Behavioral phenotype in a child with Prader-Willi syndrome and comorbid 47, XYY

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Summary

We report a 12-year-old male with Prader-Willi syndrome (PWS) and 47, XYY syndrome. Genetic work up revealed 47, XYY karyotype. PWS diagnosis was made by polymerase chain reaction methylation and maternal uniparental disomy (mUPD) was determined to be the etiology. Review of distinct behavioral features, possible interplay between the two syndromes and considerations for diagnoses are presented. To our knowledge, this is the first report of behavioral features in PWS with comorbid 47, XYY.

Keywords: Prader-Willi syndrome, 47, XYY, autism spectrum disorder, attention deficit hyperactivity disorder

1. Introduction

Prader-Willi syndrome (PWS) and 47, XYY syndrome both are rare genetic conditions and their concurrence is even rarer. Each is characterized by discrete physical and behavioral features. PWS is a neurodevelopmental disorder resulting from loss of function or deletion of genes in a particular region of chromosome 15 (critical region 15q11-q13) (1). About 70% cases are due to deletion of the gene segment on paternal chromosome 15. About 25% cases are due to maternal uniparental disomy (mUPD) which means both copies of chromosome 15 are maternally inherited instead of one from each parent (1). Other cases are attributed to translocations and genomic imprinting defects. Clinical features of PWS include neonatal hypotonia, childhood onset hyperphagia with subsequent obesity, hypogonadism, short-stature, facial dysmorphism along with significant neurological, cognitive and behavioral abnormalities. Common behavioral features in PWS are food seeking behavior, resistance to change, irritability, skin picking and temper tantrums. These are a source of significant impairment. Secondly, 47, XYY syndrome is caused by the presence of an extra Y chromosome in each cell due to nondisjunction i.e. an error during cell division. Patients may go undiagnosed and may be diagnosed during evaluation for tall stature. The XYY phenotype commonly includes tall stature, macrocephaly, macroorchidism, hypotonia, hypertelorism, and tremor (2). Behavioral abnormalities may not always be present and vary widely among affected individuals. When abnormalities do occur, patients may have learning disabilities, delayed development of speech, language and motor skills. Feature in common for the two syndromes is risk for autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD).

2. Clinical Report

We discuss a 12-year-old Caucasian male with diagnosis of PWS and 47, XYY syndrome who presented to our clinic. He was born full term to a healthy 27-year-old gravida 1, para 1 mother. Perinatal history was significant for reduced fetal movements and a three pound weight loss in mother around 38 weeks of gestation. Ultrasound showed diminished umbilical cord flow and the mother was induced but she failed to progress. Therefore, patient was delivered by emergency C-section after he showed non-reassuring heart tones. Birth weight was 2,700 g and...
APGAR scores were 6 and 7. At delivery, he had PWS specific features such as hypotonia, feeding difficulties with poor respiratory effort and received resuscitation for the same. Subsequently, he required Neonatal Intensive Care Unit (NICU) admission and treatment with surfactant for several days. Patient had micropenis and bilateral undescended testes, both commonly seen in PWS. He showed global developmental delay and intellectual disability. He sat by himself at 6 months of age, crawled at 11-12 months of age and walked independently at 19 months of age. He started speaking words at 2 years of age. He has been receiving special education. Patient received growth hormone from age 6 months to 11 years. It was stopped at 11 years at the request of the parents because of attainment of optimum growth.

According to his parents, he relies on schedule and insists on sameness. They reported- "The schedule is comforting and rules really help him navigate". When given an advanced notice and/or explanation patient was better able to tolerate deviations from the schedule or anticipated events. He has a particular interest in sports and his conversations are focused on teams and players. He is a devoted fan of a sports team and may become quite upset if they lose. Parents denied food seeking behavior. They do not restrict the range of foods he eats, but monitor his calorie intake.

Past history is significant for a 20 pounds weight gain around age 10 years. He lost the weight during an eight week hospitalization at an inpatient program for Prader Willi patients. He also had periods of increased aggression and hitting at the time and was started on escitalopram by his doctor to address his anxiety. He had an adverse reaction to the medication as demonstrated by increased irritability, tantrums, aggressiveness, restlessness and disrupted sleep. Therefore, escitalopram was discontinued. Owing to his aggression, irritability and frustration he was started on a stimulant at the time and continues to take methylphenidate to date. He achieved better symptom control, ability to articulate his feelings and internal experiences by saying things he felt rather than acting out. It also improved his attention, memory and possibly contributed to the weight loss.

On psychiatric evaluation at our clinic, his major issue was anticipatory anxiety which was evident in his repeated questioning, particularly with regards to events in future. Questioning stopped once he was reassured and knew what to anticipate. Thus, difficulty tolerating changes in routine was noted. He also demonstrated anxiety around new things and frequently asked "why?" to requests during the clinical encounter. He became very anxious when his abdomen was exposed for physical exam and was noted to have an exaggerated emotional response to disappointment. He demonstrated repetitive behavior like rubbing his forehead. C-YBOCS (Children’s Yale-brown Obsessive Compulsive Scale: Modified for ASD) score was 16 which is moderately high. Preoccupation and restricted range of interest with regards to sports and his favorite teams was noted. He did not demonstrate hyperphagia, food related obsessions, skin picking, hoarding behaviors, self-injurious behavior, suicidal ideation, impulsivity, hyperactivity, psychotic features and seizures.

Neurological exam showed high threshold for pain, temperature dysregulation, low tone and clumsiness. Patient was not overweight at the time of evaluation. His weight and height have been trending in 75th and 80th percentile respectively. Laboratory reports showed slightly raised LDL and hematocrit levels.

3. PWS and 47, XYY syndrome

The clinical history and presentation of the patient identified anticipatory anxiety as a major behavioral issue. PWS has been shown to be a highly complex psychological disorder with multiple areas of disturbance and anxiety could be a part of this symptom complex (3,4). His repetitive behavior, resistance to change and temper outbursts can be attributed to behavioral phenotype of PWS (5,6). Patient demonstrates many but not all behavioral symptoms typically seen in PWS. He did not manifest hyperphagia, food seeking behavior and skin picking which are common in PWS. It would be interesting to seek if this is a result of interplay between the two genetic disorders.

The fact that patient responded well to stimulants may indicate an underlying component of ADHD. Patient did not manifest hyperactivity and impulsivity which are common in ADHD. This also raises the question whether patients with PWS and 47, XYY have atypical presentation for ADHD. Skokauskas et al. noted ADHD-like behavior in PWS patients in their research study (7). Bardsley et al. performed a cohort study that showed higher prevalence of ADHD and ASD in men with with XYY (2). Thus, patients with 47, XYY should be evaluated for both (8). This patient has PWS and XYY, so he is at increased risk of having ADHD and ASD. The case highlights the importance of evaluating patients with PWS and comorbid 47, XYY syndrome for ADHD and ASD. PWS is a genetic syndrome in which careful attention to comorbidities and details regarding all potential behavioral and somatic manifestations can lead to a significant improvement in health.

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