Movement Disorders
CLINICAL PRACTICE

Methylphenidate Can Improve Chorea in *NKX2.1* and *ADCY5* Mutation-positive Patients—A Report of Two Children

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Benign hereditary chorea (BHC) is an autosomal dominant disorder presenting with generalized chorea involving the face, tongue, neck, trunk, or limbs, which often worsens during stress or excitement. It is caused by mutations in the *NKX2.1* gene and is characterized by an early onset, a stable or only slightly progressive course, and absence of cognitive decline.[1]

Chorea can also be the predominant feature in patients with *ADCY5* gene mutations, which manifest with a plethora of clinical features, including early childhood-onset mixed hyperkinetic movement disorder. Other characteristic signs include perioral dyskinesia, dysarthria, and hypotonia. Development can be delayed and in some severe cases there is mental retardation.[2]

Here, we report the favorable effect of methylphenidate in two boys with *NKX2.1*-related chorea and *ADCY5* gene mutation-associated disease where methylphenidate, in addition to positive effects on attention-deficit hyperactivity disorder related symptoms in the boy with *NKX2.1*-related chorea, also lead to marked and clinically meaningful improvement of chorea, gait stability, fine motor skills, and speech in both boys.

Patient 1 is now 15 years old. He was first noted to have excessive movements at the age of 6 months. Pregnancy and birth were normal. Motor milestones were delayed. Ever since he was able to walk, he had brief, abrupt, and irregular, unpredictable movements affecting the whole body and causing frequent falls. A heterozygous mutation in exon 2 of *NKX2.1* gene (c.204C>G, p.Tyr68*) had previously been found. He had hypothyroidism. He had also been diagnosed with attention deficit hyperactivity disorder on the basis of a parent-based questionnaire (Fremdbeurteilungsbogen für Aufmerksamkeits/Hyperaktivitätsstörungen [FBB-ADH]) reflecting both DSM-IV and ICD-10 diagnostic criteria commonly employed in German paediatric population with good reliability and content validity. The patient's caregiver completed the questionnaire, with results above the diagnostic threshold. However, it should be pointed out that no formal neuropsychological testing was performed.

On examination at the age of 11, he was easily distractible and inattentive. He had generalized chorea that affected the perioral and lingual muscles that increased when standing and walking and during fine finger movements. Of note, his gait was choreic with markedly impaired postural stability (Video S1a, online supporting information). Coordination was mildly impaired. Handwriting was slow and interrupted by chorea and his speech was slightly slurred and hypophonic.

The boy was initially treated with 5 mg methylphenidate bd, with some improvement. To achieve a better effect, particularly at school, we changed the dose to 7.5 mg methylphenidate in the morning and 2.5 mg in the early afternoon. Using this regime, symptoms further improved. The boy could walk unassisted and attend sport lessons. A walking aid was needed only for longer distances. Handwriting also improved and became legible. Medication was then changed to slow release methylphenidate. A dose of 36 mg methylphenidate in the morning led to a stable effect lasting the whole day (Video S1b). About a year later, at the age of 13, the positive effect of methylphenidate on chorea decreased leading to more frequent falls and increased hyperactivity. Therefore, the dose was increased to 54 mg methylphenidate, which again caused considerable improvement allowing him to walk unaided. On follow-up examination, even tandem gait could be performed. His symptoms, particularly chorea, deteriorated when he was 14 while he was still on a dosage of 54 mg slow release methylphenidate and then improved again when the dosage was increased to 72 mg mane.

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Patient 2 is now 19 years old. He has previously been described in a genetic study.[2] He presented with severe psychomotor and developmental delay, general hyperkinesia, gait instability, and episodes of weakness. Premature birth was documented. He grew up in a children's home in Bulgaria and was adopted by German foster parents at the age of 2 years. At this time, he was neither able to walk nor able to speak. At his foster parents' home, he gradually caught up and learned to walk and to speak, although voluntary control of his movements and coordination was impaired and his speech was slurred (Video S2a).

On examination, at the age of 13 years, he was hyperactive with a poor attention span and showed distractibility and increased impulsivity. There was mild stuttering and moderate dysarthria. Saccades were slightly hypometric and vertical and horizontal latencies were prolonged. He was slightly hypotonic and bradykinetic bilaterally. He had generalized chorea that affected the perioral and lingual muscles and intermittent retrocollis. There was also mild dysmetria and dysdiadochokinesia. He walked with a slight sway, but postural stability was preserved.

Genetic testing revealed a heterozygous mutation in exon 17 of the *ADCY5* gene (c.3045C>A, p.Asp1015Glu). Immediate release methylphenidate (10 mg four times a day)—later adapted to slow release methylphenidate (30 mg once daily)—significantly improved attention, concentration, and motor skills. Chorea almost completely subsided and dysarthria improved (Video S2b). Episodes of weakness also decreased in frequency and then stopped completely.

Although chorea (e.g. in Huntington disease) is typically responsive to antidopaminergic drugs, chorea in BHC has been shown to worsen by such treatment and to improve following dopaminergic medication.[3] This might be explained by nuclear imaging findings. For instance, using [^{11}C]-CFT to measure presynaptic dopamine transporter function and [^{11}C]-raclopride to determine postsynaptic D2 receptor function, positron emission tomography (PET) imaging in two *NKX2.1* gene mutation-positive patients revealed normal CFT binding, but decreased raclopride binding in the striatum.[4]

The mode of action of methylphenidate is not completely understood. Increases of extracellular dopamine in the brain appear to be most relevant.[5] Methylphenidate competitively inhibits dopamine transporters. Such blockade reduces dopamine reuptake resulting in a significant dopamine accumulation in the extracellular space.

This could be the basis of the effectiveness of methylphenidate in our patient with *NKX2.1*-related chorea overcoming reduced D2 receptor availability as outlined above. On the other hand, the effect of methylphenidate might also be explained by its proposed activating action on presynaptic D2 and D3 autoreceptors leading to a reduction of impulse triggered vesicular dopamine release, which in turn reduces dopamine signaling at postsynaptic D1 and D2 receptors causing a reduction of motor hyperactivity. It also has to be considered that methylphenidate modulates the activity of different brain regions as a function of the dopamine D2 receptor composition leading to either increases or decreases in cortical and subcortical metabolism.[6]

On the basis of the clinical course in the two cases described here and previous reports,[7,8] it is possible that methylphenidate might have direct anti-choreic properties, at least in genetically determined diseases such as *NKX2.1*-related chorea and *ADCY5* gene mutation-positive patients. As these are developing adolescents, one could not exclude the fact that many of the observed effects might have been random fluctuations in the process of becoming older. However, given the small number of patients reported so far and the fact that the clinical effects outlined in this case series were not substantiated on the basis of established rating scales and were not corroborated by independent blinded assessment more studies are needed before methylphenidate can be recommended as a treatment option for children with chorea.

Author Roles

J. Tübing, J. Bohnenpoll, Dr. J. Spiegler, Dr. T. Bäumer, Prof. J. Sperner and Prof. A. Münchau cared for the patients and initiated the treatment with methylphenidate. Prof. G. Gillessen-Kaesbach, C. Max and Prof. C. Klein were involved in the genetic analyses. J. Tübing wrote the first draft. All authors revised the paper critically.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this and that all patients gave their informed consent prior to their inclusion in the study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

A video accompanying this article is available in the supporting information here.

Video S1. (a) The video shows the patient at the age of 11. He has generalized chorea compromising fine motor control and mild dysmetria. Chorea also interferes with walking leading to a swaying gait and impaired postural control. (b) Following methylphenidate treatment, at the age of 12, choreic movements are reduced considerably. Gait stability and postural control are also markedly improved.

Video S2. (a) The first three segments are videos taken at home by the parents. They show the boy at the age of 13. They document generalized chorea while the boy is sitting on the lawn while manipulating a pocket-knife (first segment), when sitting down to have breakfast (second segment) and while lying on a carpet shortly after he had an attack of weakness (third segment). (b) This segment shows the boy in clinics a few months later while taking 30 mg slow release methylphenidate. It can be appreciated that chorea is less pronounced compared to segments 1–3. Finger and hand movements are somewhat slow and clumsy. There is dysdiadochokinesis but no dysmetria. Also, speech is normal.