N-ACETYLCYSTEINE IN TREATMENT OF TRICHTOTILLOMANIA

TRİKOTİLOMANİDE N-ASETİLSİSTEİN KULLANIMI

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Abstract

Trichotillomania is a chronic mental disorder characterized by recurrent hair-pulling. Hoarding, excoriation and trichotillomania are classified as obsessive-compulsive related disorders in DSM-5, which share similar clinical presentations, characterized by inappropriate and excessive repetitive behaviors and dysregulation of inhibitory control processes. Research evidence suggests that abnormalities in the cortico-striato-thalamic-cortical circuits are one of the key factors underlying the pathophysiology of obsessive-compulsive related disorders, including trichotillomania. Glutamate is the primary neurotransmitter within the cortico-striato-thalamic-cortical circuits. Therefore, the use of glutamate-modulating agents is subject to interest for obsessive-compulsive related disorders. N-acetylcysteine, a derivate of the amino acid L-cysteine, has been explored as potential therapy for obsessive-compulsive related disorders, including trichotillomania. Pharmacotherapies that target the prefrontal glutamatergic system, such as N-acetylcysteine, may correct the underlying pathophysiologic abnormalities and symptoms of trichotillomania. Even a limited number of studies are suggesting that N-acetylcysteine is a promising treatment option, these studies did not assess treatment effects exceeding 3-4 months treatment period. Longer term effects of N-acetylcysteine therapy in trichotillomania require further evaluation.

Keywords: N-acetylcysteine, obsessive compulsive related disorders, treatment, trichotillomania.

1. Introduction

Trichotillomania is chronic mental disorder characterized by recurrent hair-pulling. In Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of trichotillomania requires that recurrent hair-pulling must result in hair loss; an indication of an attempt to decrease or stop hair-pulling must also be necessary. Furthermore, the diagnosis of trichotillomania requires hair-pulling not to be better accounted for by another disorder or being a result of a general medical condition. Finally, for a diagnosis of trichotillomania, recurrent hair-pulling must cause significant distress or impairment in functioning. Hoarding, excoriation and trichotillomania are now categorized as obsessive-compulsive related disorders (OCRD) in DSM-5. OCRD and OCD share similar clinical presentations, characterized by inappropriate and excessive repetitive behaviors and dysregulation of inhibitory control processes, suggesting similar pathophysiology (Chamberlain et al., 2006).

Evidence suggests that abnormalities in the cortico-striato-thalamic-cortical circuits are one of the key factors underlying the pathophysiology of OCRD, including trichotillomania. Particularly, orbitofrontal cortex, anterior cingulate and ventromedial striatum hypermetabolism has been linked to OCD (Ahmari et al., 2013). Glutamate is the primary neurotransmitter within the cortico-striato-thalamic-cortical circuits and evidence suggests that abnormal glutamate metabolism is manifested in subjects with OCRD (Chakrabarty et al., 2005). Also, high levels of glutamate result in excitotoxicity and oxidative stress.
(Burdo et al., 2006). Oxidative stress markers, lipid peroxidation, have been detected in serum samples of patients with OCDDR (Ozdemir et al., 2009). Also, higher levels of oxidative stress found to be correlated with symptom severity (Chakraborty et al., 2009).

Glutamate’s role in the cortico-striato-thalamic-cortical pathway and its pro-oxidant properties supports its suggested role in the pathophysiology of trichotillomania and other OCDDR. The efficacy of glutamate modulating agents on regulating impulse control is becoming increasingly evident (Grant et al., 2009). Thus, the application of glutamate-modulating agents is of growing interest for OCDDR. More recently, N-acetylcysteine (NAC), a derivate of the amino acid L-cysteine, is promising as a potential therapy for OCDDR, including trichotillomania.

1.1. Nac

NAC is the acetylated precursor of the L-cysteine. NAC is a well-known mucolytic agent. NAC has demonstrated neurochemical, antioxidant, anti-inflammatory, mucolytic and hepatoprotective activity (Berk et al., 2013). It has been used in clinical practice for the treatment of numerous disorders. Treatment of acetaminophen intoxication, acute respiratory distress syndrome, bronchitis, chemotherapy-induced toxicity, HIV/AIDS, chemical induced nephropathy are some of the numerous treatment indications for NAC (Zafarullah et al., 2003; Atkuri et al., 2007; Millea, 2009; Radomska et al., 2012).

NAC is available in intravenous, oral and inhale forms. It has been associated with mild side effects (Atkuri et al., 2007). It has a half-life of 5.6 h after a single intravenous administration, and renal excretion clears 30% of it. NAC has a low bioavailability (almost %5). The redox exchange reactions between NAC, cysteine and cysteine proteins occur in the plasma, leading the synthesis of glutathione (Radke et al., 2012). Glutathione is an important antioxidant involved in neurotransmitter signaling (Sies, 1999).

There is growing evidence that NAC has an effect on the glutamatergic system (in the nucleus accumbens) which may target symptoms of compulsive behaviors (Kalivas, 2005). Therefore, NAC may correct the underlying pathophysiologic abnormalities and symptoms of trichotillomania. NAC increases glutathione and cysteine levels in glial cells (Mayer, 1994); therefore it may be protective to glial cell functioning during hyperglutamatergic states (Hart et al., 2004). Glial cells are capable of the clearance of glutamate from the synapse; that may be essential for the glutamate-modulating effects of NAC.

1.2. Nac and Psychiatric Disorders

NAC is a promising agent for the treatment of neuropsychiatric disorders due to the multi-factorial etiology that involves inflammatory pathways, oxidative stress, glutathione metabolism, glutamatergic transmission and mitochondrial function (Berk et al., 2013). In recent years, several controlled randomized clinical trials have demonstrated the efficiency of NAC as an adjunctive treatment option for methamphetamine, nicotine, cannabis and cocaine addiction (Van et al., 2002; LaRowe et al., 2007; Grant et al., 2010; Gray et al., 2012), pathological gambling (Grant et al., 2007), obsessive–compulsive disorder (Lafleur et al., 2006), trichotillomania and skin picking (Grant et al., 2009), schizophrenia (Lavoie et al., 2008), bipolar disorder (Berk et al., 2008) and autism (Hardan et al., 2012).

NAC was also used to modulate inflammatory pathways in central nervous system, reducing the levels of pro-inflammatory cytokines in traumatic brain injury (Beloosesky et al., 2012). NAC can modulate the levels of extracellular glutamate, which is important in excitotoxic damage models of schizophrenia and addiction (Baker et al., 2003). NAC modulates intracellular calcium, which is relevant to the dysregulation of receptor-mediated calcium release, reported in psychosis (Berk et al., 2000). It has been also demonstrated that NAC blocked amphetamine-triggered dopaminergic response in vivo and prevented the down-regulation of dopamine transporter that is highly associated with neuropsychiatric disorders (Hashimoto et al., 2004).

1.3. Nac in Treatment of Trichotillomania

Although trichotillomania has been well described, data regarding treatment options is limited. A recent meta-analytic study of randomized treatment trials in adults demonstrated that habit reversal therapy, have the greatest efficacy in the treatment of trichotillomania. Selective serotonin reuptake inhibitors are widely used in the treatment of trichotillomania, despite evidence that their efficacy is no greater than placebo (Bloch et al., 2013). A recent randomized trial has also suggested that olanzapine was more effective than placebo in adults with trichotillomania (Van Amerringen et al., 2010). Pharmacotherapies that target the prefrontal glutamatergic system, such as NAC, are promising options for correcting the underlying pathophysiologic abnormalities and symptoms of trichotillomania.

In a 12 week, double-blind, placebo-controlled trial, Grant et al. tried to determine the efficacy and tolerability of NAC in adults with trichotillomania. Their study group was composed of 50 individuals with trichotillomania (45 women and five men; with a mean age of 34.3) were administered either NAC (dosing range, 1200-2400 mg/d) or placebo for 12 weeks. Patients assigned to receive NAC had significantly greater reductions in trichotillomania symptoms. Fifty-six percent of patients “much or very much improved” with NAC use compared with 16% taking the placebo. No adverse events occurred in the NAC group, and NAC was well tolerated (Grant et al., 2009).

In another double-blind placebo-controlled trial (N=39), no significant differences in improvement between NAC and placebo groups were reported in children and adolescents with trichotillomania, both groups significantly improved (Bloch et al., 2013). In the NAC group, 25% of subjects were responded to treatment, compared to 21% in the placebo group. The authors suggest that their study results may differ from previous studies reporting a positive response to trichotillomania, due to a younger
aged sample or more severe trichotillomania symptoms among the placebo group in their study. Although research on the developmental course of trichotillomania is sparse, there is some evidence to suggest that children and adults experiencing hair pulling are fundamentally different. The authors reported that among children with trichotillomania, urge and severity of hair pulling increases with age. It has been hypothesized that NAC may work in hairpullers by reducing the frequency and intensity of the urge to pull. This hypothesis arises from the substance abuse literature, in which NAC has been demonstrated to modulate glutamate in the nucleus accumbens and reduce drug-associated cravings. If it is true that NAC acts by reducing pulling associated urges, it may be that NAC has decreased efficacy in children compared to adults.

Promising results were obtained from the case report of Rodrigues-Barata et al. (Rodrigues-Barata et al., 2012) involving two females diagnosed as trichotillomania. Both cases were non-responsive to previous psychotherapy and SSRIs. Both patients demonstrated complete regrowth of their hair within three months when supplemented with 1,200 mg/day of NAC. In another case of a 40-year-old female with trichotillomania, improvement reported with a treatment of NAC 1200 mg twice daily for three weeks (Odlaug et al., 2007). Another case of a 28-year-old male with nail biting and trichotillomania, significant improvement observed with 1,800 mg/day NAC within two weeks. Symptoms were relapsed when the failed to use the NAC for two weeks (Odlaug et al., 2007106).

Similarly, NAC was also used in another OCRD, namely, skin picking. An open-label prospective case-series (N=35) of individuals with Prader–Willi syndrome demonstrated a significant improvement in skin-picking symptoms and skin lesions in the majority of persons with 12 week NAC treatment (Miller & Angulo, 2014). Several adult case series have also reported a decrease in the frequency of skin picking behavior with NAC treatment (Grant et al., 2012; Silva-Netto et al., 2014). All the studies showed positive effect, so NAC seems like a promising treatment option for skin picking, but further controlled studies are needed.

2. Conclusion

NAC could be an effective and well tolerated treatment option for people with trichotillomania. But trichotillomania is a chronic disease which may require long term therapy. The case series in adults reported improved hair growth with NAC. The results however are mixed as one out of two controlled trials was negative for improvement. Larger clinical trials are needed to confirm the effectiveness of NAC in trichotillomania. Even several studies are suggesting that NAC is a promising treatment option; these studies did not assess treatment effects beyond 3-4 months treatment period. Longer term effects of NAC therapy require further evaluation.

References


