Combination of aripiprazole and valproate in children with tic disorders: Case series

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Tics are characterised by involuntary, repetitive movements and vocalisations that significantly impair affected children's quality of life. These disorders, primarily originating in the basal ganglia, are often misdiagnosed and inadequately treated. The exact aetiology of tic disorders is believed to involve a combination of genetic, neurobiological and environmental factors. Stress is an exacerbating factor leading to an increase in tic frequency and intensity.

We present three cases of children diagnosed with tic disorders and who exhibited substantial improvement through a combination of aripiprazole and valproate. The children, aged 7 to 15 years, had previously received various treatments with limited success. Upon switching to the combined therapy of with aripiprazole and valproate, they showed marked improvement in tic severity and associated behavioural issues. The combination treatment requires further research to validate our observations and to refine treatment protocols for children with tic disorders.

Keywords. tic disorders; aripiprazole; valproate.

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Tics are one of the most prevalent movement disorders in children.[1] The symptoms may resemble other disorders, such as behavioural disorders or seizures, hence misdiagnosis often occurs.[2] The course of tic disorders usually manifests between ages 3 to 8 years of life and may diminish when reaching adolescence.[1] However, some cases persist until adulthood and may develop into chronic and more complex conditions.[3] Tics also occur in Tourette syndrome. Tic disorders are more common in boys with a ratio of 3:1, compared with 4:1 in girls.[1]

Management of tic disorders is challenging and often requires individualised treatment.[4] Single therapy administration frequently proves ineffective, so combination therapy may be needed.[5] The use of the antipsychotics aripiprazole or risperidone is commonly used in tic disorders, accompanied by behavioural disorders.[3] The recommended combination is the use of aripiprazole with guanfacine,[4-6] but guanfacine is still rarely available in Indonesia, prompting the use of alternative combinations such as aripiprazole with valproate. While valproate has shown efficacy in reducing symptoms of Tourette and tic disorders, its combination with aripiprazole has not been extensively studied.[6]

Cases

Case 1

A 7-year-old boy, weighing 30 kg, presented with jerking movements, primarily in his hands, which interfered with his daily activities. The symptoms worsened with anxiety and were initially misdiagnosed as seizures. Previous treatments provided only temporary relief. His condition deteriorated after transferring to a new school. He was initially treated with 0.3 mg risperidone twice a day and 125 mg valproate twice a day, along with dietary interventions. He was on gluten-free diets and dairy-free diets. However, there was no significant improvement after 1 week and he also developed vocal tics. The therapy was switched to 3 mg aripiprazole and 125 mg valproate twice a day, while maintaining his gluten-free and dairy-free diet. After 1 month, he presented with a marked improvement. Movements were less frequent and limited to times of physical exertion or swimming. Over 6 months, his symptoms gradually disappeared. While on this treatment, he remained symptom-free and had no academic problems during 18 months of observation.

Case 2

The second patient, a 9-year-old boy, weighed 28 kg, experienced neck shaking along with twitching brows and tics of his hands since the age of 6. The movement was triggered initially by emotional distress. His symptoms worsened with stress, lack of sleep, and excessive video gaming. When he was unable to sleep, he would play video games and consume sugary foods. He was then initiated on 0.2 mg risperidone twice a day, which showed limited success. During this period, he also struggled with behaviour control. Switching to 2 mg aripiprazole per day and 125 mg valproate twice a day improved his emotional regulation and tic symptoms. The latter treatment was then continued to complete resolution after 3 months. No tics were noted after 1 year of observation.

Case 3

The third patient, a 15-year-old boy weighing 35 kg, developed uncontrollable lip movements and stuttering, which caused social embarrassment and withdrawal. He also experienced involuntary eyebrow-raising and several hand movements. The symptoms worsened with discomfort and fear. He was treated with 3 mg aripiprazole at night and 10 mg fluoxetine daily. After 2 weeks, he experienced nausea and new behavioural issues emerged. He was reported to have compulsive masturbation, but he was able to sleep

well at night. The treatment was then adjusted to 3 mg aripiprazole per day and 125 mg valproate twice a day. Over the course of 3 months, the tics and compulsive behaviour ceased and his speech improved. After 1 year of therapy, he showed no involuntary movements or compulsive behaviours. He also came third in a regional drawing competition representing his school.

Discussion

Our cases demonstrated chronic tic disorders persisting for over a year, with motor disturbances in various body parts. According to the DSM-V (Diagnostic and Statistical Manual of Mental Disorders - V) criteria, tic disorders must have an onset before age 18 and not be attributable to other conditions like Huntington's disease, substance use or medication side effects.[1] Chronic tic disorders are diagnosed with either motor or vocal tics persisting for at least one year while Tourette syndrome is diagnosed when both motor and vocal tics are present.[1]

Tic disorders predominantly affect boys with recent literature indicating a higher prevalence and severity in males. Comorbid conditions like obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD) are also more common in boys.[2] Tic disorders are aggravated by stress or emotional disturbances. While stereotypical movements are more rhythmic, coordinated and not aggravated by emotional disturbances, these movements are ego-syntonic or the patient usually feels comfortable with these repetitive movements.[2]

Antipsychotics play a crucial role in managing tic disorders, particularly when first-line treatments are unavailable. They block dopamine (D2) receptors, reducing tic severity by ~70%.[4] The commonly used antipsychotics include haloperidol, risperidone, pimozide, aripiprazole, olanzapine and ziprasidone.[4] Tic disorders also occur when there are imbalances of neurotransmitters (in the basal ganglia), e.g. glutamate, gamma-aminobutyric acid (GABA), and acetylcholine, which contribute to the symptoms.[5]

Disturbances or imbalances in the basal ganglia can occur through two mechanisms: direct and indirect pathways. The direct path is related to stimulation mechanisms, while the indirect pathway involves inhibitory mechanisms. The mechanism for the emergence of normal movement occurs in the basal ganglia and involves the cerebral cortex, neostriatum, globus pallidus (internal and external) and thalamus. These inhibitory and excitatory mechanisms involve two main neurotransmitters, GABA and glutamate. In individuals with tics and Tourette syndrome, the inhibitory mechanism within the basal ganglia is impaired, leading to the failure to block unnecessary signals from reaching the motor cortex. As a result, involuntary movements occur. This phenomenon is believed to arise from reduced inhibition in the basal ganglia and increased motor pathway activity, resulting in the unintended execution of movements.[7]

Dopamine plays a role in the development of tic disorders. When dopamine binds to the D1 receptor, it will activate the direct pathway which causes the thalamus to release excessive glutamate and contributes to tic movements. Conversely, when dopamine binds to D2 receptors, it will inhibit the indirect pathway, resulting in increased glutamate projections by the thalamus which causes tic disorders.[7]

Tic disorders are often exacerbated by stressors such as anxiety, emotional disturbances, and lack of sleep. Effective coping mechanisms can mitigate stress-induced symptom aggravation, but children often lack these skills, necessitating behavioural therapy alongside pharmacological treatment.[6] Aripiprazole is an atypical antipsychotic with a partial agonist action on pre-and post-synaptic dopamine receptors. This will decrease dopaminergic action which causes a reduction in symptoms. Aripiprazole has been approved for treating tic disorders in children and adolescents by the Food and Drug Administration (FDA).[4]

All three cases involved a combination of valproate for treatment of tics. Valproate enhances GABAergic activity in the basal ganglia pathways, mitigating excessive movements.[6] It also addresses impulse control disorders (ICD) that can arise from dopaminergic treatments, as seen in the third case. The combined therapy effectively controlled both tics symptoms and associated behavioural issues.[5] In the third case, the use of aripiprazole (with its partial agonist dopaminergic activity) contributed to ICD symptoms and excessive masturbation. By administering valproate, ICD symptoms were improved. Additionally, valproate blocks the calcium channels, which help suppress ICD and emotional instability, thereby reducing tics symptoms. A prior randomised controlled trial also compared valproate to aripiprazole showing that both treatments led to significant tic reduction, although the valproate group responded to treatment faster.[8] There is also a report of an interaction between aripiprazole and valproate, suggesting both medications may cause asymmetric tremors.[9] Valproate was also reported to exert little cognitive decline.[10] However, these effects were not observed in our cases and need further study.

Conclusion

The combination use of aripiprazole and valproate demonstrates efficacy in reducing tic disorders in children. Aripiprazole has been approved by the FDA for the treatment of tics in children. Its combination with valproate provides a robust therapeutic approach, which has been associated with an improvement in the symptoms of impulse control disorder. Further research is needed to explore the potential and mechanisms of this combination therapy.

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