Brief Communication

De morseir syndrome presenting as ambiguous genitalia

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ABSTRACT

Background: A 10-year-old boy presented with genital ambiguity, poor linear growth, and delayed milestones. The aim and to highlight that although rare but congenital, hypogonadotropic hypogonadism may rarely present as ambiguity. **Materials and Methods:** The patient was found to have bilateral cryptorchidism with proximal penile hypospadias, microphallus with a proportionate dwarfism with mildly delayed bone age, and karyotype 46XY. Euthyroid with normal steroid axis, growth hormone insufficient as suggested by auxology, low IGF1, and poor response to clonidine stimulation. MRI brain shows hypoplastic corpus callosum, hypoplastic anterior pituitary, and ectopic posterior pituitary bright spot. **Results:** The patient underwent laparoscopic removal of right intrabdominal testis and orchidoplexy was performed on the left one. Testicular biopsy revealed no malignancy and growth hormone replacement was initiated. The patient awaits definitive repair of hypospadias. **Conclusion:** As a provisional diagnosis of combined growth hormone and gonadotropin deficiency, most probable diagnosis is septo-optic dysplasia or de moseir syndrome leading to genital ambiguity.

Key words: Cryptorchidism, genital ambiguity, hypospadias, hypogonadotropic hypogonadism

Introduction

A 10-year-old male child born out of a consanguineous marriage, accompanied by his mother, presented for the first time in our outpatient department with a history of ambiguous genitalia and poor linear growth since birth. This condition was brought to medical attention for the first time since his birth. The patient was the youngest among his four siblings, the rest of whom were normal. The patient's mother reported no history of miscarriage or premature death of any child. The patient was born by normal spontaneous, full-term, vaginal delivery with vertex presentation, but he did not cry until 20 minutes after delivery. Probably, as a result of this perinatal hypoxic insult, the patient had delayed motor and social milestones with poor scholastic performance. The boy did not have any history of the following: Neonatal jaundice, umbilical hernia, seizures, feeding difficulties, hyper somnolence, head trauma, snake bite, any acquired cause of pituitary hormone deficiency, any chronic illness, headache, raised intracranial tension, anosmia, any trophic hormone deficiency, polyuria, or polydipsia.

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On examination, the patient's height was 102.4 cm (height SDS-5.2); the mother's height was 149.5 cm, the father was not examined as he was immobilized for life. The patient's father's upper segment to lower segment ratio was 1.04 (proportionate dwarfism). The patient's body weight was 12.7 kg. There were some dysmorphic facial features such as low set ears, hypertelorism, upward slanting eyes, and a flat occiput. There was no cleft lip or palate, no polydactly. Genital examination revealed a micropenis (SPL 2 cm) with well-formed glans, a promimal penile hypospadias, complete scrotal fusion with a well-formed sac, rugosity, and single median raphe. A single palpable gonad was present on the left side in the inguinal area, no palpable gonad was present on the right side [Figure 1]. There was

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no goiter, no visual complaints, no nystagmus, a 6/6 vision bilaterally, and the fundus examination was normal. There were no clinical features suggestive of rickets.

An X-ray of left hand wrist showed a bone age of 8 years with no evidence of epiphyseal dysgenesis. The patient was biochemically euthyroid with a TSH of 1.91 u IU/ml and free T4 of 1.28 ng/dl. The patient karyotype showed 46 XY type. Ultrasonography did not show any mullerian structures; the right gonad could not be localized. Both kidneys and pelvicalyceal system was normal. Both IGF1 levels 56.2 ng/ml and IGFBP3 2.46 ug/ml were low. A clonidine stimulation test was performed, which showed a peak growth hormone of 6.23 ng/ml at 90 minutes. Basal LH level (pooled) was 0.186 u IU/ml. The 8:00 A.M serum cortisol was 16.40 ug/dl. Other reports like liver function tests, renal function tests, and hemogram were normal. Urine examination was normal with no proteinuria. In view of growth hormone deficiency and suspected hypogonadotropic hypogonadism, an MRI hypothalamopituitary area revealed a hypoplastic anterior pituitary [Figure 2], ectopic posterior pituitary bright spot with preserved stalk [Figure 3], with aplasia of the splenium of corpus callosum [Figures 2 and 3]; however, the septum pellucidum, olfactory lobe, and sulci were normal [Figure 4].

A laparoscopic procedure was performed and intra-abdominal testis was visualized and removed. Biopsy did not show any evidence of malignancy. The patient was advised growth hormone replacement, but because of financial difficulty, his parents refused. An orchidoplexy was performed on the left side. Presently, the patient awaits a definitive hypospadias repair.

A final diagnosis of congenital combined pituitary hormone deficiency (growth hormone plus gonadotropins) due to transcription factor deficiency, most probably septo-optic dysplasia with growth hormone deficiency, also known as de morseir syndrome first described in 1956,[1]

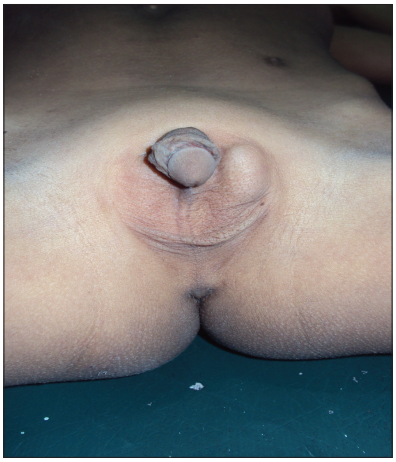

Figure 1: Microphallus with proximal penile hypospadias with chordee, left testis in scrotum post orchidopexy

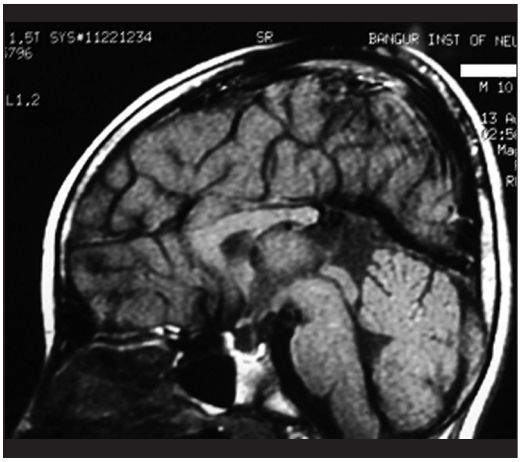

Figure 2: MRI brain showing hypoplastic pituitary with visible stalk and absent splenium of corpus callosum

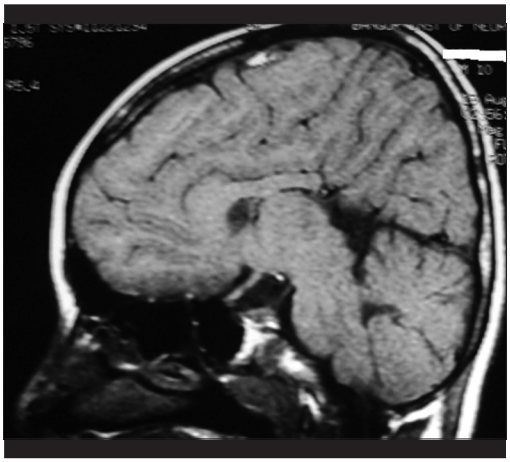

Figure 3: Ectopic bright spot

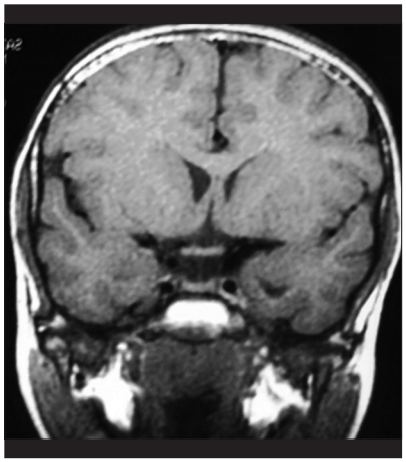

Figure 4: Normal septum pellucidum

leading to short stature and genital ambiguity was made for our patient. Congenital growth hormone deficiency and hypogonadotropic hypogonadism both have been commonly implicated as a cause for micropenis +/− cryptorchidism. However, genital ambiguity has been reported very rarely in hypogonadotropic hypogonadism[2] because of the fact that pituitary gonadotropin is essential only in the development of male external genitalia in the later part of gestation, the earlier development is gonadotropin-independent. Septo-optic dysplasia consists of a variable combination of midline defects like hypoplasia or absence of septum or corpus callosum or both, optic nerves hypoplasia/dysplasia, variable pituitary-hypothalamic dysfunction ranging from isolated deficit of pituitary hormones to pan-hypopituitarism. All these features together are rarely present in a single patient. Septo-optic dysplasia is a strong possibility because phenotypic variations can occur, and cases without optic dysplasia and normal septum pellucidum have been described previously.[3]

Other differential diagnosis would be an SF1 or DAX1 mutation leading to genital ambiguity; however, normal steroid pathway is against both the diagnosis. Moreover, growth hormone deficiency is described extremely rarely in these syndromes and MRI brain is usually normal in both these syndromes. Kallman's syndrome is also unlikely as an abnormal MRI and growth hormone deficiency goes against it. Another rare syndrome with hypopituitarism and ambiguous genitalia is Dincsoy Salih Patel Syndrome,[4] but other features of this syndrome like polydactyly, short limbs, camptodactly, and other bony anomalies were absent in our case.

Although we have tried to explain everything by a unifying diagnosis, a dual pathology cannot be ruled out, a coexisting pituitary transcription factor deficiency with a 5 alpha reductase mutation or partial androgen insensitivity theoretically could give rise to a similar phenotype; however, since the patient belonged to the pre-pubertal age group and his parents were unwilling for further tests, this could not be established.

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