CASO CLÍNICO/CASE REPORT

Hypothalamic Hamartoma Presenting as Gelastic Epilepsy: When it Goes Unnoticed

Epilepsia Gelástica como Apresentação de um Hamartoma Hipotalâmico: Quando Passa Despercebido

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Abstract

A 5-year-old boy presented with episodes of ocular retroversion occurring over the past 4 weeks. Further investigation revealed frequent bilateral epileptiform frontal activity on electroencephalogram and a nodular formation in the hypothalamus on cerebral computed tomography scan. Magnetic resonance imaging characterized the lesion as a hamartoma of the tuber cinereum. After questioning, episodes of unprovoked laughter since the first year of life, consistent with gelastic seizures, were reported. During follow-up, an increase in testicular volume was noted, and a GnRH stimulation test confirmed the diagnosis of central precocious puberty. The boy underwent treatment with anti-epileptic drugs and GnRH analogs. Surgical resection of the hamartoma was performed, resulting in cessation of seizures and behavior's improvement.

Hypothalamic hamartomas can present with precocious puberty and gelastic epilepsy. Diagnosis is challenging and often the symptoms go unnoticed for years. Long-term follow-up and multidisciplinary management are essential for optimal patient care and monitoring.

Resumo

Criança de 5 anos, sexo masculino, apresentou-se com episódios de retroversão ocular com 4 semanas de evolução. O eletroencefalograma (EEG) revelou atividade epileptiforme frontal bilateral frequente e foi identificada na tomografia computorizada cerebral uma formação nodular no hipotálamo, posteriormente caracterizada por ressonância como um hamartoma do *tuber cinereum*. Posteriormente, relatados episódios de riso descontextualizado desde o primeiro ano de vida, consistentes com crises gelásticas. No seguimento, notado aumento de volume testicular, pelo que fez prova de estimulação de GnRH que confirmou o diagnóstico de puberdade precoce central. O tratamento foi iniciado com fármacos anti-crises epiléticas e análogos de *gonadotropin-releasing hormone* (GnRH). Posteriormente, realizada a ressecção cirúrgica do hamartoma, com consequente resolução das crises e melhoria do comportamento.

Os hamartomas hipotalâmicos podem-se manifestar como puberdade precoce ou crises gelásticas. O diagnóstico é desafiador e muitas vezes os sintomas passam despercebidos durante anos, pelo que é necessário manter um seguimento multidisciplinar a longo prazo destes doentes.

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Introduction

Hypothalamic hamartomas are benign tumors that, although rare, are a well-known cause of central precocious puberty and gelastic seizures, often remaining asymptomatic for extended periods.[1]

Epilepsy in affected patients typically manifests as gelastic seizures, characterized by episodes of inappropriate laughter, which often begin early in life. The hamartoma itself directly generates this seizure type, as it is intrinsically epileptogenic due to its anatomofunctional organization. Over time, about 75% of patients with gelastic seizures will develop focal or generalized seizures, likely due to secondary epileptogenesis, which is often resistant to pharmacological treatment.[1,2]

The diagnosis is often suspected when signs of precocious puberty appear due to the involvement of GnRH-releasing neurons in the tumor. In addition, hypothalamic hamartomas are associated with a wide range of neuropsychiatric symptoms, including cognitive decline, language delay, learning disabilities, behavioral problems, and mood disorders.[3]

In general, approximately 40% of patients with neurological symptoms experience the onset of precocious puberty in childhood. In contrast, patients with an endocrine presentation tend to have milder neurological symptoms, with normal cognitive function and no evidence of epilepsy or abnormal EEG findings. This distinction may be explained, at least in part, by the higher prevalence of pedunculated hamartomas in patients presenting with endocrinological symptoms and, in contrast, the predominance of sessile hamartomas in patients presenting with neurological signs.[2,4]

Case Report

A 5-year-old boy presented to the medical care facility with an episode of ocular retroversion, involuntary movements of the head and tongue, flexed upper limbs, and drooling, lasting 1 minute. There were no tonic-clonic limb movements, sphincter incontinence, or focal deficits. The child had previously experienced several similar episodes of ocular retroversion occurring 4 weeks prior, each lasting seconds. There was no reported fever, and no history of trauma or other relevant symptoms. The child had a family history of epilepsy, with two second-degree maternal cousins and one third-degree maternal cousin affected. Adequate psychomotor development. No other significant medical history was reported. Physical examination revealed no abnormalities, and the neurological assessment was unremarkable.

An interictal electroencephalogram (EEG) recording displayed normal background activity and frequent epileptic activity in frontal regions (**Fig. 1**). A cerebral

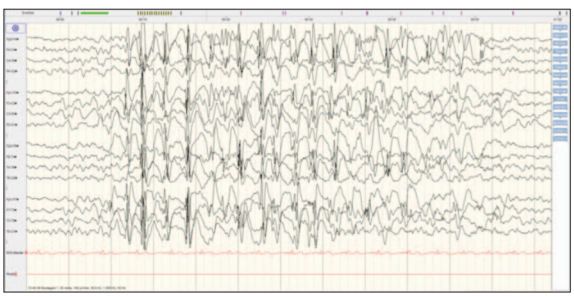

Figure 1. Interictal EEG recording showing normal background activity with frequent epileptic discharges in the frontal regions.

computed tomography (CT) scan revealed a nodular formation in the hypothalamus, measuring 14x15 mm in diameter, suggesting a hypothalamic hamartoma or a glioma. Subsequent cerebral magnetic resonance imaging (MRI) characterized the lesion as an expansive mass in the interpeduncular cistern, with well-defined borders, measuring 14.5x13x12.5 mm (**Fig. 2**). The MRI

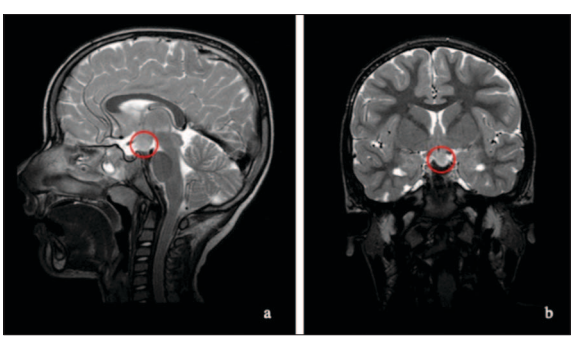

Figure 2. Cerebral MRI reveals a well-defined expansive mass in the interpeduncular cistern, measuring 14.5 × 13 × 12.5 mm, consistent with a sessile hamartoma of the tuber cinereum. The lesion displays a heterogeneous T2 signal, depicted in axial (Fig. 2a) and coronal (Fig. 2b) views.

showed a heterogeneous signal in T2 and hyperintensity in FLAIR, without any contrast enhancement. The lesion was located laterally on the left and involved the left mammillary body, suggestive of a sessile hamartoma of the tuber cinereum.

In retrospect, the parents reported that the child had been experiencing daily episodes of unprovoked laughter since the first year of life, primarily before fall-

ing asleep and during sleep, associated with purposeless movements of the upper limbs, lasting seconds, suggesting gelastic seizures. A 24-hour video-EEG monitoring recorded a total of 24 seizures, all occurring during sleep (**Fig. 3**). The ictal EEG showed 2.5 hertz generalized spike and wave with maximum parassagittal projection, sometimes wider on the left. The interictal recording showed similar epileptiform discharges in the same topography as the ictal patterns, only during sleep.

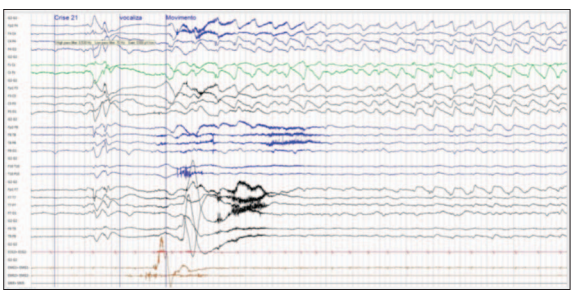

Figure 3. Video-EEG monitoring showing generalized 2.5-hertz spike-and-wave activity with maximum parassagittal projection.

During a follow-up visit, we noted an increase in bilateral testicular volume (6 mL) using the Prader orchidometer, as well as thickening and enlargement of the penis (11 cm) when measured in its stretched state. No axillary or pubic hair were present. Tanner stage G2 and P1 were noted. Hormone testing was performed: luteinizing hormone (LH) 0.2 mIU/mL (normal value (NV) 0.02-0.3 mIU/mL); follicle-stimulating hormone (FSH) <0.3 mIU/mL (NV 0.26-3 mIU/mL); testosterone <7 ng/dL (NV <3-10 ng/dL); thyroid-stimulating hormone 2,23 IU/mL (NV 0.6-5.5 IU/mL); adrenocorticotropic hormone 12.60 pg/mL (NV 6-48 pg/mL) with normal cortisol; prolactin 5.6 ng/mL (NV 3-18 ng/mL); β-human chorionic gonadotropin <2 mIU/mL (NV <5 mIU/mL). The estimated bone age (5.5 years) was similar to the chronological age (5.3 years). A gonadotropin-releasing hormone (GnRH) stimulation test showed a maximum peak level of LH at 3.22 mIU/mL, FSH at 2.69 mIU/mL, and an LH/FSH ratio of 1.19 mIU/mL, confirming the diagnosis of central precocious puberty.

The boy underwent treatment with sodium valproate titrated up to 30 mg/kg/day, resulting in inadequate seizure control. Carbamazepine was subsequently introduced as a second antiseizure drug and titrated up to 10 mg/kg/day. It was decided to initiate treatment with GnRH analogs, specifically triptorelin. After a multidisciplinary discussion, the medical team opted to perform percutaneous laser interstitial thermotherapy on the lesion. Sodium valproate was discontinued to mitigate the risk of surgical hemorrhage, with carbamazepine maintained at the maximum dose with reports of sporadic nocturnal gelastic seizures. At the three-month post-surgery follow-up, there were no further seizures observed, accompanied by an apparent improvement in behavior. Post-surgical EEG was not repeated, given the resolution of clinical complaints and the absence of further seizures.

Discussion

The presented case was an example of a sessile hypothalamic hamartoma with both neurological and endocrinological presentation. Apart from the epileptic manifestations, the patient also showed signs of central precocious puberty, with an increase in testicular volume and penile enlargement, along with hormonal abnormalities, including an LH/FSH ratio consistent with central precocious puberty.

CT typically reveals a small non-enhancing mass in the interpeduncular and suprasellar cistern, but MRI is considered the gold standard for the diagnosis, as it is able to differentiate normal hypothalamic tissue from the hamartomatous tissue. Hamartomas are typically isointense to normal gray matter on T1 and isointense to slightly hyperintense on T2/FLAIR, with the intensity directly related to the proportion of glial tissue present in the lesion. Hypothalamic hamartomas do not interfere with the blood-brain barrier, thus they do not show enhancement after contrast administration.[5]

Gelastic seizures in childhood are predominantly associated with hypothalamic hamartomas but are not exclusive, as they may also be associated with frontal or temporal lobe epilepsies. They typically show no or slight EEG changes, except for a flattening of the background activity. However, at times, diffuse paroxysmal activity or interictal focal/multifocal activity can be present.[2] The imaging and electroencephalographic findings in the case were consistent with the diagnosis.

Surgical resection of the hamartoma is considered in cases where epilepsy is refractory to pharmacological treatment, as in the presented case, or when there is progressive cognitive decline or severe behavioral problems. However, it is important to note that surgical intervention is associated with a high rate of com-

plications, making the decision for surgery a complex and careful consideration based on individual patient characteristics and symptom severity. Seizure control is achieved in approximately 50% of cases, with improvements observed in behavior and cognition.[1,3]

The patient also initiated treatment with a GnRH analogue, which is effective in patients with gonadotropin-dependent precocious puberty. Long-term follow-up and multidisciplinary management are crucial for optimizing the care of these patients.[6]

In conclusion, this case highlights the challenging diagnostic process in patients with hypothalamic hamartoma. The multidisciplinary approach proved crucial in establishing an accurate diagnosis and developing an appropriate management plan for these patients. Further studies with long-term follow-up are necessary to monitor the response to treatment and the overall clinical outcome in such cases. ■

Contributorship Statement / Declaração de Contribuição

MOP, CMag: Conception and design. MOP, CBA, CMag: Data analysis and interpretation. MOP: Writing. JF, CMel, CMei, CMag: Critical review of an important part of its intellectual content.

All authors approved the final version to be published.

MOP, CMag: Conceção e desenho. MOP, CBA, CMag: Análise e interpretação dos dados. MOP: Redação. JF, CMel, CMei, CMag: Revisão crítica de parte importante do seu conteúdo intelectual.

Todos os autores aprovaram a versão final a ser publicada.

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