Klinefelter Syndrome in Twins: It Is All in the Family

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Abstract Klinefelter’s Syndrome is a form of male hypogonadism which may present with; either a congenital chromosome abnormality; or alternatively with a mixture of 47XXY/46XY mosaics or higher-grade sex chromosomal aneuploidy as well as structurally abnormal X chromosomes. Clinically, the syndrome is characterized by findings of small, firm testes and symptoms of androgen deficiency but they may also present with azoospermia, tall stature, and bilateral painless gynecomastia. This article will describe the presentation, investigation and eventual diagnosis of identical twins with Klinefelter’s Syndrome. Both presented with varying levels of morphological features indicative of Klinefelter’s Syndrome and required further hormonal and genetic investigation. These two cases illustrate the difference in presentation of Klinefelter’s Syndrome and the challenges experienced regularly by clinicians when attempting to treat patients diagnosed with sensitive Syndromes. This is made especially difficult when there are background issues of language barriers and compliance issues.

Keywords: Klinefelter’s Syndrome, hypogonadism, twin, compliance


1. Introduction

Klinefelter’s Syndrome is a form of male hypogonadism which may present with; either a congenital chromosome abnormality; or alternatively with a mixture of 47XXY /46 XY mosaics or higher-grade sex chromosomal aneuploidy as well as structurally abnormal X chromosomes. Clinically, the syndrome is characterized by findings of small, firm testes and symptoms of androgen deficiency but they may also present with azoospermia, tall stature, and bilateral painless gynecomastia. This article will describe the presentation, investigation and eventual diagnosis of identical twins diagnosed with Klinefelter’s Syndrome.

2. Case Report

2.1. Patient 1

A 48-year-old Portuguese gentleman initially presented to his general practitioner (GP) with problems conceiving. He had noticed lack of seminal fluid during intercourse and during masturbation as the main cause for concern. He had no issues with erection and libido was normal. He was subsequently referred by the primary care route to the Urology specialists who noted this gentleman’s lack of facial hair, scanty pubic hair, as well as small testes. There were no signs of gynecomastia. He was diagnosed with hypogonadism and subsequently referred to the endocrinologists for further investigations.

He was reviewed in the endocrinology clinic three years later due to missing numerous clinic appointments. Investigations confirmed primary hypogonadism (Table 1). Cytogenetic studies conducted confirmed the presence of Klinefelter’s Syndrome and he was referred for semen analysis with future plans to discuss fertility and commencement of testosterone replacement therapy.

A bone mineral density scan revealed severe osteoporosis (Lumbar spine: T-score -3.1 & Z-score -2.9, High Fracture Risk as per WHO FRAX tool), for which he was commenced on Alendronic acid, calcium and Vitamin D supplements. These investigations were conducted sporadically over a two year period mainly due to language barriers, patient non-compliance and numerous missed clinic appointments. Despite regular contact between the endocrine department and patient’s GP there were no further follow up appointments attended and there is no confirmation of the patient’s compliance to treatment. At the time of submission this patient had not yet returned to clinic for discussion on fertility and commencement of testosterone replacement therapy.

2.2. Patient 2

A 48-year-old gentleman was referred to the endocrinology for exclusion of hypogonadism by his GP who was aware of his twin sibling’s diagnosis of Klinefelter’s Syndrome despite this being a non-hereditary...
syndrome. Initially the patient was unaware as to the reason for his referral to the endocrine clinic as he was otherwise fit and well and asymptomatic. He was an active gentleman in full-time employment and did not complain of any physical anomalies. He had reportedly good sexual function with good libido and normal erectile function. He had regular sexual intercourse but had not had any children out of choice and was therefore not complaining of any conception problems as in the previous gentleman’s case. Clinical examination did not reveal any evidence of gynaecomastia but did reveal bilaterally shrunken testes.

Given the positive finding on genital examination, he was planned for a full investigation for the possibility of hypogonadism. His results were consistent with primary hypogonadism and are listed below in Table 1. Cytogenetic studies were conducted which confirmed the presence of Klinefelter’s Syndrome. Despite having a diagnosis of Klinefelter’s Syndrome confirmed on chromosomal analysis (47, XXY) we have been unable to discuss this officially with the patient to explain the full significance of this finding and its implications as he has not attended any future appointments despite multiple communications to him. This has been communicated to his GP who is aware of the diagnosis and our investigations; with the hope that he will be able to progress with further investigations including a bone mineral density scan and for referral to counselling services and initiate treatment.

### 3. Discussion

Klinefelter syndrome is the most frequent form of primary hypogonadism with a prevalence of 1:600 in the male population [1]. Boys with this condition appear normal at birth and enter puberty normally but it is during this period where the abnormalities associated with Klinefelter begin to surface. Normally, testosterone is produced by stimulation of the Leydig cell in the testis for spermatogenesis. The pituitary luteinizing hormone (LH) produced by stimulation of the Leydig cell in the testis by the pituitary follicle stimulating hormone (FSH) is the main stimulus on the seminiferous tubules in the testis for spermatogenesis.

However, in Klinefelter syndrome, there is damage and atrophy to the seminiferous tubules [2], manifested by clinical findings of small, firm testes with volume of 2-4ml. Normal average testicular volume increase from 2ml to 15ml during puberty with average adult volume of 25ml. Consequently there is insufficient testicular growth and spermatogenesis causing variable degree of inadequate sperm production and infertility. At the same time, there is abnormality in the Leydig cells [2] in the testis and impaired testosterone production. A typical patient with Klinefelter therefore presents with low serum testosterone with high LH and FSH levels, a condition known as hypergonadotrophic hypogonadism ie primary hypogonadism. Other documented clinical features include tall stature, micropenis and bilateral painless gynaecomastia [3]. The mainstay of treatment is with testosterone replacement therapy to correct testosterone deficiency. This helps with promoting appropriate virilization, muscle growth, mood, sexual desire and protect against osteoporosis.

The diagnosis is often delayed because of various clinical forms with which the syndrome presents itself; as in this case the two siblings did not demonstrate the same levels of morphology despite being identical twins. The 47, XXY genotype results from nondisjunction of the sex chromosomes of either parent during meiotic division, while mosaicism results from nondisjunction during mitotic division after conception. The greater the number of extra X chromosomes, the greater the phenotypic consequences. The Syndrome presenting due to the presence of mosaicism has been found to be a less severe variant of the classical form (47, XXY) and the testes may be found to be of normal size [4,5].

An identical twin with Klinefelter syndrome diagnosed in adulthood was first reported by Donald A et al [6] in 1958, 16 years after the syndrome was first described. It is known that the genetic errors in Klinefelter syndrome occurs by chance, i.e. not inherited. However, with the increasing numbers of reported cases of identical twins with Klinefelter syndrome, diagnosed both in childhood and adulthood [7,8,9,10], genetic predisposition might have a role to play, though the exact mechanism is still unknown. Interestingly, as in both our patients, despite similar chromosomal analysis, most of the twins with Klinefelter syndrome exhibits different form of morphological characteristics.

Compliance issues as in this case where both individuals had a noticeably poor command of the English language has had a major impact upon the quality and efficiency of investigation, counselling and medical management. An option during the planned consultation would be to involve interpreters or bringing in family members with their consent to help with the understanding of their condition. A high standard of care is essential to assist individuals with syndromes such as Klinefelter to identify needs and requirements for an acceptable and adequate level of health and interaction in the community.

To further improve understanding and engagement, patients with Klinefelter should be encouraged to enroll with Klinefelter support groups, for example the American Association for Klinefelter Syndrome Information and Support and the Klinefelter’s Syndrome Association UK. This is an invaluable resource for providing mutual support and information to Klinefelter patients and their families, a place to meet people with similar conditions and sharing personal experiences and challenges.

Apart from monitoring of effectiveness of testosterone replacement therapy, they are also at risk of developing morbidities later in life which are not related to testosterone deficiency. These include pulmonary diseases such as chronic bronchitis, bronchiectasis, and emphysema [11], breast cancer [12], and possibly non-Hodgkin lymphoma [13]; varicose veins, leading to leg ulcers [14]; systemic lupus erythematosus [15]; and diabetes mellitus [16]. Therefore, a good understanding of their condition

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Normal Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>0.8 nmol/L</td>
<td>0.7 nmol/L</td>
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<tr>
<td>Prolactin</td>
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</tr>
<tr>
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<td>24 U/L</td>
<td>1-14 U/L</td>
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<td>TSH</td>
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<td>1.79 mU/L</td>
<td>0.3-4.2 mU/L</td>
</tr>
<tr>
<td>Free T4</td>
<td>13.1 pmol/L</td>
<td>13.5 pmol/L</td>
<td>12 - 22 pmol/L</td>
</tr>
</tbody>
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with regular engagement with health care professional is essential for lifelong follow up.

4. Conclusion

These two cases illustrate the difference in presentation of Klinefelter’s Syndrome and the challenges experienced regularly by clinicians when attempting to treat patients diagnosed with sensitive Syndromes. This is made especially difficult when there are background issues of language barriers and compliance issues.

Genetic testing should always be considered for the affected individual to establish the cause of primary hypogonadism in cases of positive findings suggesting a possible chromosomal syndrome. It may be cautious to consider genetic testing and more imperatively in the event of a twin sibling, having a non-hereditary chromosomal syndrome.

References


