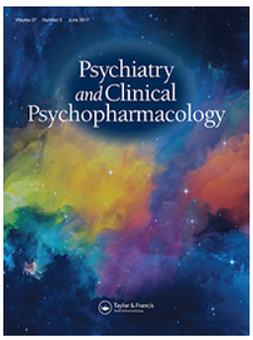

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N-acetylcysteine may reduce repetitive behaviors in children with autism: a case series

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ABSTRACT

Objective: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in social communication and interaction, and restricted, stereotypic, repetitive behaviors. Behavioral problems are common in children with ASD. Herein, we report the effect of N-acetylcysteine (NAC) treatment on repetitive behaviors in 10 children with ASD.

Methods: Ten children with ASD were assessed using the Childhood Autism Rating Scale and Aberrant Behavior Checklist (ABC). The clinical follow-up was performed with ABC and Clinical Global Impressions-Improvement (CGI-I). A total of 10 patients were initiated on NAC therapy in addition to their treatment with a stable dose of risperidone to avoid the potential adverse effects of higher doses of risperidone. Two patients discontinued NAC treatment before the third week. Eight patients were treated with an NAC dosage of 1200–2700 mg/day for 6–10 weeks.

Results: The mean age of the patients was 8.6 years. Patients received NAC treatment for a mean duration of 8.25 weeks and a mean dosage of 2100 mg/day. Improvement in stereotypic behaviors was statistically significant in addition to the improvement in mean CGI-I score ($p = .025$ and .006, respectively).

Conclusion: NAC adjunction to risperidone treatment may be helpful to reduce repetitive behaviors in children with ASD with limited adverse effects and good tolerability.

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KEYWORDS
Autism; ASD; N-acetylcysteine; NAC; repetitive behaviors

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairment in social communication and interaction, and restricted, stereotypic, repetitive behaviors [1]. Intellectual disability, irritability, aggressive behaviors, self-mutilation, emotional dysregulation, hyperactivity, and other comorbid psychiatric disorders are common in addition to the core symptoms of ASD [2]. Psychopharmacologic agents including selective serotonin reuptake inhibitors (SSRIs), antipsychotics, and psychostimulants have been used for the amelioration of associated behavioral symptoms in patients with ASD [3–6]. A number of studies have shown mild-to-good efficacy and safety of these medications in patients with ASD. Psychostimulants and atomoxetine are used for the symptoms of attention deficit-hyperactivity disorder (ADHD) [7,8]. Risperidone and aripiprazole have been shown to be effective for the treatment of behavioral problems such as irritability, aggression, and repetitive behaviors in patients with ASD [9,10]. However, a number of adverse effects including sedation, agitation, social withdrawal, emotional adverse effects, weight gain, extrapyramidal adverse effects, endocrine problems, metabolic syndrome, and long-term adverse effect tardive dyskinesia limit the use of these medications [6,11]. The adverse effect profile of neuroleptic drugs brings the need for new treatment options for ASD-related behavioral problems.

One of the recent novel molecules that seems to be promising is N-acetylcysteine (NAC). NAC is the acetaldehyde form of cysteine, which modulates glutamate metabolism and acts as an antioxidant [12]. Its glutamatergic and antioxidant effects make NAC a promising treatment option for ASD in addition to several neuropsychiatric disorders with fewer adverse effects. NAC is shown to be effective in patients with obsessive compulsive disorder (OCD) and trichotillomania (TTM) [13–15]. NAC is also promising for schizophrenia, depressive episodes of bipolar disorder and substance use disorders [15]. In contrast to a recent randomized controlled trial which reported that NAC did not show a significant improvement in social impairment in youth with ASD [16], Hardan et al. stated that NAC might be an effective agent to reduce irritability, temper tantrums, self-mutilation, and stereotypic

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behaviors in children with ASD [17]. Additionally, NAC augmentation to risperidone treatment was found effective for irritability in two other randomized controlled trials in patients with ASD [9,18].

Taken together, NAC is a promising agent for the treatment of symptoms that cause substantial disability for children with ASD and their families. Herein we report the effect of NAC on repetitive behaviors in 10 children with ASD.

Materials and method

Ten children who were referred to Zonguldak Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Department of Child and Adolescent Psychiatry between 5 March 2015 and 15 October 2015, who were diagnosed as having ASD and received NAC in addition to their routine risperidone treatment were included in this study. Treatment results were retrospectively assessed. All patients received a stable dose of risperidone for at least 4 weeks before NAC augmentation. No patients had a history of epilepsy.

We evaluated ASD by clinical interview in accordance with diagnostic and statistical manual of mental disorders-V [1] criteria and all patients were diagnosed as having ASD at a clinical level. All children were assessed using the Childhood Autism Rating Scale (CARS) [19] and Aberrant Behavior Checklist (ABC) [20] was used to assess behavioral problems. Additionally, Clinical Global Impressions-Improvement (CGI-I) was used to monitor clinical improvement. The clinical follow-up of patients was performed with ABC and CGI-I. An adverse effect scale, which was primarily based on the possible adverse effects that are documented in the package insert of NAC, was used in every clinical visit to assess the adverse effects of NAC.

A total of 10 patients were initiated on NAC therapy in addition to their treatment with risperidone. Two patients discontinued NAC treatment before the third week. Eight patients were treated with an NAC dose of 1200–2700 mg/day (mean dose: 2100 mg, SD: 453.5). These patients were followed up for between 6 and 10 weeks (mean 8.25 weeks; SD: 1.28).

Table 1. Mean scale scores of baseline and post-treatment measurements of eight patients.

	Baseline score Mean (SD)	Final score Mean (SD)	*T*	*P*
ABC hyperactivity	28.2 (9.6)	27.0 (9.7)	0.53	.613
ABC lethargy/social withdrawal	17.9 (14.0)	21.1 (15.1)	−1.43	.195
ABC stereotypic behavior	9.8 (5.2)	7.8 (5.9)	2.83	.025
ABC irritability	3.1 (3.9)	4.5 (4.2)	−1.88	.102
ABC inappropriate speech	6.8 (3.2)	7.1 (2.5)	−0.70	.504
ABC total	65.8 (31.4)	67.8 (32.4)	−0.69	.510
CGI	5.1 (1.0)	4.2 (1.5)	3.86	.006

Notes: ABC, Aberrant Behavior Checklist; CGI-I, Clinical Global Impressions-Improvement.

Data were analyzed using simple descriptive statistics. Paired *t*-test was used to compare means. *P* values less than .05 were considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences version 15.0.

Results

Seven of the 10 patients were boys (70.0%) and 3 were girls (30.0%). The mean age of the patients was 8.6 years (range: 5–14 years; SD: 2.5). The mean CARS scores of 10 patients were 42.2 (range: 33–47; SD: 4.82). All of the patients had previous psychiatric referral history and received a mean dose of 1.31 mg risperidone (range: 0.5–2.5; SD: 0.75).

Two patients discontinued treatment; one showed increased irritability with a concomitant upper airway infection in the second week of NAC treatment. The other child was discharged from treatment because of low therapeutic adherence in the 3rd week. Eight of the 10 patients used NAC for a mean duration of 8.25 weeks (SD: 1.28) and a mean dosage of 2100 mg/day (range: 1200–2700 mg; SD: 453.5).

Based on ABC, improvement in stereotypic behaviors were statistically significant ($P = .025$). However, there were no improvement in other behavioral symptoms in our group. There was significant improvement in the mean CGI-I score ($P = .006$). The mean scale scores of baseline and post-treatment ABC and CGI-I of the eight patients are given in Table 1.

There were no severe adverse effects reported. One patient had mild and transient gastrointestinal pain, and one had diarrhea; the remaining six patients reported no adverse effects during the treatment period.

Discussion

Behavioral problems and stereotyped behaviors are common in patients with ASD and usually cause further functional impairment. Although some behavioral interventions may also be beneficial in the management of these problems [2], many children with ASD may not have opportunity to access to these programs. Therefore, psychopharmacologic treatments have become important options in the management of ASD-related behavioral problems.

In our study, the stereotypic behaviors in eight children with ASD were improved significantly with NAC with tolerable adverse effects. This result is in line with previous studies. Hardan et al. reported improvement in stereotypic behaviors and irritability symptoms in a randomized controlled trial. They assumed that this improvement might be based on the recovery of the imbalance of glutathione system and the redox imbalance [17]. Other two randomized controlled studies focused on the effect of NAC for the behavioral

symptoms in ASD showed similar results. Ghanizadeh and Moghimi-Sarani found a decrease in irritability scores and Nikoo et al. reported improvement in irritability and hyperactivity symptoms in children with ASD who were treated with adjuvant NAC to risperidone [9,18]. Marler et al. reported a 4-year-old child with ASD whose self-injurious behaviors resolved after the administration of 1800 mg NAC [21].

Besides ASD, NAC is shown to be effective for the symptoms of ADHD, OCD, and impulse control disorders such as nail biting, skin picking, and TTM [13–15,22]. NAC reported to be an effective agent as an add-on therapy to SSRIs in the treatment refractory OCD [23] and a treatment option in adults with TTM [14]. Moreover, several studies reported improvement in the symptoms of schizophrenia, addiction, bipolar disorder and depressive disorders with NAC treatment [15,22]. Hardan et al. stated that NAC may be useful for treating neuropsychiatric disorders that share the common pathologic pathway, rather than being a disorder specific agent [17]. The imbalance in the glutathione system and the redox imbalance in the brain are thought to be responsible as an etiologic factor for these psychiatric disorders [13,17,21,22]. NAC is a source for cysteine and cysteine is used for glutathione synthesis. Glutathione acts as the primer antioxidant in the brain and NAC may also have a role for regulating glutamatergic function [15].

However, besides these positive results, there are also studies that reported NAC may not be effective for controlling hair pulling in children with TTM [24] – in contrast to adults [14] – as well as social impairment in youth with ASD [16] and tics in children with Tourette syndrome [25]. Further studies with larger populations are needed to show the benefits of NAC in ASD and other neurodevelopmental disorders.

NAC has a low-potential adverse effect profile with a good tolerability [17]. In our study, there were mild and transient gastrointestinal system (GIS) adverse effects in two patients. One child had to leave the study due to increased irritability in the second week of the treatment; however, it was hard to detect if the irritability was linked to NAC or the concomitant upper airway infection. This is in line with the results of previous studies that reported the most common adverse effects were GIS adverse effects [9,13,17].

Our study showed that NAC adjunction to risperidone improved stereotypic behaviors in ASD with limited adverse effects and good tolerability. However, there were no improvement in other behavioral problems such as irritability and aggression. Additionally, it is hard to generalize our results because of the limited number of the patients, concomitant use of risperidone, and the retrospective nature of the assessment.

Disclosure statement

No potential conflict of interest was reported by the authors.

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