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Mosaic Double Aneuploidy With Trisomy 21 and XYY Syndrome: A Case Report

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Abstract

Double aneuploidy involving trisomy 21 and XYY syndrome is an exceptionally rare chromosomal abnormality. Down syndrome is the most common autosomal aneuploidy, whereas XYY syndrome is a rare sex chromosome disorder. The coexistence of these two conditions may result in a complex clinical presentation, often dominated by features of trisomy 21. We report the case of a 24-month-old male presenting with typical dysmorphic features of Down syndrome and global developmental delay. Cytogenetic analysis revealed a mosaic karyotype, with 48,XYY,+21 detected in 55.1% of analyzed cells and 47,XY,+21 in 44.9%, confirming double aneuploidy. This case highlights the importance of cytogenetic analysis in patients with suspected trisomy 21 to identify additional chromosomal abnormalities that may influence prognosis and management.

Categories: Genetics, Pediatrics, Endocrinology/Diabetes/Metabolism
Keywords: aneuploidy, down syndrome, mosaicism, trisomy 21, xyy syndrome

Introduction

Down syndrome and XYY syndrome are chromosomal disorders with distinct genetic mechanisms and clinical manifestations. Down syndrome is caused by an extra copy of chromosome 21, most commonly due to maternal meiotic nondisjunction, and is characterized by intellectual disability, developmental delay, and typical dysmorphic features. XYY syndrome results from the presence of an additional Y chromosome and is often associated with tall stature and variable neurodevelopmental delays. The coexistence of these two aneuploidies is extremely rare and may lead to a complex clinical presentation requiring precise genetic evaluation.

Down syndrome and XYY syndrome are chromosomal disorders with distinct genetic mechanisms and clinical manifestations. Down syndrome, caused by an extra copy of chromosome 21, is one of the most common chromosomal disorders, occurring in approximately 1 in 700-1,000 live births. XYY syndrome, also known as Jacobs syndrome, results from the presence of an additional Y chromosome and affects approximately 1 in 1,000 male births [1].

These chromosomal abnormalities arise from errors in chromosome segregation during cell division, known as nondisjunction, resulting in an abnormal chromosome number, a condition referred to as aneuploidy. Down syndrome is commonly associated with characteristic facial features, hypotonia, congenital anomalies, and developmental delay. In contrast, XYY syndrome often presents with subtle or variable clinical manifestations, including tall stature, speech and language delays, and learning difficulties. When both abnormalities coexist, the clinical presentation may be predominantly influenced by trisomy 21, potentially obscuring features associated with the additional Y chromosome.

The coexistence of trisomy 21 and XYY syndrome is exceptionally rare, and the resulting phenotype may be difficult to distinguish clinically from Down syndrome alone. Therefore, cytogenetic analysis is essential to confirm the diagnosis and identify additional chromosomal abnormalities that may have implications for clinical follow-up, prognosis, and genetic counseling. We report a rare case of mosaic double aneuploidy involving trisomy 21 and XYY syndrome in a 24-month-old boy, highlighting the diagnostic value of karyotyping in patients presenting with features suggestive of Down syndrome.

Case Presentation

The patient is a 24-month-old male, born at term with a birth weight of 4100 g, to nonconsanguineous parents. The mother was 40 years old, and the father was 39 years old, with no family history of congenital malformations or dysmorphic syndromes. The pregnancy was complicated by gestational diabetes, anemia, and hydramnios. Delivery was performed by cesarean section due to macrosomia. The patient required three days of neonatal intensive care for perinatal asphyxia secondary to fetal infection. At 15 months of age, the patient underwent surgery for bilateral congenital cataracts, which was complicated by laryngeal dyspnea

requiring pediatric intensive care admission.

At 24 months, his weight was 10 kg, and his length was 78 cm, slightly below the 50th percentile on the growth chart of children with Down syndrome. His head circumference was 45 cm, and his chest circumference measured 49 cm. Physical examination revealed characteristic Down syndrome dysmorphic features, including generalized hypotonia, hypertelorism, bilateral strabismus with epicanthal folds, a flat nasal bridge, low-set ears, a short neck, macroglossia, and short, broad hands with clinodactyly of the fifth fingers. A single transverse palmar crease was present bilaterally, along with a sandal gap between the first and second toes (Figure *1*). Penile length measured 20 mm (-2.5 SD), and both testes were undescended. Cardiac auscultation was normal, with no cyanosis or digital clubbing.

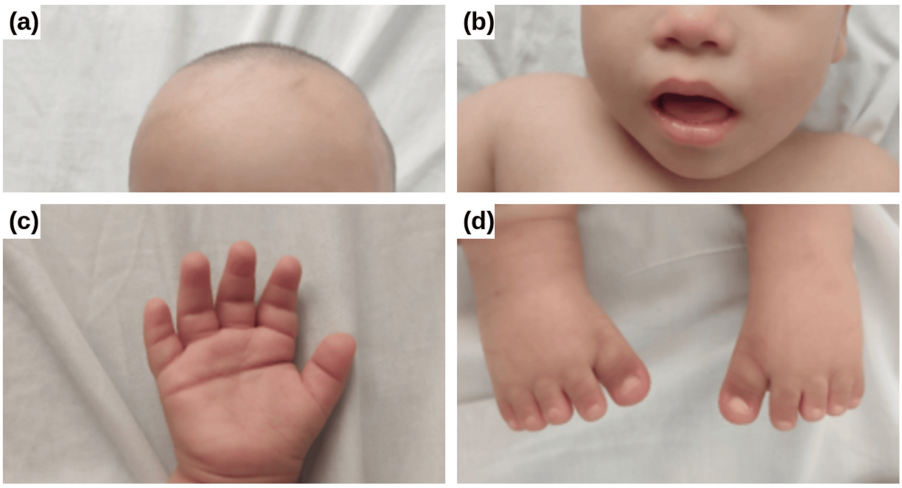


FIGURE 1: Phenotype of the patient

(a) Upper facial part: rounded head with a broad forehead. (b) Lower facial part: flattened nasal bridge, short nose, small open mouth and rounded chin. (c) Hand: short, broad hand with short fingers. (d) Feet: wide gap between the first and second toes (sandal gap).

Developmental evaluation showed global developmental delay. The patient was able to sit unsupported and creep but had not yet achieved crawling, standing, or walking. He exhibited good palmar grasp, responded to auditory stimuli, and produced babbling sounds, but had not developed expressive language.

Transthoracic echocardiography revealed no structural abnormalities. Laboratory investigations showed transient congenital hypothyroidism, while cortisol levels were normal. Serological testing for toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex virus (TORCH) was negative, and renal ultrasonography was unremarkable. A pelvic ultrasound, a barium enema, and anorectal manometry were initiated to investigate cryptorchidism and chronic constipation but remained in progress at the time of this report.

Cytogenetic analysis of peripheral blood lymphocytes using Giemsa banding revealed mosaic double aneuploidy, with 48,XYY,+21 accounting for 55.1% of the 49 analyzed cells and 47,XY,+21 accounting for 44.9% (Figure *2*). These findings established a diagnosis of mosaic double aneuploidy involving chromosomes 21 and Y.

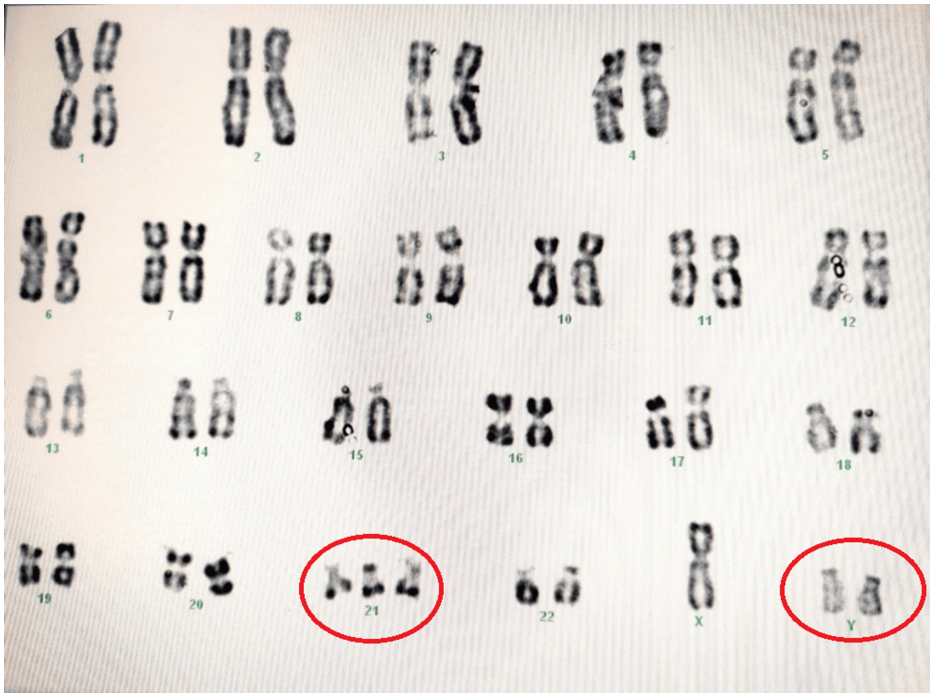


FIGURE 2: Giemsa-banded metaphase chromosomes from a lymphocyte culture showing the patient's karyotype of 48,XYY,+21

Giemsa-banded metaphase showing the 48,XYY,+21 cell line. Red circles highlight the three copies of chromosome 21 and the two Y chromosomes. Cytogenetic analysis identified two cell lines: 48,XYY,+21 (55.1%) and 47,XY,+21 (44.9%).

Discussion

Down syndrome

Down syndrome is one of the most common chromosomal disorders, occurring in 1 in 1,000 live births worldwide. It is a genetic condition caused by an extra copy of chromosome 21 that is typically due to a maternal meiotic nondisjunction event. However, about 4% of cases are caused by the unbalanced segregation of a Robertsonian translocation, and the likelihood of occurrence rises with maternal age [1]. This extra chromosome leads to both motor and intellectual developmental delays, as well as characteristic facial features, such as a flat facial profile, almond-shaped eyes with an upward slant, internal epicanthic folds, small rounded ears, a short neck, and an open mouth with a protruding, fissured tongue. The hands are usually short and broad, often with a single transverse palmar crease. Individuals with Down syndrome often exhibit hypotonia and hyperlaxity, which affect motor coordination and contribute to delayed physical development. In terms of cognitive development, they experience intellectual disabilities, language delays, and learning difficulties.

Congenital heart defects are the most common malformations in individuals with Down syndrome, present in approximately 50% of newborns. The most frequent are atrioventricular canal defects (40%) and ventricular septal defects (33%), while tetralogy of Fallot and patent ductus arteriosus are less common [2]. Gastrointestinal anomalies are the second most common congenital malformations, including duodenal atresia, annular pancreas, Hirschsprung disease, gastroesophageal reflux, imperforate anus, and celiac disease [3]. Respiratory disorders are also common, due to heart conditions, obesity, immunological dysfunction, and anatomical abnormalities. These abnormalities may include tracheal bronchus, pulmonary hypoplasia, laryngomalacia, tracheobronchomalacia, and subglottic stenosis. In fact, children with Down syndrome usually suffer from obstructive sleep apnea, pneumonia, and recurrent respiratory infections [4]. Endocrine problems are also widespread among Down syndrome individuals, including congenital hypothyroidism, type 2 diabetes, insulin resistance, obesity, short stature, and early ovarian failure in females or reduced fertility in males [5]. Renourological manifestations may include renal hypoplasia, obstructive uropathy, glomerular microcysts, decreased creatinine clearance, megaureter, vesicoureteral reflux, dysfunctional voiding and urinary retention, posterior urethral valves, hypospadias, and cryptorchidism [6]. Reported ophthalmologic and otolaryngological issues are upward-slanting eyes, epicanthus, epiblepharon, Brushfield spots, congenital cataracts, nystagmus, strabismus, refractive problems (hyperopia, myopia, astigmatism), focal retinal pigment epithelium (RPE) hyperplasia, glaucoma, keratoconus [7], glue ear, chronic ear infections, and hearing deficits that affect nearly 80% of individuals with Down syndrome [8]. Orthopedic problems are also associated with this syndrome, such as atlanto-

occipital instability, hyperflexibility, foot deformities, scoliosis, late hip dislocation, slipped capital femoral epiphysis, patellar subluxation or dislocation [9]. Dental problems are also characteristic in Down syndrome, including delayed eruption, atypical patterns of eruption, congenitally missing teeth, unusually shaped teeth, enamel defects, orthodontic problems, bruxism and periodontal disease [10]. Common skin disorders in patients with Down syndrome include atopic dermatitis, hidradenitis suppurativa, ichthyosis, lichen nitidus, psoriasis, alopecia areata, vitiligo, onychomycosis, calcinosis cutis, connective tissue nevi, dermatofibroma, melanoma, syringomas, and elastosis perforans serpiginosa. Other occasional problems are reported in the literature such as syndactyly, cerebellar hypoplasia, Dandy-Walker malformation, Moya-Moya syndrome, autoimmune arthropathy, kidney-genitourinary tract anomalies, and leukemia [11].

Down syndrome can be diagnosed both antenatally and postnatally. Antenatal diagnosis typically begins with nuchal translucency measurement and malformative features on ultrasound, quadruple screen, and cell-free DNA testing. Positive diagnosis is based on amniocentesis or chorionic villus sampling (CVS) [1]. Postnatally, the diagnosis is confirmed by cytogenetics, which identifies the extra chromosome 21.

XYY syndrome

Double Y syndrome (XYY trisomy), also known as Jacobs syndrome, is a genetic condition that affects about 1 in 1,000 male births [11]. It results from a nondisjunction event during metaphase II of paternal meiosis in spermatogenesis, leading to an additional Y chromosome. In rare cases, a post-zygotic mitotic error during early embryonic development can cause mosaicism, 46,XY/47,XYY [12].

In contrast to Down syndrome, Jacobs syndrome is not associated with specific dysmorphic features at birth. Later in childhood, it can present with characteristics such as tall stature, macrocephaly, hypertelorism, prominent glabella, large teeth, and long fingers. Children with XYY syndrome are prone to developing pulmonary and neurological conditions, such as asthma and epilepsy. Cognitive features may include intellectual disability and developmental delay, speech delays, learning difficulties, autism spectrum disorders, attention deficit hyperactivity disorder, and antisocial behavior. Genital abnormalities are also common in individuals with XYY syndrome and may include disorders of sexual development, genital dysplasia, hypogonadism, cryptorchidism, macroorchidism, scrotal hypoplasia, hypospadias, infertility, and gynecomastia [13].

Diagnosis of 47,XYY syndrome is usually delayed; it is mainly identified incidentally when genetic screening is conducted for infertility, as the condition can present with mild and variable symptoms. Approximately 85% of affected males remain undiagnosed throughout their lives [14]. However, early detection is possible through non-invasive prenatal testing, which analyzes cell-free fetal DNA from the mother's blood. Amniocentesis, a more invasive method, is less commonly used. After birth, the diagnosis is typically confirmed by karyotype analysis of the child's blood sample [15].

Double aneuploidy

Double aneuploidy refers to the coexistence of two chromosomal aneuploidies, most often involving one autosomal and one sex chromosome. In this patient, the presence of trisomy 21 in both cell lines (100% of analyzed cells) suggests a constitutional, meiotic origin, arising during gametogenesis prior to fertilization. In contrast, the additional Y chromosome was detected in only 55.1% of cells, indicating a secondary, post-zygotic mitotic nondisjunction event that occurred after fertilization in a 47,XY,+21 zygote, giving rise to the observed 48,XYY,+21/47,XY,+21 mosaicism [11]. Such independent errors are exceedingly rare, which explains why reported cases remain limited to isolated observations rather than case series.

Previous reports have described the coexistence of trisomy 21 and XYY syndrome with variable clinical presentations. Adeleke et al. reported a preterm male newborn with characteristic features of Down syndrome, extensive syndactyly, congenital cardiac abnormalities, Dandy-Walker malformation, and complete tracheal rings deformity with tracheal stenosis [11]. Similarly, Köken et al. described a five-day-old neonate with typical features of Down syndrome, jaundice, polycythemia, atrial and ventricular septal defects, and pulmonary hypertension [16]. In contrast, our patient presented at 24 months of age with characteristic features of Down syndrome, global developmental delay, bilateral congenital cataracts, and cryptorchidism. Importantly, cytogenetic analysis demonstrated two cell lines, 48,XYY,+21 and 47,XY,+21, accounting for 55.1% and 44.9% of the analyzed metaphases, respectively. This mosaic pattern highlights the cytogenetic complexity of the present case. As the clinical phenotype of double aneuploidy may be predominantly determined by trisomy 21, manifestations specifically attributable to the additional Y chromosome may be subtle or difficult to distinguish, particularly during early childhood. Therefore, clinical assessment alone may not identify the associated sex chromosome abnormality, emphasizing the importance of cytogenetic analysis for accurate diagnosis, appropriate clinical follow-up, and genetic counseling.

Conclusions

Cytogenetic analysis is crucial for confirming the diagnosis and detecting additional chromosomal abnormalities that may not be apparent from clinical presentation alone. In our patient, the identification of

mosaic double aneuploidy involving trisomy 21 and XYY syndrome highlights the importance of comprehensive chromosomal evaluation in guiding long-term care. In addition to routine surveillance for Down syndrome, recognition of the additional Y chromosome supports tailored monitoring of growth, neurodevelopment, behavioral functioning, and reproductive health. This comprehensive approach may facilitate the timely identification of age-dependent manifestations, guide genetic counseling, and support personalized multidisciplinary care. Nevertheless, the long-term prognosis of this rare chromosomal association remains uncertain, and further reports with longitudinal follow-up are needed to better characterize its clinical spectrum and management implications. Given the rarity of this chromosomal association and the limited number of reported cases, further observations and long-term follow-up are needed to clarify its phenotypic spectrum, prognostic implications, and specific management requirements.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Afaf Janati Sejjali, Laila Bouguenouch, Karim Ouldim

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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