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Case Report

Wolf–Hirschhorn (4p-) syndrome with West syndrome

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ABSTRACT

Wolf–Hirschhorn syndrome (WHS) is a chromosome disorder (4p-syndrome) which is characterized by craniofacial features and epileptic seizures. Here, we report a case of WHS with West syndrome, in whom the seizures were refractory to several antiepileptic drugs but were responsive to the addition of lamotrigine. The patient had epileptic spasms at age seven months. The interictal electroencephalogram was hypsarrhythmic. After adding lamotrigine, seizures decreased remarkably, and spasms disappeared. We have identified and described the very rare case of a girl with WHS who also developed West syndrome. In this case, adding lamotrigine to her medications effectively treated the spasms.

1. Introduction

Wolf–Hirschhorn syndrome (WHS) is a chromosomal disorder (4p-syndrome) characterized by the resemblance of craniofacial features to an ancient "Greek warrior helmet", growth delay, congenital hypotonia, mental retardation, and epileptic seizures [1]. Several patients have been diagnosed with WHS, but in whom a 4p16.3 microdeletion can be detected only by molecular probes on apparently normal chromosomes [2]. As a result of overlapping deletion analysis, the area currently regarded as the WHS critical region (WHSCR) is restricted to the 165-kb interval on 4p16.3 [3]. Three different genes have been independently described as candidates for inducing WHS. Of these, *WHSC1* overlaps the distal boundary of the WHSCR [4], whereas *WHSC2* is entirely within the WHSCR [3]. The third candidate gene, the WHSCR-flanking leucine zipper/EF-hand-containing transmembrane (*LETM1*) gene, is involved in $Ca2^{+}$ signaling; thus, it is considered an excellent candidate gene for WHS and, in particular, for WHS-associated seizures [5,6].

Epilepsy is one of the major concerns for parents and professionals caring for children with WHS. Seizures tend to occur in over 90% of the patients, with onset within the first 3 years of life and with a peak incidence at around 6–12 months of age [7]. The seizure types are unilateral clonic or tonic seizures evolving to bilateral convulsion, generalized tonic-clonic seizures, or atypical absences [1]. The epilepsy in WHS is generally well controlled with monotherapy such as phenobarbital for tonic–clonic seizures and valproate or ethosuximide for absence seizures [8]. Sodium bromide in the past has been effective for the prevention of unilateral and generalized tonic–clonic seizures and status epilepticus [9]. The electroclinical findings in epilepsy with WHS are divided into two patterns. The first pattern consists of anterior, posterior, or diffuse high voltage, 2- to 3-Hz slow waves, on which notches or spikes superimpose. This pattern is observed in both interictal and ictal periods in the patients with atypical absence or myoclonic seizures. The second pattern consists of bursts of posterior rapid, repetitive spikes. There has been only one report of a case with WHS who developed West syndrome [8], a triad of clinical signs including flexor or extensor spasms, often involving the extremities and head/neck, hypsarrhythmia on electroencephalogram (EEG), and subsequent or concurrent cognitive delay.

Here, we report a case of WHS with West syndrome, in whom the seizures were refractory to several antiepileptic drugs but were finally responsive to the addition of lamotrigine.

2. Case report

A six-year-old girl who was the first child of nonconsanguineous, healthy parents was brought to the hospital. There were no familiar histories of epilepsy or other neurological disorders. Her history included severe intrauterine growth restriction. She was born at 36 weeks gestation with a birth weight of 1360 g (−3.5 standard deviations (SD)), a body length of 39.0 cm (−2.8 SD), and a head circumference of 27.3 cm (−3.2 SD). Her Apgar score was 9 at 5 min. Abnormal craniofacial

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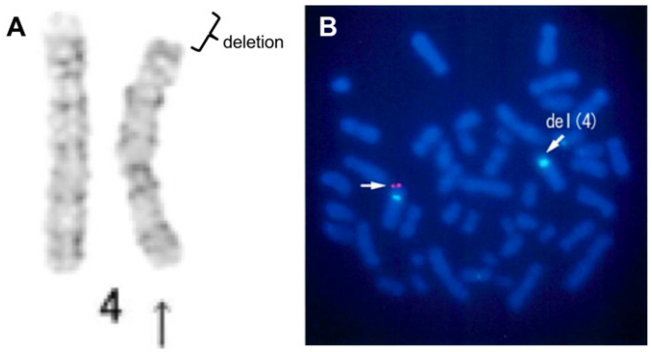

Fig. 1. Diagnostic analyses. A: The G-banding test showed the patient to have a normal 46, XX karyotype but a deletion of the most terminal portion of the short arm of chromosome 4. B: Fluorescence in situ hybridization (FISH) analysis identified a deletion of the 4p subtelomere in chromosome 4p15.3. The Wolf–Hirschhorn syndrome (WHS) critical region (WHSCR) is shown in red, and the control is shown in green.

features, including the "Greek warrior helmet" appearance her facial features involved her nose with micrognathia and low-set ears, were indicated. She was diagnosed with WHS after a G-banding test identified that her karyotype was a normal 46, XX, and there was a deletion of the most terminal portion of the short arm of chromosome 4. Fluorescence in situ hybridization (FISH) demonstrated a deletion of the 4p subtelomere, specifically in chromosome 4p15.3 (Fig. 1). Echocardiography revealed an atrial septal defect and pulmonary artery stenosis. At 2 months of age, she presented with clonic seizures involving her right arm. The interictal EEG showed spikes, sharp waves, and sharp & slow waves at multiple foci. Magnetic resonance imaging showed neither brain malformation or other structural abnormality.

Phenobarbital reduced the seizure frequency during early infancy. At age seven months, the seizures evolved to epileptic spasms that were refractory to valproate, clonazepam, and zonisamide. The interictal EEG was hypsarrhythmic (Fig. 2A). Lamotrigine and levetiracetam were able to temporarily reduce seizure frequency. Adrenocorticotropic hormone therapy was avoided because of her cardiac anomalies. The untreated epileptic spasms occurred about 50 times per day. Until age 4 years and 3 months, she was treated with clonazepam (0.15 mg/kg/day), topiramate (13 mg/kg/day), and levetiracetam (45 mg/kg/day). However, her epileptic seizures persisted. At age 4 years and 4 months, we once again tried adding lamotrigine to her other antiseizure medications. After 3 months of lamotrigine (1.0 mg/kg/day) polytherapy, seizures decreased remarkably, and epileptic spasms disappeared. At age 4 years and 6 months, the EEG demonstrated epileptic discharges consisting of spikes or sharp waves were no longer present (Fig. 2B). At the last follow-up, age 6 years and 3 months, the epileptic spasms had disappeared.

3. Discussion

To our knowledge, there had been only one patient with WHS who also developed West syndrome [8]. In that previous case, epileptic spasms appeared at age 6 months, and the patient's sleep EEG showed a hypsarrhythmic pattern interrupted by electrodecremental activity heralded by a spasm. Phenobarbital was transiently effective for the focal seizures.

In the present case, FISH revealed partial deletions of the area distal to 4p15.3 with a 4p subtelomeric probe. The proximal boundary of the WHSCR was defined by the identification of two individuals with all 4 components of the core WHS phenotype and with deletions of 4p16.3 that include the proposed candidate genes *LETM1*, *WHSC1*, and *WHSC2* [5]. However, it remains unclear whether the type and severity of seizures in patients with WHS correlates with the deletion size.

The addition of lamotrigine was effective in stopping the epileptic spasms in our patient when added to clonazepam, topiramate, and levetiracetam. The most likely mechanism underlying lamotrigine treatment is the inhibition of voltage-gated sodium channels, which stabilizes neuronal membranes and consequently modulates presynaptic neurotransmitter-like release of excitatory amino acids. Lamotrigine increases the concentration of Ca^{2+} through the activation of the phospholipase C-1,4,5-trisphosphate receptor/ryanodine receptor pathways and through calcium-/calmodulin-dependent protein kinase II activation in the dorsal root ganglionic neurons. Lamotrigine has also been shown to inhibit glutamate hyperexcitability by suppressing voltage-dependent Na^{+} and Ca^{2+} channels [10]. Recently, the *LETM1* gene was identified as

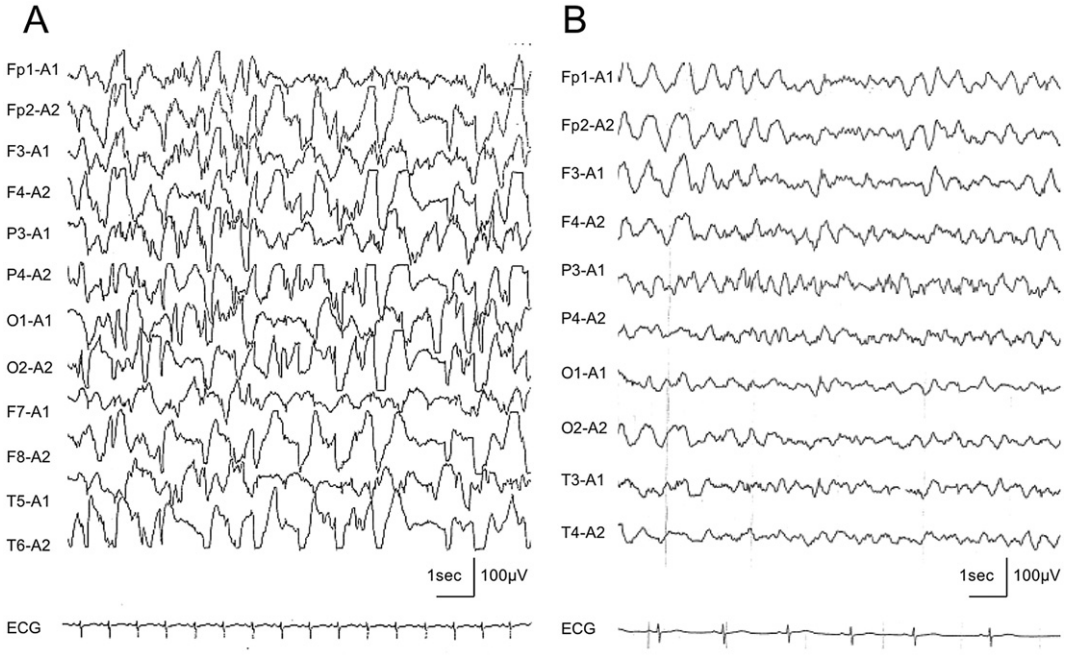

Fig. 2. Electroencephalographic (EEG) data. A: At age seven months, the patient's interictal EEG demonstrated a clear hypsarrhythmic pattern. B: At age four years, the EEG had returned to normal after lamotrigine polytherapy.

critical for the appearance of epilepsy in WHS [7,8,11]. It encodes a putative Ca^{2+} binding protein that regulates Ca^{2+} signaling and homeostasis [5]. In our patient, the addition of lamotrigine to her other antiseizure drugs might have reduced the epileptic spasms by increasing the concentration of Ca^{2+}.

In conclusion, we have identified and described the very rare case of a girl with WHS who also developed West syndrome. In this case, the addition of lamotrigine to her other antiseizure drugs effectively treated the epileptic spasms.

Conflicts of interest

None.

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