

Diagnosis of Klinefelter Syndrome in an Epileptic Patient Presented With Male Infertility in Meghalaya: A Rare Case Report

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Abstract

Klinefelter Syndrome (KS) is a hereditary illness that affects both physical and cognitive development in men. KS symptoms vary significantly, and many people are never diagnosed or treated. The classic symptom of KS is testicular failure, which is caused by a decrease in testosterone levels. A decrease in testosterone levels can result in the development of male breasts, delayed puberty, reduced facial or body hair, and, most critically, male infertility. Through hormonal therapy, early detection of KS during puberty might decrease the damage that KS can have both physically and psychologically, and have a better life living with KS. This case study describes how a regular reproductive examination of a 39-year-old tribal epileptic man from the state of Meghalaya resulted in the first known instance of KS and a diagnosis of infertility. The case emphasises the lack of understanding regarding KS and the choices available to patients with KS to father children.

Keywords: Sperm, Infertility, 47XXY, Klinefelter Syndrome

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Introduction

Klinefelter syndrome (KS) is a genetic disorder of the sex-chromosome (47, XXY) affecting males. KS prevalence varies from population to population and also on geographical areas. KS remains undiagnosed among most male population, with a few being diagnosed before puberty and about 25% being detected at a later period of their lives. Clinical presentation varies greatly and due to this reason it still remains undiagnosed in majority of men¹. Classical features of KS are androgen deficiency, azoospermia, hypogo-

nadism and elevation of FSH and LH. Learning disability, psychiatric and neurological disorders have been reported in patients with KS¹.

Additionally, excess fat deposit, reduced muscle mass, depleted bone mineral mass and risks for type 2 diabetes and other metabolic syndromes has been reported. Atrophic testicular failure is classical for men with KS. KS was first described as a syndrome by Klinefelter et al in 1942². The abnormalities are caused by non-disjunction in cell cycle. Origin of the syndrome is due to the maternal oogenesis which covers almost two-thirds and the others originated from paternal spermatogenesis which takes over the remaining third¹. Replication doubles the amount of DNA, creating 46 chromosomes with two chromatids each, before the first meiotic division (2n,4c). In the first meiotic division, known as the reduction division, homologous chromosomes (2n,4c) are segregated, and

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haploid germ cells (23 chromosomes; 1n,2c) are produced. These germ cells can be either two secondary spermatocytes (in the case of male meiosis) or one secondary oocyte and one polar body (female meiosis). In the second meiotic division (segregation of sister chromatids; 2C/C) of male meiosis, spermatids are produced, which later develop into spermatozoa. A developed (fertilised) oocyte and a second polar body are produced by the second meiotic division in female meiosis only after fertilisation. As a result, each male germ cell that enters meiosis eventually produces four spermatozoa, whereas one full cycle of female meiosis produces just one mature oocyte³. Homologous chromosomes join together and create connections known as chiasmata during prophase of meiosis I. The pseudoautosomal regions 1 and 2 on the ends of the short and long arms of the (mostly nonhomologous) X and Y chromosome pair in male meiosis (PAR1 and PAR2). Crossing over occurs when paired homologous chromosomes swap random DNA fragments at the chiasmata, causing these segments to recombine. During prophase of meiosis I, there is at least one exchange per chromosome arm during the process of crossing over, which is distributed non-randomly along the chromosomes (except for the short arms of acrocentric chromosomes). Female meioses have roughly 1.6–1.7 fold higher genome-wide recombination rates than male meioses⁴. There is a required crossover present in the PAR1 region (2.6 Mb)⁵. Meiosis does not require pairing and crossing over at the smaller (320 kb) pseudoautosomal region (PAR2) at the end of the long arms of the X and Y chromosomes^{6,7}. Crossovers serve two purposes: (1) to increase diversity within a population, and (2) to ensure proper chromosomal segregation during meiosis I⁸.

KS prevalence rises to 3-4% in infertile males and 10-12% in azoospermic patients (from 0.1 to 0.2% in male newborns)⁹. This would suggest that the growing paternal meiotic changes are connected to the KS rise. Patients with KS have a phenotype that is incredibly diverse but devoid of any noticeable facial dysmorphology that would

allow them to be mistaken for boys with normal karyotypes⁹. It is now understood that people with Klinefelter syndrome are more susceptible to comorbid conditions such as osteoporosis, neurocognitive and psychosocial symptoms, cardiovascular and metabolic disorders, which may exist in varying connections².

According to a number of longitudinal studies, males with the 47, XXY chromosome have a tendency toward linguistic deficiencies, which frequently result in scholastic challenges during the school years. The majority of 47, XXY male's exhibit language delays and somewhat delayed word expression. Additionally, these individuals demonstrate that expressive language production is more negatively impacted than understanding or receptive capabilities¹⁰. The pattern of weaknesses includes issues with oral language output, difficulties understanding complicated grammatical structures, and deficiencies in morphology, word recall skills, and oral story building. The lower mean verbal scale scores, which are much lower than performance scale scores, indicate the variety of their speech and language deficiencies¹⁰. Many misunderstanding and stigmatization circles KF about preferences in sexual orientation. However most of the patients present themselves as heterosexual men with normal sexual function.

Case Report

A 39-years-old tribal male patient from the Khasi hills district of Meghalaya, India came to the infertility centre along with his wife for the eagerness to conceive after more than 3 years of marriage. Initially, both patients were examined physically. Details of female were not included as it does not cover the aim of the paper. Medical history of the male patient showed that he was earlier diagnosed with epilepsy. Male patient physically showed testicular atrophy, high pitch voice, development of male breasts, less facial and body hair and broad hips. The patient is subjected to hormonal panel testing (Prolactin (PRL), follicle stimulating Hormone (FSH), luteinizing hormone (LH) and testosterone), andrology test (semen

analysis) and cytogenetic test (karyotyping) to confirm KS. Endocrinology findings reveal a hormonal imbalance (Table 1), leading to a provisional diagnosis of hypogonadism. A comprehensive Semen Analysis (Volume, counts, motility, and morphology) was recommended to check gonadal function, and the results indicated azoospermia (lack of sperm), which was verified by a repeat test 3 months later. To rule out any abnormalities, a cytogenetic panel test (Karyotyping) was performed. Results showed that an additional X chromosome (47,XXY vs. 46,XY) was identified. This confirmed the diagnosis of KS as given by the criteria of the World Health Organization (WHO).

Table 1. Hormonal levels and reference values of the patient

Assay	Value	Biological Reference Value
FSH	21.64	1.50 – 12.40 mIU/ml
LH	12.70	1.70 – 8.60 mIU/ml
Testosterone	1.63	1.91 – 8.41 ng/ml
Prolactin	20.18	3.45 – 17.42 ng/ml

* The Finecare™ Automated Immunofluorescent Analyzer was used to get all reference values.

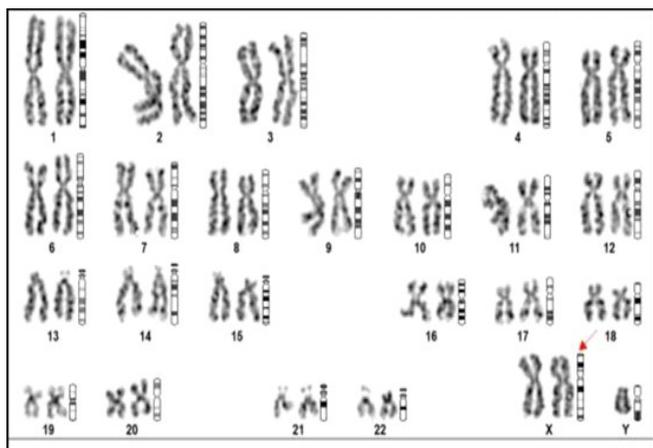


Fig 1. Karyotyping of patient peripheral venous blood showing (47,XXY)

Discussion

This report presents the first adult tribal male patient from the state of Meghalaya, India diagnosed with male infertility along with epilepsy with previous unsuspected KS as a result of fertility testing. Previous research has found a strong link between maternal age and the frequency of KS³. This example emphasizes the rarity of this illness, and correct knowledge is critical for early detection of KS in the early stages of puberty, for which testosterone supplementation can lessen the deteriorating effect of KS on the physical and mental health of young teens. Only the worst and best functioning males with KS are likely to be seen; the former are recognised early due to behavioural and linguistic issues, and the latter are due to infertility. The typical KS male may not exhibit severe stigmata, but he may have hypogonadism severe enough to prevent him from reproducing, preventing him from visiting an infertility clinic³. Depression, anxiety are the main psychological impact this disorder has on patients. The most degrading effect KS has on its patients is the inability to father offspring. With new techniques such as TESE (testicular sperm extraction) and ICSI (Intracytoplasmic sperm injection), hope is there for a promising treatment course provided that there is a suitable number of sperms present. Cryopreservation can be included in the treatment regime for future cycles.

The patient discussed in this case study initially came seeking for treatment for infertility. Following an initial investigation, the female partner's hormones were found to be normal in comparison to the male patient, indicating hypogonadism. (Table 1). Patients with KS must be monitored throughout their lives and, in the event of hypogonadism, they must receive testosterone therapy. Since these patients typically have a minor testosterone shortage, special care should be devoted to adequate titration of testosterone dosage, especially in those with mild phenotype. All testosterone formulations are successful in treating patients with KS; the decision depends on

the serum testosterone levels prior to treatment, the patient's preferences, and the attitude and background of the doctor with regard to the commercially available formulations². Analysis of semen confirmed azoospermia and genetic analysis revealed that the male possessed the 47XXY karyotype (Fig 1). Genetic counselling was advised to the couple to discuss the options available. Due to high FSH level and age, TESE was not suitable due to relatively high chance of genetic abnormalities that could occur in offspring. In cases where husband sperm could not be used, donor sperm were advised to the couple.

Conclusion

Fertility treatment is evolving with time and under the supervision of fertility specialists, patients must continuously seek out options that are available to them based on their own capacity. Fertility treatment is time bound; younger the age of couple better will be the prognosis. Awareness needs to be addressed by government as well as NGOs to educate society about KS in order to achieve early diagnosis. Techniques such as ICSI and early cryopreservation of gametes may be an option for patient with KS, but success rate varies depending upon partner fertility status.

Conflict of Interest

Authors have no conflict of interest and no grant/funding from any organization

References

1. Groth KA, Skakkebaek A, Host C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome—a clinical update. *J Clin Endocrinol Metab* 2013;98(1):20-30. [DOI:10.1210/jc.2012-2382]. Available from: <https://academic.oup.com/jcem/article/98/1/20/2823039?login=false>. Accessed on 28/2/23
2. Klinefelter HF, Reifenstein EC, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle stimulating hormone. *J Clin Endocrinol*. 1942;2(11):615-27. [DOI: 10.1210/jcem-2-11-615]. Available from :<https://academic.oup.com/jcem/article-abstract/2/11/615/2722463>. Accessed on 28/2/23
3. Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab* 88(2):622-6. [DOI:10.1210/jc.2002-021491]. Available from: <https://academic.oup.com/jcem/article/88/2/622/2845122?login=false>. Accessed on 28/2/23
4. Lynn A, Ashley T, Hassold T. Variation in human meiotic recombination. *Annu Rev Genomics Hum Genet* 2004;5:317-49. [DOI:10.1146/annurev.genom.4.070802.110217]. Available from: <https://pubmed.ncbi.nlm.nih.gov/15485352/>. Accessed on 28/2/23
5. Rappold GA. The pseudoautosomal regions of the human sex chromosomes. *Hum Genet* 1993;92:315-24. [DOI:10.1007/BF01247327]. Available from: <https://pubmed.ncbi.nlm.nih.gov/8225310/>. Accessed on 28/2/23
6. Flaquer A, Rappold GA, Wienker TF, Fischer C. The human pseudoautosomal regions: a review for genetic epidemiologists. *Eur J Hum Genet* 2008;16:771-9. Available from: <https://www.nature.com/articles/ejhg200863>. Accessed on 28/2/23
7. Li L, Hamer DH. Recombination and allelic association in the Xq/Yq homology region. *Hum Mol Genet* 1995;4:2013-6. [DOI:10.1093/hmg/4.11.2013]. Available from: <https://pubmed.ncbi.nlm.nih.gov/8589676/>. Accessed on 28/2/23
8. Handel MA, Schimenti JC. Genetics of mammalian meiosis: regulation, dynamics and impact on fertility. *Nat Rev Genet* 2010;11:124-36. [DOI:10.1038/nrg2723]. Available from: <https://www.nature.com/articles/nrg2723>. Accessed on 28/2/23
9. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* 364(9430):273-83. [DOI: 10.1016/S0140-6736(04)16678-6]. Available from:[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(04\)16678-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(04)16678-6/fulltext). Accessed on 28/2/23
10. Graham JM Jr, Bashir AS, Stark RE, Silbert A, Walzer S. Oral and written language abilities of XXY boys: implications for anticipatory guidance. *Pediatrics* 1988;81:795-806. Available from: <https://pubmed.ncbi.nlm.nih.gov/3368277/>. Accessed on 28/2/23



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