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HYPOTHALAMIC HAMARTOMA – OUR INITIAL EXPERIENCE OF TWO CASES

Neurosurgery

Dr. Raviraj Ghorpade M.Ch., Neurosurg, Department of Neurosurgery, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum, 590 010 Karnataka, India.

Dr. Pradeep N M.Ch., Neurosurg, Department of Neurosurgery, SS Institute of Medical Sciences and Research Centre,Davangere, Karnataka, India

Dr. Anitha Mahadevan M.D, Department of Pathology, NIMHANS , Bangalore ,Karnataka, India

Dr. Spoorthi. N. Sakri M.B.B.S, SS Institute of Medical Sciences and Research Centre, Davangere

ABSTRACT

Hypothalamic hamartomas (HH) are rare congenital lesions presenting with central precocious puberty (CPP), gelastic seizure (GS) and developmental delay. Hypothalamic hamartomas with CPP responds to gonadotropin releasing harmone (GnRH) analog therapy, but medical treatment is long term and expensive. Hypothalamic hamartomas with GS are refractory to medical management and surgery is good and cost effective treatment. We report two cases of HH presenting with CPP and GS who underwent surgical resection and have good results postoperatively.

KEYWORDS

Central precocious puberty; Gelastic seizures; Hypothalamic hamartoma;

INTRODUCTION

Hamartoma is a word of Greek origin, derived from *hamartion*, which means "failure of the body". It is a focal malformation which resembles a neoplasm but does not show any particular tendency to a neoplastic evolution.[1] It results from defective development in an organ and it consists of an abnormal mixture of its constituent elements. It develops and grows at practically the same rate as do the normal components of the organ of its origin. It does not compress adjacent tissues.[1] The hypothalamic hamartomas (HH) are rare congenital malformations of unknown etiology which develops between the sixth and seventh weeks of pregnancy, as non-neoplastic lesions located in the tuber cinereum. The hypothalamic hamartomas (HH) can present with neurological problems such as epileptic encephalopathy, psychomotor developmental delay, mental retardation and precocious puberty.[2,3]

The HH grows in proportion to normal brain growth and thereafter when viewed with serial imaging, their relative size to the rest of the brain remains the same. There is enormous variety in the type and severity of symptoms from patient to patient. However, symptoms become apparent during childhood in large number of patients. Clinically two phenotypes of HH are recognized: Central precocious puberty and epilepsy related neurobehavioral symptoms, but significant overlap between these phenotypes exists. For those with central precocious puberty only, symptoms may occur as early as two to three years of age. These patients present with precocious (abnormally early) development of the secondary sexual characters changes associated with puberty with or without neurological problems such as epilepsy. We present two cases of hypothalamic hamartoma with varied presentation.

Case Report 1

History and presentation

A four and half year old girl of non consanguineous parentage presented with thelarche, pubarche and menarche since 18 months. History of galactorrhoea, headache, seizure and symptoms suggestive of raised intra-cranial pressure (ICP) were absent. On clinical examination, patient was conscious, well oriented and vitals were stable. Physical examination revealed marked breast enlargement with areola and papilla separate from the contour of the breast with formation of secondary mound, scanty axillary and pubic hair. No evidence of Neurocutaneous and Craniovertebral junction (CVJ) markers. Cranium and spine examination was normal. Based on Tanner staging of puberty, patients had Tanner Stage Four Puberty corresponding to age 12 to 13 years. Patient weighed 25 Kgs and height was 121 cms (97th centile). Systemic examination revealed normal finding with regard to Cardiovascular System, Respiratory System and Per Abdomen. On Central Nervous System (CNS) examination, patient was conscious, oriented and normal higher mental function, cranial nerves, motor system and sensory system. No symptoms were observed suggestive of anterior pituitary deficiency. Further patient was subjected to relevant investigations and found to have Luteinising hormone (LH) 43.32 mIU/mL, follicular stimulating hormone (FSH) 6.67mIU/mL, Estradiol 66.19 pg/ml, normal triidothyronine (T3) (1.4 ng/mL), thyroxine (T4) (6.9 µg/dL) levels and prolactin levels (6.35), but raised thyroid stimulating hormone (TSH) (13.60 µIU/mL) and lower cortisol levels (0.73 µg/dL). Magnetic resonance imaging (MRI) scan revealed a well demarcated lesion isointense on T1, increased signal intensity on T2, non enhancing on contrast seen in Suprasellar cistern and Coronal section showed pedunculated mass hanging from Floor of third ventricle posterior to pituitary stalk.

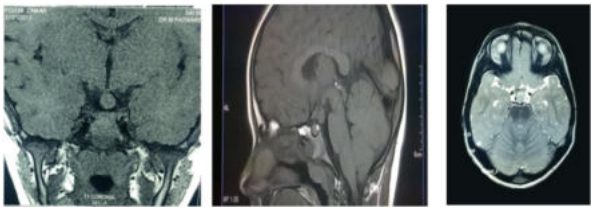

Figure 1.

Case 2

Two year old male child of non consanguineous parentage presented with generalized tonic clonic (GTC) seizures associated with inappropriate laughter persisting for one to two minutes, three to four episodes per day since three months .Parents noticed increase in size of genitals at the age of six months, aggressive behavior since the age of eight months and pubic hair at one year. On clinical examination, Child was conscious, stable vitals with occasional aggressive behavior. On physical examination, scanty pubic hair were present, penile length was 8 to 9 cm with well formed glans.

Testicular volume of 8 mL on both side and he weighed 17.6 Kgs with height 90 cms (75 to 90th percentile). He had advanced bone age corresponding to four to five years (wrist X-ray) and axillary hairs were absent. Based on Tanners stage of puberty child corresponded to Stage Three. Cranial nerves, motor and sensory systems were normal. Child had language developmental delay and psychomotor assessment could not be done as child was not co-operative. During the hospital stay, Child had two to three episodes of gelastic seizure inspite of multiple antiepileptic drugs. All the blood investigations including hormonal assay were normal except for testosterone level which was elevated (8.2 µg/mL). Electroencephalogram (EEG) showed spike and wave discharges suggestive of seizure disorder. Magnetic Resonance

Imaging of brain revealed 1.4 x 1.3x 1.4 cm T1 hypointense and T2 isointense lesions between Infundibular stalk and Mammillary bodies at suprasellar cistern which was non-enhancing on contrast suggestive of Hypothalamic hamartoma.

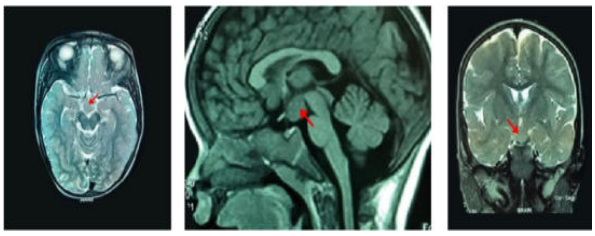

Figure 2.

Management

Based on the clinical features and investigations, Case One was diagnosed to have Central Precocious Puberty and Case Two with Gelastic Seizure and Central Precocious Puberty secondary to Hypothalamic Hamartoma. GnRH therapy was not given prior to surgery as they could not afford long term expensive treatment. As type one HH (case one) are surgically amenable and excision gives better results as compared to prolonged, expensive medical therapy. Gelastic seizure are refractory to medical treatment and progressing epilepsy causes worsening of cognitive and behavioural function, hence surgery was done in both cases. Surgery by Pterional Trans sylvian inter optico carotic approach was chosen in both cases. In both cases near total excision was attained.

Pathology

Sections from resected tissue showed cluster of ischemic and dysmorphic neurons with disorganised glial tissue. Neurons were variably positive for NeuN and synaptophysin with GFAP highlighting the interstitium and glial cell with features consistent with hypothalamic hamartoma.

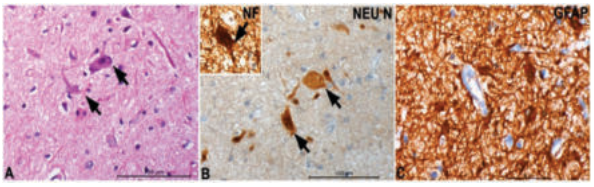

Figure 3. Microphotograph reveals clusters of large dysmorphic neurons (A) in a finely fibrillated background. The neurons are labeled by neuronal marker Neu N (B) and are seen to accumulate phosphorylated neurofilament (B, inset). Prominent gliotic stroma is highlighted by GFAP (C) [A: H&E; B: NeuN, neuronal marker, B inset: Phosphorylated neurofilament; C: GFAP immuno peroxidase. Magnification=scale bar]

Post operative course

Post operatively both patients had no complications. Case two did not have any episodes of seizure after surgery. Antiepileptic drugs were tapered to minimum dose of two primary antiepileptic drugs.

Follow up

Case one at one year- Menarche stopped three months after surgery. Regression in secondary sexual characters were noticed. At one year, she was tanner stage two. Hormonal assay was normal at the last follow-up. Case two at six months did not have any seizure episode post operatively. He is on one antiepileptic drug. There were no gross changes in the secondary sexual characters. Hormonal assay was normal.

DISCUSSION

Hamartomas are benign, focal malformation that resembles a neoplasm. Pathologically they contain the nerve cells that resemble those of the tuber cinereum along with normal glial cells. Hypothalamus appears to be most common location in CNS. Subcortical cerebral cortex and periventricular region are the other locations reported. Le marquand and Russell were the first to report hypothalamic hamartornas as congenital malformations consisting of tumour like collections of normal brain tissue lodged in an abnormal location.[4,5]

Hypothalamic hamartomas are small pedunculated growths adjoining the posterior hypothalamus, between the tuber cinereum and mamillary bodies and are extremely rare (1:200,000).[6] Incidence is same in males and females.[7] Most of patients usually present in the first or second decade of life and the same was true in our cases as both patient presented in first decade of life. Hypothalamic hamartoma fills the free space between the optic chiasm and pons and usually do not distort the hypothalamus or other parts of the base of the brain unless they are very large.[4]

Hypothalamic hamartomas can cause precocious puberty with or without complex seizures, personality disorders and mental retardation.[8] Precocious puberty is the appearance of secondary sexual characteristics before age eight in females and before age nine in males. A considerable sub-set of patients typically present with precocious puberty [35-70%] and considered relatively common in children with hypothalamic lesions. The signs of precocious puberty in girls are the appearance of the breasts, pubic and underarm hair, accelerated growth and oily skin. In boys, it is characterized by testicular growth, pubic hair, episodes of aggression, acne, and change of voice tone. Our both cases presented with precocious puberty.[4,7]

The mechanism is not very well understood. It may be from premature disappearance of normal inhibitory factors on hypothalamus, which results in Luteinising hormone releasing factor (LHRH) being released prematurely thus activating the pituitary gonadal axis. The larger hamartomas are less likely to produce precocious puberty.[4] Also precocious puberty may be due to the increase in the secretion of hypothalamic gonadotropin-releasing hormone (GnRH), resulting in changing the hormonal hypothalamus-pituitary-gonads axis. Further HH arises from the region of the tuber cinereum and is commonly associated with isosexual precocious puberty as efferent pathways that allow modulation of gonadotropins and contain releasing hormones and secretory granules are present within the floor of the third ventricle. Precocious puberty may either result from a physical pertubation of inhibitory pathways by the hamartoma or, more likely, are a direct neurosecretory process of the hamartoma itself.[9]

Gelastic seizure (GS) also known as laughing seizure was first described by Trousseau.[10] Seizure episode consists of laughter like vocalization combined with facial contraction which appears like smile. GS is first seizure manisfestation of HH. Gelastic seizure are typically associated with HH and are refractory to medical treatment despite higher doses and combination of drugs.[11]

MRI imaging is the optimal imaging study for evaluating patients presenting with CPP and HH. Hypothalamic hamartomas lesions are isointense on T1-weighted images and iso- to more commonly slightly hyperintense on T2-weighted images and do not enhance with contrast. Increased T2 signal intensity and progressive growth may indicate malignant transformation or, more likely, a different tumor. Hypothalamic hamartomas may be sessile or pedunculated. Pedunculated and smaller lesions tend to present with precocious puberty (case one), whereas sessile and larger lesions are more commonly associated with seizures (case two). In our case Magnetic Resonance Imaging showed a well demarcated lesion isointense on T1, increased signal intensity on T2, non enhancing contrast seen in suprasellar cistern.[9]

Central precocious puberty caused by HH can be managed by long acting GnRH analog therapy as it is effective with minimal complications. Since most patients present between 1-3 years of age, GnRH analogs treatment is required for 10-11 years, which is expensive. Surgical resection of HH is advisable if the initial GnRH therapy fails to suppress puberty, and it can also be considered if the patient cannot afford the expensive long term treatment with GnRH analogs, which is expensive than surgery in developing countries.

As GS is refractory to antiepileptic drugs ,ablation is considered best treatment. Ablation of HH can be done by surgery or radiosurgery.[11]

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

Pterional-trans-sylvian approach provides shortest and direct route to

the reach HH. This approach has fewer complications compared to other approaches.[14]

Roszkowski et al.[13] in their series of five patients with pterional approach. Subtemporal approach is advantageous when there is significant prepontine component, or when the lesion is adherent to the brainstem or basilar artery.[14] Albright et al.[15] have used subtemporal approach in their series of six patients. Transient oculomotor paresis has been reported in three of their patients and one patient required eye muscle surgery. Sessile HH, commonly associated with seizures, are more difficult to treat than pedunculated HH. Anterior transcallosal interforniceal approach as advocated by Rosenfeld JV.[16] has become a common approach for sessile intrahypothalamic HH, in addition to endoscopic and skull base approaches. 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. Endocrine remission even after subtotal resection of HH has been reported.[14]

Irrespective of the approach, vital anatomic structures like optic chiasma, oculomotor nerve, pituitary stalk, perforating vessels from internal carotid artery and hypothalamus can be injured during the surgery resulting in complications like impaired vision, oculomotor paresis, diabetes insipidus, hemiparesis, unconsciousness and death. Utmost care should be taken to preserve the vital structures during the surgery. Postoperative endocrine abnormalities are another concern when surgical modality is chosen as a treatment option. Several transient endocrine deficiencies have been reported in the literature, they are more common with sessile HHs where surgery is mainly indicated for intractable epilepsy. In such cases, risk of hypothalamic damage during surgery is high, explaining the high incidence of complications.[14] There is limited data available regarding postoperative endocrinopathies in pedunculated hamartomas where surgery is indicated for central precocity.

CONCLUSION

Our cases illustrate the utility of total surgical excision of HH by pterional approach in the successful management of CPP and GS with minimal complications. In developing countries, where availability and expense of long term GnRH analog therapy are an issue, surgical excision can be considered as initial treatment, which is curative and cost-effective.

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