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CASE REPORT

Gelastic seizures and hypothalamic hamartoma: a case report and review of literature

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Abstract:
Gelastic (laughing) epilepsy is characterized by recurrent unprovoked episodes of stereotyped, brief and mirthless laughter. Hypothalamic hamartoma is most often the cause of gelastic epilepsy. Hypothalamic gelastic epilepsy presenting as a progressive epileptic disease is well known, but isolated without multiple seizure types, precocious puberty, cognitive decline and behavioural problems is not usually reported. We report a case of refractory gelastic seizures associated with indolent hypothalamic hamartoma and polysyndactyly with a follow-up of 18 years. Our case highlights the possibility of underdiagnosed hypothalamic hamartomas and unrecognised gelastic epilepsy in paediatric population.

Keywords: *gelastic epilepsy, hypothalamic hamartoma, polydactaly, seizure disorder*
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Hypothalamic hamartomas (HH) are rare with an estimated prevalence rate of 1 in 50,000 to 1 in 100,000 [1]. Many paediatric neurologists may encounter only one or two cases of HH throughout their careers. It has a wide range of severity in presentation, ranging from a catastrophic epilepsy in early childhood with severe learning difficulties and behaviour problems, to a milder form of gelastic epilepsy with little or no associated cognitive difficulties [2,3]. A characteristic feature is the occurrence of laughing, or gelastic seizure (GS) [4]. Many cases are unrecognised and go undiagnosed, particularly if they are associated with other, more severe seizure types.

The aim of this report is to increase awareness of laughter as an ictal epileptic manifestation and highlight a case with an unusually benign course of hypothalamic gelastic epilepsy.

CASE REPORT

A 19 year-old Caucasian male was born with multiple congenital abnormalities. His limb abnormalities consisted of bilateral upper limb postaxial polydactyly, unilateral 4th and 5th short syndactyly on the left and a short 5th finger clinodactyly on the right. He had bilateral 2nd and 3rd partial syndactyly of the toes. His left leg was approximately 2 cm shorter than his right leg and X-rays revealed hypoplasia of the left tibia and abnormalities of both fibula. Additional features included: multiple frenula and several small hamartoma-like nodules on his gums; a Darwinian tubercle on his right ear; a curious bridge of skin lying across his anal orifice.

From 2 years of age he frequently woke up with hysterical laughing and/or crying for a few seconds after which he returned to sleep. Occasionally there was some twitching of his limbs; his mother thought he was suffering from nightmares. Infrequent episodes were noted in waking

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hours, during which he retained his consciousness. Two EEG's, including a 24 hour sleep EEG, were reported as normal. A clinical diagnosis of episodic abnormal behaviour was made and he was referred to a child clinical psychologist. During his early childhood apart from some increase in the frequency of laughing episodes there had been no change in intellectual or physical development, he was progressing along the 90th centile in weight and height and was neurodevelopmentally normal.

At 7 years of age, he had a generalized tonic clonic seizure which lasted about one minute during starvation prior to a syndactyly operation. CT brain showed no abnormalities. MRI brain showed a solid intrahypothalamic mass measuring 1cm x 1.2 cm in the maximal transverse diameter. The mass was isodense on T1 weighted imaging, slightly hyperdense on T2 weighted imaging and did not enhance with contrast. The morphology was consistent with hamartoma and the exact location was in the region of hypothalamus, particularly tuber cinereum/mamillary bodies. [Fig 1]. A diagnosis of gelastic seizures with hypothalamic hamartoma was made.

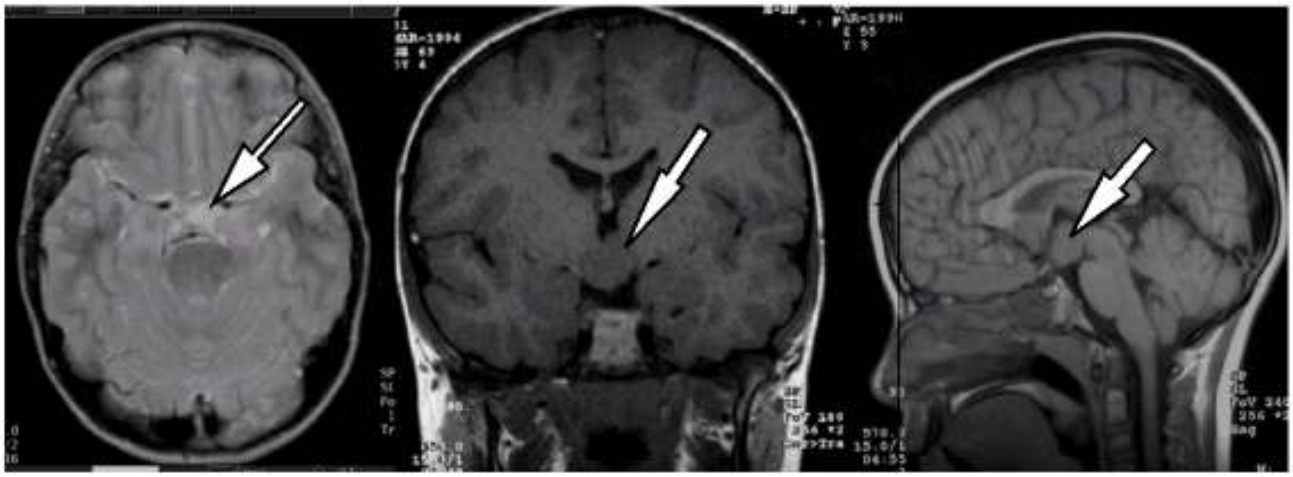

Figure 1: A) Axial T2 weighted image showing hyperdense area anterior to the midbrain B) Coronal T1 weighted image showing isodense mass in the hypothalamus C) Sagittal T1 weighted image showing isodense mass

Treatment with carbamazepine was initiated. The gelastic seizures remained refractory but infrequent (occurring from once per month to once every six months) despite various anti-epileptic drugs such as lamotrigine and topiramate. A combination of levetiracetam and lamotrigine proved to be the most effective. However, gelastic seizure freedom was never achieved. No further seizure types developed following the pre operative seizure provoked by starvation. Further EEG's including a 24 hour recording at 8 years of age were reported as normal. His fifth EEG at 15 years of age showed non-specific minor left fronto-temporal slow wave asymmetry. Episodically, there were runs of rhythmic sharp wave and sharpened theta activity over the left hemisphere maximal temporally with focal features fronto-temporally. This activity became more marked and occurred in longer runs during drowsiness before subsiding during light sleep.

At 19 years of age, apart from infrequent brief paroxysmal laughter which was well controlled on a combination of levetiracetam 750mg BD and lamotrigine 250mg BD, he was otherwise unaffected. His cognition and behaviour remained unaffected, he had completed his A levels. Neurological examination, including cranial nerves, was normal, as it had been throughout. He remained well grown and he never had visual problems or hormonal disturbances, with endocrine tests including free T4, TSH, cortisol, TRH test repeatedly normal. The hamartoma remained indolent as evidenced by serial brain MRI scans between the ages of 7 and 12.

DISCUSSION

Hypothalamic gelastic epilepsy is often a progressive epileptic seizure disorder. In the large majority of cases the laughter starts in infancy, becoming longer and more frequent over time with associated impairment of consciousness. Subsequently, patients develop seizures of various types: generalised tonic-clonic seizures, tonic seizures, drop attacks, and complex partial seizures.[2,3] Additionally, progressive cognitive and behavioural impairment develops for most patients. More than half (59%) will suffer from precocious puberty.

Ictal laughing or gelastic seizures have been reported with temporal lobe and frontal lobe seizures [3,4], but are most commonly associated with hypothalamic hamartoma. Ictal

laughing is usually brief (less than 30 seconds) and normally accompanied by feeling of mirth [4], although not always, as illustrated in our case. Given a history of brief and infrequent paroxysms of inappropriate laughter and crying, compounded with a normal neurological examination and repeated normal ictal EEG studies, alternative diagnoses including Tourette's syndrome and episodic abnormal behaviour are often made. It is understandable that the diagnosis is often missed or delayed, only after the appearance of other more conventional seizure manifestations (generalized tonic-clonic seizure in our case) and impairment of consciousness are thorough investigations carried out.

The aetiology of HH is probably one of congenital malformation or dysgenesis [3,4]. Most cases have a sporadic form of the disease, without family history or risk of recurrence and without associated congenital anomalies. However, polysyndactyly associated with HH has been reported [5,6]. On balance, we believed that our case had some form of oro-facial-digital syndrome that did not conform to common types of that disorder. There was no evidence of Pallister-Hall syndrome characterized by polydacytyly, dysplastic nails, bifid epiglottis, imperforate anus, renal anomalies, pituitary dysplasia and hypopituitarism [6].

Our patient's weight and BMI were 97th centile and greater, respectively, with no evidence of precocious puberty or hormonal disturbance. Some believe that patients with HH tend to gain weight, implying some impact on the hypothalamic axis, even if overt hormonal disturbance is not demonstrated. However, this is difficult to prove. The absence of many features such as precocious puberty, worsening seizure control, emergence of multiple seizure types, cognitive decline and behavioural problems in our patient was rather unusual and uncommon.

Lesions are best detected by MRI and may be difficult to identify by CT brain [7]. Interictal surface EEG recordings are non-specific, indeed the EEG may be completely normal. Later, epileptiform discharges and background abnormalities can be seen[7]. It is of interest that our case had an abnormal EEG at 15 years of age. Our understanding was that although the episodic activity was suspiciously epileptic in nature, rhythmic mid temporal discharges, a benign electrophysiological phenomenon, cannot be excluded.

Medical treatment with antiepileptic drugs usually has little or no effect in gelastic seizures and polytherapy may do more harm than good [3,4]. Gelastic seizures become less frequent during the first decade and may disappear entirely as other seizure types develop [8]. We believe our patient's seizure control was attributed to anti-epilepticdrugs as have been reported in 5% of cases.[3] These medications may have prevented the secondary spread or generalized seizures and therefore have value in our case as evidenced by an abnormal EEG at 15 years old.

Over time, a number of strategies to treat refactory seizures have been reported with success, for example vagal nerve stimulation (VNS) [9] and ketogenic diet. Surgery should be considered at an early age, particularly if refractory seizures are associated with deteriorating quality of life. Several types of procedure have been reported [2-4] with success, such as resective surgery, stereotactic radiosurgery (Gamma Knife), stereotactic radiofrequency thermoablation and stereotactic implantation of 125I radioactive seeds. These procedures may be curative but are technically difficult, carrying the risk of serious neurological deficit or hormonal disturbance, particularly open skull resective surgery. The risk of surgical operation outweighed the possible benefit for seizure control in our case. Clearly, if these different strategies develop further, it may be appropriate to consider in patients whose epilepsy is less severe.

Our case clearly stands against invasive surgery at early age, particularly if the child's quality of life is not compromised. The outcome of hypothalamic gelastic epilepsy may not be too grave.

CONCLUSION

Based on experiences from this case and subsequent literature review, the following conclusions can be drawn: (1) HH may present with gelastic seizures without precocious puberty, behaviour problems and cognitive deterioration; (2) congenital abnormalities, particularly polysyndactyly, may be associated with HH; (3) HH may remain indolent; (4) patients with gelastic seizures and HH can have a good quality of life.

Clinicians should be aware of laughing attacks associated with hypothalamic hamartoma and polysyndactyly. MRI Brain is essential, thus avoiding delay in diagnosis and ensuring appropriate management.

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