Brief Communication

Tale of two rare diseases

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ABSTRACT

Idiopathic Hypogonadotropic hypogonadism (IHH) phenotype is variable &various genes have been decribed in association with IHH. We describe association of IHH with mosaic trisomy 13. A 20 year old male presented with lack of development of secondary sexual characters, normal height, micropenis, small testes, gynaecomastia, absence of axillary and pubic hairs, hyposmia,synkinesis, bilateral horizontal nystagmus and high arched palate. Investigations showed low gonadotropin,low total testosterone, LH after stimulation with 100 mcg tryptorelin sc was 11.42 mU/mL at 40 min. MRI of hypothalamo-pituitary region showed normal olfactory bulb and tract but shallow olfactory sulcus . Karyotype showed homologous Robertsonian translocation of chromosome 13. This case fits classical IHH except for LH rise on stimulation.Features of Patau syndrome which is associated with trisomy 13 are absent in our case. Mosaic trisomy 13, which can otherwise be rare incidental finding , has not been described in association with IHH.Causal association of novel mutation on chromosome 13 leading to aforementioned phenotype cannot be rule out.

Key words: Idiopathic hypogonadotropic hypogonadism, mosaic trisomy13, Kallman syndrome genes, shallow olfactory

Introduction

Association of idiopathic hypogonadotropic hypogonadism (IHH) with anosmia was first described by Kallmann in 1944. It has a prevalence of 1:10,000 in general population. IHH has been described to be isolated or associated with other anomalies. So far many genes have been described. However, no gene on chromosome 13 has been described to be associated with IHH.[1]

Case Report

A 20-year-old male born of consanguineous union, resident of urban Kolkata presented with lack of development of secondary sexual characteristics. The patient was full term normal delivery with uneventful antenatal period. The neonatal period was uneventful, but history of hospitalization in infancy due to respiratory illness from which patient apparently recovered, although no past medical records could be retrieved. Growth development milestones were normally attained. There was history of hyposmia. There was no history of poor scholastic performance or other any systemic disease. On examination, height was 170 cm (97th percentile), arm span was 169 cm upper segment/lower segment ratio was 0.76, and body mass index (BMI) was 21. Facial features were normal except for high-arched palate [Figure 1]. Sense of smell tested on graded dilution of spirit revealed hyposmia. There was also synkinesis and bilateral horizontal nystagmus. Sexual maturity scores showed micropenis (stretched penile length (SPL) 4.6 cm); small testes (bilateral < 2 ml); [Figure 2] gynecomastia; and absence of facial, axillary, and pubic hairs. Systemic examination was normal. Bone age as calculated from Greulich and Pyle chart was delayed at 14 years [Figure 3]. Total testosterone was <10 ng/dl (265-800). On investigation, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) values from three pooled sample were 0.25 mIU/ml (1.7-8.6) and 1.25 mIU/ml (1.5-12.4), respectively. Morning cortisol was 7.99 μg/dl. Thyroid stimulating hormone (TSH) and free thyroxine (T4) were 3.60 μIU/ml (0.27-4.2) and 1.12 ng/dl, respectively. Stimulated LH values after 100 μg of aqueous tryptorelin inj. subcutaneously was 11.42 mIU/ml. Magnetic resonance imaging (MRI) of hypothalamo-pituitary region revealed normal olfactory bulb [Figure 4], but shallow olfactory

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.119539

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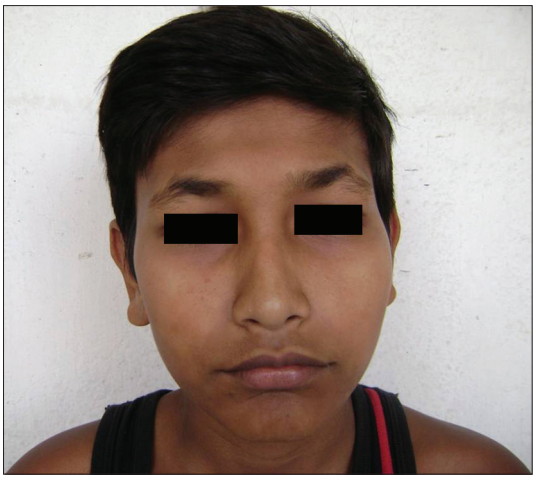

Figure 1: Normal facial features, no micropthamia, bulbous nose, hyperteorism, or any Patau syndrome phenotype

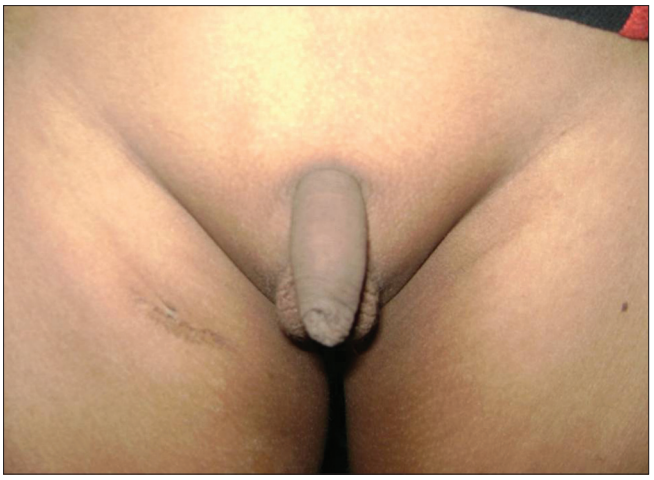

Figure 2: Micropenis and small testes

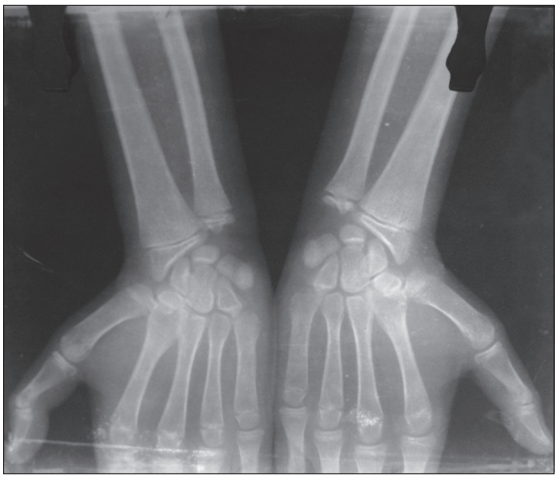

Figure 3: Delayed bone age

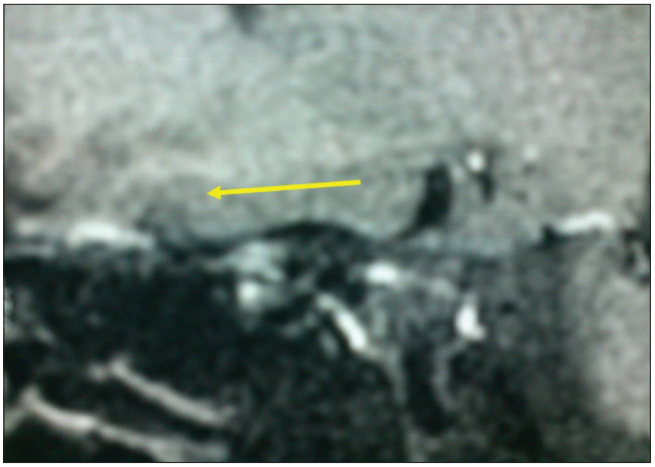

Figure 4: Olfactory bulb present

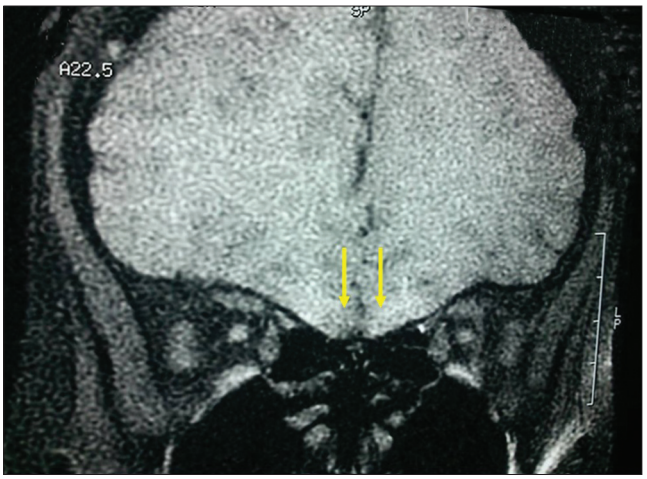

Figure 5: Shallow olfactory sulcus

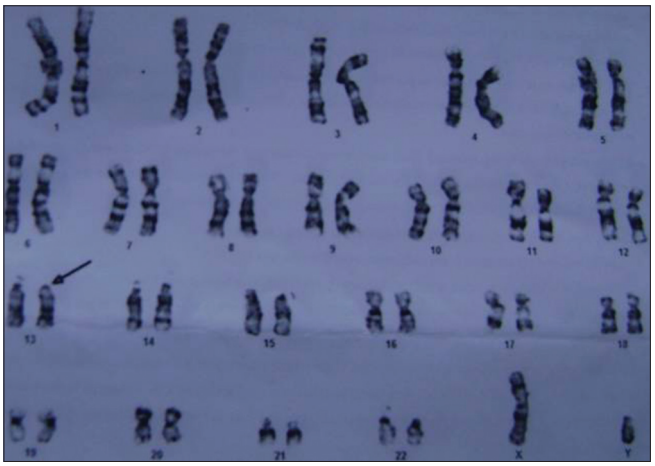

Figure 6: Deletion of chromosome 13 at band 13p10.8 and another showing trisomy 13 with homologous Robertsonian translocation

sulcus [Figure 5]. Audiometry showed no sensorineural deafness. Two dimensional (2-D) echocardiography did not reveal any cardiac anomaly. Ultrasound of abdomen does not reveal any visceral organ anomaly. Karyotype revealed two cell lines: One showing deletion of chromosome 13 at band 13p10.8 and another showing trisomy 13 with homologous Robertsonian translocation [Figure 6]. As LH rise was pubertal, patient was put on follow-up for puberty onset.

Discussion

Hypogonadism in male can either be hypergonadotropic or hypogonadotropic. Hypergonadotropic hypogonadism is caused by diseases affecting testis without any defect in gonadotropin secretion and it commonly presents with increased gonadotropin levels post puberty, while hypogonadotropic hypogonadism can be isolated or associated with defect in other pituitary hormones. Accordingly, it can be either acquired when it is commonly associated with concomitant adrenocorticotropic hormone (ACTH), growth hormone (GH), and TSH defect. Congenital IHH is caused by an isolated defect in gonadotropin-releasing hormone release, action, or both.[1] Clinically, attainment of normal height and normal morning serum cortisol makes anomaly of hypothalamo-pituitary axis less likely. Gynecomastia in IHH is seen as consequence of altered estradiol/testosterone ratio due to increased conversion of adrenal precursor to estrogen. Presence of hyposmia and synkinesis points towards Kallmann Syndrome. The inheritance can be autosomal dominant (AD), autosomal recessive (AR), and X-linked; but in the given case lack of family association likely suggests sporadic onset. Basal LH and FSH values point towards IHH. Depending on genes involved, various associations with hypogonadotropic hypogonadism have been described which include icthyosis, ear anomaly, mandibular hypoplasia,[2] severe obesity, epilepsy, renal agenesis, and CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome.[3] These association may not pertain to specific gene location and there is poor genotype phenotype correlation.[4] None of above association was present in our case. Tryptorelin stimulated LH value was in pubertal range. However, IHH cases have been described (Bauman variant) to have similar increase in LH. Such cases spontaneously enter puberty.[1] A decision of expectant follow-up of the patient for puberty onset was therefore made. Majority of familial and presumably sporadic cases of IHH with hyposmia/anosmia are due to autosomal genes.[4] Karyotype in our case showed mosaic trisomy 13. Trisomy 13 is associated with Patau syndrome. It is a rare syndrome prevalence rate of 1/10,000-20,000 and consists of microphtalmia, polydactyly, cleft palate (triad), cleft lip, low set ears, and micrognathia polydactyly.[5] Hypogonadal diseases involving midline structures like Bardet-Beidl syndrome and Pallister-Hall syndrome are therefore close differential diagnoses.[5] Only 5% of Patau syndrome has mosaic trisomy and 10% survive infancy. Survival is often attributed to mosaicism and severity of malformation.[6] Those who survive manifest growth and developmental delay. None of these features are present in the case. To best of our knowledge neither mosaic trisomy 13[7] nor any gene on chromosome 13 has been described to be associated with IHH.[1] Mosaic trisomy 13 is rare; may remain undetected especially since chromosome 13 is gene poor and possibly have clinical significance.[8]

Conclusion

An association of two very rare diseases mosaic trisomy 13 with IHH due to as yet undescribed autosomal gene cannot be ruled out.

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Cite this article as: Shukla R, Basu AK, Mandal B, Mukhopadhyay P, Maity A, Sinha A. Tale of two rare diseases. Indian J Endocr Metab 2013;17:S146-8.

Source of Support: Medical College Kolkata, **Conflict of Interest:** None declared.