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.

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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 Ca2+ 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 Ca2+ channels [10]. Recently, the LETM1 gene was identified as
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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