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Review Article

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An Overview on Klinefelter's: Clinical Features and Management in Pediatric Population

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ABSTRACT

Klinefelter syndrome is the most common sex chromosome disorder, with a prevalence of 1 in every 660 males, and despite being so prevalent, less than 30% of cases do ever get diagnosed. This is due to the very heterogeneous phenotypic presentations of the patients; failure in early identification of these patients can have dire consequences on those individuals' overall health and life quality as it is a major cause of primary hypogonadism and subsequent infertility, in addition to the increased risk of neoplasms and a plethora of other systemic conditions. Our objective was to look into the literature concerning Klinefelter's: clinical features and management in the pediatric population. PubMed database was used for articles selection, from where the papers were obtained and reviewed. The clinical presentation of Klinefelter syndrome patients can vary dramatically based on the age and severity of the disease. Most cases have near-normal phenotypes during infancy except for extreme phenotypes that could present with micro-pen undescended testis. As the child grows and reaches puberty detection rate increases as signs of normal puberty such as virilization and increase in muscle mass are usually deficient or incomplete. Most cases only picked up during adulthood who presents complaining of infertility. The treatment approach consists of testosterone therapy, assisted fertility, and early detection and treatment of associated complications.

Key words: *Klinefelter, Clinical features, Management, Complications*

INTRODUCTION

Klinefelter syndrome refers to phenotypic male individuals with additional X chromosomes. The majority of these patients have a karyotype of 47, XXY, with other variations such as 48, XXXY, 48, XXYY, and 49, XXXXY being rare and occurring in a minority of cases [1]. It is the most common sex chromosome disorder, with a prevalence of 1 in every 660 males [2, 3]. But despite being this prevalent, only a small fraction of these patients

get diagnosed, with some estimate that 70% of KS patients will remain oblivious about their condition [4], which can have dire consequences as early recognition and management play a vital role in the prevention of the disease complications chiefly primary hypogonadism. In this article, we will briefly review Klinefelter syndrome, alongside its clinical features and approach of management with special regard to the pediatric age group.

MATERIALS AND METHODS

PubMed database was used for articles selection, and the following keys were used in the mesh ((Klinefelter) AND (management)) OR (clinical features)). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; Klinefelter, clinical features, and management. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

RESULTS AND DISCUSSION

The phenotypic presentation of KS is greatly heterogeneous. It varies based on the age of presentation and severity of the condition [5], which poses a great challenge for physicians to diagnose early. Most cases have subtle and non-specific manifestations, especially in the pediatric population [6].

Most newborn babies with KS exhibit normal phenotypes and usually go undetected. Except for a small percentage of cases with the most severe disease, for example, individuals with more than 2 X chromosomes, such patients may present scrotal hypospadias, cryptorchidism, clinodactyly, or isolated micro-penis. Other less common physical findings include hypertelorism and macroglossia. Later in early childhood, young boys may experience linguistic delay and speech impairment and, therefore, may suffer from learning difficulties and have both social and behavioral problems [7, 8].

During puberty, Klinefelter syndrome is more readily diagnosed, as these individuals may have an incomplete pubertal development. Reflected by the scarcity of pubic and facial hair due to decreased or even absence of virilization. In addition, they tend to be taller with a smaller muscles mass if compared to their counterparts. Another common finding is the eunuchoid skeleton where the upper to lower body ratio is skewed to the latter; despite the variability of the symptoms mentioned above and signs, an almost universal finding is firm and small testis with a volume of <4ml, which is the result of progressive fibrosis and destruction to testicular tissue. A small exception of such findings is patients with mosaic KS with normal-sized pairs of the testis [5, 8, 9].

An overwhelming majority of KS patients go unnoticed till they reach adulthood. They present seeking medical help for infertility, and therefore semen analysis is performed, showing non-obstructive azoospermia. Other frequent complaints are due to androgen deficiency, causing both erectile and sexual dysfunction, in addition to gynecomastia [10].

Research has identified many conditions associated with KS, making affected individuals at a higher risk of such conditions. Osteoporosis and osteopenia are among the most prevalent, leading to repeated fractures during a lifetime. Another commonly affected system is the CVS ranging from benign mitral valve prolapse and varicose veins to more serious and possibly fatal IHD, DVT, and PE. in addition, numerous autoimmune diseases have been linked to KS as SLE, RA, DM type 1, and Hashimoto thyroiditis. Still, fortunately, their absolute risk remains low. As for the nervous system, essential tremors are quite common, with some estimating that it affects around 1 in every 4 KS patients. A more dreadful complication is the increased risk of cancers like non-Hodgkin lymphoma, lung cancer, and breast cancer, as patients have a 50-fold increase in their relative risk compared to the normal male population. On the other hand, studies indicate that they have a lower incidence of prostate cancer. Lastly, these patients are prone to developing both dental caries and dentofacial abnormalities [11-14].

Management

The initial step in management is establishing the diagnosis. This is achieved by measuring testosterone, FSH, and LH levels with subsequent karyotyping to make a definitive diagnosis. But we won't elaborate with further details as this is beyond the scope of this article.

With a concrete diagnosis in hand, the next step is to inform the patient and his parents of his condition and provide him with all necessary information, specifically possible complications such as infertility. Special care needs to be taken in underage boys. It requires prior discussion with the parents on the method and timing of delivery as they may opt to delay the disclosure of the diagnosis to a later age [15].

The management approach differs based on the age of presentation and severity of the condition and should be tailored to each patient's unique characteristics, needs, and phenotype. But it could broadly be classified into long-

term hormonal therapy, infertility management, lastly prevention and treatment of associated adverse complications.

Testosterone therapy

Testosterone replacement therapy is considered the cornerstone of KS management in adults. But till now, there has been a lack of guidelines on the optimal time of initiation and dosing of androgen replacement, as most KS children have a normal hormonal profile and won't exhibit any form of hypogonadism till later in life. Also, that those regimens carry with them adverse side-effects chiefly precocious puberty and its sequels, such as early closure of growth plates [16, 17].

One of the options is to start early therapy as early as infancy. This is usually the case for severe phenotypes like patients with micro-penis. Numerous data have shown that topical or systemic testosterone administration can cause penile enlargement in both girth and length. Another more commonly opted-for decision is to start when there is either clinical or a chemical indication of hypogonadism; this includes declining levels of testosterone, rising LH levels, or the symptoms mentioned above and signs. And despite the availability of a plethora of testosterone formulations in adults, pediatric options are more restricted due to the need for smaller dosing and slower tittering. Therefore, depo IM injections or topical gels and creams are the usual choices, with the initial dose being way lower than the adult's dose [16, 18].

Infertility

In the past, patients with KS were deemed infertile, and their only hope to experience parenting was through either adoption or using a donor's sperm. But with emerge of new assisted reproduction techniques, such as Fine-needle Aspiration (FNA), conventional Testicular Sperm Extraction (TESE), and microscopic testicular extraction of sperm (micro-TESE). The choice of having biological offspring became a possibility for some. These procedures briefly consist of direct retrieval of sperm from testicular tissue, which is subsequently used to fertilize on the ovum through Intra-cytoplasmic Sperm Injection (ICSI). Available data favor the use of micro-TESE as it has fewer operative complications, in addition to a higher success rate of sperm retrieval approaching 50% of the cases. This percentage could even be increased by achieving an optimal pre-operative testosterone serum level of 250 ng dl−1 [19-22].

Multiple centers started to offer peri-pubertal sperm retrieval through the technique mentioned above with cryopreservation of sperm, under the premise of a higher success rate due to normal hormonal profile and a lesser degree of fibrosis in such an age. But till now, it remains a debatable topic as multiple researchers have found out that, on the contrary, it has lower success rates and could have harmful effects on future attempts in adulthood, due to damage of the still immature spermatogenic cells during the procedure, so they advocate for the avoidance of such practice till further research is taken [10, 23, 24].

Patients with a mosaic variant of KS could benefit from peri-pubertal sperm preservation. This is because many of them have oligo-zoospermia rather than azoospermia, henceforth posing a higher chance of ejaculating sperm-containing semen. So performing semen analysis during pubertal age is advised [9, 25].

Associated conditions

Gynecomastia can have a devastating impact on patients' mental welfare, especially during adolescence, linked to depression, anxiety, and other psychological conditions. Therefore, providing treatment can positively affect patients' quality of life. The use of testosterone in the early stages of the condition can completely reverse gynecomastia. Still, as the condition progresses with time and breast tissue becomes fibrotic, testosterone monotherapy will be less efficacious, and the aid of extra surgical options may be warranted. This includes liposuction, lipolysis, and mastectomy through various approaches such as open or assisted-endoscopic. A point to keep in mind is educating the patient about the possibility of post-surgical recurrence. Other treatment modalities such as aromatase inhibitors and tamoxifen are yet to be studied in KS patients, and even when tested on other conditions had either a modest or no effect. As for breast cancer risk, there is no consensus on screening. And even though KS has a higher risk, the absolute lifetime risk remains low. Therefore, it's generally advised for routine physical examinations, and in case of suspicious findings, further mammography and biopsy are recommended [16, 26-29].

In a similar fashion to breast cancer, other forms of neoplasm, and the aforementioned co-morbid conditions such diabetes, routine screening is not recommended for asymptomatic patients. Rather having regular health checkups

with a health care provider who is aware and familiar with the possible associated conditions to KS is recommended [11].

KS patients are more vulnerable to experiencing behavioral abnormalities, having difficulties in social settings, and suffering from learning disabilities, especially in language-based domains. This could be attributed to the mild reduction in cognitive abilities observed in some patients ranging from 5-10% reduction in IQ tests. Which could require some special educational support and care in the facilities where the child is enrolled. Access to psychological support and other forms of behavioral therapies such as Social Management Training SMT have been shown to yield positive outcomes [11, 16, 30, 31].

CONCLUSION

The clinical presentation of Klinefelter syndrome patients can vary dramatically based on the age and severity of the disease. Most cases have near-normal phenotypes during infancy except for extreme phenotypes, which could have micro-pen undescended testis as the child grows and reaches puberty. The detection rate increases due to deficient or incomplete signs of normal puberty virilization and increased muscle mass. The majority of cases only picked during adulthood as they present complaining of infertility. The treatment approach consists of testosterone therapy, assisted fertility, and early detection and associated complications.

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