


Mosaic trisomy 13 and constitutional delay in puberty

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Abstract

Patau syndrome is the third most frequent chromosomal trisomy, with an estimated mortality rate that is about 50 times higher than the general neonatal mortality rate. Trisomy 13 mosaicism is a subtype that may result in a milder form of the disease, potentially leading to a longer life expectancy in these patients, allowing them to reach puberty. In this report, we discuss the case of a young boy who was evaluated for delayed puberty and karyotyping revealed mosaicism for trisomy 13. A detailed history, physical examination and appropriate laboratory studies and imaging were performed that showed a picture of suggestive of hypogonadotropic hypogonadism and an abnormal male karyotype with mosaicism for trisomy 13. To date, there is no clear explanation to the association between trisomy 13 and gonadal axis, specifically with normal imaging of pituitary. We postulate that delayed puberty could be a clinical feature of mosaic trisomy 13.

INTRODUCTION

Patau syndrome (Trisomy 13) was first described in 1960 by Dr Patau *et al.* It is the third most frequent chromosomal trisomy with an incidence of about 1/8000–12 000 births. Compared with the general neonatal mortality rate, the estimated mortality rate from trisomy 13 is about 50 times higher [1]. In total, 28% of newborns with Patau syndrome die within the first week of life, 44% in the first month and 86% by 1 year of age. Survival beyond the first year of life is unusual and exceptional beyond the first decade, with only a small number of cases experiencing pubertal age. Mortality in Patau is attributed to cardiopulmonary failure, congenital heart defects and pneumonia [1, 2].

In 5% of cases, not all cells are trisomic; some are euploid; this is known as trisomy 13 mosaicism. This entity is not well described but may lead to a milder form of the disease [3]. Delayed puberty is yet to be reported in these patients, likely owing to the short life expectancy.

In this report, we discuss a case of mosaic trisomy 13 who presented with delayed puberty. We tried to establish that there could be a possible association between mosaic trisomy 13 and constitutional delay in puberty (CDP).

CASE REPORT

A young, pleasant boy was first seen at the age of 14 years as his parents were concerned about his pubertal

development and size of genitalia. He is a product of non-consanguineous parents and had a normal natal and postnatal history. He did not suffer from any chronic medical illness and was not on any long-term medications. Growth developmental milestones were normally attained and had a good scholastic performance. There is no family history of delayed puberty or any endocrine problems.

On examination: height 166 cm (slightly below 50th percentile), weight 61.1 kg (75th percentile) (Fig. 1). He had normal facial features and a normal sense of smell. Sexual maturity scores revealed microgenitalia: stretched penile length (SPL) 4 cm and bilaterally small testes 5 ml, axillary and pubic hair tanner stage 2, no gynecomastia. Systemic examination was unremarkable, apart from kyphosis.

At a chronological age of 14, bone age corresponded to 12 years, thereby indicating a delayed bone age (Fig. 2). General laboratory investigations were all normal. Baseline hormonal assay collected in the morning time including luteinizing hormone (LH) <0.5 mIU/ml (1.7–8.6), follicular stimulating hormone (FSH) 1.2 mIU/l (1.5–12.4), testosterone level 0.8 nmol/l (0.98–38.5) and free androgen index 2.5 (40–150), all of which were below normal range. The rest of pituitary evaluation, including IGF-1, Prolactin, Cortisol AM, TSH were all normal. These findings were suggestive of either CDP or hypogonadotropic hypogonadism (HH).

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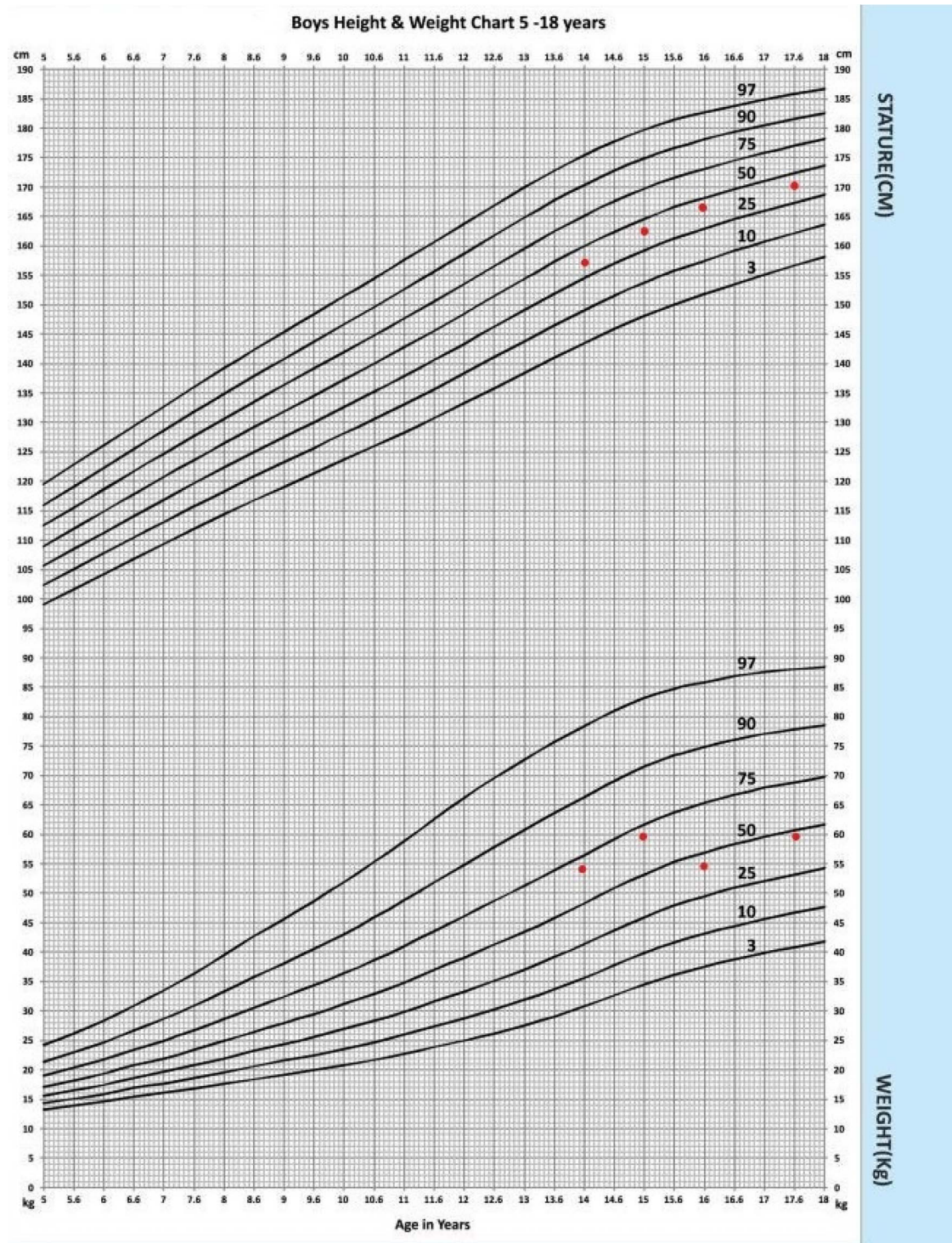


Figure 1. Growth chart: height and weight.

In patients suspected with HH chromosomal analysis to exclude congenital causes of delayed puberty is recommended. Karyotyping revealed $Mos\ 47,\ XY,\ +13$, with two cell lines: 87% of the cells having normal karyotype and the remainder with 47 chromosomes including an additional chromosome 13. Further cytogenic analysis using fluorescence *in situ* hybridization confirmed the above observation revealing 23% cells with Trisomy 13 (161/700 cells) (Fig. 3). Given the karyotype result, an

echocardiography was done, which ruled out any cardiac abnormality.

GnRH testing is generally used to differentiate between CDP and HH. The LH response to GnRH in boys with CDP usually exceeds that of HH [4–6]. In one report LH level exceeding 5.3 U/l is associated with progression in testicular volume and penile size. Following a GnRH stimulation test: LH showed an increase of up to 16 mIU/ml, FSH 9.3 mIU/L and testosterone 2.4 nmol/l. (Table 1). These

Table 1. GnRH stimulation test

	0 mins	30 mins	60 mins	90 mins	120 mins
LH	2.3	17.8	16.1	13.0	10.3
FSH	4.6	8.3	9.3	9.1	8.9
Testosterone	1.0	1.1	2.4	2.7	2.7



Figure 2. X-ray hand: bone age.



Figure 3. Karyotype: mosaic trisomy 13.

findings are in favor of CDP. Further workup included magnetic resonance imaging (MRI) Sella that showed a normal-sized pituitary gland, no supra or para-sellar masses (Fig. 4).

The patient was diagnosed with CDP, and given the size of the genitalia, he was started on a small permissive dose of testosterone (50 mg of testosterone decanoate) monthly for 3 months to assist with sexual maturity. He was advised to adopt a healthier lifestyle by incorporating more physical activity and followed up for 4 years. No further intervention was needed as he continued to



Figure 4. Normal MRI brain.

show significant improvement in sexual maturity as well as hormonal profiles. He showed normal attainment of height, weight, muscle bulk and reached puberty by the age of 17. Latest physical examination findings showed SPL of 14 cm, testicular volume of 18–20 ml and tanner stage 4 for axillary and pubic hair.

DISCUSSION

Trisomy 13 is a heterogeneous disorder encompassing multiple malformations including central nervous system, cardiac and urogenital anomalies. Characteristic features of Trisomy 13 include microphthalmia or anophthalmia, cleft lip and palate, and polydactyly [7]. The median survival time for patients with Trisomy 13 is 7–10 days, approximately 86–91% of live-born patients with this syndrome do not survive beyond the first year of life [8]. However, survival beyond the first year of life has been associated with mosaicism, which accounts 5% of these cases [9]. The phenotype and outcome of mosaic trisomy 13 is at present poorly understood [10].

The most common cause of delayed puberty is attributed to constitutional delay of growth and puberty, a self-limiting condition in which puberty starts later than usual but shows normal progression [11]. Our patient presented at the age of 14 with microgenitalia, slightly delayed bone age and initially low testosterone level but eventually showed a gradual progression in

growth. He remained within the 50th percentile for his weight and height and attained normal sexual maturation by the age of 17. He had no other congenital anomalies that are commonly associated with Patau and had a normal intellectual function.

We were able to trace one case report of a 20-year-old male with Patau syndrome and idiopathic hypogonadotropic hypogonadism (IHH). This patient presented with lack of development of secondary sexual characteristics and normal height, clinical features and biochemical parameters associated with IHH. Clinical findings commonly associated with trisomy 13 were absent in this patient. MRI brain showed a normal olfactory bulb and tract but shallow olfactory sulcus and Karyotyping revealed two cell lines: one showing deletion of chromosome 13 at band 13p10.8 and another showing trisomy 13 with homologous Robertsonian translocation [12].

To the best of our knowledge, there has been a single case report to link trisomy 13 to hypogonadotropic hypogonadism; however, there were no previous case reports that linked mosaic trisomy 13 to CDP. In summary, there could be a possible association between mosaic trisomy 13 and CDP which may present in the form of hypogonadism, and in the presence of supporting clinical evidence, trisomy 13 should be considered as one of the differential diagnoses of delayed puberty.

CONFLICT OF INTEREST STATEMENT

None declared.

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The authors have no financial relationships relevant to this article to disclose.

ETHICAL APPROVAL

Written informed consent was obtained from patients' parent. No identifiable information was added to the manuscript.

CONSENT

Written informed consent was obtained from the patients' parent for publication of this case report and any accompanying images.

GUARANATOR

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