Volume 46 ◦ Issue 3 ◦ September 2024

Cumhuriyet Medical Journal

Official Journal of Sivas Cumhuriyet University
Faculty of Medicine

e-ISSN: 1305-0028

cmj.cumhuriyet.edu.tr

Cumhuriyet Medical Journal (CMJ) is a peer-reviewed journal and is published four times a year, in March, June, September and December. It aims to provide readers with up-to-date information on basic, internal, and surgical science research, expert opinions, and diagnostic and treatment techniques. It publishes English-language articles both national and international. Using Open Journal Systems software, it is published online in an open journal publishing format. By collaborating with a nationally and internationally renowned referee group, it seeks to consistently enhance its quality and draw in a larger readership. It considers recommendations from all scientists interested in working with us to improve our journal. Cumhuriyet Medical Journal is indexed in the Index Copernicus Master List.

Cumhuriyet Medical Journal Editorial Board

Cumhuriyet Medical Journal adheres to the general rules applicable to manuscripts submitted to biomedical journals. Of all article drafts submitted to CMJ, those that are publishable are subjected to a rigorous double-blind peer review process. Every article that is submitted is checked for compliance with the submission guidelines in a preliminary review. Articles that go through this procedure are sent to the chief editor for editorial assessment. The piece that the editor-in-chief evaluates is given to the section editor. The editor of the pertinent section will designate a minimum of two reviewers. Reviewers are chosen based on their evaluation interests and areas of experience. The reviewers are not made aware of the authors' identity. Through feedback, reviewers offer recommendations to the editors on the article's scientific worth, the procedures used, and the statistical analyses performed. The statistics editor receives articles that need a more in-depth examination of statistics. The pertinent section editor provides an overall assessment based on the cumulative feedback from the reviewers. The editorial board then assesses the piece and renders a definitive decision. The website is used to send recommendations, criticisms, and comments to the writers of the articles; the referees' identities are kept private. After being returned to the authors for revision, article contents are required to be resubmitted within 15 days with the appropriate changes made.

* International Committee of Medical Journal Editors. General Rules for Manuscripts Submitted to Biomedical Journals: International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications. Last update date: October 2008. Available: http://www.icmje.org/index.html.

INFORMATION TO AUTHORS

Language

The writing language of the journal is English. Articles must be written in English and contain English and Turkish titles, abstracts and keywords. Authors whose native language is not English should get help from an expert in English and scientific writing before submitting their articles. Manuscripts that do not meet basic language standards will be returned without preliminary review.

Register

Articles must be sent to Cumhuriyet Medical Journal via Dergipark by the corresponding author. All authors must register with Dergipark. Manuscript files in Microsoft Word format (.doc, .docx) can be saved. There is no page limitation. If there is a problem while uploading the article files, the size of the article should be reduced, especially for articles containing figures. Registrations made by anyone other than the authors will not be accepted. The recording author will have taken all responsibilities in the recording and evaluation process. In case of technical problems during registration, support can be requested at cumhuriyetmedicaljournal@cumhuriyet.edu.tr.

Admission Requirements

The publications to be submitted must not have been previously published elsewhere (except for abstracts, part of a published conference, thesis studies) and must not be under evaluation by another journal. The recording author will be responsible for all authors regarding the publication of the article. It is also the responsibility of the authors

to ensure that publications issued by a particular institution have the approval of that institution. Only the acceptance letter written by the editorial office indicates the acceptance date. Subsequent correspondence and corrections will be sent to the author(s) before publication unless otherwise required. Permission must be given by all authors for the publication to be published.

Assessment

All evaluated studies must meet certain academic standards. Incoming articles will first be pre-evaluated by the journal secretary in terms of compliance with the writing rules. After the eligible articles are evaluated by the editor-in-chief, they will be evaluated by referees who are not known to the authors and are not from the same institution as the author. Author information is not shown to reviewers. Reviewers are given 7 days to accept the invitation and 15 days for evaluation. The evaluation period of your article may vary depending on the reviewers' acceptance rate.

PREPARATION OF ARTICLES

1. Title Page

- Article title (Turkish and English)
- Authors' full names, institutions and ORCID information (available at https://orcid.org/)
- Order of authors in the article
- Who is the corresponding author, contact information (e-mail address and phone number)
- Informed consent information obtained from participants included in the research.
- Author contributions (Concept, design, supervision, resources, materials, data collection, analysis, literature review, writing, critical review, other.)
- Financial support (If not, it should be written that there is none)
- If the article has been previously presented at the congress or the thesis has been published, this should be stated on the cover page. Full text printed articles are not accepted at the congress.

2. Conflict of Interest

- All contributing authors must fill out the ICMJE form individually and the completed forms must be uploaded to the online system by the corresponding author. Form is available from http://www.icmje.org/conflicts-of-interest/.

3. Copyright Transfer Form

The copyright transfer form must be signed by all authors and uploaded to the system. Cumhuriyet Medical Journal provides free access to its content from the journal's website and allows its content to be downloaded free of charge. Both anonymous and registered users can read and/or download articles. Unless otherwise noted, articles and journal content are licensed under a Creative Commons Attribution 4.0 International License.

4. Ethics Committee Approval

The pertinent approval document needs to be submitted to the system along with any articles that need to be approved by the ethics committee. A petition declaring that authorization is not needed must be signed by the relevant author and uploaded to the system for articles that do not require clearance from the ethics committee.

5. Plagiarism Report

Our journal's accepted similarity limit is 20%. The plagiarism report must also be uploaded to the system when the article is submitted.

6. Preparation of the Article

Formal rules for all types of writing:

- The length of the article depends on the type of article. Paper dimensions should be 8.5 × 11 inches with a 2.5 cm margin on all sides. Please use regular, plain font (12-point Times New Roman), justified, and number all pages consecutively. Indent or space paragraphs.
- Please number the lines.

Accepted article types:

1. **Original Research Article:** Research articles and systematic reviews, respectively; English Title, English Abstract, English Keywords, Turkish Title, Turkish Abstract, Turkish Keywords, Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgments, Authorship Contribution, Conflicts of Interest statement, References, Tables (inside the article and at the end of the article) and Figure Descriptions (figures must be uploaded to the system as separate files).
2. **Review:** Although they adhere to the format of a Research Article, they do not need to include sections on materials and methods, results, or discussion and may instead use other headings related to the topic.
3. **Case Report:** It should be structured as English Title, English Abstract, English Keywords, Turkish Title, Turkish Abstract, Turkish Keywords, Introduction, Case Report, Discussion, Conclusion, Acknowledgments, Authorship Contribution, Conflict Declaration, References, Tables and Figure Legends..

SECTIONS OF THE ARTICLE

Title and Abstract

An abstract must be provided in all articles. Abstracts of Research Articles should be structured with subheadings (Purpose, Methods, Results, and Conclusion). Word limit for abstract research paper is 250; 200 for case presentation.

Keywords

According to MESH, 3 - 5 keywords should be provided. Turkish keywords should be taken from “bilim terimleri”.

Introduction

This section should not contain subheadings.

Materials and Methods

This section should be written in enough detail to allow all procedures to be repeated. Authors should describe procedures and analytical techniques and identify the names and sources of all commercial products. It can be written by dividing it into subheadings.

In research requiring ethics committee permission, information regarding the permission (committee name, date and issue number) should be written in the materials and methods section. Case reports should include information that the informed consent/consent form was signed. Systematic review articles must comply with PRISMA guidelines. Authors should indicate this under the heading of materials and methods.

Information regarding statistical analyzes should be given under a separate subheading in this section and the statistical software used during the process should be specified.

Results

Authors should refer to appropriate tables and figures when reporting statistical findings, and findings should be presented in a logical order. The data given in the table should not be completely repeated in the text, but the important results in the table should be written in the text and then the table should be referenced.

Discussion

Conclusions

The Acknowledgements

If the study was supported by a grant or other funding, the name of the supporting organization and grant number should be stated.

All contributors who do not meet the authorship criteria recommended by the ICMJE (www.icmje.org) should be listed in the 'Acknowledgments' section.

Authorship Contribution

It is recommended that everyone listed as an author meet the 4 authorship requirements recommended by the ICMJE. These conditions:

1. Concept/design of the study; or have made a significant contribution to the collection, analysis and interpretation of data for the study;

2. Having drafted the article or made critical reviews of important intellectual content;

3. Having reviewed and approved the final version of the article before publication;

4. Agree to be responsible for all aspects of the work to ensure that questions regarding the validity and accuracy of any part of the work are appropriately investigated and resolved.

The parts of the research that the authors contributed to should be written using their first and last name initials.

Ex: Design: A.E., E.F., T.T., Data Collection: A.E., T.T.

Conflicts of Interest Statement

Identify possible conflicts of interest; if not, state that there is no conflict of interest.

References

American Medical Association 11th edition style is preferred. The rules of this reference style are;

1. References should be indicated in the article with superscript Arabic numerals after punctuation marks. You can create a superscript number in Word by highlighting the number you want and clicking the superscript button in the Font section at the top of the screen.

2. The reference list should be given as a separate page at the end of the article. It should be left aligned and arranged in numerical order. The reference list should only include references mentioned in the text.

3. Pubmed ID (PMID) or Pubmed Central ID (PMCID) records of the articles should NOT be added to the reference list.

4. It is important to write doi numbers, if any.

5. In articles with 7 or more authors, the first 3 authors should be written and et al. should be added. In articles with 6 or fewer authors, all authors must be written.

5. Example AMA 11th References

Book:

Author AA, Author BB. *Title of Book: Subtitle of Book*. Edition. Name of publisher; Year of publication.

E-Book:

Author AA, Author BB, Author CC. *Title of Book: Subtitle of Book*. Edition. Name of publisher; Year of publication. Date accessed. URL

Journal Article:

Author AA, Author BB, Author CC. Title of article: lower case letter for subtitle. *Abbreviated Title of Journal.* Year;Volume number(Issue number):page numbers. DOI.

Figures

Figure titles should be written after the references in the article, and the figures should be uploaded to the system as separate files.

Tables

Tables should be placed after the references in the text. Tables should NOT be uploaded as photographs (jpeg). It must be created using the insert table tool in Microsoft Word. The table name is above the table and explanations about the table content should be placed below the table.

Journal Boards

Editor in Chief

Ezgi AĞADAYI

Department of Medical Education, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye
ORCID: 0000-0001-9546-2483
E-mail: ezgiagadayi@cumhuriyet.edu.tr

Surgical Sciences Section Editors

Sinan SOYLU

Department of General Surgery, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye
ORCID: 0000-0002-3911-3227
E-mail: ssoylu@cumhuriyet.edu.tr

Fatih ADA

Department of Cardiovascular Surgery, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye
ORCID: 0000-0002-6953-5906
E-mail: fatihada@cumhuriyet.edu.tr

Onur AVCI

Department of Anesthesiology and Reanimation, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye
ORCID: 0000-0003-0743-754X
E-mail: onuravci@cumhuriyet.edu.tr

Mustafa KARADEMİR

Department of Neurosurgery, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye
ORCID: 0000-0002-0734-9040
E-mail: drkarademir@cumhuriyet.edu.tr

Mahmut ÖZBEY

Department of Thoracic Surgery, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye
ORCID: 0000-0001-8641-1772
E-mail: mahmutozbey@cumhuriyet.edu.tr

Hakan IŞIK

Department of Thoracic Surgery, University of Health Sciences, Gülhane Training and Research Hospital, Ankara, Türkiye
ORCID: 0000-0002-7602-4434
E-mail: hakan_hj@hotmail.com

Yavuz ALBAYRAK

Department of General Surgery, Atatürk University, Faculty of Medicine, Erzurum, Türkiye
ORCID: 0000-0002-2535-4329

Ali ÇETİN
Department of Gynecology and Obstetrics, İstanbul Haseki Haseki Training and Research Hospital, İstanbul, Türkiye

Ulaş ÇIKLA
Department of Neurological Surgery, University of Wisconsin-Madison, USA

Jose A SANCHES
Department of Dermatology, Universidade de São Paulo, Faculdade de Medicina, Brasil

Melih AKYOL
Department of Dermatology, Sivas Cumhuriyet University, Faculty of Medicine, Türkiye

Ünal ÖZÜM
Department of Neurosurgery, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye

Yavuz SİLİĞ
Department of Biochemistry, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Türkiye

Cumhuriyet Medical Journal

Official Journal of the Sivas Cumhuriyet University Faculty of Medicine

Volume 46 Issue 3 September 2024

CMJ. 2024;46(3): 156-163
DOI: 10.7197/cmj.1512299

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Technology-Based Evaluation in Parkinsonism

Selvin Balki[1,a], Emine Nacar[2,b]*, Rabia Seva Özkan[1,c], Merve Karakurt[1,d]

[1] *Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Sivas Cumhuriyet University, Sivas, Turkiye*
[2] *Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, İnönü University, Malatya, Turkiye*

**Corresponding author*

Review

History

Received: 08/07/2024
Accepted: 10/08/2024

ABSTRACT

Parkinson's disease is a neurodegenerative disorder characterized by motor and non-motor symptoms that worsen over time. Today, traditional clinical assessment methods are used to monitor disease progression and evaluate treatment responses. However, these methods are subjective and may fail to measure specific conditions. In recent years, thanks to advances in wearable technologies, smart sensors, and data analysis, technology-based approaches to the assessment of patients with Parkinson's disease have gained more attention. With these technologies, objective data can be obtained by monitoring patients' daily activities, motor functions, and symptoms. Motor symptoms such as tremor severity, rigidity, bradykinesia, postural instabilities, freezing phenomenon, and motor parameters of speech impairment can be objectively measured through these technologies. Furthermore, the ability to remotely transmit these data allows patients to be assessed in their own homes and provides continuous feedback to healthcare professionals. This review highlights the importance and potential of technology-based assessment methods in Parkinson's patients and aims to guide future research.

Keywords: Parkinson's, technological measurement, wearable technologies, intelligent sensors

Parkinsonda Teknolojik Tabanlı Değerlendirme

Derleme

Süreç

Geliş: 08/07/2024
Kabul: 10/08/2024

ÖZET

Parkinson hastalığı, motor ve motor olmayan semptomlarla karakterize nörodejeneratif bir hastalıktır ve bu semptomlar zaman içinde kötüleşir. Günümüzde hastalığın ilerleyişini izlemek ve tedavi yanıtlarını değerlendirmek için geleneksel klinik değerlendirme yöntemleri kullanılmaktadır. Ancak bu yöntemler subjektiftir ve belirli durumları ölçmede yetersiz kalabilir. Son yıllarda, giyilebilir teknolojiler, akıllı sensörler ve veri analizindeki ilerlemeler sayesinde parkinson hastalarının değerlendirilmesinde teknolojik tabanlı yaklaşımlar daha fazla dikkat çekmektedir. Bu teknolojiler sayesinde hastaların günlük aktiviteleri, motor fonksiyonları ve semptomları izlenilerek objektif veriler elde edilebilir. Tremor şiddeti, rijidite, bradikinezi, postüral instabiliteler, donma fenomeni ve konuşma bozukluğunun motor parametreleri gibi motor semptomlar bu teknolojiler aracılığıyla objektif olarak ölçülebilir. Ayrıca, bu verilerin uzaktan aktarılabilmesi, hastaların kendi evlerinde değerlendirilebilmesine olanak tanır ve sağlık uzmanlarına sürekli geri bildirim sağlar. Bu derleme, parkinson hastalarında teknolojik tabanlı değerlendirme yöntemlerinin önemini ve potansiyelini vurgulamakta ve gelecekteki araştırmalara rehberlik etmeyi amaçlamaktadır.

Anahtar Kelimeler: Parkinson, teknolojik ölçüm, giyilebilir teknolojiler, akıllı sensörler

[a] *sbalki@cumhuriyet.edu.tr* *0000-0003-4903-6349*
[b] *emine.nacar@inonu.edu.tr* *0000-0002-1172-1837*
[c] *seva.kantar@gmail.com* *0000-0001-9892-5949*
[d] *mrve_144@hotmail.com* *0000-0002-3370-7526*

How to Cite: Balki S, Nacar E, Seva Özkan R, Karakurt M. Technology-Based Evaluation in Parkinsonism. Cumhuriyet Medical Journal. 2024;46(3): 156-163.

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by typical motor symptoms including bradykinesia, hypo-/akinesis, rigidity, and resting tremor, usually with asymmetric onset.[1] The prevalence and incidence rates for PD in Europe are estimated to be approximately 108-257/100,000 and 11-19/100,000 per year, respectively.[2] In Turkey, the prevalence of PD was determined as 1.2% in a prevalence study conducted in Edirne province in 2022.[3] The incidence of PD increases with age and the majority of individuals are over 60 years of age.[4] Considering that the world population is getting older, the number of individuals with PD may exceed 12.9 million in 2040.[5] In most Parkinson's cases, the disease is idiopathic, but genetic and environmental risk factors also contribute.[6] Age is the most important risk factor for PD. In epidemiologic studies, exposure to pesticides, heavy metals, rural life and farming were listed among the risk factors, while smoking and caffeine consumption were found to be protective.[7] Although PD pathology is usually diagnosed based on motor symptoms, many non-motor symptoms also occur with the disease.[8]

Non-motor symptoms are often prominent and sometimes cause more disability than motor symptoms. The current practice for assessing motor and non-motor symptoms in patients with Parkinson's disease is the neurological examination, in which the clinician watches the patient perform specific tasks. Clinicians assign points to tasks performed by the patient with the Unified Parkinson's Disease Rating Scale (UPDRS)[1] or MDS-UPDRS (Movement Disorder Society-Sponsored Revision of the Unified PD Rating Scale).[9] With another rating scale, the Hoehn and Yahr scale (HY)[9], the clinical stage of the patient is scored between 0-5. These clinical scales are subjective and may lead to high inter-rater variability between clinicians. Clinical assessments are also based on the progression of symptoms described in patient diaries. The reliability of such reports is limited by subjectivity and patient recall bias.[10]

Accurate diagnosis of PD is vital for prognosis monitoring and treatment.[11] Early and accurate diagnosis of PD can improve the long-term quality of life of people with Parkinson's disease, while misdiagnosis of a patient leads to delays in appropriate treatment. [12, 13] Therefore, there is a need to develop accurate, objective, and continuously recordable tools to assess motor complications in PD.[11] In this context, the use of smart technologies in PD applications has increased in recent years.[14] In particular, smart technologies, such as wearable sensors, are being used to assess the progression of the disease by analyzing the symptoms of Parkinson's patients and even to detect early signs of the onset stage in the early diagnosis of PD.[15] However, no data on the percentage of smart technology use to assess motor symptoms in PD was found in the literature. Popular devices include inertial measurement units (IMUs), force and pressure plates, biopotential sensors, and optical motion capture systems.[16] IMUs usually include accelerometer and gyroscope sensors that can record the data needed to analyze symptoms.[17] Similarly, force sensors in the force plate provide information about the patient's posture and balance.[18] As a complementary method, electroencephalogram (EEG) and electromyogram (EMG) sensors measure neural activity and muscle response, respectively. Optical motion capture systems such as Vicon and Microsoft Kinect analyze body movements in patients' environments. Interconnecting these sensors has also been facilitated by the increasing use of communication protocols such as Zigbee and Bluetooth.

The increasing use of technology in the diagnosis and treatment of PD offers important opportunities to improve the quality of life of patients with Parkinson's disease by providing objective data collection, remote monitoring, and continuous follow-up.[15] Recent studies have focused on various tools that enable objective assessment of motor symptoms such as tremor, rigidity, bradykinesia, postural instability, freezing phenomenon, and speech impairment in Parkinson's disease.[19-21] In this context, the aim of the present review is to describe the main motor symptoms seen in Parkinson's disease patients and to discuss the technologically based methods used in their assessment.

Motor Symptoms in PD

The motor manifestations of the disease consist of four basic symptoms including bradykinesia, resting tremor, rigidity and postural instability, which are also used in the clinical diagnosis of the disease. In the later stages of the disease, postural changes, freezing of gait, disturbances in balance, dystonia, swallowing and speech disorders may also be observed.[22]

Tremor

Tremor is the most common symptom in PD and one of the most difficult symptoms to treat, affecting the extremities, jaw, and tongue.[23] In PD with predominant tremors in the upper extremities, postural and kinetic tremor is usually seen concurrently with resting tremors,[24] which may functionally interfere with task performance, disrupt sleep, and cause difficulties in performing activities of daily living.[25] The type of treatment depends on the cause of the tremor; therefore, an accurate diagnosis of tremor is very important. Various parameters such as the amplitude, subtle changes, activity, or tremor fluctuations of tremors cannot be effectively assessed with current clinical rating scales.[26] In addition, since tremor varies depending on emotions during the day, short-term regular outpatient follow-ups do not accurately reflect the intensity of tremors.[26] Therefore, continuous evaluation of tremors is recommended.[27]

Various sensor systems have been developed to objectively measure tremors in Parkinson's disease. These sensor systems include EMG, accelerometer, gyroscope,

goniometer, and optical motion capture systems.[28] These devices enable long-term monitoring of PD, collection of data on tremors, identification of their types, and grading of the severity of PD. However, the major disadvantage of these methods is that they are usually limited to the tremor severity of a single extremity and do not provide a comprehensive, whole-body assessment of postural tremor measurement.[29] While only the contractions in the patient's muscles are measured with EMG signals, the accelerometer measures the linear movement of the patient, the gyroscope measures the body's balance, and the goniometer measures only the range of motion of the joints. By combining these sensors, IMUs offer a new approach. Unlike previous studies, IMUs detect postural tremor.[30]

Among all movement parameters of tremors, wearable devices are used to measure the frequency of tremors.[31] In one study, a wireless motion sensor unit worn on the index finger was used to evaluate patient performance based on tasks similar to activities of daily living.[27] The recordings from the motion sensors showed that the device could be used to classify tremors as postural or kinetic and to measure tremor severity during both standard and non-standard activities. However, it was reported that larger studies are needed to obtain more reliable results because the study was performed using a small sample size.[27]

Wile et al. included 41 patients who wore smart watch devices and whose tremors were monitored within 3-6 minutes.[32] Parameters were recorded with the hands at rest and in the outstretched position. The findings from this study showed that smartwatch PD is highly specific and sensitive in differentiating postural tremors from essential tremors. Thus, smartwatch devices are useful and applicable in both clinical and community settings.[15] However, the disadvantage of this assessment may be that the monitoring time (3-6 minutes) is too short to fully characterize tremors.[32]

Another clinical study used Physilog, an ambulatory analysis method, to assess spatiotemporal parameters of gait, postural sway, physical activity, tremor, and bradykinesia.[15] The study involved 10 PD patients and 10 control subjects who undertook a 45-minute protocol of 17 typical daily activities. As a result, the estimated tremor amplitude was highly correlated with the UPDRS tremor subscore.[33]

In a recent study, Braybrook et al. used the Parkinson KinetiGraph (PKG) system to assess tremors in PD patients and developed a new algorithm to distinguish between resting and postural tremors by calculating the percentage of tremor duration presented between 09:00-18:00.[31] This algorithm not only increased the sensitivity and selectivity of assessing tremor occurrence but also analyzed the relationship between tremor and bradykinesia. In addition, this algorithm has identified a threshold value at which tremor begins to occur. It can be said that technological approaches to measuring tremors can help both researchers understand the neural mechanisms of PD and thus develop new treatments.

Rigidity

Rigidity describes the increased resistance of an extremity or axial body part to passive movement, independent of speed and direction of movement, and is one of the main symptoms seen in PD.[34] Clinically, rigidity is most commonly assessed as part of the motor section of the UPDRS.[35] However, the fact that rigidity assessment is a method used to monitor the course of motor symptoms and the efficacy of treatments in PD necessitates its evaluation with an objective and quantitative method.[35] Elastography, EMG, isokinetic dynamometry, and myotonometry are some of the methods used in the objective evaluation of rigidity.[36] Elastography is the determination of tissue stiffness by examining the images of the tissue to be evaluated with ultrasound and using an objective unit of measurement called Young's Modulus, which expresses the amount of deformation of the muscle under external force.[37] EMG evaluates the electrical fluctuations that occur based on neuromuscular activity as well as muscle responses to standard electrical stimuli and provides information about tonus, elasticity, and rigidity.[38] Isokinetic dynamometry provides information about rigidity by moving any body part at a constant speed and comparing the resistance to movement with normative data.[36] Myotonometry is a method used to measure the biomechanical and viscoelastic properties of soft tissues.[39] It records and evaluates the oscillations that occur in the soft tissue in response to small mechanical effects sent to the soft tissue.[40] In a study using myotonometry as an objective measurement tool to document the effect of deep brain stimulation in alleviating rigidity in Parkinson's patients, it was found that increased rigidity was associated with increased viscoelastic stiffness values. In addition, the use of myotonometry for objective measurement of rigidity was supported.[41]

NeuroFlexor is a clinical method that measures passive movement resistance and its neural, elastic and viscous components.[42] There are studies on its use in patients with Parkinson's disease.[43] In a study, neural and non-neural components of passive movement resistance in the wrist and finger muscles in patients with PD were investigated using the NeuroFlexor method. It was shown that stretch-induced reflex activity, not non-neural resistance, contributes to the rigidity of the wrist muscles in PD. It was concluded that NeuroFlexor is a potentially valuable clinical and research tool for measuring rigidity.[43]

In another study, the Bionics Institute Rigidity Device (BIRD) was used to measure finger rigidity. It was observed that the rigidity measured using the device was moderately compatible with the MDS-UPDRS.[44] The ability of this technique to detect changes resulting from therapeutic intervention may be useful in clinical trials or as a home monitoring tool to track symptom fluctuations. Further studies are needed to improve the robustness and usability of the device and to validate the technique in a larger group. It can be said that these technological approaches to measuring rigidity will contribute to better management of patients' treatment processes with objective and precise measurements by providing remote monitoring and continuous follow-up.

Bradykinesia

Bradykinesia is an important symptom of PD. Bradykinesia is the slowness in the initiation of voluntary movement with a gradual decrease in the speed and amplitude of repetitive actions.[45] Bradykinesia develops early or late in all patients with Parkinson's disease. Patients first develop hypokinesia, then hypokinesia progresses to bradykinesia, and finally akinesia. Akinesia is the advanced level of bradykinesia and means the inability to move. Bradykinesia and akinesia are among the most disabling symptoms in these patients. Since patients have difficulty in initiating and maintaining motor movement, their daily lives are negatively affected. It is important to evaluate bradykinesia and determine the treatment method accordingly. In addition to being equipped with accelerometers and gyroscopes, the touch screens of some smartphones provide an opportunity for bradykinesia assessment because they are very sensitive and capable of sampling many different parameters.[46, 47] In a study, accelerometers were used in the evaluation of bradykinesia and the patient's touching the touch screen at certain intervals, finger taps, and pronation-supination movements were evaluated. When the results were evaluated, it was found that all results correlated with the MDS-UPDRS, which is the gold standard tool for grading motor symptoms in Parkinson's disease patients.[48] In another study, *Leap Motion* (hand tracking device) developed to measure bradykinesia was used. Participants with Parkinson's performed wrist pronation/supination, hand opening/closing, and finger tapping tasks under different conditions. At the end of the assessments, the estimated total bradykinesia scores were found to be in strong agreement with clinical scores. The findings demonstrated that this method can objectively measure bradykinesia in agreement with clinical observation and provide reliable measures over time. Only computer and software are required to perform the assessments and it was concluded that it is suitable for both clinical and home symptom monitoring.[46]

Another study used the *SENSE-PARK* system, which consists of sensors worn by patients. The *SENSE-PARK* system consists of a set of wearable sensors (3 used during the day and 1 at night), a Wii Balance Board, software, and a smartphone application. The sensors monitor the movement of Parkinson's patients during their daily activities by collecting raw motor-related data. This sensor set, together with the algorithms developed during the *SENSE-PARK* project phase, allows the monitoring of gait, hypokinesia, dyskinesia, tremor, and sleep-related parameters. The feasibility and usability of the *SENSE-PARK* system were tested 24/7 for 12 weeks in a study involving 22 Parkinson's patients. This system was found to be very feasible in terms of patient compliance, satisfaction, and ease of use. Patients continued to participate in the program for 16 weeks and most of them requested to continue the program at the end of the study. It was found that wearing such a system increased motivation in patients by providing direct feedback about individual health status.[49] In conclusion, technology-based measurement tools play an important role in the assessment of bradykinesia. These tools can help us better assess the severity of the disease, monitor the efficacy of treatment, and improve patients' quality of daily life.

Postural Control and Mobility Problems

Decreased postural control and mobility, slipping, tripping, falling, and decreased gait in the community are common problems in PD.[50] Accurate assessment of these problems allows clinicians and researchers to monitor disease progression and response to interventions. Traditional three-dimensional video-based motion analysis systems allow comprehensive kinematic and kinetic analysis of movement in PD. These systems require relatively large spaces, are expensive, and require considerable expertise, limiting their use in the clinic and at home. *The Microsoft Kinect* is a camera-based sensor used to directly control computer games through body movement. Kinect tracks the position of the limbs and body without the need for hand controllers or power platforms. The use of a depth sensor also allows *Kinect* to capture three-dimensional motion patterns. It is recognized that this system has the potential to remotely assess movement symptoms in Parkinson's patients.[51] The accuracy of *Kinect* for measuring functional and clinically relevant movements in Parkinson's disease patients has been evaluated. This study examined standing, multidirectional reaching, stepping, and walking in place in PD and handshaking, finger tapping, foot and leg agility, chair lifting, and hand pronation in UPDRS. The results showed that the Kinect system has the potential to be a low-cost, home-based sensor for measuring movement symptoms in people with Parkinson's disease. It was reported to be able to accurately measure the timing and overall spatial characteristics of clinically relevant movements but was not able to provide the same spatial accuracy for smaller movements such as hand wringing or toe-tapping. They concluded that *Kinect* may be useful in detecting relative deterioration in both the timing and size of movements over the same period or in monitoring improvement.[52]

In a study using smartphones with Android operating systems, participants with PD were asked to ''(vocal test) say the sound 'aaah' as long as possible; (posture test) stand upright without assistance for 30 seconds; (gait test) walk twenty steps and return to the starting position; (finger tapping test) tap the screen in a regular rhythm; and (reaction time test) press the button on the screen as soon as the object appeared. Participants then took their smartphones home to perform the five tasks four times a day for one month. The device collected the measurements, and the participants met with the researcher online once a week. In the end, it was determined that Parkinson's symptoms could be measured via smartphone and they found that it had diagnostic potential.[53] In another study, a non-invasive, wearable, and wireless embedded cyber-physical system (CPS) was implemented and tested in real time for both gait analysis and postural instability detection in Parkinson's patients. The CPS takes the form of a wearable sensing system (eight EEG and eight EMG wireless smart electrodes). It is a self-wearable system without the need for patient assistance and electrode placement. The system calculates 57 different indices, estimating the

effects of muscles and motor cortex activity during movement. The processing algorithm implemented allows the system to detect critical situations during gait and thus activate corrective feedback movement. In this way, it can be used as an assistive tool even in a home environment, remotely monitoring the medication effect in Parkinson's patients, and collecting data throughout the day. Experimental results clearly show that the system can infer gait differences between Parkinson's patients and healthy individuals, including agonist-antagonist co-activation.[54]

According to these studies, technology-based measurement tools have an important role in the assessment of postural control and mobility. These tools can help us to better assess the severity of the disease, monitor the effectiveness of treatment, and improve patients' quality of daily life.

Freezing Phenomenon

Freezing phenomenon is defined as a motor impairment that causes sudden and temporary pauses in walking. It is one of the important symptoms seen in individuals with PD, especially in the elderly, preventing walking. It is observed in 50% of individuals with PD.[55] The freezing phenomenon usually occurs during the initiation of walking and turning. It also occurs in situations such as crossing a narrow road, door entrances, and individual restrictions where the patient is assigned more than one task.[56]

Traditional subjective assessment methods are the first tests used to evaluate the freezing phenomenon, but these methods do not give us quantitative information. Laboratory-based gait analysis, on the other hand, is one of the quantitative measurement methods and is a system that is applied in a standard gait laboratory or research center, where equipment such as a video recording system, 3D motion capture system, force plate, and EMG are used.[55] In a typical gait laboratory, a 3D dynamic motion capture system is applied to determine the frequency of freezing phenomena, knee and hip angle, stride length, and frequency. In this analysis method, a 3D dynamic model of the patient is prepared by placing several reflective balls on the body and using synchronized cameras. With this method, quantitative results are obtained with a highly accurate human gait analysis in a short time. The laboratory-based gait assessment method is considered a gold standard. However, due to the unpredictable nature of the freezing phenomenon, it is an extremely challenging, lengthy, and costly procedure.[57] It is difficult to use in daily assessment. Therefore, with the development of portable and wireless sensors in recent years, a low-cost and high-reliability ambulatory gait analysis system has been designed to evaluate the freezing phenomenon in PD.[58]

Ambulatory gait analysis includes wearable sensors and portable digital monitoring systems that record various parameters to assess freezing phenomena. Multiple sensors, such as Inertial Measurement Unit (IMU), Force Sensitive Resistance (FSR), and EEG, smartphone-based applications are used to detect episodes of freezing phenomenon.[59]

The IMU consists of specialized sensors for evaluating human gait, such as kinematics and kinetics. An accelerometer records the linear velocity change in 3-dimensional axes. A gyroscope has a freely rotating disc that records angular velocity when the human body is in motion.[55] The sensors can be attached to the lower limbs such as hips, knees, shins, ankles, or feet and can be used to analyze various walking disorders. Many investigators have used a combination of IMU sensors in different parts of the lower limb to assess episodes of freezing phenomena due to its small size, continuous gait signal collection, kinematics, and high reliability compared to electrophysiological (EEG and EMG) based sensors.[58] The disadvantages of IMU sensors are poor precise position calculation due to the accumulation of fundamental errors and insufficient precision of the patient-independent model.[60]

Some researchers have conducted studies on the analysis of gravity response signals using FSR sensors to detect cases of freezing phenomena.[55, 58] FSR is a typical load cell made of semiconductor material whose resistance changes when subjected to force or pressure. Due to its small size and low cost, it can be used embedded in the sole of the foot for ambulatory gait analysis. Many researchers have used FSR designs with different loading capacities in various evaluation parameters for gait analysis of toe lift, heel stride, sensitivity and freezing phenomenon.[61]

The EEG cap is an innovative, ambulatory, non-invasive technique to measure real-time physiological changes in the brain (cerebral cortex, occipital lobe) during pre-freezing phenomenon and freezing phenomenon cases in Parkinson's disease patients. By adopting this approach, some researchers have detected freezing phenomenon cases using different machine learning classifiers in EEG signals.[62]

Some researchers have used a multi-model strategy using physical and physiological sensors (IMU, FSR, EMG, and functional near-infrared sensors) to identify freezing phenomenon events online. The multi-model strategy can reduce the delay in the detection of the freezing phenomenon. This multi-model strategy can provide an in-depth and comprehensive perspective that a single sensor cannot provide. However, the integration of multiple sensors can increase system complexity and cost.[63]

It mainly consists of a triaxial accelerometer, a microcontroller with low power consumption, a bluetooth module, and an 800mA lithium battery that can support the operation of the node for 10 hours. Acceleration measurements are received by a microcontroller at a frequency of 200 Hz via the IIC bus, which then transmits them to the Bluetooth module and transmits the data to the smartphone. This system is one of the technologically based techniques that can be used in the detection of freezing phenomenon attacks in Parkinson's disease. According to research on sensor placement, it has been

found that the waist is a better location for sensor placement than other areas such as thighs, legs, feet, and chest. Thanks to its small size, patients will not feel discomfort when they wear this sensor node.[64]

According to the studies, technologically based systems facilitate the detection of frostbite phenomena. These systems may contribute to quantitatively assessing the frostbite phenomenon and improve the quality of daily life of patients.

Speech Disorders

PD is characterized by speech disorders, among many other symptoms. Studies have shown that symptoms related to PD-specific speech disorders may include reduced language flexibility, longer pauses, and monotonous and slow speech. Technology-based methods have been useful in sensitively capturing differences between Parkinson's patients and healthy controls in symptoms such as maximum vocalization time, vocalization coefficient, and facial tremor.[65]

One of the prominent examples of smartphone-related evaluations is the mPower study on PD.[66] This study was conducted with the use of the built-in microphone of the smartphone. The vocal activity recorded by the smartphone is a continuous vocalization process in which participants are instructed to say "Aaaaah" into the microphone and are asked to speak into the microphone at a constant volume for up to 10 seconds. Data from this event include audio files containing measurements from the telephone microphone for the 10-second sustained vocalization and a 5-second countdown before the event.[66] An automated speech assessment is also proposed as part of tests such as posture analysis, gait assessment, finger tapping, and reaction time using commercially available smartphone applications to monitor Parkinson's symptoms in the home environment. With such technology-based assessments, it has become easier to detect Parkinson's symptoms.

Conclusion

This review highlights the importance of technology-based assessments in the diagnosis and management of PD. Compared to traditional methods, technological approaches provide more precise, objective and continuous data tracking, allowing a better understanding of disease progression. In particular, wearable devices, mobile applications and artificial intelligence-based analyses support clinical assessments and increase patients' independence in their daily lives.

The findings show that technology has become an indispensable tool in PH management. However, it should be kept in mind that studies in this field are still in their infancy and more research is needed. Especially in our country, although the prevalence of PD is quite high, the number of studies in this field is limited. This situation requires taking steps to expand the use of technology in the treatment of PD in our country. For this purpose, university-industry collaborations should be established to support the development of new need-oriented technologies. Neurologists, doctors, physical therapists and other healthcare professionals should be informed about technological developments. The technological solutions developed should be integrated into the existing health system and their accessibility should be increased. By participating in international studies, information sharing should be ensured and joint projects should be developed.

In conclusion, the importance of technology in the management of PD cannot be underestimated. In the future, technology-based assessments are expected to develop further and be more widely used in the diagnosis, follow-up and treatment of PD. In particular, it is thought that studies to be conducted in this field in our country will not only improve the quality of life of our patients, but also strengthen the effectiveness of our healthcare system and contribute to our country having a voice in the international arena in this field.

References

1. Fahn S. Unified Parkinson's disease rating scale. *Recent developments in Parkinson's disease*. 1987:153-63.
2. Balestrino R, Schapira A. Parkinson disease. *European journal of neurology*. 2020;27(1):27-42. doi: 10.1111/ene.14108.
3. Güler, S., Caylan, A., Turan, F. N., & Dağdeviren, N. (2022). Prevalence and Clinical Features of Idiopathic Parkinson's Disease in Western Turkey. Archives of Neuropsychiatry, 59(2), 98. doi: 10.29399/npa.27486.
4. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement disorders*. 2014;29(13):1583-90. doi: 10.1002/mds.25945.
5. Dorsey ER, Bloem BR. The Parkinson pandemic—a call to action. *JAMA neurology*. 2018;75(1):9-10. doi: 10.1001/jamaneurol.2017.3299.
6. Dorsey ER, Elbaz A, Nichols E, Abbasi N, Abd-Allah F, Abdelalim A, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2018;17(11):939-53. doi: 10.1016/S1474-4422(18)30295-3.
7. Jankovic J, Tan EK. Parkinson's disease: etiopathogenesis and treatment. *Journal of Neurology, Neurosurgery & Psychiatry.* 2020;91(8):795-808. doi: 10.1136/jnnp-2019-322338.
8. Wolters EC. Variability in the clinical expression of Parkinson's disease. *Journal of the neurological sciences.* 2008;266(1-2):197-203. doi: 10.1016/j.jns.2007.08.016.
9. Hoehn MM. Commentary: Parkinsonism: Onset, progression, and mortality. *Neurology*. 1998;50:318-. doi: 10.1212/wnl.50.2.318.
10. Ozanne A, Johansson D, Hällgren Graneheim U, Malmgren K, Bergquist F, Alt Murphy M. Wearables in epilepsy and Parkinson's disease—a focus group study. *Acta Neurologica Scandinavica*. 2018;137(2):188-94. doi: 10.1111/ane.12798.
11. Qu Y, Zhang T, Duo Y, Chen L, Li X. Identification and quantitative assessment of motor complications in Parkinson's disease using the Parkinson's KinetiGraph™. *Frontiers in Aging Neuroscience*. 2023;15. doi: 10.3389/fnagi.2023.1142268.
12. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson's disease: challenges and opportunities. *Movement Disorders*. 2016;31(9):1272-82. doi: 10.1002/mds.26642.

13. Rovini E, Maremmani C, Cavallo F. How wearable sensors can support Parkinson's disease diagnosis and treatment: a systematic review. *Frontiers in neuroscience*. 2017;11:555. doi: 10.3389/fnins.2017.00555.
14. Di Lazzaro G, Ricci M, Al-Wardat M, Schirinzi T, Scalise S, Giannini F, et al. Technology-based objective measures detect subclinical axial signs in untreated, de novo Parkinson's disease. *Journal of Parkinson's disease.* 2020;10(1):113-22. doi: 10.3233/JPD-191758
15. Godinho C, Domingos J, Cunha G, Santos AT, Fernandes RM, Abreu D, et al. A systematic review of the characteristics and validity of monitoring technologies to assess Parkinson's disease. *Journal of neuroengineering and rehabilitation.* 2016;13:1-10. doi: 10.1186/s12984-016-0136-7.
16. Özen D, Karakaya MG, Yenişehir S, Çıtak İ. Parkinsonlu Hastalarda Teknoloji Temelli Yürüyüş Değerlendirmelerinin Literatür Analizi Literature Analysis Of Technology-Based Gait Assessment In Patients With Parkinson Disease. Full Text Book.56.
17. Moreau C, Rouaud T, Grabli D, Benatru I, Remy P, Marques A-R, et al. Overview on wearable sensors for the management of Parkinson's disease. *NPJ Parkinson's Disease*. 2023;9(1):153. doi: 10.1038/s41531-023-00585-y.
18. Suppa A, Kita A, Leodori G, Zampogna A, Nicolini E, Lorenzi P, et al. L-DOPA and freezing of gait in Parkinson's disease: Objective assessment through a wearable wireless system. *Frontiers in neurology.* 2017;8:406. doi: 10.3389/fneur.2017.00406.
19. Bove F, Di Lazzaro G, Mulas D, Cocciolillo F, Di Giuda D, Bentivoglio AR. A role for accelerometry in the differential diagnosis of tremor syndromes. *Functional neurology.* 2018;33(1):45. doi: 10.11138/fneur/2018.33.1.045
20. Delrobaei M, Tran S, Gilmore G, McIsaac K, Jog M. Characterization of multi-joint upper limb movements in a single task to assess bradykinesia. *Journal of the neurological sciences*. 2016;368:337-42. doi: 10.1016/j.jns.2016.07.056.
21. Ricci M, Giannini F, Saggio G, Cenci C, Di Lazzaro G, Pisani A, editors. A novel analytical approach to assess dyskinesia in patients with Parkinson disease. *2018 IEEE international symposium on medical measurements and applications (MeMeA)*. 2018; (pp. 1-5), IEEE. doi: 10.1109/MeMeA.2018.8438666.
22. Kaya D, Soyukibar TE. Parkinson's Disease and Parkinsonism. *The Journal of Turkish Family Physician.* 2022;13(4):182-92. doi: 10.15511/tjtfp.22.00482
23. Jankovic J. Parkinson's disease: clinical features and diagnosis. *Journal of neurology, neurosurgery & psychiatry.* 2008;79(4):368-76. doi: 10.1136/jnnp.2007.131045.
24. Kraus P, Lemke M, Reichmann H. Kinetic tremor in Parkinson's disease–an underrated symptom. *Journal of neural transmission*. 2006;113:845-53. doi: 10.1007/s00702-005-0354-9.
25. Fleischman DA, Wilson RS, Schneider JA, Bienias JL, Bennett DA. Parkinsonian signs and functional disability in old age. *Experimental aging research*. 2007;33(1):59-76. doi: 10.1080/03610730601006370.
26. Rigas G, Tzallas AT, Tsipouras MG, Bougia P, Tripoliti EE, Baga D, et al. Assessment of tremor activity in the Parkinson's disease using a set of wearable sensors. *IEEE Transactions on Information Technology in Biomedicine.* 2012;16(3):478-87. doi: 10.1109/TITB.2011.2182616.
27. Heldman DA, Jankovic J, Vaillancourt DE, Prodoehl J, Elble RJ, Giuffrida JP. Essential tremor quantification during activities of daily living. *Parkinsonism & related disorders*. 2011;17(7):537-42. doi: 10.1016/j.parkreldis.2011.04.017.
28. Delrobaei M, Memar S, Pieterman M, Stratton TW, McIsaac K, Jog M. Towards remote monitoring of Parkinson's disease tremor using wearable motion capture systems. *Journal of the neurological sciences.* 2018;384:38-45. doi: 10.1016/j.jns.2017.11.004.
29. Grimaldi G, Manto M-U, Manto M. *Tremor: from pathogenesis to treatment*: Morgan & Claypool Publishers; 2008.
30. Rahimi F, Bee C, South A, Debicki D, Jog M, editors. Variability of hand tremor in rest and in posture—A pilot study. *In 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*; 2011: IEEE. doi: 10.1109/IEMBS.2011.6090067.
31. Braybrook M, O'Connor S, Churchward P, Perera T, Farzanehfar P, Horne M. An ambulatory tremor score for Parkinson's disease. *Journal of Parkinson's disease*. 2016;6(4):723-31. doi: 10.3233/JPD-160898.
32. Wile DJ, Ranawaya R, Kiss ZH. Smart watch accelerometry for analysis and diagnosis of tremor. *Journal of neuroscience methods*. 2014;230:1-4. doi: 10.1016/j.jneumeth.2014.04. 021.
33. Salarian A, Russmann H, Wider C, Burkhard PR, Vingerhoets FJ, Aminian K. Quantification of tremor and bradykinesia in Parkinson's disease using a novel ambulatory monitoring system. *IEEE Transactions on biomedical engineering.* 2007;54(2):313-22. doi: 10.1109/TBME.2006.886670
34. Tysnes O-B, Storstein A. Epidemiology of Parkinson's disease. *Journal of neural transmission*. 2017;124:901-5. doi: 10.1007/s00702-017-1686-y.
35. Teshuva I, Hillel I, Gazit E, Giladi N, Mirelman A, Hausdorff JM. Using wearables to assess bradykinesia and rigidity in patients with Parkinson's disease: a focused, narrative review of the literature. *Journal of Neural Transmission*. 2019;126:699-710. doi: 10.1007/s00702-019-02017-9.
36. Ferreira-Sánchez MdR, Moreno-Verdú M, Cano-de-La-Cuerda R. Quantitative measurement of rigidity in Parkinson's disease: a systematic review. *Sensors*. 2020;20(3):880. doi: 10.3390/s20030880.
37. Gao J, He W, Du L-J, Li S, Cheng L-G, Shih G, et al. Ultrasound strain elastography in assessment of resting biceps brachii muscle stiffness in patients with Parkinson's disease: a primary observation. *Clinical Imaging*. 2016;40(3):440-4. doi: 10.1016/j.clinimag.2015.12.008.
38. López-de-Celis C, Pérez-Bellmunt A, Bueno-Gracia E, Fanlo-Mazas P, Zárate-Tejero CA, Llurda-Almuzara L, et al. Effect of diacutaneous fibrolysis on the muscular properties of gastrocnemius muscle. *PLoS One*. 2020;15(12):e0243225. doi: 10.1371/journal.pone.0243225.
39. Kisilewicz A, Madeleine P, Ignasiak Z, Ciszek B, Kawczynski A, Larsen RG. Eccentric exercise reduces upper trapezius muscle stiffness assessed by shear wave elastography and myotonometry. *Frontiers in Bioengineering and Biotechnology*. 2020;8:928. doi: 10.3389/fbioe.2020.00928.
40. Agyapong-Badu S, Warner M, Samuel D, Stokes M. Practical considerations for standardized recording of muscle mechanical properties using a myometric device: Recording site, muscle length, state of contraction and prior activity. *Journal of Musculoskeletal Research.* 2018;21(02):1850010. doi: 10.1142/S0218957718500100.
41. Rätsep T, Asser T. Changes in viscoelastic properties of skeletal muscles induced by subthalamic stimulation in patients with Parkinson's disease. *Clinical biomechanics.* 2011;26(2):213-7. doi: 10.1016/j.clinbiomech.2010.09.014.
42. Gäverth J, Sandgren M, Lindberg PG, Forssberg H, Eliasson A-C. Test-retest and inter-rater reliability of a method to measure wrist and finger spasticity. *Journal of rehabilitation medicine*. 2013;45(7):630-6. doi: 10.2340/16501977-1160.

43. Zetterberg H, Frykberg GE, Gäverth J, Lindberg P. Neural and nonneural contributions to wrist rigidity in Parkinson's disease: an explorative study using the NeuroFlexor. *BioMed research international.* 2015;2015. doi: 10.1155/2015/276182.
44. Perera T, Lee W-L, Jones M, Tan JL, Proud EL, Begg A, et al. A palm-worn device to quantify rigidity in Parkinson's disease. *Journal of neuroscience methods*. 2019;317:113-20. doi: 10.1016/j.jneumeth.2019.02.006.
45. Reichmann H. Clinical criteria for the diagnosis of Parkinson's disease. *Neurodegenerative diseases*. 2010;7(5):284-90. doi: 10.1159/000314478.
46. Lee WL, Sinclair NC, Jones M, Tan JL, Proud EL, Peppard R, et al. Objective evaluation of bradykinesia in Parkinson's disease using an inexpensive marker-less motion tracking system. *Physiological measurement*. 2019;40(1):014004. doi: 10.1088/1361-6579/aafef2.
47. Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. *Journal of Parkinson's disease*. 2012;2(1):47-55. doi: 10.3233/JPD-2012-11071.
48. Kassavetis P, Saifee TA, Roussos G, Drougkas L, Kojovic M, Rothwell JC, et al. Developing a tool for remote digital assessment of Parkinson's disease. *Movement disorders clinical practice.* 2016;3(1):59-64. doi: 10.1002/mdc3.12239.
49. Ferreira JJ, Godinho C, Santos AT, Domingos J, Abreu D, Lobo R, et al. Quantitative home-based assessment of Parkinson's symptoms: The SENSE-PARK feasibility and usability study. *BMC neurology*. 2015;15:1-7. doi: 10.1186/s12883-015-0343-z.
50. Lord S, Galna B, Godfrey A, Burn D, Rochester L, editors. Patterns of daily ambulatory activity differ in early Parkinson's disease compared with controls. *16th International Congress of Parkinson's Disease and Movement Disorders*; 2012: Newcastle University.
51. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Movement disorders: official journal of the Movement Disorder Society.* 2008;23(15):2129-70. doi: 10.1002/mds.22340.
52. Galna B, Barry G, Jackson D, Mhiripiri D, Olivier P, Rochester L. Accuracy of the Microsoft Kinect sensor for measuring movement in people with Parkinson's disease. *Gait & posture*. 2014;39(4):1062-8. doi: 10.1016/j.gaitpost.2014. 01.008.
53. Arora S, Venkataraman V, Zhan A, Donohue S, Biglan KM, Dorsey ER, et al. Detecting and monitoring the symptoms of Parkinson's disease using smartphones: A pilot study. *Parkinsonism & related disorders.* 2015;21(6):650-3. doi: 10.1016/j.parkreldis.2015.02.026.
54. De Venuto D, Annese VF, Mezzina G, Defazio G. FPGA-based embedded cyber-physical platform to assess gait and postural stability in Parkinson's disease. *IEEE Transactions on Components, Packaging and Manufacturing Technology.* 2018;8(7):1167-79. doi: 10.1109/TCPMT.2018.2810103
55. Bansal SK, Basumatary B, Bansal R, Sahani AK. Techniques for the detection and management of freezing of gait in Parkinson's disease–A systematic review and future perspectives. *MethodsX*. 2023;10:102106. doi: 10.1016/j.mex.2023.102106.
56. Giladi N, Kao R, Fahn S. Freezing phenomenon in patients with parkinsonian syndromes. *Movement disorders: official journal of the Movement Disorder Society.* 1997;12(3):302-5. doi: 10.1002/mds.870120307.
57. Morris J. Accelerometry—A technique for the measurement of human body movements. *Journal of biomechanics*. 1973;6(6):729-36. doi: 10.1016/0021-9290(73)90029-8.
58. Han JH, Lee WJ, Ahn TB, Jeon BS, Park KS, editors. Gait analysis for freezing detection in patients with movement disorder using three dimensional acceleration system. *Proceedings of the 25th Annual International Conference of the IEEE Engineering in Medicine and Biology Society* (IEEE Cat No 03CH37439); 2003: IEEE. doi: 10.1109/IEMBS.2003.1279781.
59. Moore ST, MacDougall HG, Ondo WG. Ambulatory monitoring of freezing of gait in Parkinson's disease. *Journal of neuroscience methods*. 2008;167(2):340-8. doi: 10.1016/j.jneumeth.2007.08.023.
60. Niazmand K, Tonn K, Zhao Y, Fietzek U, Schroeteler F, Ziegler K, et al., editors. Freezing of Gait detection in Parkinson's disease using accelerometer based smart clothes. *2011 IEEE Biomedical Circuits and Systems Conference (BioCAS)*; 2011: Ieee. doi: 10.1109/BioCAS.2011.6107762.
61. Popovic M, Djuric-Jovicic M, Radovanovic S, Petrovic I, Kostic V. A simple method to assess freezing of gait in Parkinson's disease patients. *Brazilian Journal of Medical and Biological Research*. 2010;43:883-9. doi: 10.1590/s0100-879x2010007500077.
62. Handojoseno AA, Gilat M, Ly QT, Chamtie H, Shine JM, Nguyen TN, et al., editors. An EEG study of turning freeze in Parkinson's disease patients: The alteration of brain dynamic on the motor and visual cortex. *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*; 2015: IEEE. doi: 10.1109/EMBC.2015.7319910.
63. Delval A, Snijders AH, Weerdesteyn V, Duysens JE, Defebvre L, Giladi N, et al. Objective detection of subtle freezing of gait episodes in Parkinson's disease. *Movement Disorders*. 2010;25(11):1684-93. doi: 10.1002/mds.23159.
64. Kim H, Lee HJ, Lee W, Kwon S, Kim SK, Jeon HS, et al., editors. Unconstrained detection of freezing of Gait in Parkinson's disease patients using smartphone. *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC);* 2015: IEEE. doi: 10.1109/EMBC.2015.7319209.
65. Godino-Llorente J, Shattuck-Hufnagel S, Choi J, Moro-Velázquez L, Gómez-García J. Towards the identification of Idiopathic Parkinson's Disease from the speech. *New articulatory kinetic biomarkers*. PloS one. 2017;12(12):e0189583. doi: 10.1371/journal.pone.0189583.
66. Bot BM, Suver C, Neto EC, Kellen M, Klein A, Bare C, et al. The mPower study, Parkinson disease mobile data collected using ResearchKit. *Scientific data*. 2016;3(1):1-9. doi: 10.1038/sdata.2016.11.

CMJ. 2024; 46(3): 164-168
DOI: 10.7197/cmj.1511986

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Intraoperative Lung Mechanics in Post-Covid Healthy Pregnants Who Required Cesarean Section: An Observational Study

Fatih Balcı[1,a,*], Ahmet Cemil İsbir[2,b], Oğuz Gündoğdu[2,c], Onur Avcı[2,d], Sinan Gürsoy[2,e], İclal Özdemir Kol[2,f], Kenan Kaygusuz[2,g]

[1] *Clinic of Anesthesiology and Reanimation, Zara State Hospital, Sivas, Turkiye*
[2] *Department of Anesthesiology and Reanimation, Sivas Cumhuriyet University, School of Medicine, Sivas, Turkiye*

**Corresponding author*

Research Article

History

Received: 07/07/2024
Accepted: 06/08/2024

ABSTRACT

Objective: This study aimed to investigate whether lung mechanics were affected in patients recovering from Covid-19 without ARDS (Acute Respiratory Distress Syndrome) who did not undergo lung imaging during the active infection period.

Methods: Patients who underwent cesarean section under general anaesthesia were included in the study. The study included 100 patients divided into two groups: those who had recovered from Covid-19 within the last year (group 1, n=50) and those who had never experienced Covid-19 infection (group 2, n=50). Peak pressure (Ppeak), plateau pressure (Pplato), dynamic compliance (Cdyn), and positive end-expiratory pressure (PEEP) values, measured by the anesthesia machine, were recorded at specified time intervals following intubation.

Results: Comparisons of Ppeak, Pplato, ΔP (Driver pressure), Cdyn, and R (Airway resistance) data at specified times (1 min, 5 min, 10 min, 20 min, 30 min, and 40 min) showed no significant differences between the groups (p>0.05).

Conclusion: During the cesarean section, no significant differences in lung mechanics were found between the COVID-19-recovered pregnant group and those who had never experienced COVID-19 infection.

Keywords: *Covid-19, Cesarean section, Respiratory mechanics*

Sezaryen Gerekli Post-Covid Sağlıklı Gebelerde İntraoperatif Akciğer Mekanikleri: Gözlemsel Bir Çalışma

Araştırma Makalesi

Süreç

Geliş: 07/07/2024
Kabul: 06/08/2024

ÖZET

Amaç: Bu çalışmanın amacı aktif enfeksiyon süresi boyunca akciğer görüntüleme yapılmamış ve ARDS (Akut Respiratuar Distres Sendromu) olmadan Covid-19'dan iyileşen hastalarda akciğer mekaniklerinin etkilenip etkilenmediğini göstermektir.

Yöntem: Genel anestezi altında sezaryen yapılan hastalar çalışmaya dahil edilmiştir. Çalışmaya alınan 100 hasta iki gruba ayrıldı: Son 1 yıl içinde Covid-19 enfeksiyonu geçirip iyileşmiş hastalar (grup 1, n:50) ve kontrol grubu olarak hiç Covid-19 enfeksiyonu geçirmemiş hastalar (grup 2 n:50). Genel anestezi altında opere olan hastalarda MAP (ortalama arteryal basınç), HR (kalp hızı) ve SpO_2 (oksijen satürasyonu) değerleri hasta takip formunda belirli zamanlarda ölçüldü ve kaydedildi. Entübasyon sonrası 1.dakikadan itibaren belirtilen zaman aralıklarında anestezi makinesi tarafından ölçülen tepe basıncı (Ppeak), plato basıncı (Pplato), dinamik kompliyans (C_{dyn}) ve ekspirasyon sonu pozitif basınç (PEEP) değerleri kaydedildi.

Bulgular: Her iki gruptaki bireylerden belirli zamanlarda elde edilen Ppeak, Pplato, ΔP (sürücü basıncı), C_{dyn} ve R (havayolu direnci) verileri karşılaştırıldığında gruplar arası anlamlı fark bulunmamıştır. Grup 1 ve Grup 2'ye ait farklı zamanlarda elde edilen Pplato, ΔP ve R ölçümleri istatistiksel olarak anlamsız bulunmuştur.

Sonuç: Sezaryen sırasında, COVID-19'dan kurtulan gebe grubu ile COVID-19 enfeksiyonunu hiç yaşamamış olanlar arasında akciğer mekanikleri açısından önemli bir fark bulunmamıştır.

Anahtar Kelimeler: *Covid-19, Sezaryen, Akciğer mekanikleri*

[a] *fatihbalci05@gmail.com* *0000-0002-9005-6758*
[b] *cemilisbir@hotmail.com* *0000-0003-4094-7584*
[c] *droguzgundogdu@gmail.com* *0000-0002-8864-0015*
[d] *dronuravci@gmail.com* *0000-0003-0743-754X*
[e] *gungursoy@gmail.com* *0000-0003-0259-9750*
[f] *driclal@gmail.com* *0000-0001-8247-440X*
[g] *kaygusuzkenan@gmail.com* *0000-0002-0745-4633*

How to Cite: Balcı F, İsbir AC, Gündoğdu O, Avcı O, Gürsoy S, Özdemir Kol İ, Kaygusuz K. Intraoperative Lung Mechanics in Post-Covid Healthy Pregnants Who Required Cesarean Section: An Observational Study. Cumhuriyet Medical Journal. 2024; 46(3): 164-168

Introduction

Lung mechanics refers to lung function as measured by changes in pressure and flow. These measurements encompass static compliance, airway resistance, plateau pressure and driving pressure.[1]

Compliance signifies the change in volume per unit pressure change and is indicative of alveolar expansibility; higher compliance values correlate with greater alveolar distensibility.[2] Airway resistance measures the pressure required to generate 1 liter/minute of gas flow through the airways, increasing as airway diameter decreases, thereby reflecting the degree of airway obstruction.[3] The ratio of the difference between peak inspiratory pressure and plateau pressure to flow determines resistance.[1] ΔP, or driving pressure, represents the difference between plateau pressure and PEEP, with ΔP <15 cmH2O recommended as safe;[4] lower driving pressure correlates with reduced risk of ventilator-induced lung injury.[5] Plateau pressure is measured in the absence of gas flow and indicates the pressure needed to maintain tidal volume in the lungs.[6]

Cdyn decreases due to conditions such as airway or endotracheal tube obstruction caused by secretions, bronchospasm, or tube kinking.[7] However, pregnancy has no impact on dynamic compliance.[8,9]

Several studies have explored the impact of Covid-19 infection on lung mechanics, particularly in Covid-19-associated ARDS (CARDS) patients, demonstrating significant lung impairment in cases with evident lung involvement.[10–12] Pulmonary mechanics were found to be affected in these patients with lung involvement. This requires clarification of two issues that have not yet been studied: The possible effects on lung mechanics in non-ARDS patients in whom lung involvement cannot be visualized by any imaging modality and in patients who have recovered from the infection.

This study was conducted during cesarean section procedures in pregnant patients. Its objective was to investigate whether lung mechanics were affected in patients recovering from Covid-19 without ARDS who did not undergo lung imaging during the active infection period.

Material and Methods

This observational study enrolled pregnant females classified as American Society of Anesthesiologists (ASA) II who had recovered from Covid-19 between October 2021 and October 2022, alongside ASA II pregnant females without prior Covid-19 infection. Informed consent was obtained from all participants. The study received Sivas Cumhuriyet University Clinical Research Ethics Committee approval on 28.09.2021 (Decision No. 2021-09/03). The study followed the principles of the Declaration of Helsinki.

The present study included patients with chronic lung disease such as chronic obstructive pulmonary disease, asthma, interstitial lung disease, hypertension, pulmonary hypertension, lower or upper respiratory tract infection, history of lung surgery, single lung, beta 2 agonists, patients using bronchodilators such as anticholinergics and theophylline or inhaled/oral corticosteroids, patients using drugs that cause bronchospasm such as beta-blockers, patients with unstable hemodynamics; patients whose consent for the study could not be obtained or who refused to participate in the study were excluded from the study. Patients with unstable hemodynamics, intraoperative hemodynamic instability, or requiring endotracheal tube exchange were excluded.

The 100 patients included in the study were divided into two groups: Patients who had Covid-19 infection in the last 1 year and recovered (group 1, n:50) and patients who had never had Covid-19 infection as the control group (group 2 n:50).

Preoperatively, MAP, HR, and SpO2 were recorded, and standard 5-lead electrocardiography monitoring was performed in the operating room. Intravenous (i.v.) NaCl 0.9% infusion of 10 ml/kg/h in the first hour and 5 ml/kg/h thereafter was started and preoxygenation was administered with 100% oxygen for 3-5 minutes.

All patients underwent standard general anesthesia protocol. Under this standard general anesthesia protocol, 4-6 mg/kg thiopental sodium i.v. and 0.5 mg/kg rocuronium i.v. were administered. Patients were intubated with an appropriate endotracheal tube after adequate depth of anesthesia and ventilation with a mask was achieved. Subsequent to endotracheal intubation, routine mechanical ventilator settings were as follows: tidal volume: 6 mL/kg, respiratory frequency: 12/min, PEEP: 5 cmH_20, fresh gas flow: 3 L/min, gas setting: 2% sevoflurane in a mixture of 50% air and 50% oxygen. After clamping the umbilical cord, 1µg/kg fentanyl was administered to the mother.

MAP, HR and SpO_2 values were documented preop (before induction) and at the time of induction in the patient follow-up form in patients operated under general anesthesia. The same values were measured and documented at 1 minute, 5 minutes, 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, 60 minutes after intubation. Ppeak, Pplato, C_{dyn} and PEEP values measured by the anesthesia machine (GE Healthcare brand, Carestation 620) were documented at specified time intervals starting from the 1st minute after intubation. ΔP and R values, which were the other data compared between the groups, were calculated, and documented for certain time intervals with the formulas mentioned below.

ΔP = Pplato – PEEP

Flow rate= Tidal Volume / Inspiration time

R= Ppeak-Pplato/ Flow rate (cmH_20/L/sec)

Statistical analysis

The study aimed for a power of 0.80 with α=0.05, considering d=0.60, and included 50 patients in each group (patient and control groups, respectively). A total of 100 people were included in the study. The data obtained from our study were analyzed using the SPSS (version 22.0) software package. When the assumptions for parametric tests were met (Kolmogorov-Smirnov test), the significance of the difference between two means was used to compare measurements obtained from two independent groups. When the assumptions for parametric tests were not met, the Mann-Whitney U test was used for comparisons between two independent groups. The Chi-square test was employed for the evaluation of categorical data. The data are

presented in tables as arithmetic mean and standard deviation, with an alpha level of 0.05 considered for statistical significance.

Results

The mean age of patients was 30.77±6.39 years in Group 1 and 30.22±5.38 years in Group 2 (p>0.05).

In terms of smoking status, 46 patients in Group 1 and 49 patients in Group 2 were smokers (p>0.05). Additionally, no statistically significant differences were observed between the two groups regarding body mass index (BMI) and gestational week (p>0.05).

The mean duration of COVID-19 infection in Group 1 patients was 7.91±4.33 months. A total of 27 patients were asymptomatic, 23 experienced mild symptoms such as fever, joint pain, runny nose, and weakness, while 5 patients required hospitalization; none had a history of intensive care unit admission.

No significant differences were observed between the groups when comparing HR, MAP and SpO2 values at specified times (preoperative, post-induction, 1 min, 5 min, 10 min, 20 min, 30 min, and 40 min) (p>0.05).

Similarly, when comparing Ppeak, Pplato, ΔP, Cdyn, and R data obtained from patients at specific times (1 min, 5 min, 10 min, 20 min, 30 min, and 40 min), no significant differences were found between the groups (p>0.05).

Intra-group comparisons of measurements at specified times for Group 1 and Group 2 revealed significant decreases in HR and MAP measurements towards the end of the operation in both groups.

No statistically significant differences were found in Pplato, ΔP, and R measurements at different times within Group 1 and Group 2 (p>0.05).

However, the increase in Cdyn values towards the end of surgery was found to be statistically significant in both groups (p<0.05).

Differences in SpO2, MAP, and Cdyn values observed during the study were attributed to routine anesthesia procedures such as laryngoscopy, endotracheal intubation, and PEEP application. Further comprehensive studies involving larger patient cohorts are recommended to explore the long-term pulmonary implications of Covid-19 infection in recovering patients.

***Table 1**. Statistical data for comparison of HR, MAP and SpO2 values between groups*

	Grup 1			Grup 2		
	Mean ± SD			Mean ± SD		
	HR	MAP	spO2	HR	MAP	spO2
Preoperation	95.52±15.51	92.56±10.70	97.15±1.22	94.42±16.77	97.38±16.56	97.02±1.20
Induction	111.24±19.84	95.28±12.26	98.31±1.54	104.7±18.59	99.74±17.98	98.22±1.20
1st min.	113.68±23.17	101.78±15.45	98.78±1.09	114.48±17.74	105,7±21.29	98.76±1.02
5th min.	106.91±14.51	93.52±17.90	98.63±1.07	106.3±16.77	100.28±18.04	98.46±0.93
10th min.	103.42±13.98	85.98±11.79	98.61±1.16	100.4±17.10	90,7±14.44	98.6±0.75
20th min.	101.16±18.16	81.63±12	98.63±1.06	100±15.70	87.68±13.64	98.46±0.93
30th min.	100.79±11.68	82.2±9.12	98.65±1.20	99.91±17.83	89.33±21.02	98.44±0.82
40th min.	98±10.13	82.66±7.84	98.33±1.03	98.6±21.43	97.4±17.54	98.4±0.54

HR:Heart Rate, MAP:Mean Arterial Pressure, SpO_2:Peripheral Oxygen Saturation, min.:Minute

***Table 2.** Statistical data for comparison of Ppeak, Pplato, ΔP, Cdyn and R values between groups*

	Grup 1					Grup 2				
	Mean ± SD					Mean ± SD				
	Ppeak	Pplato	ΔP	Cdyn	R	Ppeak	Pplato	ΔP	Cdyn	R
1st min.	18.1±2.62	15.71±2.75	10.71±2.78	37.62±7.98	9.1±10.29	18.92±3.77	16.72±3.60	11.78±3.59	36.75±8.37	7.1±4.25
5th min.	17.17±2.33	15.08±2.64	10.12±2.71	40.28±7.81	7±4.67	18.44±3.25	16.26±3.28	11.34±3.31	37.36±8.57	7.25±3.50
10th min.	17.26±2.43	15.08±2.74	10.15±2.76	40.19±7.90	7.24±4.98	17.84±2.89	15.76±3.06	10.78±3.07	39.26±7.77	6.88±3.70
20th min.	17.14±2.18	15.1±2.43	10.12±2.40	40.15±6.83	6.81±4.19	17.62±2.60	15.68±3.01	10.72±2.86	39.75±7.04	6.31±3.20
30th min.	17.68±2.56	15.68±2.72	10.68±2.72	38.73±7.62	6.59±4.95	18.2±3.09	16.29±2.74	11.2±2.70	39.3±7.90	7.86±6.40
40th min.	18±1.67	17±1.67	12±1.67	37.08±3.14	3.36±0.25	17.4±2.70	16±2.12	11±2.12	40.32±9.67	4.66±2.93

Ppeak: Peak pressure, Pplato: plateau pressure, ΔP: Cdyn: dynamic compliance, R: airway resistance, min.:minute

***Table 3.** Statistical evaluation of MAP and HR values measured at different times within the groups*

	Grup 1		Grup 2	
	Mean±SD		Mean±SD	
	HR	MAP	HR	MAP
Preoperation	107.93±18.20	91.1±10.39	105.25±19.85	105.29±19
Induction	96.6±14.11	93.93±11.34	93.54±16.79	108.58±19.49
1st min.	113.72±15.60	100.44±15.40	114.2±20.08	115.25±19.70
5th min.	105.89±10.29	92.93±22.14	108.7±18.89	104.37±20.26
10th min.	100.65±11.13	85.68±12.06	101.83±21.03	94.04±17.73
20th min.	98.03±19.29	78.89±8.66	101.54±17.87	92.87±15.24
30th min.	100.79±11.68	82.2±9.12	99.91±17.83	89.33±21.02
	p=0001	p=0.001	p=0.001	p=0.001

HR:Heart Rate, MAP:Mean Arterial Pressure, min.:Minute

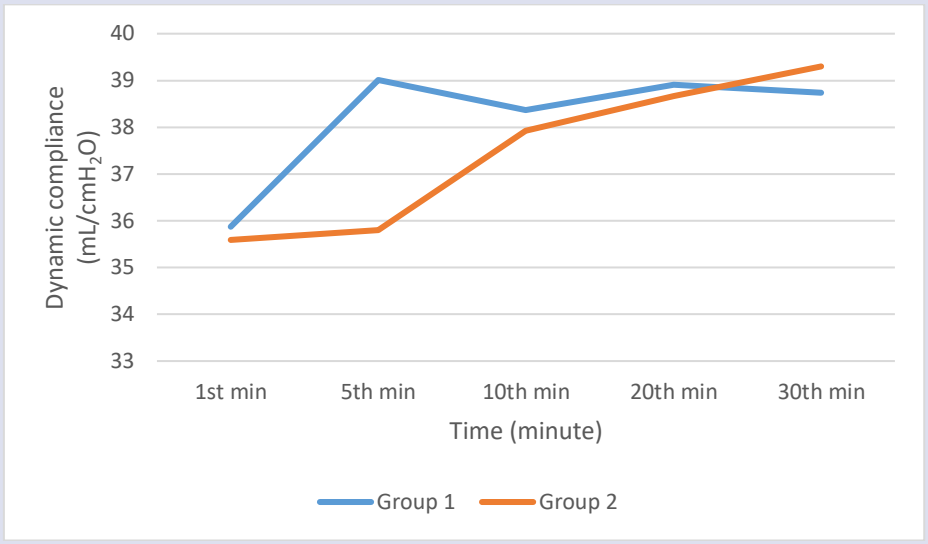

Figure 1: The change in Cdyn. values during the surgery

Discussion

The study results indicated no significant difference in intraoperative lung mechanics among patients who had recovered from COVID-19. Cdyn values increased in both patient groups later in the operation. The significant difference in HR, MAP, and SpO2 measurements was interpreted as elevations secondary to intubation.

It is known that static and dynamic lung compliance and inspiratory muscle strength are not affected by pregnancy.[8] Therefore, these data will not present any differences in the patients in our study due to pregnancy.

Although there are a few studies in the literature investigating the effects of infection on lung mechanics in COVID-19-associated ARDS cases, studies on lung mechanics in patients with COVID-19 and recovered surgery are limited. Since the first definition of ARDS in 1967, extensive studies have shown that the underlying lung injury may be due to a variety of physiological changes, including alveolar collapse, decreased lung compliance, increased pulmonary vascular resistance, and impaired gas exchange.[13] Ferrando et al. studied parameters such as Pplato, ΔP, and lung compliance in mild, moderate, and severe CARDS patients. The study revealed that Pplato values were significantly lower in patients with mild ARDS, whereas no difference was found between the other data. The same study also found that respiratory parameters (compliance, Pplato, ΔP) of CARDS patients and non-COVID However, it was reported following the study that lung compliance may vary in COVID-19 patients. L and F phenotypes were identified in COVID-19 patients accordingly.[14] Based on these findings, Puah et al. studied phenotype and mortality. COVID-19 patients admitted to intensive care were divided into two groups: patients with low and high complexity. They reported that there was no difference in oxygenation at baseline in the two patient groups after intubation, but Pplato and ΔP were higher in the patient group with low compliance. There was no significant change in the lung compliance values of patients with low compliance at baseline on day 7. However, patients initially classified as having high compliance had a significant reduction in lung compliance. The researchers reported that mortality was also significantly higher in patients in the high-complexity group compared to the low-complexity group at baseline.[12] However, a different result was obtained from the study by Yıldırım et al. In their study on lung mechanics in mechanically ventilated CARDS patients, Pplato and ΔP were significantly higher in deceased patients, while lung compliance data were significantly lower. When the patients were divided into two groups with drive pressure below and above 15 cmH2O, the mortality rate on day 28 was lower in the group with drive pressure below 15 cmH2O.[15] However, the study by Puah et al. showed that the lung compliance of patients with initially high compliance rapidly decreased and mortality rates of patients in this group were found to be high. In fact, the mortality rates of patients with low lung compliance in the study by Yildirim et al. were also high.

The positive effect of low ΔP values on mortality in ARDS patients is established.[16] It is critical whether the same is also applicable to CARDS patients followed up in intensive care. Boscolo et al. sought to answer this question and found a direct relationship between ΔP and mortality. Increasing ΔP from 10 cmH2O to 14 cmH2O in CARDS patients resulted in significantly increased mortality rates in the intensive care unit.[17] It was also reported that intraoperative low ΔP values were associated with decreased postoperative respiratory complications in patients followed.[18] The reason for the high ΔP in ARDS patients is that the lung volume participating in respiration, i.e., the functional lung volume, is reduced. Likewise, lung pathologies such as atelectasis, consolidation, bullae, effusion, fibrosis, barotrauma, or atelectotrauma are associated with increased ΔP. The present study, in which we investigated the possible pulmonary effects of COVID-19 in patients who recovered from COVID-19 without ARDS and in whom lung imaging could not be performed, showed no difference in ΔP values between the two groups, suggesting that patients recovered completely without any lung pathology.

When the measurements obtained at different times of the groups were compared among themselves, MAP and HR measurements of both groups were found to be higher in the first minutes of the operation compared to the later measurements, and this difference was found to be statistically significant. This is explained by the increase in MAP-HR measurements as a sympathoadrenergic response to endotracheal intubation and the suppression of this response after cord clamping and i.v. opioid administration.

When SpO2 measurements obtained at different times in participants with and without COVID-19 were analyzed, all SpO2 measurements obtained after induction in both groups were found to be higher than the pre-induction measurements, and this difference was found to be statistically significant. This difference may be attributed to insufflation with 100% FiO2 at the beginning of induction and intubation and positive pressure ventilation with 50% FiO2 values afterward.

Cdyn values measured at different time intervals in patients with and without COVID-19 were found to be increased in the later stages of surgery compared to the beginning. There was a significant difference in both groups. Decreasing Ppeak values later in the operation account for increasing compliance. It was also stated in the review published by Öz et al. that the application of continuous positive airway pressure and PEEP will increase lung compliance.[19] With the data available on Cdyn, we conclude that lung compliance increases in the later stages of the operation, regardless of COVID-19 history.

All of these studies report changes in lung mechanics seen in CARDS patients. The present study focused on the lung mechanics of patients who had COVID-19 without ARDS. These patients were also patients who had not undergone lung imaging during their active disease.

Limitations

This study has several limitations. Since the patients were pregnant, lung imaging was not performed. We endeavored to investigate whether the lungs of these patients were affected. The extent of lung involvement remains unknown. Additionally, there are no other studies in the literature investigating the intraoperative respiratory mechanics of patients who have had COVID-19. Studies related to respiratory mechanics are generally conducted on patients with CARDS.

Conclusions

Covid-19 has known or unknown effects on systems other than the respiratory system. We attempted to reveal possible respiratory system effects by studying intraoperative lung mechanics in patients who had the disease and could not undergo lung imaging. This study was conducted during cesarean surgeries in pregnant patients. The findings indicate no significant differences in lung mechanics between the Covid-19-recovered patient group and the control group.

References

1. Hess DR, Faarc R. Respiratory Mechanics in Mechanically Ventilated Patients. *Respir Care*. 2014;59(11):1773-1794. doi:10.4187/RESPCARE.03410
2. Dikmen Y. *Mekanik Ventilasyon-Klinik Uygulama Temelleri*. (Dikmen Y, ed.). Güneş Tıp Kitabevleri; 2012.
3. Robb J. Physiological changes occurring with positive pressure ventilation: part one. *Intensive Crit Care Nurs*. 1997;13(5):293-307. doi:10.1016/S0964-3397(97)80493-4
4. Baldomero AK, Skarda PK, Marini JJ. Driving Pressure: Defining the Range. *Respir Care*. 2019;64(8):883-889. doi:10.4187/RESPCARE.06599
5. Bugedo G, Retamal J, Bruhn A. Driving pressure: A marker of severity, a safety limit, or a goal for mechanical ventilation? *Crit Care*. 2017;21(1):1-7. doi:10.1186/s13054-017-1779-x
6. Morgan G, Mikhail M, Butterworth JF, Mackey DC, Wasnick JD. *Morgan&Mikhail Klinik Anesteziyoloji*. 5.th. (Cuhruk FH, ed.). McGraw-Hill; 2015.
7. Yarkın T. Mekanik Ventilasyon Sırasında Solunum Monitörizasyonu. *Yoğun Bakım Derg*. 2007;7(7):322-327.
8. Jensen D, Webb KA, Davies GAL, O'donnell DE. Mechanical ventilatory constraints during incremental cycle exercise in human pregnancy: implications for respiratory sensation. *J Physiol*. 2008;586:4735-4750. doi:10.1113/jphysiol.2008. 158154
9. McAuliffe F, Kametas N, Costello J, Rafferty GF, Greenough A, Nicolaides K. Respiratory function in singleton and twin pregnancy. *BJOG An Int J Obstet Gynaecol*. 2002;109(7):765-769. doi:10.1111/J.1471-0528.2002.01515.X
10. Ferrando C, Suarez-Sipmann F, Mellado-Artigas R, et al. Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS. *Intensive Care Med*. 2020;46(12):2200-2211. doi:10.1007/s00134-020-06192-2
11. Baedorf Kassis E, Schaefer MS, Maley JH, et al. Transpulmonary pressure measurements and lung mechanics in patients with early ARDS and SARS-CoV-2. *J Crit Care*. 2021;63:106-112. doi:10.1016/J.JCRC.2021.02.005
12. Puah SH, Cove ME, Phua J, et al. Association between lung compliance phenotypes and mortality in covid-19 patients with acute respiratory distress syndrome. *Ann Acad Med Singapore*. 2021;50(9):686-694. doi:10.47102/ANNALS-ACADMEDSG.202112 9
13. Swenson KE, Swenson ER. Pathophysiology of Acute Respiratory Distress Syndrome and COVID-19 Lung Injury. *Crit Care Clin*. 2021;37(4):749-776. doi:10.1016/J.CCC.2021 .05.003
14. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020;46(6):1099-1102. doi:10.1007/S00134-020-06033-2/FIGURES/1
15. Yildirim S, Cinleti BA, Saygili SM, Senel E, Ediboglu O, Kirakli C. The effect of driving pressures in COVID-19 ARDS: Lower may still be better as in classic ARDS. *Respir Investig*. 2021;59(5):628-634. doi:10.1016/j.resinv.2021.06.002
16. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med*. 2016;42(12):1865-1876. doi:10.1007/S00134-016-4571-5/TABLES/3
17. Boscolo A, Sella N, Lorenzoni G, et al. Static compliance and driving pressure are associated with ICU mortality in intubated COVID-19 ARDS. *Crit Care*. 2021;25(1):1-8. doi:10.1186/S13054-021-03667-6/TABLES/2
18. Ladha K, Melo MFV, McLean DJ, et al. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. *BMJ*. 2015;351. doi:10.1136/BMJ.H3646
19. Öz H, Köksal GM. Mekanik Ventìlasyon. 2006;8(1):37-46.

CMJ. 2024; 46(3): 169-177
DOI: 10.7197/cmj.1424299

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Examination of Subclinical Neurological Involvement in Patients with Psoriasis Vulgaris

Sibel Berksoy Hayta[1,a], Burhanettin Çiğdem[2,b], Rukiye Yasak Güner[3,c,*], Şeyda Figül Gökçe[2,d], Melih Akyol[3,e]

[1] *Private practice, Adana, Turkiye*
[2] *Department of Neurology, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Turkiye*
[3] *Department of Dermatology, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Turkiye*

**Corresponding author*

Research Article

History

Received: 23/01/2024
Accepted: 08/08/2024

ABSTRACT

Objective: The aim of this study is to evaluate cognitive functions of patients with psoriasis in terms of subclinical neurological involvement using p300 method, and to reveal the correlation between the disease duration and severity if any.

Methods: 40 patients with psoriasis vulgaris and 40 healthy individuals were included in the study. Standard mini mental test and beck depression inventory were applied to the groups. PASI values and DLQI values of psoriasis patients were calculated. P300 measurements of both groups were recorded and assessed in order to evaluate the cognitive functions.

Results: There was no statistically significant difference between the healthy and psoriasis groups in terms of PzLat, PzAmp, CzLat and CzAmp values (p=0.681, p=0.301, p=0.138, p=0.739, respectively). When it was compared in terms of PASI values, there was no statistically significant difference in the patient group in terms of PzLat, PzAmp, CzLat and CzAmp values (p=0.211, p=0.422, p=0.106, p=0.305, respectively). When evaluated according to disease duration, there was no statistically significant difference between the groups in terms of PzLat, PzAmp, CzLat and CzAmp values (p=0.901, p=0.244, p=0.632, p=0.868, respectively).

Conclusion: Cognitive functions in psoriasis patients are not affected by the presence, severity and duration of the disease. As far as we know, the present study is the first study using electrophysiological P300 method in evaluating the cognitive functions in patients with psoriasis.

Keywords: Psoriasis, cognition, P300, neurophysiological test, cognitive dysfunction

Psoriasis Vulgaris Hastalarında Subklinik Nörolojik Tutulumun İncelenmesi

Araştırma Makalesi

Süreç

Geliş: 23/01/2024
Kabul: 08/08/2024

ÖZET

Amaç: Bu çalışmanın amacı, psoriasis hastalarında subklinik nörolojik tutulum açısından bilişsel fonksiyonları P300 yöntemi ile değerlendirmek ve hastalık süresi ve şiddeti arasındaki ilişkiyi ortaya koymaktır.

Yöntem: Çalışmaya 40 psoriasis vulgaris hastası ve 40 sağlıklı birey dahil edilmiştir. Her iki gruba standart mini mental test ve Beck Depresyon Envanteri uygulanmıştır. Psoriasis hastalarının PAŞİ (Psoriasis Alan ve Şiddet İndeksi) ve DYKİ (Dermatoloji Yaşam Kalitesi İndeksi) değerleri hesaplanmıştır. Her iki grubun P300 ölçümleri kaydedilmiş ve bilişsel fonksiyonları değerlendirmek amacıyla analiz edilmiştir.

Bulgular: Sağlıklı ve psoriasis grupları arasında PzLat, PzAmp, CzLat ve CzAmp değerleri açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (sırasıyla p=0.681, p=0.301, p=0.138, p=0.739). PAŞİ değerleri açısından karşılaştırıldığında, hasta grubunda PzLat, PzAmp, CzLat ve CzAmp değerleri açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (sırasıyla p=0.211, p=0.422, p=0.106, p=0.305). Hastalık süresine göre değerlendirildiğinde, gruplar arasında PzLat, PzAmp, CzLat ve CzAmp değerleri açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (sırasıyla p=0.901, p=0.244, p=0.632, p=0.868).

Sonuç: Psoriasis hastalarında bilişsel fonksiyonlar, hastalığın varlığı, şiddeti ve süresi ile etkilenmemektedir. Bildiğimiz kadarıyla, mevcut çalışma psoriasis hastalarında bilişsel fonksiyonları değerlendirmede elektrofizyolojik P300 yöntemini kullanan ilk çalışmadır.

Anahtar Kelimeler: Psoriasis, biliş, P300, nörofizyolojik test, bilişsel disfonksiyon

[a] *drberksoy@gmail.com* *0000-0002-6185-6094*
[b] *bcigdem@cumhuriyet.edu.tr* *0000-0003-4941-9497*
[c] *rky.guner@gmail.com* *0000-0002-5154-4652*
[d] *figulgokce@gmail.com* *0000-0002-2719-0428*
[e] *melakyol@gmail.com* *0000-0001-7912-0651*

How to Cite: Berksoy Hayta S, Çiğdem B, Yasak Güner R, Gökçe ŞF, Akyol M. Examination of Subclinical Neurological Involvement in Patients with Psoriasis Vulgaris. Cumhuriyet Medical Journal. 2024;46(3): 169-177

Introduction

Psoriasis is a commonly seen disease characterized by chronic inflammation. Its prevalence in the general population is accepted to be 2-3%.[1] Tissue reaction seen in psoriasis covers severe inflammatory component and abnormal keratinocyte differentiation along with complex immunological reaction. It has been reported that 75% of patients with psoriasis have at least one comorbid condition other than skin involvement such as hypertension, diabetes, cardiovascular diseases, uveitis, inflammatory bowel diseases, osteoporosis, and chronic obstructive pulmonary disease.[2] Although information about neurological comorbidities in patients with psoriasis is limited, many neurological and psychological disorders such as epilepsy, migraine, depression, cognitive disorders, and sleep disorders have been defined.[3,4] Therefore, psoriasis is assessed as a multisystem disease rather than a skin disease in recent years.[5]

The brain-skin axis (neurocutaneous relationship) is very important in understanding inflammatory skin diseases. Inflammation is a catalyst for the development of cognitive functions and neurodegenerative diseases. There are studies showing that proinflammatory processes have roles in the development of neurodegenerative diseases and affect cognitive functions over time.[6-11]

Chronic inflammation is an important risk factor for diseases accompanied by dementia and cognitive insufficiency such as Alzheimer's disease (AD).[12] Inflammatory cytokines can prepare the ground for cognitive function changes by increasing neuronal stress due to the reasons such as contribution to atherogenesis development, formation of microvascular damage, increased vascular permeability, causing endothelial dysfunction.[11,12] There are studies reporting that high values of some cytokines such as TNF alpha, IL1 beta, and IL6 playing an important role also in pathogenesis of psoriasis in Alzheimer's disease are related to regression in cognitive functions.[13,14]

Processing information is very important for detecting and evaluating the cognitive functions such as attention, learning, memory, language generation and executive functions.[15] In the recent period, there are several studies about the effects of psoriasis on cognitive functions. In psoriasis, different aspects of cognition may be impaired. Disruption in visual and verbal memory and attention, slowed psychomotor speed, and decrease in cortical thickness with brain imaging methods are some of them.[14,15] Along with studies supporting that cognitive functions are impaired, there are also studies reporting that they are not affected.[11,12]

Both the presence of cardiometabolic comorbidities and the presence of genetic characteristics and inflammation close to AD can include psoriasis patients in the risk group for the development of cognitive dysfunction and dementia. However, information about cognitive dysfunction and the development of dementia along with psoriasis is limited and controversial.[12] To evaluate cognitive functions in patients with psoriasis, many verbal, visual, auditory tests have been used but P300 method in which electrophysiological measurements are conducted has never been used.

The objective of this study is to assess the cognitive functions of patients with psoriasis., who has no known psychiatric and neurological diseases and has normal neurological examination, in terms of subclinical neurological involvement using P300 method which is an electrophysiological test and to reveal the correlation between the disease duration and severity if any.

Material and Method

Study Groups

The number of patients and control groups to be included in the study was determined with power analysis. In calculation of sample size made considering confidence interval of 95% and error of 5%, values were taken as alpha=0.05 and beta=0.20. The power of the test was found to be p = 0.8024.

The present study is a prospective cross-sectional study involving 40 psoriasis vulgaris patients and 40 voluntary healthy individuals who were matched for age and gender. The patients over 18 years of age who have no known additional diseases that may affect cognitive functions other than psoriasis (neurological, psychological, infectious, drug addition, malignancy and/or diseases related to other systems, hospital records and patient anamnesis were taken as basis) and those who had normal neurological examination were included in the study. Patients whose beck depression inventory (BDI) total scores were over 17 were considered as clinical depressions at the limit and patients whose standard mini mental test (SMMT) scores were below 24 were considered as the onset of dementia and illiterate individuals were not included in the study.

Patient and healthy control groups were evaluated in the dermatology outpatient clinic and the prepared demographic data form and beck depression inventory were filled out. After calculating the psoriasis area and severity index (PASI) for patients and filling the dermatology life quality index (DLQI), P300 wave measurements were conducted after the mini mental test application in neurology outpatient clinic.

Statistical analysis

After making the parametric test assumptions in statistical evaluation (Kolmogorov-Smirnov), the significance test of the difference between two mean values and Tukey test will be used in independent groups. When parametric test assumptions were not met, the Mann Whitney U test was used. In order to determine the correlation between the P300 amplitude and latency values of psoriasis patients with and without subclinical involvement and disease severity, correlation analysis and Spearman correlation coefficient and Chi Square test were used in the

comparison of the data obtained by counting and the significance level was taken as 0.05.

PASI

This metric stands out as one of the most widely employed tools for gauging the severity of psoriasis. The value is the sum of the products of PASI for the four parts of the body (Head-neck, lower and upper extremities, body). While maximum value of PASI is 72, its minimum value is 0. Higher scores indicate greater severity of the clinical lesions.[16]

SMMT

This test is a widely used screening test to evaluate cognitive functions and is the most commonly used test for dementia screening. Validity and reliability studies of the Turkish version were conducted by Gungen et al., in 2002. It is composed of eleven questions and evaluated over 30 points. Scores between twenty-four-thirty points are compatible with normal dementia, scores between 18-23 points are compatible with mild dementia, and scores of 17 points and lower are compatible with severe dementia. It tests orientation, memory, attention, calculation, remembering, language, motor function and perception, and visuospatial capabilities. Its easy and fast applicability is its major advantage.[17]

SMMT, based on education level, was applied to the patient group and healthy control group.

BDI

It's a self-assessment tool utilized with both healthy individuals and psychiatric patients. Its aim is to assess the risk of depression and gauge the severity and alteration of depressive symptoms. The patients fill out the scale on their own and respond by marking on the scale. This self-report form, including a total of 21 items, provides a four-point Likert type measurement. Each item gets a gradually increasing point between 0-3 and the total score is obtained by adding them. A high overall score indicates greater severity of depression. The scale, originally devised by Beck et al., underwent adaptation, validation, and reliability assessments specific to the Turkish population.[18]

DLQI

It is the first health-related quality of life scale published specific to dermatology. It is the most important and widely used one among the dermatology-specific tests and its application is very practical. It is a simple, short, understandable questionnaire for patients and can be used in daily routine clinical studies. The questionnaire is composed of 10 questions with 4 possible answers. At the beginning, it was validated initially by comparing with the normal population and it showed high sensitivity, repeatability, and internal consistency. Turkish validity and reliability of DLQI were conducted by Ozturkcan et al.[19]

P300

Long-latency evoked potentials related to cognitive functions are called as cognitive evoked potentials (EP) or endogenous event-related potentials (ERPs). P300 is the best known of the ERPs. P300 is associated with distinguishing two different stimuli. These potential changes occur in necessary conditions when the distinguishing target stimulus from the non-target stimulus with subject's selective attention; therefore, event-related EP do not depend on the stimulus but depend on the subject, subject's attention, consciousness and cognitive condition. It is observed approximately 300 ms after the presence of the target stimulus. It is believed that these potentials reflect neuronal activity related to the functional work of the brain. Although which structures P300 wave originated from has not been revealed exactly, it has been suggested that these structures may be diencephalon, medial temporal lobe structures, various neocortical areas, and hippocampus.[20] It is suggested that the time elapsed for P300 wave latency will lead to the time that the brain needs to recognize and classify the stimulus and the measurement of the amplitude of this wave can guide in evaluating the decision making ability of the brain. It has been reported in the literature that while P300 wave amplitude (Amp) changes reflect the degree or quality of information processing, latency (Lat) changes provide information about cognition ability, attention and instantaneous memory capacity. P300 is used as an objective measure of cognitive functions.

P300 waves reach to the highest amplitude values on the midline when the positive electrode is located in the central (Cz) and parietal (Pz) position in the records made on the scalp. P300 latency ranges between wide ranges such as 250-600 ms in normal individuals. P300 abnormalities (latency elongation, amplitude decrease) are evaluated as evidence of cognitive dysfunction. P300 is used in the cognitive evaluation of various neurological and psychiatric disease groups. [21]

The stimulation method used in obtaining ERPs is the "odd ball paradigm" based on the principle of distinguishing recurrent stimuli in random or less frequent order among the frequent stimulations. When the subject is encounter with a sparse stimulus, he/she is asked to count them or push a button. The wave forming at this time is P300. P300 forms when the stimulus is not given occasionally into the same type of stimulus sequence given at regular intervals and the person pays attention to these. [22]

Obtaining P300 records

P300 records were conducted in an isolated room in the Electrophysiology Laboratory in Neurology Department of Medical Faculty Hospital in Sivas Cumhuriyet University. Before the records, patients and controls were informed about the procedures to be applied and their consents were obtained. In addition, they were asked not to move as much as possible during the procedure, to avoid movements such as chewing and swallowing, not to move eyeballs and eyelids and to close their eyes slightly. The recordings were carried out in a quiet environment by allowing the patients to sit in a comfortable chair. All P300 records were made using Natus brand Nicolet EDX model 2 port EMG/UP device in a silent environment when the person was in sitting position and by placing active electrodes in AG/AGCl disk structure to Cz and Pz and placing reference electrodes on

the right and left ear lobe. It was arranged as the impedances of the electrodes were below 5 ohms, the frequency was 1 Hz, amplification was 50 mv/unit and analysis time was 100 msn/unit for a total of 1000 msn. Stimulation method, the standard odd ball paradigm, was in the form of distinguishing thin (2kHz) tone sounds and rarer sounds occurring with the frequency of 20% between the thick sound (1kHz) tones repeated with the frequency of 80%. The stimulus in the severity obtained by adding 80 dB to the hearing threshold was given to both ears regularly every 2 seconds. Stimuli repeating rarely were randomly distributed among the recurrent ones. The patient was asked to press the button he/she was holding in these rare stimuli. In order to evaluate both latency and amplitudes, Cz and Pz points were taken as the active recording points. In the obtained trace, P300 Lat and Amp were determined.

Results

40 patients with psoriasis as patient group and 40 healthy individuals as the control group who were similar in terms of age and gender were included in the study.

There was no statistically significant difference between the control and patient groups in terms of PzLat, PzAmp, CzLat and CzAmp values (p=0.681, p=0.301, p=0.138, and p=0.739, respectively) (Table 1) (Figure 1).

Table 1. PzLat, PzAmp, CzLat and CzAmp values between control and patient groups

Groups		n	Mean	Std. Deviation	Std. Error Mean	p
PzLat	**Healthy**	40	351,40	23,50	3,71	0.681
	Psoriasis	40	354,10	34,09	5,39	
PzAmp	**Healthy**	40	6,45	2,11	0,33	0.301
	Psoriasis	40	7,35	5,01	0,79	
CzLat	**Healthy**	40	344,30	25,41	4,01	0.138
	Psoriasis	40	354,12	32,81	5,18	
CzAmp	**Healthy**	40	7,17	2,78	0,44	0.739
	Psoriasis	40	7,48	5,01	0,79	

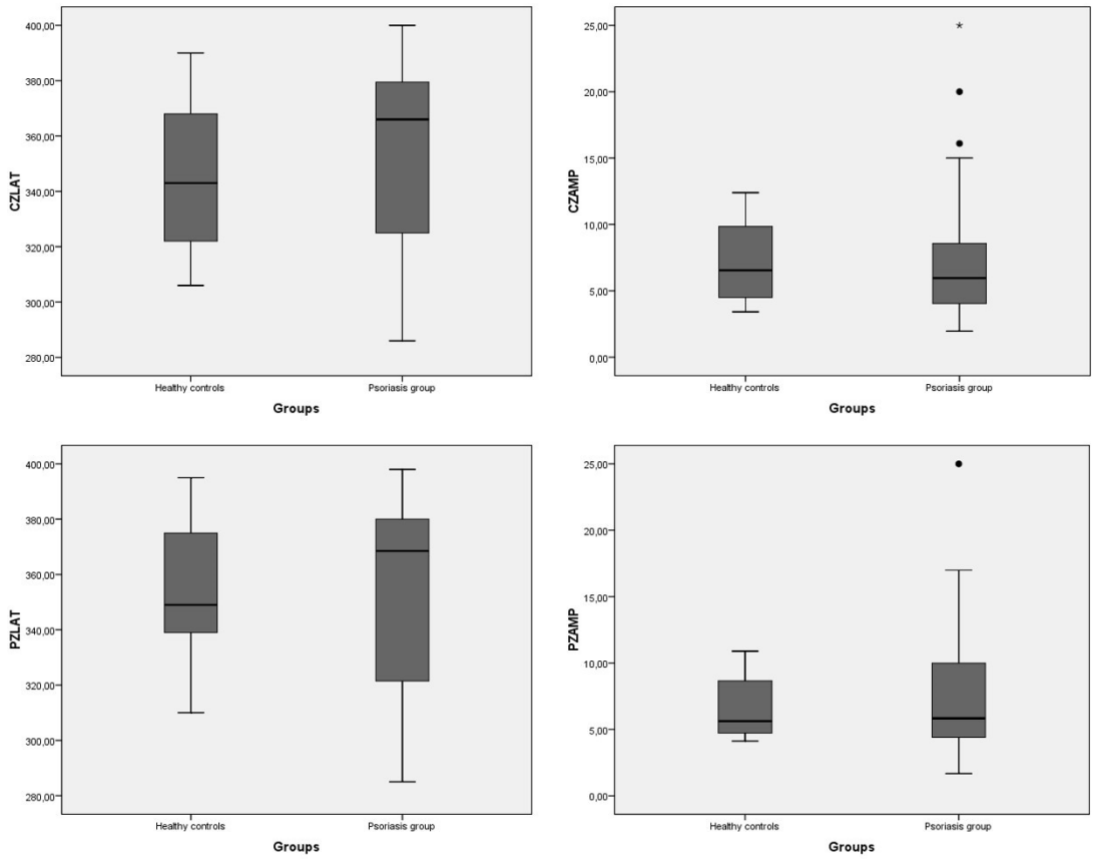

Figure 1. Comparison of PzLat, PzAmp, CzLat, and CzAmp values between control and patient groups

No statistically meaningful distinction was observed between healthy women and women with psoriasis in terms of PzLat, PzAmp, CzLat, and CzAmp values (p=0.774, p=0.740, p=0.521, and p=0.982, respectively). There was no statistically significant difference between healthy men and men with psoriasis in terms of PzLat, PzAmp, and CzAmp values (p=0.183, p=0.323, and p=0.327, respectively) but there was a statistically significant difference between control and patient groups in men in terms of CzLat (p=0.019). Mean CzLat in psoriasis man group was found to be exceeding the mean CzLat of men in the control group (Figure 2-3).

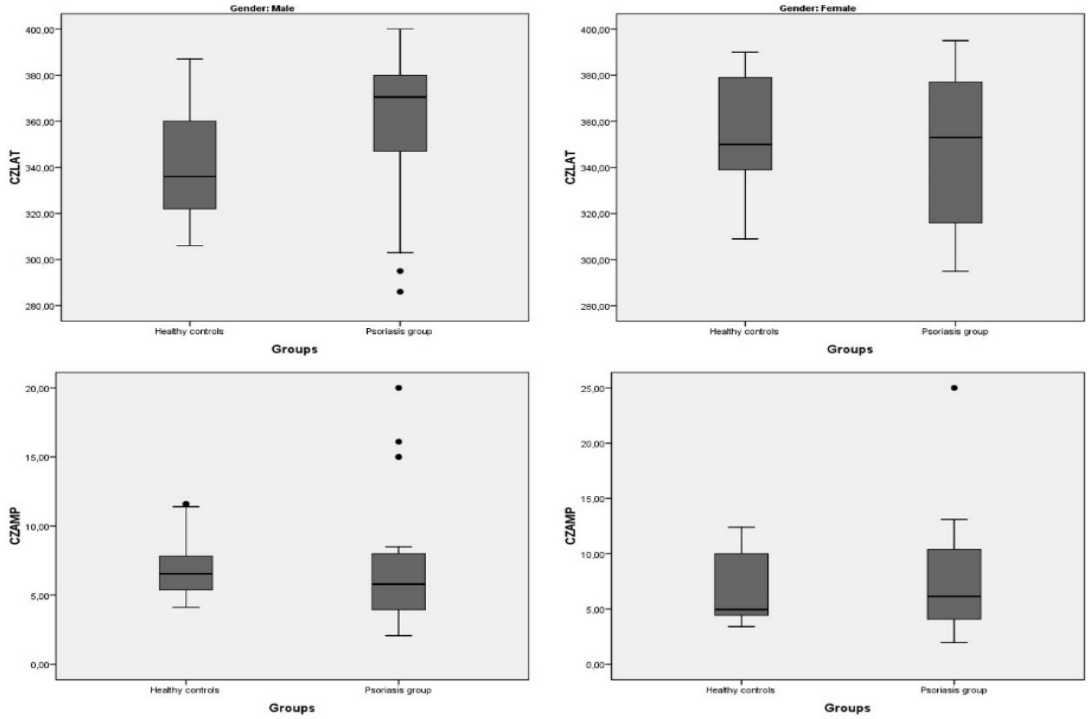

Figure 2. Cz Latency and Amplitude values in patient and control groups in terms of gender

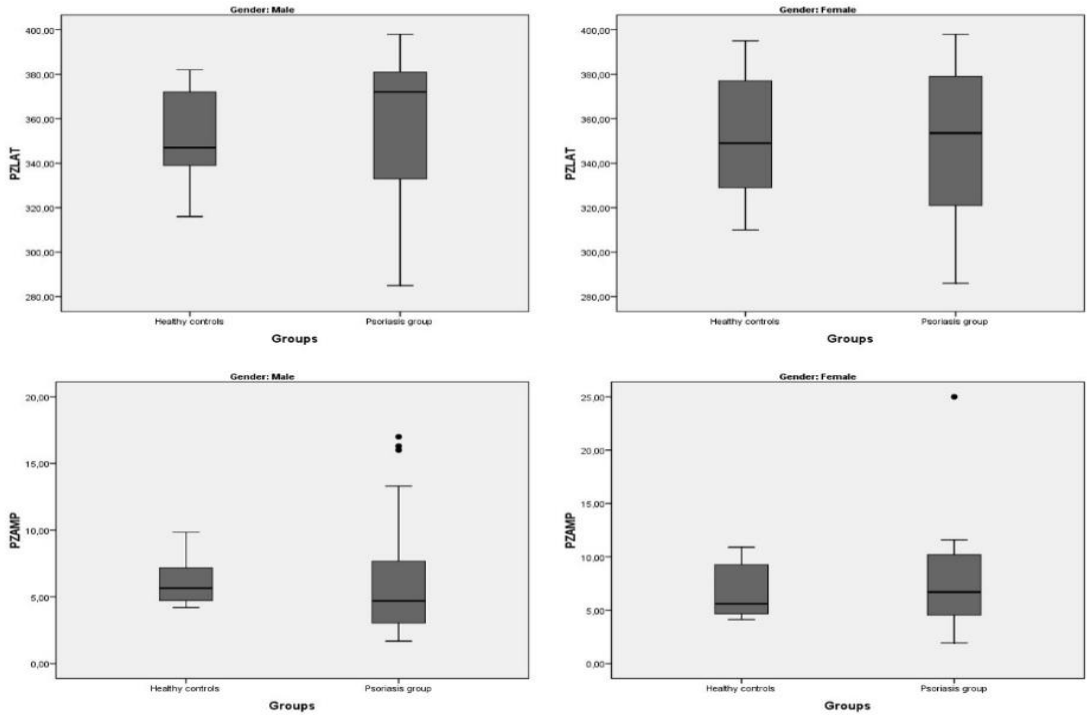

Figure 3. Pz Latency and Amplitude values in patient and control groups in terms of gender

When the patient group was analyzed statistically within itself

No statistically significant difference was found in PzLat, PzAmp, CzLat and CzAmp values (p=0.677, p=0.229, p=0.476, p=0.697, respectively) of patient group in terms of gender.

When those in the patient group were divided and compared as those whose PASI values were below 10 and those with PASI values of 10 or more, there was no statistically significant difference in the patient group in terms of PzLat, PzAmp, CzLat, and CzAmp values (p=0.211, p=0.422, p=0.106, and p=0.305, respectively).

When the patients with psoriasis were divided into two groups and assessed as those whose disease duration were below 10 years and those with disease duration of 10 years and more, there was no statistically significant difference between the groups in terms of PzLat, PzAmp, CzLat and CzAmp values (p=0.901, p=0.244, p=0.632, and p=0.868, respectively).

Discussion

Studies conducted in recent years have revealed that psoriasis is not only a skin and joint disease but also a systemic inflammatory condition. In patients with psoriasis, an increase is observed in cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, obesity, and metabolic syndrome. Patients report that there is a significant decrease also in their physical activity, cognitive functions and quality of life. Experimental studies on psoriasis draw attention to the coexistence of psychology, neuroendocrinology, and immunology in the etiology of the disease.[1,2,23,24]

The fact that epidermis and neural plaque is originated from the same embryonal leaf, the ectoderm caused the establishment of the correlation between skin and central nervous system. Many studies have emphasized the importance of psychoneuroimmunological factors in dermatological diseases such as psoriasis. Since the brain and skin have the same development origin, they are exposed to the effect of similar hormones and neurotransmitters.[5] Starting from these information, it is concluded that dermatological diseases can affect cognitive functions. There are studies showing that cognitive functions are also affected in Behcet's disease, which is a chronic inflammatory disease like psoriasis.[20,21] In literature, various verbal, visual, auditory tests and some imaging methods have been used to evaluate cognitive functions of patients with psoriasis. There are conflicting results in these studies conducted on cognitive function disorders in psoriasis. Although most of the studies have reported data showing that cognitive functions are impaired in patients with psoriasis, there are also data showing that they are not affected.

In their study, Gisondi et al.,[14] examined cognitive performance in patients with chronic plaque psoriasis via neuropsychological tests. In their study, they reported that 44% of 41 psoriasis patients and 11% of 37 controls had mild cognitive impairment. In the study by Colgecen et al.,[11], Beck depression inventory was filled by patient and control groups and Montreal Cognitive Asssessment (MoCA) test was applied to all participants. MoCA test results showed that patients with psoriasis had mild cognitive impairment. It was determined that visuospatial functions and executive functions were significantly affected in psoriasis patients. In their study conducted with 50 patients with psoriasis and healthy controls who were similar in terms of age and gender, Innamorati et al.,[25] reported that patient group exhibited deterioration in cognitive performance and high levels of anxiety and depression symptoms and showed impaired quality of life. In their study conducted by Marek-Jozefowicz et al.,[15] on 97 psoriasis patients and 91 healthy individuals, Marek-Jozefowicz et al.,[15] used the Trail Making Test and the Stroop test to evaluate dorsolateral prefrontal cortex functions. It was emphasized that the problem in the neuropsychological tests evaluating memory and cognitive functions of patients was evident. There are studies in the literature reporting that treatments based on teaching cognitive strategies can support patients with psoriasis therapeutically.[26-28] In the present study, cognitive functions were evaluated with P300 method and no difference was observed with patients with psoriasis and healthy controls. The study conducted by Pezzolo et al.,[12] with 318 psoriasis patients and 9678 individuals without psoriasis, which supports the present study. In this population-based study, it was reported that cognitive test scores and volumetric and microstructural measurements of the brain were not affected by the presence of psoriasis.

When P300 was compared between the patient and control groups in terms of gender, it was found that while no difference was found in p300 evaluation of the female patients with psoriasis and female controls, mean CzLat in male patient group with psoriasis was higher compared to mean CzLat of men in the control group. In a systematic review study conducted on the effect gender on P300, 2143 articles in 2000-2018 were evaluated. As a result of this evaluation, the first result was that there may be p300 changes between genders, the second finding was that there were inconsistent results on gender effect. While more P300 amplitude changes were mentioned in women in half of the studies, the other half states that gender had no effect on p300 and the number of studies showing higher p300 amplitudes in male gender was limited. The third finding was that the results for p300 amplitude were best recorded on centro-parietal region. These differences were reported to be caused by the neuroanatomical differences between the brain cortex and hemispheres between women and men, functional differences such as establishment of intra-hemispheric connections by men and establishment of inter-hemispheric connections by women, level differences of sex steroids and may be the study methodology.[29-31] There are studies reporting that low estrogen (E2) hormone levels play a role in the etiology of dementia in women. It remains uncertain whether the association between low estrogen levels and cognitive decline and dementia stems from the direct impact of E2 deficiency on neurons, or its indirect

influence on other physiological systems, particularly the immune system.

It was reported that long disease duration in patients with psoriasis may be correlated with significantly poor results in neuropsychological tests. This can be explained by changes in central nervous system (CNS), especially in prefrontal cortex and the negative effects of inflammatory factors (cytokines, cortisol) on the nervous system. It was shown that cortisol may have neurotoxic effects especially for hippocampal neurons involved in memory and emotional processes. This hypothesis was supported with the data obtained from numerous studies determining that nervous, immune and endocrine systems acted like a functional union and systems communicated and interacted with each other using neurotransmitters, hormones or cytokines and impairments in this interaction affected the systems.[15,33] Interleukin (IL) -1, IL-2 and IL-6 receptors are found in hypothalamus and hippocampus structure. IL-1 and IL-6 are produced at consistently low concentrations in neurons and glia. The hypothalamic-pituitary-adrenal (HPA) axis is stimulated at all levels by proinflammatory cytokines. During somatic problems observed to increase in the synthesis of proinflammatory cytokines, the development risk of depression symptoms was documented. Cytokines regulate brain function and affect sleep patterns, appetite and cognitive functions.[34-38] In psychological level, the early onset of skin disease can be a dysfunctional, depressive cognitive schema element.[15] It was shown that hippocampus and medial temporal lobes of patients with high systemic inflammatory markers having an effect on cognitive functions were lower than the patients with lower inflammatory markers.[6] In the study conducted by Jung et al.,[39] to investigate the effects of cytokines on cognition, they showed that while inflammatory cytokines such as IL-1 and TNF alpha negatively affected the cognitive functions, anti-inflammatory cytokines such as IL- 10 and IFN gamma had positive effects on cognitive functions. In studies where cytokine measurements were not conducted, it was reported that the deterioration in cognitive functions in psoriasis patients was not correlated with severity and/or the last inflammation period of the disease.[11,14,15] Among these studies, in the study by Marek-Jozefowicz et al. [15], they reported that severity of psoriasis disease did not affect cognitive disorders and the presence of long-term disease was the main factor for cognitive dysfunction. In other words, the longer the disease lasts, the greater the brain damage. In the present study, it was observed that both severity and duration of psoriasis disease did not affect cognitive functions.

Conclusion

Cognitive functions are not affected by the presence of the disease in psoriasis patients. Despite its limitations, to the best of our knowledge, this study represents the initial attempt to assess cognitive function in individuals with psoriasis vulgaris using the P300 method.

Limitations

Although it was seen in the present study that disease severity (PASI) did not affect P300, inflammatory cytokine levels such as IL-1, IL-6, and TNF alpha that will determine the inflammation indicator and severity were not measured.

In terms of revealing the differences between genders, parameters considering the gender- related characteristics (gender hormones etc.) were not used in the present study.

Acknowledgments

The authors thank Assistant Prof. Ziynet Çınar for her assistance.

Ethics committee approval

The study was conducted with the approval of Sivas Cumhuriyet University Clinical Research Ethics Committee (2017-01/24).

Conflict of interest

No conflict of interest was declared by the authors.

Financial disclosure

This study was supported by Coordination Department of Scientific Research Projects of Sivas Cumhuriyet University (CUBAP). Project number: T764.

References

1. Akyol M, Alper S, Atakan N, Bülbül Başkan E, Gürer MA, Koç E, Onsun N, Ozarmagan G, Şentürk N, Yaylı S. Turkey Psoriasis Treatment Guide-2016. Türkderm-Arch Turk Dermatol Venerology. 2016;50(1):1-56.
2. Bu J, Ding R, Zhou L, Chen X, Shen E. Epidemiology of Psoriasis and Comorbid Diseases: A Narrative Review. Front. Immunol. 2022;13: 880201.
3. Amanat M, Salehi M, Rezaei N. Neurological and psychiatric disorders in psoriasis. Rev Neurosci. 2018; 29(7):805-13.
4. Biçici F, Berksoy Hayta S, Akyol M, Özçelik S, Ziynet Çınar Z. Evaluation of sleep quality in patients with psoriasis. Türkderm- Arch Turk Dermatol Venerology. 2015; 49: 208-12.
5. Berksoy Hayta S, Güner R, Akyol M, Albayrak F, Kuğu N, Özçelik S. Increased expressed emotion in patients with psoriasis. Neuropsychiatria and Neuropsychologia. 2018: 13(1);9-16.
6. Bettcher BM, Kramer JH. Longitudinal Inflammation, Cognitive Decline, and Alzheimer's Disease: A Mini-Review. Clin Pharmacol Ther. 2014; 96(4): 464-9.
7. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 2000; 908:244-54.
8. Eikelenboom P, Hoozemans JJ, Veerhuis R, van Exel E, Rozemuller AJ, van Gool WA. Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer's disease. Alzheimers Res Ther. 2012;4:15.
9. Kravitz BA, Corrada MM, Kawas CH. Elevated C-reactive protein levels are associated with prevalent dementia in the oldest-old. Alzheimers Dement. 2009;5:318-23.
10. Bettcher BM, Wilheim R, Rigby T, Green R, Miller JW, Racine CA, Yaffe K, Miller BL, Kramer JH. C-reactive protein is related to memory and medial temporal

brain volume in older adults. Brain Behav Immun. 2012;26:103-8.
11. Çölgeçen E, Çelikbilek A, Taslak Keskin D. Cognitive Impairment in Patients with Psoriasis: A Cross-Sectional Study Using the Montreal Cognitive Assessment. Am J Clin Dermatol. 2016;17:413-9.
12. Pezzolo E, Mutlu U, Vernooij MW, Dowlatshahi EA, Gisondi P, Girolomoni G, Tamar Nijsten T, Ikram A, Wakkee M. Psoriasis is not associated with cognition, brain imaging markers and risk of dementia: the Rotterdam Study. 10.1016/j.jaad.2018.07.046
13. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, Culliford D, Perry VH. Systemic inflammation and disease progression in Alzheimer disease. Neurology. 2009;73(10):768-74.
14. Gisondi P, Sala F, Alessandrini F, Avesani V, Zoccatelli G, Beltramello A, Moretto G, Gambina G, Girolomoni G. Mild cognitive impairment in patients with moderate to severe chronic plaque psoriasis. Dermatology.2014;228(1):78-85.
15. Marek-Jozefowicz L, Jaracz M, Placek W, Czajkowski R, Borkowska A. Cognitive impairment in patients with severe psoriasis. Adv Dermatol Allergol. 2017;34(2):120-5.
16. Langley RG, Ellis CN. Evaluating psoriasis with Psoriasis Area and Severity Index, Psoriasis Global Assessment and Lattice System Physicans Global Assessment. J Am Acad Dermatol. 2004;51:563-9.
17. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Reliability and Validity of The Standardized Mini Mental State Examination in The Diagnosis of Mild Dementia in Turkish Population. Türk Psikiyatri Dergisi. 2002; 13(4):273-81.
18. Hisli N. Validity and reliability of Beck depression inventory for university students. Back depresyon envanterinin üniversite öğrencileri için geçerliği, güvenirliği.*Turkish Journal of Psychology* . 1989;7:3-13.
19. Öztürkcan S, Ermertcan A, Eser E, Şahin MT. Cross validation of Turkish version of Dermatology Life Quality Index (DLQI). International Journal of Dermatology. 2006;45(11):1300-7.
20. Gökçay F, Celebisoy N, Kisabay A, Kumral E, Akyürekli O. P300 and neuropsychological evaluation in Behçet's disease with and without neurological manifestations. J Neurol. 2004;251 :676-9.
21. Keçeci H, Akyol M. P300 in Behcet's Patients without Neurological Manifestations. The Canadian journal of neurological sciences. 2001; 28(1):66-9.
22. Melynyte S, Wang GY, Griskova-Bulanova I. Gender effect on auditory P300: A systematic review. International Journal of Psychophsiology. 2018;133:55-65.
23. Imamoglu B, Berksoy Hayta S, Guner R, Akyol M, Ozcelik S. Metabolic syndrome may be an important comorbidity in patients with seborrheic dermatitis. Arch Med Sci Atheroscler Dis. 2016;1(1):e158–e161.
24. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006; 55: 829-35.
25. Innamorati M, Quinto RM, Lester D, Iani L, Graceffa D, Bonifati C. Cognitive impairment in patients with psoriasis: A matched case-control study. J Psychosom Res. 2018;105:99-105.
26. Panasiti MS, Ponsi G, Monachesi B, Lorenzini L, Panasiti V, Aglioti SM. Cognitive load and emotional processing in psoriasis: a thermal imaging study. Experimental Brain Research. 2019;237:211-22.
27. Piaserico S, Marinello E, Dessi A, Linder MD, Coccarielli D, Peserico A. Efficacy of Biofeedback and Cognitive-behavioural Therapy in Psoriatic PatientsA Single-blind, Randomized and Controlled Study with Added Narrow-band Ultraviolet B Therapy. Acta Derm Venereol. 2016;96(217):91-5.
28. van Beugen S, Ferwerda M, Spillekom-van Koulil S, Smit JV, Zeeuwen-Franssen ME, Kroft EB, de Jong EM, Otero ME, Donders AR, van de Kerkhof PC, van Middendorp H, Evers AW. Tailored Therapist-Guided Internet-Based Cognitive Behavioral Treatment for Psoriasis: A Randomized Controlled Trial. Psychother Psychosom. 2016;85(5):297-307.
29. Melynyte S, Wang GY, Griskova-Bulanova I. Gender effect on auditory P300: A systematic review. International Journal of Psychophsiology. 2018;133:55-65.
30. Leah H. Rubin L, Neigh GN, Sundermann EE, Xu Y, Scully EP, Maki PM. Sex Differences in Neurocognitive Function in Adults with HIV: Patterns, Predictors, and Mechanisms. Current Psychiatry Reports. 2019;21:94.
31. Hillerer KM, Slattery DA, Pletzer B. Neurobiological mechanisms underlying sex-related differences in stress-related disorders: Effects of neuroactive steroids on the hippocampus. Frontiers in Neuroendocrinology. 2019:100796.
32. Au A, Feher A, McPhee L, Jessa A, Oh S, Einstein G. Estrogens, inflammation and cognition. Front Neuroendocrinol. 2016;40:87-100.
33. Zhu TH, Nakamura M, Farahnik B, Abrouk M, Lee K, Singh R, Gevorgyan A, Koo J, Bhutani T. The Role of the Nervous System in the Pathophysiology of Psoriasis: A Review of Cases of Psoriasis Remission or Improvement Following Denervation Injury. Am J Clin Dermatol. 2016;17(3):257-63.
34. Joachim RA, Kuhlmei A, Dinh QT. Neuronal plasticity of the "brain-skin connection": stress-triggered up-regulation of neuropeptides in dorsal root ganglia and skin via nevre growth factor-dependent pathways. J Mol Med 2004;85:1369-78.
35. Schmid-Ott G, Jaeger B, Meyer S, et al. Different expression of cytokine and membrane molecules by circulating lymphocytes on acute mental stress in patients with atopic dermatitis in comparison with healthy controls. J Allergy Clin Immunol. 2001;108:455-62.
36. Evers AW, Verhoeven EW, Kraaimaat FW, et al. How stres gets under the skin: cortisol and stress reactivity in psoriasis. Br J Dermatol. 2010;163:986-91.

37. Al Abadie MS, Kent GG, Gawkrodger DJ. The relationship between stress and the onset and exacerbation of psoriasis and other skin conditions. Br J Dermatol. 1994;130:199-203.
38. Fordham B, Griffith C, Bundy C. Can stress reduction interventions improve psoriasis? A review. Psychol Health Med. 2013;18:501-14.
39. Jung YH, Shin NY, Jang JH, Lee WJ, Lee D, Choi Y, Choi SH, Kang DH. Relationships among stress, emotional intelligence, cognitive intelligence, and cytokines. Medicine (Baltimore). 2019; 98(18): e15345.

CMJ. 2024; 46(3): 178-185
DOI: 10.7197/cmj.1524213

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Evaluation of the Relationship of HBsAg Serum Plasma Values with HBV DNA and Other Serologic Markers in the Diagnosis of Hepatitis B

Hamdi Karahan[1,a], Cem Çelik[1,b*]

[1]*Department of Medical Microbiology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Turkiye*
**Corresponding author*

Research Article

History

Received: 29/07/2024
Accepted: 10/09/2024

ABSTRACT

Objective: Hepatitis B virus (HBV) infections cause a major public health problem worldwide diagnosis and treatment of HBV infection is an important issue. Detection of HBV DNA by polymerase chain reaction (PCR) and demonstration of viral replication together with serologic and biochemical indicators are very useful in diagnosis and treatment. In this study, we aimed to evaluate the relationship between HBsAg serum concentration values and other serologic parameters related to HBV in the diagnosis of hepatitis B.

Methods: HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, and Anti HBe values obtained from blood sera taken from patients in Sivas Cumhuriyet University Application and Research Hospital Microbiology Laboratory between 2012-2020 were retrospectively analyzed from laboratory records.

Results: A positive correlation was found between HBsAg serum titers and HBV DNA and between HBeAg and HBV DNA. It was found that HBV DNA positivity rates increased as HBsAg titers increased. Similarly, it was found that HBc IgG positivity increased as HBsAg titers increased. HBeAg positivity increased with increasing HBsAg titers up to a certain point, while HBeAg positivity decreased after a certain titer. When HBV DNA results were compared with HBeAg results, the relationship between the two values was found to be significant.

Conclusion: We think that it is useful to investigate the relationship between serum concentrations of HBsAg and HBV DNA and other serologic parameters in the accurate identification of HBV infection and monitoring of treatment.

Keywords: HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, Anti HBe

Hepatit B Tanısında HBsAg Serum Plazma Değerlerinin HBV DNA ve Diğer Serolojik Belirteçlerle İlişkisinin Değerlendirilmesi

Araştırma Makalesi

Süreç

Geliş: 29/07/2024
Kabul: 10/09/2024

ÖZET

Amaç: Hepatit B virüsü (HBV) enfeksiyonları tüm dünyada çok önemli bir toplum sağlığı problemi oluşturmaktadır. HBV enfeksiyonunun tanı ve tedavisi önemli bir konudur. HBV DNA'nın polimeraz zincir reaksiyonu (PCR) yöntemi ile saptanarak viral replikasyonun gösterilmesi, serolojik ve biyokimyasal göstergelerle birlikte tanı ve tedavinin takibinde oldukça yararlıdır. Bu çalışmada, Hepatit B tanısında HBsAg serum konsantrasyon değerlerinin, HBV ile ilgili diğer serolojik parametreler ile karşılaştırılarak aralarındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Yöntem: Sivas Cumhuriyet Üniversitesi Uygulama ve Araştırma Hastanesi Mikrobiyoloji Laboratuvarına 2012–2020 yıllarında hastalardan alınan kan serumlarından elde edilen HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg ve Anti HBe değerleri laboratuvar kayıtlarından geriye dönük olarak incelenmiştir.

Bulgular: HBsAg serum titreleri ile HBV DNA arasında ve HBeAg ile HBV DNA arasında pozitif bir ilişki bulunmuştur. HBsAg titreleri arttıkça HBV DNA pozitiflik oranlarının arttığı görülmüştür. Aynı şekilde HBsAg titreleri arttıkça HBc IgG pozitifliklerinin arttığı tespit edilmiştir. Belirli bir noktaya kadar artan HBsAg titreleri ile HBeAg pozitifliği artarken, belirli bir titreden sonra HBeAg pozitifliği düşmüştür. HBV DNA sonuçları ile HBeAg sonuçları karşılaştırıldığında iki değer arasındaki ilişki önemli bulunmuştur.

Sonuç: HBV enfeksiyonun doğru bir şekilde tanımlanmasında ve tedavinin izlenmesinde HBsAg'nin serum konsantrasyonlarının, HBV DNA ve diğer serolojik parametreler ile ilişkilerinin araştırılmasının yararlı olduğunu düşünmekteyiz.

Anahtar Kelimeler: HBsAg, HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, Anti HBe

[a] *hmdkrhn@gmail.com* *0000-0002-4801-2217* [b] *cemcelik58@gmail.com* *0000-0002-7141-5874*

How to Cite: Karahan H, Çelik C. Evaluation of the Relationship of HBsAg Serum Plasma Values with HBV DNA and Other Serologic Markers in the Diagnosis of Hepatitis B. Cumhuriyet Medical Journal, 2024; 46(3): 178-185.

Introduction

Hepatitis B virus (HBV) infections are a very important public health problem all over the world. Many people around the world are infected with HBV and 300 million people are chronically infected. Approximately one million people die each year due to HBV infection and HBV-related complications[1].

Liver diseases caused by HBV are one of the important health problems all over the world[2]. HBV infection can lead to a wide range of liver diseases, from HBV carriage to liver cirrhosis and hepatocellular carcinoma[3].

Differences in the virus or patients cause different clinical manifestations of HBV infection. The clinical presentation of HBV infection depends on the age of infection, the genetic structure of the virus, the presence of other viral hepatitis viruses, and the immune status of the host. While 90% of infections acquired in the neonatal period become chronic, the rate of chronicity is 25-30% until the age of 5 and less than 5% in adulthood[4].

Diagnosis and treatment of HBV infection is an important issue. Detection of viral replication by polymerase chain reaction (PCR) of Hepatitis B virus deoxyribonucleic acid (HBV DNA), together with other serologic indicators, is very useful in diagnosis and monitoring of treatment[5]. In recent years, it has become important to investigate the relationship between serum concentrations of Hepatitis B surface antigen (HBsAg) and HBV DNA and other serologic parameters[6]. Molecular, serological, and biochemical tests are used together in the diagnosis, clinical, and treatment management of HBV infection[7]. This study aimed to evaluate the relationship between HBsAg serum concentration values and HBV DNA, Anti HBc IgG (Hepatitis B virus core G antibody), Anti HBc IgM (Hepatitis B virus core M antibody), HBeAg (Hepatitis B virus e antigen) and Anti HBe (Hepatitis B virus e antibody) in the diagnosis of Hepatitis B.

Materials and Methods

In this study, HBsAg, HBV DNA, anti-HBc IgG, anti-HBc IgM, HBeAg, and anti-HBe levels obtained from blood sera of patients of different age and gender groups in Sivas Cumhuriyet University Application and Research Hospital Microbiology Laboratory between 2012 and 2020 were retrospectively analyzed from laboratory records.

In the study, the blood samples analyzed were evaluated once a year for each patient; repeated patient results within the same year were not evaluated. In addition to HBsAg positivity, patients with one or more positive anti HCV, anti HDV and anti HIV tests were excluded from the study to avoid confusion in the evaluation of other study parameters.

In this study, the presence of antigen/antibody used in HBV diagnosis in serology tests was analyzed. Blood samples taken from the patients in EDTA tubes were separated by centrifugation without waiting. HBsAg, Anti HBc, Anti HBc IgM, HBe Ag, Anti HBe, HBe IgM, HBe Ag, Anti HBe, tests of serum samples from 2012-2019 were analyzed using the Chemiluminescent Microparticle Enzyme Immunoassay (CMIA) method by the procedure recommended by the manufacturer (Architect System, Abbott, Germany). HBsAg, Anti HBc, Anti HBc, Anti HBc IgM, HBeAg, Anti HBe, tests from serum samples in the 2019-2020 years were analyzed using the electrochemilluminescence Immunoassay (ECLIA) method by the procedure recommended by the manufacturer (Roche Diagnostics, Germany).

Each stage of the study was conducted with ethical principles. Before the application, the necessary permissions were obtained from the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (dated 25.05.2022, numbered 11/41).

Statistical Analysis

The data obtained from this study were uploaded to the SPSS program (ver:22.0). In the evaluation of the data, when the parametric test assumptions were fulfilled (Kolmogorov-Smirnov), the significance test of the difference between two means was used when comparing the measurements obtained from two independent groups, Man Whitney U test was used when the parametric test assumptions were not fulfilled, Correlation analysis was used to determine the relationships between variables, Khi-Square test was used in 2x2 and multi compartment arrangements in the evaluation of data obtained by counting, and the error level was taken as 0.05.

Results

In this study, a total of 3788 patients were tested for HBsAg and HBV DNA. Of these patients, 1536 were female (40.6%) and 2252 were male (59.4%). In the 3788 patients in the study, the youngest age was 0 and the oldest age was 94, with a mean age of 49.43 years. The mean age was 49.65 years for females and 49.30 years for males. HBV DNA, Anti HBc IgG, Anti HBc IgM, HBeAg, and Anti HBe tests were performed in the patient group included in the study and their relationships with HBs Ag titers were compared (Table 1-6).

HBV DNA positivity rate of individuals with HBsAg titer <1 IU/ml was 1.3% and the negativity rate was 98.7%, while HBV DNA positivity rates increased as HBsAg titers increased. When the HBsAg titers and HBV DNA cross table were examined in detail, the relationship between HBV DNA positivity according to titers was found to be significant (X^2=1913.70) (p=0.001) (Table 1).

Table 1. HBsAg Titer and HBV DNA Cross Table

HBsAg Titer (IU/ml)		HBV DNA			
		Negative	Positive	Pos./Neg.	Total
<1 IU/ml	Number of patients	1299	17	0	1316
	%	98.7	1.3	0	100.0
1-10 IU/ml	Number of patients	102	11	0	113
	%	90.3	9.7	0	100,0
11-100 IU/ml	Number of patients	153	185	1	339
	%	45.1	54.6	0.3	100.0
101-1000 IU/ml	Number of patients	0	4	0	4
	%	0	100.0	0	100.0
1001-2000 IU/ml	Number of patients	32	162	0	194
	%	16.5	83.5	0	100.0
2001-4000 IU/ml	Number of patients	199	628	4	831
	%	23.9	75.6	0.5	100.0
4001-5000 IU/ml	Number of patients	133	493	0	626
	%	21.2	78.8	0	100.0
>5001 IU/ml	Number of patients	106	259	0	365
	%	29.0	71.0	0	100
Total	Number of patients	2024	1759	5	3788
	%	53.4	46.4	0.2	100.0

When the cross tabulation of HBsAg titers and Anti HBc IgG is analyzed, it is seen that HBc IgG positivity increases as HBsAg titers increase. While HBc IgG positivity was 68.6% at HBsAg titer <1 IU/ml, this rate reached up to 100% as the titers increased. Accordingly, the relationship between HBsAg titers and anti HBc IgG was found to be significant (X^2=489.20) (p=0.001) (Table 2).

Table 2. HBsAg Titer and HBc IgG Cross Table

HBsAg Titer (IU/ml)		HBc IgG		
		Negative	Positive	Total
<1 IU/ml	Number of patients	160	350	510
	%	31.4	68.6	100.0
1-10 IU/ml	Number of patients	14	29	43
	%	32.6	67.4	100.0
11-100 IU/ml	Number of patients	9	165	174
	%	5.2	93.8	100.0
101-1000 IU/ml	Number of patients	0	2	2
	%	0	100.0	100.0
1001-2000 IU/ml	Number of patients	0	127	127
	%	0	99.2	100.0
2001-4000 IU/ml	Number of patients	2	550	552
	%	0.4	99.6	100.0
4001-5000 IU/ml	Number of patients	2	417	419
	%	0.5	99.5	100.0
>5001 IU/ml	Number of patients	0	247	247
	%	0	100.0	100.0
Total	Number of patients	187	1887	2074
	%	9.2	90.8	100.0

The first antibody that develops against hepatitis B Cor antigen is Anti HBcIgM. This antibody disappears after a while and is replaced by HBcIgG. When HBsAg titers and Anti HBcIgM values were analyzed in our study, Anti HBcIgM positivity was found between 0% and 7% in HBsAg titers. (X^2=71.14)(p=0.021) (Table 3).

Table 3. HBsAg Titer and HBcIgM Cross Table

HBsAg Titer (IU/ml)		HBcIgM			
		Negative	Positive	Pos./Neg.	Total
<1 IU/ml	Number of patients	501	10	1	512
	%	97.8	1.9	0.3	100.0
1-10 IU/ml	Number of patients	42	1	0	43
	%	97.7	2.3	0	100.0
11-100 IU/ml	Number of patients	164	11	0	175
	%	93.7	6.3	0	100.0
101-1000 IU/ml	Number of patients	2	0	0	2
	%	100.0	0	0	100.0
1001-2000 IU/ml	Number of patients	119	9	0	128
	%	93.0	7.0	0	100.0
2001-4000 IU/ml	Number of patients	542	11	0	553
	%	98.8	2.0	0	100.0
4001-5000 IU/ml	Number of patients	415	5	0	420
	%	98.8	1.2	0	100.0
>5001 IU/ml	Number of patients	247	0	0	247
	%	100.0	0	0	100.0
Total	Number of patients	2032	47	1	2080
	%	97.3	2.3	0.04	100.0

HBeAg is formed during similar periods as HBsAg. HBeAg disappears and Anti HBe is formed in certain groups during the progression of the disease. When the HBsAg titers and HBeAg cross-tabulation were examined, HBeAg positivity ranging from 0.5% to 32.7% was observed at different HBsAg titers. While HBeAg positivity increased with increasing HBsAg titers up to a certain point, HBeAg positivity decreased after a certain titer (X^2=297.81)(p=0.001) (Table 4).

Table 4. HBsAg Titer and HBeAg Cross Table

HBsAg Titer (IU/ml)		HBeAg		
		Negative	Positive	Total
<1 IU/ml	Number of patients	590	3	593
	%	99.5	0.5	100.0
1-10 IU/ml	Number of patients	51	1	52
	%	98.1	1.9	100.0
11-100 IU/ml	Number of patients	167	56	223
	%	74.9	25.1	100.0
101-1000 IU/ml	Number of patients	2	0	2
	%	100.0	0	100.0
1001-2000 IU/ml	Number of patients	105	51	156
	%	67.3	32.7	100.0
2001-4000 IU/ml	Number of patients	582	85	667
	%	87.3	12.7	100.0
4001-5000 IU/ml	Number of patients	508	14	522
	%	97.3	2.7	100.0
>5001 IU/ml	Number of patients	297	7	304
	%	97.7	2.3	100.0
Total	Number of patients	2302	217	2519
	%	91.4	8.6	100.0

When the HBsAg titers and Anti HBe cross table are analyzed, it is seen that Anti HBe positivity increases as HBsAg titers increase. Anti HBe positivity, which was 21.4% at HBsAg <1 IU/ml, increased to 74.3% as the titers increased. The relationship between HBsAg titers and Anti HBe was found to be significant (X^2=374.06) (p=0.001) (Table 5).

Table 5. HBsAg Titer and Anti-HBe Cross Table

HBsAg Titer (IU/ml)		Anti-HBe Negative	Anti-HBe Positive	Total
<1 IU/ml	Number of patients	447	122	569
	%	78.6	21.4	100.0
1-10 IU/ml	Number of patients	28	22	50
	%	56.0	44.0	100.0
11-100 IU/ml	Number of patients	120	99	219
	%	54.8	45.2	100.0
101-1000 IU/ml	Number of patients	1	1	2
	%	50.0	50.0	100.0
1001-2000 IU/ml	Number of patients	69	86	155
	%	44.5	55.5	100.0
2001-4000 IU/ml	Number of patients	238	419	657
	%	36.2	63.8	100.0
4001-5000 IU/ml	Number of patients	133	384	517
	%	25.7	74.3	100.0
>5001 IU/ml	Number of patients	109	193	302
	%	36.1	63.9	100.0
Total	Number of patients	1145	1326	2471
	%	46.3	53.7	100.0

When HBV DNA results were compared with HBeAg results, HBeAg positivity was found to be 2.5% in HBV DNA negative patients, while this rate was 13.5% in HBV DNA positive patients. When HBV DNA results were compared with HBeAg results, the relationship between the two values was found to be significant (X^2=95.43) (p=0.001) (Table 6).

Table 6. HBV DNA and HBeAg Cross Table

HBVDNA		HBeAg Negative	HBeAg Positive	Total
Negative	Number of patients	1073	27	1100
	%	97.5	2.5	100.0
Positive	Number of patients	1221	190	1411
	%	86.5	13.5	100.0
Pos.Neg.	Number of patients	4	0	4
	%	100.0	0	100.0
Total	Number of patients	2298	217	2515
	%	91.4	8.6	100.0

Discussion

The issue of which serologic and virologic tests to use in the diagnosis of HBV-related diseases is important. The diagnosis of HBV is based on clinical, biochemical, histological and serological findings[8].

HBsAg is the first antigen of the virus detected in the diagnosis of acute hepatitis B. Primary HBV infection can

be serologically determined by the appearance of HBsAg and HBeAg. Clinical symptoms appear around 10 weeks after infection and during this period elevated liver enzymes and anti-HBc IgM antibodies are detected. Shortly after the appearance of HBsAg, HBeAg also appears. The presence of HBeAg is associated with transmissibility and active viral infection. When HBeAg disappears, Anti-HBe appears and remains positive for years. In acute hepatitis B, there may be a window period when both HBeAg and Anti HBe are negative. Anti-HBc IgM is positive during the window period and is therefore important. Anti-HBc IgM level decreases within 12-48 weeks, while Anti-HBc IgG level increases and can be positive in serum for life. Detection of Anti-HBc IgG and Anti-HBs IgG antibodies together is an indication that the disease has been transmitted and immunity is formed. Anti HBcTotal and anti HBs tests are not useful in diagnosis. Because they are indicators of previous infection. Persistent HBsAg positivity for at least 6 months suggests the presence of chronic hepatitis B[9].

The treatment of chronic HBV infections is difficult and complex. Due to the persistence of HBV covalently closed circular DNA (cccDNA), most patients require indefinite treatment. A durable treatment response often fails to develop. Therefore, efforts to prevent the disease and to screen risk groups are of vital importance[10]. Measurement of HBV DNA load and serum HBsAg is important in accurately defining HBV infection, monitoring treatment, and determining prognosis. Sağlık et al.[11] reported a positive correlation between HBsAg measurement values and HBV DNA levels in chronic hepatitis B patients. Zhu et al.[12] reported a positive correlation between increasing HBV load and serum HBsAg levels in patients divided into 3 groups according to HBV DNA load. Demirelli et al.[13] investigated the relationship between serum HBsAg and HBV DNA in 71 patients treated for chronic hepatitis B infection. Researchers have found a positive correlation between serum HBsAg levels and HBV DNA in patients. In our study, similar results were obtained between HBsAg serum titer and HBV DNA. As HBsAg titer increased, the HBV DNA positivity rate increased.

Karra et al.[14] categorized HBV infection into 4 phases: immune tolerance phase, immune clearance phase, low replicative phase, and HBeAg negative hepatitis. In a total of 976 HBV-associated patients, the investigators reported that HBsAg titers were different in each phase of HBV infection, and HBsAg and HBV DNA levels were significantly correlated in all groups. Özaras et al.[15] performed HBsAg quantitation and HBV DNA measurements at certain weeks in 18 patients with chronic hepatitis B receiving pegylated interferon ± lamivudine and reported a significant correlation between these results. Researchers have reported that the HBsAg test is associated with HBV DNA and may be a valuable marker during the monitoring of the effectiveness of HBV treatment. Similarly, in our study, the HBV DNA positivity rate increased as the HBsAg titer increased. The relationship between HBsAg titers and HBV DNA positivity was found to be significant ($p<0.05$).

The presence of HBe Ag antigen is associated with increased infectivity and an increased risk of chronic hepatitis b carriers progressing to cirrhosis. The HBe Ag antigen can be used to help monitor the evolution of chronic HBV[8]. Shao et al.[16] evaluated HBV DNA levels in HBeAg positive and negative patients in their study. The researchers found HBeAg test positive in 178 and negative in 35 of 213 patients with HBV DNA levels above 10^5 copies/mL. In our study, similar results were obtained between HBV DNA and HBeAg status similar to Shao et al. HBV DNA was found positive in 190 of 217 HBeAg positive patients. Wang et al.[17] grouped 1020 patients into HbeAg positive and HbeAg negative groups and high and low HBV DNA levels. The researchers reported that when the HBeAg level was higher than 16.15 S/CO, they were four times more likely to have high HBV DNA levels. Bizim çalışmamızda HBeAg pozitif olan hastaların büyük çoğunluğunda HBV DNA pozitif bulunması yönünden Wang ve arkadaşlarının çalışmasının sonuçları ile benzer görünmektedir. Çeviker et al.[18] formed two groups according to HBeAg positive and negative status among 231 patients diagnosed with chronic hepatitis B. Among these patients, 198 were anti HBe positive and 33 were HBeAg positive. HBV DNA levels were found to be significantly higher in HBeAg positive patients. The results of our study seem to be similar to the results of this study.

HBV inactive carriers are difficult to differentiate from HBeAg negative patients. Martinot-Peignoux et al.[19] classified 129 HBeAg-negative CHB patients as inactive carriers, active carriers and reactivation patients. The researchers reported that combined HBsAg and HBV DNA cut-off values should be applied to baseline measurements and HBsAg should be included in the monitoring of asymptomatic HBeAg-negative CHB patients. Akın et al.[20] reported HBeAg negative anti HBe positive results in 94% of 233 patients and HBV DNA positive results in 13 patients. In our study, 90.7% of HBeAg negative patients were also found to be anti HBe positive. The results of the study by Akın et al. and the anti HBe positivity in our study seem to be similar. Tezcan Ülger et al.[21] compared HBV DNA results with HBeAg results in 91 patients with chronic hepatitis B and reported that the relationship between HBsAg measurement values and HBV DNA levels was statistically significant. The researchers found that HBsAg levels in HBeAg positive patients were significantly higher than HBeAg negative patients.

In cases where HBsAg is negative, the presence of HBV DNA at low titer is known as latent HBV. Even if the HBsAg test is negative, HBV may be present in the body in some patients. These patients may continue to be infectious. Savcı et al.[22] reported that they found isolated HBV DNA positivity (occult hepatitis B infection) in 18 of 160 HBsAg negative patients on hemodialysis. Latent HBV infection is a significant threat to the safety of the blood supply. Svicher et al.[23] investigated occult HBV infection in their study. HBsAg and nucleic acid tests were performed on a total of 422278 blood donors. The researchers reported that they identified occult HBV in 26 of them. In our study,

of the 1316 patients with HBsAg titer <1 IU/ml, 1299 were HBV DNA negative and 17 were HBV DNA positive. Our study results are similar to the results of the above studies in this respect.

Isolated anti HBc positivity may be indicative of different conditions ranging from false reactivity to chronic HBV infection. Further investigation and monitoring are important in these patients. Bozdemir et al.[24] retrospectively analyzed the serologic parameters of 22333 patients whose HBsAg, anti HBc, and anti HBs tests were performed on the same date. It was reported that isolated anti-HBc positivity was detected in 837 (3.74%) of these patients. Of 180 patients who were tested for HBV DNA, 16 (8.8%) were found to be positive. In our study, anti HBcIgM test was performed in 2090 of 3788 patients. Anti HBcIgM test was found to be negative in 2032 patients, positive in 47 patients, and pos. neg in 1 patient. HBV DNA positivity was found to be higher in our study compared to this study.

HBsAg as an indicator of HBV infection is being evaluated. The clinical use of plasma concentrations of serum HBsAg is becoming increasingly important. HBsAg and other serologic parameters alone are insufficient in the evaluation of the course of HBV infection, response to antiviral treatment, and prognosis. Detection of HBV DNA is recognized as the most sensitive method in treatment and follow-up. A positive correlation has been found between HBsAg serum titers and HBV DNA and between HBeAg and HBV DNA. We think that HBV DNA levels are very important in the accurate identification of HBV infection and monitoring of treatment.

Conflicts of interest

There are no conflicts of interest in this work.

Authors' contributions

HK: Analyses, design, supervision, resources, materials, data collection, literature review, reporting. CÇ: Project administration, concept, Writing – review and editing, Research, Methodology, Verification.

References

1. Martyn E, Eisen S, Longley N, et al. The forgotten people: Hepatitis B virus (HBV) infection as a priority for the inclusion health agenda. Elife. 2023; 12:e81070. doi: 10.7554/eLife.81070.
2. Güçlü E, Geyik MF. Hepatitis B infection and prevention. Konuralp Med J. 2012; 4(2): 54-58.
3. Rizzo GEM, Cabibbo G, Craxì A. Hepatitis B virus-associated hepatocellular carcinoma. Viruses. 202214(5):986. doi: 10.3390/v14050986.
4. Akhan S, Aynıoğlu A, Çağatay A, et al. Management of chronic hepatitis B virus infection: A consensus report of the study group for viral hepatitis of the Turkish society of clinical microbiology and infectious diseases. Klimik Derg. 2014; 27(Suppl 1):2-18. doi: 10.5152/kd.2014.26
5. Guvenir M, Arikan A. Hepatitis B virus: from diagnosis to treatment. Pol J Microbiol. 2020;69(4):391-399. doi: 10.33073/pjm-2020-044.
6. Nguyen T, Desmond P, Locarnini S. The role of quantitative hepatitis B serology in the natural history and management of chronic hepatitis B. Hepatol Int. 2009;3(Suppl 1):5-15. doi: 10.1007/s12072-009-9149-7.
7. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560–1599. doi: 10.1002/hep.29800.
8. Krajden M, McNabb G, Petric M. The laboratory diagnosis of hepatitis B virus. Can J Infect Dis Med Microbiol. 2005;16(2):65-72. doi: 10.1155/2005/450574.
9. Uysal RC, Çalık BY, Tercan U, Arslantaş, D. Hepatitis B &Hepatitis C infections. Türk Tıp Öğrencileri Araştırma Dergisi. 2020;2(2):108-112.
10. Leowattana W, Leowattana T. Chronic hepatitis B: New potential therapeutic drugs target. World J Virol. 2022;11(1):57-72. doi: 10.5501/wjv.v11.i1.57.
11. Sağlık I, Mutlu D, Öngüt G, et al. Comparison of HBsAg and HBeAg levels with HBV DNA and ALT levels in patients with chronic hepatitis B infections. Viral Hepat J. 2013;19(3):119-122. doi:10.4274Vhd.84856.
12. Zhu HY, Zhang XS. Relationship between HBV DNA load and levels of serum HBsAg in patients with chronic hepatitis B. Eur Rev Med Pharmacol Sci. 2016;20(10):2061-2064.
13. Demirelli M, Tülek N, Temocin F, Yücel D, Erdinç Ş, Ertem G. Investigation of the association of serum quantitative HBsAg levels with viral load in chronic hepatitis B patients receiving treatment. Pamukkale Med J. 2020;13(3): 569-578. doi.org/10.31362/patd.691645.
14. Karra VK, Chowdhury SJ, Ruttala R, Polipalli SK, Kar P. Clinical significance of quantitative HBsAg titres and its correlation with HBV DNA levels in the natural history of hepatitis B virus infection. J Clin Exp Hepatol. 2016;6(3):209-215. doi: 10.1016/j.jceh.2016.07.002.
15. Ozaras R, Tabak F, Tahan V, et al. Correlation of quantitative assay of HBsAg and HBV DNA levels during chronic HBV treatment. Dig Dis Sci. 2008;53(11):2995-2998. doi: 10.1007/s10620-008-0263-5.
16. Shao J, Wei L, Wang H, et al. Relationship between hepatitis B virus DNA levels and liver histology in patients with chronic hepatitis B. World J Gastroenterol. 2007;13(14):2104-2107. doi: 10.3748/wjg.v13.i14.2104.
17. Wang N, Zheng J, Huang Y, Pu X, Jiang L, Yang J. A Predictive model to evaluate the HbeAg positivity of chronic hepatitis B virus patients in clinics: A cross-sectional study. Medicina (Kaunas). 2022;58(9):1279. doi: 10.3390/medicina58091279.
18. Çeviker SA, Günal Ö, Kılıç SS, Köksal E. The relationship between serum HBV DNA levels, Hbeag status, biochemical parameters, liver ınflammation and fibrosis severity in patients with chronic hepatitis B. KSU Med J. 2020;15(1):32-36. doi.org/10.17517/ksutfd.566288
19. Martinot-Peignoux M, Lapalus M, Laouénan C, et al. Prediction of disease reactivation in asymptomatic hepatitis B e antigen-negative chronic hepatitis B patients using baseline serum measurements of HBsAg and HBV-DNA. J Clin Virol. 2013;58(2):401-407. doi: 10.1016/j.jcv.2013.08.010.
20. Akın P, Özbay G, Şentürk H, et al. Asyptomatic "healthy" HBsAg carrier state in Turkey. Cerrahpaşa J Med.1998;29(3):141-144.
21. Tezcan Ülger S, Delialioğlu N, Kandemir Ö, Ovla Çelikcan HD. Quantitative determination of HBsAg levels in chronically infected patients with hepatitis B virus. Türk Mikrobiyol Cem Derg. 2018;48(1):60-65. doi:10.5222/TMCD.2018.060.
22. Savcı Ü, Bulut Y. Polymerase chain reaction with investigation of occult Hepatitis B infection in hemodialysis patients. Turk J Clin Lab. 2015;6(1):19-23.

23. Svicher V, Cento V, Bernassola M, et al. Novel HBsAg markers tightly correlate with occult HBV infection and strongly affect HBsAg detection. Antiviral Res. 2012;93(1):86-93. doi: 10.1016/j.antiviral.2011.10.022.

24. Bozdemir T, Zeytinoğlu Türkeş A, Sertöz R, Altuğlu İ. Evaluation of 'anti-HBc only' serological pattern detected in patients admitted to Ege University Hospital. Ege Journal of Medicine. 2016;55(4):180-183.

CMJ, 2024; 46(3): 186-190
DOI: 10.7197/cmj.1520709

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Evaluation of Neonates Hospitalized with Indirect Hyperbilirubinaemia

Hikmet Coşkun[1,a,*], Fatih Bolat[2,b]

[1] *Department of Child Health and Diseases, Neonatology Department, Adana City Training and Research Hospital, Adana, Türkiye*
[2] *Department of Child Health and Diseases, Neonatology Department, Medical Park Pendik Hospital, Istanbul, Türkiye*
**Corresponding author*

Research Article

History

Received: 24/07/2024
Accepted: 10/09/2024

ABSTRACT

Objective: Neonatal jaundice is a common problem and is the most common cause of hospitalization. We aimed to determine the characteristics and etiological factors of late preterm and term newborns hospitalized due to indirect hyperbilirubinemia.
Methods: Late preterm and term newborns hospitalized between January 1,2009 and December 31,2014 with a diagnosis of indirect hyperbilirubinemia were included. Demographic and clinical characteristics, duration, and patterns of treatment were obtained retrospectively. Etiological factors were determined.
Result: Late preterm and term infants with indirect hyperbilirubinemia were included (n=412). 54.6% of the patients were male, 40.8 % were first babies, the mean gestational age was 38.3±1.1 weeks, and the mean birth weight was 3031±520 grams. 84.5 % were exclusively breastfed. The time of presentation was 4.6 ±2.6 days, and the serum total bilirubin level was 18.6 ±4.7 mg/dl. ABO incompatibility was found in 29 %, dehydration in 10.7 %, and Rh incompatibility in 7.1% of the patients. The mean duration of hospitalization was 3.1 ±2.2 days, and the mean duration of phototherapy was 44.8±22.8 hours. 16 patients received intravenous immunoglobulin. An exchange transfusion was performed in 14 patients. In the group with a serum total bilirubin level of ≥ 20 mg/dl, male gender and normal spontaneous vaginal delivery were statistically significantly higher than the group with a serum total bilirubin level below 20 mg/dl (p = 0.02 for both).
Conclusion: Indirect hyperbilirubinaemia, which is common in the neonatal period, should be recognized early and is a treatable condition. We should promptly identify and treat the cause before complications arise.

Keywords: Etiological factors, indirect hyperbilirubinemia, newborn

İndirekt Hiperbilirübinemi Tanısı ile Hospitalize Edilmiş Yenidoğanların Değerlendirilmesi

Araştırma Makalesi

Süreç

Geliş: 24/07/2024
Kabul: 10/09/2024

ÖZET

Amaç: Sarılık yenidoğan döneminde sık karşılaşılan sorundur ve hastane yatışlarının en sık nedenidir. Bu çalışmada, indirekt hiperbilirübinemi nedeni ile hospitalize edilen geç preterm ve term yenidoğanların özelliklerini ortaya koymak ve etiyolojik faktörlerini belirlemek amaçlanmıştır.
Yöntem: İndirekt hiperbilirübinemi tanısı ile 1 Ocak 2009-31 Aralık 2014 tarihleri arasında hastaneye yatırılan geç preterm ve term yenidoğanlar çalışmaya alındı. Hastaların demografik ve klinik özellikleri, tedavi süreleri ve şekilleri retrospektif hasta dosyalarından elde edildi. Etiyolojik faktörler belirlendi.
Bulgular: 1 Ocak 2009-31 Aralık 2014 tarihleri arasında hastanemiz yenidoğan yoğun bakım ünitesinde takip edilmiş 4831 hastanın 412'si dahil edilme kriterlerini karşılayan indirekt hiperbilirübinemili geç preterm ve term bebeklerdi. Hastaların %54,6'sı erkek, %40,8'i ilk bebek, doğum haftası ortalama 38,3±1,1 ve doğum ağırlığı 3031±520 gram olarak saptandı. Vakaların %84,5'i yalnızca anne sütü alıyordu. Başvuru zamanı 4,6±2,6 gün ve serum total bilirübin düzeyi 18,6±4,7 mg/dl idi. Hastaların %29'unda ABO uyuşmazlığı, %10,7'sinde dehidratasyon ve %7,1'inde Rh uyuşmazlığı vardı. Ortalama yatış süresi 3,1±2,2 gün ve fototerapi süresi 44,8±22,8 saat olarak bulundu. 16 hastaya intravenöz immünglobülin verilmişti. 14 hastaya kan değişimi yapılmıştı. Serum total bilirübin düzeyi ≥20 mg/dl olan grupta erkek cinsiyet ve normal spontan vajinal yol ile doğan bebek serum total bilirübin düzeyi 20 mg/dl'nin altında olan gruptan istatistiksel olarak anlamlı yüksek saptandı (her ikisi için p=0,02).
Sonuç: Yenidoğan döneminin sık görülen indirekt hiperbilirübinemi erken fark edilmesi gereken ve tedavi edilebilir bir durumdur. Nedeni hızlıca saptanmalı ve komplikasyon gelişmeden tedavi edilmelidir.

Anahtar Kelimeler: Etyolojik faktörler, indirekt hiperbilirübinemi, yenidoğan

[a] *defnehikmet00@gmail.com* *0009-0003-6243-4138* [b] *fatihbolat74@gmail.com* *0000-0002-8363-2139*

How to Cite: Coşkun H, Bolat F. Evaluation of Neonates Hospitalized with Indirect Hyperbilirubinaemia. Cumhuriyet Medical Journal. 2024;46(3):186-190

Introduction

The most prevalent reason for hospitalization during the first week after birth is jaundice, which affects 60 % of full-term newborns and 80 % of preterm infants. Numerous factors, including gestational age, birth weight, race, geographic location, genetic background and concomitant illnesses, might affect the intensity and duration of jaundice in neonates. The chance of having excessive bilirubin levels rises in tandem with the number of risk factors. Serum total bilirubin (STB) levels above 17 mg/dL after the 72nd hour is significant in late preterm and term newborns; levels above 20 mg/dL are critical; levels above 25 mg/dL are excessive; and levels above 30 mg/dL are classified as dangerous hyperbilirubinemia.[1,2] The American Academy of Pediatrics (AAP) suggests that, in order to lower hospital admissions and the risk of kernicterus associated with indirect hyperbilirubinemia, every healthcare facility identify risk factors prior to discharge and establish a protocol for detecting and monitoring the rate of bilirubin increase.[2] The goals are to stop bilirubin levels from rising too high, reduce the chance of brain injury, and end kernicterus instances. In the process of developing an indirect hyperbilirubinemia monitoring protocol in our hospital, this study intends to assess and compare the etiologies, bilirubin levels, and demographic, clinical, and laboratory characteristics of late preterm and term infants diagnosed with indirect hyperbilirubinemia who are admitted to our neonatal unit.

Materials and Methods

This retrospective analysis comprised 412 late preterm and term neonates who were observed in our neonatal intensive care unit from January 1, 2009, to December 31, 2014, for indirect hyperbilirubinemia. Those with congenital cardiac disease, metabolic disorders, chromosomal abnormalities, and sepsis monitoring were not included in the sample, nor were babies delivered before 37 weeks or beyond 40 weeks. Only infants born between 37 and 40 weeks who were diagnosed with indirect hyperbilirubinemia were included. This study collected the following information from patient files and hospital systems: gender, gestational age, time of hospital admission, weight at birth, feeding technique, mode and location of delivery, birth order, day the baby was brought to the hospital, length of hospital stay and the day the family noticed jaundice. comprehensive blood count, serum total bilirubin, direct bilirubin levels, C-reactive protein (CRP), venous hematocrit and reticulocyte values, maternal and neonatal blood groups, presence of reducing substances in urine, thyroid-stimulating hormone level, pyruvate kinase and glucose-6-phosphate dehydrogenase (G6PD) levels, and direct Coombs test results were among the laboratory data collected. Patient records also contained details regarding the therapies that the patients received, including the length of phototherapy, intravenous immunoglobulin (IVIG), and exchange transfusion.

Statistical Analysis

The SPSS (Statistical Package for Social Sciences) for Windows 15.0 application was used to undertake the statistical analysis of the results. Descriptive statistical analysis was used to assess the demographic features. The comparison of qualitative and quantitative data was done using descriptive statistical techniques (mean, standard deviation, median, minimum, and maximum), as well as Student's t-test, Chi-square test, and Fisher's exact test. The significance level was set at $p < 0.05$.

Ethical Approval: The Cumhuriyet University Ethics Committee granted its approval for the study (Decision No. 04/07, Date: 2015).

Result

Among the 4,831 patients monitored in our hospital's neonatal intensive care unit from January 1, 2009 to December 31, 2014; 412 were late preterm and term infants diagnosed with indirect hyperbilirubinemia**.** Of these patients, 81 (19.7 %) were referred from other facilities, and 331 (80.3 %) were born in our hospital. Forty-eight percent of the patients were first-born males, making up 54.6 % of the patient population. The mother's age ranged from 16 to 44 years on average, and 62.9 % of the babies were born naturally through spontaneous vaginal delivery (NSVD). The average birth weight was 3,034 +/- 529 grams, and the average gestational age was 38.3 +/- 1.1 weeks. Eighty-four percent of the babies were nursed exclusively. Within the first week, 75% of the patients were admitted to the hospital; admissions took place on days 1 through 16 days (on average, the 4th day). Table 1 provides a summary of the patients' indirect hyperbilirubinemia causes. The average period of phototherapy for the patients was 48 hours, and their average serum total bilirubin (STB) level was 18.6 mg/dL. Sixty-four (15.5 %) of our patients had a direct Coombs test that was positive. Intravenous immunoglobulin (IVIG) treatment was administered to sixteen patients who had significant hyperbilirubinemia (>20 mg/dL) as a result of blood group incompatibility and STB levels at the exchange transfusion threshold. With mean STB levels of 32.8 +/- 14 (26-47) mg/dL, a total of 14 patients underwent exchange transfusion; three of these patients underwent exchange transfusion after IVIG treatment. Eighty percent of the newborns receiving exchange transfusions were delivered naturally by vaginal delivery (NSVD), and the average time of the transfusions was between 2.9 and 1.2 days. Six of these babies were incompatible with ABO, five were incompatible with Rh, and three were incompatible with both ABO and Rh (Table 2). Both male newborns and those born via normal spontaneous vaginal delivery (NSVD) were substantially more likely to be in the severe hyperbilirubinemia group ($p=0.02$) when the patients were split into two groups based on their STB values (<20 mg/dl ve ≥20 mg/dl). In the group with severe hyperbilirubinemia, there were statistically significantly more patients with G6PD deficits and urinary tract infections ($p = 0.07$ for both). Patients with STB 20 mg/dL had substantially lower hematocrit levels than those with STB <20 mg/dL ($p = 0.04$). Severe hyperbilirubinemia was present in 33.6 % of individuals with ABO incompatibility and 14.1% of individuals with Rh incompatibility. Regarding additional risk variables including dehydration, feeding technique, Rh incompatibility, and ABO incompatibility, no significant differences were seen between the groups (Table 3). Out of the 412 patients that underwent phototherapy, 12% had diarrhea, 15% had skin rashes, and 2 had necrotizing enterocolitis sepsis after receiving an exchange transfusion. During the transfusion, a patient's bradycardia and apnea were noted as causes of death.

Table 1. Identifiable causes of indirect hyperbilirubinaemia in patients

Etiological factors	n (%)
ABO mismatch	122 (29.6)
Dehydration	45 (10.9)
Rh incompatibility	30 (7.2)
Urinary tract infection	12 (2.9)
G6PD deficiency	12 (2.9)
Hypothyroidism	5 (1.2)
Cephal haematoma	4 (0.9)
Surrenal haematoma	4 (0.9)
Polycythemia	4 (0.9)
ABO+Rh incompatibility	3 (0.7)
Hereditary spherocytosis	2 (0.4)
Galactosemia	2 (0.4)
Unidentified cause	167 (40.5)

G6PD: glucose 6 phosphate dehydrogenase

Table 2. Some laboratory results and treatment methods of the patients

Total serum bilirubin (mg/dl)	18.6 (8-47)
Direct bilirubin (mg/dl)	0.6 (0.1-8)
Haematocrit (%)	49.8 (23-72)
Leucocytes (n)	11170 (3400-47000)
Reticulocyte (%)	1 (0-18)
Duration of phototherapy (hours)	48 (12-168)
Blood exchange n (%)	14 (3.4%)
IVIG treatment n (%)	16 (3.9%)

Values were given as mean (minimum-maximum) and n (%).
IVIG: intravenous immunoglobulin

Table 3. Comparison of the groups with and without severe hyperbilirubinaemia in terms of demographic, clinical and laboratory data

n(%)	STB<20 mg/dl (n=284)	STB≥20 mg/dl (n=128)	p
Gender			
Female	166 (58.5)	59 (46.1)	0.02*
Male	118 (41.5)	69 (53.9)	
Mode of delivery			
Normal	168 (59.2)	91 (71.1)	0.02*
Sectio	116 (40.8)	37 (28.9)	
Gestational age	38.28±1.3	38.2±1.1	0.72
Dehydration	31 (10.9)	12 (9.4)	0.63
Diet			
Breast milk	236 (83.1)	112 (87.5)	
Formula milk	7 (2.5)	2 (1.6)	0.51
Mix tipe milk	41 (14.4)	14 (10.9)	
Hematocrit	50.6±8.6	47.9±8.7	0.04*
Leukocyte count	10595±4750	12626±5449	0.053
ABO incompatibility	79 (27.9)	43 (33.6)	0.23
Rhincompatibility	25 (8.8)	18 (14.1)	0.11
Urinary infection	4 (1.4)	8 (6.2)	0.07
G6PD defisity	4 (1.4)	8 (6.2)	0.07
D.coombs positive	41 (14.4)	23 (18)	0.36

*p<0.05, STB:serum total bilirübin, G6PD: glukoz 6 fosfat dehidrogenaz

Discussion

Talk about one of the most prevalent conditions in the newborn stage is jaundice. It affects 60 % of full-term babies, and 5–10 % of these instances necessitate hospital care. Male gender, breastfeeding, being the first child, early discharge of the mother and child after delivery, and pathological weight loss are risk factors for developing jaundice that requires medical attention.[3-6] Studies show that jaundice exhibits regional, ethnic, and cultural variances, and that each nation must establish its own guidelines for treating jaundice.[4] In wealthy nations, mother-child pairs' postpartum hospital stays have gotten shorter, especially in the last ten years. But as a result, infants with indirect hyperbilirubinemia are being readmitted at a significantly higher rate after being discharged.[6, 7] Neonatal jaundice is known to affect male infants more frequently than female neonates, with a male-to-female ratio of 1 to 1.5.[2,8] In a similar vein, male newborns accounted for 54.6 % of the cases in our study. First-born parents' inexperience with baby care and feeding, along with the delayed increase in breast milk supply following the first birth, are the likely causes of the greater frequency of newborn jaundice in these children.[1,9] Bülbül et al., however, discovered that having a first child did not increase the risk.[10] Although 40.8 % of the newborns in our study were the first in their families, there was no evidence linking this to an increased risk of high bilirubin levels. As opposed to cesarean sections, the American Academy of Pediatrics (AAP) states that having a normal spontaneous vaginal delivery (NSVD) increases the risk of high bilirubin levels.[2] While Phuapradit et al. could not detect a link between the technique of delivery and jaundice,[13] other research[11,12] corroborate the AAP data. According to our research, babies delivered via NSVD had statistically considerably higher STB values than babies delivered by cesarean surgery. G6PD deficiency, subgroup incompatibility, and ABO and Rh incompatibility are the most frequent hemolytic causes of indirect hyperbilirubinemia.[14,15] ABO incompatibility was found in 11.1% and Rh incompatibility in 7.4% of patients with indirect hyperbilirubinemia, according to Kâini et al.[16] Indirect hyperbilirubinemia was seen in 21.3% of ABO incompatibility cases, according to Sarici et al.[17] ABO incompatibility affected 29% of our patient population, while Rh incompatibility affected 7.2%. Of them, six individuals had ABO incompatibility and five had Rh incompatibility; significant hemolysis was seen in both groups. This suggests that blood group screening should be done on patients who have indirect hyperbilirubinemia. The most prevalent erythrocyte enzyme deficit in the world, G6PD deficiency is linked to kernicterus and indirect hyperbilirubinemia.[18,19] G6PD deficiency was found to be 2.8% in our study. It is well known that infants who are solely breastfed are more likely to develop jaundice. According to the Schneider study, 2% of breastfed newborns and 0.3% of formula-fed infants had severe jaundice, while 14% of breastfed infants and 4% of formula-fed infants had mild jaundice.[20] Hyperbilirubinemia was found in 28% of term newborns who were fed solely breast milk, according to Bhat et al.[21] We found no evidence of a substantial relationship between dietary status and bilirubin levels in our investigation. For certain cases, the etiology of indirect hyperbilirubinemia remains unknown despite the identification of numerous factors. In Canadian research, 64% of 258 individuals with severe hyperbilirubinemia had no known etiology.[22] Urinary tract infection (UTI) and congenital hypothyroidism have been found to have rates of 4%, 7.5%, and 1.2–3.9%, respectively, among other etiologic causes in neonates with jaundice.[23–25] As etiologic variables, we discovered hypothyroidism in 5% of the patients and UTI in 2.8 % of them. With evolving technology, phototherapy has been applied more broadly and more successfully in the treatment of infant jaundice.[4,26] From the time of their admission to the clinic, all of the patients in our study received phototherapy. If the STB level is more than 25 mg/dl in healthy term neonates, exchange transfusion is advised.[10,27] According to reports in the literature, newborns who received exchange transfusions had STB levels ranging from 26 to 38 mg/dl.[7,10] The most frequent reason for infants receiving exchange transfusions has been determined to be ABO incompatibility.[10,28–30] ABO incompatibility was revealed to be the most common reason in 3.4 % of our patients (mean STB levels of 31.1 mg/dl), who underwent exchange transfusion.

Conclusion

In summary, indirect hyperbilirubinemia is a significant and prevalent illness that affects newborns. A thorough investigation of the underlying reason is necessary. In order to stop difficulties from developing, it's also critical to identify patients as soon as possible and start the proper treatment. Not one acknowledgement.

References

1. Anderson NB, Calkins KL. Neonatal Indirect Hyperbilirubinemia. Neoreviews. 2020;21(11):e749-60.
2. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297-316.
3. Lo YS, Lu CC, Chen LY, Tsai LT. Clinical studies of neonatal hyperbilirubinemia treated with blood exchange transfusion. Gaoxiong Yi Xue Ke Xue Za Zhi. 1990;6(10):556-64.
4. Gartner LM, Herschel M. Jaundice and breastfeeding. Pediatr Clin North Am. 2001;48(2):389-99.
5. Newman TB, Maisels MJ. Evaluation and treatment of jaundice in the term newborn: a kinder, gentler approach. Pediatrics. 1992;89(5 Pt 1):809-18.
6. Burgos AE, Schmitt SK, Stevenson DK, Phibbs CS. Readmission for neonatal jaundice in California, 1991-2000: trends and implications. Pediatrics. 2008;121(4):e864-9.
7. Kaplan M, Bromiker R, Schimmel MS, Algur N, Hammerman C. Evaluation of discharge management in the prediction of hyperbilirubinemia: the Jerusalem experience. J Pediatr. 2007;150(4):412-7.
8. Polat A, Öktem F, Koç H. Evaluation of 963 neonates with hyperbilirubinemia. Türkiye clinical Pediatri 2.2. 1993:26-30.

9. Bravi F, Wiens F, Decarli A, Dal Pont A, Agostoni C, Ferraroni M. Impact of maternal nutrition on breast-milk composition: a systematic review. Am J Clin Nutr. 2016;104(3):646-62.
10. Bülbül A, Okan F, Cigerci N, Nuhoğlu A. Clinical characteristics and causes of exchange transfusion in term neonates with hyperbilirubinemia. Turk Arch Ped. 2007:107-11.
11. Trikalinos TA, Chung M, Lau J, Ip S. Systematic review of screening for bilirubin encephalopathy in neonates. Pediatrics. 2009;124(4):1162-71.
12. Donneborg ML, Hansen BM, Vandborg PK, Rodrigo-Domingo M, Ebbesen F. Extreme neonatal hyperbilirubinemia and kernicterus spectrum disorder in Denmark during the years 2000-2015. J Perinatol. 2020;40(2):194-202.
13. Phuapradit W, Chaturachinda K, Auntlamai S. Risk factors for neonatal hyperbilirubinemia. J Med Assoc Thai. 1993;76(8):424-8.
14. Stoll BJ, Kliegman RM. Jaundice and hyperbilirubinemia in the newborn. In: Behrman RE, Jenson HB. editor. Nelson Textbook of Pediatrics. Philadelphia, 2003:592-6.
15. Sahoo T, Sahoo M, Gulla KM, Gupta M. Rh Alloimmunisation: Current Updates in Antenatal and Postnatal Management. Indian J Pediatr. 2020;87(12):1018-28.
16. Kaini NR, Chaudhary D, Adhikary V, Bhattacharya S, Lamsal M. Overview of cases and prevalence of jaundice in neonatal intensive care unit. Nepal Med Coll J. 2006;8(2):133-5.
17. Sarici SU, Yurdakök M, Serdar MA, Oran O, Erdem G, Tekinalp G, et al. An early (sixth-hour) serum bilirubin measurement is useful in predicting the development of significant hyperbilirubinemia and severe ABO hemolytic disease in a selective high-risk population of newborns with ABO incompatibility. Pediatrics. 2002;109(4):e53.
18. Eissa AA, Haji BA, Al-Doski AA. G6PD Deficiency Prevalence as a Cause of Neonatal Jaundice in a Neonatal Ward in Dohuk, Iraq. Am J Perinatol. 2021;38(6):575-80.
19. M Abo El Fotoh WM, Rizk MS. Prevalence of glucose-6-phosphate dehydrogenase deficiency in jaundiced Egyptian neonates. J Matern Fetal Neonatal Med. 2016;29(23):3834-7.
20. Schneider AP 2nd. Breast milk jaundice in the newborn. A real entity. JAMA. 1986;255(23):3270-4
21. Bhat SR, Lewis P, David A, Liza SM. Dehydration and hypernatremia in breast-fed term healthy neonates. Indian J Pediatr. 2006;73(1):39-41.
22. Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ. 2006;175(6):587-90.
23. Bilgen H, Ozek E, Unver T, Biyikli N, Alpay H, Cebeci D. Urinary tract infection and hyperbilirubinemia. Turk J Pediatr. 2006;48(1):51-5.
24. Deger I, Ertuğrul S, Yolbaş I, Tekin R. Evaluation of urinary tract infections in neonatal indirect hyperbilirubinemia. Minerva Pediatr (Torino). 2022;74(5):562-7.
25. Baz AMK, El-Agamy OAE, Ibrahim AM. Incidence of urinary tract infection in neonates with significant indirect Hyperbilirubinemia of unknown etiology: case-control study. Ital J Pediatr. 2021;47(1):35.
26. Gartner LM, Lee KS, Keenan WJ, White NB Jr, Bryla DA. Effect of phototherapy on albumin binding of bilirubin. Pediatrics. 1985;75(2 Pt 2):401-6.
27. Sharma DC, Rai S, Mehra A, Kaur MM, Sao S, Gaur A, et al. Study of 25 cases of exchange transfusion by reconstituted blood in hemolytic disease of newborn. Asian J Transfus Sci. 2007;1(2):56-8.
28. Watchko JF. ABO hemolytic disease of the newborn: a need for clarity and consistency in diagnosis. J Perinatol. 2023;43(2):242-7.
29. Khurana R, Batra P, Faridi M, Khan N. Revisiting ABO incompatibility as a risk factor for significant neonatal hyperbilirubinemia. Trop Doct. 2019;49(3):201-4.
30. Murki S, Kumar P. Blood exchange transfusion for infants with severe neonatal hyperbilirubinemia. Semin Perinatol. 2011;35(3):175-84.

CMJ, 2024;46(3): 191-197
DOI: 10.7197/cmj.1539366

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Ultrasound Guided Lateral Crossed Pin Fixation in Pediatric Supracondylar Humerus Fractures

Seyran Kılınç[1,a,*], Özhan Pazarcı[2,b], Muhammed Yasir Altunışık[3,c], Burak Aydın[4,d], Sefa Aktı[1,e]

[1]*Department of Orthopedics and Traumatology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Turkey*
[2] *Department of Orthopedics and Traumatology, Adana City Training and Research Hospital, Adana, Turkey*
[3] *Department of Orthopedics and Traumatology, Gaziantep Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Turkey*
[4]*Department of Orthopedics and Traumatology, Sivas Numune Hospital, Sivas, Turkey*

**Corresponding author*

Research Article

History

Received: 29/08/2024
Accepted: 10/09/2024

ABSTRACT

Objective: In our study, we aimed to test the preventability of radial nerve injury in the ultrasound-guided lateral cross pinning technique.

Methods: The study included 30 patients who were admitted to our clinic between September 2019 and September 2020 due to supracondylar humerus fractures and underwent closed reduction with the lateral cross pinning technique under ultrasonography. Demographic and clinical data of the patients were retrieved from the patient files and recorded.

Results: Fifteen (50%) of the 30 patients included in the study were girls. The patients' mean age was 59.2±33.9 months. While 3.3% of the patients had flexion-type injuries, 30.0% had Gartland Type 2, 40.0% had Type 3, and 26.7% had Type 4 injuries. Eighteen patients (60%) had fractures in their left extremities. Type 4 fractures exhibited the biggest difference among all fracture types in comparison of the arm diameters of the fractured and contralateral sides (17.1%±5.5%; p=0.013). In the comparison of the proximal K-wire and the radial nerve (PWRN) to the lateral condyle and the radial nerve (LCRN) distance ratio, the difference was the highest in Type 2 fractures (23.3%±8.0%; p=0.027). None of the patients encountered postoperative iatrogenic radial nerve injury.

Conclusion: In pediatric patients with supracondylar humerus fractures, the swelling of the extremity increases with the severity of the fracture. The ultrasound-guided lateral cross pinning technique is a reliable method in terms of ease of application and the determination of the nerve line to create a safe zone, especially in elbow injuries with excessive swelling.

Keywords: Humeral supracondylar fracture, lateral cross pinning, pediatric, ultrasonography.

Pediatrik Suprakondiler Humerus Kırıklarında Ultrasound Eşliğinde Lateral Çapraz Pinleme

Araştırma Makalesi

Süreç

Geliş: 29/08/2024
Kabul: 10/09/2024

ÖZET

Amaç: Çalışmamız da Ultrasound (USG) eşliğinde lateral çapraz pinleme tekniği ile radial sinir hasarının önlenebilirliliği test edilmesi amaçlanmıştır.

Yöntem: Eylül 2019- Eylül 2020 yılları arasında kliniğimize başvuran çocuk humerus suprakondiler kırık tanısı konan ve USG eşliğinde lateral çapraz pinleme yapılan 30 hasta ile çalışma yapıldı. Hastaların demografik ve klinik verileri hasta dosyalarından elde edilerek kaydedildi.

Bulgular: Çalışmaya alınan 30 hastanın 15 (%50.0) ı kız çocuktan oluşmakta olup ortalama yaş 59.2±33.9 ay idi. 18 hasta (%60.0) sol extremiteden kırık geçirmişti. Hastaların %3,3 ü flexiyon tip, %30,0 tip 2 , %40,0 tip3 , %26,7 si tip4 yaralanma mevcuttu. Kırık tipi ile contralateral/Kırık extremite çap farkı oranı karşılaştırıldığında tip4 kırıkların çap farkı ortalamalarının daha yüksek olduğu bulunmuştur (17.1±5.5) (p=0.013). Kırık tipleri ile Wire-Radial/Condyle-Radial sinir mesafe farkı oranı karşılaştırıldığında tip 2 kırıklarında wire-sinir oranı arasındaki mesafenin en uzun olduğu bulunmuştur (23.3±8.0) (p=0.027). Hiçbir hastada postoperatif iyatrojenik radial sinir yaralanması görülmemiştir.

Sonuç: Pediatrik Suprakondiler humerus kırıklı hastaların kırık tipi ile extremite şişlik oranının arttığı görülmektedir. USG eşliğinde lateral çapraz pinleme tekniği uygulama kolaylığı ve özellikle aşırı şişlik gözlenen dirsek yaralanmalarında sinir hattının belirlenip güvenli bir alan oluşturması açısından güvenilir bir yöntem olarak karşımıza çıkmaktadır.

Anahtar Kelimeler: Humerus suprakondiler kırık, lateral çapraz pinleme, pediatrik, ultrasonografisi.

[a] *seyrankilinc@hotmail.com* *0000-0003-0144-0916*
[b] *dr.pazarci@gmail.com* *0000-0002-2345-0827*
[c] *yasiraltun@msn.com* *0000-0002-3080-8946*
[d] *drburakaydin12@gmail.com* *0000-0002-4353-8893*
[e] *sefa.akti@gmail.com* *0000-0001-8873-1358*

How to Cite: Kılınç S, Pazarcı Ö, Altunışık MY, Aydın B, Aktı S. Ultrasound-Guided Lateral Crossed-Pin Fixation in Pediatric Supracondylar Humerus Fractures. Cumhuriyet Medical Journal. 2024; 46(3): 191-197

Introduction

Supracondylar fractures of the humerus are common traumas during childhood and are associated with malunion, neurovascular complications, and morbidity due to compartment syndrome. These fractures account for 16% of all pediatric fractures and two-thirds of the hospitalizations for pediatric elbow injuries.[1] A correct understanding of supracondylar fractures is essential for the success of the treatment and the reduction of complications.[2]

Nondisplaced fractures are first treated with a posterior splint followed by a long arm cast. Closed reduction and percutaneous pinning are the treatment of choice for displaced or unstable fractures. Percutaneous pinning may be performed using the lateral-medial cross, lateral divergent, or lateral cross technique. While these techniques have been compared in several studies in the literature, debates about the advantages and disadvantages of these techniques still continue.[3,4] The main advantage of using the cross pin technique is to provide greater stability, which prevents secondary fracture displacement and misalignment. However, it has been reported that the prevalence of ulnar nerve injury increases by 4.3 times with lateral-medial cross pinning.[4]

Some authors suggested that the best way to prevent iatrogenic ulnar nerve injury was to avoid medial nailing and recommended lateral cross pinning as an alternative method.[5-7] However, this method raises concerns about the risk of radial nerve injury in the supracondylar region created by the wire sent from the proximal.[8]

In this study, our primary aim was to evaluate the feasibility and reliability of the ultrasound-guided lateral cross pinning technique in pediatric supracondylar fractures. We also aimed to determine the relationship of the proximal wire with the radial nerve and assess its effectiveness in reducing the risk of iatrogenic nerve injury. Considering that the study to be conducted in this context is the first in the literature, our results can provide valuable contributions to the literature.

Patients and Methods

The study was started following the approval of the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (Decided Number:2020-10/06, Date:21.10.2020). Thirty-two patients admitted to the Department of Orthopedics and Traumatology at the Faculty of Medicine of Sivas Cumhuriyet University due to supracondylar humerus fracture between September 2019 and September 2020 were included in the study. One patient was later excluded due to preoperative radial nerve palsy and another due to the requirement of open reduction. The study was continued with a total of 30 patients who underwent closed reduction with the lateral cross pinning technique under ultrasonography (USG). Demographic and clinical information of the patients including age, gender, fracture type according to the modified Gartland classification,[9,10] fracture side, concomitant injuries, arm diameters of the fractured and contralateral sides, the distance between the lateral condyle and the radial nerve (LCRN), the distance between the proximal K-wire and the radial nerve (PWRN), duration of surgery, the time between fracture diagnosis and surgery, and postoperative complications of the nerve were retrieved from the patient files and recorded.

Surgical technique

All patients were operated on in the supine position under general anesthesia by the same pediatric orthopedic surgeon after the surgery conditions were met. Before the surgery, the area where the radial nerve laterally crossed the humerus in the fractured extremity was determined and marked under USG. After assessing the quality of the closed reduction with fluoroscopy, Kirschner wires (K-wires) were sent from the lateral condyle to the humeral body. A K-wire was sent from the proximal shaft of the humerus to the medial condyle using the appropriate K-wire configuration, provided that the advancement line was below the mark determined under the fluoroscopic guidance. The quality and stability of the reduction were checked under fluoroscopy (**Fig. 1**). The LCRN distance where it laterally crossed the humerus, the PWRN distance, the arm diameter at the marked radial nerve level in the fractured extremity, and the arm diameter at the level where the radial nerve crossed the humerus in the contralateral extremity were measured and recorded (**Fig. 2**). The surgery was ended after placing the patients in a long arm cast at 70 degrees.

Statistical analyses were carried out using the SPSS v.23 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as percentage, mean and standard deviation. The Kruskal-Wallis test was employed in analyzing the relationship between the fracture type and the duration of surgery, the arm diameter difference between the fractured/contralateral side, and the PWRN to LCRN distance ratio, while correlation analysis was used in the evaluation of the relationship between the arm diameter difference between the fractured/contralateral side and the PWRN/LCRN distance ratio. The level of significance was assumed at the $p<0.05$ level.

Results

Fifteen (50%) of the 30 patients included in the study were girls. The patients' mean age was 59.2±33.9 months (range: 17.0 to 137.0 months). Twelve (40.0%) of the participants had Type 3 fractures, while 18 patients (60%) had fractures in their left extremities. Two patients (6.7%) had concomitant ipsilateral torus fractures of the distal radius. The mean diameter of the fractured arm was 20.7±3.2 cm (range: 17.0 to 33.0 cm), while the mean diameter of the contralateral arm was 18.3±3.0 cm (range: 15.0 to 30.5 cm). The mean difference between the diameters of the fractured and contralateral arms was

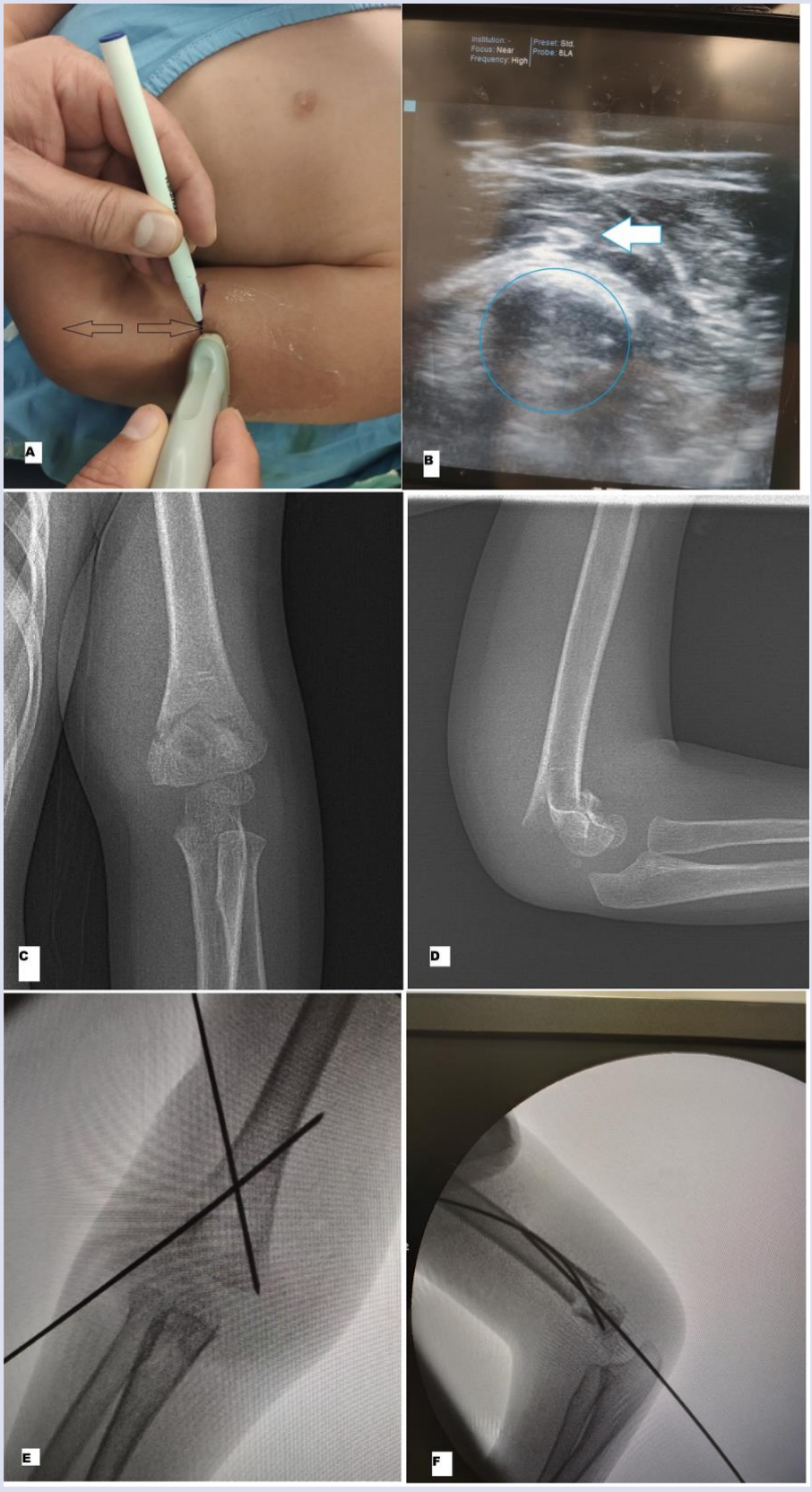

Fig. 1. Supracondylar humerus fracture in a 5-year-old girl. A. Using ultrasonography, the place where the radial nerve crosses the humerus is determined (black arrows: safe zone). B. Ultrasonogram of the patient (white arrow: radial nerve, blue circle: humerus). C. Preoperative AP X-ray image. D. Preoperative lateral X-ray image. E. Intraoperative AP fluoroscopy image. F. Intraoperative lateral fluoroscopy image.

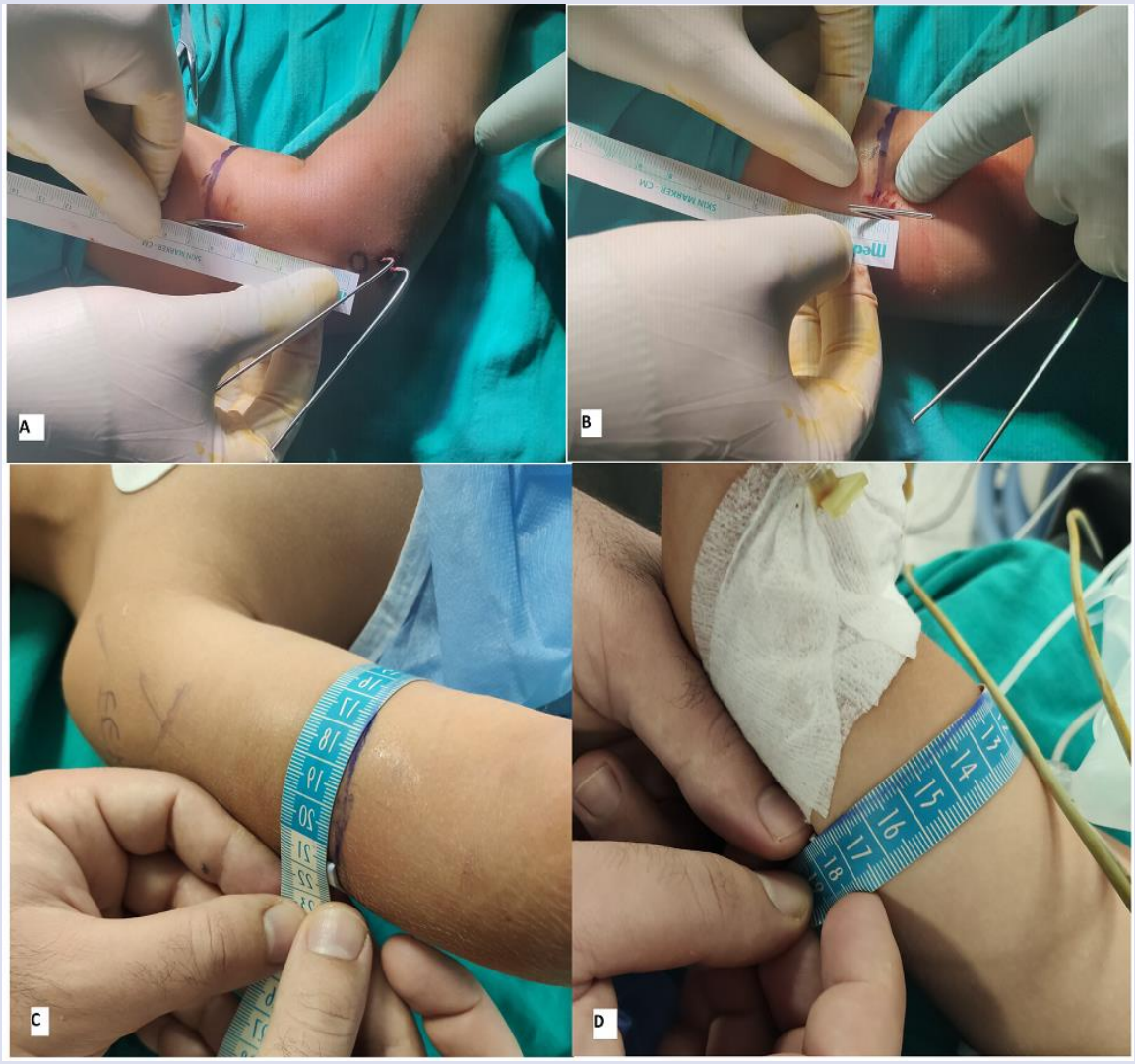

Fig. 2. Postoperative measurements. A. Lateral condyle-radial nerve (LCRN) distance. B. Proximal-lateral K-wire-radial nerve (PWRN) distance. C. Arm diameter in the fractured extremity. D. Arm diameter in the contralateral extremity.

13.2%±6.5% (range: 2.8% to 30.5%). The mean LCRN distance was 6.3±1.5cm (range: 4.0 to 11.1 cm), whereas the mean PWRN distance was 1.0±0.6 cm (range: 0.4 to 3.5 cm). The mean PWRN/LCRN distance ratio was 17.1%±7.7% (range: 6.2% to 38.8%). The mean duration of surgery was 39.8±11.6 minutes (range: 25.0 to 60.0 minutes). The time elapsed between the diagnosis of fracture and the surgery was over six hours in 56.7% (n=17) of the patients. Pin tract infection developed in 20.0% (n=6) of the patients. Recovery after the removal of the K-wire was achieved with appropriate antibiotic therapy (Table 1).

Since there was only one patient with a flexion-type fracture in the study, this was not included in the analyses. Type 4 fractures had a higher duration of surgery than other fracture types, with a mean duration of 45.0±8.8 minutes (p=0.76). Again, Type 4 fractures had the biggest difference among all fracture types in the comparison of the arm diameters of the fractured and contralateral sides (17.1%±5.5%), exhibiting a statistical significance (p=0.013). In comparison of the PWRN to LCRN distance ratio, the difference was the highest in Type 2 fractures (23.3%±8.0%; p=0.027) (Table 2). There was a negative, moderate, non-significant correlation between the arm diameter difference between the fractured/contralateral side and the PWRN/LCRN distance ratio (r=-0.34, p>0.05).

Table 1. Descriptive characteristics of the study patients (n=30).

	Percentage (n)	Mean±SD	Range
Gender			
Female	50.0 (15)		
Male	50.0 (15)		
Age (months)		59.2±33.9	17.0-137.0
Fracture type			
Flexion	3.3 (1)		
Type 2	30.0 (9)		
Type 3	40.0 (12)		
Type 4	26.7 (8)		
Fracture side			
Right	40.0 (12)		
Left	60.0 (18)		
Concomitant injuries			
Yes	6.7 (2)		
No	93.3 (28)		
Arm diameter of the fractured side (cm)		20.7±3.2	17.0-33.0
Arm diameter of the contralateral side (cm)		18.3±3.0	15.0-30.5
Arm diameter difference between the fractured/contralateral side (%)		13.2±6.5	2.8-30.5
LCRN distance (cm)		6.3±1.5	4.0-11.1
PWRN distance (cm)		1.0±0.6	0.4-3.5
PWRN/LCRN distance ratio (%)		17.1±7.7	6.2-38.8
Duration of surgery (minutes)		39.8±11.6	25.0-60.0
Time to surgery			
≤ 6 hours	43.3 (13)		
6-12 hours	56.7 (17)		
Postop complications			
Yes	20.0 (6)		
No	80.0 (24)		

LCRN: lateral condyle-radial nerve, PWRN: proximal wire-radial nerve.

Table 2. Duration of surgery, arm diameter difference between the fractured/contralateral side, and the PWRN/LCRN distance ratio according to fracture types.

Fracture type	Duration of surgery (mean±SD)	Arm diameter difference between the fractured/contralateral side (mean±SD)	PWRN/LCRN distance ratio (mean±SD)
Type 2	34.4±10.7	8.2±3.3	23.3±8.0
Type 3	38.7±11.8	14.8±6.9	14.4±6.5
Type 4	45.0±8.8	17.1±5.5	14.1±5.8
p	0.76	**0.013**	**0.027**

LCRN: lateral condyle-radial nerve, PWRN: proximal wire-radial nerve.
Significant p values are written in bold.

Discussion

The strength of our study is its presentation of a USG-guided lateral cross pinning method for the first time in the literature. In addition, radial nerve distance measurements were made according to fracture types and the changes in the arm diameter due to edema. Closed reduction and percutaneous pinning are widely accepted methods in the treatment of displaced supracondylar fractures of the humerus in children. Although different configurations exist for fixation, biomechanical studies suggest cross-configuration as the most suitable one for stabilization.[11,12] The main purpose of the current study is based on determining the location of the radial nerve with the help of USG and minimizing the iatrogenic radial nerve damage during the advancement of the wire from the proximal to the lateral.

Ultrasonography is widely used in musculoskeletal diseases. Recently, the tendency among orthopedists to use USG in the diagnosis and follow-up phases of pediatric patients has increased.[13-15] Soldado et al. designed their study on the detection of the ulnar nerve with USG and then cross insertion of the K-wire.[15] The authors did not record any iatrogenic nerve manifestations, however, they mentioned of technical difficulties since they had to

manipulate the ulnar nerve when sending the wire from the medial. The advantages of the technique are that the patients who underwent USG during the study are performed by us and that the evaluation is easy. This ease depends on the fact that the anatomical region where the radial nerve crosses the distal humerus is located on a flat surface increases the ease of USG and the comprehensibility of the learning curve.

Some authors recommend the lateral cross pinning method as it prevents ulnar nerve injury and is as effective as cross pinning.[7] However, the advancement of the wire from the proximal to the lateral in lateral cross pinning poses a risk for radial nerve injury.[16] Superolateral insertion of the pin to reduce nerve injury risks has been recommended as an alternative in studies that are based on clinical experience and radiological analysis.[17-19]

In a study in which radial nerve damage occurred as a result of lateral cross pinning, the authors mentioned that the technique is not widely used and the literature information about the 'safe zone' is scarce.[16] In addition, the authors focused on the need to be attentive when sending the wire and the need to determine the location with USG if necessary. We believe that our study will contribute to the literature in this context. In our study, the safe zone was determined intraoperatively for each patient, so that the phenotypic traits of the patient are evaluated and individual safe zones are determined. These assessments helped us provide a standardized approach to individual independent measurements and parameters such as age, gender, and trauma-related swelling. Since the measurements were performed during anesthetic procedures, it did not cause any loss of extra time or cost, while no neurological damages were observed in the patients.

Symptoms such as extensive ecchymosis, soft tissue swelling, and skin shrinkage in humeral supracondylar fractures indicate severe trauma.[20] The swelling can cause difficulties in determining the anatomical location during wire delivery. We can conclude from our study that as the severity of the trauma increases, the diameter of the fractured arm increases significantly compared to the contralateral arm. Although this increase is considered an expected finding, a significant decrease is observed between the distance of the superolateral K-wire and the radial nerve after reduction. This is explained by the view that the superior K-wire moves proximally in a swollen arm to provide the appropriate configuration. By creating a safe zone under ultrasonography guidance and keeping the wire within this zone, the nerve damage was prevented.

Despite reports suggesting that the distance between the radial nerve and the proximal wire is sufficient and that it will not cause iatrogenic nerve damage, some researchers asserted that the radial nerve may be injured during the placement of the proximal wire.[19,21] We did not encounter any nerve damage in our patients postoperatively. However, we observed that the proximal wire approached the upper limit of the safe zone with a significant increase in arm diameter, especially in patients with Type 4 fractures. This has shown us that the risk of nerve injury may increase further in patients of advanced trauma with an increased arm diameter and that USG is of great help in this regard.

The study's retrospective design and the small number of patients included in it may be considered a limitation. Further larger prospective series is mandatory to support our results.

In conclusion

The detection of the radial nerve by USG is an easy and applicable method in pediatric patients with supracondylar humerus fractures. The swelling of the extremity increases with the severity of the fracture in pediatric patients with supracondylar humerus fractures. This situation decreases inversely with the distance of the proximal K wire from the radial nerve. The ultrasound-guided lateral cross pinning technique is a reliable and effective method in terms of determining the nerve line and creating a safe zone, especially in elbow injuries with excessive swelling.

Declaration of conflicting interests: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

Authors' Contributions:

SK: Conceptualization, Data curation, Formal Analysis, Writing – original draft.

OP: Data curation, Writing –review & editing.

MYA: Formal Analysis, Writing – original draft.

BA: Data curation, Writing – review & editing.

SA: Writing – review & editing.

References

1. Cheng JC, Shen WY. Limb fracture pattern in different pediatric age groups: a study of 3,350 children. J Orthop Trauma. 1993;7(1):15–22.
2. Brubacher JW, Dodds SD. Pediatric supracondylar fractures of the distal humerus. Curr Rev Musculoskelet Med. 2008;1(3-4):190-196.
3. Prashant K , Lakhotia D , Bhattacharyya TD , Mahanta AK , Ravoof A . A comparative study of two percutaneous pinning techniques (lateral vs medial-lateral) for Gartland type III pediatric supracondylar fracture of the humerus. J Orthop Traumatol. 2016;17(3):223-229.
4. Woratanarat P , Angsanuntsukh C , Rattanasiri S et al. Meta-analysis of pinning in supracondylar fracture of the humerus in children. J Orthop Trauma. 2012;26(1):48-53.
5. Rizk AS, Kandil MI. Conventional versus lateral cross-pinning (Dorgan's technique) for fixation of displaced pediatric supracondylar humeral fractures: a randomized comparative study. Egypt Orthop J. 2018;53:348-58.
6. Dekker AE, Krijnen P, Schipper IB. Results of crossed versus lateral entry K-wire fixation of displaced pediatric

supracondylar humeral fractures: A systematic review and meta-analysis. Injury. 2016 Nov;47(11):2391-2398.
7. Altay MA, Erturk C, Isikan UE. Comparison of traditional and Dorgan's lateral cross-wiring of supracondylar humerus fractures in children. Saudi Med J. 2010; 31:793–796.
8. Brighton B , Abzug JM , Ho CA , Ritzman TF . Current strategies for the management of pediatric supracondylar humerus fractures: tips and techniques for successful closed treatment. Instr Course Lect. 2016;65:353-360
9. Gartland JJ. Management of supracondylar fractures of the humerus in children. Surg Gynecol Obstet. 1959 Aug;109(2):145-54.
10. Leitch KK, Kay RM, Femino JD, Tolo VT, Storer SK, Skaggs DL. Treatment of multidirectionally unstable supracondylar humeral fractures in children. A modified Gartland type-IV fracture. J Bone Joint Surg Am. 2006 May;88(5):980-5.
11. S.S. Lee, A.T. Mahar, D. Miesen, P.O. Newton. Displaced pediatric supracondylar humerus fractures: biomechanical analysis of percutaneous pinning techniques. J Pediatr Orthop. 2002;22; 440-443.
12. Feng, Chao MD; Guo, Yuan MD; Zhu, Zhenhua MD; Zhang, Jianli MD; Wang, Yukun MD. Biomechanical Analysis of Supracondylar Humerus Fracture Pinning for Fractures With Coronal Lateral Obliquity, Journal of Pediatric Orthopaedics. 2012; 32(2);196-200.
13. Vanderhave KL, Brighton B, Casey V, Montijo H, Scannell B. Applications of musculoskeletal ultrasonography in pediatric patients. J Am Acad Orthop Surg. 2014 Nov;22(11):691-8.
14. Altay MA, Erturk C, Altay M, Belhan O, Isikan UE. Ultrasonographic examination of the radial and ulnar nerves after percutaneous cross-wiring of supracondylar humerus fractures in children: a prospective, randomized controlled study. J Pediatr Orthop B. 2011 Sep;20(5):334-40.
15. Soldado F, Knorr J, Haddad S, et al. Ultrasound-guided Percutaneous Medial Pinning of Pediatric Supracondylar Humeral Fractures to avoid Ulnar Nerve Injury. Arch Bone Jt Surg. 2015;3(3):169-172.
16. Gangadharan S, Rathinam B, Madhuri V. Radial nerve safety in Dorgan's lateral cross-pinning of the supracondylar humeral fracture in children: a case report and cadaveric study. J Pediatr Orthop B. 2014 Nov;23(6):579-83.
17. Bloom T, Zhao C, Mehta A, Thakur U, Koerner J, Sabharwal S. Safe zone for superolateral entry pin into the distal humerus in children: an MRI analysis. Clin Orthop Relat Res. 2014 Dec;472(12):3779-88.
18. Nielsen E, Andras LM, Skaggs DL. Quantifying the Location of the Radial Nerve in Children for Intraoperative Use. J Pediatr Orthop. 2018 May/Jun;38(5):292-5.
19. Queally JM, Paramanathan N, Walsh JC, Moran CJ, Shannon FJ, D'Souza LG . Dorgan's lateral cross-wiring of supracondylar fractures of the humerus in children: a retrospective review. Injury. 2010;41:568–571
20. Vaquero-Picado A, González-Morán G, Moraleda L. Management of supracondylar fractures of the humerus in children. EFORT Open Rev. 2018;3(10):526-540.
21. Eberhardt O, Fernandez F, Ilchmann T, Parsch K. Cross pinning of supracondylar fractures from a lateral approach. Stabilization achieved with safety. J Child Orthop. 2007;1:127–133.

CMJ. 2024; 46(3): 198-204
DOI: 10.7197/cmj.1539734

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Determination of Etiology and Risk Factors in Patients Applying to Our Outpatient Clinic for Weight Loss

Ayşe Münevver Mühürdaroğlu[1,a]*, Seyit İbrahim Akdağ[2,b], Mercan Taştemur[3,c]

[1]*Division of Endocrinology, Department of Internal Medicine, Ankara Training and Research Hospital, Ankara, Turkiye*
[2]*Department of Internal Medicine, Etlik City Hospital, Ankara, Turkiye*
[3]*Division of Geriatrics, Department of Internal Medicine, Bilkent City Hospital, Ankara, Turkiye*
**Corresponding author*

Research Article

History

Received: 28/08/2024
Accepted: 29/09/2024

ABSTRACT

Objective: This study aims to determine the etiological factors and risk factors of 100 adult patients who applied to our outpatient clinic for weight loss.

Methods: Data were collected retrospectively, and age, gender, blood pressure, anthropometric measurements, and laboratory findings were analyzed. Patients with type 1 and type 2 diabetes, those using lipid-lowering drugs, patients with renal or hepatic insufficiency, pregnant individuals, or those under the age of 18 were excluded from the study.

Results: 79% of the patients were female, and according to the body mass index (BMI) classification, 29% were overweight, 39% had stage 1 obesity, 23% had stage 2 obesity, and 9% had stage 3 obesity. A significant difference was found in HOMA-IR values between BMI groups (p=0.002), and as BMI increased, insulin resistance also increased. There were statistically significant differences in fasting plasma glucose (FPG), insulin, LDL, and vitamin D levels between BMI groups. However, no significant relationship was found between smoking and BMI.

Conclusion: In conclusion, the study found a significant relationship between obesity, insulin resistance, and some biochemical parameters, emphasizing that these findings should be considered in the management and treatment of obesity.

Keywords: Obesity, Insulin Resistance, Body Mass Index, Risk Factors

Polikliniğimize Kilo Vermek İçin Başvuran Hastalarda Etiyoloji ve Risk Faktörlerinin Belirlenmesi

Araştırma Makalesi

Süreç

Geliş: 28/08/2024
Kabul: 29/09/2024

ÖZET

Amaç: Bu çalışma, kilo vermek amacıyla polikliniğimize başvuran 100 yetişkin hastanın etiyolojik faktörlerini ve risk faktörlerini belirlemeyi amaçlamaktadır.

Yöntem: Veriler retrospektif olarak toplanmış ve yaş, cinsiyet, kan basıncı, antropometrik ölçümler ve laboratuvar bulguları analiz edilmiştir. Çalışmaya tip 1 ve tip 2 diyabeti olan, lipid düşürücü ilaç kullanan, renal veya hepatik yetmezliği olan, hamile veya 18 yaş altındaki hastalar dâhil edilmemiştir.

Bulgular: Hastaların %79'u kadın olup, vücut kitle indeksi (VKİ) sınıflamasına göre %29'u fazla kilolu, %39'u evre 1 obez, %23'ü evre 2 obez ve %9'u evre 3 obez olarak sınıflandırılmıştır. HOMA-IR değerlerinde, VKİ grupları arasında anlamlı fark bulunmuş (p=0.002), VKİ arttıkça insülin direnci de artmıştır. VKİ grupları arasında açlık plazma glikozu, insülin, LDL ve D vitamini düzeylerinde istatistiksel olarak anlamlı farklılıklar bulunmuştur. Ancak, sigara kullanımı ile VKİ arasında anlamlı bir ilişki saptanmamıştır.

Sonuç: Sonuç olarak, çalışmada obezite ile insülin direnci ve bazı biyokimyasal parametreler arasında belirgin bir ilişki olduğu saptanmış, bu bulguların obezite yönetimi ve tedavisinde dikkate alınması gerektiği vurgulanmıştır.

Anahtar Kelimeler: Obezite, İnsülin Direnci, Vücut Kitle İndeksi, Risk Faktörleri

**This research was presented as an oral presentation at the 3rd Internal Medicine Congress of the Health Sciences University (Sağlık Bilimleri Üniversitesi 3. İç Hastalıkları Kongresi)*

[a] *aysemunevver_86@hotmail.com* *0009-0007-8255-1832*
[b] *iakdag16@gmail.com* *0000-0003-3388-2989*
[c] *dr.tastemur@gmail.com* *0000-0003-0320-4095*

How to Cite: Mühürdaroğlu AM, Akdağ Sİ, Taştemur M. Determination of Etiology and Risk Factors in Patients Applying to Our Outpatient Clinic for Weight Loss. *Cumhuriyet Medical Journal, 2024; 46(3): 198-204.*

Introduction

The morbidity and mortality associated with being overweight have been recognized by the medical profession since the time of Hippocrates. [1] According to the World Health Organization (WHO), obesity is defined as "excessive or abnormal accumulation of fat that is hazardous to health". It has reached epidemic proportions worldwide and is the most serious public health problem of the 21st century. [2,3] While obesity was once considered a problem of developed countries, its prevalence is rapidly increasing in developing countries and in our own, due to the adoption of western lifestyles, widespread consumption of fast food, and decreased energy expenditure compared to increased energy intake. [4]

There is a clear association between obesity and increased central adiposity and an elevated risk of morbidity and mortality. Obesity has a deleterious impact on numerous biochemical markers, including fasting blood glucose, insulin resistance, and cholesterol levels. When left untreated, it has adverse effects on all organs and systems in the body, particularly the endocrine and cardiovascular systems. There is a strong association between obesity and a number of other health conditions, including metabolic syndrome, prediabetes, type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular disease, nonalcoholic fatty liver disease, polycystic ovary syndrome, female infertility, male hypogonadism, sleep apnea, asthma, osteoarthritis, depression, and a number of cancers, including endometrial, breast, and gallbladder cancers in women and colon, rectum, and prostate cancer in men.[5,6]

The rapid change in lifestyle in our country has resulted in a critical prevalence of obesity exceeding 30%, which represents a significant threat to public health. The Endocrine and Metabolic Society of Turkey (TEMS) recommends that all individuals over the age of 18 should undergo screening for obesity. In clinical practice, the most commonly employed methods for assessing obesity are Body Mass Index (BMI) and waist circumference measurements. BMI classifications are based on the risk of cardiometabolic disease. Furthermore, there is a strong correlation between waist circumference and the amount of intra-abdominal adiposity. [7-9]

The objective of this study was to determine the obesity-related risk factors in male and female patients over the age of 18 years who applied to our outpatient clinic with the desire to lose weight and who had no known comorbidities.

Materials and Methods

The study was designed as a retrospective study. The archival data of 100 male and female patients over the age of 18 who applied to the Internal Medicine Outpatient Clinic of Health Sciences University Ankara Dışkapı Training and Research Hospital between 01 December 2016 and 01 June 2017 with the desire to lose weight were subjected to analysis.

The following data were obtained from the patients' files: age, gender, medical history, blood pressure, anthropometric measurements and laboratory data. The study excluded patients younger than 18 years of age, pregnant women, and patients with known disease. This included patients with type 1 DM and type 2 DM who were on medication, patients on antilipidemic drugs, patients with renal failure or hepatic failure, patients with myocardial infarction or stroke, patients with a body mass index (BMI) of less than 25 kg/m², and those for whom archival information was not available.

In this outpatient clinic, patients' heights were measured by removing their shoes and using a meter affixed to the wall. Waist and hip circumferences were gauged with a non-stretchable tape measure over thin clothing. The waist measurement was taken at the midpoint of the last costa and iliac crest, while the hip measurement was taken over the trochanter major, identifying the widest diameter. Body mass index (BMI) is calculated by dividing an individual's weight (in kilograms) by the square of their height (in metres). The classification of BMI is based on the recommendations of the National Institutes of Health (NIH) and the World Health Organization (WHO) (Table 1).[10,11].

Table 1. Classification of body mass index

BMI (kg/m)²	Class
<18.5	Underweight
≥18.5 to 24.9	Normal weight
≥25 to 29.9	Overweight
≥30	Obesity
30 to 34.9	Obesity class 1
35 to 39.9	Obesity class 2
≥40	Obesity class 3

All biochemical analyses were conducted in the Biochemistry Laboratory of Dışkapı Yıldırım Beyazıt Training and Research Hospital, following a minimum of eight hours of fasting. The haemograms were determined using a Becman Coulter LH 780 automatic blood count apparatus. The lipid levels were determined by an enzymatic method on a Roche Cobas 6000 Hitachi c501 autoanalyzer. The levels of high-density lipoprotein (HDL) and triglycerides (TG) were quantified, and the level of low-density lipoprotein (LDL) was calculated indirectly using the Friedewald formula (LDL = TK - (HDL + TG/5)). The levels of urea, creatinine, AST, ALT, iron, iron-binding capacity, ferritin, glucose, folic acid, TSH, St4, B12 and vitamin D were determined using the Roche Cobas 6000 Hitachi c501 autoanalyzer. Insulin levels were quantified by means of a chemiluminescent enzyme immunoassay in a Siemens Immulite 2000 autoanalyzer. Insulin resistance was calculated using the HOMA-IR formula (fasting

glucose (mg/dl) x fasting insulin (µIU/mL) / 405). Values of 2.5 and above were considered significant.

The study was approved by the Clinical Research Ethics Committee of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital with decision no. 124 dated 06/12/2018.

Statistical analysis was conducted using the SPSS 22.0 software package. The descriptive statistics of all data collected in the study were calculated. The assumption of normality was tested for continuous quantitative variables using the Kolmogorov-Smirnov and Shapiro-Wilk tests. One-way ANOVA and Kruskal-Wallis tests were employed for the comparison of quantitative variables between groups. A p-value of less than 0.05 was considered statistically significant at the 95% confidence interval.

Results

The study population comprised 100 patients who had sought treatment at the internal medicine outpatient clinic with a desire to lose weight between the specified dates. The study cohort was 79% female. The analysis of the participants according to their body mass index (BMI) revealed the following distribution: 29 individuals (29%) were classified as overweight, 39 (39%) as having stage 1 obesity, 23 (23%) as having stage 2 obesity, and 9 (3%) as having stage 3 obesity. No statistically significant difference was observed in the BMI grouping according to gender (p=0.680). The demographic and blood parameters of female and male patients are presented in Table 2.

Table 2. Distribution of demographic and blood parameters of patients according to gender

Parameters (Median (min-max))	Female	Male
Age	32.00 (18-78)	29.00 (18-64)
FPG	90.00 (69-155)	92.00 (61-115)
PPG	94.00 (61-218)	101.00 (70-219)
Insulin	9.30 (0.57-82.10)	10.90 (4.15-53.20)
HDL	48.00 (31-78)	41.00 (28-141)
LDL (Mean ± SD)	126.77 ± 30.09	124.80 ± 39.72
Triglyceride	126.00 (46-310)	171.00 (36-663)
TSH	2.22 (0.38-6.20)	1.80 (0.45-104.00)
sT4	0.84 (0.50-1.22)	0.79 (0.20-3.70)
Urea	22.00 (12-43)	26.00 (19-42)
Creatinine	0.79 (0.50-1.10)	0.90 (0.70-1.20)
ALT	19.00 (9-43)	23.00 (12-39)
AST	18.00 (7-56)	28.00 (18-82)
Vitamin D	11.20 (5.60-46.30)	12.50 (6.40-27.20)
HGB	13.40 (8.10-15.80)	16.10 (14.10-17.80)
Ferritin	15.00 (1.40-93.50)	44.50 (15.20-148)
Vitamin B12	215.00 (97-1500)	188.00 (107-394)
Body weight (kg)	87.00 (66-140)	100.00 (76-134)
Height (m)	161.00 (150-185)	178.00 (165-186)
Waist circumference (cm, Mean ± SD)	96.35 ± 15.48	102.33 ± 12.10
Hip circumference (cm)	116.00 (96-150)	116.00 (99-140)
Waist/hip ratio (Mean ± SD)	0.83 ± 0.06	0.88 ± 0.09
SBP	110.00 (80-140)	120.00 (90-150)
DBP	70.00 (50-90)	70.00 (60-100)
BMI distribution (n, %)		
Obesity class 1	31 (79.4%)	8 (20.6%)
Obesity class 2	19 (82.6%)	4 (17.4%)
Obesity class 3	8 (88.8%)	1 (11.2%)

FPG: Fasting plasma glucose, PPG: postprandial glucose, HDL: high density lipoprotein, LDL: low density lipoprotein, ALT: alanine transaminase, AST: aspartate transferase, TSH: thyroid stimulating hormone, HGB: hemoglobin, SBP: systolic blood pressure, DBP: diastolic blood pressure

A notable discrepancy was observed between HOMA-IR values and BMI groups (p=0.002). As the BMI group increased, so too did the HOMA-IR values. The median (min-max) values according to the groups were 1.57 (0.5-5.7) in the overweight individuals, 2.19 (0.55-20.20) in the stage 1 obese group, 2.80 (1.09-12.7) in the stage 2 obese group and 3.06 (0.42-6.2) in the stage 3 obese group.

Among the overweight individuals included in the study, 41.3% of the stage 1 obese group, 30.7% of the stage 2 obese group, 26% of the stage 3 obese group and 22.2% of the stage 1 obese group were smokers. No statistically significant correlation was observed between smoking status and BMI (p = 0.580).

Table 3 illustrates the distribution of demographic and blood parameters of the patients according to BMI groups. Significant differences were observed between fasting plasma glucose, insulin value, LDL and vitamin D results and BMI group (p=0.040; p<0.001; p=0.040; p=0.049, respectively).

No significant difference was observed in waist/hip ratio according to BMI groups (p=0.130). Similarly, there was no significant difference in systolic and diastolic blood pressure results according to BMI groups (p=0.080 and p=0.330, respectively).

Discussion

In this study, a comprehensive range of demographic data, blood parameters and anthropometric measurement results were extracted from the medical records of patients who had sought advice from the internal medicine outpatient clinic regarding weight loss. The differences between these values according to BMI groups were then subjected to detailed analysis.

The gender distribution of the 100 patients included in the study was 79% female and 21% male. The proportion of male patients was 7% in the study by Bulur et al. (2022), while the study by Akbaş et al. (2022) found this figure to be 11%. Furthermore, the data from the Turkish Health Survey conducted in Turkey in 2022 revealed that the prevalence of obesity was 20.2%. It was observed that 23.6% of women were obese and 30.9% were pre-obese, while 16.8% of men were obese and 40.4% were pre-obese.[14] In our study, the highest proportion of women was in stage 1 obese, while men were most frequently in the overweight group. In the study by Bulur et al., stage 1 obesity was found to be more prevalent in women, while stage 2 obesity was more common in men. This differs from the findings of our study.[12] Another study by Saygın et al. observed that the majority of both men and women were in the overweight category.[15]

In the Turkish Hypertension Prevalence Study, the mean values of blood pressure were found to be 127.9 ± 21.1 mmHg for systolic and 81.4 ± 12.7 mmHg for diastolic. A gender-based analysis of the distribution revealed mean values for SDB of 126.2 ± 17.4 mmHg in men and 129.8 ± 24.2 mmHg in women. The mean values for diastolic blood pressure (DBP) were 80.8 ± 11.0 mmHg in men and 82.0 ± 14.3 mmHg in women. Additionally, the prevalence of hypertension in Turkey was determined to be 31.8%. The prevalence of hypertension was higher in women (36.1%) than in men (27.5%). (16) In our study, no significant difference was observed between genders in terms of systolic or diastolic blood pressure values. No significant difference was identified between BMI groups in terms of blood pressure measurements. There is a strong association between obesity and elevated blood pressure, which can lead to hypertension. Furthermore, obesity is a significant risk factor for cardiovascular disease due to its adverse effects on insulin resistance and other cardiometabolic processes.^(17–19) As our study did not include a normal weight control group, we are unable to ascertain the impact of overweight on blood pressure in comparison with normal weight. However, the blood pressure values of our participants were comparable across BMI groups.

The risk of impaired glucose tolerance or type 2 diabetes increases in proportion to the degree of body weight excess. The NHANES study, conducted over a period of three decades, revealed that an increase in BMI over time was the most significant of the three covariates (age, race/ethnicity, BMI) studied in relation to the rising prevalence of diabetes.

Evidence suggests that weight loss achieved through lifestyle interventions can reduce the risk of developing type 2 diabetes and improve glycemic management, potentially leading to remission in patients with diabetes mellitus.

In our study, as BMI groups increased, fasting plasma glucose and HOMA-IR values also increased significantly. There is a robust correlation between obesity and coronary heart disease. A meta-analysis indicates that there is a 29 percent increase in the risk of coronary heart disease for every five-unit increase in BMI. The elevated risk of cardiovascular disease in obese patients is further compounded by the frequent coexistence of risk factors such as hypertension, dyslipidaemia and diabetes. The precise extent to which obesity is the sole contributing factor remains uncertain. One explanation for the lack of a significant increase in blood LDL-C levels in obese patients is the capacity of adipose tissue to expand and store cholesterol. A dyslipidaemia, including elevated triglycerides, reduced HDL-C, elevated non-HDL-C, elevated apoB, elevated LDL particle number and elevated small dense LDL particles, is typically observed in individuals with obesity.[23] A significant difference was identified between BMI groups and LDL values.

In their study, Uysal et al. identified a correlation between BMI and impaired liver function tests in patients presenting to an obesity outpatient clinic for weight loss. However, other studies have also indicated that serum aminotransferase activities are associated with the severity of fatty liver in obese patients. of fatty liver in obese patients.[25] Salvaggio et al. demonstrated that serum activity ratios of liver enzymes were significantly correlated with body weight and BMI values.[26] There is no significant difference was observed between BMI groups and liver function tests.

Table 3. Distribution of demographic and blood parameters of patients according to BMI groups

Parameters (Median (min-max))	Overweight	Obesity Class 1	Obesity Class 2	Obesity Class 3	p
Age	28.00 (18-61)	35.00 (18-71)	35.00 (19-78)	36.00 (22-59)	0.130
FPG	86.0 (61-133)	90.00 (72-155)	92.00 (71-136)	97.00 (76-115)	**0.040**
PPG	91.0 (61-149)	94.00 (71-219)	104.0 (64-218)	96.00 (64-151)	0.090
Insulin	7.8 (0.57-25.4)	9.90 (3.1-82.1)	13.07 (4.11-53.2)	11.2 (2.24-29.3)	**<0.001**
HDL	48.00 (31-141)	44.00 (28-78)	44.00 (28-78)	45.00 (32-67)	0.890
LDL (Mean ± SD)	114.17 ± 29.82	130.58 ± 34.80	137.34 ± 29.31	119.22 ± 22.98	**0.040**
Triglyceride	107.00 (36-300)	134.0 (60-592)	130.00 (62-663)	173.00 (75-226)	0.160
TSH	2.3 (0.45-104)	1.80 (0.62-6.2)	2.24 (0.38-4.6)	2.1 (0.8-3.8)	0.620
sT4	0.80 (0.5-0.98)	0.88 (0.20-3.7)	0.80 (0.60-1.10)	0.9 (0.5-1.22)	0.200
Urea	23.00 (13-42)	24.00 (12-38)	24.00 (19-43)	27.00 (17-34)	0.650
Creatinine	0.80 (0.6-1.08)	0.80 (0.6-1.16)	0.80 (0.5-1.2)	0.78 (0.6-1.07)	0.800
ALT	20.00 (12-39)	21.00 (11-43)	20.00 (9-30)	18.00 (14-39)	0.710
AST	20.00 (7-82)	21.00 (7-51)	19.00 (7-41)	21.00 (13-28)	0.970
Vitamin D	13.40 (7.5-27.2)	11.00 (6.5-46.3)	10.10 (6.4-16.5)	11.90 (5.6-23.2)	**0.049**
HGB	13.5 (10.7-17.8)	13.60 (8.1-17)	13.8 (10.3-17.5)	13.3 (12.5-15.8)	0.790
Ferritin	17.60 (2.10-148)	17.5 (1.4-128.1)	63.00 (20-232)	55.0 (12.6-64.3)	0.530
Vitamin B12	227 (115-1500)	175.0 (114-550)	199.0 (97-435)	193.0 (150-270)	0.070
Body weight (kg)	78.0 (66-100)	88.0 (75-159)	94.0 (83-134)	116.0 (94-140)	**<0.001**
Height (m)	165.0 (155-186)	164.0 (155-183)	160.0 (153-185)	162.0 (150-174)	0.110
Waist circumference (cm, Mean±SD)	89.86 ± 10.71	95.30 ± 16.51	104.52 ± 9.04	114.88 ± 11.75	**<0.001**
Hip circumference (cm)	107.0 (97-125)	114.0 (96-134)	125.0 (101-140)	130.0 (111-150)	**<0.001**
Waist/hip ratio (Mean ± SD)	0.82 ± 0.07	0.85 ± 0.07	0.85 ± 0.07	0.87 ± 0.07	0.130
SBP	110.0 (80-140)	110.0 (90-150)	120.0 (100-140)	110.0 (90-150)	0.080
DBP	70.0 (50-90)	70.0 (50-100)	70.0 (60-90)	70.0 (50-90)	0.330

FPG: Fasting plasma glucose, PPG: postprandial glucose, HDL: high density lipoprotein, LDL: low density lipoprotein, ALT: alanine transaminase, AST: aspartate transferase, TSH: thyroid stimulating hormone, HGB: hemoglobin, SBP: systolic blood pressure, DBP: diastolic blood pressure

It has been documented in the literature that the marked increase in the incidence of end-stage renal disease is concurrent with the rise in obesity. In the study by Gomez-Ambrosi et al., creatinine levels rose in direct proportion to obesity among the normal weight, preobese and obese groups. Obesity-related glomerulopathy is characterised by glomerular enlargement and mesangial enlargement. It has been suggested that obesity-related glomerulopathy may be reversible with weight loss. The present study did not identify any statistically significant differences between BMI groups and urea and creatinine values. It is recommended that further studies be conducted with a larger number of patients.

Serum 25(OH)D levels are approximately 20% lower in individuals with obesity compared to those with a normal body mass index (BMI). There is an inverse relationship between serum 25(OH)D levels and BMI, as well as fat mass. Vitamin D plays a pivotal role in bone health and may also exert significant influence over immune and other physiological systems. A deficiency of vitamin D is a common occurrence among obese individuals, regardless of age, ethnicity or geographical location. This may not necessarily indicate a clinical issue. Obese individuals require higher loading doses of vitamin D to achieve the same serum 25-hydroxyvitamin D levels as those of normal weight.[31] Our study revealed a significant difference between BMI groups and vitamin D levels, consistent with the findings of previous research.

In conclusion, obesity represents a significant public health challenge in the coming century. It is essential to elucidate the underlying mechanisms and examine the laboratory values associated with it, with the aim of preventing its adverse consequences.

Conflicts of interest

There are no conflicts of interest in this work.

References

1. Okka B, Durduran Y. Obesity in the Ancient Greek and Byzantine Periods. *Turkiye Klinikleri J Med Ethics* . 2013;21(3):111-117.
2. WHO Consultation on Obesity, World Health Organization, Programme of Nutrition, Family and Reproductive Health. *Obesity : Preventing and Managing the Global Epidemic : Report of a WHO Consultation on Obesity*.; 1997. Accessed July 25, 2024. https://iris.who.int/handle/10665/63854
3. World Health Organization. *Obesity*. Accessed July 25, 2024. https://www.who.int/health-topics/obesity#tab=tab_1
4. Gergerlioğlu U. Evaluation of Obesity Taxes in the Context of Some OECD Countries. *Journal of Economic and Social Research*. 2016;12(2):149-166.
5. Turkish Society of Cardiology. *Coronary Heart Disease Prevention and Treatment Guidelines*; 2002.
6. Haslam DW, James WPT. Obesity. *Lancet*. 2005;366(9492):1197-1209. doi:10.1016/S0140-6736(05)67483-1
7. TEMD Obesity LMHÇG. *Obesity Diagnosis and Treatment Guideline*. 8th ed.; 2019.
8. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(25 Suppl 2):S102-38. doi:10.1161/01.cir.0000437739.71477.ee
9. Prospective Studies Collaboration, Whitlock G, Lewington S, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373(9669):1083-1096. doi:10.1016/S0140-6736(09)60318-4
10. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253.
11. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res*. 1998;6 Suppl 2:51S-209S.
12. Bulur Ş, Çeçen S, Eren F. Anthropometric and Biochemical Characteristics of Individuals Applying to the Department of Sports Physiology with Overweight Complaint. *Journal of ADU Faculty of Medicine*. 2014;15(1):29-35.
13. Akbas F, Usta Atmaca H, Karadas E, Yildiz I, Okten IN. Evaluation of Data from the Obesity Outpatient Clinic at the End of the Second Year as a Newly Formed Unit in Istanbul Training and Research Hospital. *Istanbul Medical Journal*. 2013;14(4):253-256. doi:10.5152/imj.2013.69672
14. *Turkey Health Survey*; 2022. Accessed July 27, 2024. https://data.tuik.gov.tr/Bulten/Index?p=Turkiye-Saglik-Arastirmasi-2022-49747
15. Saygın M, Öztürk Ö, Akbulut S, Kılınç F, Saygın RR. Prevalence of obesity in patients applying to the diet outpatient clinic of Süleyman Demirel University Faculty of Medicine Hospital. *SDU Medical Faculty Derg* . 2015;22(3):53-59.
16. Altun B, Arici M, Nergizoglu G, et al. Prevalence, awareness, treatment and control of hypertension in Turkey (the PatenT study) in 2003. *J Hypertens*. 2005;23(10):1817-1823. doi:10.1097/01.hjh.0000176789.89505.59
17. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362
18. Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. *JAMA*. 2009;302(4):401-411. doi:10.1001/jama.2009.1060
19. Huang Z, Willett WC, Manson JE, et al. Body weight, weight change, and risk for hypertension in women. *Ann Intern Med*. 1998;128(2):81-88. doi:10.7326/0003-4819-128-2-199801150-00001

20. Menke A, Rust KF, Fradkin J, Cheng YJ, Cowie CC. Associations between trends in race/ethnicity, aging, and body mass index with diabetes prevalence in the United States: a series of cross-sectional studies. *Ann Intern Med*. 2014;161(5):328-335. doi:10.7326/M14-0286
21. Uusitupa M, Khan TA, Viguiliouk E, et al. Prevention of Type 2 Diabetes by Lifestyle Changes: A Systematic Review and Meta-Analysis. *Nutrients*. 2019;11(11). doi:10.3390/nu11112611
22. Bogers RP, Bemelmans WJE, Hoogenveen RT, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med*. 2007;167(16):1720-1728. doi:10.1001/archinte.167.16.1720
23. Bays HE, Kirkpatrick C, Maki KC, et al. Obesity, dyslipidemia, and cardiovascular disease: A joint expert review from the Obesity Medicine Association and the National Lipid Association 2024. *Obesity Pillars*. 2024;10:100108. doi:10.1016/j.obpill.2024.100108
24. Uysal A. *Investigation of the Correlation Between Obesity and Liver Function Tests in Obese Cases*. Specialization Thesis. Taksim Training and Research Hospital; 2005.
25. Fishbein MH, Miner M, Mogren C, Chalekson J. The Spectrum of Fatty Liver in Obese Children and The Relationship of Serum Aminotransferases to Severity of Steatosis. *J Pediatr Gastroenterol Nutr*. 2003;36(1):54-61. doi:10.1097/00005176-200301000-00012
26. Salvaggio A, Periti M, Miano L, Tavanelli M, Marzorati D. Body mass index and liver enzyme activity in serum. *Clin Chem*. 1991;37(5):720-723.
27. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: A systematic review and meta-analysis. *Kidney Int*. 2008;73(1):19-33. doi:10.1038/sj.ki.5002586
28. Gómez-Ambrosi J, González-Crespo I, Catalán V, et al. Clinical usefulness of abdominal bioimpedance (ViScan) in the determination of visceral fat and its application in the diagnosis and management of obesity and its comorbidities. *Clinical Nutrition*. 2018;37(2):580-589. doi:10.1016/j.clnu.2017.01.010
29. Shen W wen, Chen H mei, Chen H, Xu F, Li L shi, Liu Z hong. Obesity-related glomerulopathy: body mass index and proteinuria. *Clin J Am Soc Nephrol*. 2010;5(8):1401-1409. doi:10.2215/CJN.01370210
30. Walsh JS, Evans AL, Bowles S, et al. Free 25-hydroxyvitamin D is low in obesity, but there are no adverse associations with bone health. *Am J Clin Nutr*. 2016;103(6):1465-1471. doi:10.3945/ajcn.115.120139
31. Walsh JS, Bowles S, Evans AL. Vitamin D in obesity. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(6):389-394. doi:10.1097/MED.0000000000000371

CMJ. 2024;46(3): 205-207
DOI: 10.7197/cmj.1458402

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

A Rare Complication After Spinal Anesthesia: Intracranial Subdural Hematoma

Fatma Hançer Çelik[1,a], Necmi Baykan[1,b,*], Ömer Salt[1,c], Rukiye Aytekin[1,d], Gözde Yılmaz[1,e]

[1]*Department of Emergency Medicine, Kayseri City Hospital, Kayseri, Turkiye*
**Corresponding author*

Case Report

History

Received: 25/03/2024
Accepted: 25/06/2024

ABSTRACT

Acute & chronic intracranial subdural hematoma is usually caused by trauma. However, it is a rare and serious complication after spinal anesthesia. A 38-year-old woman was brought to the emergency department by her relatives with complaints of sudden change in consciousness. It was learned that the patient gave birth by cesarean section under spinal anesthesia 3 days ago. It was anamnesized that there was no abnormality in the operation, the patient had a headache during the follow-up in the service and was diagnosed as post-dural puncture headache, analgesics were prescribed and she was discharged with recommendations. It was determined that the headaches continued after discharge and sudden change in consciousness occurred 2 hours after discharge. On physical examination, the patient was intubated because of poor general condition and Glasgow coma scale score of 8. The patient had 4/2 anisocoria on the left side. A brain CT scan showed a 6 mm subacute subdural hematoma in the left frontotemporoparietal region at the widest part. There was an 8 mm shift effect to the right of the midline, the sulci were obliterated and the cerebral tissue was mildly edematous. The patient was consulted to neurosurgery because of subacute subdural hematoma, shifting and anisocoria and was transferred to neurosurgery intensive care unit for emergency craniotomy and hematoma evacuation. This case report describes an acute subdural hematoma after spinal anesthesia and emphasizes that when using spinal anesthesia, it should be kept in mind that headache does not always mean hypotensive headache associated with spinal anesthesia and that a catastrophic complication of subdural hematoma may also occur.

Keywords: Spinal Anesthesia, Subdural Hematoma, Headache

Spinal Anestezi Sonrası Nadir Bir Komplikasyon: İntrakraniyal Subdural Hematom

Olgu Sunumu

Süreç

Geliş: 25/03/2024
Kabul: 25/06/2024

ÖZET

Akut ve kronik intrakraniyal subdural hematom genellikle travma nedeniyle oluşur. Ancak spinal anestezi sonrası nadir ve ciddi bir komplikasyondur. 38 yaşında kadın hasta yakınları tarafından ani bilinç değişikliği şikayeti ile acil servise getirildi. Hastanın 3 gün önce spinal anestezi altında sezaryen ile doğum yaptığı öğrenildi. Operasyonda herhangi bir anormallik olmadığı, hastanın servisteki takibi sırasında baş ağrısı olduğu ve post-dural ponksiyon baş ağrısı tanısı aldığı, analjezik reçete edildiği ve önerilerle taburcu edildiği öğrenildi. Taburcu olduktan sonra baş ağrısının devam ettiği ve taburcu olduktan 2 saat sonra ani bilinç değişikliği olduğu tespit edildi. Fizik muayenede genel durumu kötü ve Glasgow koma skalası skoru 8 olan hasta entübe edildi. Hastanın sol tarafında 4/2 anizokori vardı. Beyin BT taramasında sol frontotemporoparietal bölgede en geniş yerinde 6 mm subakut subdural hematom görüldü. Orta hattın sağına doğru 8 mm'lik bir kayma etkisi vardı, sulkuslar oblitereydi ve serebral doku hafif ödemliydi. Hasta subakut subdural hematom, şift ve anizokori nedeniyle beyin cerrahisine konsülte edildi ve acil kraniotomi ve hematom tahliyesi için beyin cerrahisi yoğun bakım ünitesine transfer edildi. Bu olgu sunumu spinal anestezi sonrası gelişen akut subdural hematomu tanımlamakta ve spinal anestezi kullanırken baş ağrısının her zaman spinal anesteziye bağlı hipotansif baş ağrısı anlamına gelmediğini ve subdural hematom gibi katastrofik bir komplikasyonun da oluşabileceğini akılda tutmak gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Spinal Anestezi, Subdural Hematom, Baş ağrısı

[a] *ftmhncr91f@gmail.com* *0009-0003-4421-5791*
[b] drnecmibaykan@gmail.com *0000-0002-6845-9550*
[c] *dromersalt@gmail.com* *0000-0002-5557-6627*
[d] *drrukiyeaytekin51@gmail.com* *0009-0007-7139-1562*
[e] *beau_gozde@hotmail.com* *0009-0003-0032-4398*

How to Cite: Hançer Çelik F, Baykan N, Salt Ö, Aytekin R, Yılmaz G. A Rare Complication After Spinal Anesthesia: Intracranial Subdural Hematoma, Cumhuriyet Medical Journal, 2024;46(3): 205-207.

Introduction

Acute & chronic intracranial subdural hematoma is usually caused by trauma. However, it is a rare and serious complication after spinal anesthesia. Intracranial bleeding with subdural hematoma after spinal anesthesia is a rare and fatal complication with a reported incidence of 1 in 500000 obstetric populations.[1] Symptoms of subdural hematoma are due to mass effect and displacement of structures. Spinal anesthesia has the advantage of avoiding the side effects of general anesthesia and allowing the patient to be awake during the surgical procedure. It is especially popular in obstetric surgery and delivery.[2] Post-dural puncture headache after spinal anesthesia is a known complication of neurocranial blockade.[3] Other complications include nausea, ringing in the ears, dizziness and photophobia. Symptoms usually resolve spontaneously when treated with bed rest and analgesics or within five days. The diagnostic criterion for post-dural puncture headache is postural headache that occurs or intensifies after 15 minutes of standing and resolves with lying down.[4]

Case Presentation

A 38-year-old woman was brought to the emergency department by her relatives with complaints of sudden change in consciousness. It was learned that the patient gave birth by cesarean section under spinal anesthesia 3 days ago. Spinal anesthesia was given by 25G Quincke's spinal needle, and 8 mg of hyperbaric bupivacaine was used. A total of two attempts were taken for dural puncture. It was anamnesized that there was no abnormality in the operation, the patient had a headache during the follow-up in the service and was diagnosed as post-dural puncture headache, analgesics were prescribed and she was discharged with recommendations. It was determined that the headaches continued after discharge and sudden change in consciousness occurred 2 hours after discharge. She had a history of hypertension. The patient's history was negative for any condition that could cause subdural hemorrhage such as arteriovenous malformation, bleeding disorder, alcohol and drug abuse except hypertension. At the time of admission, vital signs were fever 36 °C, blood pressure 160/90 mmHg, pulse 70/min, SpO_2 99%, fingerstick blood glucose 124 mg/dl. On physical examination, the patient was intubated because of poor general condition and Glasgow coma scale score of 8. The patient had 4/2 anisocoria on the left side. Laboratory tests revealed no pathology. A brain CT scan showed a 6 mm subacute subdural hematoma in the left frontotemporoparietal region at the widest part. There was an 8 mm shift effect to the right of the midline, the sulci were obliterated and the cerebral tissue was mildly edematous (Figure 1). No pathology was detected in other CT imaging studies performed for exclusion. The patient was consulted to neurosurgery because of subacute subdural hematoma, shifting and anisocoria and was transferred to neurosurgery intensive care unit for emergency craniotomy and hematoma evacuation. Cranioplasty was performed after resorption of the brain edema. The patient was intubated for 3 days and then extubated and transferred to the ward and was discharged with recovery after he had no problems in the ward follow-up.

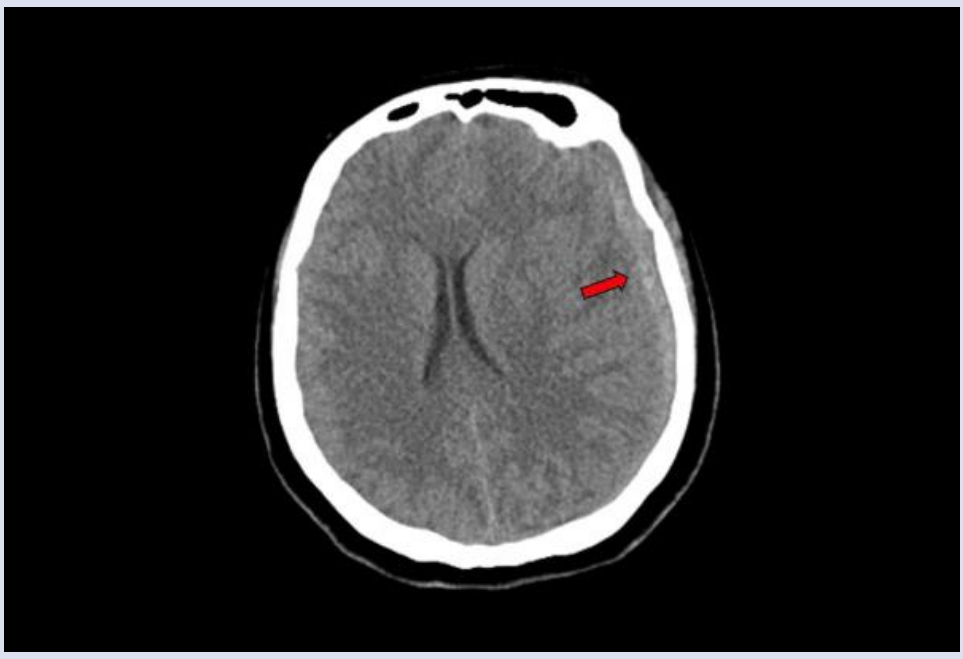

Figure 1. Brain CT image of the patient (A subdural hematoma is marked with a red arrow.)

Discussion

Intracranial subdural hematoma is a result of dural puncture, which is a rare but serious complication after epidural and spinal anesthesia. This may occur during obstetric neuraxial anesthesia, especially in young and healthy women, and the consequences can be serious.[5] Loss of cerebrospinal fluid (CSF) due to epidural and spinal anesthesia may shift the brain caudally, causing rupture of intracranial subdural veins and subdural hemorrhage.[6] Symptoms of subdural hematoma are related to mass effect and displacement of structures.

Post-dural puncture headache is caused by loss of CSF as a result of dural puncture and worsens with the effect of gravity when the patient stands upright and relieves when the patient is supine. Secondly, vasodilatation occurs in response to decreased intracranial pressure due to CSF loss and causes headache; more than 85% resolve within six weeks.[7] Persistent postpartum headache is usually caused by common causes such as tension-type headache and migraine. This is one of the common types of headache that women frequently encounter in the postpartum period. Especially tension-type headache and migraine may occur prominently in this period and it is a common problem among women with long-term headache.[8] Refractory or recurrent post-dural puncture headache, especially when associated with neurologic symptoms, may require neurology or neurosurgery consultation with cerebral neuroimaging. When this is the clinical situation, it is important to further investigate the cause of the headache in order to determine appropriate treatment strategies.

Development of intracranial subdural hematoma after spinal anesthesia has been reported, although it is rare.[7] This complication is a condition in which early diagnosis is important and therefore the nature of headache after spinal anesthesia should be carefully considered. If any change in the headache is noticed, a thorough neurologic examination should be performed as soon as possible, taking into account the possibility of intracranial subdural hematoma. This may positively affect the prognosis by providing early diagnosis of a potentially serious complication.

This case report describes an acute subdural hematoma after spinal anesthesia and emphasizes that when using spinal anesthesia, it should be kept in mind that headache does not always mean hypotensive headache associated with spinal anesthesia and that a catastrophic complication of subdural hematoma may also occur.

References

1. Kshirsagar SJ, Pande AH, Naik SV, Kamble NM. Intracranial hypotension with subdural hematoma after spinal anesthesia in obstetric patient: A rare but fatal complication. Saudi J Anaesth. 2024;18(1):114-6.
2. Szeto V, Kosirog J, Eilbert W. Intracranial subdural hematoma after epidural anesthesia: a case report and review of the literature. International Journal of Emergency Medicine. 2018;11:1-4.
3. Van de Velde M, Schepers R, Berends N, Vandermeersch E, De Buck F. Ten years of experience with accidental dural puncture and post-dural puncture headache in a tertiary obstetric anaesthesia department. International journal of obstetric anesthesia. 2008;17(4):329-35.
4. Apfel C, Saxena A, Cakmakkaya O, Gaiser R, George E, Radke O. Prevention of postdural puncture headache after accidental dural puncture: a quantitative systematic review. British journal of anaesthesia. 2010;105(3):255-63.
5. Vaughan D, Stirrup C, Robinson P. Cranial subdural haematoma associated with dural puncture in labour. British journal of anaesthesia. 2000;84(4):518-20.
6. Ferrari L, De Sevin F, Vigue J, Granry J, Preckel M, editors. Hématome sous-dural intracrânien après brèche dure-mérienne en obstétrique. Annales françaises d'anesthésie et de réanimation; 2001: Elsevier.
7. Cuypers V, Van de Velde M, Devroe S. Intracranial subdural haematoma following neuraxial anaesthesia in the obstetric population: a literature review with analysis of 56 reported cases. International journal of obstetric anesthesia. 2016;25:58-65.
8. Nolte C, Lehmann T. Postpartum headache resulting from bilateral chronic subdural hematoma after dural puncture. The American journal of emergency medicine. 2004;22(3):241-2.

CMJ. 2024;46(3): 208-210
DOI: 10.7197/cmj.1325127

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Ectopic Pancreas in The Gallbladder Associated With Chronic Chalculous Cholecystitis: Case Report

Ali Mızrak[1,a,*]

[1] *Clinic of Medical Pathology, Sultangazi Haseki Training and Research Hospital, İstanbul, Turkiye*
**Corresponding author*

Case Report

History

Received: 12/07/2023
Accepted: 16/07/2024

ABSTRACT

Heterotopia is defined as the presence of a tissue outside of its natural location. Ectopic or heterotopic pancreatic tissue is a form of choristoma and is considered an embryological abnormality. Stomach, duodenum, jejunum and spleen are common localizations. The gallbladder is a very rare localization. In this case report, ectopic pancreatic tissue observed in the gallbladder of a 41-year-old patient who is diagnosed with chronic calculous cholecystitis who underwent surgery is discussed in the light of current literature.

Keywords: Chronic calculous cholecystitis, ectopic pancreas, gall bladder

Kronik Taşlı Kolesistit Hastasında Safra Kesesinde Ektopik Pankreas Dokusu: Olgu Sunumu

Olgu Sunumu

Süreç

Geliş: 12/07/2023
Kabul: 16/07/2024

ÖZET

Heterotopi bir dokunun doğal yerleşim yeri dışında lokalize olmasıdır. Ektopik veya heterotopik pankreas dokusu bir koristom şeklidir ve embriyolojik anomalilerden sayılmaktadır. Mide, duodenum, jejunum ve dalak sık görülen lokalizasyondur. Safra kesesi ise oldukça nadir bir lokalizasyondur. Bu olgu sunumunda 41 (kırk bir) yaşında kronik taşlı kolesistit tanısı konularak opere edilen hastanın safra kesesinde izlenen ektopik pankreas dokusu, mevcut literatür bilgileri ışığında tartışılmıştır.

Anahtar Kelimeler: Kronik taşlı kolesistit, ektopik pankreas, safra kesesi

[a] *dralimizrak@gmail.com* *0000-0002-1096-1660*

How to Cite: Mızrak A. Ectopic Pancreas in the Gallbladder Associated with Chronic Chalculous Cholecystitis: Case Report. Cumhuriyet Medical Journal. 2024; 46(3): 208-210.

Introduction

Ectopic or heterotopic pancreatic tissue is defined as pancreatic tissue that has no vascular, neural or anatomical connection with the pancreas. It is considered an embryological developmental abnormality and is thought to develop during the fusion of the dorsal and ventral pancreas.[1] Ectopic pancreatic tissue is frequently encountered in the stomach, duodenum, jejunum and spleen in autopsy series or incidentally.[2,3] On the other hand, gallbladder localization is quite rare and has been reported in a small number of case reports.[1-7]

Case Report

A forty-one (41) year old male patient applied with complaints of abdominal pain, nausea and bloating. On physical examination, tenderness to palpation was observed in the right upper abdomen. In blood tests, AST (22 µ /l), ALT (29 µ /L) and GGT (22 µ /l) levels were within normal limits whereas ALP (113 µ /L) was elevated. In the ultrasonographic examination, several stones were observed in the gallbladder, and the largest one was 12 mm in diameter. The patient was diagnosed with chronic calculous cholecystitis and underwent laparoscopic cholecystectomy.

Pathological examination revealed that the gallbladder was 45 mm long and 25 mm in diameter. The mucosal surface was white-grey in colour, and the wall thickness was 8 mm at its thickest point. A solid nodule with a diameter of 5 mm, was observed in the neck area of the gallbladder.

In microscopic evaluation focal mucosal ulceration of the gallbladder and inflammation rich in mononuclear cells was noted in lamina propria. Hypertrophy was observed in the muscular layer. Focal areas of fibrosis were seen. These findings were consistent with chronic cholecystitis. In addition, pancreatic tissue was observed in the gallbladder, separated from the surrounding tissue by a smooth border (Figure 1) and without causing significant inflammation around it. The ectopic pancreatic tissue was 5 mm in diameter and was located under the muscular layer. Duct and acini were observed in the pancreatic tissue (Figure 2). With these findings, a diagnosis of ectopic pancreas was made in addition to chronic cholecystitis.

Discussion

Ectopic pancreatic tissue is considered an embryological developmental abnormality and is thought to develop during the fusion of the dorsal and ventral pancreas.[1,2] On the other hand, there is information that abnormalities in the Notch signalling pathway are associated with ectopic pancreas.[2,7] Although it is relatively common in the stomach, small intestine and Meckel's diverticulum, it is rare in the gallbladder. It was first reported in the gallbladder by Otschkin in 1916, and more than 30 cases have been reported since then.[5]

Most patients are over the age of forty and it is more common in women.[5] The sizes of heterotopic pancreatic tissue in the gallbladder reported in the literature vary between 1 mm and 10 mm.[3] It can be located in the fundus, body and neck regions of the gallbladder. Approximately half of the patients have gallbladder stones.[5] Microscopically, according to von Heinrich classification; those containing acinus, ductus and islets of Langerhans are Type 1; those containing only ducts and acinus are type 2; Those containing only proliferating ducts without containing endocrine elements and exocrine acini are classified as Type 3.[1-7]

In our case, the pancreatic tissue was 5 mm in diameter and was located in the neck of the gallbladder. Histologically, it contains acini and ductus. Therefore, it can be considered type 2 according to the von Heinrich classification. Although the clinical significance of ectopic pancreatic tissue is not clearly known, tumours of pancreatic origin can develop in these ectopic tissues, and those located in the neck of the gallbladder may cause obstruction.[7]

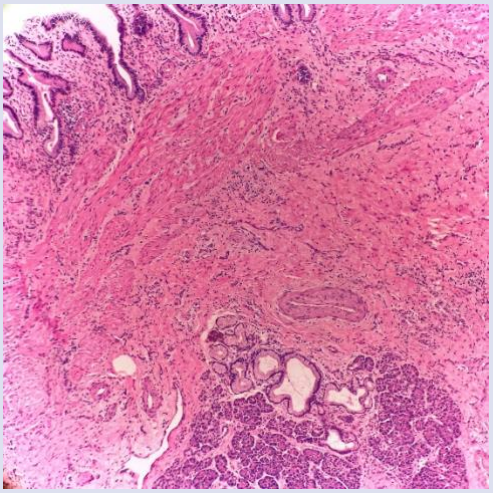

Figure 1: Ectopic pancreatic tissue under the muscular layer in the gallbladder (H&E 40)

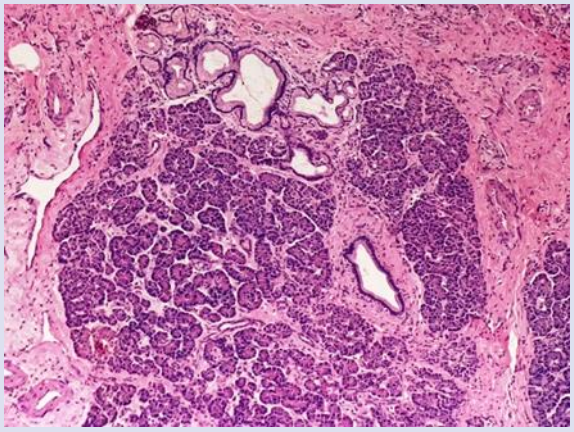

Figure 2: Pancreatic ducts and acini (H&E x400)

References

1. Chatziantoniou G, Tzikos G, Ioannidis A, Loukousia A, Raptou G, Michalopoulos A, Paramythiotis D. The rare entity of ectopic pancreatic tissue in the gallbladder: A case report. Ann Med Surg (Lond). 2022 Apr 29;77:103698. doi: 10.1016/j.amsu.2022.103698.
2. Lauricella S, Dell'Ovo A, Coppola A et al. Heterotopic Pancreatic Tissue in the Gallbladder: a Report of a Very Rare Case. J Gastrointest Cancer. 2021 Sep;52(3):1175-1179. doi: 10.1007/s12029-021-00663-5.
3. Elhence P, Bansal R, Agrawal N. Heterotopic pancreas in gall bladder associated with chronic cholecystolithiasis. Int J Appl Basic Med Res. 2012 Jul;2(2):142-3. doi: 10.4103/2229-516X.106360.
4. Şerboiu CS, Aliuș C, Dumitru A, Țăpoi D, Costache M, Nica AE, Alexandra-Ana M, Antoniac I, Grădinaru S. Gallbladder Pancreatic Heterotopia-The Importance of Diagnostic Imaging in Managing Intraoperative Findings. Medicina (Kaunas). 2023 Aug 1;59(8):1407. doi: 10.3390/medicina59081407.
5. Aborajooh E, Ghayada IKK, Lafi YMI. Heterotopic Pancreas in the Gallbladder: Case Report and Literature Review. Case Rep Med. 2021 Jan 30;2021:6611291. doi: 10.1155/2021/6611291.
6. Al-Janabi MH, Ismail L, Wassouf MY, Sulaiman J, Salloum R, Al-Shehabi Z. Heterotopic pancreatic tissue in the gall bladder neck and lymph node surrounding cystic duct identified during cholecystectomy for chronic calculous cholecystitis: a rare case report from Syria. Oxf Med Case Reports. 2022 Jun 23;2022(6):omac068. doi: 10.1093/omcr/omac068.
7. Weppner JL, Wilson MR, Ricca R, Lucha PA Jr. Heterotopic pancreatic tissue obstructing the gallbladder neck: a case report. JOP. 2009 Sep 4;10(5):532-4.

CMJ. 2024; 46(3): 211-213
DOI: 10.7197/cmj.1448397

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Diaphragmatic Mesothelial Cyst And Percutaneous Ethanol Sclerotherapy: In A Young Girl**

Levent Cankorkmaz[1,a,*], İsmail Şalk[2,b], Mehmet H. Atalar[2,c]

[1] *Department of Pediatric Surgery, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Turkiye*

[2] *Department of Radiolgy, Sivas Cumhuriyet University, Faculty of Medicine, Sivas, Turkiye*

**Corresponding Author*

**This study was presented at the 16th Congress of Hungarian Association of Pediatric Surgeons, October 14th – 16th, September 2017, in Szeged, Hungary.

Case Report

History

Received: 11/03/2024
Accepted: 27/07/2024

ABSTRACT

Diaphragmatic mesothelial cysts are rare congenital lesions that are lined with mesothelial cells. The diagnosis might be problematic because of their rarity and anatomic location. We report a case of with a diaphragmatic cyst in a 6–year–old girl. In this case, the cyst was found incidentally. We found a thin-wall, homogeneous cyst, which was between the lateral aspects of the liver and diaphragm with radiological imaging. The patient was planned for cyst aspiration and ethanol sclerotherapy was made based on the imaging findings. The cyst was aspirated and then performed ethanol sclerotherapy. The cytological findings of the cyst fluid were appeared to be degenerated histiocytes and mesothelial cells. If treatment is needed, percutaneous treatment is conceivable as the first choice of technique.

Keywords: Mesothelial cyst, Child, Ethanol Sclerotherapy

Bir Kız Çocukta Diyafragmatik Mezotelyal Kist ve Perkütan Etanol Skleroterapisi

Olgu Sunumu

Süreç

Geliş: 11/03/2024
Kabul: 27/07/2024

ÖZET

Diyafragmatik mezotelyal kistler, mezotelyal hücrelerle döşeli, nadir görülen konjenital lezyonlardır. Nadir görülmeleri ve anatomik yerleşimleri nedeniyle tanıları sorunlu olabilir. Biz 6 yaşında diyafragma kisti olan kız çocuğu olguyu sunuyoruz. Bu vakada kist tesadüfen tespit edilmişti. Radyolojik görüntülemede karaciğer laterali ile diyafram arasında ince duvarlı, homojen kist saptandı. Görüntüleme bulgularına göre hastaya kist aspirasyonu planlandı ve etanol skleroterapi uygulandı. Kist aspire edildi ve ardından etanol skleroterapi uygulandı. Kist sıvısının sitolojisinde dejenere histiositler ve mezotelyal hücreler saptandı. Lezyonlarda tedavi gerekiyorsa perkütan tedavi ilk seçenek olarak düşünülebilir.

Anahtar Kelimeler: Mezotelial kist, Çocuk, Etanol skleroterapi

[a] *lcankorkmaz@gmail.com* *0000-0003-1525-1470*
[b] *ismailsalk@gmail.com* *0000-0002-5156-6923*
[c] *mhatalar@gmail.com* *0000-0003-3076-8072*

How to Cite: Cankorkmaz L, Şalk İ, Atalar MH. Diaphragmatic Mesothelial Cyst And Percutaneous Ethanol Sclerotherapy: In A Young Girl. Cumhuriyet Medical Journal. 2024;46(3): 211-213

Introduction

Diaphragmatic mesothelial cysts (DMC) are uncommon congenital lesions, especially for pediatric patients lined by mesothelial cells. The diagnosis might be problematic because of their rarity and anatomic location.[1,2] MC in small size is usually asymptomatic and diagnosis is generally based on the imaging.[2] We report a case of a diaphragmatic cyst in a 6–year–old girl. US is the initial diagnostic examination for children, and it has been reported that the finding of a thin- walled and bilobate cyst in the posterolateral aspect of the right costophrenic angle, and an extracapsular location of the liver is very suggestive of the diagnosis.[1]

Case Report

In our case, the chief complaint was abdominal pain, and the cyst had been found incidentally by Ultrasonography (US). There was not a family history of hydatid cysts or trauma. We performed US and computed tomography (CT) (Figure 1-2). It was found in the US, a thin-wall, homogeneous cyst, which was between the lateral aspects of the liver and diaphragm determined with CT. The dimension of the cyst was 35X25X55 mm (ML-AP-CC). Laboratory investigations yielded normal results.

The patient was planned for cyst aspiration and ethanol sclerotherapy was made based on the imaging findings because she had abdominal pain. The cyst was aspirated and then performed ethanol sclerotherapy. The cytological findings of the cyst fluid were appeared to be degenerated histiocytes and mesothelial cells, features of a cystic fluid. Ethanol was chosen as the sclerosing solution because it has been commonly used for sclerosing hepatic, renal, and splenic hydatid cysts safely and successfully.[3,4] Cyst disappeared completely in case after the procedure, in follow-up was nonproblematic.

Discussion

Diaphragmatic masses present a radiological challenge because of cysts' infrequency and the difficulty of establishing exact anatomical relationships concerning neighboring structures such as the pleura, lungs, spleen, or liver, where the disease is much more frequent.[5] Diaphragmatic mesothelial cysts arise from coelomic remnants. Other cystic lesions of the diaphragm include bronchogenic cysts, teratoma, and hydatid cysts. Mesothelial cysts may also be detected in organs such as the spleen, adrenal gland, ovary, falciform ligament, vaginal process of the testicle, and mesentery.[6] Surgery may be necessary if the cyst is large or symptomatic. If treatment is needed, percutaneous treatment is conceivable as the first choice of technique.

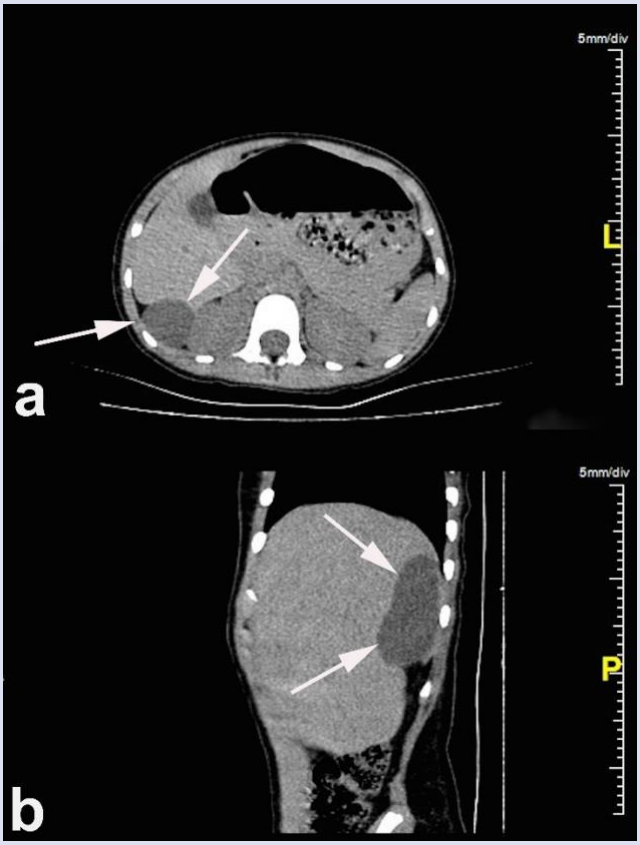

Figure 1: Pretreatment axial (a) and sagittal reformatted (b) computed tomography images show diaphragmatic mesothelial cyst (arrows).

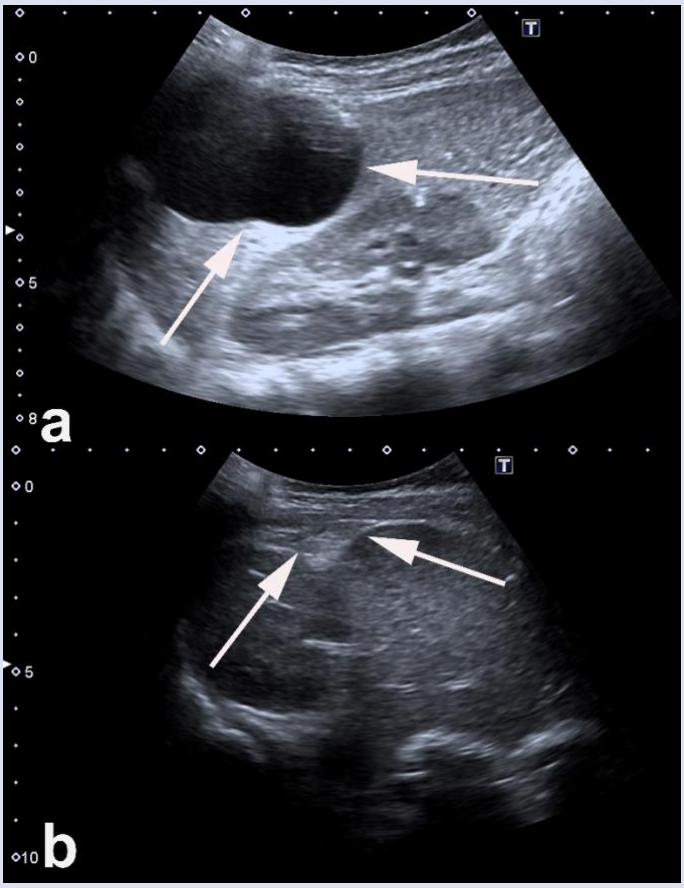

Figure 2: Ultrasound images, (a) pretreatment image shows cystic lesion (arrows) with thin hyperechoic wall, and (b) post-treatment image shows after complete aspirated of diaphragmatic mesothelial cyst (arrows).

References

1. Akinci D, Akhan O, Ozmen M, Ozkan OS, Karcaaltincaba M. Diaphragmatic mesothelial cysts in children: radiologic findings and percutaneous ethanol sclerotherapy. AJR Am J Roentgenol. 2005; 185(4): 873-7.
2. Yang M, Xiang B, Xie XL, Li KW, Li FY. Retroperitoneal mesothelial cyst misdiagnosed as a congenital choledochal cyst for an infant patient: A case report and literature review. Int J Surg Case Rep. 2020; 71:176-178. doi: 10.1016/j.ijscr.2020.04.075.
3. Bean WJ, Rodan BA. Hepatic cysts: treatment with alcohol. AJR 1985; 144:237–241.
4. Akinci D, Akhan O, Ozmen M, et al. Long-term results of single-session percutaneous drainage and ethanol sclerotherapy in simple renal cysts. Eur J Radiol 2005; 54: 298–302.
5. Esparza Estaún J, González Alfageme A, Sáenz Bañuelos J. Radiological appearance of diaphragmatic mesothelial cysts. Pediatr Radiol 33, 855–858 (2003). Doi: 10.1007/s00247-003-1014-6.
6. Estaun JE, Alfageme AG, Banuelos JS. Radiologic appearance of diaphragmatic mesothelial cysts. Pediatr Radiol. 2003; 33: 855–858.

CMJ, 2024;46(3): 214-216
DOI: 10.7197/cmj.1453153

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

A Rare Cause of Pseudoarthrosis: Costal Exocytosis on Facing Surfaces of Each Other

Hüseyin Alper Kızıloğlu[1,a,*]
[1]*Department of Radiology, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Türkiye.*

**Corresponding author*

Case Report

History

Received: 15/03/2024
Accepted: 27/07/2024

ABSTRACT

Osteochondromas are common asymptomatic lesions. The development of chondroid malignancies from cartilage caps has rarely been described. Costal osteochondromas are relatively rare lesions. The incidence of osteochondromas in flat bones is approximately less than 5% of all osteochondromas. Osteochondroma originating from two adjacent ribs and forming a joint with each other is a phenomenon described for the first time in the literature.

Keywords: Costa, Rare, Exocytosis

Psödoartrozun Nadir Bir Nedeni: Birbirine Bakan Yüzeylerde Kostal Ekzositoz

Olgu Sunumu

Süreç

Geliş: 15/03/2024
Kabul: 27/07/2024

ÖZET

Osteokondromlar sık görülen asemptomatik lezyonlardır. Kıkırdak keplerinden malignitelerinin gelişimi nadiren tanımlanmıştır. Kostal osteokondromlar nispeten nadir görülen lezyonlardır. Yassı kemiklerde osteokondrom görülme sıklığı tüm osteokondromların yaklaşık %5'inden azdır. Bizim vakamız, komşu iki kostadan köken alan ve birbirleriyle eklem oluşturan bir olgudur ve literatürde ilk kez tanımlanmıştır.

Anahtar Kelimeler: Costa, Nadir, Ekzositoz

[a] *alperkzloglu@hotmail.com* *0000-0002-6921-8716*

How to Cite: Kızıloğlu HA. A Rare Cause of Pseudoarthrosis: Costal Osteochondroma on Facing Surfaces of Each Other, Cumhuriyet Medical Journal, 2014;46(3): 214-216.

Introduction

Osteochondroma is a relatively common lesion. It constitutes 10-15% of all bone tumors and approximately 35% of benign bone tumors.[1] It is usually asymptomatic and if isolated, the probability of malignant transformation is very low. Osteochondromas differ from other exocytosis because they have cartilage cap.[1] Osteochondromas develop in adolescence, but they generally do not increase in size with advancing age. They can be seen at any age and are usually detected incidentally. They are usually sporadic but may accompany diaphyseal achalasia and Trevor disease. [1] Malignant transformation develops from the cartilage cap and is approximately 1% in sporadic solitary osteochondromas. However, in case of heterogeneous multiple exocytosis, the malignancy rate is much higher (5%-25%).[2] Although it is usually asymptomatic, the symptom occurs due to mechanical effect and malignant transformation. Osteochondromas are generally observed in the appendicular skeleton and around the knee.[2] Although osteochondromas are common tumors of bones, they are rarely observed in the ribs.[3] Radiologically, osteochondromas are seen as sessile or pedunculated. The diagnosis comes to mind when the continuity of the cortex and medulla from the bone of origin is demonstrated. By demonstrating the cartilage cap of varying thickness, the diagnosis is made almost without the need for histopathological verification. Radiologically, attention is paid to the cartilage cap thickness and monitored. In the differential diagnosis, it is most often confused with osteophytic spur formation. In this case, attention is paid to the patient's age, other degenerative findings of the joint, and whether the protrusion is towards the joint. While osteochondromas grow opposite to the joint, osteophytic spur formations grow towards the joint.

Case Report

A 49-year-old male patient is undergoing a thorax computed tomography (CT) examination due to follow-up of a solitary pulmonary nodule. Incidentally, in the 7th-8th grade in the right hemithorax posterior. Exocytosis is observed on the sides of the ribs facing each other. Pseudoarticulation is observed at the level of exocytosis. The extension of exocytosis is towards the lung. The cartilage cap cannot be observed in the available images (Fig. 1). Upon patient request, the lesions are removed and osteochondroma is confirmed histopathologically. Although follow-up was recommended due to the patient's obsessive nature, the patient preferred to undergo surgery.

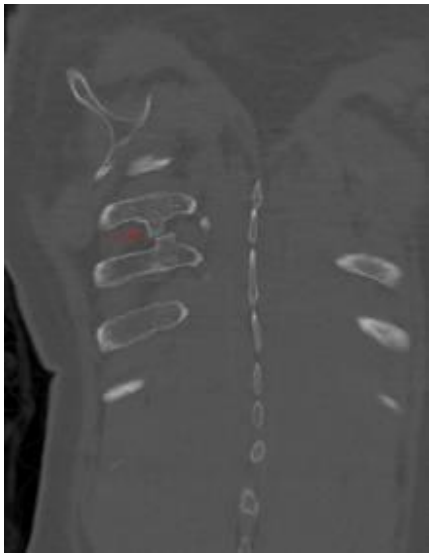

Figure 1.a. In the coronal CT image, exocytosis and pseudoarticulation are observed in the 7th and 8th ribs (red arrow).

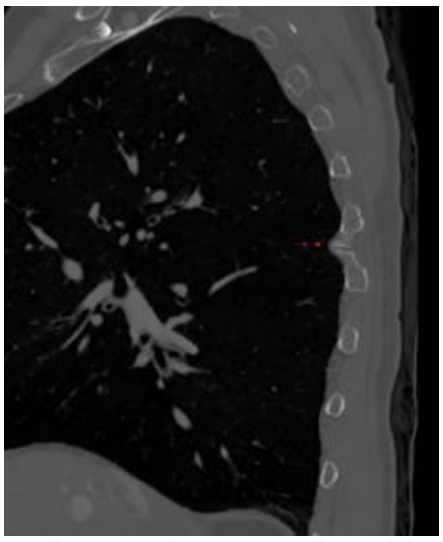

Figure 1.b. In sagittal sections, it is observed that both exocytosis is directed towards the lung (red arrow).

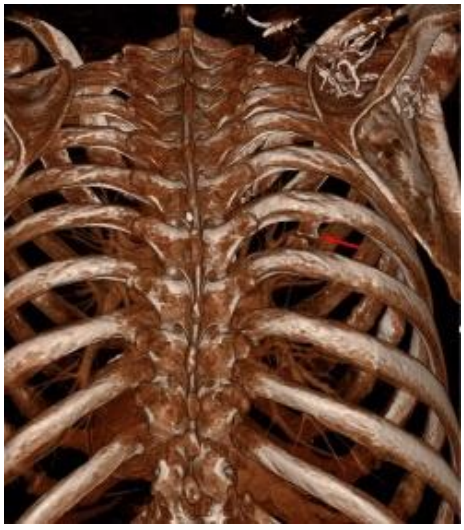

Figure 1.c. Lesions are observed in the 3D reformatted image (red arrow).

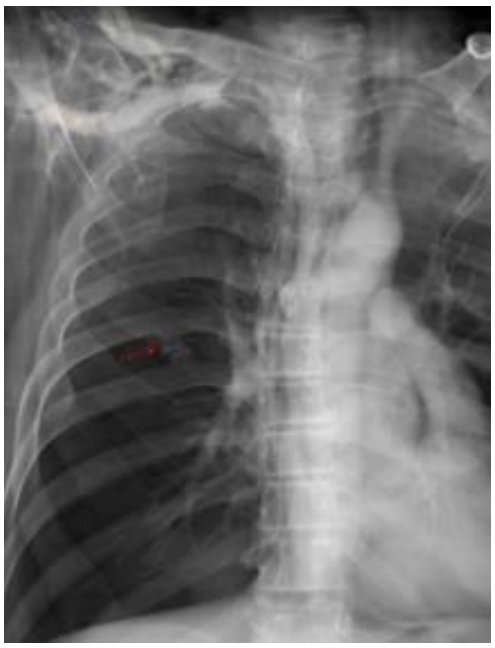

Figure 1.d. Lesions are observed in the X-ray section obtained from the CT image (red arrow).

Discussion

Around half of all primary chest wall tumors are non-cancerous, with osteochondroma (exostosis) being the most frequent type. These tumors are often without symptoms, but in rare cases, they can lead to pneumothorax, hemothorax, diaphragm rupture, empyema, and lung damage. Spontaneous pneumothorax is typically caused by the unprovoked rupture of a pulmonary bleb or by the pressure exerted by an osteochondroma on the lung tissue.

Although osteochondromas are relatively common lesions, costal osteochondromas are rare lesions. The probability of malignant transformation in osteochondromas is quite low. It is monitored radiologically by cartilage cap thickness. Their treatments are mostly related to the compression effect.

There are case reports about costal osteochondromas in the literature.[3,4,5] Studies in the literature are related to its size, its compression effect and the symptoms it creates. There are also cases in the literature that cause rare complications such as spontaneous pneumothorax.[6] Although our case is asymptomatic, it is valuable in that it presents an atypical morphology.

Conclusion

There are current publications about costal osteochondroma in the literature.[3,4] However, there is no publication in the literature where two osteochondromas form pseudoarticulation. We described the first case report.

References

1. WHO Classification of Tumours Editorial Board, Who Classification of Tumours Editorial. Soft Tissue and Bone Tumours. (2020) ISBN: 9789283245025 - Google Books
2. Lee J, Yao L, Wirth C. MR Imaging of Solitary Osteochondromas: Report of Eight Cases. AJR Am J Roentgenol. 1987;149(3):557-60. doi:10.2214/ajr.149.3.557 – Pubmed
3. Morales LC, Cardona Ortegón JD, Pinzón Valderrama BA, Jiménez Uribe AM, Mora Bendeck NG, Fierro Ávila F. Osteochondroma of the Rib: A Potentially Life-Threatening Benign Tumor. Cureus. 2023;15(9):e45449. Published 2023 Sep 18. doi:10.7759/cureus.45449
4. Tiwari C, Borkar N, Hussain N, Khubchandani N. Solitary osteochondroma of the rib: An unusual chest wall tumor in the pediatric age group. J Cancer Res Ther. 2023;19(5):1423-1425. doi:10.4103/jcrt.jcrt_679_21
5. Jilowa S, Paliwal P, Kapur A, Verma GC. Exostosis of Rib: Case Report of an Extremely Rare Giant Osteochondroma at an Unusual Site, Radiopathological Correlation with Brief Review of Literature. *Indian J Radiol Imaging*. 2021;31(3):740-744. Published 2021 Nov 13. doi:10.1055/s-0041-1736406
6. Lin CY, Chang CC, Chuang MT. Spontaneous Haemothorax Secondary to Rib Exostosis. *Heart Lung Circ*. 2017;26(8):e62-e63. doi:10.1016/j.hlc.2017.02.005

CMJ. 2024;46(3):217-221
DOI: 10.7197/cmj.1498748

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Grief Accompanied by Suicidal Thoughts After Traumatic Loss in Adolescent: A Case Report

Özlem Şireli[1,a,*], İrem Naz Yazarlı[1,b], Elif Abanoz[1,c], Ayla Uzun Çiçek[1,d], Cansu Mercan Işık[1,e], Mehmet Çolak[2,f]

[1] *Sivas Cumhuriyet University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Sivas, Turkey*
[2] *Child and Adolescent Psychiatry, Freelance Physician, Izmir, Turkey*

**Corresponding author*

Case Report

History

Received: 10/06/2024
Accepted: 30/07/2024

ABSTRACT

Grief is a normal process that occurs following the irreversible loss of a loved one. This process, characterized by painful experiences, varies widely and is influenced by numerous factors, including the identity of the deceased, the circumstances of their death, the individual characteristics of the bereaved, and the availability of support systems. The suddenness and violence of a loss can disrupt the normal grieving process, leading to the manifestation of traumatic symptoms. This phenomenon, referred to as "traumatic grief" in the literature, is associated with an increased risk of various psychiatric disorders, including major depression, anxiety disorders, and post-traumatic stress disorder. The death of a parent represents a profound loss for an adolescent, complicating their coping mechanisms and significantly impacting their psychological well-being. Parental loss alone is a significant risk factor for suicidal behavior in adolescents. When a parent's death is traumatic, it can further exacerbate this risk, leading to suicidal thoughts and behaviors by disrupting the normal grief process, even in adolescents who were previously mentally healthy. This article presents the diagnosis and treatment of a 17-year-old female who exhibited active suicidal thoughts and behaviors after her father was killed with a firearm. The objective of this case report is to explore the atypical grief symptoms that can follow traumatic losses during adolescence and to assess the effectiveness of holistic approaches that combine supportive psychotherapy with pharmacotherapy in treating such cases.

Keywords: Adolescent, traumatic grief, suicide

Ergende Travmatik Kayıp Sonrası İntihar Düşüncelerinin Eşlik Ettiği Yas: Olgu Sunumu

Olgu Sunumu

Süreç

Geliş: 10/06/2024
Kabul: 30/07/2024

ÖZET

Yas, sevilen birinin geri dönüşümsüz kaybı sonrasında yaşanan normal bir süreçtir. Acı deneyimler içeren bu süreç, ölen kişinin kimliği, ölüm şekli, kayıp yaşayan kişinin bireysel özellikleri, destek sistemleri gibi birçok etmenle ilişkili olarak farklı biçimlerde yaşantılanabilir. Kayıp şeklinin ani ve şiddet içeren şekilde olması, olağan yas sürecini etkileyerek bireyin kayıp sürecinde travmatik belirti ve bulgular yaşamasına neden olabilir. Literatürde "travmatik yas" olarak tanımlanan bu süreç, major depresyon, anksiyete bozuklukları, posttravmatik stres bozukluğu başta olmak üzere birçok psikiyatrik hastalık açısından risk teşkil etmektedir. Ebeveynin ölümü ergen için benliğin baş etmesini zorlayan ağır bir kayıptır. Tek başına ebeveyn kaybı, ergenlerde intihar davranışı için önemli risk faktörüdür. Ebeveynin travmatik kaybı, ruhsal açıdan sağlıklı bir ergende dahi olağan yas sürecini bozarak ebeveyn ölümü sonrası intihar düşünce ve davranışlarına neden olabilir. Bu yazıda, babasının ateşli silahla öldürülmesi sonrasında aktif intihar düşünce ve davranışlar ile çocuk ve ergen psikiyatri polikliniğine başvuran 17 yaşında bir kadın hastanın tanı ve tedavi süreci anlatılacaktır. Bu olgu sunumunun amacı, ergenlik dönemindeki travmatik kayıplar sonrası olağan dışı yas bulgularının gözden geçirilmesi ve tedavide farmakoterapinin yanı sıra destekleyici psikoterapinin uygulandığı bütüncül yaklaşımların etkinliğinin değerlendirilmesidir.

Anahtar Kelimeler: Ergen, travmatik yas, intihar

[a] *ozlemsireli@cumhuriyet.edu.tr* *0000-0002-5549-4154*
[b] *irem.yazarli16@gmail.com* *0009-0005-7784-9234*
[c] *elifabanoz_17@hotmail.com* *0000-0002-9214-4735*
[d] *aylauzun@cumhuriyet.edu.tr* *0000-0003-2274-3457*
[e] *dr.cansumercan@gmail.com* *0000-0001-9437-3024*
[f] *memocolak@gmail.com* *0000-0003-4880-3892*

How to Cite: Şireli Ö, Yazarlı İN, Abanoz E, Uzun Çiçek A, Mercan Işık C, Çolak M. Grief Accompanied by Suicidal Thoughts After Traumatic Loss in Adolescent: A Case Report, Cumhuriyet Medical Journal. 2024;46(3): 217-221

Introduction

Grief is the subjective reactions that an individual experience after irreversible loss(s). Freud (1917) defines grief as a reaction to the loss of a loved one or some abstract-ideal values such as country, freedom, ideal.[1] Although the reactions given after the loss include individual differences, most of the symptoms that occur in the normal mourning process show similar characteristics.[2-3]

Freud (1917) described the normal mourning process by drawing parallels to melancholia. After losing a loved one, individuals often experience a loss of interest in the external world, similar to melancholia, an inability to form new attachments as they feel nothing can replace the deceased, and a cessation of efforts related to the lost individual.[1] However, unlike melancholia, normal mourning does not involve a decline in self-esteem. Theorists posit that the normal mourning process involves several common phases, each marked by similar cognitive, emotional, and behavioral symptoms.[3-7] In the initial stages of grief, individuals typically experience shock and numbness, often accompanied by denial of the death.[3-5] While they recognize the loss, they may behave as if it did not occur. Anger is a prominent emotion during these early stages, often directed at the deceased or at others.[5]As grief progresses, individuals actively experience and process their emotions, leading to periods dominated by feelings of hopelessness and pessimism. These stages, known as the acceptance phase, involve reflecting on the relationship with the deceased and attempting to keep memories alive. In a healthy mourning process, these phases eventually lead to a reduction in preoccupation with the deceased, acceptance of the loss, increased interest in the external world, and adaptation.[6-7] The grief process can become complicated if an individual remains stuck in any stage, exhibits exaggerated grief reactions, or fails to complete the expected phases of mourning. [2,8-10]

Normal grief reactions do not necessitate treatment, as they are part of a natural and essential process. However, complicated grief is a clinical condition that requires both diagnosis and intervention. Pathological grief, encompassing abnormal grief reactions, is referred to by various terms in the literature, including “complicated grief,” “unresolved grief,” and “chronic grief,” due to its manifestation through diverse symptoms and presentations. In the DSM-5-TR, it is classified as "Prolonged Grief Disorder." According to the diagnostic criteria, the individual's exaggerated grief reactions, relative to cultural, religious norms, and age, must significantly impair work and social functioning, with symptoms persisting for at least one year in adults and six months in children after the loss.[11] Although not specifically defined in the DSM-5, the term “traumatic grief” is also used in the literature to describe pathological grief reactions.[12]

Traumatic grief is characterized by the symptoms and findings that emerge in individuals following the sudden, unexpected, and often horrifying or violent death of a loved one.[13] A key feature distinguishing traumatic grief from pathological or complicated grief is the traumatizing nature of the separation experience.[12] The simultaneous occurrence of trauma and loss significantly alters an individual's worldview and coping mechanisms, impeding the normal grief resolution process. This condition often involves an excessive preoccupation with the deceased and separation anxiety that severely affects daily functioning.[14]According to Parkers (2001), a diagnosis of traumatic grief requires symptoms affecting psychosocial functionality to persist for at least two months. Prigerson et al. (1997) further identify traumatic grief as a risk factor for both physical and mental disorders.[15] Research indicates that traumatic grief may precede major depression (MD) and post-traumatic stress disorder (PTSD) and is associated with a heightened risk of suicide.[16-17]

While normal grief typically does not necessitate treatment, complicated and/or traumatic grief is a clinical condition requiring therapeutic intervention. Identifying the clinical features of grief is crucial for both completing the grief resolution process and preventing the development of subsequent mental disorders. This article explores the diagnosis and treatment of a case involving traumatic loss, where the patient exhibited active suicidal thoughts and sought help at a child and adolescent psychiatry outpatient clinic following the loss. The objective of this case report is to examine the atypical grief symptoms following traumatic losses in adolescence and to evaluate the effectiveness of holistic approaches combining supportive psychotherapy with pharmacotherapy. Informed consent was obtained from the patient and her parents for the study.

Case Report

A 17-year-old female patient, referred to as Z, accompanied by her mother, presented to the child and adolescent psychiatry outpatient clinic with complaints of temper tantrums and suicidal ideation.

According to the history provided by the mother, Z's father and grandfather had been murdered two and a half months before. It was revealed that Z's father was killed by his brother with a firearm over a property dispute while working in the field. Upon learning of her father's death via phone, Z exhibited extreme distress, including screaming, throwing herself on the ground, and stomping. She was inconsolable for an extended period, marked by persistent crying and shouting. At the funeral the following day, Z fainted twice consecutively and was removed from the ceremony. Upon regaining consciousness, she screamed and cried, exclaiming, "No, my father cannot die," and lashed out at individuals offering condolences.

Z's mother reported that her daughter's intense anger persisted for days. From the onset, she reacted violently when her father's death was mentioned, shouting,

swearing, and crying at home. She blamed her grandmother and aunts for her father's death, frequently sending them abusive messages. Efforts by relatives, including her mother, to console her were met with denials and accusations, such as "My father is not dead" and "You are lying." Normally attentive to her diet and exercise, Z began binge eating, expressing fatalistic thoughts like, "I'm going to die anyway, leave me alone, I'll eat whatever I want." She frequently talked about death and left notes indicating her intent to commit suicide. Her sleep was significantly disturbed, with difficulty falling asleep and a preference for sleeping with her mother. Despite previously enjoying school, she now avoided it, could not attend classes, and spent hours crying in the counselor's office.

Continued temper tantrums and suicidal ideation led Z's mother to insist on psychological intervention. After two sessions, Z refused further therapy, claiming, "This is not helping me at all." Repeated mentions of her father resulted in emergency hospital visits due to trembling, shortness of breath, and fainting. A child and adolescent psychiatrist at an external center prescribed medication (dideral tb) for as-needed use, but Z refused to take it, citing its ineffectiveness.

Z's psychosocial, developmental, and family history revealed that she was born at term via normal delivery without complications during pregnancy and delivery. Her language, cognitive, motor, and communication development were age-appropriate. She began kindergarten at age 4 and maintained good relationships with teachers and peers throughout her schooling, consistently performing well academically. As a young child, Z was affectionate, outgoing, responsible, and exhibited normal premorbid characteristics. The mother, a 47-year-old anesthesia technician, voluntarily stopped working after Z's birth. She had a history of breast cancer diagnosed when Z was 7, which was successfully treated over two years, and currently had no medical illnesses. The father, who was 52 years old at the time of his death, was a science teacher with no medical illnesses. Z was an only child, and her mother had been her primary caregiver since birth. Both parents had a very close relationship with Z, with the father being particularly affectionate and attentive. There was no history of psychiatric illness in the family.

During the psychiatric examination, the patient, Z, displayed physical characteristics appropriate for her age but showed a decline in self-care. Her mood was depressed, and her affect was consistent with her mood. When discussing the "loss of her father," she became agitated, repeatedly stating, "no, he is not dead," accompanied by shortness of breath and tremors. She demonstrated normal intelligence and full orientation but was easily distractible. Her thought content was marked by excessive preoccupation with her father, thoughts about the meaninglessness of life, denial, persistent ruminations about her father's death, and pervasive suicidal ideation. The Beier Sentence Completion Test revealed expressions of longing and love for her father, as well as feelings of despair and pessimism about death being a form of salvation and life being meaningless. The Child Depression Inventory (CDI) score was 39, and the Beck Anxiety Inventory (BAI) score was 38.

The psychiatric evaluation concluded that Z experienced her father's sudden and violent death as a traumatic loss, leading to denial and complicating her grief process. Psychiatric interviews were planned to control the patient's active suicidal thoughts, to reduce depressive symptoms, to support the grief process regarding the loss of the father, and to strengthen the mother's attitude and behavioral skills, initially twice a week and then once a week. In order to control the patient's agitation and tantrums, medication was started as risperidone 1 mg/day and alprazolam 0.5 mg/day.

In the second evaluation, it was noted that Z's sleep patterns had normalized, and her temper tantrums had decreased. However, her active suicidal thoughts persisted, and she continued to make plans for suicide. She reported feeling temporarily better while at school with friends and when talking to her counselor. Z expressed anger towards her mother, perceiving her sadness and tears as if "something bad had happened," which intensified Z's distress. The mother, experiencing helplessness, burnout, and difficulty sleeping, was referred to a psychiatrist to support her grief process. The school counselor was informed of Z's clinical status and given recommendations for supportive strategies. An agreement was made with Z to ensure her safety, and sertraline 50 mg/day was added to her treatment regimen.

By the third and fourth interviews, Z's depressive symptoms had decreased, her attendance and participation in school had improved, and she began preparing for exams and spending time with a newly adopted cat. Z was more engaged in the interviews but avoided discussing her father. Her anxiety spiked in situations that reminded her of her father, causing tearfulness. She reported intrusive thoughts about her father's death, hypervigilance to loud noises, and episodes of palpitations and shortness of breath. Risperidone was replaced with aripiprazole 5 mg/day due to weight gain and increased appetite, and alprazolam was discontinued by the fourth week. Her medication was adjusted to sertraline 100 mg/day and aripiprazole 5 mg/day. The mother's condition improved, and she received further recommendations to support Z's grief process.

During psychiatric, interviews Z was encouraged to express her anger towards those she blamed for her father's death. Emotional catharsis techniques were employed to help her acknowledge her feelings of sadness and helplessness. Approximately three months into treatment (at the end of 10 treatment sessions), Z began to accept her father's death, marking the end of her denial phase. Supportive interventions were intensified during periods of acute sadness in the acceptance process. The relationship with her father was explored, and a memory formulation was developed. As Z's external support systems were strengthened, her father-related activities diminished. She started spending more time with friends

and engaging in sports activities, indicating a positive trajectory in her grief resolution.

Currently, Z's psychiatric follow-up and treatment has been ongoing for 10 months (20 treatment sessions) and psychiatric interviews are conducted every 4 weeks. Her anxiety symptoms have improved (BAI score: 6), suicidal thoughts have ended, and depressive symptoms have decreased considerably (CDI score: 17). Drug treatment continues as sertraline 50 mg/day and aripipirazole 2.5 mg/day with decreasing doses. During the interviews, Z has shown increased comfort in discussing the loss of her father and expressing her related emotions and thoughts, indicating a resolution of her conflict regarding the loss. Her social and academic functioning has greatly improved. She receives support in coping with her father's absence and in formulating future plans. Z has decided to pursue a career as a veterinarian and is actively preparing for university entrance exams.

Discussion

In this study, the traumatic grief process of an adolescent female who lost her father as a result of his murder with a firearm was examined.

The diagnosis of traumatic grief remains a contentious issue. It is crucial to accurately diagnose and treat traumatic grief as it often co-occurs with other mental disorders such as major depression (MD), anxiety disorders, and post-traumatic stress disorder (PTSD). This condition significantly impacts functionality and increases the risk of suicide.[15-17] According to Parkers' (2001) diagnostic criteria for traumatic grief, the diagnosis requires a “sudden, violent death of a relative and excessive preoccupation (longing, searching, yearning) with the deceased”.[14] Additionally, there must be at least four specific symptoms of traumatization, including a sense of meaninglessness about the future, emotional numbness, shock, difficulty accepting the death, feelings that life is empty, a sense that a part of oneself is missing, an inability to envision a meaningful life without the deceased, feelings that the world is falling apart, insecurity, beliefs of harming the deceased, and extreme pain and anger related to the death. Symptoms must persist for at least two months to affect psychosocial functioning. In this case, the patient experienced the sudden and violent death of her father by gunshot, exhibited excessive preoccupations such as longing and searching for her father, had difficulty accepting the death, experienced extreme anger and pain, believed she could not continue life without her father, made suicide plans, felt life had lost its meaning, and these symptoms persisted for 2.5 months following the loss.

Differentiating traumatic grief from MD and PTSD is challenging due to overlapping symptoms. Research indicates that the unexpected death of a close person is a significant risk factor for anxiety disorders, MD, and PTSD.[18] However, researchers emphasize that traumatic and/or complicated grief has distinct clinical features.[19] According to Prigerson and colleagues (2009), a key feature of traumatic grief not present in MD and PTSD is the feeling of longing.[20] While PTSD centers on overlearned fear, the primary reaction to loss in traumatic grief is longing. In traumatic and/or complicated grief, the negative mood is associated with longing for the deceased and memories, whereas in MD, there is a pervasive dysphoria with an inability to experience positive emotions, and no avoidance behaviors related to reminders of the loss are present.[21]In this case, the primary emotion was longing, and avoidance behaviors were related to situations and thoughts about the loss. The depressive mood was triggered by memories and thoughts about the father and fluctuated, with no anhedonia when distanced from reminders about the father, which allowed the exclusion of PTSD and MD diagnoses.

While normal grief does not require treatment, traumatic grief necessitates intervention as it is a precursor to other mental disorders, affects psychosocial functioning, and increases the risk of suicide.[22] In this case, the initial psychiatric evaluation revealed a high risk of suicide, significant anxiety, and depressive symptoms. With medication and grief-oriented, supportive psychotherapy, the patient's clinical symptoms improved, and her social and academic functioning enhanced. The therapy aimed to help the patient confront the loss, cope with the pain, accept the death while preserving positive memories, and make future plans. For children and adolescents to complete the grief process, it is essential to include their parents in the grief process through psychoeducation.[23] Z's mother was directed to receive specialized support to complete her grief process and was included in Z's treatment through psychoeducation.

Conclusion

This article examines the diagnosis and treatment of traumatic grief. While normal grief does not necessitate treatment, traumatic grief is a condition requiring both diagnosis and intervention. Traumatic grief is not currently included in diagnostic systems, and its diagnostic criteria remain unclear. Despite concerns that the medicalization of normal grief reactions might lead to stigmatization and unnecessary interventions, substantial evidence supports the benefits of clarifying diagnoses and implementing early interventions. In clinical evaluations of traumatic grief, identifying risk groups and adopting appropriate treatment approaches can prevent complications such as suicide. Early and targeted interventions enable patients to complete the grieving process and enhance their psychosocial functioning.

References

1. Freud S. *Mourning and melancholia*. The standard edition of the complete psychological works of Sigmund Freud,1917, 237-258.
2. Lindemann E. Symptomatology and management of acute grief. *Am J Psychiatry*. 1944; 101: 141-148.
3. Engel GL. Is grief a disease? A challenge for medical research. *Psychosom. Med*. 1960; 22:18-25.

4. Bowlby J, Parkes C. *Separation and Loss within the Family*. In Anthony EJ (ed.) *The Child in His Family*. New York: Whiley, 1970.
5. Volkan V. Normal and pathological grief reactions—a guide for the family physician. *Virginia Med*. 1966;93: 651–656.
6. Kübler-Ross E. *On Death and Dying*. Collier Books Macmillan Publishing, 1969.
7. Worden W. *Grief counselling and grief therapy: A handbook for the mental health practitioner.* New York, Brunner-Routlege, 2001.
8. Çevik A, Öncü B. Normal ve patolojik yas kliniğinin çok boyutlu incelenmesi ve tedavi ilkeleri. *Psikiyatri Bülteni*.1995;3(3):109-14. *(Turkish article).*
9. Lindemann E. Symptomatology and management of acute grief. *Pastoral Psychology*. 1963; 14(6): 8-18.
10. Horowitz MJ, Siegel B, Holen A, Bonanno GA, Milbrath C, Stinson CH. Diagnostic criteria for complicated grief disorder. *Am J Psychiatry*. 1997; 154: 904-910.
11. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, fifth edition, text revision*. Washington: American Psychiatric Association, 2022.
12. Prigerson HG, Shear MK, Jacobs SC, et al. Consensus criteria for Traumatic Grief: A preliminary empirical test. *Br J Psychiatry*. 1999;174: 67–73. https://doi.org/ 10.1192/bjp.174.1.67.
13. Jacobs S, Mazure C, Prigerson H. Diagnostic criteria for traumatic grief. *Death Stud*.2000; 24(3): 185–199. https://doi.org/10.1080/074811800200531.
14. Parkes CM. *A historical overview of the scientific study of bereavement*. In: Stroebe MS, Hansson RO, Stroebe W, Schut H (eds.). *Handbook for bereavement research: Consequences, coping, and care.* Washington, DC. APA, 2001.
15. Prigerson HG, Bierhals AJ, Kasl SV et al. Traumatic grief as a risk factor for mental and physical morbidity. *Am J Psychiatry*. 1997; 154: 616-623.
16. Hensley PL (2006). Treatment of bereavement-related depression and traumatic grief. *J Affect Disord*. 2006; 92(1): 117-124. https://doi.org/10.1016/j.jad.2005.12.041.
17. Melhem NM, Day N, Shear MK, Day R, Reynolds III CF, Brent D. Traumatic grief among adolescents exposed to a peer's suicide. *Am J Psychiatry*. 2004; 161(8): 1411-1416. https://doi.org/10.1176/appi.ajp.161.8.1411.
18. Keyes KM, Pratt C, Galea S, McLaughlin KA, Koenen KC, Shear MK. The burden of loss: Unexpected death of a loved one and psychiatric disorders across the life course in a national study. *Am J Psychiatry*. 2014;171(8); 864–871. https://doi.org/10.1176/appi.ajp.2014.13081132.
19. Simon NM, Shear MK, Reynolds CF et al. Commentary on evidence in support of a grief-related condition as a DSM diagnosis. *Depression and Anxiety*. 2020;37(1):9-16. https://doi.org/10.1002/da.22985.
20. Prigerson HG, Horowitz MJ, Jacobs SC et al. Prolonged grief disorder: Psychometric validation of criteria proposed for DSM-V and ICD-11. *PLoS Med*. 2009;6(8): e1000121. https://doi.org/10.1371/journal.pmed.1000121.
21. Baker AW, Keshaviah A, Horenstein A et al. The role of avoidance in complicated grief: A detailed examination of the grief-related avoidance questionnaire (GRAQ) in a large sample of individuals with complicated grief. *J Loss Trauma*. 2016; 21(6): 533–547. https://doi.org/10.1080/15325024. 2016.1157412.
22. Jacobs S. *Traumatic grief: Diagnosis, treatment, and prevention*. Routledge, 2016.
23. Mannarino AP, Cohen JA. Traumatic loss in children and adolescents. *J Child Adolesc Trauma*. 2011; *4*:22-33. https://doi.org/10.1080/19361521.2011.545048.

CMJ. 2024;46(3):222-225
DOI: 10.7197/cmj.1524426

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Pruritus: An Overlooked Symptom of Spinal Tumors

Dilara Bulut Gökten[1,a,*], Murat Gokten[2,b], Rıdvan Mercan[1,c]

[1] *Department of Rheumatology, Tekirdag Namik Kemal University, Faculty of Medicine, Tekirdağ, Turkiye*
[2] *Department of Neurosurgery, Tekirdag City Hospital, Tekirdağ, Turkiye*

**Corresponding author*

Case Report

History

Received: 29/07/2024
Accepted: 11/09/2024

ABSTRACT

A 65-year-old female patient, with no known diseases and no regular medication usage, presented with a complaint of itching that had been ongoing for the past two years. Itching initially started in approximately five cm areas on the bilateral below-knee flexor surfaces. The patient, whose complaints persisted, was referred to the internal medicine outpatient clinic by dermatology. On physical examination, erythematous excoriated papules were observed in the areas affected by itching. The patient's blood sugar, liver and kidney function tests, complete blood count, erythrocyte sedimentation rate, thyroid function tests, urinalysis, stool parasitology were all normal or negative. The patient reported a sensation of coldness in the same area, was referred to neurosurgery to investigate the etiology of possible neuropathic itching. The patient's spinal imaging, revealed a spinal mass. She underwent surgery performed by a neurosurgeon, during which the spinal mass was completely removed. She reported that her itching had completely disappeared post-operatively. The concept of itching as a variant of pain is not very new. Any damage occurring in the central nervous system or peripheral nervous system that affects the neurons responsible for transmitting and processing itch can lead to neuropathic itching. Focusing on spinal cord pathologies, any condition that damages the spinal cord may cause itching, depending on the level of damage. In cases of itching with dermatomal localization, where pain, hot or cold sensations, and paroxysmal itching are present, additional imaging methods or investigations for etiology should be performed.

Keywords: pruritus, neuropathic, spinal tumor, itching

Kaşıntı: Spinal Tümörlerin Gözden Kaçan Bir Belirtisi

Olgu Sunumu

Süreç

Geliş: 29/07/2024
Kabul: 11/09/2024

ÖZET

Bilinen herhangi bir hastalığı olmayan ve düzenli ilaç kullanımı olmayan 65 yaşında kadın hasta, iki yıldır devam eden kaşıntı şikayeti ile başvurdu. Kaşıntı başlangıçta iki taraflı diz altı fleksör yüzeylerinde yaklaşık beş santimetrelik alanda başlamıştı. Fizik muayenede kaşıntının olduğu bölgelerde eritematöz ekskoriye papüller görüldü. Hastanın kan şekeri, karaciğer ve böbrek fonksiyon testleri, tam kan sayımı, eritrosit sedimantasyon hızı, tiroid fonksiyon testleri, idrar tahlili, dışkı parazitolojisi normal idi. Aynı bölgede soğukluk hissi bildiren hasta, olası nöropatik kaşıntının etiyolojisinin araştırılması için beyin cerrahisine yönlendirildi. Hastanın görüntülemesinde spinal tümör saptandı. Beyin cerrahisi tarafından gerçekleştirilen ameliyatta omurga kitlesi çıkarıldı ve hasta, ameliyat sonrası kaşıntılarının tamamen kaybolduğunu bildirdi. Ağrının bir çeşidi olarak kaşıntı kavramı çok yeni olmamakla birlikte, merkezi veya periferik sinir sisteminde meydana gelen ve kaşıntının işlenmesinden sorumlu nöronları etkileyen herhangi bir hasar, nöropatik kaşıntıya yol açabilir. Omurilik patolojilerine odaklanacak olursak, spinal korda zarar veren herhangi bir durum, hasarın derecesine bağlı olarak kaşıntıya neden olabilir. Ağrı, sıcak veya soğuk hissi, paroksismal kaşıntının olduğu dermatomal kaşıntı durumlarında ek görüntüleme yöntemleri veya etiyolojiye yönelik araştırmalar yapılmalıdır.

Anahtar Kelimeler: pruritus, nöropatik, spinal tümör, kaşıntı

[a] *dilarabulutgokten@gmail.com* *0000-0002-9226-7532*
[b] *mrtgokten@gmail.com* *0000-0002-5659-4763*
[c] *mercanridvan@hotmail.com* *0000-0003-1537-2192*

How to Cite: Bulut Gökten D, Gökten M, Mercan R. Pruritus: An Overlooked Symptom of Spinal Tumors, Cumhuriyet Medical Journal. 2024;46(3): 222-225.

Introduction

In the 17th century, Samuel Hafenreffer defined itch as "an unpleasant sensation that arouses the desire or reflex to scratch." Chronic itch is often associated with pain due to its complex nature.[1]Severe itching is a rare symptom that can occur during the course of various diseases, and its mechanism and treatment are not yet fully understood. It can manifest directly in primary dermatological conditions such as dermatitis, psoriasis, drug reactions, and insect bites, or secondarily in systemic diseases such as cholestasis, uremia, malignancies, and infections.

The difference between chronic itching and pain lies in the perception they create. Pain induces avoidance, whereas itching is relieved by mechanical stimulation of the affected area.[2] Neuropathic pruritus is defined as a debilitating form of chronic itching, about which not much is known to date. This condition may develop as a result of various neurological events and is associated with damage to the somatosensory nervous system, accounting for approximately 10% of chronic itching cases.[3] Syringomyelia, transverse myelitis, radiculopathies, thoracic spine masses, brain tumors, strokes, and abscesses are among the conditions associated with neuropathic itching to date.[4] Other findings that suggest the itching seen in these conditions is of neurogenic origin include burning and stinging pains accompanied by persistent itching, sensations of wetness, electric shocks, numbness, tingling, and a severe cold sensation.[5]

Neuropathic pruritus, associated with spinal cord problems and known as the "ice-pack sign," has been described in the literature. Patients report relief by placing ice blocks on the affected areas. This condition is generally observed in the upper back, neck, and, rarely, the upper chest regions.[6]

In this case report, we will describe the journey of a patient who had been experiencing severe itching for two years. The patient was initially referred to the internal medicine outpatient clinic for the investigation of systemic diseases, eventually diagnosed with a spinal tumor, and subsequently underwent surgery.

This report aims to contribute to the literature by emphasizing the importance of a comprehensive and multidisciplinary approach in diagnosing atypical causes of pruritus. It highlights the diagnostic challenges and the need for healthcare providers to consider rare but serious underlying conditions, such as spinal tumors, in patients with unexplained chronic itching. Additionally, it underscores the role of thorough clinical evaluation and appropriate use of diagnostic imaging in uncovering unexpected etiologies that may not be immediately apparent in routine clinical practice.

Case Report

A 65-year-old female patient, with no known diseases and no regular medication usage, presented to the dermatology clinic with a complaint of itching that had been ongoing for the past two years and was gradually increasing in severity. The itching initially started in approximately five cm areas on the bilateral below-knee flexor surfaces and then spread to the surrounding areas. Intense scratching led to the development of excoriated papules in the affected regions. Topical corticosteroids and antihistamines were prescribed in the dermatology clinic, but these treatments elicited no response. The patient, who had no symptoms other than itching, did not have any notable features in her family history.

The patient, whose complaints persisted, was referred to the internal medicine outpatient clinic by dermatology for the investigation of possible systemic diseases. On physical examination, erythematous excoriated papules were observed in the areas affected by itching, along with post-inflammatory hypopigmented and hyperpigmented areas secondary to scratching. (see Figure 1) The patient's fasting blood sugar, aspartate aminotransferase, alanine aminotransferase, creatinine, alkaline phosphatase, complete blood count, erythrocyte sedimentation rate, thyroid function tests, urinalysis, stool parasitology, and tests for anti-HIV, HBs-Ag, anti-HBs, anti-HBc, and anti-HCV were all normal or negative. The dermatologist was contacted again, and a swab was taken from the excoriated papules for bacterial and viral cultures, but no growth was observed. A punch biopsy sample taken during follow-up showed mild hyperkeratosis and superficial keratinocyte necrosis. The pathology report indicated that the sample was compatible with excoriated dermatitis. The patient, who was no longer under follow-up by dermatology, reported a sensation of coldness and occasional electric shocks in the same area, as well as lower back pain that worsened, particularly when standing, in addition to the itching. Given these additional symptoms, the patient was referred to neurosurgery to investigate the etiology of possible neuropathic itching.

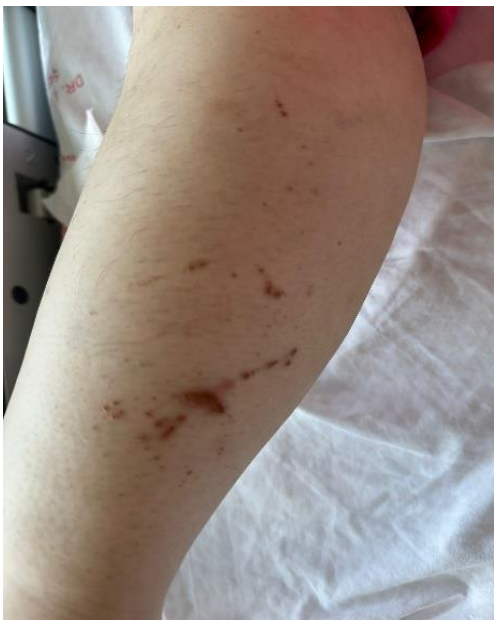

Figure 1.Erythematous excoriated papules secondary to itching.

The patient's spinal MRI, taken at the neurosurgery outpatient clinic, revealed a spinal mass (see Figure 2). The patient underwent surgery performed by a neurosurgeon, during which the spinal mass was completely removed without complications. Pathological analysis confirmed the diagnosis of meningioma. One month after the surgery, the patient returned to the internal medicine clinic for a follow-up visit. She reported that her itching and lower back pain had completely disappeared post-operatively.

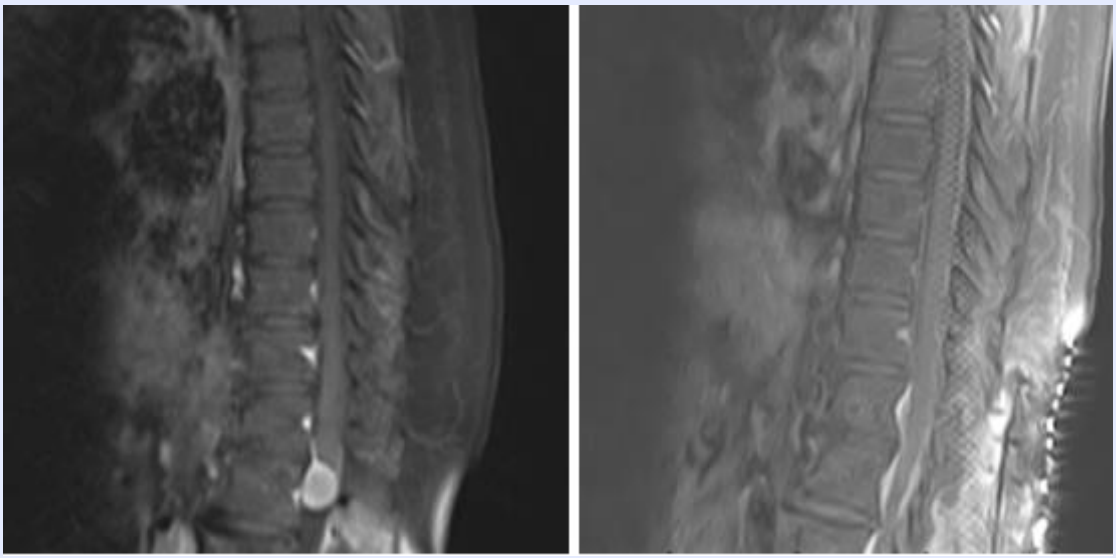

Figure 2. Preoperative and postoperative images of spinal tumor of patient.

Discussion

Explanations regarding the neural basis of itching and pain are not yet clear in the literature. It is known that the neural pathways for itch involve an itch-specific labeled line. These pathways include mechanosensitive C fibers and myelinated polymodal C fibers. Centers related to itch in the central nervous system include the somatosensory cortex, accessory somatosensory cortex, and insula.[7] The concept of itching as a variant of pain is not very new. Any damage occurring in the central nervous system (CNS) or peripheral nervous system (PNS) that affects the neurons responsible for transmitting and processing itch can lead to neuropathic itching.[8]

In the literature, causes of neuropathic itching related to PNS involvement include herpes zoster, small fiber neuropathy, notalgia paresthetica, neuropathic anogenital itching, post-burn itching, and ganglioneuropathies. Spinal pathologies such as transverse myelitis, cavernous hemangiomas, and ependymomas are also noted. Additionally, CNS-related causes include uremic itching, neuropathic itching that develops after cerebrovascular accidents (CVA), brain abscesses, aneurysms, and various brain tumors.[9]

Among the cases of neuropathic pruritus reported so far, brachioradial pruritus has been observed to predominate. Heyl was the first to describe brachioradial pruritus in the literature, examining 14 cases and associating this itching with cervical nerve compression.[10] The first case in which brachioradial pruritus was associated with a spinal tumor was described by Kavak et al. in our country. In this case, the patient's main complaint was defined as neck pain and a burning sensation accompanied by itching in the affected area. An MRI taken following the report of burning sensations revealed a spinal mass.[11] Similarly, in our case, the patient experienced an electric shock sensation and lower back pain in addition to the itching. These complaints led us to suspect neuropathic itching, and spinal imaging revealed a mass. The neurosurgeon also attributed the lower back pain to dural irritation and extradural nerve root compression caused by the tumor's mass effect.

Focusing on spinal cord pathologies, any condition that damages the spinal cord may cause itching, depending on the level of damage. For instance, an intramedullary spinal tumor was detected in a 19-month-old child who complained of localized itching in the neck, shoulder, and arm, without any other complaints or diseases.[12] In another case, paroxysmal itching resulting from Chiari malformation and syringomyelia was reported in a 16-year-old woman.[13] In cavernous hemangiomas, hemosiderin-laden macrophages can cause ectopic transmission in adjacent nerves, leading to severe itching in these lesions.[2] In cases of itching with dermatomal

localization, where pain, hot or cold sensations, and paroxysmal itching are present, additional imaging methods or investigations for etiology should be performed. Gliosis, tumor-induced spinal cord compression, and damage to the skin may be underlying causes of itching.

There are no specific guideline recommendations for the treatment of neuropathic itch. Diagnosis and treatment can be quite challenging for clinicians, and management should be multidisciplinary. Both pharmacological and non-pharmacological treatment methods have been suggested. Pharmacological treatments include topical glucocorticosteroids, calcineurin inhibitors, and anesthetics. Systemic treatments include anticonvulsants, opioids, antihistamines, and serotonin receptor blockers.[12] In our case, since the primary cause was a spinal mass, the patient's complaints completely disappeared after surgery.

Conclusion

Neuropathic itch is a subtle and debilitating cause of systemic itching, often unaccompanied by specific skin lesions. Many cases of neuropathic itch go undiagnosed and unreported. Clinical suspicion is crucial for diagnosis, and radiological or functional investigations may be necessary in selected cases.

List of Abbreviations

MRI: magnetic resonance imaging, CNS: central nervous system, PNS: peripheral nervous system, CVA: cerebrovascular accidents

Declarations

Ethics approval and consent to participate: A consent has been taken from subject regarding writing of this case report.

Competing interests: none

Funding: none

Authors' contributions: DBG: data collection, writing, idea; MG: data collection, surgery; RM: idea, supervision

References

1. Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. The neurobiology of itch. Nat Rev Neurosci. 2006;7(7):535-47.
2. Dey DD, Landrum O, Oaklander AL. Central neuropathic itch from spinal-cord cavernous hemangioma: a human case, a possible animal model, and hypotheses about pathogenesis. Pain. 2005;113(1-2):233-7.
3. Meixiong J, Dong X, Weng H-J. Neuropathic Itch. Cells. 2020;9(10):2263.
4. Oaklander AL. Neuropathic itch. Semin Cutan Med Surg. 2011;30(2):87-92.
5. Goodkin R, Wingard E, Bernhard JD. Brachioradial pruritus: Cervical spine disease and neurogenic/neurogenic pruritus. Journal of the American Academy of Dermatology. 2003;48(4):521-4.
6. Bernhard JD, Bordeaux JS. Medical pearl: the ice-pack sign in brachioradial pruritus. J Am Acad Dermatol. 2005;52(6):1073.
7. Ikoma A, Cevikbas F, Kempkes C, Steinhoff M. Anatomy and neurophysiology of pruritus. Semin Cutan Med Surg. 2011;30(2):64-70.
8. Ju T, Yosipovitch G. Neuropathic pruritus associated with brain disorders. Itch. 2020;5(3):e37.
9. Misery L. Neuropathic Pruritus Secondary to Brain and Spinal Cord Tumors. In: Misery L, Ständer S, editors. Pruritus. Cham: Springer International Publishing; 2016. p. 215-7.
10. Heyl T. Brachioradial Pruritus. Archives of Dermatology. 1983;119(2):115-6.
11. Kavak A, Dosoglu M. Can a spinal cord tumor cause brachioradial pruritus? Journal of the American Academy of Dermatology. 2002;46(3):437-40.
12. Poddar S, Mondal H, Podder I. Aetiology, pathogenesis and management of neuropathic itch: A narrative review with recent updates. Indian J Dermatol Venereol Leprol. 2023;90(1):5-18.
13. Morimoto T, Yabuki S, Kugimoto Y, Asami A. Paroxysmal Itching in Syringomyelia with Chiari Malformation (Type I): A Case Report. Orthopedics & Traumatology. 2008;57(4):647-51.

CMJ. 2023; 45(1): 81-86
DOI: 10.7197/cmj.1137978

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Effect of Coronavirus Disease 2019 on Fluorine-18 fluorodeoxyglucose Uptake of Endocrine Organs

Ogün Bülbül[1,a,*] , Sibel Göksel[1,b], Demet Nak[1,c]

[1] *Department of Nuclear Medicine, Recep Tayyip Erdogan University, Faculty of Medicine, Rize, Turkiye*

**Corresponding author*

Research Article

History

Received: 29/06/2022
Accepted: 13/02/2023

ABSTRACT

Objective: The new type of Coronavirus (SARS-CoV-2) damages cells by using the angiotensin converting enzyme-2 (ACE2) as a receptor to adhere and go through the cell membrane. It is known that some of the endocrine organs express ACE2 and these organs are potential targets for Coronavirus 2019 disease (Covid-19). This study aimed to investigate the effect of Covid-19 on Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) uptake of endocrine system organs.

Methods: Sixteen patients who had Covid-19 underwent ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) later, 77 patients who did not have Covid-19 underwent ^{18}F-FDG PET/CT between March 2020-October 2021 were included. SUVmax and SUVmean of the pituitary, thyroid, adrenal gland, pancreas, and testis measured from the PET/CT of the patients who had Covid-19 were compared with SUVmax, and SUVmean measured from the same organs in PET/CT images of the patients who had not Covid-19.

Results: Pancreatic mean SUVmax was significantly higher in patients who had Covid-19 than in patients who did not (p= 0.035). Pancreatic mean SUVmean was slightly higher in patients who had Covid-19 than in patients who did not, but this difference was not statistically significant (p= 0.072). No significant difference was found between the SUVmax and SUVmean values of the pituitary gland, thyroid gland, adrenal gland, and testis in patients who had Covid-19 and did not have.

Conclusion: It was thought that the pancreas might have been affected in the course of Covid-19 due to the higher mean SUVmean values of the pancreas in patients who had Covid- 19.

Keywords: Covid-19, endocrine system, FDG, PET/CT

Covid-19 Enfeksiyonu Sonrası Endokrin Organların F-18 Florodeoksiglukoz Tutulumundaki Değişiklikler

Araştırma Makalesi

Süreç

Geliş: 29/06/2022
Kabul: 13/02/2023

ÖZET

Amaç: Yeni tip koronavirüs (SARS-CoV-2) anjiyotension dönüştürücü enzim-2'yi (ACE2)reseptör olarak kullanarak hücreye tutunur, hücre membranı geçer ve hücreye zarar verir. Bazı endokrin organların ACE2 eksprese ettiği bilinmektedir ve bu organlar Covid-19 için hedef olma potansiyeline sahiptir. Bu çalışmada Covid-19'un endokrin sistem organlarındaki F-18 florodeoksiglukoz (^{18}F-FDG) tutulumuna etkisini araştırmak amaçlanmıştır.

Yöntem: Mart 2020-Ekim 2021 arasında Covid-19 geçirip sonrasında ^{18}F-FDG PET/BT çekimi yapılan 16 hasta ile Covid-19 geçirmeyen 77 hastanın verileri analiz edildi. Covid-19 geçiren ve geçirmeyen hastaların hipofiz bezi, tiroid bezi, adrenal bez, pankreas ve testislerinden ölçülen SUVmax ve SUVmean değerleri karşılaştırıldı.

Bulgular: Covid-19 geçiren hastaların ortalama pankreas SUVmax değeri Covid-19 geçirmeyen hastalarınkinden daha yüksekti (p= 0.032). Covid-19 geçiren hastaların ortalama pankreas SUVmean değeri Covid-19 geçirmeyen hastalarınkinden daha yüksekti ancak bu fark istatistiksel olarak anlamlı düzeyde değildi (p= 0.072). Covid-19 geçiren ve geçirmeyen hastaların hipofiz bezi, tiroid bezi, sürrenal bez ve testislerinden ölçülen SUVmax ve SUVmean değerleri arasında anlamlı düzeyde farklılık saptanmadı.

Sonuç: Covid-19 geçiren hastalarda ortalama pankreas SUVmean değerinin daha yüksek olması nedeniyle pankreasın Covid-19 sürecinde etkilenmiş olabileceği düşünüldü.

Anahtar Kelimeler: Covid-19, endokrin sistem, FDG, PET/BT

[a] *ogunbulbulbulbulogun38@gmail.com* *0000-0002-4154-8801*
[b] *sibelkandemirgoksel@gmail.com* *0000-0003-2584-1386*
[c] *demetnak139133@gmail.com* *0000-0002-9756-7788*

How to Cite: Bülbül O, Göksel S, Nak D. Effect of Coronavirus Disease 2019 on Fluorine-18 fluorodeoxyglucose Uptake of Endocrine Organs. Cumhuriyet Medical Journal. 2023;45(1): 81-86.

Introduction

The Coronavirus 2019 disease (Covid-19), which emerged in Wuhan, China, in December 2019, spread all over the world in a short time, and the World Health Organization (WHO) declared Covid 19 a pandemic on March 11, 2020. The new type of coronavirus (SARS-CoV-2), the causative agent of Covid-19 (1), has mutated, revealing new, more infectious variants (Alpha, Beta, Gamma, Delta, and Omicron, etc.) (2-4).

Covid-19 usually manifests itself with mild upper respiratory tract infections or is asymptomatic in people with a robust immune system and no severe comorbidities (5). The most frequently affected organ system in severe cases is the pulmonary system (5,6). However, many extrapulmonary manifestations have been reported (5). Hyperthyroidism and hypothyroidism are among the best-known effects of Covid-19 on the endocrine system (7,8). The effect of Covid-19 on other endocrine organs other than the thyroid gland has not yet been clarified. It was revealed in the severe acute respiratory syndrome (SARS) epidemic in 2003 that the coronavirus could affect the endocrine system (9). It is known that Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) has a high uptake in inflammatory pathologies. Therefore, in the presence of inflammation in endocrine organs, ^{18}F-FDG uptake of these organs may increase. This study aims to investigate the effect of Covid-19 on ^{18}F-FDG uptake/glucose metabolism of endocrine system organs.

Material and Method

All patients who underwent ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) in our hospital and applied to the Covid-19 pandemic outpatient clinic between March 2020 and October 2021 were identified. Among these patients, those who did not have a real-time polymerase chain reaction (RT-PCR) test were excluded. Finally, 93 patients who underwent ^{18}F-FDG PET/CT in our clinic and whose RT-PCR was studied from nasal and throat swabs for Covid-19 for any reason were included in the study. During this period, PET/CT was not performed on patients with symptoms such as fever, cough, sore throat that may be associated with Covid-19, unless the RT-PCR result was negative. Maximum standardized uptake value (SUVmax) and mean standardized uptake value (SUVmean) (threshold of 40% of SUVmax) were calculated by placing a circular region of interest (ROI) in the localization of the pituitary fossa, thyroid gland, pancreas, adrenal gland and testes of male patients on PET/CT fusion images (Figure 1). Patients with ^{18}F-FDG uptake suggest primary malignancy associated with the aforementioned endocrine organs or metastasis in these organs were excluded. Since four of 16 patients who had Covid-19 had pancreatic cancer, SUV measurements were not made from the pancreas of these patients. Since the hypothalamus, pineal gland, parathyroid glands, and ovaries could not be distinguished in ^{18}F-FDG PET/CT, SUV values of these organs could not be calculated.

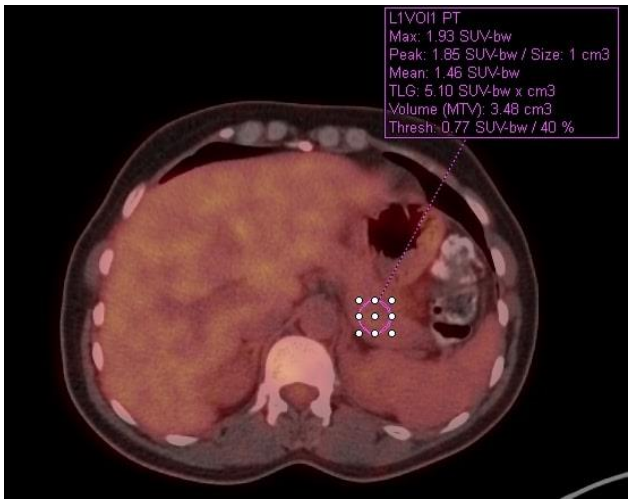

Figure 1. Calculation of the SUVmax and SUVmean from the endocrine organs using circular region of interest

^{18}F-FDG was injected intravenously at a 3.7 MBq/kg (0.1 mCi/kg) dose to patients with blood glucose levels below 200 mg/dl after fasting for at least 4-6 hours. Before PET/CT, the patients rested for 60 minutes in a single room. PET/CT images were obtained from the vertex to the upper thigh (Siemens Biograph mCT 20). First, low-dose CT images were acquired with 120 kVp, 50 mAs, iodine-containing oral contrast, and free-breathing protocol. Then, PET images were obtained with a 2 min/bed position in three-dimensional mode. A nuclear medicine physician with five years of oncological PET/CT experience evaluated images at the Siemens syngo.via workstation.

SUVmax and SUVmean values of the pituitary, thyroid, adrenal gland, pancreas, and testis measured from the first PET/CT performed in the post-Covid-19 period of patients had Covid-19 were compared with SUVmax, and SUVmean values measured from the areas mentioned earlier in PET/CT images performed during the staging phase of the diseases of the patients who had not Covid-19. The independent sample t-test was used to make this comparison. Only eight patients with Covid-19 had PET/CT images before Covid-19. The SUVmax and SUVmean values obtained from the previously mentioned endocrine organs from these patients' pre- and post-Covid-19 images were compared. The Wilcoxon test was used to make this comparison. In all statistical tests, $p < 0.05$ was considered statistically significant. All Statistical analyzes were performed with SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Post-infective PET/CT imaging of patients who had Covid-19 was performed median of 130 (45-284) days after nasal and throat swab RT-PCR results. Detailed demographic information is in Table 1.

Only six of 16 patients who had Covid-19 did not receive oncological treatment at the time of post-Covid-19 PET/CT, and imaging was performed for cancer staging in these patients; In the other ten patients, the imaging purpose was to evaluate treatment response. Pancreatic mean SUVmax value was slightly higher in patients who had Covid-19 (2.1 ± 0.3) than in patients who did not (1.9 ± 0.4) (p= 0.035) (Table 2). In addition, pancreatic mean SUVmean value was slightly higher in patients who had Covid-19 (1.6 ± 0.3) than in patients who did not (1.4 ± 0.3), but this difference was not statistically significant (p= 0.072). SUVmax and SUVmean values of the pituitary gland, thyroid gland, adrenal gland, and testis did not differ between the patients who had Covid-19 and who did not (Table 2).

Table 1. Patient characteristics

	Patients infected by Covid-19	**Patients not infected by Covid-19**	P value
Gender			
Female	6	22	0.479
Male	10	55	
Primary malignancy			
	Lung, 5 (31%)	Lung, 24 (31%)	
	Pancreas, 4 (25)	Unknown primary, 9 (11)	
	Breast, 3 (19)	Larynx, 6 (7)	
	Others, 4 (25)	Others, 39 (51)	
Age (years), Mean ± SD	65 ± 11	66 ± 13	0.737
Blood glucose level during FDG injection (mg/dL), Mean ± SD	104 ± 15	102 ± 18	0.624
Dose of FDG (MBq), Mean ± SD	274 ± 85 (7.4 ± 2.3 mCi)	285 ± 48 (7.7 ± 1.3 mCi)	0.416

Covid-19: Coronavirus disease 2019, FDG: Fluorodeoxyglucose

Table 2. SUVmax and SUVmean values of the endocrine organs

	Patients infected by Covid-19 (n=16)	**Patients not infected by Covid-19 (n=77)**	**p-value**
	Mean ± SD	Mean ± SD	
Pituitary gland			
SUVmax	2.6 ± 0.6	2.8 ± 0.7	0.506
SUVmean	1.8 ± 0.4	2.0 ± 0.5	0.361
Thyroid gland			
SUVmax	2.2 ± 0.8	2.0 ± 0.5	0.228
SUVmean	1.6 ± 0.7	1.6 ± 0.4	0.964
***Pancreas**			
SUVmax	2.1 ± 0.3	1.9 ± 0.4	**0.035**
SUVmean	1.6 ± 0.3	1.4 ± 0.3	0.072
Adrenal gland			
SUVmax	2.1 ± 0.4	2.3 ± 0.6	0.175
SUVmean	1.6 ± 0.4	1.6 ± 0.4	0.948
Testicle			
SUVmax	2.9 ± 0.8	3.2 ± 0.6	0.598
SUVmean	1.9 ± 0.6	2.5 ± 0.8	0.207

SUV: standardized uptake value, Covid-19: Coronavirus disease 2019, SD: Standard deviation

***** n=12 for postinfected group, because 4 patients had focal F-18 FDG uptake in pancreas due to pancreatic cancer.

No significant difference was found between the SUVmax and SUVmean values of the pituitary gland, thyroid gland, adrenal gland, pancreas, and testis before and after Covid-19 in 8 patients who had Covid-19 and had PET/CT examination both before and after infection (Table 3).

Table 3. SUVmax and SUVmean values of the endocrine organs befere and after Covid-19 (n=8)

	Before Covid-19		After Covid-19		p-value
	Mean ± SD	Median (min - max)	Mean ± SD	Median (min-max)	
Pituitary gland					
SUVmax	2.7 ± 0.6	2.7 (1.9 – 3.4)	2.6 ± 0.5	2.3 (2.0 – 3.2)	0.596
SUVmean	1.9 ± 0.4	1.9 (1.5 – 2.6)	1.8 ± 0.3	1.6 (1.5 – 2.2)	0.129
Thyroid gland					
SUVmax	1.8 ± 0.4	2.0 (1.2 – 2.4)	2.1 ± 0.6	2.3 (1.2 – 2.6)	0.416
SUVmean	1.6 ± 0.3	1.6 (1.1 – 1.9)	1.6 ± 0.4	1.7 (1.1 – 2.0)	0.414
Pancreas					
SUVmax	1.9 ± 0.5	1.9 (1.4 – 2.7)	2.1 ± 0.3	2.1 (1.6 – 2.5)	0.115
SUVmean	1.0 ± 0.6	1.2 (0.9 – 1.7)	1.6 ± 0.3	1.5 (1.3 – 2.1)	0.114
Adrenal gland					
SUVmax	2.1 ± 0.5	2.1 (1.4 – 2.8)	2.2 ± 0.4	2.2 (1.7 – 2.7)	0.734
SUVmean	1.7 ± 0.5	1.6 (1.2 – 2.5)	1.8 ± 0.4	1.7 (1.1 – 2.3)	1.000
Testicle					
SUVmax	3.5 ± 0.8	3.7 (2.4 – 4.3)	2.9 ± 0.7	3.0 (2.1 – 3.4)	0.068
SUVmean	2.3 ± 0.4	2.4 (1.8 – 2.7)	1.9 ± 0.4	2.0 (1.5 – 2.3)	0.144

SUV: standardized uptake value, Covid-19: Coronavirus disease 2019

Discussion

In the light of the information obtained from the SARS epidemic, the endocrine system was thought to be a potential target for SARS-CoV-2 (9). Findings of central adrenal insufficiency in some patients after SARS epidemic, thyroid follicular epithelial damage and decrease in TSH in some patients, presence of SARS-CoV in pancreatic tissue, increase in prolactin, luteinizing hormone and follicle-stimulating hormone, decrease in estrogen and progesterone after SARS in women, the demonstration of microscopic damage to the testicular tissue of patients who died from SARS and the high angiotensin converting enzyme-2 (ACE2) expression in the testis were the basis of this thought (9). Clinically, it has been shown in some retrospective studies that Covid-19 can cause endocrinological problems, especially thyroid dysfunction (10,11).

Considering this information, we examined whether there were changes in the glucose metabolisms of the endocrine system organs after Covid-19. Pancreatic SUVmax values of patients who had Covid-19 were slightly higher than those who did not (p= 0.035). Among these patients, SUV measurement was not performed in the pancreas of 4 patients with primary pancreatic cancer. None of the remaining 12 patients had focal or diffuse pathological ^{18}F-FDG uptake in their pancreas. Five of these patients had lung cancer, but none had a history of immunotherapy that could cause pancreatitis. Wang et al. reported elevated pancreatic enzymes in 17% of 52 patients hospitalized for Covid-19 pneumonia (12). Bruno et al. showed that 8.5% of the 70 patients hospitalized for Covid-19 who had pneumonia had elevated pancreatic enzymes (13). In the two studies mentioned, the patients had no acute pancreatitis clinically. Since the patients in our study applied to the hospital for cancer staging or oncological treatment response evaluation, amylase and lipase laboratory test results were not available in the routine clinical evaluation of the patients. Therefore, the relationship between pancreatic ^{18}F-FDG uptake after Covid-19 and pancreatic enzymes could not be examined. The expression of ACE2 messenger RNA in pancreatic tissue (14,15) and the presence of case reports about Covid-19-associated acute pancreatitis (16-18) suggest that the pancreas may be vulnerable to the attack of SARS-CoV-2. We think that the mild SUVmax elevation, which we detected after Covid-19 in the pancreas, may be related to mild inflammation.

Lania et al. detected thyrotoxicosis in 20.2% of the 287 Covid-19 patients who were hospitalized (10). They found overt thyrotoxicosis in 53.4% of the patients with thyrotoxicosis. They reported an inverse correlation between thyroid stimulatin hormone (TSH) and interleukin 6 (rho= −0.41; p < 0.001). The same study reported that 5.2% of the patients had hypothyroidism. Our study showed no difference between SUVmax and SUVmean of the thyroid glands of patients who had and did not have Covid-19. There was no difference between pre-Covid-19 and post-Covid-19 SUVmax and SUVmean of the thyroid glands of the eight patients who underwent PET/CT before and after Covid-19. The patients' history of hospitalization due to Covid-19, serum TSH, free T3 and free T4 hormones, and thyroid antibody levels during the PET/CT were unknown. The small number of patients in this study and perhaps the fact that most of the patients had mild Covid-19 may be the reason why there was no diffuse increase in ^{18}F-FDG uptake in the thyroid gland. Also, Albano et al. reported that the most common pathology in patients with diffuse ^{18}F-FDG uptake in the thyroid gland is thyroiditis (19). However, not all patients

with thyroiditis may show diffuse ^{18}F-FDG uptake. For this reason, we think that the presence of thyroiditis cannot be definitively excluded in the patients in our study who had Covid-19.

In their review, Frara et al. reported that cases of pituitary apoplexy, syndrome of inappropriate antidiuretic hormone, and hypophysitis associated with Covid-19 have not yet been proven (20). Similarly, Covid-19-related adrenal gland and testicular inflammation have not been proven. In our study, there was no difference between the SUVmax and SUVmean values of the pituitary, adrenal gland, and testis in patients who had and did not have Covid-19.

Study Limitations

Our study has some limitations. The small number of patients who had and did not have Covid-19 is is an important factor that may affect the results of statistical analysis. The high number of patients who had PET/CT scans both before and after Covid-19 could have enabled us to more accurately evaluate the effect of Covid-19 on ^{18}F-FDG uptake of endocrine organs. Because the laboratory test results associated with organs whose SUV values were measured were absent in our study, we could not evaluate the glucose uptake of these organs parallel to test results such as thyroid function tests, amylase, and lipase. In addition, among the patients included in our study, asymptomatic carriers who did not have a PCR test and the presence of patients with false negative or false positive PCR test results cannot be definitively excluded.

Conclusion

The pancreas, like many organs, is a possible target for SARS-CoV2 due to its expression of ACE2 mRNA. In our study, the slightly higher ^{18}F-FDG uptake in pancreas in the patients who had Covid-19 compared to those who did not have the disease suggested that the pancreas may have been affected in the course of Covid-19.

Ethics Committee Approval: This study was approved by Ethics Committee and conducted according to the principles of the Declaration of Helsinki (Decision date: 14.12.2021, approval number: 2021/213).

Informed Consent: The ethical committee waived the requirement for informed consent as the study was retrospective.

Authors' Contributions: Concept- O.B. ; Design- O.B., S.G., D.N. ; Supervision: O.B. ; Data Collection and Processing: O.B., S.G., D.N. ; Analysis and/or Interpretation: O.B, S.G., D.N. ; Literature Search: O.B., ; Writing: O.B.

Conflicting of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Sanyal S. How SARS-CoV-2 (COVID-19) spreads within infected hosts - what we know so far. Emerg Top Life Sci. 2020;4:371-8.
2. Wang X, Powell CA. How to translate the knowledge of COVID-19 into the prevention of Omicron variants. Clin Transl Med. 2021;11:e680.
3. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, Planchais C, Porrot F, Robillard N, Puech J, Prot M, Gallais F, Gantner P, Velay A, Le Guen J, Kassis-Chikhani N, Edriss D, Belec L, Seve A, Courtellemont L, Péré H, Hocqueloux L, Fafi-Kremer S, Prazuck T, Mouquet H, Bruel T, Simon-Lorière E, Rey FA, Schwartz O. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature. 2021;596:276-280.
4. Abdool Karim SS, de Oliveira T. New SARS-CoV-2 Variants - Clinical, Public Health, and Vaccine Implications. N Engl J Med. 2021;384:1866-68.
5. Johnson KD, Harris C, Cain JK, Hummer C, Goyal H, Perisetti A. Pulmonary and Extra-Pulmonary Clinical Manifestations of COVID-19. Front Med (Lausanne). 2020;7:526.
6. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med. 2020;35:1545-49.
7. Lisco G, De Tullio A, Jirillo E, Giagulli VA, De Pergola G, Guastamacchia E, Triggiani V. Thyroid and COVID-19: a review on pathophysiological, clinical and organizational aspects. J Endocrinol Invest. 2021;44:1801-14.
8. Speer G, Somogyi P. Thyroid complications of sars and coronavirus disease 2019 (Covid-19). Endocr J. 2021;68:129–36.
9. Mongioì LM, Barbagallo F, Condorelli RA, Cannarella R, Aversa A, La Vignera S, Calogero AE. Possible long-term endocrine-metabolic complications in COVID-19: lesson from the SARS model. Endocrine. 2020;68:467–70.
10. Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G. Thyrotoxicosis in patients with COVID-19: The THYRCOV study. Eur J Endocrinol. 2020;183:381–7.
11. Scappaticcio L, Pitoia F, Esposito K, Piccardo A, Trimboli P. Impact of COVID-19 on the thyroid gland: an update. Rev Endocr Metab Disord. 2021;22:803–15.
12. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. Gastroenterology. 2020;159:367–70.
13. Bruno G, Fabrizio C, Santoro CR, Buccoliero GB. Pancreatic injury in the course of coronavirus disease 2019: A not-so-rare occurrence. J Med Virol. 2021;93:74–5.
14. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol. 2020;18:2128-30.
15. Kusmartseva I, Wu W, Syed F, Van Der Heide V, Jorgensen M, Joseph P, Tang X, Candelario-Jalil E, Yang C, Nick H, Harbert JL, Posgai AL, Paulsen JD, Lloyd R, Cechin S, Pugliese A, Campbell-Thompson M, Vander

Heide RS, Evans-Molina C, Homann D, Atkinson MA. Expression of SARS-CoV-2 Entry Factors in the Pancreas of Normal Organ Donors and Individuals with COVID-19. Cell Metab. 2020;32:1041-51.
16. Hadi A, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, Gluud LL. Coronavirus Disease-19 (COVID-19) associated with severe acute pancreatitis: Case report on three family members. Pancreatology. 2020;20:665-7.
17. Eldaly AS, Fath AR, Mashaly SM, Elhadi M. Acute pancreatitis associated with severe acute respiratory syndrome coronavirus-2 infection: a case report and review of the literature. J Med Case Rep. 2021;15: 1–12.
18. Aloysius MM, Thatti A, Gupta A, Sharma N, Bansal P, Goyal H. COVID-19 presenting as acute pancreatitis. Pancreatology. 2020;20:1026-7.
19. Albano D, Treglia G, Giovanella L, Giubbini R, Bertagna F. Detection of thyroiditis on PET/CT imaging: a systematic review. Hormones. 2020;19:341–9.
20. Frara S, Allora A, Castellino L, di Filippo L, Loli P, Giustina A. COVID-19 and the pituitary. Pituitary. 2021;24:465–81.

This article has an erratum in issue 45(3) because of a typo during layout. This is the corrected article.