Continuous giggling and autistic disorder associated with hypothalamic hamartoma

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Summary

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Summary : We present the case of a child affected since early infancy from recurring episodes of giggling mixed with stereotypical behaviours, mingled with head drops, and eventually with falls, in the context of an autistic disorder. Scalp video-EEG recordings revealed an epileptic encephalopathy with generalized slow spike-and-wave complexes alternating with electrodecremental periods, which generally corresponded to the onset of the aforementioned clinical sequences. A resection of a hypothalamic hamartoma was achieved at the age of two. Since then, after 22 months of follow-up, the child is totally free from the giggling and the drops, and the autistic behaviour significantly improved during the second year of follow-up. This case illustrates the difficulties to recognize some subtle ictal manifestations during infancy and childhood, and encourages the early surgical treatment of hypothalamic hamartomas when associated with epileptic encephalopathy and when technically possible.

Keywords : giggling, gelastic seizures, hypothalamic hamartoma, autism

ARTICLE

Introduction

The syndrome of hypothalamic hamartoma and epilepsy is distinguished by early-onset drug resistant seizures - mainly gelastic seizures, partial complex seizures, and drop attacks - linked to significant cognitive and behavioural disturbances [1-3]. Intrinsic epileptogenicity inside the hamartomas has been demonstrated by means of stereo-EEG and depth recordings [3-5] and ictal SPECT [5-7]. After early discouraging results [1], cumulative experience indicates promising results on sporadic cases and series of patients in whom the hamartoma (the epileptogenic lesion) has been removed or neutralized, mainly by means of surgical resection [3, 7-13], or gamma-knife radiotherapy [14]. Resective surgery can be technically difficult, particularly when the hamartomas have a sessile attachment (which is the most frequent form associated with epilepsy) and may carry a higher acute morbidity (even mortality); a worthy improvement of both seizures and behavioural disturbances has been shown in patients operated on, particularly if resection is complete or subtotal [3].

Case report

CCJ came under our observation at the age of 23 months. Previous history revealed a normal pregnancy and delivery, and no significant family history for epilepsy or neurological diseases. Physical and neurological examinations were normal. Cognitive and behavioral disturbances were evident. Parents had noticed that since birth the infant frequently emitted an unnatural cackle. From the age of three months, he also occasionally presented slight head noddings. These events were not taken into consideration until the age of 21 months, when more clear and intense episodes appeared many times per day. At the time of our evaluation, the main complaint was from unexpected head drops and eventual falls.
We performed a 24-hour video-EEG monitoring, using a BMSI 5000 Nicolet system. Interictal EEG consisted of very frequent paroxysmal activity with generalized slow spike-and-wave (SSW) complexes and bilateral irregular regional discharges on poorly organized wakefulness and sleep EEG patterns. Forty-four seizures were analysed in the context of a continuous stereotypical symptomatology recurring every few minutes during wakefulness and sleep. A spectrum of sequential symptoms could be recognized (video-EEG sequences). First (gelastic phase), the child began to giggle, sometimes mixed with a cackling whine, and tended to sit himself up and flap his arms while intermittently continuing to giggle. On other occasions he presented hyperpnea and rocking. Secondly (partial complex phase), he reduced his activity and presented some stereotypical slow-motion behaviours, such as clapping, caressing objects, or inclining the head while looking out of the corner of his eye. Thirdly (atonic phase), after some seconds of general arrest of activity, he exhibited a sudden forward head drop, occasionally affecting also the trunk. All of these symptoms sometimes presented themselves in a less precise sequence. Several nocturnal episodes included vomiting. Ictal EEG frequently consisted of a generalized attenuation of the paroxysmal activity which tended to persist while the gigging and complex symptoms continued. Occasionally, a clear-cut electrodecremental response was noticed at the beginning of the symptoms, but more frequently, only a partial reduction of the SW discharges was observed. The drops were related to a high amplitude diffuse slow transient followed by a sequence of low-voltage fast activity. Valproid acid therapy partially reduced EEG discharges, but gigging and stereotypes persisted.

The behavioural observation of the patient allowed us to diagnose (according to DSM-IV criteria) an autistic disorder. The most striking features were poor social interaction (he had no ocular contact, and did not share any interest for activities with others); poor communication (he was mute, non communicative and showed no symbolic play); and restrictive, repetitive and stereotypical behaviour with motor mannerisms.

An MRI examination revealed a well defined mass with a diameter of 1.5 cm, isointense to gray matter, attached to the tuber cinereum and the mamillary bodies, imprinting the floor of the third ventricle. No gadolinium enhancement was observed. Endocrinological study did not show any signs of precocious puberty. Because of the natural poor prognosis of the hypothalamic hamartoma and epilepsy syndrome, resection of the lesion was performed at the age of 2 years. Access to the mass was achieved through a right frontotemporal craniotomy. The floor of the third ventricle was opened and virtually complete removal of the tumor was performed. There were no significant neurological or neuroradiological (early or delayed) complications. Histopathologic analysis of the resected tissue showed typical features of hypothalamic hamartoma.

Over the following 22 months, on valproid acid therapy, serial video-EEG evaluations have revealed a complete control of gigging and the drops, and a consistent EEG normalization with preserved physiological background rhythms, normal sleep organization, and disappearance of paroxysmal discharges. A mild right fronto-temporal slowing has been related to previous craniotomy. The mental and psychopathological follow-up has shown evolutive changes. Since the surgery the bizarre cyclical behavioural sequences have no been longer observed, but initially he continued to show autistic features. At the age of 3 years and 3 months, the Battelle developmental inventory disclosed a developmental quotient of 33, equivalent to a global developmental age of 14 months, with a disproportion among cognitive (12 months), language (11.5 months), social (4 months), and motor (23 months) areas. At that age, the main psychopathological features were a restrictive span of behaviours and interests and an altered communication, although he had began to develop echolalic language and to improve his social interaction. He presented frequent bouts of rage with aggression towards himself as well as others, frequently related with refusal to eat. A new evaluation at the age of 3 years, 9 months disclosed a significant improvement of autistic behaviour. He did not show stereotypes, he had developed reciprocal interaction with the parents, language referential bisyllables, and symbolic play. Developmental delay, attention difficulties, restlessness and opposition to others persisted, but the diagnosis of PDD was no longer sustained.

Discussion

We described the case of a young child with a complex epileptic picture and an autistic disorder associated with a hypothalamic hamartoma. He experienced a complete cessation of seizures and EEG epileptiform activity and a significant-although delayed-improvement of the PDD after surgical resection of the lesion.

The hypothalamus, due to its connections to the amygdala, hippocampus, thalamus, and brainstem reticular formation, has a decisive role in the functioning of the rhinencephalic, limbic, autonomic and...
endocrine systems [15]. According to clinical and experimental knowledge, some of the highlights of the classical picture of hypothalamic hamartoma and epilepsy syndrome, such as gelastic seizures, EEG pattern with slow spike-and-wave complexes, and disturbed behaviour, may be related both to the location and the epileptogenicity of the lesion, causing disruption of thalamo-cortical and limbic circuits [16, 17]. In patients with this epileptic syndrome, a paroxysmal diencephalic dysfunction has indeed been documented as a hormonal and autonomic (sympathetic) release during the seizures [6, 18].

The main signs of our patient were the repetitive giggling since birth, the sequential bizarre behaviours, and the head and trunk drops in the context of an EEG epileptic encephalopathy. In patients with hypothalamic hamartoma gelastic seizures are the most distinctive epileptic feature. They can manifest themselves in different ways: as unnatural or inappropriate laughing or smiling [4, 6, 19, 20]; a pressure to laugh, (as described in adults with small hamartomas) [21]; or an early onset giggling, as in our case [2, 5, 7]. The latter symptom can be easily overlooked by parents and caregivers [2, 7]. Gelastic symptoms can be associated with other peculiar signs, such as crying [19] and running [5, 8]. Regarding the bizarre cyclical behaviours observed in our case during the video-EEG analysis, it was not entirely possible to differentiate them as complex epileptic automatons or signs of PDD itself. Nevertheless, their striking sequential association to the clearer epileptic signs as well as their disappearance after the resection of the hamartoma suggest an intrinsic relation to the seizure activity. Remarkable periodicity of spells characterized by giggling followed by other symptoms (hyperpnea and "cooing" respiration) has been previously observed in a child with hypothalamic hamartoma and epilepsy of neonatal onset [7]. Some authors have stressed the possibility of under-recognized "ictal stereotypes" in children [22, 23]. Deonna et al. [24] demonstrated a right orbito-frontal ictal onset on invasive subdural EEG recording in a boy with "behavioural seizures", mainly characterized by slow rhythmic clapping, vocalizations and staring. The head and trunk atomic drops recorded in our case were clinically similar to those observed in children with age-dependent epileptic encephalopathies such as Lennox-Gastaut syndrome. Those ictal phenomena could be explained by a rapid subcortical reticular involvement [3]. Atonic seizures in children with hypothalamic hamartoma have also been related to secondary epileptogenesis [4]. The most striking EEG features recorded in our child were an ictal pattern consisting of very frequent generalized SSW discharges plus irregular poorly distributed regional discharges, which experienced a paradoxical attenuation when the paroxysmal behavioural symptoms began. Surface EEG generalized attenuation is a common ictal pattern of gelastic seizures associated with hypothalamic hamartoma [2, 4]; no EEG ictal changes are also a possible finding [5, 6]. Munari et al. [4] demonstrated that diffuse flattening of the surface trace during laughing fits corresponded to low-voltage fast activity in the stereo-EEG recording inside the hamartoma.

Resection of the lesion in patients with the syndrome of hypothalamic hamartoma and epilepsy has been related to a significant improvement regarding seizures [3, 7-13], as well as behaviour and cognition [3, 5, 8-12]. In a recent series of Palmini et al. [3], 2 out of 13 patients remained seizure-free, 11 patients achieved a greater than 90% reduction of major seizures (drop attacks and generalized tonic-clonic seizures), and three cases experienced a dramatic improvement in behaviour and cognition.

In children with PDD and focal epileptogenic cortical lesions, PDD symptoms may or may not improve after epilepsy surgery, even if the surgery is successful with respect to seizure control [24]. In patients with hypothalamic hamartoma, the PDD has been directly related to the epileptic encephalopathy [20]; the social and affective/emotional disturbances has been associated to a possible disruption of neuronal connections between hypothalamus, cortical association areas, and hippocampus [25]. Although the neurobiology of autism is still poorly established, there is evidence pointing to a disorder of neural network organization [26]. Sporadic reports describe limbic lesions [27] or impaired pituitary functioning [28] in patients with autism. In our case, the significant behavioural improvement was delayed more than one year after surgery, whereas control of seizures and EEG paroxysmal dysfunction was immediate. That improvement was greater than that which may occur as a natural evolution in some children with autism at this age.

The HH, as an epileptogenic diencephalic lesion, can constitute a model which reproduces in some aspects the physiopathology of the age-dependent epileptic encephalopathies. In cases with associated autistic features, ictal semiology such as complex automatons may be hardly differentiated from symptoms of the PDD itself. The expected malignant evolution of the epilepsy and the autistic disorder may be reversed after the removal of the hamartoma.

CONCLUSION

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