Low-Dose Aripiprazole and Risperidone for Treating Problem Behavior in Children With Pitt-Hopkins Syndrome

To the Editors:

Pitt-Hopkins syndrome (PTHS) is a neurodevelopmental disorder characterized by moderate to severe intellectual disability, pronounced language delay, epilepsy, episodic hyperventilation and/or breath-holding, constipation, severe myopia and facial dysmorphism with microcephaly, deep-set eyes, broad nasal bridge, and tented upper lip.[1,2] It is an autosomal dominant disorder caused by haploinsufficiency of the *TCF4* gene (transcription factor 4), located on 18q21.2.[1] TCF4 protein is highly expressed during early human development throughout the central nervous system and is said to be involved in intellectual disability, epilepsy, autism, and schizophrenia.[2,3] Overall prevalence of PTHS is unknown.[1,4] The behavioral phenotype is characterized by features of autism spectrum disorder and frequent motor stereotypies, such as body rocking, hand biting, and hand-washing movements.[1,3,5] Sleep problems are described as problems falling asleep, problems sleeping the whole night through, and night terrors. The disorder is often associated with feeding difficulties and an anxious or agitated disposition.[5] Maladaptive behaviors, such as shouting, outbursts of aggression, and self-injury, may occur.[1,3] As far as we know, there is no literature on the psychopharmacological treatment of these emotional and behavioral problems. This report describes 2 sisters with PTHS who were treated with low doses of aripiprazole and risperidone in an open-label trial. Written informed consent was obtained from the parents.

CASE REPORTS

Patient A showed an early developmental delay with hypotonia and a wide-based gait. She was diagnosed with PTHS at the age of 10 years. Child psychiatric assessment 1 year later showed severe intellectual disability, severe language delay, and features of autism spectrum disorder with poor contact, verbal perseveration, and echolalia. At the age of 13 years, her parents consulted with a child psychiatrist because of increased agitation and perseveration, anxieties associated with unanticipated changes in routine, and anhedonia. There was considerable distress for the child as well as for her parents, and a trial therapy of aripiprazole at low dose (0.5 mg/d) was started (weight 37.6 kg). A beneficial effect was seen the next day. Two weeks later, the dose was augmented to 0.5 mg twice daily. Another 3 weeks later, the dose of aripiprazole was lowered to 0.4 mg twice daily because of fatigue and falling asleep early. A year later, the anxieties and anhedonia were still under control with the current dose; the falling asleep early persisted.

Patient B is patients A's 2 years younger sister and had a similar delay of early development. She was diagnosed with severe intellectual disability, absent active language development, and autism spectrum disorder and was diagnosed with PTHS at the age of 9 years. She showed motor stereotypies, a short attention span, and frequent temper tantrums. Because of sleeping problems during her first years, several medicines (melatonin, clobazam, ethyl loflazepate, and chloral hydrate) were prescribed by child neurologists. Because of little or paradoxical effects, these products were stopped. At the age of 6½ years, she was seen by a child neurologist for sleeping problems, hyperactive behavior, shouting, unprovoked excessive laughing, aggression, and self-injury. Risperidone was started and augmented to a dose of 0.25 mg twice daily (weight 22.1 kg). Because of increased fears after startup of risperidone (anxiety attacks, being afraid to go to bed alone), the dose was lowered to 0.1 mg in the morning and 0.15 mg at night a few weeks later. The fears disappeared, but the previously described symptoms returned. After a dose adjustment to 0.2 mg twice daily, 3 months after startup, the patient slept better, but her behavior was not yet under control. Because of the behavioral difficulties with agitation, the dose of risperidone was augmented to 0.25 mg twice daily, a month later. This resulted in a paradoxical effect with anxiety attacks, upon which the dose of risperidone was lowered to 0.25 mg in the morning and 0.2 mg at night a few weeks later. At the age of 8 years 10 months, the parents consulted with a child psychiatrist because of increased agitation when confronted with changes, hurting other children, groaning, shouting, and hand biting. A slow switchover of risperidone to aripiprazole (1 mg/d for a body weight of 25.5 kg) resulted in sleepless nights and agitation during the day. A dose adjustment 2½ weeks later, combining risperidone (0.1 mg in the morning and 0.2 mg at night) and aripiprazole (0.5 mg twice daily), left the girl quiet, relaxed, and content. The shouting diminished, and she slept better. The groaning remained. After a dose increase of aripiprazole to 1 mg in the morning and 0.5 mg at night a month and a half later, temper tantrums and agitation increased. Two months later, doses were adjusted to risperidone 0.1 mg in the morning and 0.2 mg at night and aripiprazole 0.6 mg in the morning and 0.5 mg at night. Because of agitation and behavioral problems at school, a dose increase of aripiprazole 0.7 mg in the morning and 0.5 mg at night was attempted 2 weeks later, retaining the dose of risperidone. Because of increased shouting and aggression a year and a half later, the dose of aripiprazole was reduced to 0.4 mg twice daily, in combination with risperidone 0.1 mg twice daily (for a body weight of 33.8 kg), with favorable effect on the behavioral difficulties. Motor stereotypies remained.

Up to December 2016 MEDLINE, Web of Science, EMBASE, Cochrane, and PsycINFO were searched for studies on the pharmacological treatment of behavioral problems in PTHS. The combination of MeSH terms "Pitt-Hopkins syndrome" and "Problem Behavior" or "Pitt-Hopkins syndrome" and "Drug Therapy" delivered no results. The search terms were broadened to the MeSH term "Pitt-Hopkins syndrome" (MEDLINE 30 results [77 without MeSH terms], Web of Science 139, EMBASE 108, Cochrane 1, and PsycINFO 21 results). Thirteen relevant articles were selected.

DISCUSSION

When behavior modification for self-injury or anxieties in PTHS proves to be insufficient, there are no guidelines on psychopharmacological treatment.[4,6] It is necessary for one to fall back on general clinical guidelines for pharmacological treatment of problem behavior in intellectual disability and/or autism. A recent meta-analysis indicated that short-term use of antipsychotics can have a positive effect on problem behavior in intellectually disabled children.[7] In order to minimize adverse effects, it is recommended to start with a very low dose, to increase the dose very slowly, and to use the lowest effective dose.[8] In children with intellectual disability, problem behavior, and autism, there is evidence for the efficacy of atypical antipsychotics in the short term.[7,9,10] Risperidone can have a positive effect on irritability, social withdrawal, hyperactivity, and stereotyped behavior. There is a risk of weight gain, and the effect of long-term treatment is unknown.[7]

Aripiprazole in daily doses of 2 to 15 mg in short-term treatment can have a positive effect on irritability, hyperactivity, and stereotypies.[11] The risk of adverse effects, such as weight gain, drooling, somnolence, headaches, increased prolactin, and extrapyramidal symptoms, is real.[8,9] The positive effect may persist after discontinuation of aripiprazole.[11] Risperidone is a dopamine D_2 receptor and 5-HT_2 receptor antagonist. Aripiprazole is a partial dopamine D_2 and 5-HT_{1A} receptor agonist and a 5-HT_2 receptor antagonist and is seen as a dopamine system stabilizer. It may act as an antagonist when the synaptic concentration of dopamine is elevated or may act as a D_2 receptor agonist when the concentrations of dopamine are low.[9] A dopamine imbalance in different regions of the brain could lead to autistic behavior, whereby both hypoactivity and hyperactivity of the dopamine system are suggested.[12–17] The positive effect of very low doses of atypical antipsychotics and increase of complaints with dose augmentation in this open-label trial (n = 2) suggest that the balance of the dopamine system in these children with PTHS is complex and very sensitive. This could potentially be linked to the function of the *TCF4* gene, responsible for PTHS. Variants of this gene may be involved in altered dopaminergic transmission in schizophrenia.[18] Genome-wide studies have shown that variants of *TCF4* are associated with a higher risk of schizophrenia.[19,20] A mutation in the *TCF4* gene could affect the dopamine system in children with PTHS, possibly leading to hypersensitivity to small dose changes of atypical antipsychotics. Further research in this area is needed.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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Rhabdomyolysis of Multifactorial Origin in Schizophrenia
Antipsychotics, Statins, Trauma

To the Editors:

Rhabdomyolysis is a serious syndrome caused by direct or indirect muscle injury. It results from the death of muscle fibers and release of their contents into the bloodstream (creatine kinase, potassium, phosphorus, myoglobin, etc). The symptoms are varied: muscular pain, weakness, dark urine, general feeling of malaise, fever, tachycardia, and so on.[1] A prompt diagnosis is recommended to prevent future serious complications (such as acute renal failure, shock, or even death).

There are many causes of rhabdomyolysis, such as genetic, endocrine, infection, intense exercise, trauma, drugs, and so on.[1] Antipsychotics and statins have been found to induce rhabdomyolysis, with cases involving these drugs being the most published.[2]

We describe a clinical case with several characteristics: (*a*) severe psychiatric disorder, (*b*) various types of medications (statin, antipsychotics, benzodiazepine, and anticholinergic), and (*c*) severe rhabdomyolysis with positive outcome.

CASE REPORT

The patient was a man aged 67 years who was institutionalized since the age of 6 years. A clinical history of illness since adolescence was reported. He was diagnosed as having residual schizophrenia (CIE-10). He has no additional psychiatric diagnosis. He has received a variety of treatments but with no response. For 6 years up to date, he has been taking the following: fluphenazine decanoate, 1 vial of 25 mg every 4 weeks; biperiden, 1 vial of 5 mg, every 4 weeks: quetiapine 300 mg, 1 tablet every 24 hours; and biperiden 4 mg slow release, 1 tablet every 24 hours. The patient's clinical picture is characterized predominantly by defective