Case Report

Surgical excision of hypothalamic hamartoma in a twenty months old boy with precocious puberty

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ABSTRACT

A twenty months old boy presented to our department with true precocious puberty due to hypothalamic hamartoma. Total surgical excision of pedunculated hypothalamic hamartoma was done successfully by the pterional trans-sylvian approach as he could not afford medical management. Patient had uneventful post-operative course with normalization of serum testosterone levels and regression of secondary sexual characters.

Key words: Hypothalamic hamartoma, precocious puberty, surgical management

Introduction

Central precocious puberty (CPP) caused by hypothalamic hamartoma (HH) is a rare disease. Hypothalamic hamartomas are benign lesions, which can clinically present as CPP and/or gelastic seizures and behaviour abnormality. The cause of CPP due to HH can be due to expression of stimulatory factors like gonadotropin releasing hormone (GnRH), transforming growth factor (TGF) alpha and TGF beta[1,2] or due to larger size and contact with infundibulum/tuber cinerum.[2] Treatment options include long term GnRH analog therapy[3] or microsurgical resection.[4] Long-term therapy with GnRH analogs has become the mainstay of treatment, and it acts by delaying/suppressing puberty till the age of 12-13 years.[5] Surgical resection is curative and is advisable if the initial GnRH therapy fails to suppress puberty. There are less than 70 cases reported for microsurgical resection of HH causing precocious puberty.

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Case Report

Presentation

A twenty months old boy presented with a history of growth spurt and secondary sexual characters like pubic hair, enlarged penis and scrotum, change of voice since one year. There was no history suggestive of seizures or hypopituitarism. On clinical examination, the child's height was 92 centimetres (cm) and weight was 18 kilogram. His preoperative growth velocity was 12.5 cm/year. The patient was classified as Tanner stage 3 of puberty with a testicular volume of 10 ml on both sides, stretched penile length of 9.5 cm and pubic hair stage 3. His endocrine evaluation was suggestive of CPP [Table 1]. His bone age was advanced and corresponding to 5 years (Greulich and Pyle atlas) of age. Magnetic resonance Imaging (MRI) of brain revealed HH of size 2 x 1.8 cm [Figure 1]. GnRH therapy was not given to this patient before surgery as he could not afford the long term treatment which is expensive. Surgical excision of HH was chosen by parents after knowing about the procedure, risks and complications.

Surgery

After giving general anaesthesia, the head was rotated 30 degrees to the left and neck mildly extended. Head was placed on a horseshoe headrest and no skull fixation device was used to hold the head, in view of the thin

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Table 1: Endocrine evaluation before and after surgery of the patient in the study

Investigation	Preoperative	Postoperative (1 week)	Postoperative (18 months)	Reference range
L.H (m IU/ml)	9.91	2.61	<0.1	<0.10-6.00
F.S.H (mIU/ml)	6.39	1.27	0.73	0.30 – 2.00
Testosterone (ng/dl)	668.89	86.87	<2.50	2.5-25
T3 (ng/ml)			2.29	0.8 – 2.53
T4 (μg/dl)	12.4		13.3	7.0-13.1
TSH (μIU/ml)	1.62		2.11	0.55-7.1
FT4 (ng/dl)			1.77	0.76-2.0
FT3 (pg/ml)			5.88	2.4 – 6.7
Synacthen test (250 μg)				
0 minute cortisol (μg/dL)			7.2	4.3 – 22.4
60 minute cortisol (μg/dL)			27.3	> 18 μg/dL
Clonidine Stimulation test				
0 minute GH (ng/ml)			0.22	
30 minute GH (ng/ml)			0.5	> 10 ng/ml
60 minute GH (ng/ml)			4.6	> 10 ng/ml
90 minute GH (ng/ml)			3.2	> 10 ng/ml
120 minute GH (ng/ml)			0.8	> 10 ng/ml

L.H.: Luteinizing hormone, F.S.H.: Follicle stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, GH: Growth hormone

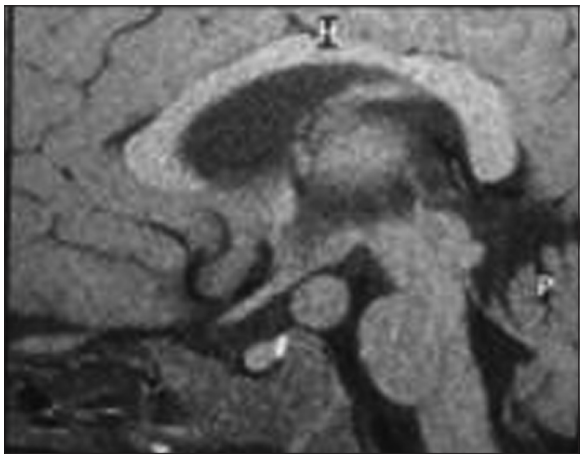

Figure 1: Pre-operative Magnetic Resonance imaging of brain showing hypothalamic hamartoma

skull. Right pterional craniotomy was done and trans-sylvian approach was taken. HH was identified through the space between the optic nerve and internal carotid artery [Figure 2a]. Intraoperatively, there was a pedunculated HH. Pituitary stalk was identified initially and preserved. Under microscopic vision, the tumor was initially debulked in piecemeal manner and then the remaining tumor was removed enbloc [Figure 2b]. Total excision of HH was done and no injury to the pituitary stalk or hypothalamus occurred during surgery. Total blood loss during the entire procedure was less than 50 ml.

Pathology

Microscopic examination of the excised specimen revealed a mostly fibrillary glial matrix that exhibited vague nodularity with delicate bands of connective tissue surrounding the nodules. There were aggregates of benign looking unipolar as well as multipolar neurons and also scattered lone ganglion cells, embedded in the fibrillary matrix. Also there were a few collections of astrocytes with anisokaryosis and oligodendrocytes with cytoplasmic vacuoles [Figures 3a and b]. The histologic picture was consistent with hamartoma.

Postoperative course

Post operatively patient had no complications. He was discharged on eigth post operative day. Patient was evaluated radiologically and by assessing hormone levels. Post-operative MRI brain revealed complete excision of HH [Figure 4]. Post operative serum testosterone level at one week has decreased to 86.87 ng/dl from 668.89 ng/dl [Table 1].

Follow-up

After surgery his growth spurt has stopped, pubic hair has disappeared by 6 months, testicular volume has regressed to 4-5 ml bilaterally by 18 months. At 18 months follow-up, serum testosterone level has decreased to 2.5 ng/dl suggesting regression of puberty. His presurgical growth velocity has decreased from 12.75 cm/year to post surgical growth velocity of 5 cm/year. Post operative evaluation for hypopituitarism at 18 months post surgery revealed normal thyroid and adrenal function. Growth hormone evaluation was done with clonidine stimulation test which has shown subnormal stimulation of growth hormone [Table 1]. Growth hormone stimulation by insulin tolerance test was not done due to lack of consent from parents. No other complications like diabetes insipidus or disorders of

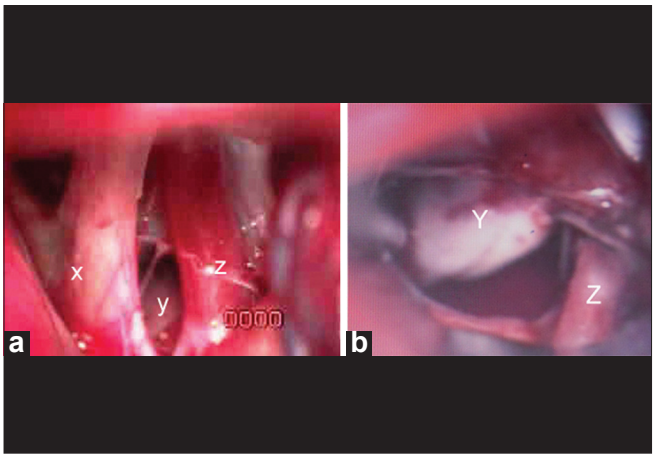

Figure 2: (a) Intraoperative photograph showing hypothalamic hamartoma(y) identified between optic chiasma(x) and internal carotid artery(z). (b) Hypothalamic hamartoma(y) being removed en-bloc after initial debulking

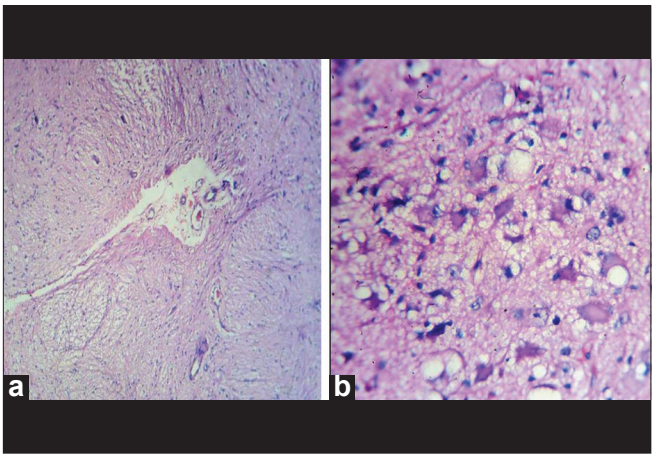

Figure 3: (a) Disorganized nodular aggregates of neuronal, glial and fibrous tissue (H and E, ×100). (b) Normal looking, variably sized bi and multipolar neurons and ganglion cells (H and E, ×400)

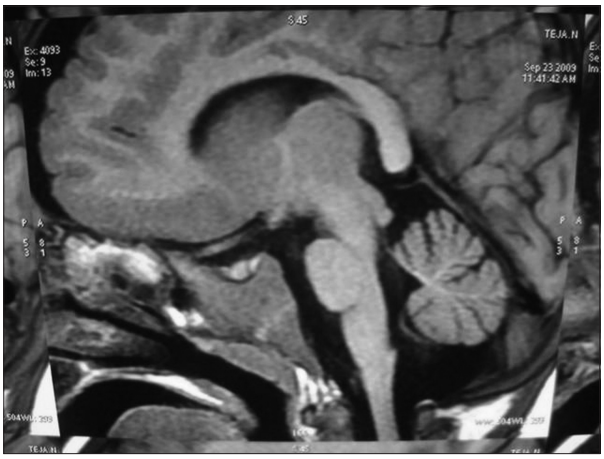

Figure 4: Post-operative magnetic resonance imaging brain showing complete excision of hypothalamic hamartoma

appetite regulation occurred during 18 months of follow up.

Discussion

Central precocious puberty caused by HH is a rare endocrine disease often managed by long acting GnRH analog therapy as the frontline treatment because it is highly effective with least complications. Since most patients present between 1-3 years of age, treatment with GnRH analogs is required for 10-11 years, which is expensive. Surgical resection of HH is advisable if the initial GnRH therapy fails to suppress puberty, reduce bone age advancement and it can also be considered if the patient cannot afford the long term treatment with GnRH analogs, which is 5-10 fold expensive than surgery in developing countries.[5,6]

Complete microsurgical resection of HH is curative in CPP as reported previously.[6-14] HH associated with CPP are more likely of pedunculated type, while HH associated with seizures are more of sessile type.[5] HH associated with CPP can be approached either by the pterional[6,9,10] or by the subtemporal approach[12] compared to sessile intrahypothalamic HH associated with epilepsy, which are approached by trans-callosal, endoscopic, orbito-zygomatic routes.[15]

Pterional-trans-sylvian approach offers the shortest and direct route to the HH, leading to higher chances of relieving the endocrine symptoms with fewer complications and is well versed with most of the neurosurgeons. Extending the craniotomy to a pterional- orbitozygomatic approach gives better access to larger and complex lesions. Transient third nerve palsy in two patients and diabetes insipidus in one patient has been reported by Roszkowski *et al*, in their series of five patients with pterional approach.[6] Subtemporal approach is advantageous when there is significant prepontine component,[16] or when the lesion is adherent to the brainstem or basilar artery.[12] Albright *et al*, have used subtemporal approach in their series of six patients.[12] Transient oculomotor paresis has been reported in three of their patients and one patient required eye muscle surgery.[12] Sessile HH, commonly associated with seizures, are more difficult to treat than pedunculated HH. Anterior transcallosal interforniceal approach as advocated by J.V.Rosenfeld has become a common approach for sessile intrahypothalamic HH, in addition to endoscopic and skull base approaches.[15,17] Failure to achieve endocrine remission after surgery is rare, since HH associated with precocious puberty is usually pedunculated and total excision of HH is possible.[6-10]

Endocrine remission even after subtotal resection of HH has been reported.[18,19]

Irrespective of the approach, vital anatomic structures including optic chiasma, oculomotor nerve, pituitary stalk, perforating vessels from internal carotid artery and hypothalamus can be injured during the surgery resulting in decreased vision, oculomotor paresis, diabetes insipidus, hemiparesis, unconsciousness and death. Great care should be taken to preserve these structures during the surgery. Postoperative endocrine consequences are another concern when opting for surgical modality as a treatment option in these cases of HH with CPP. Though several transient endocrine deficiencies have been reported in the literature,[20] they are more common with sessile intrahypothlamic HHs where surgery is mainly indicated for intractable epilepsy. In these cases, risk of hypothalamic damage during surgery is high, explaining the high incidence of complications. There is limited data available regarding postoperative endocrinopathies in pedunculated hamartomas where surgery is indicated for central precocity. In the present case, postoperative evaluation for hypopituitarism reveals normal thyroid and adrenal function with subnormal stimulation of growth hormone after clonidine stimulation test. Taking into consideration his normal growth velocity, re-evaluation for growth hormone axis and follow up for growth velocity will explain whether it is a surgical consequence or it is a physiological deceleration of GH axis either due to the lack of pre-existing sex steroid stimulation, or due to the relatively advanced bone age.

Since the first report of successful surgery for HH in CPP,[21] less than 70 cases have been reported. The present case illustrates the utility of total surgical excision of pedunculated HH by pterional approach in the successful management of CPP with least complications. In developing countries, where availability and expense of long term GnRH analog therapy are an issue, and if there is pedunculated HH, surgical excision can be considered as initial treatment, which is curative and cost-effective.

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