Cryptorchidism Due to Chromosome 5q Inversion Duplication

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Abstract
We present a 15 year old boy who was born out of a non consanguineous marriage, and presented with bilateral cryptorchidism, mental retardation, facial dysmorphism, hypergonadotrophic hypogonadism with failure of anatomical and biochemical localisation of testes. Karyotype analysis showed 46 XY with inverted duplication on chromosome 5q22-31.

Introduction
Cryptorchidism was first described in 1786 by Hunter and has been recognised for centuries.¹ Cryptorchidism has been reported in 1-2% of full term infants.² The exact cause of an undescended testicle isn’t known. A combination of genetics, endocrine, anatomical, and iatrogenic factors can affect descent of testes and cause cryptorchidism.³ Cryptorchidism has been seen in sex chromosomal abnormalities like Klinefelter’s syndrome.⁴ However, autosomal abnormalities also have associated with cryptorchidism.⁵ Aberrations in chromosome 5 have been reported with various phenotypic abnormality and cryptorchidism.⁶ Here we report a case of 15 year old boy who had dysmorphic features, mental retardation, cryptorchidism, vanishing testis, hypergonadotrophic hypogonadism and abnormality in chromosome 5q.

Case Report
A 15 year old boy was operated at 5 years of age by orchidopexy for bilateral cryptorchidism noticed at 2 years of age. During recent follow up treating surgeon noticed absence of testis and patient was referred to endocrinologist for evaluation.

He was born of a non consanguineous marriage as a full term normal delivery. There was history of birth asphyxia. His motor and social milestones were delayed. He also had delayed dentition. The patient had mental retardation (IQ-50). He could perceive various smells. There was no development of facial hair. He had no symptoms suggestive of other anterior pituitary deficiencies.

On examination he had facial dysmorphism with low set ears, broad nose, flat nasal ridge, hypertelorism, microglossia, high arched palate, multiple black naevi, abnormal dentition, feminine fat distribution, and eunuchoid proportions (Upper segment: lower segment- 0.80) (Figures 1 and 2). Testes were not palpable, however were felt initially and orchidopexy was done. Stretched penile length was 7 cm. There were few pubic hairs at base of penis (P1, G1 on Tanner puberty staging) and no axillary hair. There were no gynaecomastia. Hormonal evaluation revealed hypergonadotrophic hypogonadism (S. testosterone- 0.08 ng/ml , LH-44.56 u/l, FSH- 52.91 u/l ). MRI abdomen and pelvis failed to show any testes. hCG stimulation test showed no response indicating absence of functional testicular tissue. His thyroid hormone test (FT3-4.03 pg/ml, FT4-1.37 ng/ml, TSH- 1.92 μiu/ml) and adrenal function test (basal cortisol- 5.84 μg/dl and post-ACTH stimulated cortisol- 18.79 μg/dl) were normal. MRI brain
showed normal pituitary (8X12X11 mm) and olfactory bulbs. Karyotype showed 46, XY configuration with chromosome 5 q inversion duplication (Figure 3).

**Discussion**

Normal hypothalamic-pituitary-gonadal axis is a prerequisite for testicular descent. In our patient increased gonadotropins, normal thyroid and adrenal function; and normal pituitary on MRI brain excluded possibility of panhypopituitarism and septo-optic dysplasia. Mutation of FGFR2, which is associated with facial dysmorphism, mental retardation and normo-osmic hypogonadotrophic hypogonadism also excluded with increased gonadotropin levels. Testosterone is also necessary for continued migration, especially during the inguinoscrotal phase. Testosterone biosynthetic defects were excluded by the absence of ambiguous genitalia, and androgen receptor defects by low testosterone level.

Association of cryptorchidism has been reported in various chromosomal abnormalities. The XY karyotype excluded the possibility of Klinefelters syndrome. Phenotypic presentation similar to our case has been reported in literature with chromosome 5q aberrations. Chromosome 5q encodes for Great (G-protein-coupled receptor affecting testis descent) gene, which is a seven-transmembrane receptor. The Great gene is highly expressed in the gubernaculum, the ligament that controls testicular movement during development, and therefore may be responsible for mediating hormonal signals that affect testicular descent. The Great mutant receptor fails to respond to Insulin like factor – 3 (INSL3) causing cryptorchidism. However, inversion duplication of chromosome 5q as seen in our case has not been previously reported in literature, whether this is a part of the spectrum of contiguous gene syndromes seen in chromosome 5 disorders is conjectural. Our patient did not have anaemia or haematological abnormalities seen with abnormalities of chromosome 5p.

Vanishing testes in our patient remains unexplained. Most often cause of testicular regression is unknown,
vascular malformations and torsion have been implicated in testicular regression.\(^8\) Whether the same occurred in our patient or was part of the smoldering process of testicular involution due to this rare chromosomal abnormality is at best conjectural at this point of time. The familial occurrence of the disease and the association of this phenotype with 46,XY gonadal dysgenesis has led to the suggestion that genetic factors, which play a role in testicular determination, may be involved.\(^9\) The patient is started on testosterone supplementation.

References