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Jacob's Syndrome and Deficiency of 11-Beta-Hydroxylase Enzyme Association Revealed by a Statural Advance: A Case Report

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Abstract

47XYY syndrome is a rare sex chromosome variant with an extra Y chromosome. Most patients with a 47XYY karyotype have a normal phenotype. This disorder seems to be associated with a higher risk of developing behavior and cognitive problems, tall stature and infertility in adulthood. We report here a rare case of 47, XYY syndrome associated with an 11-beta-hydroxylase deficiency revealed by a stature advance along with precocious puberty after obtaining informed consent from parents. To our knowledge, this is the first case reported in the literature.

Keywords

Jacob's Syndrome, 47XYY Syndrome, 11-Beta-Hydroxylase Deficiency

1. Introduction

Jacob's or 47, XYY or XYY or YY syndrome is an uncommon male chromosomal anomaly. It is characterised by the presence of an extra Y chromosome in a male. The normal male karyotype is 46, XY. However, in this syndrome, the person's chromosomal pattern is 47, XYY, as a result of an erroneous cell division before or after conception. Most patients with a 47, XYY karyotype have a normal phenotype, and therefore the diagnosis is usually delayed or incidental, they are medium to large and tend to have normal fertility. They may also have developmental delay, language and behaviour issues [1] [2].

We report the case of a child who was admitted to the Pediatric Endocrinology Department of the Hassan II University Hospital in Fez for the management of a stature advance associated with precocious puberty signs.

2. Case Presentation

A 3 years and 10 months old boy, born from a 2nd degree consanguineous marriage and having a similar case history in his paternal cousin, was admitted to our hospital for the management of a stature-weight advance with a weight of 29 kg (+3 SD), a height of 133 cm (+3 SD) associated with precocious puberty signs: A pubic hair stage III of tanner, a penis of 9 cm, normal testicles and a rough voice, along with arterial hypertension of 150/100mmhg on several occasions.

Blood tests showed a testosterone level at 6 ng/ml, an 8 am cortisol level low at 2.9 ug/dl, an ACTH level high at 1250 pg/ml and a kalemia level at 3.1 meq/l. So as to rule out an 11-beta-hydroxylase enzyme deficiency given the high blood pressure levels associated with hypokalaemia, the deoxycorticosterone (DOC) level came back high at 2599 pg/ml, *i.e.* 16*N. the karyotype matched Jacob's syndrome with 47, XYY.

Bone age was estimated at 14 years, abdominal ultrasound showed bilateral adrenal hypertrophy and an organomegaly of 8 years of age.

In terms of treatment, 15 mg/d hydrocortisone was prescribed for the child with a good evolution.

Further assessment and a psychiatric consultation are planned to evaluate the patient's psychological state. In addition, a genetic consultation is planned for genetic counselling.

3. Discussion

Jacob's or 47, XYY or XYY or YY syndrome is a rare and less common male chromosomal abnormality, affecting approximately 1 in 1000 male newborns [2]. This incidence appears to be relatively common in males worldwide [3].

It is the second most common sex chromosomal disorder in males—after Klinefelter's syndrome—characterised by the presence of an extra Y chromosome in males and is always paternally inherited. The first case was incidentally discovered by a cytogeneticist, Sandberg, *et al.* in 1961 [4]. In our case, it was discovered by the presence of precocious pseudo-puberty signs associated with an advanced stature.

Jacob's syndrome is the result of non-disjunction at metaphase II of paternal meiosis during spermatogenesis with an extra copy of the Y chromosome which, if involved in fertilisation, will result in the child carrying an extra Y chromosome in all cells. In some rare cases, there may be an error in post-zygotic mitosis during early embryonic development that produces a 46, XY/47, XYY mosaic [5] [6].

The diagnosis of this syndrome is usually late, with the average age of diagnosis being about 17 years [3], whereas our patient's age was 3 years and 10 months.

In 1970, some studies showed that people with 47XYY were particularly numerous in penal and psychiatric institutions [7] [8]. Later on, these studies were recognized as having significant methodological faults [7].

It is currently reported that patients with a 47XYY karyotype have cognitive

and behavioural impairments, including delayed language and movement development, impulsivity, poor attention and impaired social interaction along with an increased risk of autism spectrum disorders [5] [7] [9] [10]. In our case, we did not find these abnormalities at this age (3 years and 10 months). A special psychomotor evaluation was suggested as well as a regular follow-up.

47, XYY patients are also more likely than the general population to be diagnosed with asthma, seizure disorders and tremors [3]. Adult males may have infertility and low libido history [5].

Physical examination findings may vary, as the phenotypic expressions of syndrome 47, XYY are very variable [5]. The most common findings on physical examination are large stature, as was the case in our patient, macrocephaly, hypertelorism, hypotonia and clinodactyly [11]. About half of such patients may have flat feet, a minority of patients have dental anomalies such as underbite and macrodontia, while it is estimated that about 85% of 47, XYY males are never diagnosed [11] [12].

Atrophied testes may be observed, but the external genitalia may also appear normal [5]. Thus, in our case, the pubic hair was classified as tanner stage III, the penis at 9 cm and the testes as normal, making an aspect of precocious puberty secondary to 11-beta-hydroxylase enzyme deficiency which is a genetic disease of autosomal recessive inheritance with an incidence of 1/200,000 in the general population [13].

11-b-hydroxylase is required for the hydroxylation of 11-deoxycortisol (compound S) to cortisol in the glucocorticoid pathway and deoxycorticosterone (DOC) to corticosterone in the mineralocorticoid pathway. Its deficiency thus leads to a defect in cortisol and aldosterone synthesis, accumulation of the upstream metabolites compound S and DOC, and excess synthesis of adrenal androgens by the only possible metabolic pathway [13]. In girls, the diagnosis is made at birth in the presence of virilisation of the external genitalia without salt loss, whereas in boys, the diagnosis is often delayed and established by an early pseudo-pubertal presentation occurring most often at the age of 2 - 4 years [13] [14] [15]. The hypersecretion of DOC and its metabolites known for their mineralocorticoid action can lead to high blood pressure and hypokalaemia, which is the case in our patient.

Indeed, the diagnosis of 11-beta-hydroxylase enzyme deficiency is based on the elevation of compound S and baseline DOC or after stimulation by ACTH. The molecular study establishes the diagnosis of the disease by proving the mutation in the CYP11B1 gene. Glucocorticoid treatment is usually prescribed to control hyperandrogenism, as was the case in our patient.

The lifetime of patients with 47, XXY syndrome is shorter than that of patients with a normal karyotype and may be due to an increased risk of cancer, lung, neurological and unspecified diseases, and also to the high-risk behaviour and trauma that have been reported in men with 47, XXY syndrome [3].

The diagnosis of 47, XYY syndrome can be made during the prenatal period using cell-free fetal DNA [12]. This technique has been shown to be very accu-

rate in detecting sex chromosome aneuploidies. Amniocentesis is a more invasive method of prenatal diagnosis and is therefore no longer the preferred method [12]. After childbirth, the diagnosis is established by analysing the karyotype from a sample of the patient's blood.

Families who receive a prenatal diagnosis of 47, XYY syndrome should receive genetic counselling to help them understand the condition.

Treatment for this syndrome is usually limited to support, taking into account the patient's comorbidities. Men with infertility should be thoroughly evaluated by a qualified reproductive endocrinologist [5].

4. Conclusions

47XYY syndrome is the most common aneuploidy after Klinefelter syndrome. To date, men with 47XYY syndrome have been shown to have a characteristic physical phenotype, including tall stature and cognitive and behavioural deficits, with an increased risk of autism spectrum disorders and infertility in adulthood.

As far as we know, this is the first case reported in the literature associating Jacob's syndrome and 11-beta-hydroxylase enzyme deficiency. Further studies are needed to investigate the mechanism of this association.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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