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A Boy 45X/46XY Mosaicism with ADHD: A Case Report

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Abstract

45X/46XY mosaicism is a rare chromosome disease. The apparent prevalence of males and females with 45X/46XY is 5.6 and 2.1 per 100,000 liveborn males and females. We present a boy who had a developmental delay with hypospadias. He was referred to pediatric genetics and was diagnosed with 45X/46XY mosaicism by peripheral blood chromosome examination. During serial rehabilitation programs, his speech delay was caught up. But his poor attention and hyperactivity are obvious progressively. We should pay attention to these patients, not only physical conditions but also psychological problems.

Keywords

45X/46XY Mosaicism, ADHD, Developmental Delay

1. Background

45X/46XY mosaicism is a rare sex chromosome abnormality. The apparent prevalence was 5.6 per 100,000 liveborn males and 2.1 per 100,000 liveborn females. [1] 45X/46XY patients reveal a wide range of phenotypes, from the normal female phenotype, which is usually considered Turner syndrome (TS), ambiguous genitalia, to the male phenotype with normal external genitalia. [2] Patients with Turner syndrome are at a higher risk for gonadal insufficiency, congenital heart and renal anomalies, acquired autoimmune conditions, poor linear growth, neurocognitive deficits, and a variety of other medical and psychological conditions [3]. There are some reports of poor linear growth, dysmorphic features commonly associated with Turner syndrome, congenital heart disease, and renal anomalies in individuals with male phenotype or ambiguous genitalia, although these are primarily case reports or descriptive studies without a comparison group, making it difficult to quantify the relative risk [4] [5]. They all grow up with different degrees

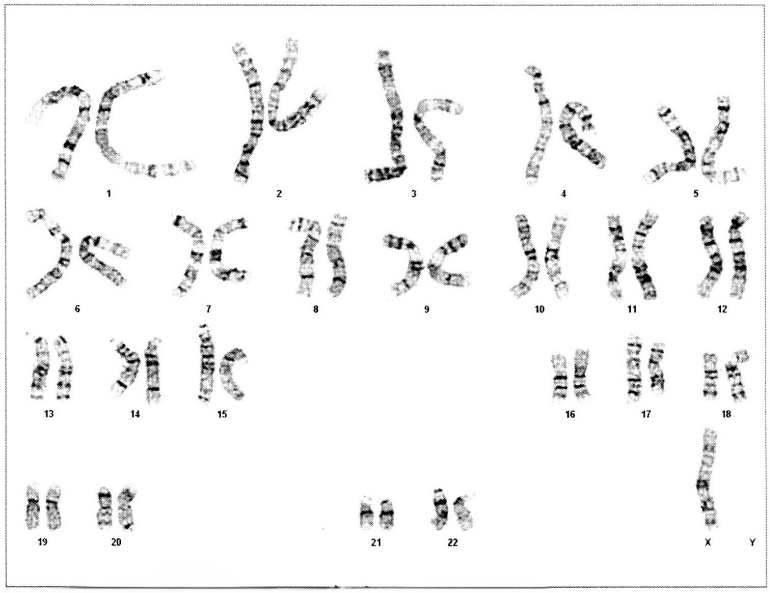
of short stature, especially in the female phenotype patients. [6]. Some female patients have clitoromegaly or no masculine appearance of external genitalia. Patients with male phenotype have hypospadias combined with or without cryptorchidism or small testicles. Gonadal dysgenesis is common in these patients. [6] [7] Gonadoblastoma risk is high in these patients as well. Growth hormone therapy is suggested for these patients with short stature. They should be routinely followed up for late-onset infertility and tumors. [7] However, less is known about the learning profiles, psychological risks, autoimmunity, or cardiometabolic disease in patients with male phenotype or ambiguous genitalia. So, we report this case to reveal neurodevelopmental aspects associated with the chromosome abnormality that we should also pay attention to.

2. Case Report

A boy aged 2 years and 5 months came to our clinic with his mother, who asked for a developmental evaluation because his speech development was not very well. He was found to have hypospadias since he was one month old. Then, he was referred to see a pediatric geneticist. Due to his light iris color and hypospadias with bend chordee, the genetic doctor highly suspected he had chromosome disease. Indeed, to the end, his chromosome exam showed 45X/46XY mosaicism (55%/45%). (**Figure 1**) He received an operation of urethroplasty with correction of chordee when he was one year old.

After a complete developmental evaluation, Peabody Developmental Motor Scales-Second Edition (PDMS-2) showed that he had the fine motor ability of a 1.8 - 1.11-year-old child, which was about 21%. Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) revealed speech comprehension & expression ability equaled to 1.9 years old child, which was about 2%. During the evaluation, therapists found that this boy had difficulty calming down, hyperactivity, and poor attention. According to this finding, he received speech therapy and occupational therapy (OT) for several months. When he was 3 years and 6 months old, he got 2nd developmental evaluation. The Sensory Integration Functions Assessment Scale showed he is a child with overall sensory integration dysfunction, especially in attention, hyperactivity, sensory management, sensory process, emotion, and behaviors. Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) showed Full-Scale IQ (FSIQ) 84 (14%), Verbal Comprehension Index (VCI) 88 (21%), Visual Space Index (VSI) 88 (21%), Working Memory Index (WMI) 82 (12%). Leiter International Performance Scale-Revised (Leiter R) showed his activity and impulse levels were higher. On the Werry-Weiss-Peters Activity Scale (WWPAS), he got 78, higher than the average of 47. Overall, the report showed his fine motor development was borderline delayed, combined with sensory integration (SI) dysfunction and symptoms of attention-deficit/hyperactivity disorder (ADHD). After that, he got OT and psychotherapy (PSY) for several months. When he was 4 years and 5 months, he got 3rd developmental evaluation. His fine motor and SI conditions were borderline delayed, but the symptoms of ADHD

persisted. His OT and PSY were continued. He also received art therapy for his ADHD condition. When he was 5 years 6 months old, he received 4th developmental evaluation. WISC IV showed FSIQ 84 (14%), VCI 93 (32%), VSI 85 (16%), WMI 66 (1%), Fluid reasoning index (FRI) 80 (9%) and Processing speed index (PSI) 108 (70%). Leiter R showed that his activity, impulse, attention, emotion, and adaptability were clinically significant. Chinese Version of the Swanson, Nolan, and Pelham Version IV Scale for ADHD (SNAP IV) revealed higher scores in attention, impulse, and hyperactivity aspects. His ADHD was diagnosed. No fine motor delay was found, but SI dysfunction persisted. Her mother had mentioned, "he is easily distracted by external noises, moves almost like an engine, often runs around, climbs up and down, is hyperactive, prefers to have things happening throughout the day, has difficulty calming down, and often interrupts by something, blurt out words without thinking". She was worried about his hyperactivity condition more than his physical condition. She hoped that his son could improve through early intervention and rehabilitation programs.



Chromosome Counts	44	45	46	47	Total
No. of Cells		11	9		20

Karyotype: 45,X,1qh+[11]/46,XY,1qh+[9]

Interpretation:

This study was performed on metaphase chromosomes from culture of PHA-stimulated peripheral blood lymphocytes. Twenty cells in metaphase were identified and analyzed. Eleven cells showed a karyotype of monosomy X [45,X,1qh+]. The remaining 9 cells showed a normal male karyotype [46,XY,1qh+]. The 1qh+ is a normal variant. Please correlate the cytogenetic finding with the client's clinical condition.

Figure 1. Interpretation of metaphase chromosomes from the culture of PHA-stimulated peripheral blood lymphocytes.

This case study has been confirmed by the Institutional Review Board (IRB). IRB proved that we don't need to inform his parents because there is no issue of personal data being leaked.

3. Discussion

There are few studies that mentioned children with mosaic monosomy X and Y chromosome material presented as different kinds of phenotype, ranging from normal female phenotype and ambiguous genitalia to normal male phenotype. [8] [9] According to the largest cohort study of 45, X/46, XY boys with normal or mild genital anomaly, they not only have short stature and gonadal dysfunction, they also have multisystem problems. [4] Such as congenital heart disease, structural renal disease, autoimmunity, dysmorphic features, multiple otitis media, orthopedic defect and psychomotor delay. But this paper didn't mention the details of psychomotor delay, which only happened in 10% of their study group. They suggest initial screening at diagnosis includes external genitalia, Turner syndrome (TS) dysmorphic features, skeletal defect, and psychomotor evaluation. Annual follow-up exams include pubertal progression, growth hormone monitor, testicular function, testicular tumor evaluation, autoimmune and metabolic evaluation, ENT, renal, cardiac or orthopedic follow-up depending on the initial evaluation, and proposition of fertility preservation at the end of puberty. [4]

TS is a phenotype of mosaic monosomy X and Y chromosome material. In studies of children with TS, the prevalence of attention-deficit/hyperactivity disorder (ADHD) has been reported to be around 24% [10] [11], in comparison to 1.8% in girls in the general population. [12] In another adult TS study, 7% of participants reached the diagnosis of ADHD [13], which can be compared to 2.5 - 3.5% of adult women in the general population [14] [15]. Overall, the prevalence of ADHD in TS is higher than in the normal population. According to a meta-analysis study in 2020, the prevalence of ADHD in children aged 3 to 12 years is 7.6%, and 5.6% of teenagers aged 12 to 18 years [16]. A systemic review study of ADHD in adults showed that males have more prevalence as compared to females [17].

Another study of X/XY children showed none in the X/XY 7 group were diagnosed with learning disability (LD), but the occurrence of LD in the X/XY female group was similar to that seen in TS [18]. Just as TS [3], LD involves nonverbal learning disability, lower performance IQ, articulation problems, reduced visual-motor performance, decreased coordination, and ADHD. X/XY female group of LD probably reflects the relative predominance of 45, X cell line compared to 46, XY in their brains and causing the similarity to female children with TS. As far as I know, the karyotype of brain cells has never been evaluated in children with TS or with those with X/XY syndrome. It may explain why our patient had ADHD.

The presence of 45,X cell line explains how X/XY children have abnormalities similar to girls with TS, so these children require clinical evaluation similar to that performed in girls with TS, including cardiovascular, renal, endocrine, growth

and development, autoimmune, psychological, and educational evaluation.

4. Conclusion

In our case, he had ADHD symptoms since 3y/o 6 months and was diagnosed with ADHD since 5y/o 6 months. This disease became the dominant problem, causing his learning disability. X/XY children require clinical evaluation just as that performed in female children with TS, including cardiovascular, renal, endocrine, growth and development, autoimmune, psychological, and educational evaluation. We suggest further reports can focus on psychological and educational fields.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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