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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*

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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

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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*

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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	

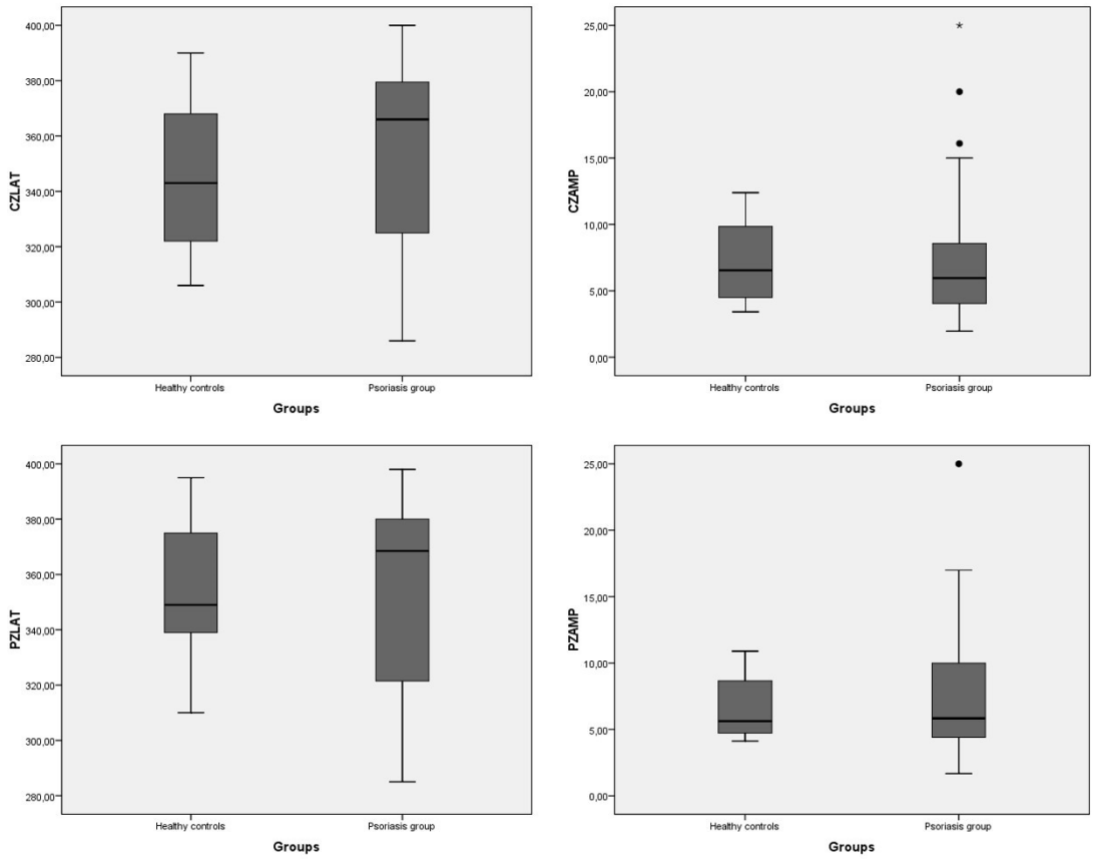

Figure 1. Comparison of PzLat, PzAmp, CzLat, and CzAmp values between control and patient groups

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).

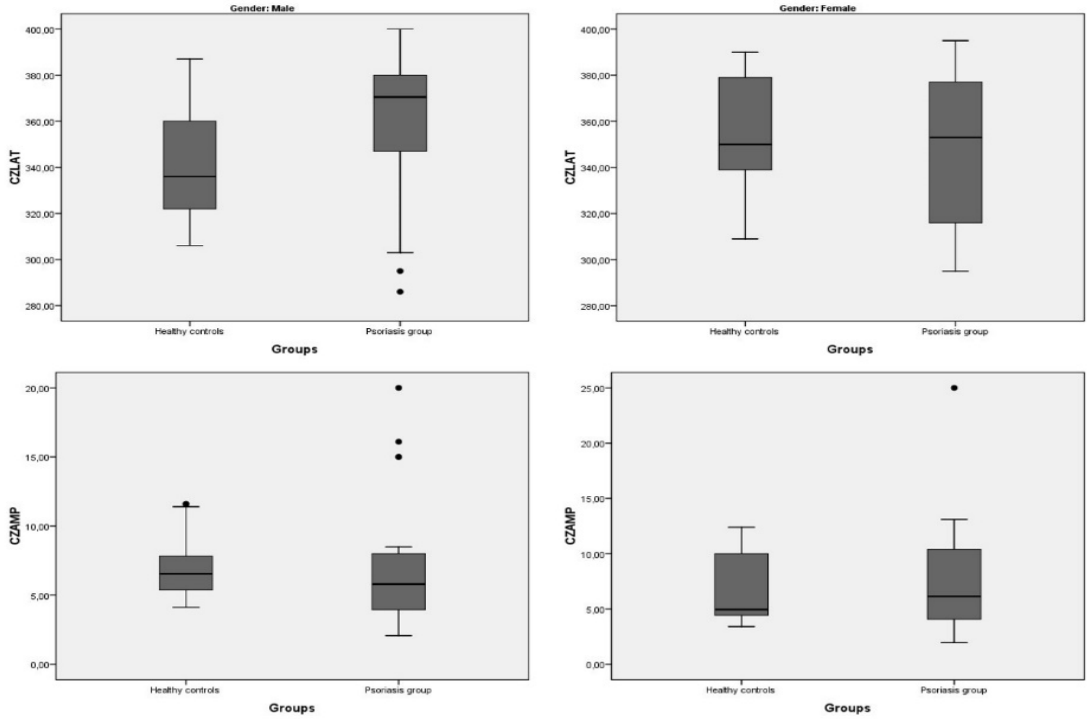

Figure 2. Cz Latency and Amplitude values in patient and control groups in terms of gender

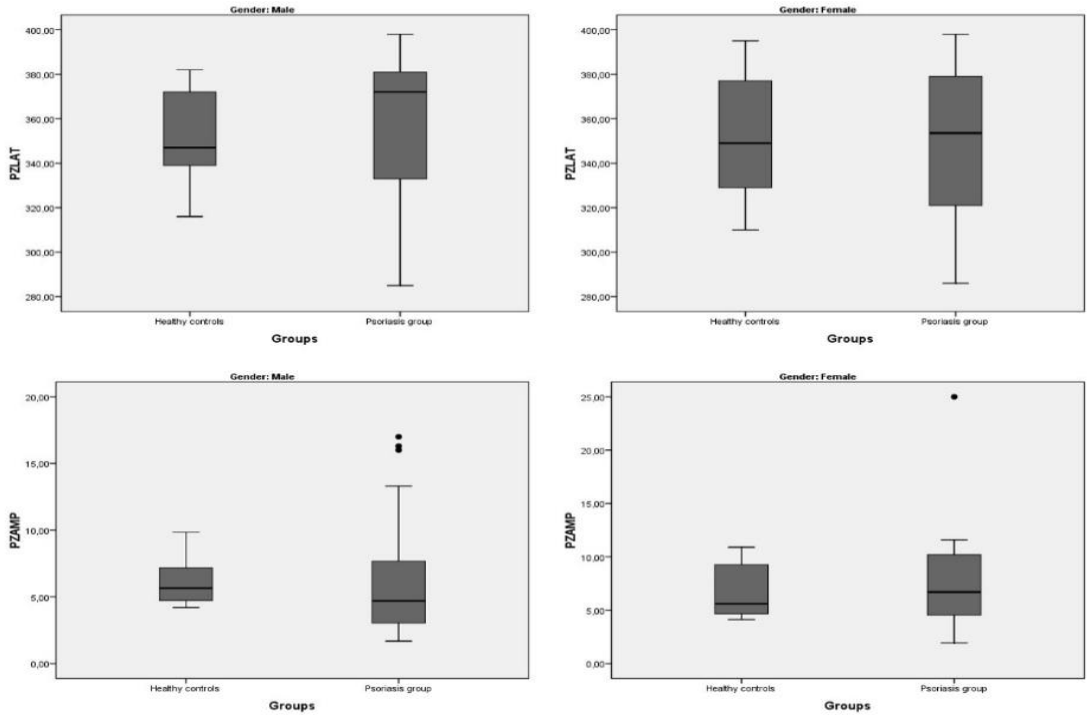

Figure 3. Pz Latency and Amplitude values in patient and control groups in terms of gender

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.

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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.

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