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Klinefelter's syndrome with renal tubular acidosis: impact on height

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ABSTRACT

A 19-year-old Indian man presented with a history of proximal muscle weakness, knock knees and gynaecomastia. On examination, he had features of rickets and bilateral small testes. Karyotyping revealed a chromosomal pattern of 47,XXX, confirming the diagnosis of Klinefelter's syndrome. He was also found to have hyperchloraemic metabolic acidosis with hypokalaemia, hypophosphataemia, phosphaturia and glycosuria, which favoured a diagnosis of proximal renal tubular acidosis. Patients with Klinefelter's syndrome typically have a tall stature due to androgen deficiency, resulting in unfused epiphyses and an additional X chromosome. However, this patient had a short stature due to associated proximal renal tubular acidosis. To the best of our knowledge, this is the second case of Klinefelter's syndrome with short stature due to associated renal tubular acidosis reported in the literature. This report highlights the need to consider other causes when patients with Klinefelter's syndrome present with a short stature.

Keywords: Klinefelter's syndrome, proximal renal tubular acidosis, short stature

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INTRODUCTION

Klinefelter's syndrome is a common condition seen in approximately one in 500 to one in 1,000 male births. Most cases are inconspicuous before puberty. The post-pubertal syndrome is characterised by small testes, with the testicular volume ranging from 1–4 ml. Men with Klinefelter's syndrome tend to be tall and have eunuchoid body proportions due to androgen deficiency, which leads to unfused epiphyses and the presence of three pseudoautosomal short stature homeobox genes (one in each X chromosome and one in the Y chromosome).⁽¹⁾ Apart from having a tall stature, most of them have gynaecomastia (bilateral and usually painless) due to androgen deficiency and excessive aromatase activity. They also have problems with language and learning.



Fig. 1 Photograph of the patient on presentation shows Tanner Stage 5 bilateral gynaecomastia.

Fertility is the main issue in the later years. Most are infertile because of azoospermia.^(2,3) Elevated serum follicle stimulating hormone (FSH) levels with low testosterone, small testes and bilateral gynaecomastia are suggestive of Klinefelter's syndrome, and its diagnosis is confirmed by karyotyping.⁽⁴⁾

Renal tubular acidosis is characterised by hyperchloraemic metabolic acidosis with various electrolyte abnormalities.⁽⁵⁾ Type 1 or distal renal tubular acidosis is a result of acid secretion failure in the distal tubules of the kidneys. The kidneys are unable to acidify the urine to a pH value of less than 5.5 in the presence of systemic metabolic acidosis, or after acid loading. Type 2 or proximal renal tubular acidosis is a result of impaired bicarbonate re-absorption in the proximal tubules of the kidneys, which are the primary areas of bicarbonate re-absorption. These patients present with hypophosphataemia, hypokalaemia, renal glycosuria (glycosuria with a normal plasma glucose concentration) and aminoaciduria.⁽⁶⁾ In this report, we present a patient with both Klinefelter's syndrome and short stature due to proximal renal tubular acidosis.

CASE REPORT

A 19-year-old Indian man presented to the endocrine outpatient department with a history of progressive knock knees and proximal muscle weakness of two years' duration. His other concern was an increase in the size of both the breasts without any pain or secretion over the past three years. He was born of a second-degree

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Fig. 2 Radiograph of the pelvis shows triradiate pelvis.

consanguineous marriage and had normal siblings. There was a history of delay in developmental milestones. He also gave a history of polyuria and polydipsia, but no history of renal stones, bone fracture, periodic paralysis or eye symptoms.

On examination, the patient was short-statured, measuring 148 cm in height, which was three standard deviations below the mean height, and his height-for-age corresponded to 11 years. He had bilateral gynaecomastia at Tanner Stage 5, with no tenderness or discharge from the nipples (Fig. 1). Both the upper and the lower limbs had severe proximal muscle weakness. The skeletal examination showed a widening of both the wrist joints, knock knees and arachnodactyly. Both the testes were small in size, with a volume of 2 ml each, and the stretch penile length was 5 cm, with pubic hair at Tanner Stage 3. The rest of the examination was unremarkable. There was no thyroid swelling and no presence of cystine crystal in the eyes. His bone age was 14 years.

The laboratory investigations were as follows: post-prandial plasma glucose 119 mg/dl (6.61 mmol/L) (normal values [NV] 80–140 mg/dl and 4.4–7.7 mmol/L), serum potassium 2.7 mmol/l (NV 3.5–5.0 mmol/l), serum bicarbonate 16 mmol/l (NV 22–29 mmol/l), serum chloride 108 mmol/l (NV 95–105 mmol/l), serum creatinine 1.4 mg/dl (NV 0.5–1.4 mg/dl), serum calcium 9.1 mg/dl (NV 8.3–10.2 mg/dl), serum albumin 4.3 g/dl (NV 3.5–5.3 g/dl), serum 25 (OH) vitamin D 21.9 ng/ml (NV > 20 ng/ml) and parathyroid hormone plasma (iced sample) 53.7 pg/ml (NV 8.0–74 pg/ml), serum phosphorous 2.2 mg/dl (NV 2.5–4.5 mg/dl), serum alkaline phosphatase 1,226 u/l (NV 60–125 u/l), serum FSH 91.2 IU/L (NV 0.8–11 IU/L), serum testosterone 22.5 ng/dl (NV 212–1,030 ng/dl). The urine dipstick for glucose was positive. Tubular maximum phosphate



Fig. 3 Photograph shows the patient after the Webster procedure.

reabsorption per glomerular filtration rate was 1.8 mg (NV 2.5–4.5 mg), which was suggestive of phosphaturia. Karyotyping showed a chromosomal pattern of 47,XXY. The radiological examination showed triradiate pelvis and genu valgum (Fig. 2). A diagnosis of Klinefelter's syndrome was considered based on the clinical findings and karyotyping. The patient had features of rickets with proximal muscle weakness and lower limb deformities. He also had biochemical hyperchloraemic metabolic acidosis with hypokalaemia, hypophosphataemia and glycosuria. A diagnosis of proximal renal tubular acidosis was considered but the aetiological workup for this was negative. He was initiated on replacement therapy with activated vitamin D₃, potassium, phosphate and alkaline, as well as androgen therapy for his hypogonadism. He underwent breast correction surgery using the Webster technique (Fig. 3), and has been on follow-up for over a year. There has been modest correction of the polyuria and polydipsia, as well as a significant improvement in his proximal muscle weakness. However, there has been no change in his height or skeletal deformities.

DISCUSSION

Klinefelter's syndrome is one of the common causes of male hypogonadism. The most prevalent karyotype in men with Klinefelter's syndrome is 47,XXY. This is usually due to first meiotic non-disjunction in either of the parents.⁽⁷⁾ Men with Klinefelter's syndrome commonly have azoospermia. A testicular biopsy usually shows an absence of spermatogenesis with hyalinisation of the seminiferous tubules.⁽¹⁾ The degree of hyalinisation varies from patient to patient. There is a higher prevalence of malignancies, such as breast cancer, mediastinal germ cell tumours and non-Hodgkin's lymphoma, associated with Klinefelter's syndrome.⁽⁸⁾ Autoimmune diseases are more common in patients with Klinefelter's syndrome,⁽⁹⁾ and diabetes mellitus

also occurs more frequently.⁽¹⁰⁾ Osteoporosis is seen in a quarter of patients with Klinefelter's syndrome.⁽¹¹⁾

Renal tubular acidosis is characterised by hyperchloraemic metabolic acidosis, which occurs when there is a renal tubular defect with little effect on glomerular functions. In Type 1 or distal renal tubular acidosis, a failure in acid secretion in the distal tubules of the kidneys results in the inability of the renal system to acidify urine, whereas in Type 2 or proximal renal tubular acidosis, bicarbonate re-absorption is impaired in the proximal tubules of the kidneys. Hence, these patients present with multiple electrolyte abnormalities.⁽¹²⁾ Renal tubular acidosis may be a result of cystinosis, tyrosinaemia, hereditary fructose intolerance, galactosaemia, glycogen storage disease (Type I) or Wilson's disease, or it may be due to heavy metal poisoning such as lead, copper or mercury poisoning. The management of proximal renal tubular acidosis includes alkali therapy, phosphate supplementation and the replacement of potassium and active vitamin D.

The presence of renal tubular acidosis in patients with Klinefelter's syndrome is rare. To the best of our knowledge, this is the second time that such an association is being reported. Matteini et al reported a case of Klinefelter's syndrome associated with idiopathic renal tubular acidosis.⁽¹³⁾ Short stature in a patient with Klinefelter's syndrome due to growth hormone deficiency has also been reported.⁽¹⁴⁾ An association between X-linked hypophosphataemic rickets and Klinefelter's syndrome has previously been described.⁽¹⁵⁾ In our patient, the rare association between renal tubular acidosis and Klinefelter's syndrome had resulted in the loss of height, which accounted for the short stature.

In conclusion, other causes have to be considered in patients with Klinefelter's syndrome and short stature. Therapy should be directed toward the aetiology of

short stature, in addition to treating hypogonadism with androgen therapy.

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