Epilepsy and hypothalamic hamartoma: look at the hand Pallister-Hall syndrome

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Summary

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Summary : We report the case of a 29-year-old patient, who suffered from drug resistant laughing seizures since childhood. The clinical examination was normal, except for sequelae of hand and feet surgery during infancy for post-axial polydactyly. Cerebral MRI showed a hypothalamic hamartoma. The association of complex limb abnormalities with hypothalamic hamartoma lead to the diagnosis of Pallister-Hall syndrome. This syndrome is related to a mutation of gene GLI3, located on chromosome 7p13, and its inheritance is autosomal dominant. In the case of laughing seizures, a cerebral MRI should be performed to look for a hypothalamic hamartoma. The observation of such lesions indicates the necessity of standard radiographies of the hands and feet, to search for associated abnormalities. These findings might help to recognize a Pallister-Hall syndrome, thus allowing genetic counseling.

Keywords : Pallister-Hall syndrome, magnetic resonance imaging, hypothalamic hamartoma

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Case report

A 29-year-old patient, who suffered from drug resistant laughing seizures (gelastic seizures) since childhood, was referred to the neurology department for evaluation. She was born at full term following an uncomplicated pregnancy. Post-axial hexadactyly involving the hands and feet was noted at birth, and was surgically corrected during childhood. Psychomotor development was normal. First seizures started in childhood and were characterized by a feeling of "deja-vu", inappropriate laughing followed by agitation. They lasted less than one minute. At 13 years of age, a new type of seizure was described: staring, gestural, with oro-alimentary automatisms, left conjugate deviation of the head and eyes, and post-ictal confusion with right nose wiping. These lasted for several minutes. The two types of seizures actually occurred in clusters, almost every day. Valproic acid, phenobarbital, carbamazepine, phenytoin, clonazepam, clobazam, vigabatrin, gabapentine and lamotrigine were all ineffective.

Clinical examination was normal, and there was no mental retardation. Interictal EEG showed bi-temporal slow activity and bi-temporal sharp waves with right predominance. EEG performed during the seizures with automatisms showed an ictal discharge in the temporal, parietal and central regions with a right predominance. Cerebral MRI scan (figure 1) showed a 2 cm tuber cinereum mass, mildly hypointense on T1-weighted images and hyperintense on T2-weighted images to gray matter. The lesion was non-calcified and there was no enhancement after contrast media administration. These imaging findings, associated with gelastic seizures, are characteristic of hypothalamic hamartoma [1, 2].

X-rays of the hands and feet (figure 2) showed syndactyly of the third and fourth metacarpals and of the third and fourth metatarsals with short fourth metacarpals.
Cardiac and abdominal ultrasound examinations and endocrinological examinations showed no other abnormalities.

The clinical and radiological abnormalities of the limbs associated with the hypothalamic hamartoma suggest the diagnosis of Pallister-Hall syndrome [3].

Her son presented the same clinical symptomatology and also underwent a cerebral MRI scan, X-rays of the hands and feet, cardiac and abdominal ultrasound examinations and endocrinological examination, which revealed a hypothalamic hamartoma associated with complex limb abnormalities.

Genetic analysis of both patients confirmed the diagnosis of Pallister-Hall syndrome, with a mutation of gene GLI3, located on chromosome 7p13.

Familial investigations found 10 other subjects having complex limbs abnormalities but no gelastic seizures (figure 3). None underwent cerebral MRI scan.

**Discussion**

Magnetic resonance imaging showed an hypothalamic hamartoma, with a hypothalamic mass, isointense with gray matter on T1 weighted images, no enhancement after gadolinium administration, and isointense or slightly hyperintense on T2-weighted images [4].

Recently Arita *et al.* [5] described two categories of hypothalamic hamatomas based on MR findings: the "parahypothalamic type", which is only attached to the floor of the third ventricle, and is generally associated with precocious puberty, and the "intrahypothalamic type", in which the hamartoma involves the hypothalamus, and is generally associated with seizures. Clinically these consist of gelastic seizures, but other types of seizures (drop attacks, tonic-clonic seizures) occur in the course of the illness, and mental retardation then appears [1].

Ictal depth electrode recordings from the hamartoma have shown that gelastic seizures are associated with ictal discharges within the lesion [6]. These results have been confirmed by ictal SPECT studies showing hyperperfusion in the hamartoma [7] and by MRI spectroscopic studies demonstrating neuronal damage in the hamartoma [8].

In the case of drug resistant epilepsy, the treatment of hypothalamic hamatomas includes surgical resection of the lesion, but this is often associated with morbidity. More recently, stereotactic radiosurgery has been used, with promising results [9].

The association of hypothalamic hamartoma with hand abnormalities, including post-axial polydactyly, oligodactyly, short fourth metacarpals and syndactyly leads to the diagnosis of Pallister-Hall syndrome [10].

This syndrome was first described in 1980 [3], and combines the presence of hypothalamic hamartoma, hypopituitarism, post-axial polydactyly and imperforate anus. There is an important range of phenotypic variability [11], and many other abnormalities have since been described, including: laryngeal cleft, bifid epiglottis, renal dysplasia, cardiac malformations and lung dysplasia [10, 12]. The clinical presentation ranges from polysyndactyly associated with asymptomatic hypothalamic hamartoma to neonatally lethal malformations including holoprosencephaly [3, 11]. The discovery of malformations on prenatal ultrasonographic examination suggests the diagnosis of Pallister-Hall syndrome [13, 14].

This syndrome is due to a mutation of the gene GLI3, located on chromosome 7p13, and its inheritance is autosomal dominant [15].

**CONCLUSION**

In the case of laughing seizures, a cerebral MRI should be performed to search for a hypothalamic hamartoma. The presence of this lesion should indicate standard X-ray of the hands and feet, to search for associated abnormalities. These findings might help in the diagnosis of Pallister-Hall syndrome, thus
allowing genetic counseling.

REFERENCES


