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Case Report

Turner Syndrome Complicated by a *NONO* Gene Variant

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Abstract

Non-POU domain-containing octamer-binding (*NONO*)-associated X-linked intellectual disability syndrome (NAXIS) is a rare disorder characterized by findings that include cardiomyopathy, feeding difficulties, intellectual disability, and seizures that has previously been reported only in males. Here, we describe a girl with Turner syndrome (TS) due to (45,X/46,X,r(X)) mosaicism. She demonstrates typical features of TS, such as a bicuspid aortic valve and growth failure, but also displays symptoms not typical of TS that are more severe than expected in classic TS. Whole-exome sequencing revealed a likely pathogenic variant in the *NONO* gene, providing an explanation for her unexpected symptoms. This case highlights the importance of considering an evaluation for X-linked disorders in individuals with TS presenting with atypical symptoms, as this can assist the family and the medical team with expectant management.

Key Words: *NONO* gene, Turner syndrome, *NONO*-associated X-linked ID syndrome

Abbreviations: NAXIS, *NONO*-associated X-linked intellectual disability syndrome; *NONO*, non-POU domain-containing octamer-binding; r(X), ring X chromosome; TS, Turner syndrome; *XIST*, X-inactive-specific transcript.

Introduction

Turner syndrome (TS) is a chromosomal disorder, most commonly monosomy X, that affects 1 in 2500 live female births [1]. Girls present with short stature, characteristic dysmorphic features, cardiac defects, renal malformations, and hypogonadism secondary to dysgenetic ovaries [2]. Care for individuals with TS is multidisciplinary and involves input from multiple subspecialties both for symptom management and anticipatory care. Typically, overall intelligence in these individuals is considered normal [2].

Non-POU domain-containing octamer-binding (*NONO*)-associated X-linked intellectual disability syndrome (herein referred to as NAXIS) is a rare X-linked intellectual disability syndrome (<25 reported cases) characterized by features overlapping with TS, such as cardiac defects and growth failure, but also seizures, hypotonia, and feeding difficulties. Diagnosis of NAXIS involves identification of variants in the causative gene and thus are not diagnosed via karyotype. We present a girl with mosaic TS due to a ring X chromosome and an atypical presentation subsequently diagnosed with NAXIS.

Case Presentation

A female neonate, born at 35 weeks' gestation via emergent cesarean delivery for nonreassuring fetal heart tracings, was suspected of having TS based on noninvasive prenatal screening. The pregnancy was complicated by intrauterine growth restriction, and she was born weighing 1400 g. Postnatal echocardiogram revealed a bicuspid aortic valve and, later, a juxtaductal coarctation of the aorta requiring intervention. Renal ultrasound revealed a horseshoe kidney with mild hydronephrosis. Her newborn course was complicated by episodes of hypoglycemia, hyperbilirubinemia requiring phototherapy, thrombocytopenia, and vocal cord paralysis requiring nasogastric tube feedings. By age 7 months, she developed severe mitral stenosis requiring valvuloplasty.

Postnatal karyotype revealed a 45,X[4], 46,X + r(X)[16] mosaicism, confirmed by interphase fluorescence in situ hybridization (62.5% 46,X,r(X) and 37.5% 45,X). A single-nucleotide variation microarray identified a pathogenic terminal deletion on Xp22.33-p11.23, a pathogenic terminal deletion of Xq21.2-q27, and a duplication of 11p15.4 of uncertain significance on the ring chromosome. The X-inactive-specific transcript (*XIST*) gene was present on the ring X, so it was expected that her phenotype would be similar to that of monosomy X due to preferential inactivation of the abnormal X chromosome.

Despite the presence of the *XIST* on the ring chromosome, the patient exhibited global developmental delays and poor symmetric growth by age 1 year (Fig. 1). She was demonstrating poor weight gain despite fortified feeds via a gastrostomy tube and was receiving occupational therapy, speech therapy, and physical therapy. Additional complications included hip dysplasia, conductive hearing loss, reflux and aspiration pneumonia requiring a Nissen fundoplication, and obstructive sleep apnea with laryngomalacia. Early physical examinations conducted by the geneticist revealed dysmorphic features including mild redundant nuchal skin, shortened fifth metatarsals, pes planus, hypotonia, widened maxillary alveolus, and a down-turned mouth, but no lymphedema of the extremities, neck webbing, stigmata of neurocutaneous disease, Madelung deformity, or shortened fifth metacarpals characteristic of TS. At age 2 years, she continued to demonstrate poor growth and

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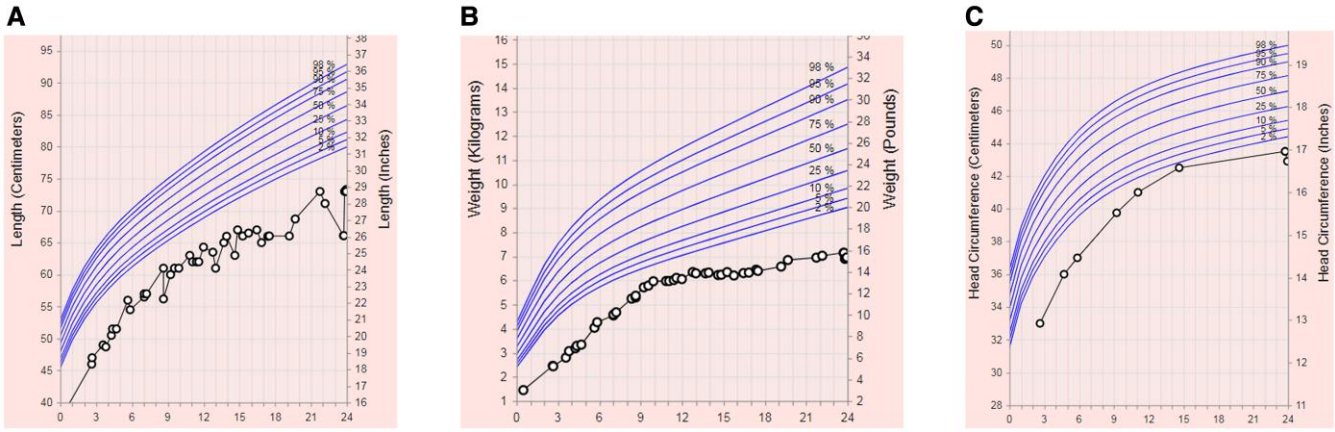

Figure 1. Anthropometric data for birth through 24 months using standards from the World Health Organization: A, length; B, weight; C, head circumference. Source: World Health Organization Growth Chart Standards.

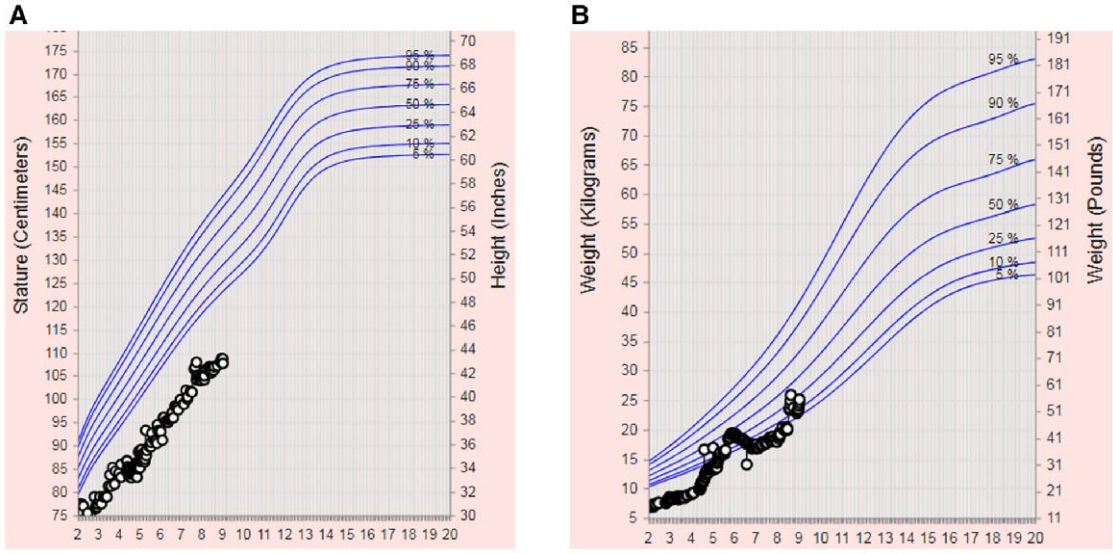

Figure 2. Anthropometric data for age 24 months to 9 years: A, Height on Centers for Disease Control (CDC) growth chart; B, weight on CDC growth chart. Source: Centers for Disease Control Growth Chart Standards.

was started on growth hormone under the indication of TS. At age 4 years, she developed autoimmune pancytopenia requiring intravenous immunoglobulin, transfusions, filgrastim, and glucocorticoids with multiple relapses. Also at this time, she developed recurrent staring episodes that were initially observed in infancy that had now reemerged.

Diagnostic Assessment

Prompted by the mixture of developmental delays and staring episodes, whole-exome sequencing was conducted that identified a likely pathogenic gene variant (c.1136_1137delAG: p.Glu379AlafsX54 in exon 11) in the *NONO* gene, a frameshift variant that is predicted to result in protein truncation. This variant is consistent with a diagnosis of NAXIS.

Treatment

The patient's staring episodes were diagnosed as nonlesional focal epilepsy from the right posterior quadrant and were treated with antiepileptic pharmacotherapy. Growth hormone therapy, interrupted between years 3.75 and 6.8 due to poor weight gain and pancytopenia treatment, was resumed and is ongoing. Autoimmune pancytopenia is monitored regularly.

Outcome and Follow-up

As part of continued management of her epilepsy, a magnetic resonance image of her brain was obtained. This revealed nonspecific hyperintensities in the subcortical/deep white matter. There were no reported abnormalities seen in the thalamic, hypothalamic, or pituitary regions. Her epilepsy remains well controlled.

She is responding to growth hormone well on a current growth hormone dosage of 0.36 mg/kg/week. She is growing at a rate of 5 cm/year (Fig. 2). Her pancytopenia remains stable.

Discussion

While classic TS is characterized by monosomy X, a subset of patients (6%-7%) instead have a ring X chromosome (r(X)) [3]. When a ring chromosome is present, much of the clinical

presentation depends on whether part of the genetic material deleted in forming the ring includes the *XIST* gene locus. When the *XIST* gene is preserved on the r(X), this typically leads to preferential inactivation of the abnormal X chromosome, which mitigates the effect of the abnormal chromosome resulting in a phenotype similar to monosomy X [2]. It is when the *XIST* is included in the genetic material deleted in forming the r(X) that individuals have a more severe phenotype, with an increase in cognitive difficulties and congenital malformations because the abnormal X chromosome is expressed rather than inactivated. Our patient, despite an intact *XIST*, displayed profound developmental and cognitive impairment unusual for someone whose r(X) has an intact *XIST* with other findings not typical of TS, such as seizures, hypotonia, and feeding difficulties ultimately found to have a variant in the *NONO* gene, which we now believe is the etiology of these additional findings.

The *NONO* gene, located on chromosome Xq13.1, is involved in gene regulation including genes involved in neuronal synapse [4, 5]. Loss-of-function variants cause NAXIS [6, 7]. This disorder is characterized by intellectual disability, dysmorphic facies, hypotonia, structural changes to the brain, and cardiac defects [4, 6]. Seizures, gastroesophageal reflux, and hematologic abnormalities, all of which were seen in our patient, have also been reported [4, 8].

To our knowledge, this is the first reported female case of *NAXIS*. There are 130 developmental disorder–associated genes located on the X chromosome, and variants in these are thought to result in X-linked developmental disorders, thus affecting predominantly males [9]. However, some literature suggests that skewed X inactivation and semi-dominant variants in females allows some women to display a phenotype of these disorders to some degree [9]. Our case demonstrates that co-occurrence with TS is another mechanism for females to be affected by an X-linked disorder. For example, Kaczorowska et al [10] describe a case of a girl with classic monosomy X TS who was also found to have a variant in the dystrophin gene resulting in an unusual presentation of a female with Duchenne muscular dystrophy. Our patient's autoimmune pancytopenia, while not specifically described in NAXIS, may represent a novel association.

Our patient underscores the importance of avoiding anchoring bias in attributing unusual symptomatology to a known underlying condition. For example, Vieira et al [11] describe a 16-year-old girl with cardiac abnormalities, failure to thrive, ear infections, and growth difficulties attributed to known neurofibromatosis; however, she was later found to have TS diagnosed secondary to primary amenorrhea, which likely contributed to components of her phenotype. Meena et al [12] report a girl evaluated for short stature and primary amenorrhea found to have TS, a common cause of both of these concerns, but with imaging that revealed Mayer-Rokitansky-Küster-Hauser syndrome that may have been overlooked if a further workup had not been pursued. Last, Bouayed Abdelmoula et al [13] describe a patient case of TS with hair loss found to have alopecia universalis, which is unusual as TS is instead associated with alopecia areata.

The present case highlights the importance in considering X-linked disorders in individuals with TS who present with an atypical phenotype not fully explained by a sole diagnosis of TS and the need for further investigation. It also underscores the need to avoid anchoring bias and pursue further genetic testing when an individual's clinical presentation deviates from expected findings of an established genetic diagnosis. Identification of the presence of these disorders in children with TS provides more of an opportunity for genetic counseling to help guide the family through additional medical issues their children may experience in addition to those associated with TS.

Learning Points

- Children with TS secondary to a ring chromosome that have an intact *XIST* gene locus do not typically display cognitive difficulties as a result of TS itself.
- Children with NAXIS typically present with developmental delay, dysmorphic facial features, cardiomyopathy, structural brain changes, hypotonia, and feeding difficulties.
- For children with TS who have atypical findings not expected from their genotype, consideration should be made to test for other X-linked disorders that are thought to predominantly affect males.

Contributors

Both authors made individual contributions to authorship. A.K. and P.S. were involved in manuscript creation and submission. P.S. was involved in the diagnosis and management of this patient. Both authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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