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Macroorchidism and central *precocious* puberty associated with cytotoxic lesion in the corpus callosum in a child

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Abstract
Background: Bilateral macroorchidism is a rare presentation and this could be idiopathic, genetic or endocrine dysfunction.
Case report: We report a 7 year old boy who presented with bilateral macro-orchidism and central *precocious* puberty. Physical examination showed both height and weight above 95th centiles and enlarged testes. Bone age was 14 years and ultrasonography revealed grossly enlarged testes with normal echogenecity. Serum testosterone, LH and FSH levels were consistent with *precocious* puberty. MRI brain showed cytotoxic lesion in the corpus callosum which disappeared on follow-up imaging at 6 months.
Discussion: Benign idiopathic macro-orchidism is diagnosed by exclusion. Genetic syndromes usually associated with mental retardation and dysmorphic features. Endocrine causes include hypothyroidism, congenital adrenal hyperplasia, FSH secreting pituitary adenoma and rarely aromatase deficiency. Bilateral primary testicular neoplasms are other rare cause. Central *precocious* puberty can present with enlarged testes but compared to idiopathic macroorchidism the testicular volume is not very high as in this case.
Conclusion: This case describes occurrence of *precocious* puberty associated with massively enlarged testes and unusual finding of cytotoxic lesion in the corpus callosum. This case emphasize the importance of early diagnosis and treatment to preserve adult height, halt the puberty and possibly testicular enlargement.

Keywords: Macro-orchidism, megalotestes, *precocious* puberty, cytotoxic lesion, corpus, callosum

Introduction
Macro-orchidism and megalo-testes are defined as enlarged testes with a volume greater than twice the normal adult testicular volume, which is usually 25 ml. Bilateral macro-orchidism could be idiopathic, genetic or due to endocrine dysfunction.

Case Study
7 year old boy presented to the endocrinology unit with a history of testicular enlargement. He is a third child of non-consanguineous marriage, had a normal birth and peri-natal history. During the early childhood, at the age of 8 months, he underwent left orchidopexy and surgery for bilateral hydrocele with patent processes vaginalis.
Mother noticed gradual enlargement of both testes since two years old. As there is no pain, they did not seek any treatment until now. Recently he complained of discomfort and heaviness in the scrotum. Mother also noticed growth of public hair and facial hair since last year. He had no behavioural change, but less than average in the class. He is the tallest among his peers. He had no history of headache, vomiting, visual discomfort or seizures.
On Examination his height was 147 cm and weight was 31 Kg; both parameters were above 95th centiles on CDC chart. He has no dysmorphic feature or skin pigmentation. His sexual maturity score was Tanner stage 2 for pubic hair, axillary hair stage 1 with a testicular volume of more than 30 ml bilaterally and a stretched penile length of 7 cm (Figure 1). Rest of the examination was unremarkable.
Investigations revealed normal biochemistry including serum electrolytes and haemoglobin. Hormone analysis showed high testosterone levels for his age (Table 1).

Bone age was 14 years compared to his chronological age of 7 years (Figure 2). Ultrasound scan revealed grossly enlarged testes (Right side volume of 64ml and left side volume of 74 ml) with normal echogenicity and vascularity. Both testes had small cysts. His liver, spleen, kidneys were ultrasonically normal.

Magnetic resonance imaging (MRI) of testes confirms grossly enlarged testes with homogeneous enhancement and T_2 high signal intensity and T_1 isointensity. There are multiple cysts of various sizes in both testis, largest in left tests measuring 8mmx 5mm in size. There was no testicular or extra testicular solid or cystic masses or hydrocele or regional lymph node enlargement. MRI brain showed enlarged pituitary gland with convex upper margin (6.5x10.5x11 mm with volume of 380mm3 - normal volume 210mm3). Imaging appearance of splenium of corpus callosum suggestive of cytotoxic lesion of the Corpus callosum. (Figure 3)

Bilateral macro-orchidism with gonadotrophin dependent *precocious* puberty associated with poor IQ was diagnosed. Follow up MRI brain in 6 months showed no focal lesions. Previously noted cytotoxic lesion in spleium of the corpus calloum was not evident in the repeat MRI. (Figure 4)

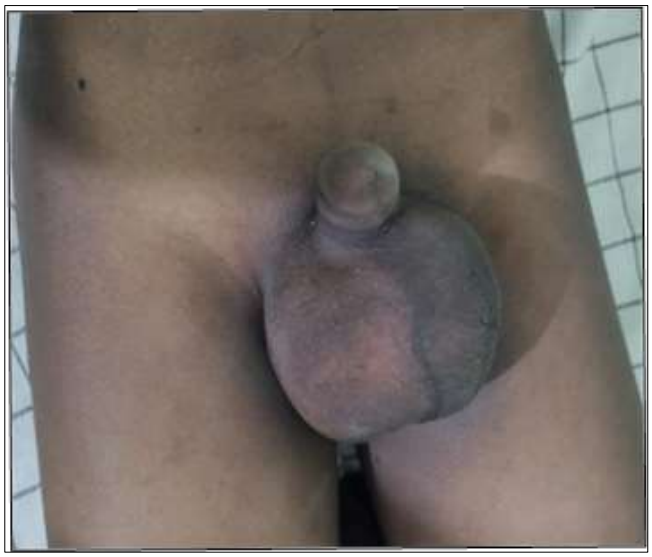

Fig 1: Bilateral grossly enlarged testes on genital examination

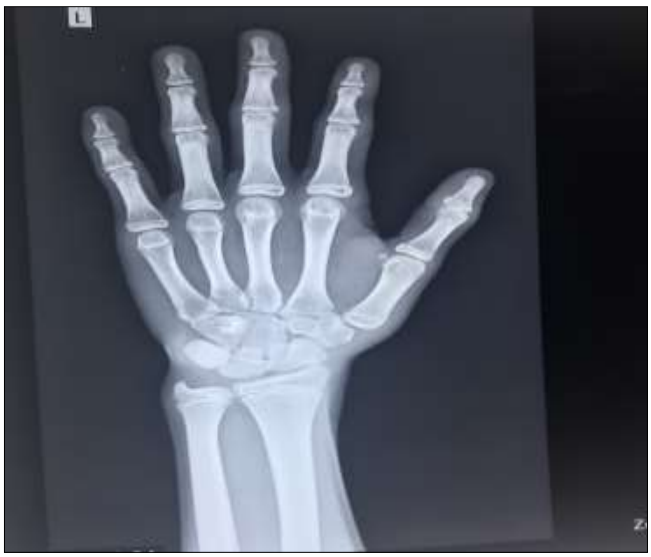

Fig 2: Bone age of 14 years on X ray left hand

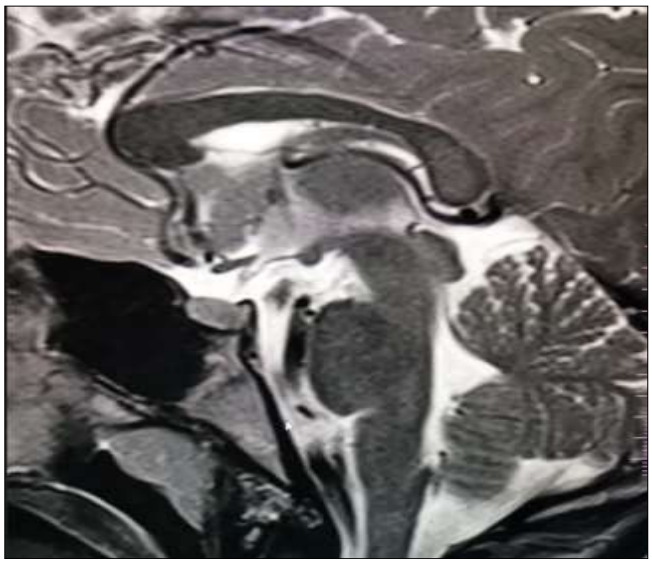

Fig 3: MRI brain showing enlarged pituitary gland and cytotoxic lesion of the Corpus callosum

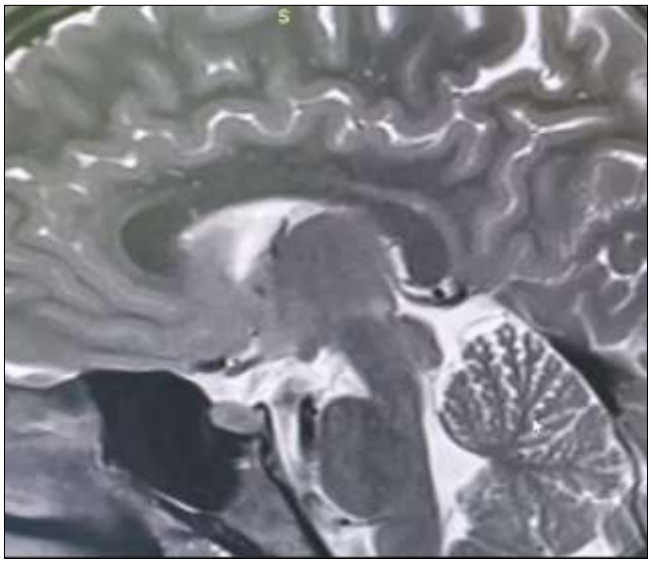

Fig 4: Follow-up MRI brain showing enlarged pituitary gland with normal corpus callosum

Table 1: Hormone profile of the patient

Tests	Results	Normal Range for age
Testosterone	11.1	0.007 - 0.277 nmol/L
FSH	15.12	0 -5 iu/L
LH	0.404	<0.02 - 0.3 iu/L
TSH	2.39	0.5 - 5 mu/L
Free T4	1.639	0.8 - 2 ng/dL
17 OHP	3	<3.6nmol/L
TSH-thyroid stimulating hormone	TRH- thyrotrophic hormone FSH - follicular stimulating hormone	LH - leutinizing hormone OHP - hydroxyprogesterone

Discussion

Macro-orchidism and megalo-testes are defined as enlarged testes with a volume greater than twice the normal adult testicular volume, which is usually 25ml. Testicular volume is commonly measured by Prader orchidometer. Unilateral macro-orchidism is usually caused by a testicular tumour or rarely as a compensatory hypertrophy when contralateral testis has been removed. Bilateral macro-orchidism could be idiopathic, genetic or due to endocrine dysfunction. Benign idiopathic macro-orchidism is diagnosed by exclusion. In this rare condition, testes are symmetrically enlarged and have normal consistency. Compared to *precocious* puberty, the testicular size is markedly large in the idiopathic macro-orchidism. This condition has been reported in pubertal age, but very few cases are reported in pre-pubertal age [1].

Genetic causes for macro-orchidism includes fragile X syndrome, X linked macro-orchidism with marfanoid habitus, Atkin-Flaitz-Patil-Smith's X linked mental retardation, trisomy 20p and fragile X phenotype with acquired central nervous system lesion. Genetic syndromes usually associated with mental retardation and dysmorphic features. McCune-Albright syndrome, a rare sporadic genetic disorder could present with bilateral macro-orchidism. The classical triad of polyostotic bone dysplasia, cafe-au-lait skin spots and endocrine dysfunction frequently associated with peripheral *precocious* puberty [2].

Hypothyroidism has been reported in several case reports of macro-orchidism. This is commonly seen in pre-pubertal children and most will have clinical signs and symptoms of hypothyroidism [2]. Biochemical evaluation generally reveals elevated TSH, prolactin, FSH and LH but testosterone within the normal range for the prepubertal age. The pathogenesis was thought to be stimulation of hypothalamus and release of TRH secondary to low thyroxine. This in turn increases TSH and prolactin, which determines release of gonadotropins and testicular enlargement, and on the other hand inhibits steroidogenesis of Leydig cells and keep the testosterone within normal range [3]. With thyroxine replacement therapy, endocrine abnormalities can regress, but the size of the testes could reduce or remain same.

Untreated or poorly controlled congenital adrenal hyperplasia could result in hyperplasia of adrenal remnants and asymmetrical nodular testicular masses. Even appropriate therapy may not reduce the testicular volume in this longstanding androgen stimulation. FSH secreting pituitary adenoma has been reported in few cases of macro-orchidism [4]. Pituitary surgery normalise FSH and testicular size. Rarely aromatase deficiency could present with large testes as a result of deficient conversion of androgen to oestrogen. Bilateral primary testicular neoplasms are other rare causes [1].

Clinical assessment and laboratory evaluation are important for early diagnosis. This includes hormone profile, tumour markers, genetic testing and imaging. Early diagnosis may reduce the incidence of X linked mental retardation in affected families. Ultrasonography and magnetic resonance imaging are commonly used as radiological evaluation. The latter will be useful to exclude intracranial lesions associated with *precocious* puberty. The most common finding is hypothalamic hamartoma in central *precocious* puberty [5].

MRI imaging of brain in this boy showed cytotoxic lesion of corpus callosum. Although numerous underlying etiologies have been identified, these lesions appear to result from a stereotyped cascade of cytokines and stimulated cells. This inflammatory process increase glutamate levels in extracellular fluid and results in cytotoxic oedema involving astrocytes and neurones. It appears that the reason the splenium of the corpus callosum is preferentially affected is the presence of a high density of oligodendrocytes expressing large numbers of glutamate affected receptors [6]. These transient lesions are seen in a wide variety of clinical settings, including patients with seizures or metabolic disturbances [7]. Significance of these lesions in this boy with macro-orchidsm is not clear. The follow-up MRI in 6 months showed no lesions, confirming transient nature of this lesion.

The goal of treating *precocious* puberty is to stop, possibly reverse the onset of puberty and preserve adult height. For gonadotrophin dependent *precocious* puberty, GnRH agonist can be used to suppress pituitary FSH and LH secretion. The decision to treat depends on several factors; age of the child, rate of pubertal progression, height velocity and rate of skeletal maturation [8, 9]. This child had skeletal maturation of 14 years on bone age x-ray and decision was taken not to initiate GnRH analog. He was referred to community paediatrician for further support with regard to his poor performance and clinic follow up was arranged to monitor his clinical parameters.

Conclusion

This case describes occurrence of *precocious* puberty associated with massively enlarged testes and unusual finding of cytotoxic lesion in the corpus callosum. This case emphasize the importance of early diagnosis and treatment to preserve adult height, halt the puberty and possibly testicular enlargement.

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Author's Contribution

Not available

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