Case Report

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A Rare Case of XXXXY Syndrome with a (4;19) Translocation from Northeast Iran

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Running Title XXXXY Syndrome and Translocation (4; 19) (p16.2; q13.3)

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ABSTRACT

49, XXXXY syndrome is a rare chromosomal abnormality, often considered a variant of Klinefelter syndrome. Commonly referred to as Fraccaro syndrome, it is characterized by a unique phenotype and more severe clinical features compared to Klinefelter syndrome, including developmental delays, intellectual disabilities, and a range of congenital anomalies. We present the case of a 13-year-old boy from northeastern Iran with a confirmed karyotype of 49, XXXXY. Cytogenetic analysis revealed a unique feature: a concomitant t(4;19)(p16.2;q13.3) translocation, which has not been reported in previous studies. The patient exhibited key clinical features, including intellectual disability, speech difficulties, developmental delays, short stature, and facial abnormalities such as deep-set eyes and a prominent nasal tip. Additional findings included a small penis, testicular atrophy, recurrent severe urinary tract infections, a history of patent ductus arteriosus (PDA), dental malformations, and hypotonia.

The karyotype of 49, XXXXY, along with the observed clinical features, facilitated the diagnosis of Fraccaro syndrome. The identification of the novel t(4;19)(p16.2;q13.3) translocation adds a unique aspect to this case and highlights the need for further research to understand the potential impact of additional chromosomal abnormalities on this rare syndrome.

Introduction

49, XXXXY syndrome, also known as Fraccaro syndrome, is a rare X chromosome aneuploidy with an estimated incidence of approximately 1 in 85,000–100,000 male births. First described by Fraccaro et al. in 1960, this syndrome is recognized as a severe variant of Klinefelter syndrome, though it exhibits distinct and more severe clinical features [1–4]. This condition results from maternal nondisjunction of the X chromosome during meiosis I and II, theoretically leading to an egg with four X chromosomes. When such an egg is fertilized by a Y-bearing sperm, the resulting embryo develops with a 49, XXXXY karyotype [5].

The characteristic phenotype of 49, XXXXY syndrome includes musculoskeletal abnormalities, intellectual disabilities, hypogonadism, and a range of congenital anomalies. Additional features include distinctive facial characteristics, short stature, cardiac defects,

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genital abnormalities, and varying degrees of speech and cognitive impairment. Unlike classical Klinefelter syndrome, 49, XXXXY syndrome is associated with distinct intellectual disabilities and facial features [6–7].

The biological mechanisms underlying 49, XXXXY syndrome are thought to involve two primary hypotheses. The first posits that the increased dosage of active genes located in regions of the X chromosome that escape inactivation plays a critical role. The second hypothesis focuses on the asynchronous replication of the additional X chromosomes. These chromosomal alterations may disrupt the precise regulation of gene expression, affecting both the quantity and timing of essential genetic activity [8]. Notably, studies suggest that maternal age does not influence the occurrence of this syndrome [9].

To date, over 100 cases of 49, XXXXY syndrome have been reported worldwide. In Iran, six cases had been documented as of 2023 [10]. In this report, we present the seventh documented case of 49, XXXXY syndrome in a 13-year-old male from northeastern Iran, referred to the cytogenetic laboratory at Ghaem Hospital in Mashhad. Notably, none of the previous studies have reported a concomitant (4;19) translocation, which is a unique feature observed in our patient.

Case presentation

A 13-year-old Iranian male was referred to the cytogenetics laboratory at Ghaem Hospital, Mashhad, Iran, for genetic evaluation due to multiple congenital anomalies, developmental delays, and intellectual disabilities. The patient was born preterm at 32 weeks of gestation via cesarean section due to oligohydramnios, with a birth weight of 2.1 kg, placing him below the 5th percentile for gestational age. The parents are non-consanguineous, and the patient has an older brother who is healthy. At the time of delivery, the mother was 28 years old, and the father was 29 years old.

The patient experienced developmental delays, beginning to crawl at 1.5 years of age and achieving independent walking thereafter. Currently, the patient's gait is normal. Speech development was also delayed, with persistent articulation difficulties for certain words, which have not improved despite multiple sessions of speech therapy. Intellectual development remains delayed, as evidenced by speech difficulties and learning challenges. Sensory evaluations have shown normal auditory and visual function. At present, the patient's height is 140 cm (falling between the 3rd and 10th percentiles for age in the Iranian population), and his weight is 48 kg (between the 25th and 50th percentiles).

t 15 months of age, the patient underwent surgical correction of a patent ductus arteriosus (PDA). He has a history of recurrent and severe urinary tract infections (UTIs) and urinary hesitancy, which have persisted since early childhood. Physical examination revealed short stature, a short neck, deep-set eyes, a prominent

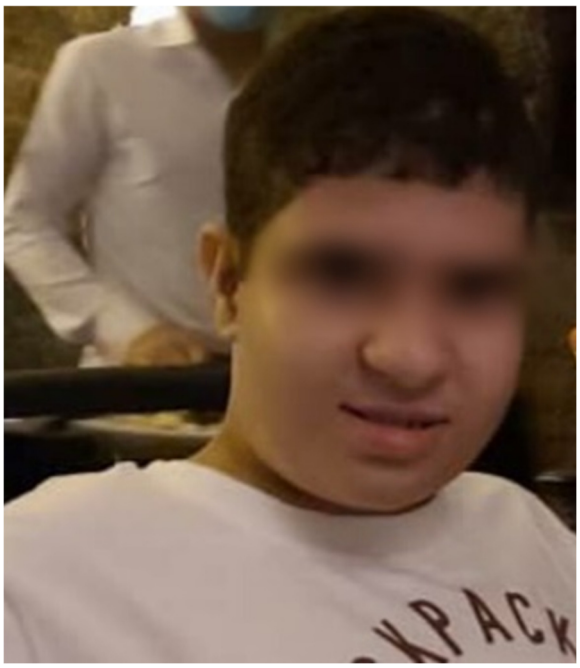

Fig. 1. Facial features of the patient

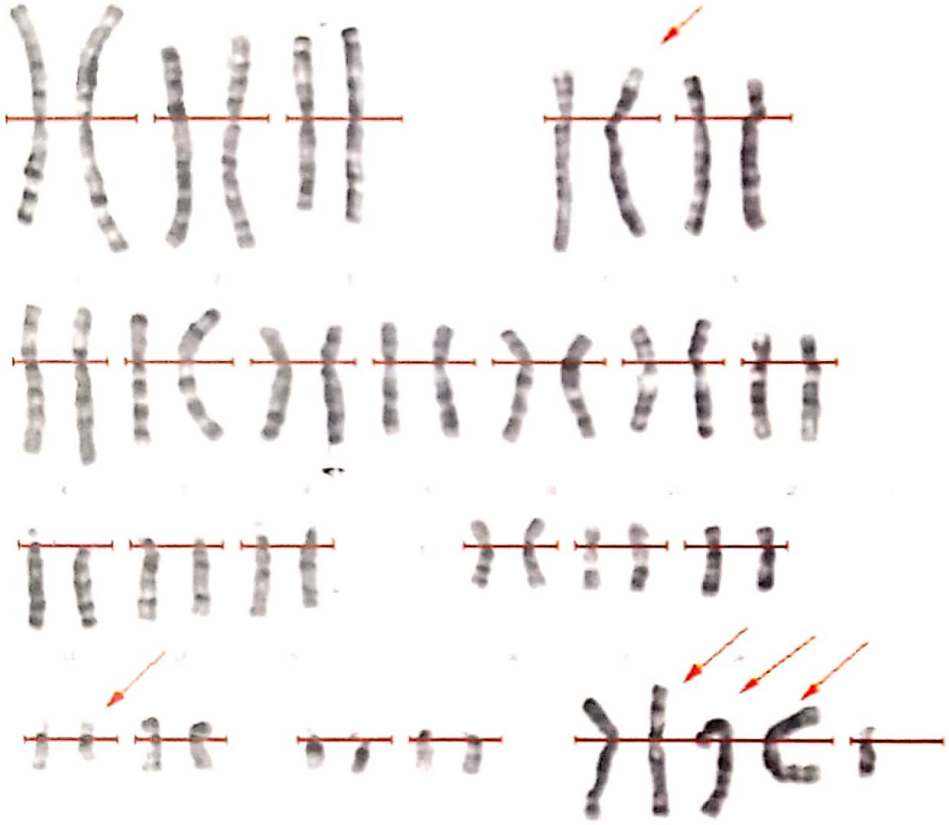

Fig. 2. Chromosome analysis of peripheral blood sample. The result showed that a karyotype of 49, XXXXY and t (4;19) (p16.2; q13.3).

nasal tip, and dental malformations (Figure 1). Additionally, testicular atrophy was noted, along with the presence of a small penis.

The maternal family history is significant for neonatal death due to pulmonary hypoplasia and cleft palate in two of her siblings. The paternal family history includes a cousin with Down syndrome. However, the exact syndrome identified in the patient has not been detected in the family. Both parents are phenotypically normal.

During cytogenetic examination, chromosome analysis of a peripheral blood sample using the high-resolution G-banding method was conducted for this patient. The results showed that the patient had a karyotype of 49, XXXXY. In addition, t(4;19) (p16.2;q13.3) was detected in this patient (Figure 2).

Discussion

This study presents the case of a 13-year-old male from northeastern Iran diagnosed with 49, XXXXY syndrome (Fraccaro syndrome), accompanied by a novel t(4;19)(p16.2;q13.3) translocation, which, to the best of our knowledge, has not been previously reported. Globally, approximately 100 cases of 49, XXXXY syndrome have been identified, including six in Iran. Reported cases span an age range from 2 months to 45 years, with clinical presentations varying in symptoms and manifestations across studies [10].

In six studies conducted in Iran, hypotonia emerged as the most commonly reported clinical feature, which was similarly observed in the current patient. Speech impediments, another frequently reported symptom, were identified in two Iranian cases and in studies such as Peet et al., which described severe speech difficulties [8,10]. The patient in the present study also exhibited speech difficulties, particularly in articulating certain words, with no significant improvement despite multiple speech therapy sessions. Intellectual and cognitive impairments, including learning difficulties, were evident in this case, consistent with earlier reports. However, microcephaly, observed in other cases, was absent [11].

MS Al Araim et al. reported a case in Oman with abnormal genitalia and cardiac defects [12], both of which were observed in the current patient. The patient also had a history of congenital heart defects, specifically patent ductus arteriosus (PDA), which required surgical correction. This finding aligns with

other reported cases [13-14]. In contrast, conditions such as cleft palate, diabetes, hypothyroidism, and cataracts—documented by Wei L et al. in China [15]— were not observed in the current case. Dental malformations, a feature described by Rajabzadeh et al. [10], were present in the current patient. Bone malformations, such as abnormalities in the hands or feet, were not detected in this patient. However, the patient exhibited other typical features of the syndrome, including short stature and a short neck.

The patient also experienced recurrent urinary tract infections, a symptom that has persisted over time. Although recurrent infections are less commonly reported in individuals with 49, XXXXY syndrome, Peet et al. described frequent upper respiratory infections, including multiple episodes of pneumonia [8]. These findings suggest a potential predisposition in some patients to recurrent infections, warranting further investigation to better understand this susceptibility.

Consistent with prior studies, this case supports the lack of correlation between maternal age and 49, XXXXY syndrome. The patient's maternal age was below 30 years, corroborating findings by Lia et al., who similarly reported no association between maternal age and the syndrome [9]. Furthermore, preterm delivery due to oligohydramnios, as noted in studies such as Peet et al., along with birth weights below the 5th percentile, were observed in this case [8].

A novel (4;19)(p16.2;q13.3) translocation was identified in this patient's karyotype analysis. This finding has not been previously reported in association with 49, XXXXY syndrome. Although the clinical significance of this translocation is currently unclear, Yanjie Qian et al. demonstrated that microdeletions in the 4p16.2 region in children are associated with congenital anomalies and developmental delays [16]. It is plausible that this translocation may disrupt critical genes at these breakpoints. However, the potential implications of this translocation were not further analyzed in this study. Additional research is necessary to elucidate its impact and clinical relevance.

Reports of additional chromosomal translocations in individuals with 49, XXXXY syndrome have been documented in the literature. Lomelino et al. described a 9-year-old male with a concomitant (3;15) translocation, while de la Chapelle et al. reported a male with 49, XXXXY and a balanced (4;11) translocation. Notably, in both cases, the translocations were inherited and identified in other family members. However, in the present study, it was not possible to evaluate family members for the presence of the (4;19)(p16.2;q13.3) translocation [17-18].

Parental cytogenetic testing was not performed in this case, limiting our ability to determine whether the t(4;19) translocation is inherited or de novo. While the family history did not reveal any known genetic conditions, we cannot exclude the possibility of an inherited rearrangement, which represents a limitation of our study. Future cases should include parental studies to better clarify the nature and clinical significance of such translocations.

Conclusion

Overall, individuals with 49, XXXXY syndrome are distinct from those with Klinefelter syndrome, exhibiting unique clinical and genetic features. These patients should undergo comprehensive clinical and cytogenetic evaluations to facilitate early detection and diagnosis. Special attention should be given to identifying cardiac defects and considering surgical and medical treatments to optimize growth and development.

Ethical Considerations

Ethics Approval

The study was approved by the Ethics Committee of MUMS, and informed consent was obtained from the patient.

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Conflict of Interests

The authors have no conflict of interest to declare.

Data availability

All data have been included in the manuscript and will be made available upon its publication.

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