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Clinical Aspects and Management of Klinefelter Syndrome in the Pediatric Age Group

Asma Ayed Alanazi[1], Fahad Abdullah Wajdi[2], Mohammed Saleh Al Issa[3], Albandari Abdulrahman Fallatah[3], Abdulrazaq Oudah Shaker[4], Abeer Abdalaziz Al Hatim[5], Mona Khalid Alqubali[6], Reem Hamoud Alshammari[7], Buthaynah Abdullah Alghasham[8], Hassan Yousef Almohammedali[9]*, Hanan Abdullah Alrashidi[10], Mohammed Anwar S Bawazier[11]

[1]Faculty of Medicine, Vision Colleges, Riyadh, KSA.
[2]Department of Pediatrics, Maternity and Children Hospital, Makkah, KSA.
[3]Department of Pediatrics, Al Yamama Hospital, Riyadh, KSA.
[4]Department of Pediatrics, King Fahad Hospital, Albaha, KSA.
[5]Department of Pediatrics, Adderyiah Hospital, Riyadh, KSA.
[6]Faculty of Medicine, Tabuk University, Tabuk, KSA.
[7]Department of Pediatrics, Maternity and Children Hospital, Hail, KSA.
[8]Faculty of Medicine, Unaizah College of Medicine, Unaizah, KSA.
[9]Faculty of Medicine, Ibn Sina National College of Medicine, Jeddah, KSA.
[10]NICY Department, Alyamammah hospital, Riyadh, KSA.
[11]Faculty of Medicine, King Abdulaziz University, Jeddah, KSA.

***E-mail** ✉ Dr.hasanyousef.2021@gmail.com

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ABSTRACT

Klinefelter syndrome is the most common sex chromosome anomaly, occurring in approximately 1 in 660 males, yet fewer than 30% of individuals are diagnosed. This low diagnosis rate is due to the wide variability in the phenotypic presentation of the condition. The failure to detect Klinefelter syndrome early can lead to significant health complications, including primary hypogonadism, infertility, and an elevated risk of various cancers and other systemic diseases. This study aimed to review the existing literature on Klinefelter syndrome, focusing on its clinical features and its management in the pediatric population. Articles were selected and reviewed from the PubMed database. Klinefelter syndrome manifests in a wide range of clinical presentations that vary based on the age of the patient and the severity of the disease. During infancy, most cases appear phenotypically normal, although extreme cases may present with conditions such as microphallus and undescended testes. As children approach puberty, the rate of diagnosis increases due to the insufficient development of typical pubertal features, such as virilization and muscle mass. Many cases remain undiagnosed until adulthood, usually when individuals seek medical help for infertility. Management strategies include testosterone replacement therapy, assisted reproductive techniques, and early intervention to address associated complications.

Keywords: Klinefelter syndrome, Clinical presentation, Treatment, Complications

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Introduction

Klinefelter syndrome (KS) is a genetic disorder in males where there is an extra X chromosome, typically resulting in a 47, XXY karyotype. Other variations, such as 48, XXXY, 48, XXYY, and 49, XXXXY, are less common [1]. It is the most frequent sex chromosome anomaly, with an occurrence rate of approximately 1 in 660 male births [2, 3]. Despite its prevalence, a significant number of individuals with KS remain undiagnosed, with some estimates suggesting that as many as 70% of affected individuals are unaware of their condition [4]. This lack of diagnosis can lead to serious health issues, as timely detection and intervention are crucial to mitigate

complications like primary hypogonadism. This paper seeks to explore Klinefelter syndrome, including its clinical manifestations and management strategies, with an emphasis on the pediatric population.

Materials and Methods

A systematic search was conducted in the PubMed database using the following search terms: ((Klinefelter) AND (management)) OR (clinical features). Articles were selected based on their focus on one or more of the following topics: Klinefelter syndrome, clinical features, and management. Studies that did not address these core topics were excluded from this review.

Results and Discussion

Klinefelter syndrome (KS) presents a highly variable phenotype, with the severity and age of onset influencing clinical manifestation [5]. This variability often complicates early diagnosis, particularly in pediatric patients. In many cases, KS remains undetected in newborns due to subtle or absent symptoms, except in those with more severe karyotypic variations, such as those with additional X chromosomes. These individuals may present with distinct physical features like scrotal hypospadias, cryptorchidism, clinodactyly, or isolated micro-penis. Rarely, other signs such as hypertelorism and macroglossia may also be noted.

In early childhood, children with KS may exhibit developmental delays, particularly in language and speech, which can lead to academic struggles as well as social and behavioral challenges [6, 7].

As children with KS reach puberty, the syndrome becomes easier to diagnose due to incomplete or absent pubertal development. These individuals typically show reduced virilization, evidenced by a lack of facial and pubic hair. They may also be taller than their peers but have smaller muscle mass. One key characteristic of KS is the eunuchoid body habitus, where the upper-to-lower body ratio is disproportionate, with longer legs. A hallmark of KS is the presence of small, firm testes with a volume of less than 4 ml, a result of fibrosis and progressive testicular damage. However, in patients with mosaic KS, testicular size may appear normal [5, 8, 9].

Most cases of KS remain undiagnosed until adulthood, with the primary reason for seeking medical help being infertility. A semen analysis often reveals non-obstructive azoospermia. Other common complaints include symptoms of androgen deficiency, such as erectile dysfunction, sexual issues, and gynecomastia [10].

Patients with KS are at higher risk for several associated conditions, including osteoporosis and osteopenia, which can lead to frequent fractures. Cardiovascular issues are also common, ranging from benign mitral valve prolapse and varicose veins to more severe conditions like ischemic heart disease (IHD), deep vein thrombosis (DVT), and pulmonary embolism (PE). Furthermore, autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (DM), and Hashimoto's thyroiditis are more common in this population, although their absolute risk remains relatively low. Neurological issues are frequent, with essential tremor being notably common, affecting approximately 25% of individuals with KS.

One of the more concerning complications of KS is the increased susceptibility to certain cancers, particularly non-Hodgkin lymphoma, lung cancer, and breast cancer, with a 50-fold higher relative risk compared to the general male population. Interestingly, the incidence of prostate cancer in KS patients is lower than in the general population. Additionally, dental problems such as dental caries and dentofacial abnormalities are prevalent in those affected by KS [11-14].

Management

The first step in managing Klinefelter syndrome (KS) is to establish a definitive diagnosis. This typically involves measuring testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels, followed by karyotyping. However, detailed diagnostic procedures are beyond the scope of this article.

Once the diagnosis is confirmed, the next crucial step is to inform both the patient and their parents about the condition and its potential complications, particularly infertility. In pediatric cases, special consideration must be given to the timing and method of disclosure. Discussions with the parents about when and how to reveal the diagnosis are important, as some may choose to delay disclosure until a later age [15].

Management strategies should be personalized based on the patient's age, the severity of the condition, and their specific needs. However, the broad approach can be divided into three main categories: long-term hormonal therapy, infertility management, and the prevention and treatment of associated complications.

Testosterone therapy

Testosterone replacement therapy (TRT) is a cornerstone of KS management in adults. However, there is no consensus on the optimal timing or dosing for androgen replacement, particularly in children with KS, as many initially have normal hormone levels and do not develop hypogonadism until later in life. Moreover, androgen therapy, especially if initiated too early, can lead to side effects such as precocious puberty and early closure of the growth plates [16, 17].

For more severe phenotypes, such as patients with a micro-penis, early testosterone therapy can be started in infancy. Research has shown that both topical and systemic testosterone can lead to penile growth, both in length and girth. In other cases, therapy is typically initiated when clinical or biochemical signs of hypogonadism, such as declining testosterone levels or elevated LH levels, appear. While adults have access to a variety of testosterone formulations, pediatric options are more limited, requiring smaller doses and slower titration. Depo intramuscular injections or topical gels and creams are often used, starting at lower doses than those prescribed for adults [16, 18].

Infertility management

Historically, individuals with KS were considered infertile, and adoption or sperm donation were their only options for having biological children. However, advances in assisted reproduction have opened new possibilities. Techniques such as fine-needle aspiration (FNA), conventional testicular sperm extraction (TESE), and micro-TESE have made it possible for some individuals with KS to father biological children. These procedures involve the direct retrieval of sperm from testicular tissue, which is then used to fertilize an egg via intra-cytoplasmic sperm injection (ICSI).

Among these techniques, micro-TESE is the preferred method due to its lower risk of complications and higher sperm retrieval success rate, which approaches 50%. This success rate can be further improved if the patient achieves an optimal pre-operative testosterone level of 250 ng/dl [19-22].

Peri-Pubertal sperm retrieval and cryopreservation

Several medical centers have started offering sperm retrieval procedures in peri-pubertal individuals, coupled with sperm cryopreservation, under the assumption that it may yield better success due to the presence of a more favorable hormonal profile and reduced fibrosis in younger individuals. However, this approach is still controversial, with some studies suggesting that the procedure could be less effective and potentially harmful. Concerns arise from the possibility of damaging immature sperm cells during the retrieval process, which could impact future fertility. As a result, some experts advocate for further research before routinely offering this option to younger patients [10, 23, 24].

Mosaic klinefelter syndrome

Patients with mosaic Klinefelter syndrome may benefit more from sperm preservation before puberty. Many of these individuals experience oligozoospermia (a low sperm count) rather than azoospermia (absence of sperm), meaning they have a higher chance of producing sperm that can be used for fertilization. Thus, semen analysis during puberty is recommended for these patients to determine sperm count and assess fertility potential [9, 25].

Gynecomastia and other associated conditions

Gynecomastia is a significant concern for many KS patients, particularly during adolescence, as it can negatively affect mental health, leading to depression, anxiety, and other psychological issues. Early testosterone treatment can often reverse the condition, but if left untreated, the breast tissue may become fibrotic, making testosterone therapy less effective. In these cases, surgical options, such as liposuction or mastectomy, may be necessary. Patients should be informed about the possibility of recurrence after surgery. Other medications like aromatase inhibitors and tamoxifen have shown limited effectiveness in treating gynecomastia in KS, and no conclusive evidence supports their use. While KS patients are at a higher risk for certain cancers, such as breast cancer, the overall risk remains low. Routine screening for breast cancer is not universally recommended, but regular check-ups with a healthcare provider knowledgeable about KS-associated risks are essential for early detection and intervention [16, 26-29].

For other conditions linked to KS, such as diabetes and neoplasms, routine screening is generally not recommended for asymptomatic patients. Instead, ongoing health assessments with a provider familiar with KS are advised to monitor for potential complications [11].

Cognitive and behavioral support

Individuals with KS are more prone to behavioral issues, difficulties in social interactions, and learning disabilities, particularly in language-based areas. Some studies suggest a mild decline in cognitive function, with IQ scores averaging a 5-10% reduction compared to peers. As a result, many KS patients require specialized educational support. Psychological support and behavioral therapies, including social management training (SMT), have been found to improve outcomes in this population, helping them navigate social and academic challenges more effectively [11, 16, 30, 31].

Conclusion

The clinical manifestation of Klinefelter syndrome (KS) can vary widely, depending on the age of onset and severity of the condition. During infancy, most cases exhibit near-normal phenotypes, with only severe forms, such as micro-penis and undescended testis, presenting more distinct features. As the individual reaches puberty, the detection rate increases due to incomplete or absent signs of typical pubertal development, such as virilization and increased muscle mass. Most KS cases are not identified until adulthood, often when individuals seek help for infertility. The management strategy for KS includes testosterone replacement therapy, assisted reproductive techniques, and early identification and treatment of related complications.

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