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Case Report

Medication Treatment in an Adolescent Female with *FOXP1* Mutation -

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ABSTRACT

FOXP1 mutations/deletions are associated with Intellectual Disability (ID), language impairment, behavior problems, autism spectrum disorder (ASD) features, and dysmorphic facial features. As the FOXP1-phenotype continues to be characterized, it is important to document and evaluate psychopharmacological treatments that may help to manage the behavioral symptoms in affected patients. This case report describes the medication management of a 16-year-old female with a *FOXP1* mutation, ID, Attention-Deficit/Hyperactivity Disorder (ADHD), obsessive-compulsive behavior, anxiety, and language delays. Her medications included methylphenidate extended release for ADHD management, aripiprazole for mood stabilization and aggressive behaviors, and clomipramine for obsessive-compulsive behaviors.

Keywords: *FOXP1* gene; Medication management; Psychopharmacology; Autism; ASD; *FOXP1* related neurodevelopmental disorder; *FOXP1* syndrome

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by two core symptom domains: impaired social communication and the presence of restricted, repetitive patterns of behavior or interests [1]. ASD is highly heterogeneous with varied expressivity and differences in the severity of clinical symptoms and functional impairments as well as high genetic heterogeneity. Several genes have been found to be associated with ASD, including FOXP1, but more genes remain to be discovered. Recent studies have shown the functional convergence among ASD-related genes on pathways that are involved in synaptic development, plasticity and signaling, raising the hope of new therapeutic strategies that may be effective for different forms of ASD [2-4]. Behavioral therapy and educational interventions remain the first-line treatment for ASD; however, pharmacological treatment can be effective for managing a wide array of behavioral features. Genetic testing is the standard of care recommended for all children diagnosed with ASD and more than 25% of children with ASD have an identified genetic cause [5]. Therefore, carefully documenting psychopharmacological management of children with specific genetic causes of ASD is needed in this era of genomics [6].

Since the initial description of a boy with a deletion of the *FOXP1* gene by Pariani, et al. (2009) [7-17] at least 18 more patients have been reported in the literature. The *FOXP1* gene belongs to sub family P of the Forkhead box (FOX) transcription factor family. Forkhead box transcription factors play important roles in the regulation of tissue- and cell type-specific gene transcription during development through adulthood. The FOXP1 protein contains DNA-binding- and protein-protein binding-domains [18] and is a transcriptional repressor, necessary for the proper development of the brain, heart, and lung in mammals [19,20].

Clinical characterization of individuals with *FOXP1* mutations/deletion describes associations with intelectual disability (ID) with or without ASD features, as well as with moderate to severe language delays that particularly affect expressive language. Most patients have articulation difficulties and some have verbal dyspraxia. Common dysmorphic features include broad forehead, down-slanting palpebral fissures, and a short nose with a broad tip, macrocephaly, frontal hair upsweep, and prominent digit pads. Behavioral problems include irritability, hyperactivity, mild to moderate aggression, and restricted and repetitive behaviors. The FOXP1-phenotype remains to be well characterized using systematic and prospective assessments and to date, there are no reports about potential treatments.

Here, we describe the pharmacological treatment of a previously reported patient [17] in order to begin documenting effective psychopharmacological regimens in individuals with *FOXP1* alterations.

CASE AND TREATMENT

The patient is a 16-year-old female with a *de novo FOXP1* variant c.1267_1268delGT (p.V423Hfs*37) discovered on whole exome sequencing. She has a history of ASD, ID, Attention-Deficit/Hyperactivity Disorder (ADHD) with predominantly inattentive symptoms, obsessive-compulsive behavior, anxiety, and expressive language delay with articulation difficulties. The patient's heterozygous *de novo FOXP1* variant was determined to be pathogenic and considered to be the etiology of her ID and ASD.

The patient was born at 37 weeks gestation to a 32-year-old mother with prenatal care. She was delivered via C-section secondary to concerns about oligohydramnios and pre-eclampsia. The patient's parents did not recall the APGAR scores, and the birth records were not available. At birth, she was noted to have a 2-vessel umbilical cord and significant hypotonia, but did not require resuscitation and was able to be discharged from the hospital with her mother three days after birth. Her birth weight was five 5 pounds, 4 ounces. There were no neonatal complications.

The hypotonia persisted through infancy and initially lead to the diagnosis of cerebral palsy. She was evaluated for neuromuscular disorders including testing for muscular dystrophy, mitochondrial disorders, and nerve conduction studies which were all normal. She was noted to have delays in achieving motor and language milestones as well as deficits in adaptive self-help skills. She did not begin crawling until 12 months, walking occurred at 20 months, and her first word was not until 24 months. The patient was toilet trained during the day at 5 years old (she still has intermittent nocturnal enuresis) and could dress herself by 10 years old although she continues to need help manipulating buttons.

Behaviorally, the patient has problems with inattention and was diagnosed with ADHD at age 7. She also has difficulty with social communication and social relatedness in addition to her expressive language deficits. She has restricted interests and repetitive/compulsive behaviors, which include using tape to laminate year book photos which she keeps with her and "treats like they are her [living] friends" - she talks to them, feeds them, and puts them to sleep. She re-laminates the pages up to three times a day making the photos appear worn and hard to visualize by other people. She also has rigid adherence to her routines and will become upset if they are disrupted. She exhibits oppositional behavior and outbursts triggered by frustration. She sometimes acts out aggressively (such as yelling, pounding on the walls, throwing things, hitting and stomping her feet) during these outbursts. She does not have any self-stimulatory or self-injurious behaviors. The patient has been in special education throughout her schooling. An Autism Diagnostic Observation

Figure 1: 15-year-old female with *FOXP1* mutation.
Facial features include: mild ptosis, facial hypotonia, prominent upper lip, open-mouth stance, micrognathia, a gap between her upper central incisors, high arched palate, and a slightly low-set and posteriorly-rotated ears with underdeveloped earlobes bilaterally.

Schedule (ADOS) assessment at the age of 12 years had a total score of 14 consistent with the diagnosis of ASD. A cognitive assessment at 14 years-old with the Wechsler Intelligence Scale for Children-fourth edition (WISC-IV), resulted in a full-scale IQ of 54 with a verbal comprehension index of 59, perceptual reasoning index score of 67, working memory index score of 50, and processing speed index score of 70.

On exam, the patient had normal vital signs. Her growth parameters were in the average range with a height of 162 cm (47 %ile), weight 54.4 kg (59 %ile), and BMI 20.87 kg/ m2 (61 %ile). She was noted to be macrocephalic (+4 SD; 58.5 cm), with dysmorphic facial features including mild ptosis, facial hypotonia, prominent upper lip, an open-mouth stance, micrognathia, a gap between her upper central incisors, and a high arched palate. Her ears were slightly low-set and posteriorly rotated with underdeveloped earlobes bilaterally. She had a bridged palmar crease on the left hand, and high arches on both feet. Her muscle tone, bulk, and strength were normal in the extremities. No foot drag was noted while walking or running although she has a history of a mild right foot drag. Her gait was wide based and she had trouble balancing on either foot, and with tandem walking. The rest of her physical exam was within normal limits. She was cooperative throughout the exam, and answered questions directed to her in short sentences, but had poorly modulated eye contact. Her speech was about 50% intelligible due to articulation difficulties. She did not exhibit any aggressive behaviors on the exam.

Previous investigations done in addition to the neuromuscular workup included an electroencephalogram (EEG), which was within normal limits, and magnetic resonance imaging (MRI) of her brain, which showed multiple non-enhancing subcortical and deep white matter abnormalities, as well as a venous angioma in the left frontal lobe. A Chromosomal Microarray Analysis (CMA) in 2012 did not detect any pathogenic aberrations. The CMA was followed by whole exome sequencing, which found the *de novo* heterozygous c.1267_1268delGT variant in the *FOXP1* gene as noted.

Pharmacotherapy interventions to address the patient's ADHD, anxiety, and obsessive-compulsive behaviors, and aggression have included methylphenidate ER, sertraline, clomipramine, and aripiprazole. To target attention deficit, methylphenidate ER 36 mg daily was used successfully for several years, beginning at age 10. Brief periods off methylphenidate ER were attempted, but the patient's mother noted that with the medicine she was more focused, with improved mood, and less oppositional.

A trial of sertraline 25 mg daily was started at age 14 initially in an attempt to decrease anxiety and compulsive behaviors. The patient did not have noticeable improvements on the 25 mg dose after about 2 months, so the dose was increased to 50 mg, which caused activation and worsening aggression and obsessive-compulsive behaviors. Sertraline was then tapered and discontinued and the behaviors returned to baseline.

Aripiprazole 1 mg daily was then added to the methylphenidate ER 36 mg at age 14 to address mood dysregulation and aggression. She had only mild improvement after two months, so the dose was increased to 2 mg. On aripiprazole 2 mg daily, the patient had significantly fewer outbursts. Although outbursts still occurred, they involved yelling and the aggression subsided almost entirely. Side effects with aripiprazole included increased appetite and weight gain of approximately 15 pounds.

Obsessive-compulsive behaviors still needed to be addressed more directly as they significantly disrupted her functioning at both school and home. After adapting to the increased dose of aripiprazole, clomipramine 25 mg was added at bedtime, which dramatically decreased her obsessive-compulsive symptoms within 2 weeks. However, she had an increase in nocturnal enuresis (from every two weeks at baseline to every other day) and the clomipramine dose was switched from bedtime to morning. After nine months on clomipramine 25 mg, her obsessive symptoms increased again and the dose was titrated to 50 mg daily. However, the increased dose resulted in behavioral activation and was reduced back to 25 mg.

By 15 years old, the patient's treatment with methylphenidate ER was discontinued due to lack of efficacy and she continued on aripiprazole 2 mg and clomipramine 25 mg daily. With advancing age and likely pubertal onset, her aggressive and compulsive symptoms were significantly exacerbated, required dose titrations of both medicines. By 16 years old, the patient was on aripiprazole 10 mg and clomipramine 100 mg daily with good effect and without significant tolerability issues.

DISCUSSION

Selective Serotonin Reuptake Inhibitors (SSRIs), such as sertraline, have been used therapeutically in patients with idiopathic

ASD and Fragile X syndrome to target repetitive behaviors with mixed success. In typically developing children and adults, on the other hand, sertraline has demonstrated efficacy for treating symptoms of anxiety, depression, and Obsessive-Compulsive Disorder (OCD). However, a significant percentage of typically developing children, as well as children with ASD and other neurodevelopmental disorders, may experience hyperarousal or behavioral activation with SSRIs. Hyperarousal associated with SSRIs can include worsening symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, psychomotor restlessness, hypomania/mania, worsening depression, and suicidal ideation [21]. Treatment with sertraline was attempted in our patient and while lower doses were ineffective despite an adequate trial, she became activated at 50 mg and the medication had to be discontinued. Another SSRI, citalopram, did not effectively treat repetitive behaviors in a large multi-centered controlled trial in children with ASD and several patients also demonstrated hyperarousal [22]. While our experience with this patient is not adequate to make medication treatment recommendations, it is clear that SSRIs, if used, should be monitored carefully.

Clomipramine is a tricyclic antidepressant which also blocks serotonin reuptake [23] and is FDA approved for the treatment of OCD in children over 10 years of age. However, limited evidence exists to support its use in children with developmental disabilities [24]. Our patient with the *FOXP1* mutation initially benefited from taking clomipramine, but again appeared sensitive to increased blockade of serotonin reuptake and became activated. Unlike with sertraline, lower doses appeared at least partially effective and clomipramine 25 mg was then continued. As the patient aged and advanced in her development, she has challenged again with higher doses of clomipramine and eventually came to tolerate up to 100 mg daily with good effect. It is, of course, unknown what role *FOXP1* mutations play in predicting efficacy or tolerability to serotonergic medication.

Methylphenidate ER is a psychostimulant medication used to treat ADHD symptoms that acts mainly on dopaminergic systems [25]. A Study assessing the effects of methylphenidate in children with ASD have found improvements in ADHD symptoms [25]. Our patient with the *FOXP1* mutation was also reported to have improved mood while on methylphenidate.

Aripiprazole is a partial agonist at the dopamine and is FDA approved for the treatment of irritability in children with ASD [26]. Research assessing the effects of aripiprazole in children with ASD has shown reductions in hyperactivity and stereotypy in addition to irritability. Irritability in patients with ASD can manifest as aggression, tantrums, rapidly changing moods, and self-injurious behaviors [27,28]. Aripiprazole significantly helped our patient to decrease her aggressive behaviors, although the dose needed to eventually be titrated to 10 mg daily. Evidence from large randomized controlled trials of aripiprazole suggests that doses between 5 and 15 mg daily are effective at targeting irritability in ASD. Possible side effects of aripiprazole include weight gain, which can be associated with metabolic syndrome (eg: elevated fasting glucose, abnormal lipid profiles), as well as extrapyramidal symptoms such as tremor, psychomotor hyperactivity, akathisia, and dyskinesia [28]. Our patient gained 15 pounds after starting aripiprazole, but fasting glucose and lipid profile remained stable.

Future translational studies in animal and human neuronal model systems may provide new insights into the pathogenesis and treatment of patients with *FOXP1* variants. A mouse model (brain-specific *Foxp1* deletion) has shown disruption of the developing striatum and the hippocampus as well as reduced excitability and an imbalance of excitatory to inhibitory input in CA1 hippocampal neurons [29]. *Foxp1* KO mice also show various cognitive and social deficits, in addition to repetitive and hyperactive behaviors similar to those described in affected humans [29]. Additional clinical studies are still needed to determine the nature and extent of the cognitive, behavioral and medical phenotype in children and adolescents with *FOXP1* variants. However, clarifying the cellular and synaptic deficits associated with *FOXP1* variants, and preclinical studies of targeted treatments, will eventually inform clinical trials to develop more refined psychopharmacological interventions for affected individuals.

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