CASE REPORT

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Use of Clonidine in Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorder Comorbidity: Report of 3 Cases

Rahime Duygu Temeltürk[1], Gökçen İlçioğlu Ekici[2], Gökçe Yağmur Efendi[3], Birim Günay Kılıç[1]

[1]Department of Child and Adolescent Psychiatry, Ankara University, Faculty of Medicine, Ankara, Turkey; [2]Department of Child and Adolescent Psychiatry, Ankara Bilkent City Hospital, Ankara, Turkey; [3]Department of Child and Adolescent Psychiatry, Şanlıurfa Mehmet Akif İnan Training and Research Hospital, Şanlıurfa, Turkey

ABSTRACT

Clonidine has been widely used in child and adolescent psychiatry, especially in attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), which are recently categorized under neurodevelopmental disorders. However, it is not recommended as a first-line medication for treatment, and current data on the use of clonidine are limited. Herein, we present 3 cases with ADHD and ASD comorbidity, if any, as well as other neurodevelopmental disorders, including intellectual disability and Tourette's disorder, treated with clonidine. At the second-month follow-up, substantial improvements were observed in subscale scores of Conners's Parent Rating Scale-Revised Long Form, and Autism Behavior Checklist. Our case report indicated that clonidine is well tolerated, safe, and effective in improving both ADHD- and ASD-related symptoms as well as disruptive, aggressive behaviors and tics in children with multiple neurodevelopmental disorders.

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INTRODUCTION

Clonidine was first approved in the 1960s for the treatment of hypertension. Since then, it has been used for other indications such as Tourette's syndrome (TS), autism spectrum disorder (ASD), and attention deficit/hyperactivity disorder (ADHD) in the field of child and adolescent mental health.[1-4] Clonidine is an alpha-2 adrenergic agonist and regulates noradrenergic systems directly acting on presynaptic autoreceptors of locus coeruleus neurons, which decreases noradrenaline release and indirectly stimulates postsynaptic alpha-2 adrenergic receptors in the prefrontal cortex.[5] Both mechanisms reduce hyperactivity, impulsiveness, and aggressive behaviors, which are frequently observed in ADHD and ASD.[2,3,5,6]

Research has revealed that over half of children and adolescents with ASD have ADHD comorbidity.[7] In children with both diagnoses, atomoxetine and methylphenidate are generally used for their ADHD symptoms; however, as it is known, efficacy is lower and side effects emerge more frequently, especially in children with intellectual disability (ID).[8] Besides, risperidone and aripiprazole are used for their other frequent symptoms, such as irritability, aggression, sleep problems, and stereotypes. Nevertheless, atypical antipsychotics are of concern due to their metabolic side effects.[9]

Considering the reasons mentioned above, an alpha-2 agonist such as clonidine might be an alternative and ideal preference. It is used with increasing frequency in treating psychiatric disorders; however, our knowledge regarding the effects of clonidine on special groups is still insufficient, especially in cases with multiple neurodevelopmental disorders.

All 3 cases had a diagnosis of ASD accompanied by ADHD in common, who applied to Ankara University Faculty of Medicine, Department of Child and Adolescent Psychiatry Outpatient Clinic. All of them exhibited persistent and refractory aggressive behavior that remained unresponsive to alternative pharmacological interventions. Case 1 at the school-age stage had a prior follow-up in different centers. Upon his first visit to our facility, clonidine treatment was initiated. The other 2 cases were adolescents who had been under our outpatient care since early childhood and were prescribed clonidine during their follow-up period. Hence, to demonstrate the effects of clonidine in child

Corresponding author: Rahime Duygu Temeltürk, e-mail: rduygukaydok@gmail.com

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and adolescent psychiatry practice, 3 cases are presented before and after clonidine treatment with a description of the symptoms related to psychiatric disorders. Informed consent was provided by the parents for this case report.

Before and after 2 months of treatment, each case was evaluated regarding ADHD and ASD core symptoms, irritability, oppositional, and conduct behaviors. As assessment tools, Conners's Parent Rating Scale-Revised Long Form (CPRS-R/L), and Autism Behavior Checklist (ABC)were used. Written informed consent was obtained from the parents of each case for publication.

CASE PRESENTATION

Case 1

A 7-year-old boy had been followed at other medical centers for different periods before applying to our child psychiatry department with his parents. His parents complained about his inattention and distractibility problems during homework, disruptive and aggressive behaviors (e.g., physical hitting) in the classroom and at home, involuntary motor movements (shoulder shrugging, eye blinking), and disturbing noisy sounds such as sniffling and grunts. After our psychiatric evaluation, he was diagnosed with ASD, ADHD, and TS. His current medications prescribed in other child psychiatry outpatient clinics included atomoxetine, risperidone, and haloperidol. These pharmacological treatments slightly reduce the severity of motor-vocal tics, hyperactivity, irritability, and conduct problems that disrupt the social adaptation. Therefore, to decrease aggressive behaviors and tic symptoms, we started on clonidine 0.025 mg treatment combined with atomoxetine 25 mg per day. We gradually increased the dose to 0.1 mg (divided into 2) and 40 mg per day, respectively. After 2 months, Yale Global Tic Severity Scale (YGTSS) score results showed significant attenuation in motor (−32%, from 25 to 17) and vocal (−50%, from 20 to 10) tic scores, and the level of impairment in functionality decreased from 30 to 10. Furthermore, there were significant improvements in CPRS-Inattentive (−54.54%, from 22 to 10), CPRS-Hyperactive/Impulsive (−38.88%, from 18 to 11), and CPRS-Combined (−47.5%, from 40 to 21) subscale scores and in the ABC scale (−23.68%, from 114 to 87 on total scores, and −43.75%, from 16 to 9 on Social and Adaptive Skills scores).

MAIN POINTS

- The comorbidity of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) is highly prevalent among children and adolescents.
- Clonidine demonstrates favorable tolerability, safety, and efficacy profiles in ameliorating symptoms related with both ASD and ADHD.
- The administration of Clonidine treatment results in a substantial reduction of tic symptoms and displays enhanced therapeutic efficacy in children with ASD, ADHD and Tourette's syndrome comorbidity.
- Clonidine is a crucial alternative pharmaceutical option for the treatment of children with multiple neurodevelopmental disorders.

Case 2

A 15-year-old male patient has been followed up at our clinic since he was 2 years of age. He was diagnosed with ADHD, moderate ID, and ASD. Throughout his treatment process, a variety of pharmacological agents (atomoxetine, risperidone, and haloperidol-biperiden) had been used for his hyperactivity, impulsivity, and irritability symptoms; however, he still had severe aggressive behaviors such as biting and hitting. He also had difficulties with sleep maintenance. Therefore, to reduce these behavioral problems, clonidine (0.05 mg/day) was started, while haloperidol (presently used) treatment was gradually reduced. Six weeks later, we increased the dose to 0.3 mg/day, which was continued as the maintenance dose. Two months after treatment, CPRS subscale scores decreased significantly compared to the previous state—40% (from 25 to 15), 45.45% (from 22 to 12), 42.55% (from 47 to 27) in CPRS-Inattentive, CPRS-Hyperactive/Impulsive, and CPRS-Combined subscales, respectively. Additionally, there were reductions in ABC Total (−13.9%, from 151 to 130) and Social and Adaptive Skills (−22.72%, from 22 to 17) scores.

Case 3

An adolescent boy aged 14 diagnosed with ASD, ADHD, and moderate ID has been followed up at our outpatient clinic since his early childhood. During this long-term follow-up period, multiple pharmacological treatments were used besides psychosocial interventions. Initially, methylphenidate treatment was started to reduce hyperactivity complaints but had to be stopped due to side effects such as restlessness and sleep disturbances. Risperidone and aripiprazole were used to decrease aggressive self-harm behaviors, motor stereotypes, and insomnia; however, these treatments could not be continued because of side effects such as increased appetite and body weight. Thus, after these negative experiences, it was agreed to start with the initial dose of 0.1 mg/day clonidine for his treatment and increase it to 0.4 mg/day. At the end of the second month, positive changes were also determined in this case. The CPRS-Inattentive (−30.76%, from 26 to 18), CPRS-Hyperactive/Impulsive (−41.66%, from 24 to 14), and CPRS-Combined (−64%, from 50 to 18) subscale scores and ABC (−16.91%, from 136 to 113 on total and −20%, from 20 to 16 on Social and Adaptive Skills) scores were significantly better compared to before clonidine treatment.

DISCUSSION

After an 8-week course of treatment, substantial improvements in ADHD and ASD core symptoms, disruptive

behaviors, and aggressive problems were obtained in all 3 cases. Besides, oppositional behaviors and conduct problems, which could be comorbid situations in ADHD, showed substantial decreases. Moreover, sleep problems in the second and third cases were significantly better compared with their initial state. Finally, comparing the tic severity before and after treatment in case 1, a significant reduction in the YGTSS score was recorded.

To date, various studies have been conducted on clonidine, although there are few compared to other medical treatments for the coexistence of ASD and ADHD. In a randomized, double-blind, placebo-controlled study, significant improvements were found in the hyperactivity and irritability symptoms of children with ASD with clonidine use in parent and teacher reports.[10] In a more recent randomized controlled trial, another alpha-2 agonist, extended-release guanfacine, was used instead of clonidine in children and adolescents with ASD and ADHD. After 8 weeks of treatment, it was determined that there were significant attenuation in the hyperactivity, impulsivity, and distractibility symptoms, and their general functionality was improved.[11]

While examining the effect of clonidine on positive outcomes for sleep disorders among children with ADHD and ASD, promising results have been reported with clonidine. It was announced that the use of clonidine at bedtime benefitted the reduction of sleep disturbances associated with ADHD or its treatment.[12] An open-labeled retrospective study was conducted to examine the effect of clonidine in children with ASD. It was established that clonidine was effective on sleep issues by facilitating sleep initiation and maintenance. Additionally, ADHD symptoms, emotion regulation problems, and aggression levels were relatively improved in those children.[13] Finally, a recent systematic review addressing clonidine usage for behavioral disturbances in ASD concluded that clonidine was relatively insufficient for recommendation in this group. However, researchers suggest that among children and adolescents with ASD, those with symptoms such as hyperactivity, impulsivity, sleep problems, aggression, and self-harming behaviors have the most potential to benefit from the treatment.[2]

Our case report results indicated that clonidine reduced tic symptoms and was a more helpful treatment in cases with ADHD, ASD, and TS comorbidities. This finding is consistent with previous research that provides evidence for the effectiveness of clonidine on tic symptoms among children with ADHD.[3,14]

It has been observed that clonidine was well tolerated, and no significant side effects were experienced in most cases. Sedation and fatigue, the most common side effects, could even be desired in some patients.[10,11,13] Similarly, there were no significant side effects other than sedation in our patients.

Although both guanfacine and clonidine are effective agents as monotherapy or augmentation agents for ADHD, in many countries, such as Australia and Canada, only guanfacine is approved as a treatment option.[15] Although guanfacine is generally preferred over clonidine for treating ADHD and ASD due to its more favorable side effect profile, greater selectivity for relevant receptors, superior efficacy in clinical trials, and once-daily dosing convenience,[16] to date, no study directly supports the assertion that guanfacine is superior to clonidine in a head-to-head comparison.[17] Until recently, approval from the Turkish Pharmaceuticals and Medical Devices Agency was mandatory for both guanfacine and clonidine for psychiatric conditions in Turkey. Due to this additional and often time-consuming step in the process of obtaining drugs, their usage was limited in Turkey. However, extended-release guanfacine has only recently entered our clinical practice. Hence, guanfacine may become a substantial alternative medicine in Turkey, especially for children with intellectual disabilities, ASD, and ADHD. On the other hand, clonidine exhibits robust binding and activity at presynaptic alpha-2 adrenergic receptors, with a potency approximately tenfold greater than that of guanfacine at these specific receptor sites. This nonselective pharmacological profile and potent presynaptic actions are thought to play a significant role in clonidine's pronounced sedative effects for targeting aggressive behaviors and sleep disturbances.[2,5]

In these case series, we focused mainly on the beneficial effects of clonidine in children and adolescents with comorbid ASD and ADHD. All 3 cases clinically showed improvements in core ASD and ADHD symptoms and associated behavioral problems. Clonidine is an essential alternative drug to be considered for treating children with multiple neurodevelopmental disorders. However, it is important to acknowledge certain limitations in this case report. First, the limited scope of this case report, encompassing only 3 cases, poses potential constraints on the generalizability of the findings to a broader population. Additionally, the absence of a control group or comparison to alternative treatments prevents a direct assessment of clonidine superiority over other interventions. Furthermore, the duration of follow-up was relatively short, preventing a comprehensive evaluation of the long-term effects and sustainability of clonidine therapy. Finally, subjective measures and reliance on caregiver reports introduce potential bias and may not capture the full range of outcomes. Further research with larger sample sizes, controlled designs, longer follow-up periods, and objective outcome measures is warranted to provide a more robust understanding of the effectiveness and limitations of clonidine in children and adolescents. Additionally, investigating the mechanisms of action underlying clonidine's therapeutic effects and incorporating objective outcome measures would contribute to more precise evaluation and evidence-based

guidelines for optimizing the clinical management of neurodevelopmental disorders.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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