Case Report

Surgical treatment for infantile spasms (West syndrome): a case report

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Keywords

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Abstract

We report the case of a 10-month-old boy with developmental regression parallel to apparition of symmetrical flexion spasms and hypsarrhythmia, characteristic of West syndrome. Brain magnetic resonance imaging showed an expansive entorhinal and right parahippocampal lesion. A right temporal lobectomy was performed. Pathological examination showed the presence of a low-grade oligodendrocyte-like glioneuronal tumor with a *BRAF V600E* genetic variant.

Our case highlights the role of the *BRAF V600E* genetic variant in the development of this refractory epileptic syndrome. In addition, it shows that surgery offers a potentially curative treatment for epilepsy in the subgroup of children with a focal brain lesion, particularly if surgical treatment is performed early.

Introduction

West syndrome is an epileptic encephalopathy specific to infants characterized by a triad of spasm clusters, hypsarrhythmia pattern on electroencephalogram (EEG) and developmental delay or regression. About 58% of patients present an identifiable etiology, including non-chromosomal brain malformations (53%), perinatal vascular, infectious or toxic injuries (25%), genetic abnormalities (17%) and other (5%) (1).

West syndrome is rarely caused by brain tumors, but their recognition is essential because the long-term epileptic and oncological prognosis is better with early surgical treatment (1-5).

Clinical case

A male infant was born at term from non-consanguineous parents, with a normal antenatal history and fetal ultrasounds. Neonatal adaptation was normal and developmental milestones were achieved. Family history was unremarkable. At the age of 10 months, the patient suddenly presented several breaks in eye contact with nodding flexion spasms, symmetric extension spasms of the four limbs and ocular revulsions, followed by crying. The neurological examination revealed weak eye contact, transient social smile and irritability. When pulled to a sitting position, axial hypotonia with poor head control and loss of sitting position was noted. Continuous video-EEG confirmed the diagnosis of West syndrome supported by interictal hypsarrhythmia during wakefulness and sleep, and several symmetrical spasm clusters. There was initially no lateralizing element on the EEG. Treatment by vigabatrin (up to 150 mg/kg/d) was initiated, leading to the disappearance of the spasms but persistence of the hypsarrhythmia on EEG after 12 days. Further treatment by adrenocorticotropic hormone (ACTH 6 UI/kg/2d) allowed improvement of the hypsarrhythmia after 10 days but lateralized interictal epileptiform discharges were then recorded during sleep, with right high voltage spike-and-waves. At that point, psychomotor abilities of the child started to improve.

The diagnosis of tuberous sclerosis complex was evoked but unlikely as he had no hypomelanotic macules. The urinary organic acid profile was normal. The brain magnetic resonance imaging (MRI) showed an expansive cortico-subcortical entorhinal and right parahippocampal lesion (Figure 1) associated with T2-weighted magnetic susceptibility phenomena, suggesting the presence of right calcifications, without contrast uptake. The methionine positron emission tomography scan revealed a hypermetabolic lesion.

Given the severe clinical presentation of epileptic encephalopathy, the association of right epileptic activities with a corresponding right temporal lesion justified a right temporal lobectomy at the age of 12 months, after multidisciplinary discussion.

The histological analysis of the sample found a low-grade oligodendrocyte-like lesion presenting "branched" vascularization and calcifications (Figure 2). The molecular assessment, based on a Next Generation Sequencing (NGS) analysis of a "Cancer panel", revealed the presence of a *BRAF*V600E mutation in the tumor cells. Follow-up via brain MRI confirmed the complete resection of the tumor with no recurrence over a period of three years.

At the age of four, the child has a normal motor and language development and is seizure-free without any antiepileptic drug.

Discussion

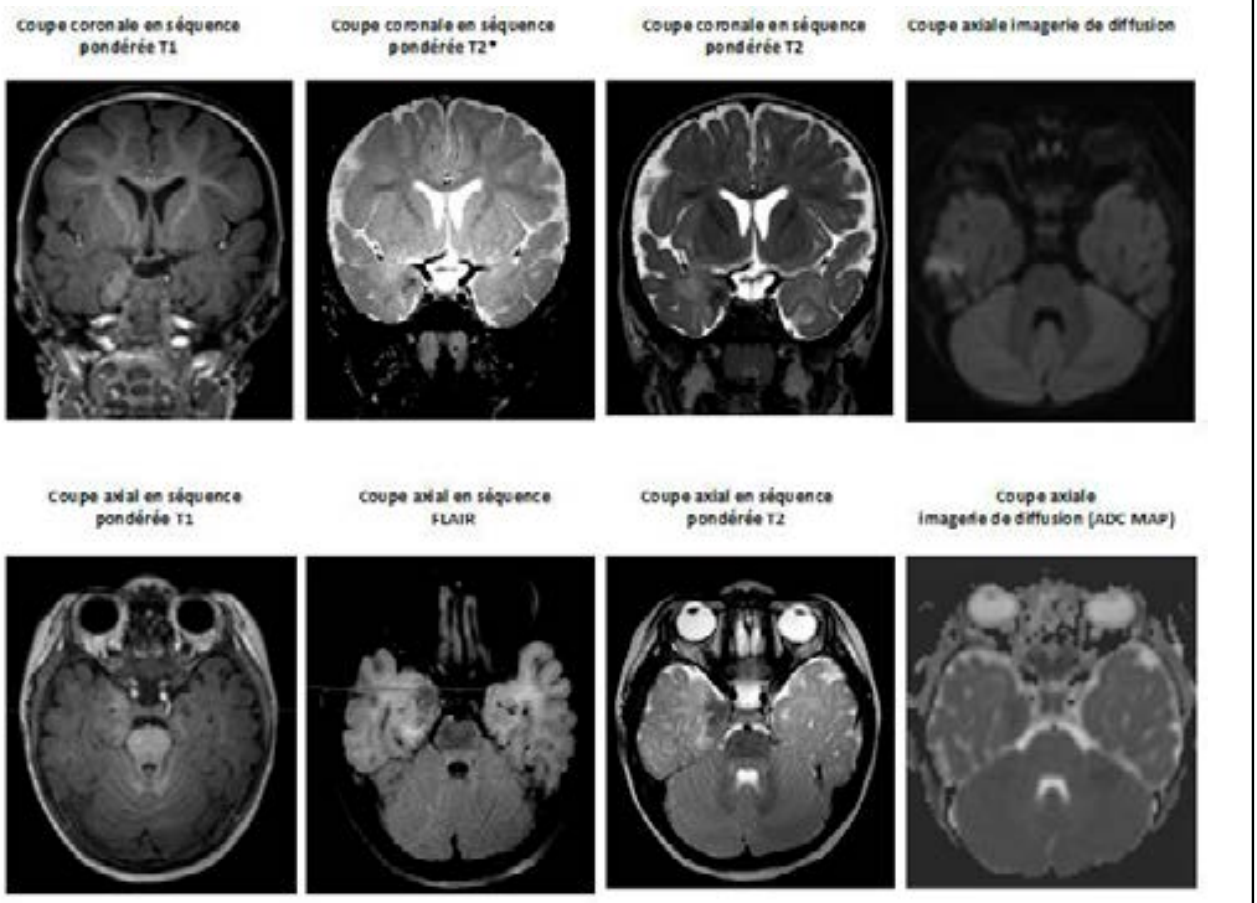
We report a case of West syndrome revealing a right mesiotemporal oligodendrocyte-like tumor, which was successfully treated by resective surgery. The child is seizure-free since then and could recover a normal development, illustrating the efficacy of surgical treatment in West syndrome caused by a single brain lesion.

The concept of epileptic encephalopathy states that the epileptic activity in itself can contribute to cognitive and behavioral disorders beyond what might be expected from the underlying pathology (6). Therefore cognitive disabilities are likely to get worse over time. This concept implies that antiepileptic drugs should eliminate not only seizures but also interictal epileptic activity on EEG, i.e. hypsarrhythmia in the case of West syndrome. Our case illustrates

Figure 1. **Cranial MRI**

MRI examination without administration of contrast agent (from left to right) using an axial and coronal plane with T1 weighted image sequence, a coronal plane with T2* weighted image sequence, axial FLAIR, coronal and axial planes with T2 weighted image sequence, and an axial plane with TRACE and ADC MAP-type diffusion imaging.

Hypersignal lesion to the cortex in T1 weighted image sequence centered on the right internal tem-poral cortex ; having a hyposignal appearance in T2* weighted image sequence, suggesting either hemosiderin deposition or a calcic content, hyposignal in appearance in FLAIR image sequence; characterized by a hyposignal appearance in T2 weighted image sequence surrounded by a dis-crete hypersignal area of perilesional edema; without restriction of diffusion coefficients in diffusion imaging.



this notion. As soon as the flexion spasms and hypsarrhythmia appeared, the patient showed developmental regression. The psychomotor skills were not improved by vigabatrin, which was efficient to treat the seizures but not the hypsarrhythmia. Interestingly, the child dramatically improved his performances with resolution of hypsarrhythmia after ACTH treatment and the resection of the brain tumor. His neurological development is now normal.

Several divergent opinions have evolved over the last decades regarding the treatment of infantile spasms. ACTH is used for the short-term treatment of infantile spasms but there is insufficient evidence to recommend the optimum dosage and duration of treatment (2).

Vigabatrin is possibly effective with a response rate of 30% and may be the treatment of choice in tuberous sclerosis with more than 50% patients seizure-free (2). A recent international multicentric, randomized trial found that combination therapy with hormonal therapy (ACTH or prednisone) and vigabatrin is significantly more effective than hormonal therapy alone to treat spasms (2).

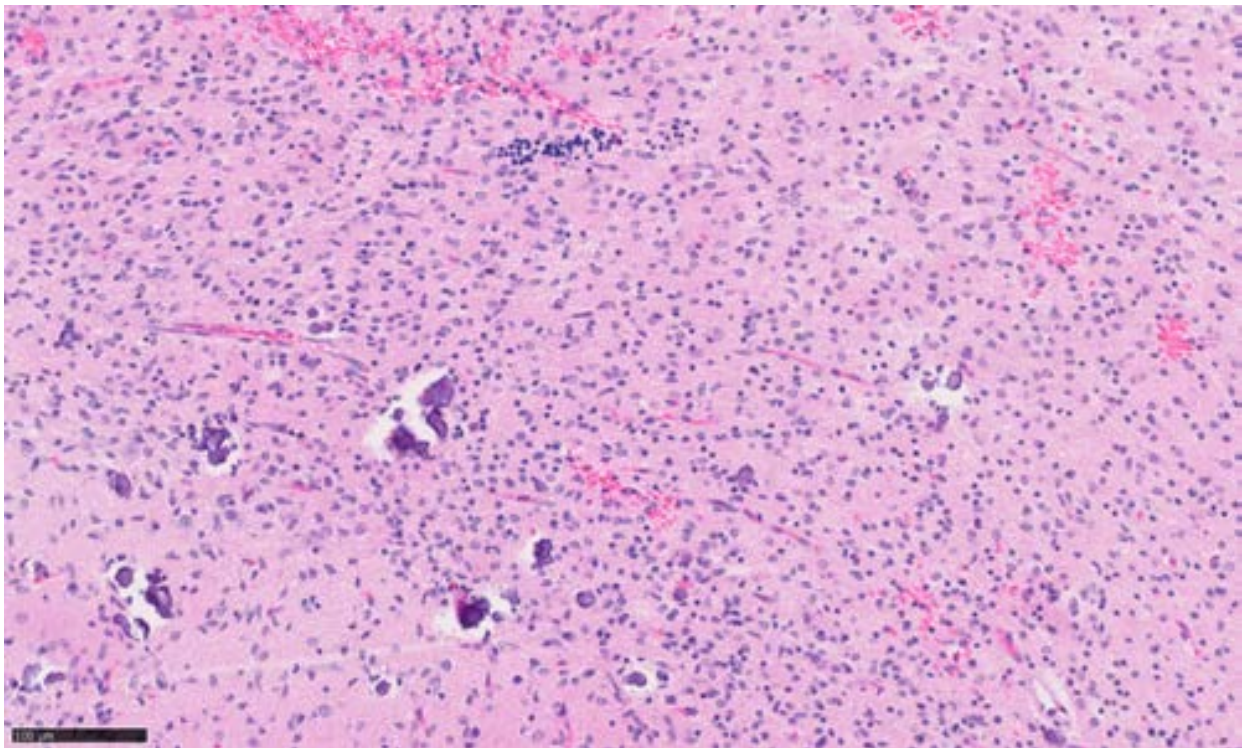
Moreover, in well-selected cases, a surgical treatment should also be considered. Obviously, the risk-benefit ratio favors an aggressive treatment (hormonal therapy or surgery) for the purposes of eliminating interictal epileptic activity and spams and therefore improving developmental outcome.

During the first three years of life, epilepsy has an incidence of 0.2% (7). Early childhood epilepsy has many different etiologies, with the thread of negative and persistent repercussions on health and quality of life. Almost 40% of children with epilepsy onset before three years present an abnormality - either a specific diagnosis (such as a cerebral malformation, tumor, metabolic disease, genetic disease, clinical dysmorphic syndrome) or a developmental delay of unknown etiology. This fact corroborates the necessity of performing a brain MRI in case of early-life epilepsy. Some of those children could develop a severe form of epilepsy such as West syndrome (7).

In 2018, a prospective observational study was conducted on 509 patients with epilepsy starting before the age of one year (8). They were divided into two groups of about 250 patients—those with infantile spasms (initially or within the first year), and those presenting another type of early onset epilepsy. The age of epilepsy onset was more widely distributed and occurred earlier in patients with early onset epilepsy without infantile spasms than in those with spasms (median of four versus six months) (8).The genetic analyses of 92 patients with infantile spasms revealed 50 known pathogenic variants (8). These genes were gathered according to the common biological pathways, the molecular functions they govern, and the cellular compartments where they are expressed. This revealed significant differences between the two groups. In the group of patients affected by infantile spasms, mutations of genes involved in cell body function, such as the Golgi apparatus and endoplasmic reticulum, were found, while the other group showed genetic abnormalities expressed in the axons, dendrites, nodes of Ranvier and synapses. Three molecular functions were overrepresented in the patients affected by infantile spasms, namely protein-protein interactions, the formation of molecular complexes, and the phosphorylation of proteins by protein kinases. The *BRAF*V600E genetic variant expressed by the tumor cells of our patient belongs to the last category of protein kinases.

In most patients, West syndrome appears before the age of one year, with peak incidence at six months of age. Irrespective of the etiology, the site of the cortical lesions influences the age of infantile spasms onset, depending on the cerebral lobe affected. Interestingly, the occurrence of this

Figure 2. Anatomopathological image illustrating the «oligodendrocyte-like » part.
Highly-vascular tumor proliferation in the form of a fine capillary network, associated with the presence of calcifications, consisting of oligodendrocyte-like cells with consistent nuclei or of cells with more fusiform, ovoid nuclei.



encephalopathy follows the normal maturation timeline of the central nervous system. Thus, the lesions in the occipital lobes are symptomatic earlier than the parietal/temporal lobes, which are symptomatic earlier than the frontal lobes. Most isolated cortical lesions are found in the temporal and parietal lobes, which coincide with the peak incidence of six months (9).

In addition, irrespective of the cause, patients born prematurely will develop spasms later and proportional to their prematurity, which strongly supports the hypothesis that this syndrome arises at a specific stage of brain development (8).

It appears then that in order to develop West syndrome rather than another type of epilepsy, different factors must come into play, such as the stage of cerebral maturation as well as specific metabolic pathways that are altered concurrently.

Some patients with West syndrome are candidates for a surgical tailored resection, when a focal epileptic onset zone is demonstrated. Those patients show comparable rates of epilepsy control than patients affected by other types of refractory epilepsy, with approximately 69% of patients seizure-free at six months and 50% at five years (10). Indeed underlying etiologies are similar, with 70% of brain malformations (cortical dysplasia, hemimegalencephaly, tuberous sclerosis), 13% of ischemia and rare cases of temporal low grade tumors (10). Nevertheless, the persistence of preoperative hypsarrhythmia is associated with poor outcome of mortality and cognitive development (10). Surgical treatment for infantile spasms with focal onset offers better control of epilepsy when performed earlier (<36 months) rather than later (>50 months) (4). The ideal surgical candidate carries a single MRI lesion or a single region of abnormal glucose metabolism concordant with the epileptic focus on EEG and clinical signs of lateralization during seizures or spasms (5).

Conclusion

West syndrome is a severe epileptic encephalopathy reputed to be refractory with a poor developmental outcome. In the case of West syndrome caused by a single brain lesion, early resective surgery offers a potentially curative treatment of epilepsy followed by a normal development outcome.

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