

Olgu serisi / Case series

The efficiency and safety of N-acetylcysteine augmentation in the autistic children with severe irritability and aggression: six cases

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ABSTRACT

Autism spectrum disorder (ASD) is characterized by deficits in social interactions and communication, and restricted and stereotypic behaviors. A growing body of evidence has identified metabolic pathways and glutamatergic neurotransmission affecting oxidative stress levels as potential targets of drug development in autism spectrum disorders. N-acetylcysteine (NAC) is an antioxidant that modulate glutamate and reduce oxidative stress, both associated with the pathophysiology of ASD. N-acetylcysteine has been identified as a potential treatment agent for irritability and self-injurious behaviors in autism. In this case report, we report six cases of autism with severe symptoms of irritability and aggression, two of them responded well to N-acetylcysteine treatment, two of them responded partially and while two did not. (*Anatolian Journal of Psychiatry* 2020; 21(2):218-221)

Keywords: autism, irritability, N-Acetylcysteine, aggression

Şiddetli irritabilite ve saldırganlığı olan otistik çocuklarda N-asetilsistein augmentasyonunun etkinliği ve güvenilirliği: Altı olgu

ÖZ

Otizm spektrum bozukluğu (OSB) sosyal-iletişimsel alanda belirgin yetersizlikler ve sınırlı, yineleyici davranışlar ve ilgi alanları ile karakterizedir. Gittikçe artan sayıda kanıt, glutamaterjik nörotransmisyonu ve oksidatif stres düzeylerini etkileyen metabolik yolları otizm spektrum bozukluklarında ilaç gelişiminin potansiyel hedefleri olarak tanımlamıştır. N-asetilsistein (NAC), ikisi de OSB'nin patofizyolojisi ile ilişkili olarak glutamata modüle eden ve oksidatif stresi azaltan bir antioksidandır. N-asetilsistein, otizmde irritabilite ve kendine zarar verme davranışları için potansiyel bir tedavi ajanı olarak tanımlanmıştır. Bu olgu sunumunda ağır saldırganlık ve irritabilite belirtileri olan altı otizmlili hastada N-asetilsistein tedavisi sunulmuştur. Altı olgunun ikisi tedaviye iyi yanıt verirken, diğer ikisinde kısmi yanıt saptanmıştır. İki olgu ise tedaviye yanıt vermemiştir. (*Anadolu Psikiyatri Derg* 2020; 21(2):218-221)

Anahtar sözcükler: Otizm, irritabilite, N-asetilsistein, agresyon

INTRODUCTION

In the pathogenesis of autism spectrum disorder (ASD), it has been hypothesized that oxidative stress due to glutathione deficiency is a potential causal factor.¹ Glutathione is one of the most

substantial antioxidants which inhibits cell damage caused by the components such as heavy metals, lipid peroxides and free radicals. N-acetylcysteine (NAC), a glutathione precursor, is used with many different indications to treat a wide range of disorders as lung diseases,

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heavy metal and paracetamol intoxication.^{2,3}

NAC is also used as a glutamatergic modulator and antioxidant.³ Due to its neuroprotective effects, its clinical use has included the treatment of different psychiatric disorders such as trichotillomania, onychophagia, Tourette's disorder, cannabis related cravings and ASD.¹ In the limited research, NAC was found to be well tolerated without any serious adverse effect. Although it is not effective for treating core symptoms of autism, it improves irritability and aggression symptoms. This finding is important because the current Food and Drug Administration (FDA) approved agents may cause serious adverse effects (metabolic abnormalities, weight gain, and tardive dyskinesia), that have limited their use.⁴ Based upon these data and the lack of severe associated adverse effects, NAC seemed to be helpful for targeting aggression symptoms in ASD. Here we report six cases of autism with severe symptoms of irritability and aggression, four of them responded to NAC treatment, while two did not. The Clinical Global Impression Scale (CGI-S) was used to measure the treatment response.

CASE 1

A 12-year-old female patient had been visiting routinely our outpatient clinic since she was diagnosed with ASD. She did not benefit from the valproic acid, risperidone and gabapentin treatment for aggression and irritability symptoms. She was on haloperidol 10 mg/day, quetiapine 600 mg/day and aripiprazole 20 mg/day when she was applied to our outpatient clinic again. She was overactive during the visit and constantly hit herself and her mother. A CGI-S score of 7 (among the most extremely ill patients) was determined in terms of the irritability. NAC 600 mg twice a day was added to the current treatment. One month later, it was observed that her hyperactivity continued, but the aggressive and self-injurious behaviors were partially reduced. No adverse effect was reported associated with the treatment.

CASE 2

A 17-year-old female patient, was diagnosed with autism and severe mental retardation 10 years ago. She had taken medications such as high doses of mirtazapine, quetiapine, aripiprazole, amisulpride, diazepam for irritability symptoms. However, her parents reported that she did not benefit. She was on haloperidol 20 mg/day,

chlorpromazine 100 mg/day, biperiden 4 mg/day, risperidone 4 mg/day, valproic acid 1000 mg/day at her last visit to our clinic. She was screaming and had aggressive and self-mutilative behaviors such as biting her arms, and hitting her mother during the interview. The CGI-S score was 7 (among the most extremely ill patients). NAC 600 mg twice a day was added to her current treatment. It was observed that the biting and screaming behaviors continued in the same manner after 1 month, but hitting the family members decreased. The CGI-I score was 3 (minimally improved). The severity of side effects was 1 (none). The current NAC treatment of the patient was increased to 900 mg twice a day. There was no change in CGI scores after one month. She continues NAC augmentation.

CASE 3

A 13-year-old male patient was diagnosed with autism eight years ago. He had been on methylphenidate, risperidone and aripiprazole treatment since the age of six. Due to not benefit from the medication, the current treatment was switched to risperidone 4 mg/day and haloperidol 10 mg/day. He initially had responded to the treatment but then the treatment response was decreased and he was applied again with complaints of aggression, self-harm and hyperactivity. He was screaming, trying to hit himself and biting his mother during the evaluation. NAC 600 mg twice a day was added. After two weeks, the treatment was stopped because his family reported that self-harm symptoms did not improve and they wanted to stop the medication.

CASE 4

A 9 year-old female patient, with the diagnoses of autism and severe mental retardation, had used olanzapine and aripiprazole for irritability symptoms. The current treatment was risperidone 2 mg/day. She had aggressive and self-mutilative behaviors such as biting her arms and hitting her head. She was spitting to her mother. The CGI-S score was 5 (markedly ill) on the assessment of irritability. NAC 200 mg twice a day was added to her current treatment. After 4 weeks, it was observed that the symptoms of the patient decreased. The CGI score was 3. There was no side effect. She still continues NAC augmentation.

CASE 5

A 13-year-old Iranian male patient with ASD

applied our outpatient clinic with symptoms of aggression. Previously, risperidone and haloperidol treatments were applied in high doses. The current treatment was risperidone 4 mg/day. He had self mutilative behaviors like biting and hitting himself. He also hit his mother when she tried to stop him. NAC 600 mg twice a day was added to his current treatment. After three weeks, there was no improvement in his symptoms. Due to the side effect of being weakness, NAC treatment was stopped.

CASE 6

A 13-year-old male patient, with the diagnosis of autism and moderate mental retardation, visited our outpatient clinic for irritability and aggression. Previously, risperidone, quetiapine, haloperidol, diazepam and short-acting methylphenidate treatments were applied in high doses. Due to not benefit from the medications, the treatment was switched to valproate 600 mg/day, olanzapine 25 mg/day and short-acting methylphenidate 10 mg/day. However, symptoms did not improve. NAC 600 mg twice a day was added. After four weeks, aggression, self-harm and hyperactivity symptoms decreased partially. She continues NAC augmentation with the consent and request of the family.

CGI scores of all cases have shown in Table 1.

DISCUSSION

In the present case report, these outcomes suggest advantages of adding NAC to the treatment regimen of children with autism, particularly those who poorly respond to the current medications. In all cases, NAC was added to the treatment as a single drug to avoid confounding benefits of other drugs. We also take into account how long patients have been using previous treatments.

N-Acetylcysteine (NAC) targets several factors involved in the pathophysiology of multiple neuropsychiatric disorders including the antioxidant glutathione, glutamatergic transmission, inflammatory pathways, apoptosis, and mitochondrial function.³ In the literature, NAC was used as an augmentation therapy for many psychiatric disorders such as obsessive-compul-

sive disorder, schizophrenia, bipolar disorder, depression, and substance abuse.^{2,3} There is limited research about its efficiency in autism. In one study, monotherapy of NAC has been shown to reduce aggression in autistic children.⁴ However, in another study demonstrated that there was no benefit of adjunctive N-acetyl cysteine in treating autistic disorder.⁵ There are also studies about its augmentation to risperidone, and reported to be effective to reduce signs of aggression in autism.^{6,7} In addition, there is a case report suggesting the benefits of NAC augmentation in self injurious behavior in autism,⁸ and another case report indicating decreasing in aggressive behaviors and improving in social interaction after adding NAC treatment.⁹

The action of NAC may be associated with two mechanisms: modulation of glutamatergic system and antioxidation⁴. NAC modulates the glutamatergic system by increasing in extracellular cystine (oxidized form of cysteine), which lead to an increase in glutamate shuttle to the out of cell by the glutamate-cystine antiporter. This action stimulates the inhibitory type 2/3 metabotropic glutamate receptors.¹⁰ Both metabotropic and ionotropic receptors may play a role in aggression. Among glutamate receptors, NMDA receptors seem to be the most promising targets for pharmacological intervention in treating aggression.¹¹

In six cases we reported who did not benefit from a large number of psychotropic medications for serious aggression and self-harm, it was observed that there was a significant or much improvement in two cases, at least a clinical improvement in two cases and no benefit in two cases. Side effect occurred only in one patient. These data demonstrate beneficial effects without serious adverse effects of adding NAC to the treatment for treating irritability in children with autistic disorder.

Conclusion

Regarding its safety profile and beneficial effects, clinicians may consider adding NAC to the treatment regimen in autistic children who respond poorly to conventional treatments. To assess the safety and long term efficacy of NAC in children with autistic disorder, clinical trials with also larger sample sizes are needed.

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Table 1. Evaluation of treatment responses in terms of age, gender, NAC dose and irritability and aggression

	Age/gender	NAC dosage/day	CGI-S before NAC treatment	CGI-s after NAC treatment	CGI-I	The severity of side effects
Case 1	12 / F	1200 mg	7	4	2	1
Case 2	17 / F	1200 mg	7	5	3	1
Case 3	13 / M	1200 mg	7	7	4	1
Case 4	9 / F	400 mg	5	3	2	1
Case 5	13 / M	1200 mg	7	7	4	3
Case 6	13 / M	1200 mg	7	6	3	1

CGI-S: Clinical Global Impression-Severity of illness; 0=Not assessed, 1=Normal, 2=Borderline mentally ill, 3=Mildly ill, 4=Moderately ill, 5=Markedly ill, 6=Severely ill, 7=Among the most extremely ill patients

CGI-I: Clinical Global Impression-Global improvement; 0=Not assessed, 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Minimally worse, 6=Much worse, 7=Very much worse

The severity of side effects: (1) none, (2) do not significantly interfere with patient functioning, (3) significantly interferes with patient functioning, (4) outweighs therapeutic effect

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