■ Clinical commentary

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Epileptic Disorders

Possible critical region associated with late-onset spasms in 17p13.1–p13.2 microdeletion syndrome: a report of two new cases and review of the literature

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ABSTRACT

17p13.1-2 microdeletion syndrome is a congenital anomaly syndrome with characteristic facial features and multiple malformations. The prevalence of epilepsy with 17p13.1–2 microdeletion is low, with only one case reported for late-onset spasms. Late-onset spasms is one of the rare epilepsy syndromes and one of the developmental epileptic encephalopathies requiring urgent treatment. We experienced two cases of 17p13.1-2 microdeletion syndrome, one of which presented with epileptic spasms in cluster at 18 months of age. EEG showed symmetrical hypsarrhythmia during interictal periods and a paroxysmal fast wave superimposed on widespread slow waves during seizures, leading to the diagnosis of late-onset spasms. Another case had no epilepsy. Comparing the extent of deletion in the two cases with that of previous reports, the involvement of the *USP6* gene was suspected. However, the accumulation of additional case reports is needed to confirm the genetic involvement in late-onset spasms.

Key words: 17p13.1–13.2 microdeletion, late-onset spasms, epileptic spasms, *USP6*, NMDA

The 17p13.1 microdeletion syndrome is a congenital syndrome with characteristic facial features, including a flat face, straight eyelid fissures, interocular segregation, a broad nasal bridge and backward-rotated ears as well as intellectual disability, ocular hypertelorism and coloboma, sacrocaudal skin depression, scoliosis, accessory or inverted nipple, pectus excavatum and congenital heart disease [1]. There are 16 previous case reports associated with 17p13.1 microdeletion [2-8], three of which are related to epilepsy; myoclonic epilepsy, focal epilepsy and late-onset spasms (LOS). LOS is one of the rare epileptic syndromes, affecting about 3-5 per 10,000 live births, and is a developmental epileptic encephalopathy that requires urgent treatment and pathogenetic investigation [9]. Recently, the genetic pathogenesis of epilepsy has been studied using methods, such as comparative genomic hybridization (CGH) array and whole-exome analysis, and treatments for the causative

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pathology have been developed. This technique has revealed microdeletions, such as 2q24.3, 5q14.3, 9p34, *etc*., also related to the development of LOS [10]. The purpose of the present report was to describe two further cases of 17p13.1-p13.2 microdeletion syndrome.

Case studies

Written informed consent for publication was obtained from the parents.

Case 1

The patient, a boy, was born at 41 weeks and six days without fetal distress. His family history was unremarkable. Immediately after birth, he displayed abnormal eye movements. He was admitted to hospital for a thorough examination at six months, because he showed a lack of neck control, visual fixation and severe developmental delay. He had a peculiar facial appearance with telecanthus, strabismus, a low nasal bridge, low-set ears and a high arched palate. In addition, pectus excavatum, accessory nipple, right-sided cryptorchidism and a sacrocaudal dimple were observed. MRI of the brain at six months showed underdevelopment of the frontal lobe and global cerebral hypomyelination. Spinal MRI showed a cutaneous depression in the sacrocaudal region with no continuity with the spinal cavity. Sleep EEG revealed vertex sharp transients and 14-Hz bilateral spindles, without epileptiform discharges. Ophthalmological examination revealed bilateral myopic astigmatism and a left choroidal coloboma. Chromosome G staining revealed 46, XY, inv (9) (p12q13), which was thought to be a normal variation. At six months of age, we performed CGH array (analysed using 60K, Agilent Technologies SurePrint G3 Human CGH array) to investigate a multiple malformation syndrome and detected a 17p13.1–p13.2 microdeletion spanning about 3.03 Mb (chr17:4,537,516–7,576,822) [hg19]. This region encompasses 116 genes. The parents did not wish to be examined. At 18 months of age, the patient started showing a movement which involved raising of both upper limbs in clusters, mainly when drowsy, lasting approximately 10-15 minutes. The patient showed developmental arrest. EEG showed symmetrical hypsarrhythmia during interictal periods both in wakefulness and sleep (*figure 1A*). Ictal EEG revealed a paroxysmal fast wave superimposed on widespread slow waves (*figure 1B*), leading to the diagnosis of LOS. Epileptic spasms were treated with antiseizure drugs, such as valproate, topiramate and clobazam, however, the patient remained refractory to treatment. The abnormal eye movement was not associated with any detectable scalp EEG change and continues to persist at the age of three years.

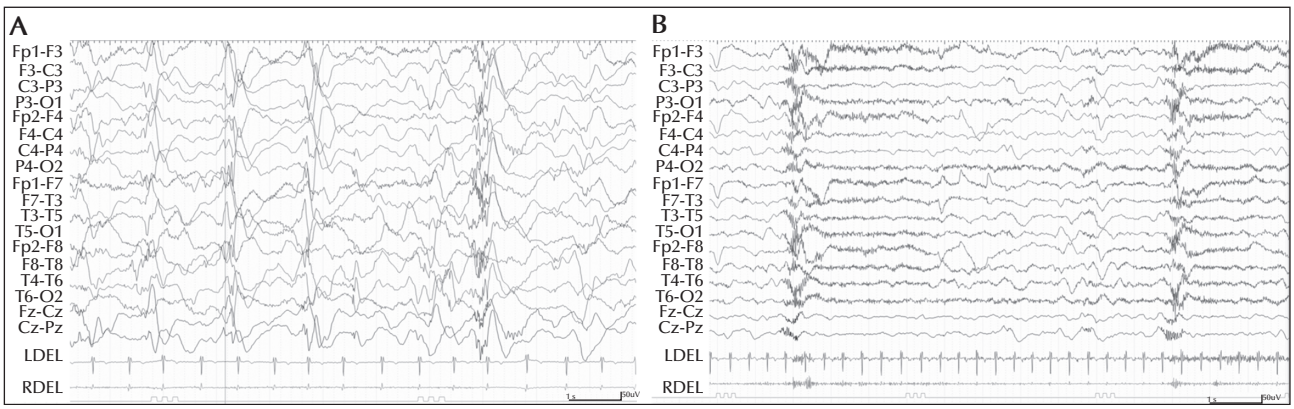
Case 2

The patient, a boy, was delivered normally at a gestational age of 41 weeks and five days, with a birth weight of 3,140 g. Family history was unremarkable. He was under observation at a public health centre because of a lack of neck control at a four-month check-up. At two years of age, speech and motor delay became apparent, and the child was admitted to our hospital at two years and three months of age for a close examination of developmental delay. The examination revealed a peculiar facial appearance with backward-rotated ears, high arched palate, retrognathia and micrognathia, as well as amblyopia, sacral dimple and mildly decreased muscle tone. Cranial MRI findings at two years and three months showed no evidence of structural abnormalities or delayed myelination. Sleep EEG showed vertex sharp transients and 14-Hz bilateral spindles, however, no epileptiform discharges. At the age of 10 years, we performed CGH array (analysed using 60K, Agilent Technologies SurePrint G3 Human CGH array) to investigate a multiple malformation syndrome and detected a 17p13.1–p13.2 microdeletion spanning about 1.31 Mb (chr17:5,931,990–7,247,070)[hg19]. This region encompasses 16 genes. Fluorescence *in situ* hybridization (FISH) on samples from both parents showed no obvious deletion and his genetic alteration was found to be *de novo*. No epilepsy developed during the course of the disease.

Discussion

In this study, we report two cases with deletions in the 17p13.1–p13.2 region, both of which had characteristic symptoms and findings in common but differed significantly in terms of epilepsy. One patient had LOS, while the other did not have epilepsy, suggesting that the difference in the extent of deletion may play a role in the development of LOS.

To our knowledge, 16 cases with deletions in the 17p13.1– p13.2 region have been reported as of 2020 [1]. Among them, five cases had deletions spanning both 17p13.1 and 17p13.2. Three of the previously reported cases had epilepsy. One case had focal impaired awareness seizures, well controlled with oxcarbazepine [1], and another myoclonic seizures, controlled by valproic acid and lamotrigine administration [5]. Komoike *et al*. reported a case of LOS in which the extent of deletion was similar to that of our Case 1, and proposed the following genes to be



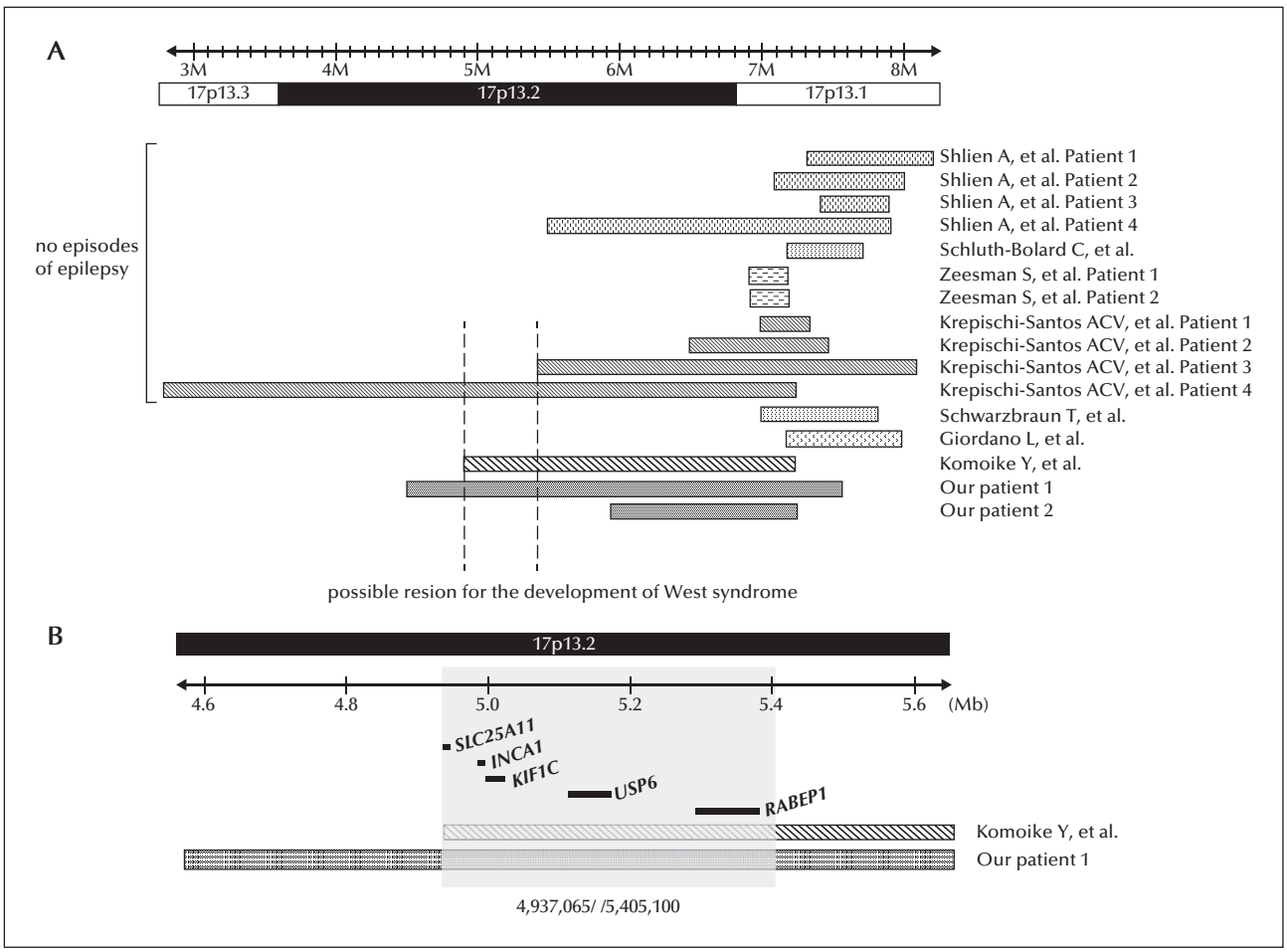
■ **Figure 1.** EEG was performed using the international 10 20 electrode system, reformatted to longitudinal bipolar montage; electromyography (EMG) electrodes were attached to the deltoid muscles bilaterally. (A) At 18 months of age, interictal EEG during the awake state showed symmetrical hypsarrhythmia. (B) At 18 months of age, ictal EEG showed a paroxysmal fast wave superimposed on widespread slow waves that appeared periodically, corresponding to the movement of raising both upper limbs. EMG revealed a crescendo-decrescendo sequence with a diamond-shaped configuration associated with diffuse triphasic slow waves. LDEL: left deltoid muscle; RDEL: right deltoid muscle.

involved in the epilepsy: *KCTD11/REN*, *GPS2*, *GABARAP* and *DLG4/PSD95* [6]. The other two cases were not described as developmental and epileptic encephalopathy, at least not with a treatment-resistant course [1, 5]. The locations of the deleted regions and epilepsy-related genes in previous reports are shown in *figure 2* [1]. Affected genes that are common to the case of Komoike *et al*. and our Case 1, not reported in the other cases, are *SLC25A11*, *INCA1*, *KIF1C*, *USP6*, and *RABEP1*. There are no reports showing an association between these genes and epilepsy, however, *USP6* may be important for the development of LOS. Ubiquitin-specific protease (USP) 6 is a hominoid-specific protein deubiquitinase containing Tre-2/USP6, BUB2, and Cdc16 and USP domains [11]. Its genomic location is prone to chromosomal breakage and translocation events, as well as genomic rearrangement, and *USP6* is consequently down-regulated. This rearrangement and down-regulation may lead to intellectual impairment and aberrations in social behaviour, such as intellectual disability and autism spectrum disorder [12, 13]. Recent studies on *USP6* transgenic mice have shown that ubiquitination of N-methyl-D-aspartate (NMDA) receptors is suppressed in the cerebral cortex, and that *USP6* overexpression leads to increased expression and stabilization of NMDA receptors on the cell surface [11]. Conversely, dysfunction of *USP6* also leads to the accumulation of neurotoxic substances, such as glutamate [11]. In our Case 1, the *USP6* gene deletion may destabilize NMDA receptors, leading to the repeated activation of NMDA receptors by excessive accumulation of glutamate, a neurotoxic substance. These mechanisms may be involved in the development of epileptic spasms. The fourth case in the study by Krepischi-Santos *et al*. [3] demonstrated a deletion covering a larger region, including *USP6*, however, this was a mosaic deletion and may not have played a role in epilepsy.

The present report has limitations; it is based on inferences from only two cases and does not allow for definitive conclusions. The involvement of additional genes cannot be ruled out because we did not perform a comprehensive genetic analysis. However, in the future, further case reports may provide confirmation of the genetic involvement in LOS.

Conclusion

In the present study, we describe two further cases of 17p13.1–p13.2 microdeletion syndrome. We speculate on the pathogenesis of LOS, considering the deletion region in these two cases and previous reports. By comparing the extent of the deletion with previous reports, *USP6* gene involvement is suspected. We hypothesize that the decrease in NMDA receptor expression and destabilization, and accumulation of neurotoxic substances caused by the *USP6* gene deletion might be involved in the development of LOS, however, owing to the small number of cases, this hypothesis remains to be confirmed. Therefore, further research is warranted, for instance, with the use of *USP6* knockout mice. ■



■ **Figure 2.** (A) Schematic representation of the genetic deletions in patients described in the literature. (B) Enlargement of the region that may be involved in the development of late-onset spasms, and the possible epilepsy-related genes within this region (modified from *figure 5* in [1]).

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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The authors declare no conflicts of interest.

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TEST YOURSELF

(1) What are the characteristic clinical features of 17p13.1 microdeletion syndrome?

(2) What is the incidence of 17p13.1 microdeletion syndrome, and how often are late-onset spasms associated with the syndrome?

(3) What are the possible mechanisms involved in the development of late-onset spasms associated with 17p13.1 microdeletion syndrome?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.