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The clinical spectrum and natural history of gelastic epilepsy-hypothalamic hamartoma syndrome

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Outcome;
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Summary

Purpose: To delineate the clinical spectrum and patterns of evolution of epilepsy with gelastic seizures related to hypothalamic hamartoma (HH).
Patients and methods: We evaluated patients with HH, observed between 1986 and 2002 for whom at least one ictal video-EEG or EEG recording of gelastic seizures was available.
Results: Six subjects (four male, two female) with sessile HH between 0.8 and 1.7 cm in diameter were identified. The onset of gelastic seizures was between 2 months and 20 years. It evolved to secondary generalized epilepsy in one case, and to drug-resistant partial epilepsy in the other five from 2 to 13 years after onset. No patient showed precocious puberty. Severe cognitive impairment developed in the patient with secondary generalized epilepsy, and a mild cognitive defect in two others. Patients with an HH below 1 cm did not show neuropsychological or behavioural disturbances. Drug resistance occurred in all cases. Surgical removal of HH markedly improved the clinical evolution in two patients.
Conclusions: Gelastic epilepsy-HH syndrome can differ in severity and evolution. A catastrophic evolution and drug resistance can be reversed by surgical or by gamma-knife ablation of HH.

Introduction

It was first recognized in 1873 that compulsive bursts of laughter could be epileptic in nature.[1] Almost a century later, Daly and Mulder[2] coined the term "gelastic epilepsy" in their report of two cases in which laughter was a fixed feature of the seizure pattern. A brief history of early reports on gelastic epilepsy can be found in Gumpert et al.[3] In 1971, the criteria for the diagnosis of gelastic seizures (GS) were established.[4]

Gelastic seizures are rare; they are usually associated with other seizure types and can be restricted to a limited period during the evolution of an epi-

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leptic syndrome.[5–8] Some patients may also have crying or ''dacrystic'' seizures.[6] Gelastic seizures have been reported, albeit rarely, in temporal[8] and frontal[9] lobe epilepsies, but the interest of this rare seizure type lies in its association with hypothalamic hamartomas (HH).[10–14]

In 1988 Berkovic et al.[15] provided the first comprehensive description of HH and ictal laughter, namely, ''early-onset gelastic epilepsy, hypothalamic harmatoma and precocious puberty syndrome''. This condition typically results in a catastrophic epileptic encephalopathy, which is usually refractory to antiepileptic therapy, but in most cases it is reversed by surgical excision,[16–19] radiofrequency thermocoagulation[20] or gamma-knife surgery of the HH.[21–23] Therefore, despite its rarity, this syndrome is of clinical relevance and an early diagnosis is important. Moreover, it provides a model for the study of epileptic mechanisms.[24] Indeed, GS originates from the HH,[20,25] and the HH seems to determine the evolution to a refractory epilepsy with multiple seizure types, either focal (frontal and/or temporal) or generalized. The latter frequently lead to symptomatic generalized epilepsy that mimics Lennox-Gastaut syndrome, and includes intractable epilepsy, cognitive impairment and severe behavioural disturbances.[15,26,27] Consequently, the epileptic syndrome described by Berkovic et al.[15] is also a model for pervasive autistic developmental disorders of childhood.[28] In addition, HH is itself the cause of precocious puberty and of autonomic ictal symptoms.[29,30]

The gelastic epilepsy-HH syndrome may determine a less severe epileptic disorder: precocious puberty is a not constant feature and, is probably infrequent.[31] Only some cases progress to secondary generalized epilepsy, and cognitive and behavioural disturbances can be mild or even absent. Thus, the severity of HH-related gelastic epilepsy ranges from a mild, drug-resistant, epilepsy in which GS are characterized by a simple ''pressure to laugh''[32] in otherwise normal patients, up to the catastrophic picture described by Berkovic et al.[15] It has been suggested that this spectrum of severity is related to the size of the HH.[32,33]

The aim of our study was to re-evaluate our patients with HH-related GS, and to delineate the spectrum of severity and the evolution of this syndrome, also in relation to therapeutic options.

Patients and methods

All data refer to patients with epilepsy characterized by GS and HH attending our Epilepsy Centre between 1986 and 2002. Some of these cases have been reported elsewhere.[31,33,34] Gelastic seizure was diagnosed according to Gascon and Lombroso,[4] namely ''GS is a stereotypic recurrence of ictal laughter inadapted to context, associated with other signs compatible with seizure and with ictal/interictal EEG abnormalities''. The study entry criteria were: GS as the only type of seizures referred, onset of epilepsy with GS, or GS as the most clinically relevant ictal phenomenon for at least 1 year, and recording of at least one GS by means of video-EEG or by EEG and directly observed by one of the authors.

Patients were also investigated for other seizure types and their onset age. All subjects underwent at least one brain MRI with a 0.5 or 1.5 T superconductive magnet, a spin-echo multiecho sequence and T1-PD- and T2-weighted images, by using 3-mm sections, in axial, transverse and coronal planes. Another T1-weighted sequence was used after intravenous injection of paramagnetic contrast medium (Gd-DTPA) (see Ref. [34] for further information about MRI procedures). We defined an HH ''small'' if it was less than 1 cm in diameter. Interictal ^{99m}Tc-HMPAO single photo emission computed tomography (SPECT) was performed in three cases. Adult patients underwent a battery of neuropsychological tests, according to our routine protocol.

Results

Between 1986 and 2002 we examined six patients (four male and two female) affected by HH-related GS. Their clinical data are listed in Table 1.

MRI findings

Detailed radiological findings of patients 1–4 and 6 are reported elsewhere.[34] In all cases, HH was sessile and attached to the hypothalamus. The diameter of HH ranged from 0.8 to 1.7 cm. The mass arises from the hypothalamus, and is attached to the tuber cinereum, between the pituitary stalk and the mamillary bodies. The mass was isointense to gray matter on T1-weighted images and was variably hyperintense on PD- and T2-weighted images, with no enhancement after Gd-DTPA administration, thereby demonstrating the integrity of blood–brain barrier. The mass extended upwards and pressed on the floor of the third ventricle in cases 2 and 4–6, and extended downwards into the interpeduncular cistern in case 3. In patient 1, the lesion extended upwards and downwards thereby displacing the hypothalamus and distorting the third ventricle.