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N-acetylcysteine in trichotillomania as an alternative treatment option

Trikotillomanide alternatif bir tedavi seçeneği olarak N-asetilsistein

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Abstract

We aimed to examine trichotillomania (TTM), a rarely seen disorder, and N-acetylcysteine (NAC), an agent used as a treatment option, in the light of literature in the present study. Trichotillomania is the compulsive urge to pull out one's own hair persistently and leading to noticeable hair loss. Contrary to what is expected, it is a more frequently detected disorder characterized by compulsive hair pull-outs and of great importance not only due to physical appearance but also due to its associated psychosocial problems. Metabolic functions of N-acetylcysteine are effective either as antioxidant (forming up glutathione which is an endogenous antioxidant) or as glutamatergic agent. Due to these effects, N-acetylcysteine was administrated in as oxidative stress related schizophrenia and bipolar disorders as well as trichotillomania characterized by compulsive symptoms and in eating nail. Administration of N-acetylcysteine in cases with psychiatric disorders was reported in clinical researches such as case report and open label studies. In the literature, the efficiency of N-acetylcysteine in the treatment of trichotillomania was demonstrated in 3 studies as case report, double blind and placebo controlled researches. N-acetylcysteine may be a promising and ideal treatment option in the mono or combined treatment of diseases such as trichotillomania due to its efficiency, and cost affectivity, but it also does not lead to adverse effects.

Keywords: Trichotillomania, N-acetylcysteine, glutamate, antioxidants

Özet

Bu yazıda, günlük pratikte sık karşılaşılan bir bozukluk olmayan trikotillomani (TTM) ve tedavisinde kullanılan N-asetilsistein'in (NAC) literatür ışığında gözden geçirilmesi amaçlanmıştır. Trikotillomani kişinin tekrarlayıcı olarak ve belirgin saçsız alanlar oluşturacak şekilde saçlarını yolmasıdır. Trikotillomani sanıldığının aksine daha sık görülen, kompulsif saç yolmalarla karakterize sadece fiziksel görünüm açısından değil yaşattığı psikososyal sorunlar nedeniyle önemli bir ruhsal bozukluktur. N-Asetilsistein metabolik fonksiyonlarını, ya antioksidan (endojen antioksidan olan glutatyon oluşturarak) ya da glutamaterjik düzenleyici olarak gösterir. Bu etkileri nedeniyle N-Asetilsistein; oksidatif stres ile ilişkili şizofreni, bipolar gibi bozukluklarda, ayrıca kompulsif belirtiler ile karakterize trikotillomani, tırnak yeme gibi bozukluklarda kullanılmıştır. N-Asetilsistein'in psikiyatrik hastalıklarda kullanımı; olgu sunumu, açık-etiketli pilot çalışmalar ve çalışmalar gibi klinik araştırmalarla bildirilmiştir. Literatürde N-Asetilsistein'in trikotillomani tedavisinde etkinliği; 3 çalışmada olgu sunumu ve çift-kör, plasebo-kontrollü araştırmalar ile gösterilmiştir. N-Asetilsistein gerek etkinliği, gerek ucuz olması ve yan etkilere yol açmaması nedeniyle; Trikotillomani gibi hastalıkların tekli ya da kombine tedavisinde umut verici ve ideal bir tedavi seçeneği olabilir.

Anahtar sözcükler: Trikotillomani, N-asetilsistein, glutamat, antioksidanlar

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Introduction

We aimed to examine trichotillomania (TTM), a rarely seen disorder, and N-acetylcysteine (NAC), an agent used as a treatment option, in the light of literature in the present study. Firstly NAC, later on TTM was detailed and NAC administration would be evaluated in TTM.

N-acetylcysteine: NAC, glutathione (GSH-y-glutamyl) as an antioxidant has been used in the treatment of paracetemol intoxication over 30 years [1]. On the other hand, it is commonly administrated in cases with chronic obstructive pulmonary disease as a mucolytic agent [2].

Mechanisms of action: NAC metabolically affects two major physiological functions.

As an antioxidant: Antioxidant effect is demonstrated with glutathione proliferation which is a very efficient endogenous antioxidant. N-acetylcysteine is primarily converted to cysteine. Acetylcysteine is transformed to cysteine and cysteine combines with glutamate thereby forming up glutathione. GSH is a potent antioxidant playing a role in immune system [1, 3]. NAC increases cysteine and glutathione levels in glial cells [4]. In animal based studies, it was demonstrated that NAC easily passed through blood-brain barrier and increased GSH level in brain [5]. Although GSH is sold in the market, administration of oral cysteine and GSH does not either increase GSH levels or increases in a very low level. However, administration of oral NAC increases plasma cysteine levels thereby causing the proliferation in plasma GSH level [6]. As in many patients, oxidative damage gains importance in the etiology of psychiatric patients. There are numerous studies in which oxidative stress plays a significant role in patients presenting with obsessive compulsive disorder (OCD) [7, 8, 9]. In case of lipid peroxidation increase [7, 8], antioxidant deficiency, vitamin E [7], catalase, glutathioneperoxidase and selenium deficiency, superoxide dismutase increase [8] and excessive oxidative situation, some modifications [9] were detected. Therefore, in many psychiatric cases for whom oxidative damage was substantial, NAC was administrated [3].

Glutamate regulation: NAC is of great metabolic importance to regulate glutamate. As a prior-end substrate of NAC glutamate, cysteine is administrated. With these functions, NAC has a treating effect upon psychiatric syndromes characterized by impulsive/compulsivity [3]. For preventing the compulsive behaviors, it was considered to be associated with the regulation of extracellular glutamate concentration in nucleus accumbense [10]. Clinical studies support that such glutamatergic modulators as NAC have effects upon the treatment of recurrent or compulsive diseases [11, 12]. There are also other evidences in those patients presenting with obsessive compulsive disorder, supporting that some gluthamergic abnormalities were available [13, 14]. In addition, NAC leads to the release of interleukins (İL-6, İL-1β) and tumor necrosis factor (TNF-α) which are pro and anti-inflammatory mediators. In the studies, the importance of these mediators was stressed in bipolar depression and schizophrenia patophysiology particulary in depression [15, 16]. Mechanism of action of NAC may be explained with inflammatory cytokines production in psychiatric patients undergoing NAC treatment. This may be directly associated with inflammatory pathway or oxidative process with inflammation [1].

Administration of NAC in psychiatric diseases was reported with clinical researches such as case report, open-label pilot studies and double blind placebo controlled studies. It was also used in addiction therapies [17, 18, 19], schizophrenia [6, 20], bipolar disorders [21], pathologic gambling [22], pathologic nail eating [23] as well as pathologic skin pull-out [11] either single or supporting treatment.

Trichotillomania

Trichotillomania was first defined by Francois Hallopeau, a French dermatologist, in 1889 [24, 25]. TMM is the compulsive urge to pull out one's own hair persistently and leading to noticeable hair loss. The word "Trichotillomania" is derived from two Greek words: Hair (trich) and pulling-out (tillo), disease like impulse (mania) [26, 27]. In all hairy sites, pull-out may occur, and in both children and adults, pull-out site is generally scalp followed by eyebrow and eyelash [27, 28].

In DSM-IV-TR, Trichotillomania was classified as an impulse control disorder. Criteria for Trichotillomania diagnosis are as follows:

1. Recurrent pull-out of hairs by one's own leading to pronounced hair loss.
2. Gradually increasing stress emotion before or during hair pull-out.
3. Taking pleasure while pulling out hair, achieving satisfaction or relaxing.
4. This disorder cannot be explained with another mental disorder and not associated with a general medical situation.
5. Such a disorder results in clinical distress or social, professional or substantial functional problem [29].

In DSM-IV-TR Trichotillomania was classified as an impulse control disorder, however, this classification is still controversial. Trichotillomania is claimed to be available in obsessive compulsive disorders (OCD), and a kind of behavioral addiction, and that it seems as addiction and that it is associated with some people in evolutionary perspective [26].

Suggested Criteria for DSM-5:

1. Recurrent hair pull-out causing hair loss, such a disorder results in clinical distress or social, professional or substantial functional problem.
2. This disorder is not associated with physiological state due to drug addiction and a general medical situation (for instance; dermatological cases).
3. Hair pulling-out is not limited to another mental disorder (for instance; hair pulling-out due to postural dysmorphic disorder appearance, hair pulling-out due to symmetric anxiety in case of obsessive-compulsive disorder).

Changes recommended for diagnosis: In Section 1, the word "pronounced" was removed, 2nd and 3rd sections were wholly eliminated, medical exclusion sentence was renewed and psychiatric disorder hierarchy criteria were added. The sections 2nd and 3rd, "Gradually increasing stress emotion before or during hair pull-out, Taking pleasure while pulling out hair, achieving satisfaction or relaxing" were not evaluated as universal [30].

TTM incidence is not exactly known but it is reported to affect the population in 0.6-1% ratio [31]. In a study held by Christenson on college students, the prevelance was detected to be 0.6% [32]. In other studies, life long occuring ratios were detected to be 4.4% in adult psychiatric patients and in 4.6% of patients with obsessive compulsive disorder [33, 34].

It is more frequent in women compared to men. It generally starts in childhood and puberty period however, it was also reported in late periods [27].

Etiology

Trichotillomania etiology is not still known. Numerous factors were claimed to be relevant. Except oxidative damage and biochemical factors in brain, psychological problems such as deficient social functions, labor dissatisfaction and impaired quality of life are generally detected in patients with TTM. Mother-child problems, isolophobia, and new object losses are significant factors [32, 35].

Associated disorders are many mental diseases particularly obsessive personality disorder, Borderline Personality Disorder and depression [27]. This disease is

phenomenologically and neuro-biologically associated with obsessive personality disorder [27, 36]. In TTM, as in obsessive personality disorder, chronic and undesired conditions are detected. In Trichotillomania, different from obsessive personality disorder, no obsessive thoughts are available and compulsive activity is limited with an action (hair pull-out) [27].

The primary method in Trichotillomania is clinical contact and observation.

Treatment: There is no consensus on the best treatment option. Knowing the exact behavior of the patient in Trichotillomania is of importance in detecting the factors directing or contributing to the behavior, and in conceptualizing prior control strategies and in planning treatment [26].

In TTM treatment, the efficiency of klomipran-a tricyclic antidepressant, was detected however patient compliance was poor. SSRI was used in first level treatment however there are no benefit reports for this use [37]. Due to similarity of TTM with obsessive personality disorder, those agents effective in obsessive personality disorder such as fluoksetin, paroksetin, fluvoksamin, sitalopram and essitalopram were used in the treatment [38-42]. Combined treatment with Fluvoksamine and NAC led to dramatic healing in hair combing and compulsive washing control [43].

Other alternative treatment combinations include such neuroleptics as Naltreaksone, pimozid [44, 45]. Positive results were reported with Risperidon and olanzapin [46, 47]. Another option for Trichotillomania treatment is cognitive and behaviorist therapy [25, 35, 48].

Treatment for reversing the familiarities includes the procedures such as teaching the patient how to become aware of hair pull-out related conditions or stressors, and relaxation training and closing hands tightly when pull-out is likely to occur or when it happens in order for preventing it [49].

Use of N-acetylcysteine in Trichotillomania

3 studies were detected in the literature for NAC use in Trichotillomania. In the first study by Odlaug and Grant, NAC treatment was detected to be useful on a 28 year old man and a 40 year old woman. In these cases, the agent was administrated 1800 mg/day for 10 and 13 weeks [11].

In a double blind, placebo controlled study performed by Grant et al. [50], 50 patients (45 women and 5 men) underwent NAC treatment. During 6 weeks, in placebo and patient group, 1200 mg/day, and during the subsequent week 2400 mg/day NAC was delivered. Approximately half of the samples (28) 18 SSRI, 8 SNGI and 2 were exposed to stimulating treatment and 4 patients were involved in psychotherapy. NAC was combined with these treatments. Compared to placebo, NAC was detected to reduce TTM symptoms. There were no adverse effects in NAC group.

In the second study by Barata et al. [51], it was demonstrated that in 2 female patients with TTM (23 and 19 years old) NAC treatment was useful.

The first patient did not benefit from fluoccytin and psychotherapy. In the second month following the treatment on the frontal region where hair pull-out occurred hair was regrown, and for 6 months this situation was ongoing. In the history of the patient, it was reported to be associated with the death of mother of the patient during childhood. The second patient was pulling out her hairs since 9 years old and various treatments were applied until TTM diagnosis was finalized but no results were acquired. With NAC administration during 3 months, hairs were exactly regrown. No other adverse effects were detected in these two cases during treatment.

Trichotillomania is the compulsive urge to pull out one’s own hair persistently and leading to noticeable hair loss. Contrary to what is expected, it is a more frequently detected disorder characterized by compulsive hair pull-outs and of great importance not

only due to physical appearance but also due to its associated psychosocial problems. Although not absolutely diagnosed and impulsive control disorder is available in DSM, the similarity with OCD group and other disorders of addiction is noticeable, as well. This is associated with its reduced prevalence. Comorbid is a factor we should consider for treatment in mental cases.

N-acetylcysteine is an antioxidant which has recently gained importance. NAC plays a role in forming gluthatione, a body antioxidant, and in regulating gluthamatergic system. With this task, they may be useful mono therapy or supporting strategy for oxidative stress related psychiatric disorders (such as schizophrenia and bipolar disorder) and/or psychiatric syndromes characterized by impulsive/compulsive symptoms (for example, Trichotillomania, nail eating, drug abuse, pathologic gambling etc.).

Trichotillomania should be evaluated for such modifications in etiopathogenesis and functional problems and treatment plan should be done. Although efficient treatment is not certain, those studies with N-acetylcysteine are promising. These studies are insufficient but in order for disclosing clear results, more complicated studies should be performed on more participants.

In conclusion; N-acetylcysteine may be a promising and ideal treatment option in single or combined treatment of disease such as Trichotillomania.

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