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Paroxysmal tonic eye deviation: an atypical presentation of hypothalamic hamartoma

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ABSTRACT – Hypothalamic hamartoma is a rare developmental non-neoplastic malformation, often characterised by early onset gelastic seizures and later progressive cognitive and behavioural deterioration. In this case study, we have examined a child who presented with an atypical onset of benign paroxysmal gaze deviation between two to three months of age. The patient subsequently developed gelastic seizures at age 13. Based on the observation that hypothalamic hamartomas do not involve any functional region involved in eye motility, we speculate that both gaze deviation and gelastic seizures are a manifestation of the epileptogenic nature of the hypothalamic hamartoma. *[Published with video sequences]*

Key words: hypothalamic, hamartoma, gelastic seizures, epilepsy, paroxysmal gaze deviation, Pallister-Hall syndrome

Hypothalamic hamartoma (HH) is a congenital malformation affecting the hypothalamus that is frequently associated with early onset epileptic seizures, such as gelastic seizures (GS), and, sometimes, precocious puberty. The evolution can be variable but in most cases seizures become refractory to medical therapy. Other seizure types (focal and/or generalised) develop during the clinical course and the progression is characterized by the onset of a catastrophic epileptic encephalopathy with significant cognitive and behavioural problems (Berkovic *et al.*, 1988).

Case study

This child was born to healthy non-consanguineous parents. Pregnancy, delivery and neonatal period were unremarkable. The only findings of note were both birth weight and head circumference which appeared at the upper limits of the normal range. At the age of two months, the child began to present episodes of leftward paroxysmal gaze deviation, less frequently upward, preceded by minimal eyelid closure *(see video sequence 1)*. The frequency was high during the day, occurring in clusters of three days

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separated by intervals of around 15-20 days. The episodes disappeared completely after several hours of sleep. No alteration of consciousness or any other manifestation was detectable except for mild irritability.

Extensive laboratory and metabolic investigations (including T3, free T4, THS, CSF analysis, urinary organic acids, urinary and plasma amino acids, lactic and pyruvic acids) were unremarkable. Neurological and neuro-ophthalmogical examinations (ocular, orthoptic and visual evoked potentials) were normal. Video-EEG monitoring was also performed during the episodes and was normal. No interictal epileptiform paroxysmal activity was found.

MRI showed a voluminous sessile hypothalamic hamartoma, with an upper margin not clearly distinguished from the deep left hemispheric brain matter, and a lower part characterized by clearly defined edges. These edges were located in the suprasellar cistern, the interpeduncular cistern and the pre-pontine cistern reaching the level of the junction between the upper and middle third of the anterior margin of the pons *(figure 1)*.

Endocrinological evaluation to detect precocious puberty or other disturbances associated with this condition was normal. Also, genetic testing for Pallister-Hall syndrome (GLI3 mutation) was found to be negative.

The paroxysmal episodes disappeared spontaneously when he was three months of age. Until the age of 13 months he was in good general health, psychomotor development and neurological findings continued to be normal and no other paroxysmal manifestation occurred.

From the age of 13 months he began to present very frequent (every 10-15 minutes) daily episodes when he was awake, characterized by a guttural coughing sound (similar to the onset of crying or laughter), which were not associated with any alteration of consciousness *(see video sequence 2)*. These episodes were brief, stereotyped and not related to the environmental context. Psychomotor instability was evident after the events and the child seemed to be disturbed, looking for physical contact with his mother. No interictal or ictal epileptiform abnormalities were found during the video-EEG monitoring. Six months after the onset of the episodes the child was reported to have normal neurological and psychomotor development (GQ = 90 evaluated with Griffiths scale).

Discussion

Hypothalamic hamartoma (HH) is a rare developmental non-neoplastic malformation commonly associated with gelastic seizures (GS). The prevalence is about 1-2 per 100,000, which could be an underestimation of the true prevalence of the disease (Kerrigan *et al.*, 2005), which has recently increased with the advances in neuroimaging techniques. The typical clinical picture of HH is usually characterized by epilepsy, mental retardation with behavioural disorders and endocrinological problems (precocious puberty). HH is usually sporadic and only rarely associated with the autosomal dominant Pallister-Hall syndrome (PHS). GS are the more specific ictal feature associated with this malformation and tend to be more frequent at the onset, being the only symptom of the disease at that time. Furthermore, GS may occur very early, even from the first day of life (Freeman *et al.*, 2003; Brandberg *et al.*, 2004; Shahar *et al.*, 2007). They can be more difficult to recognize in very young children since they may be erroneously interpreted as real laughing or crying episodes or confused with normal infantile abdominal colic.

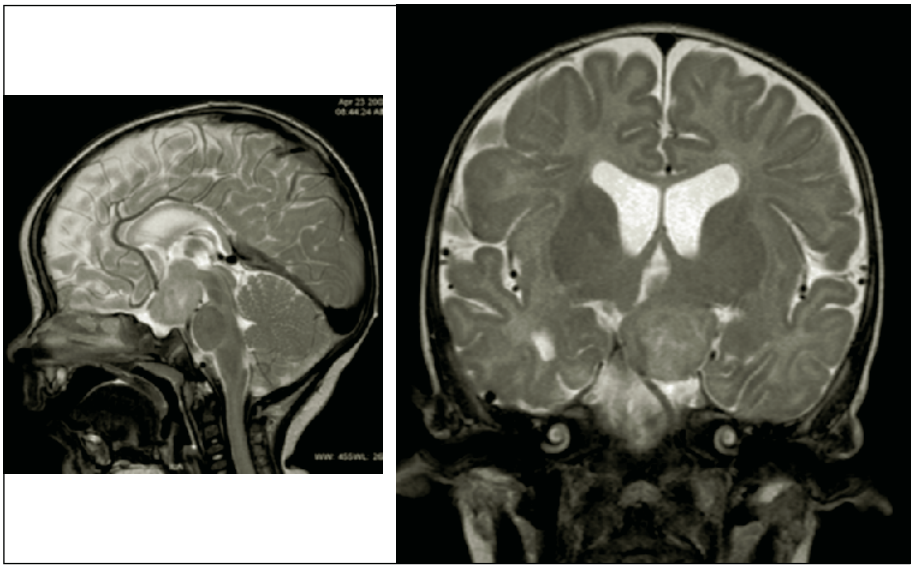

Figure 1. Sagittal (**A**) and coronal (**B**) fast spin-echo T2-weighted images (1.5T, TR = 5,022 ms, TE = 100 ms) show a huge mass attached with a wide sessile base to the inferior surface of the hypothalamus which is mildly hyperintense with respect to the cortex.

Also, they may present with little or no epileptiform abnormalities based on the scalp EEG.

In our case, clinical onset was characterized by a paroxysmal disorder consisting of very brief gaze deviation occurring in clusters, several times during the day, which disappeared spontaneously after one month. In very young children non-epileptic paroxysmal manifestations are common and usually considered to be benign.

Paroxysmal tonic upgaze deviation has been described as an age-dependent manifestation characterized by onset in infancy of periods of short conjugate upward deviation of the eyes without deterioration and with eventual improvement. This syndrome is usually classified as a benign transient movement disorder in children (Ouvrier and Billson, 2005). Nevertheless, paroxysmal gaze deviation may also be an early sign of more widespread neurological dysfunction and has been reported in association with specific inflammatory or compressive lesions involving the periaqueductal grey structure (Spalice *et al.*, 2000; Senbil *et al.*, 2009). Due to a lack of specific clinical features, we were unable to classify the paroxysmal gaze manifestation presented by our patient as paroxysmal tonic upgaze *per se*.

Whereas abnormal vertical eye movement is believed to be controlled by the periaqueductal region in patients with HH, the effect on eye movement was more difficult to understand in our patient since the HH was not shown to interefere with any functional region involved in eye motility.

Partial seizures are widely accepted to be part of the clinical picture of HH (Kahane *et al.*, 2003) and can be of different types (partial motor, partial complex). They tend to occur later than GS and are usually associated with detectable EEG abnormalities, documenting the focal onset arising from the cortical areas (frontal and temporal lobe) adjacent to the malformation. Some studies using stereotactic intracerebral EEG recordings (Kahane *et al.*, 2003; Fenoglio *et al.*, 2007) and functional neuroimaging (SPECT) have effectively demonstrated that HH is intrinsically epileptogenic (Di Fazio and Davis, 2000) and could be responsible for the onset of seizures even if no EEG scalp abnormalities are found.

We suggest that both paroxysmal disorders (gaze deviation and GS), which presented at different ages in our patient, could be interpreted as a manifestation of the epileptogenic HH. The spontaneous regression of initial gaze deviation and the later occurrence of the GS may thus be interpreted in terms of the different clinical expression of the same disease due to progressive cerebral maturation with age. This case therefore represents a form of HH with atypical onset characterised by early onset of a clinically "benign" condition (in terms of spontaneous regression, normal neurological and psychomotor development) which is the first sign of a less "benign" brain lesion. □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

Legends for video sequences

Video sequence 1
At three months of age, the patient experienced very brief episodes (lasting for a few seconds) of leftward paroxysmal gaze deviation preceded by minimal eyelid closure, more evident on the right. The EEG recording was found to be normal during the episodes.

Video sequence 2
At 13 months of age, the patient experienced very brief, stereotyped episodes characterized by a guttural coughing sound (similar to the onset of crying or laughter), not associated with any alteration of consciousness. Psychomotor instability was evident after the events and the child seemed to be disturbed, looking for physical contact with his mother. The EEG recording was found to be normal during the episodes.

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