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Case Report

West syndrome in three patients with brain injury and a benign course

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ABSTRACT

Infants with West Syndrome and underlying structural pathology typically experience persistent symptomatic focal seizures and intellectual disability. We performed a retrospective case review of 84 patients with West Syndrome evaluated at one institution between 1990 and 2013. From this group we identified three patients with West syndrome and congenital hemiplegia who later developed genetic epilepsy features and had normal intellectual development. This outcome is highly unusual and raises important questions about the relationship and possible influence of genetic epilepsy in patients with pre-existent West Syndrome and brain injury.

1. Background

West Syndrome (WS) typically presents between the ages of 4 and 9 months with symmetric spasms, hypsarrhythmia and multifocal epileptiform discharges occurring in both cerebral hemispheres on EEG [1]. This pattern usually has a favorable prognosis with early spasm and hypsarrhythmia disappearance, and normal neurological development. The available literature supports the observation that normal or near normal development occurs in only 15–25%of patients with infantile spasms [2]. In contrast, a similarly favorable outcome in "symptomatic" or "with proven a symptomatic etiology" WS [1] is decidedly unusual. While genetic benign epilepsy can occur in patients with structural brain lesions symptomatic WS carries an exceptionally poor prognosis and is unlikely to evolve favorably [3].

We report three patients with early-acquired congenital hemiplegia who were diagnosed with WS yet had an excellent outcome. All three subsequently developed electroclinical features of the focal epilepsies of unknown etiology, one with occipital epilepsy and two with subclinical rolandic epileptiform discharges on EEG in both the injured and healthy cerebral hemispheres. One patient also had benign neonatal convulsions. Their courses raise important questions about the co-occurrence and relationship of both disorders in the same patient.

2. Case study

We performed a retrospective case review of 84 patients with infantile spasms followed at the Child Neurology Unit of the Maggiore Hospital of Bologna from 1990 to 2013.

From this group we identified 10 patients with congenital hemiplegia and WS. This subgroup yielded three patients who evolved with normal intelligence. At their first presentation, patients were tested using the Mental Scale of the Bayley Scale of Infant Development. Subsequent intellectual assessments employed the Leiter International Performance Scale of non-verbal intelligence. Adaptive functioning at school and social development assessment was provided by the parents. Neuromotor development was assessed clinically through the neurological examination. The three subjects had a mean of follow-up of 179 months (range 113–274 months). Seven additional patients (4 male; 3 female) evidenced intractable epilepsy and developmental delay at the end of the follow-up period (mean - 156 months; range - 102–254 months). Based on their course, they were excluded from the analysis. Patients provided a written informed consent.

2.1. Patient 1

A.C. was a male born at 41-week gestation after an uncomplicated pregnancy and delivery. Neurological development was delayed but cognition was normal. Clusters of epileptic spasms began at age 7 months. Awake EEG revealed unilateral hypsarrhythmia with intermixed electroclinical spasms (Fig. 1A). The hypsarrhythmia reappeared between spasms.

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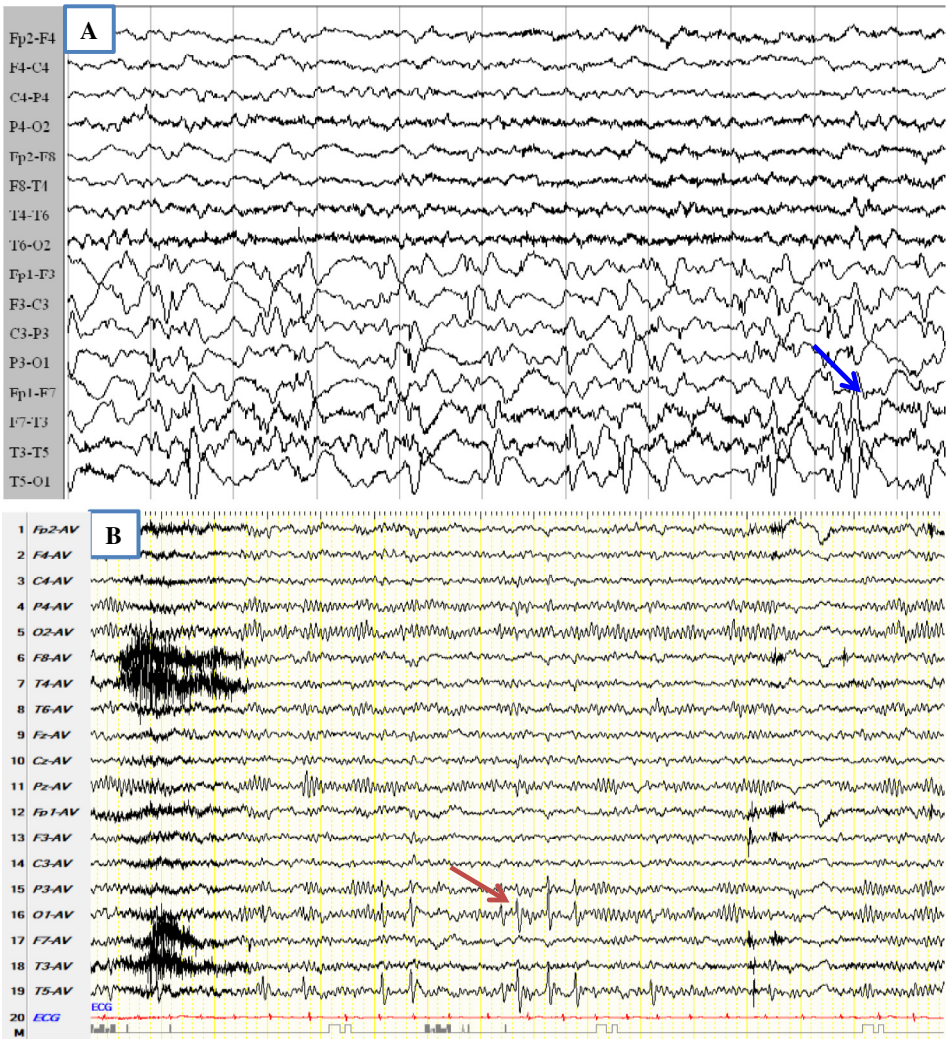

Fig. 1. EEG recording of a patient with WS and at follow-up. **A. Patient 1.** Awake EEG (sens 14.0 microV/mm; TC 0.10 s; HFF 50 Hz; paper speed 20 s/pg) several days after spasm onset (age 7 month) showing unilateral left hemisphere hypsarrhythmia with intermixed electroclinical spasm (blue arrow). **B. Patient 1.** Interictal awake EEG (sens 15.0 microV/mm; TC 0.10 s; HFF 70 Hz; paper speed 30 s/pg) at age 2 years 8 months revealing left temporo-occipital sharp waves (red arrow) that attenuate with eye opening. (For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this chapter.)

The neurological examination revealed motor and postural asymmetry consistent with a right hemiplegia. Laboratory, metabolic studies and ARX, CDKL5 and STXBP1 gene testing were normal. Brain MRI revealed a large porencephalic cavity in the left temporal–parietal region. He was successfully treated with IM synthetic ACTH 0.025 ml/kg per day utilizing a scalar dose protocol for 45 days which produced complete spasm remission and disappearance of the hypsarrhythmia. Following resolution of the spasms and hypsarrhytmia there was a gradual clinical improvement, both cognitive and psychosocial skills. At age 2 years 8 months, the patient experienced a single focal seizure characterized by blurred vision, mouth and eye deviation and preserved consciousness. An interictal EEG revealed left temporo-occipital paroxysmal abnormalities (Fig. 1B). No therapy was administered. At age 11 years and 3 months a second similar focal seizure occurred leading to the diagnosis of occipital epilepsy; the EEG was unchanged. No therapy was administered and there were no further seizures. The patient is currently age 13 years and 1 month and has normal intellect with excellent psychosocial outcome.

2.2. Patient 2

M.L. was a male born at 40-week gestation by Caesarean section after a pregnancy complicated by recurrent threatened miscarriage. Benign neonatal seizures appeared shortly after birth and responded promptly to phenobarbital (no gene testing was performed). Neurological development was delayed but cognition was normal. Clusters of epileptic spasms appeared at age 7 months. The waking interictal EEG revealed bilateral hypsarrhythmia (Fig. 2A). Polygraphic recording of the clusters revealed bilateral spasms coincident with the disappearance of the hypsarrhythmia and onset of diffuse rapid rhythms. Hypsarrhythmic EEG findings reappeared between spasms (Fig. 2B).

The neurological examination revealed motor and postural asymmetries associated with right hemiplegia. Brain MRI revealed multiple areas of altered signal in the left temporal region and basal ganglia. Laboratory, metabolic studies and ARX, CDKL5 and STXBP1 gene testing were normal. Intramuscular synthetic ACTH produced complete cessation of spasms and disappearance of the hypsarrhythmia. Treatment with phenobarbital was continued. Gradual clinical improvement, both cognitive and psychosocial skills, followed the disappearance of the spasms and hypsarrhythmia was observed.

At age 4 years and 9 months diphasic sharp waves with a positive frontal dipole in bipolar and referential montages, were observed from the healthy right hemisphere without clinical seizures (Fig. 3A). The EEG normalized at age 5 years. Frequent seizures re-appeared at age 14 years and were characterized by right arm paresthesias that responded to oxcarbazepine (30 mg/kg/die). An EEG was normal. The

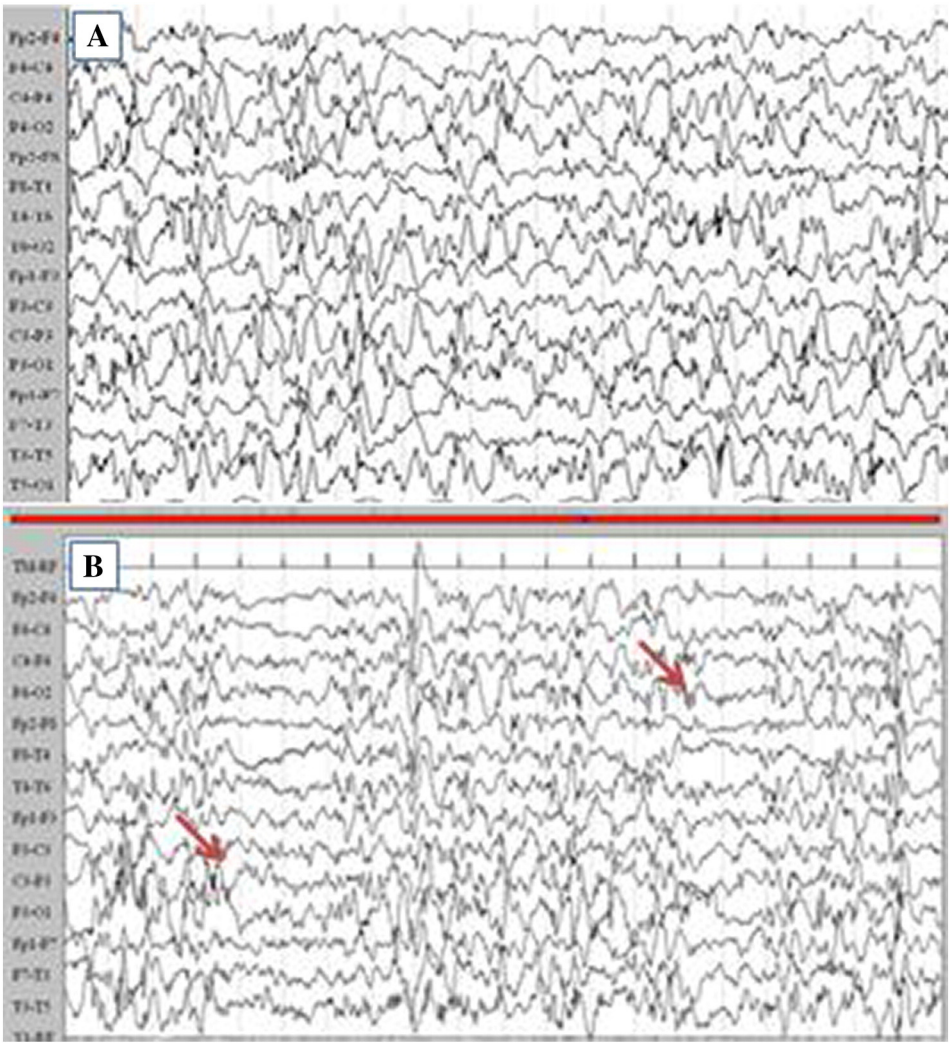

Fig. 2. Interictal and ictal EEG recording during WS in Patient 2. (A) Interictal EEG during sleep (sens 14.0 microV/mm; TC 0.10 s; HFF 50 Hz; paper speed 20 s/pg) of several days after spasm onset (age 7 month) showing bilateral hypsarrhythmia. **B. Patient 2**: Ictal awake EEG (sens 14.0 microV/mm; TC 0.10 s; HFF 50 Hz; paper speed 20 s/pg) several days after spasm onset (age 7 month) showing two consecutive bilateral spasms (red arrows). Diffuse rapid rhythms and attenuation is concomitant with each spasm. The hypsarrhythmia returned between spasms. (For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this chapter.)

patient is now age 23 years 5 months and has normal intellect with excellent psychosocial outcome.

2.3. Patient 3

A.M. was a male born at 32-week gestation by Caesarean delivery. Neurological development was delayed but cognitive ability was preserved. Clusters of epileptic spasms began at age 8 months. The awake interictal EEG revealed bilateral hypsarrhythmia. Polygraphic recording of a typical cluster revealed bilateral spasms associated with disappearance of the hypsarrhythmia and diffusely rapid rhythms. The neurological examination revealed motor and postural asymmetry attributable to a right hemiplegia. Laboratory, metabolic studies and ARX, CDKL5 and STXBP1 gene testing were normal. Brain MRI revealed diffuse cortical atrophy seen predominantly in the left hemisphere.

Vigabatrin (150 mg/kg/die) produced incomplete seizure control. Subsequent treatment with IM synthetic ACTH induced spasm remission and disappearance of all EEG abnormalities. Vigabatrin was subsequently withdrawn leading to a steady improvement in cognitive development.

At age 4 years 7 months an EEG revealed rolandic spikes arising independently in both cerebral hemispheres without clinical seizures (Fig. 3B). The EEG normalized seven years later. The patient is now age 10 years 1 month and has normal intellect with excellent psychosocial outcome.

3. Discussion

We report three patients with a favorable evolution despite an initial presentation of congenital hemiplegia and WS. All subsequently went on to manifest childhood epilepsies characterized by either occipital seizures or interictal rolandic discharges. One also had benign neonatal convulsion. None of the other seven patients with congenital hemiplegia and WS had EEG changes characteristic of the benign focal epilepsies or experienced similarly favorable neurodevelopmental outcomes. This evolution is both rare and unpredictable in infancy. We did not observe any markers in infancy that distinguished these three patients from the others in the cohort.

The long-term emergence of both focal epilepsy and the benign clinical course after an initial presentation of WS in patients with brain injury raises several important clinical issues. Firstly, this favorable evolution is inconsistent with the tacit assumption that the genetic focal epilepsies are unlikely to manifest in patients with WS and structural brain lesions. This situation is not entirely unexpected however as the existence of structural lesions in patients with focal and

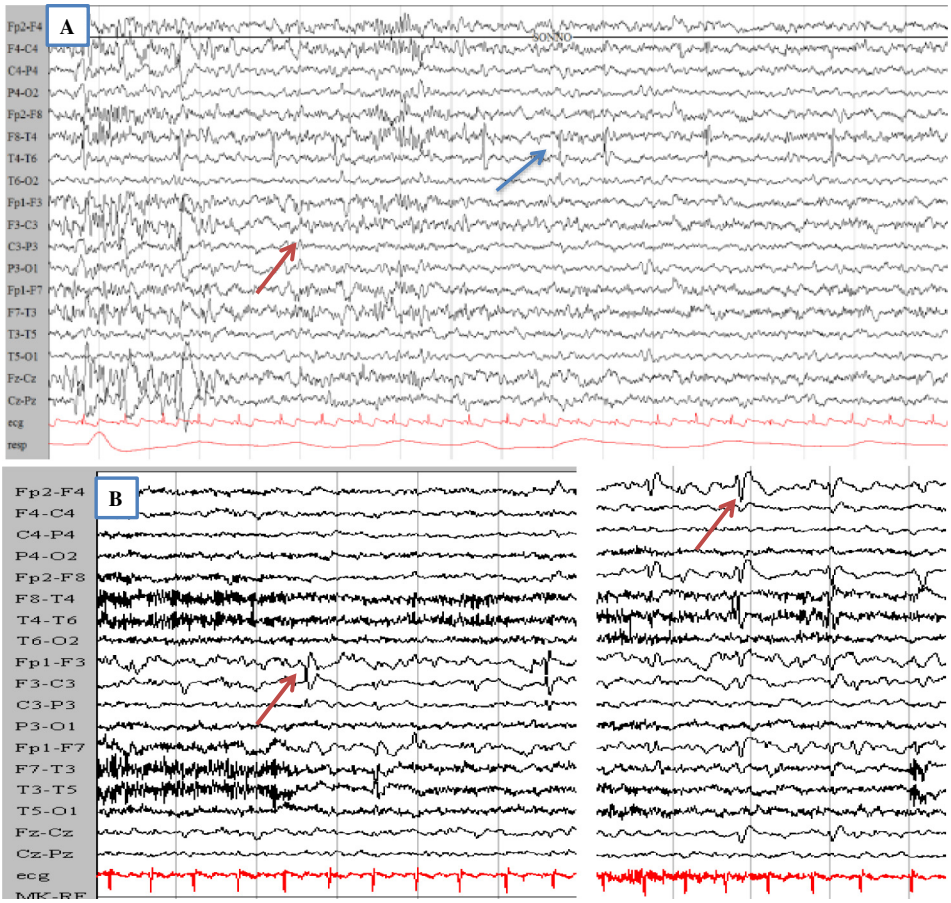

Fig. 3. Rolandic spikes in Patients 3 during follow-up. (A). Interictal awake EEG (sens 14.0 microV/mm; TC 0.10s; HFF 50 Hz; paper speed 20 s/pg) at age 4 years 7 months of age showing rolandic spikes in the healthy right hemisphere (red arrow). (B). Two examples of the interictal awake EEG (sens 14.0 microV/mm; TC 0.10 s; HFF 50 Hz; paper speed 20 s/pg) at age 4 years 7 months showing rolandic spikes in the injured and healthy hemispheres (red arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the online version of this chapter.)

generalized epilepsy associated with genetic origins is a well-recognized phenomenon [3]. Patients with WS due to an underlying stroke and a favorable long-term course have also been described [4]. A 14 year old girl with rolandic seizures after a traumatic brain injury reportedly had a good outcome [3].

The full preservation of long-term cognitive status in patients with structural hemispheric brain injury is even more unusual, particularly for patients with an epileptic encephalopathy. Thus, while structural pathology in patients with benign focal epilepsies is well described, prevalence of the overall combination of structural brain pathology, infantile spasms, epileptic encephalopathy and normal cognition is relatively unknown.

Similar EEG abnormalities were identified in the normal sibling of one of our patients (patient No. 3) provide additional confirmation that the patient's focal epilepsy was genetic rather than symptomatic in origin. While it is possible that an acquired cortical lesion could somehow activate an underlying genetic predisposition [5], focal epileptiform discharges on EEG characteristic of benign focal epilepsy in our cases did not arise in structurally abnormal tissue and were functionally independent. This situation is therefore similar to patients with successful excisional surgical procedures for focal epilepsy due to a structural lesion who also experience combined remission of a benign focal epileptiform discharge on EEG [3].

Our first patient exhibited interictal epileptiform discharges in proximity to a prior cerebral infarction. This could be interpreted as a symptomatic process. While several studies have shown morphological differentiation between genetically determined and symptomatic rolandic discharges, no firm consensus has been established. We note however that the appearance and disappearance of rolandic discharges in our patients was more consistent with the typical maturational course of an genetic focal epilepsy.

The rapid and complete response of WSto medical treatment in all three patients is more typical of genetic focal WS. We recognize however that although rare, a rapid response to corticosteroid therapy in patients with symptomatic WS may occur. However all three of our steroid-responsive symptomatic patients also ultimately exhibited EEG features of benign focal epilepsy. Furthermore, the EEG features of WS in our patients were remarkably similar to those described for the non-symptomatic WS [1]. In fact, the interictal EEG showed a hypsarrhythmia recovering between each spasm cluster and disappearing relatively early.

Our sample is obviously too small to make any inferences beyond noting the association, but investigating a larger cohort might further document the frequency of this improbable association and better assess its significance. We recognize that the absence of comprehensive genetic screening in all three patients is a limitation of our study. However, our goal was not to describe a new genetic syndrome but rather to bring attention to the good clinical outcome in three patients with West syndrome who shared several important characteristics. Genetic diagnosis is a future goal in this population. While the rapid and complete treatment response would be expected to significantly diminish the burden of epileptic encephalopathy, it should not alter the

cognitive prognosis of early-acquired unilateral hemispheric destruction. The probability of a completely normal intellect in patients with brain injury and WS with brain injury is unusual and we do not have a good explanation. We speculate that their acquired lesions somehow promoted a different and more favorable pathway for inter-hemispheric reorganization [6]. We note further that a focal epileptiform discharge in structurally preserved contralateral cortex in all three patients was not associated with adverse cognitive consequences.

Declaration of interest

None of the authors has any conflict of interest to disclose.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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