Case Reports

Ring chromosome 15 syndrome presenting with gonadotropin dependent precocious puberty

***B C Lakmini[1], J Suntharesan[1], U A M D de Silva[1], Navoda Atapattu[2]**

Sri Lanka Journal of Child Health, 2021; **50**(4): 718-720
DOI: http://doi.org/10.4038/sljch.v50i4.9896
(Key words: Ring chromosome 15, Central precocious puberty)

Introduction

Deletion of genetic material at the two ends of the chromosomes with fusion leads to a ring chromosome. Clinical phenotype depends on the amount of genetic material lost[1]. Common phenotype consists of triangular facies with associated dysmorphism, intrauterine growth restriction (IUGR), short stature, neurocognitive abnormalities and congenital malformations including café-au-lait macules, cardiac, eye, ear and musculoskeletal abnormalities[1]. Gonadotropin dependent precocious puberty is uncommon in males without underlying aetiology and has not been reported previously with ring chromosome 15 syndrome. Here we report a 6-year-old child who presented with gonadotropin dependent precocious puberty with 46, XY, r15 karyotype

Case report

A 6-year-old boy presented with progressive pubic hair growth and lengthening of penis over 2-month duration. He did not have headache, vomiting, unsteady gait, behavioural abnormalities or polyuria. He never had episodes of wheezing or shortness of breath.

He is the 2nd born to non-consanguineous healthy parents with one elder healthy brother. He was born at 38 weeks of gestational age with a birth weight of 2.1kg and a 45cm length. He did not have any immediate post-natal complications. However, he was under the developmental rehabilitation care for global developmental delay. Current developmental age is 3–4 years. Child was diagnosed with congenital diaphragmatic hernia at the age of 4 years.

On examination, child had short stature. Height was 111.5 cm (below 3rd centile) which was well below the mid-parental height. He had triangular facies (Figure 1) with downward slanting eyes and epicanthic folds and associated brachydactyly and fifth finger clinodactyly (Figure 2). There were no café-au-lait spots or bone abnormalities suggestive of fibrous dysplasia. There was no hepatomegaly. Neurological examination was clinically normal including the fundus

.

Figure 1: ***Short stature and triangular facies***

**Permission given by parents to publish photograph*

[1]*Senior Registrar in Paediatric Endocrinology,* [2]*Consultant Paediatric Endocrinologist, Lady Ridgeway Hospital for Children, Colombo, Sri Lanka*
**Correspondence:* chamilk87@gmail.com

https://orcid.org/0000-0002-3015-4161

(Received on 27 August 2020: Accepted after revision on 16 October 2020)
The authors declare that there are no conflicts of interest.
Personal funding was used for the project.

Figure 2: shows hypoplastic thumb, clinodactyly and brachydactyly

Pubic hair distribution was Tanner stage 2 with 5.5 cm of stretched penile length. Bilateral testes were 5ml in volume with normal consistency.

Hormonal evaluation showed gonadotropin dependent puberty with a luteinizing hormone (LH) level of 1.14 IU/L and a follicular stimulating hormone (FSH) level of 6.11 IU/L. Serum testosterone was 12.06nmol/L. Serum alpha feto protein (AFP) and beta human chorionic gonadotropin (β HCG) were normal (1.36ng/ml and <0.7miu/ml respectively)

Bone age was compatible with the chronological age. Mediastinum was normal on chest x-ray. Ultrasound scan (USS) of the abdomen and scrotum revealed normally echogenic liver and testes. Magnetic resonance imaging (MRI) of the brain showed no abnormalities except pubertal pituitary enlargement. Karyotype showed 46, XY, r15 (Figure 3).

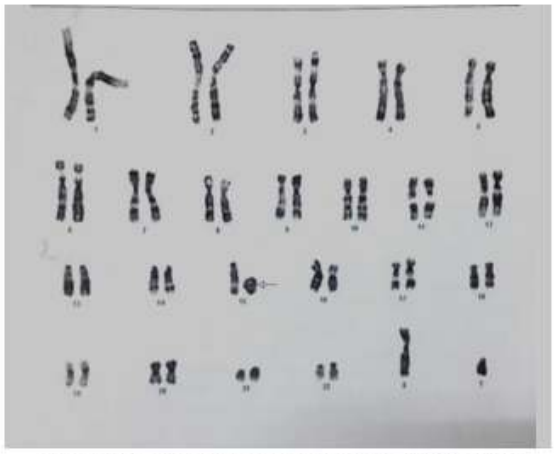

Figure 3: Karyotype 46, XY, r15

Hearing and ophthalmic assessments were normal.

Subcutaneous GnRH analogue (3.6mg; 4 weekly) was started with the view of suppressing the central precocious puberty.

Discussion

Ring chromosome 15 syndrome is a rare genetic syndrome resulting from loss of genetic material during ring formation. Ring chromosome 15 syndrome was first described in 1966 and less than 100 cases have been reported worldwide up to now[1,2]. Genomic region 15q26 is the commonest breakpoint. Alterations in the genetic material in this region is associated with growth abnormalities, Silver-Russell syndrome and congenital diaphragmatic hernia. Abnormalities in Synemin (encoded by the SYNM gene) and tetratricopeptide repeat domain 23 (TTC23) are associated with musculoskeletal defects such as clinodactyly, brachydactyly and abnormal body proportions[2]. Delayed diagnosis and misdiagnosis are common due to its varied nonspecific presentation. Median age of diagnosis is 7 years[2]. Reported endocrine abnormalities associated with ring chromosome 15 syndrome are growth retardation mainly due to IGF1R abnormalities and hypogonadotropic hypogonadism[1].

Common features of ring chromosome 15 syndrome described in the literature are short stature, microcephaly, low birth weight and birth length, triangular facies and brachymesophalangy with associated developmental delay and learning disability[1,2]. The case described in this report has all these commonly described clinical features. However, the amount of genetic material is less in this case as there were no other severe congenital cardiac renal or other abnormalities. Our child also had congenital diaphragmatic hernia which is a common association with 15q26 breakpoint[3].

Gonadotropin dependent precocious puberty in a male child is uncommon. It can be secondary to germ cell or liver tumour or brain malformation[4]. In our child mediastinum, liver, gonadal and brain imaging were normal and tumour markers were negative. To our knowledge, gonadotropin dependent precocious puberty has not been previously described with ring chromosome 15 syndrome. However, Makorin ring finger 3 gene (MKRN3) located on chromosome 15 has an inhibitory effect on GnRH secretion and acts as a controller on onset of puberty. Paternally inherited MKRN3 defects are associated with central precocious puberty. Hence this may be the possible hypothesis of central precocious puberty in ring chromosome 15 syndrome.

Due to its rarity, more description of cases may provide further knowledge on the spectrum of ring chromosome 15 syndrome.

Reference

1. Xu F, Zou CC, Liang L, Huang XM, Shao YN. Ring chromosome 15 syndrome: case report and literature review. *Hong Kong Journal of Paediatrics* 2011; **16**:175-9.

2. Paz-y-Mino C, Guevara-Aguirre J, Paz-y-Mino A, Velarde F, Armendariz-Castillo I, Yumiceba V, *et al.* Ring chromosome 15-cytogenetics and mapping arrays: a case report and review of the literature. *Journal of Medical Case Reports* 2018; **12**:340. https://doi.org/10.1186/s13256-018-1879-5
PMid: 30442194 PMCid: PMC6238305

3. Klaassens M, van Dooren M, Eussen HJ, Douben H, den. Dekker AT, Lee C, *et al.* Congenital diaphragmatic hernia and chromosome 15q26: determination of a candidate region by use of florescent in situ hybridization and array-based comparative genomic hybridization. *American Journal of Human Genetics* 2005; **76**:877-82. https://doi.org/10.1086/429842
PMid: 15750894 PMCid: PMC1199376

4. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Archives of Disease in Childhood* 1970; **45**:13-23. https://doi.org/10.1136/adc.45.239.13
PMid: 5440182 PMCid: PMC2020414