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Case Report

Successful treatment of migrating partial seizures in Wolf–Hirschhorn syndrome with bromide

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Abstract

A girl with mild psychomotor developmental delay developed right or left hemiclonic convulsion at 10 months of age. One month later, clusters of hemiclonic or bilateral tonic seizures with eyelid twitching emerged, resulting in status epilepticus. Treatment with phenobarbital and potassium bromide completely terminated the seizures within 10 days. Ictal electroencephalography revealed a migrating focus of rhythmic 3–4 Hz waves from the right temporal to right frontal regions and then to the left frontal regions. Genetic analysis was conducted based on the characteristic facial appearance of the patient, which identified a 2.1-Mb terminal deletion on chromosome 4p. This is the first case of Wolf–Hirschhorn syndrome complicated by epilepsy with migrating partial seizures.

Keywords: Status epilepticus; 4p-Syndrome; Bromide; Migrating partial seizures in infancy

1. Introduction

4p-Syndrome or Wolf–Hirschhorn syndrome (WHS) is a contiguous gene deletion syndrome characterized by a distinctive facial appearance, growth impairment, intellectual disability, and seizures [1]. Individuals with various deletion sizes demonstrate that critical genes for these core manifestations reside within the 1.9 Mb terminal of the short arm of chromosome 4. Haploinsufficiency of *LETM1* at 1.9 Mb from the telomere was considered to be responsible for the seizure phenotype; however, another seizure locus has also been postulated in the 0.76–1.3 Mb region [2].

Migrating partial seizures in infancy (MPSI) is an epileptic syndrome with typical onset before 6 months of age. It is characterized by an ictal electroencephalography (EEG) pattern of polymorphic, rhythmic epileptiform discharges independently and sequentially arising from both hemispheres. Mutations in genes encoding subunits of Na^+ and K^+ channels, Na^+–Cl^- cotransporter, and glutamate transporter, have been identified to be responsible for MPSI.

Seizures in WHS and MPSI are often refractory to anti-epileptics; however, bromide is effective for seizure control in both of these entities [3,4]. Here we report the case of a WHS whose seizure phenotypes were compatible with those of MPSI and were successfully controlled with potassium bromide (KBr).

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2. Case report

The girl was born to non-consanguineous parents at 38 gestational weeks with 1538 (−3.6 SD) g birth weight, 40.0 (−4.0 SD) cm body length, and 29.4 (−2.5 SD) cm head circumference. She was intubated and tube fed for 1 week; however, thereafter, her clinical course was unremarkable. She gained social smile at 2 months of age, head control at 4 months, rolling abilities at 9 months, and sat unsupported at 10 months. Her developmental quotient was assessed as 39 by Enjoji developmental scale (Tokyo, Japan, 1976). G-band chromosomal analysis revealed normal female karyotype of 46, XX. Intermittent ocular convergence appeared at 3–6 months but spontaneously disappeared.

She experienced her first convulsive seizure at 10 months, which was preceded by recurrent vomiting and manifested with left facial twitching and successive propagation to left clonic hemiconvulsion. Two weeks later, right clonic hemiconvulsion with ocular deviation to the right side developed. These episodes lasted >30 min and were terminated with an injection of antiepileptic agents. EEG and brain magnetic resonance imaging were unremarkable; 9 mg/kg/d carbamazepine was initiated. However, recurrent episodes of sudden gazing with smacking and stereotypic limbs movements emerged 1 week later, with each one lasting up to several minutes and occasionally accompanied by cyanosis. These episodes increased in frequency within a few days and were not completely suppressed by 0.3 mg/kg/h midazolam infusion. The patient was then transferred to Tottori University Hospital when seizures repeatedly appeared with right eyelid twitching, oral smacking, clonic movements to extremities on the right side, and occasional bilateral involvement. On examination, the patient was 66.5 (−1.8 SD) cm in height, 6.6 (−2.2 SD) kg in weight, and 40.0 cm (−2.9 SD) in head circumference. Frontal and glabellar bossing, arched eyebrows, and a short philtrum were noted. Although mild, generalized hypotonia was noted, the patient could track moving objects with both eyes and vertically elevated her head in the prone position during inter-ictal periods.

Ictal video-EEG was recorded after admission when a seizure type involving the right eyelid twitching, tonic elevation of the lower limbs in flexion, and intermittent elevation of both upper limbs was predominant. On EEG during wakefulness, right temporal slow waves appeared first, which then migrated to the right frontopolar area (Fig. 1A). The right eyelid twitching insidiously appeared at this point; tonic elevation of lower limbs with left predominance emerged when slow activity was augmented (Fig. 1B). This lasted for approximately 1 min, followed by a clinical appearance of motionless staring associated with bifrontal slow activity on EEG (Fig. 1C). Within 1 min, upper limbs were raised in the extension posture; tonic elevation of lower limbs in flexion posture also appeared (Fig. 1D). Upper limb elevation lasted for <1 s and repeated with an interval of approximately 10 s. This phase lasted for 1 min, followed by an unresponsive state for several minutes (Fig. 1E). The patient then resumed responses to visual and tactile stimuli and the usual body movements (Fig. 1F). On some occasions, such seizures occurred in clusters without recovery of consciousness and could be regarded as status epilepticus. Under continuous midazolam infusion, phenobarbital and KBr were initiated on admission day 2 and 4, respectively. The seizure frequency rapidly decreased over 2 days and disappeared after day 8 (Fig. 2). Slow waves on inter-ictal EEG gradually ameliorated. We terminated midazolam infusion without seizure recurrence. The patient has been seizure free for 7 months; her developmental quotient was assessed as 35 at 1 year and 5 months of age, when she could handle toys with both hands in unsupported sitting posture.

After informed consent was obtained from the parents, genetic analyses was conducted based on the facial characteristics. Fluorescent in situ hybridization analysis for WHS revealed a deletion of one of the 4p terminal regions, whose size was assessed as 2.1 Mb by comparative genomic hybridization (CGH) array analysis (Fig. 3).

3. Discussion

Approximately 90% of WHS patients suffer from epilepsies, most often during infancy with seizure types of generalized tonic–clonic, clonic, or alternating hemiconvulsions as well as myoclonus, tonic spasms, or complex partial seizures. Particularly, half of WHS patients experience status epilepticus by 3 years of age, which can be fatal [1]. The seizure type of prolonged hemiconvulsions in the present patient was compatible with these features. However, the development of migrating partial seizures in WHS has never been reported. The findings of ictal EEG were reminiscent of those in MPSI in that polymorphic and rhythmic slow waves alternatively emerged in ipsilateral and contralateral hemispheres [5]. Meanwhile, epileptic foci in WHS are usually located in the parietal lobe and less frequently in the central or occipital regions, not in the fronto-temporal regions as seen in the present patient [6,7].

Another characteristic issue in our patient was that she had a 2.1 Mb 4p terminal deletion, which is a relatively small size among WHS patients. Shimizu et al. found that deletions >6 Mb resulted in earlier epilepsy onset and susceptibility to status epilepticus [2]. Conversely, another report revealed no correlation between the deletion size and seizure type, severity, and onset age of epilepsy [1]. In the 1.9 Mb terminal of the 4p16.3 chromosomal region responsible for WHS phe-