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Case Report: Down-Klinefelter Syndrome in A Saudi Child

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Abstract

Down-Klinefelter Syndrome is an exceptionally rare chromosomal disorder that arises from the coexistence of two distinct genetic anomalies: Down syndrome (trisomy 21) and Klinefelter syndrome (47, XXY). The patient is a 3-year-old male with a rare and complex chromosomal condition resulting from mosaic Down syndrome and Klinefelter syndrome (48, XXY+21). The child has a history of congenital heart disease (CHD), which necessitated surgical intervention. Post-surgical recovery has been complicated, including significant morbidity such as a left foot amputation caused by a crossed vasoconstriction reflex. The patient underwent several investigations to elucidate the extent of their complex medical issues. A Doppler ultrasound revealed limited arterial flow in the left lower limb post-ECMO, with only partial arterial signals detected. Down-Klinefelter syndrome is a rare chromosomal abnormality that combines features of Down syndrome and Klinefelter syndrome. Documented complications include hypothyroidism, infantile spasms, gastrointestinal dysfunction, and congenital heart disease. To date, more than 70 cases of double aneuploidy have been reported in the literature.

Keywords: Patients; Down sindrome; Chromosomal; Disorder; Genetic abnormality

Introduction

Down-Klinefelter Syndrome is an exceptionally rare chromosomal disorder that arises from the coexistence of two distinct genetic anomalies: Down syndrome (trisomy 21) and Klinefelter syndrome (47, XXY). This coexistence brings some difficulty into an understanding of the disorders as people with this dual diagnosis have a broad range of physical, cognitive, and endocrine abnormalities [1]. This is particularly because the condition is very rare and has attracted focus in genetics, pediatrics and clinical medicine because of the insights it brings on chromosomal interactions and developmental effects. Down syndrome results from a type of nondisjunction, through which affected persons will have 47 chromosomes, with an extra chromosome 21. It is among the known chromosomal disorders such as intellectual disability, hypotonia, cognitive delays, facial abnormalities, and a huge inclination of congenital abnormalities [2]. On the other hand, Klinefelter syndrome arises due to presence of an extra X chromosome; and results in an individual having 47 chromosomes. This condition interconnects testicular dysfunction, infertility, increased height, gynecomastia, and learning difficulties predilection [3]. Down-Klinefelter Syndrome therefore arises from a combination of trisomy 21 and aneuploidy involving an extra X chromosome, giving the chromosomal constitution of 48;XXY,+21. It is a very rare karyotype, and can be a direct result of complicated nondisjunction occurrences during gamete formation [4]. Namely, errors during the maternal or paternal meiosis may lead to a gamete with both karyotypes trisomy 21 and XXY - the combination of which forms the hybrid disease after fusion. The clinical manifestation of Down-Klinefelter Syndrome point to a hybrid of the features of Down syndrome and Klinefelter Syndrome [5]. Concerning Down syndrome, the sufferers have intellectual disability, facial abnormalities like flattened faces, upward slanting eyes, and small nose, and increased risk of developing congenital heart disease, hypothyroidism, and some form of haematological disorders including leukaemia [6]. Further, the hypotonia that is typical of Down syndrome is also in people with this dual disorder as well. Hence from the Klinefelter syndrome view, affected males have chances of being tall, having small testes, low testosterone, gynecomastia and are often infertile [7]. The endocrine dysfunctions that define Klinefelter syndrome, namely hypogonadism and the related osteoporosis often present with additional complications that can present in Down syndrome, including health risk factors. The case of Down-Klinefelter Syndrome, due to the similarity in presentations of both Down and Klinefelter Syndromes, is relatively rare and may, therefore, be diagnosed quite a challenge. For a diagnosis, formal karyotype or chromosomal analysis including cytogenetics is done and it reveals the specific 48,XXY,+21 karyotype [8]. There have been improvements in non-invasive prenatal testing and next generation sequencing which increase the possibility of early detection; however, such double anomalies are very rare to be detected during a routine screening. The findings suggest that about 80% of KS males harbour the karyotype 47, XXY and 20% of them have other higher-grade chromosome aneuploidies such as 46, XY/47, XXY mosaicism or structurally abnormal X chromosomes. KS is the most frequent sex-chromosome disturbance and has been estimated to occurs in around one neonate male per 600 [9]. Discrepancies in number of chromosomes characterise a cytogenetic abnormality known as chromosome aneuploidy. Of all the chromosomal disorders, aneuploidy is the commonest and clinically significant. It is, thus, trisomy 21 that is most common, affecting about 0.3% of all live births [10]. Whole-arm double aneuploidy in which one chromosome is trisomic and the other is monosomic results from two instances of meiotic nondisjunction. The two aneuploidies described herein could be paternal or maternal in origin and they could be the same or be different [11].

Case presentation

Patient Profile

- ***Age***: 3 years old.
- ***Gender***: Male.
- ***Nationality***: Saudi.
- ***Medical History***: Mosaic Down syndrome and Klinefelter syndrome (48, XXY+21).
- ***Presenting Complaints***: Post-surgical complications, recurrent respiratory infections, and low oxygen saturation.

Clinical History

The patient is a 3-year-old male with a rare and complex chromosomal condition resulting from mosaic Down syndrome and Klinefelter syndrome (48, XXY+21). The child has a history of congenital heart disease (CHD), which necessitated surgical intervention. Post-surgical recovery has been complicated, including significant morbidity such as a left foot amputation caused by a crossed vasoconstriction reflex.

Medical History

The patient has a complex medical history that includes genetic conditions including mosaic Down syndrome and Klinefelter syndrome (48, XXY+21), alongside congenital heart disease (CHD) with a complete atrioventricular septal defect (CAVSD) surgically repaired and subsequent complications, including pulmonary hypertension and right ventricular dysfunction managed with central arterial-venous extracorporeal membrane oxygenation (AV ECMO) support and decannulation. Cardiac problems necessitated permanent pacemaker placement for bradycardia. Neurologically, the patient has a history of infantile spasms managed with Keppra and valproic acid, severe psychomotor impairment, and left vocal cord paralysis following open-heart surgery. Renal concerns include acute renal failure requiring dialysis, now resolved, and chronic kidney disease (Stage II) requiring monitoring. Gastrointestinal issues involve gastroesophageal reflux disease (GERD) with esophageal motility disturbances, delayed gastric emptying, and severe swallowing dysfunction with silent aspiration, necessitating NG tube feeding. Limb complications include left distal foot gangrene, leading to midfoot amputation, with bone overgrowth and growth arrest in the left tibia and fibula. Respiratory history includes COVID-19-related bronchopneumonia requiring two PICU admissions; the patient is now stable on minimal oxygen. The patient exhibits dysmorphic facial features consistent with Down and Klinefelter syndromes, is stable on 0.5-1 L nasal cannula oxygen but experiences occasional desaturations when agitated, and has ENT findings of significant arytenoid erythema and edema with secretions and left vocal cord immobility. Neurologically, there is severe developmental delay with an inability to achieve motor milestones, and musculoskeletal issues include a left foot amputation with bone overgrowth, fibular prominence on the right side, and bilateral proximal tibial growth arrest.

Clinical Examination

- ***Vital Signs:***
  - Stable on 0.5-1 L nasal cannula oxygen.
  - Occasional desaturations observed when agitated.
- ***General Appearance:***
  - Dysmorphic facial features consistent with Down and Klinefelter syndromes.
- ***ENT Findings:***
  - Significant arytenoid erythema and edema with secretions.
  - Left vocal cord immobility.
- ***Neurological:***
  - Severe developmental delay with inability to achieve motor milestones.
- ***Musculoskeletal:***
  - Left foot amputation with residual complications.
  - Bone overgrowth in the left tibia and fibula.
  - Right fibular prominence and bilateral proximal tibial growth arrest.
- ***Respiratory:***
  - Stable oxygenation on low-flow nasal cannula but occasional desaturations during distress.

Investigations and Diagnosis

The patient underwent several investigations to elucidate the extent of their complex medical issues. A Doppler ultrasound revealed limited arterial flow in the left lower limb post-ECMO, with only partial arterial signals detected. This finding was further evaluated with a CT angiogram, which confirmed patent right and left common femoral arteries but showed limited visualization of distal arteries on the left side, correlating with the history of left foot gangrene and amputation. Upper gastrointestinal (GI) endoscopy demonstrated esophageal motility disturbance and delayed gastric emptying, contributing to feeding difficulties and recurrent chest infections. A swallow study revealed severe pharyngeal dysphagia with a high aspiration risk, necessitating nasogastric (NG) tube feeding despite prior recommendations for a pureed diet. Radiological findings indicated growth arrest in the left tibia and fibula, further complicating the patient's musculoskeletal development. Based on the clinical evaluation and investigations, the following diagnoses were established: mosaic Down syndrome and Klinefelter syndrome, recurrent respiratory infections (including COVID-19 with bronchopneumonia), left vocal cord paralysis with silent aspiration, and left foot amputation due to gangrene. Additionally, the patient was diagnosed with congenital heart disease (post-surgical repair of complete atrioventricular septal defect) with pacemaker dependency, severe psychomotor delay and developmental disabilities, chronic kidney disease (Stage II), and hypothyroidism. These findings underscore the multifaceted nature of the patient's condition, requiring a multidisciplinary approach to management. The patient's management requires a comprehensive multidisciplinary approach to address the multiple systems affected. Nutritional support is prioritized through NG tube feeding to prevent aspiration, alongside minimal oxygen support to maintain respiratory stability. Regular monitoring for respiratory infections is crucial, with PICU care available for severe exacerbations. Wound and skin care for the left foot amputation site includes daily saline cleaning and Flamazine dressing to prevent infection and promote healing. Family and genetic counseling sessions are vital to discuss the prognosis, potential complications, and the possibility of further surgical interventions, including limb revision. While developmental therapy is recommended for long-term follow-up, the patient's current physical limitations restrict active rehabilitation options. Regular follow-ups with ENT specialists are required to manage vocal cord paralysis, along with cardiology for pacemaker and congenital heart disease (CHD) monitoring, nephrology for chronic kidney disease (CKD), and pulmonology for ongoing respiratory care.

Discussion

The first reported case of double aneuploidy, including Down-Klinefelter syndrome, was documented in 1959 by Ford et al. Double aneuploidy, a rare genetic condition, occurs in approximately 0.098% of affected individuals. In such cases, the clinical features of Down syndrome typically dominate during the neonatal period, while traits of Klinefelter syndrome often emerge later [12]. The latter commonly affects testicular function, leading to hypogonadism, which may present as cryptorchidism or micropenis in neonates. However, most males with Klinefelter syndrome appear phenotypically normal until adulthood, when symptoms such as gynecomastia or infertility prompt further investigation. Congenital heart disease (CHD) is occasionally associated with Down-Klinefelter syndrome. Reported cases of double aneuploidy often include typical Down syndrome features but lack significant thyroid, digestive, or cardiovascular complications [13]. In contrast, some cases exhibit repeated chest infections and other isolated abnormalities, as seen in our patient. In another study, a patient with Down-Klinefelter syndrome presented with recurrent respiratory infections, small stature, and no gastrointestinal or cardiovascular abnormalities. Unique findings in our case include the presence of hypothyroidism, infantile spasms, recurrent chest infections, and Stage II CKD. The crossed vasoconstriction reflex leading to limb amputation is an unusual feature, further distinguishing this case from previously reported instances. Additionally, our patient presents with congenital heart disease requiring pacemaker dependency, which is a rare complication in cases of Down-Klinefelter syndrome [14].

Conclusion

Down-Klinefelter syndrome is a rare chromosomal abnormality that combines features of Down syndrome and Klinefelter syndrome. Documented complications include hypothyroidism, infantile spasms, gastrointestinal dysfunction, and congenital heart disease. To date, more than 70 cases of double aneuploidy have been reported in the literature. However, our case is unique in presenting with crossed vasoconstriction reflex leading to limb amputation and the presence of Stage II CKD, which have not been previously

described.

Conflict of Interest

The authors declare no conflict of interest.

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This study received no specific funding.

Consent for Publication

Written informed consent was obtained from the patient's parents to publish this case report.

Ethical Approval

Ethical approval for this case report was granted by the Ethics Committee of King Fahad Medical City, Riyadh (IRB: 16-422), in November 2024.

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