■ Case vignette

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Subtotal hemispherotomy for late-onset spasms after anti-myelin oligodendrocyte glycoprotein antibody-positive acute haemorrhagic leukoencephalitis

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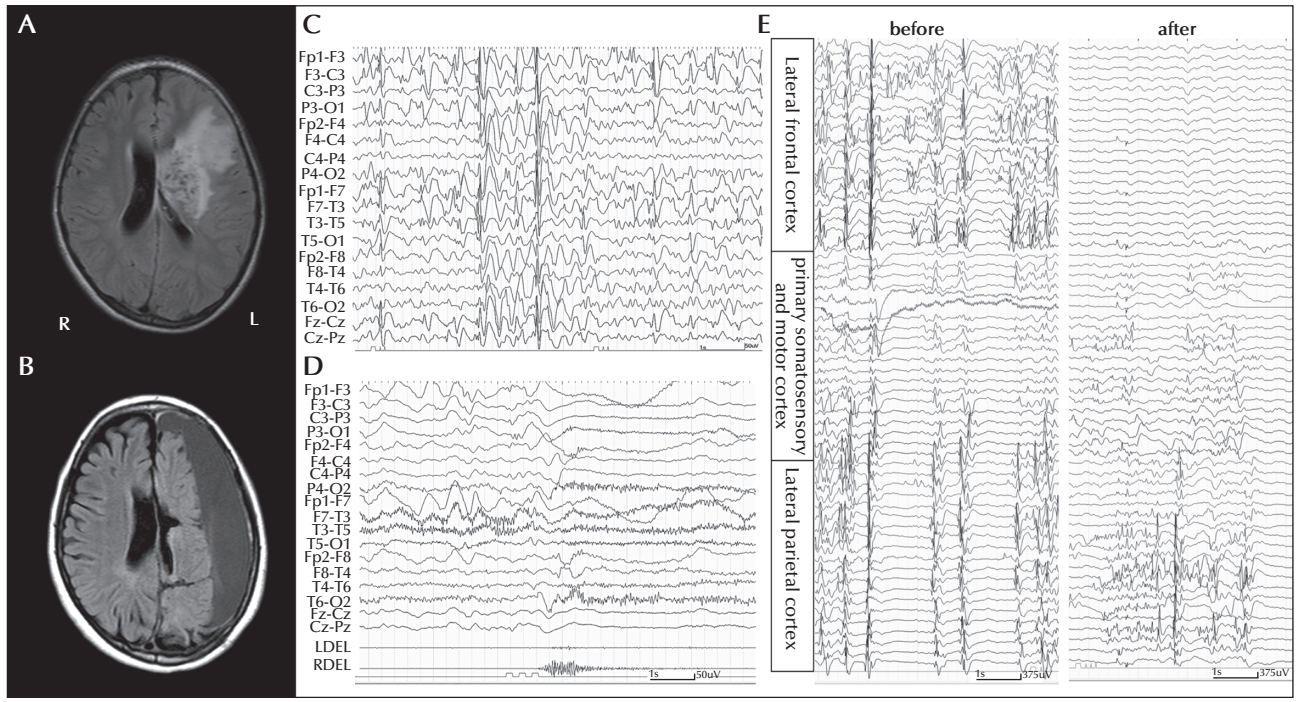
Acute haemorrhagic leukoencephalitis (AHLE) is an acquired demyelinating disease first reported by Hurst in 1941 that generally develops after infection or vaccination. Its course is rapidly progressive, and diagnosis is based on the collation of clinical symptoms and imaging and histological findings [1, 2]. Few studies have reported cases of paediatric AHLE, and the neurological prognosis of surviving patients remains unclear. We herein report a case of anti-myelin oligodendrocyte glycoprotein (MOG) antibody-positive AHLE with a focus on prognosis after epilepsy surgery for post-encephalitic late-onset spasms (LOS).

The patient was six years old at the onset of AHLE. The patient's condition improved without recurrence after several courses of high-dose immunoglobulin therapy and intravenous methylprednisolone pulse therapy, and prednisolone (*figure 1A*). At the onset of encephalitis, she showed aphasia and could express only a few words, and the number of words increased with the progression of treatment.

EEG showed paroxysmal discharges mainly over the left frontal region, five months after the onset of encephalitis. The EEG findings gradually worsened; the spike-and-wave discharges spread to the left hemisphere, and further spread to the contralateral side. With worsening EEG findings, attention deficit in daily life was observed, even after oral levetiracetam and valproic acid administration. A movement comprising sequential raising of the right shoulder and forward bending of the head appeared 14 months after the onset of encephalitis. The seizure type was confirmed as epileptic spasm (ES), and the patient was diagnosed with LOS (*figure 1C, D*). Intellectual regression, restlessness, and attention deficit were also observed, along with difficulty in calculation and writing, which the patient was capable of before LOS onset. ES temporarily disappeared with adrenocorticotropic hormone therapy, but relapsed four months later.

Subtraction ictal single-photon emission computed tomography co-registered to MRI demonstrated an increase in blood flow from the left frontal to parietal lobe. Fluoro-2-deoxy-D-glucose positron emission tomography revealed a massive reduction in glucose metabolism in the left cerebral hemisphere. Magnetoencephalography estimated dipoles over a wide area in the left hemisphere. The Wada test revealed that the dominant hemisphere of language and memory had shifted to the right side, but



■ **Figure 1.** FLAIR images at the onset of AHLE (A), after left subtotal hemispherotomy (B). At the onset of AHLE, extensive high-signal intensity regions can be observed in the left basal ganglia, and frontal and temporal lobes. A similar hyperintense region can also found in the white matter of the right frontal lobe. (C, D) Scalp EEG performed 14 months after the onset of AHLE using the international 10–20 electrode system and reformatted to the longitudinal bipolar montage. The electromyography electrodes were attached to the deltoid muscles bilaterally. Interictal EEG (C) showing diffuse, left-hemisphere dominant, high-amplitude spike-and-wave complexes. Ictal EEG (D) recorded during an epileptic spasm revealed that general attenuation or spikes preceded the left temporal lesion, and diffuse slow waves periodically appeared predominantly in the left hemisphere on video-EEG. Electromyography (EMG) revealed a crescendo-decrescendo sequence with a diamond-shaped configuration associated with diffuse triphasic slow waves. (E) Intraoperative electrocorticography (ECoG); performed with a bandpass filter of 0.016–300 Hz and a sampling rate of 2000 Hz, before (left) and after subtotal hemispherotomy (right). Intraoperative electrocorticography (ECoG) revealed repetitive spikes mainly over the frontal and parietal lobes before subtotal hemispherotomy. Although the spikes over the frontal lobe disappeared after subtotal hemispherotomy, those over the parietal lobe remained.AHLE: acute haemorrhagic leukoencephalitis; FLAIR: fluid-attenuated inversion recovery: R: right; L: left; LOS: late-onset spasms; LDEL: left deltoid muscle; RDEL: right deltoid muscle.

functional MRI revealed that the left hemisphere retained control of motor function. Left subtotal hemispherotomy, including temporo-parieto-occipital disconnection, prefrontal disconnection, and corpus callosotomy of the central part, was performed 21 months after onset of encephalitis (*figure 1E*).

Although a slight tonic movement of the right shoulder was observed, this was clearly different from the movement seen before surgery. Though EEG was evaluated in the presence of subdural hygroma, no new EEG findings or slight attenuation consistent with the movement was noted. An electromyogram showed a contraction of the right deltoid muscle for about 3-4 seconds. It was difficult to characterize the movement as epileptic spasms (Engel Class I-C). The Kyoto Scale of Psychological Development, utilized three months post-AHLE onset (at the time of transfer), revealed a developmental index of 69. The preoperative full scale intelligence quotient (FSIQ) score, derived from the Wechsler intelligence test (fourth edition), was 65. Five months postoperatively, this score increased to 67. The intellectual and behavioural regression also improved.

We later found that the patient's serum tested positive for anti-MOG antibody (detected using cell-based-assay) at the onset of AHLE. No mutations were observed in complement-related genes.

This is the first case report in which the long-term neurological prognosis after AHLE was evaluated with respect to epilepsy. Residual seizures accompanied by EEG discharges were not observed after surgery. Moreover, the patient was later found to be anti-MOG antibody positive.

AHLE has been associated with astrocyte damage at lesion sites [3] and deficiency in complement factor I, which is thought to control local inflammation in the brain [4]. AHLE causes destructive lesions over a wide area of the brain due to the above-mentioned pathophysiological mechanism. Similarly, ES is known to develop after acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), impairing a wide range of areas [5]. The formation of a multilobar abnormal network between the cortico-cortical and cortico-subcortical structures during recovery from extensive injury is postulated to trigger ES onset [6]. The occurrence of ES has also been reported in cases of Rasmussen encephalitis with extensive hemispheric lesions [7]. Subtotal hemispherotomy ameliorated LOS in this patient. Intraoperative electrocorticography indicated that the interictal spikes spared the motor area. A case series revealed that multilobar drug-resistant epilepsy had multifocal epileptogenicity that skipped the motor area [8]. The authors proposed that the chronology of myelination is a potential mechanism for skipping the motor area; the primary motor area undergoes myelination before birth, while the association fibre pathways undergo gradual myelination after birth.

Moreover, we later found that the serum at the onset of AHLE was positive for anti-MOG antibody. Anti-MOG antibody-positive cases have been reported repeatedly in various inflammatory demyelinating diseases of the CNS [9], however, anti-MOG antibody-positivity has not been reported in AHLE. Anti-MOG antibody-positive inflammatory demyelinating diseases of the paediatric CNS are considered highly responsive to prednisolone, although disease recurrence has been reported [10]. Our patient responded well to prednisolone and her condition improved without recurrence, however, it is essential to continue careful patient monitoring. ■

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

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None of the authors have any conflicts of interest to declare.

References

1. Hurst EW. Acute hemorrhagic leucoencephalitis: a previously undefined entity. *Med J Aust* 1941; 2: 1-6.

2. Rosman NP, Gottlieb SM, Bernstein CA. Acute hemorrhagic leukoencephalitis: recovery and reversal of magnetic resonance imaging findings in a child. *J Child Neurol* 1997; 12: 448-54.

3. Robinson CA, Adiele RC, Tham M, Lucchinetti CF, Popescu BF. Early and widespread injury of astrocytes in the absence of demyelination in acute hemorrhagic leukoencephalitis. *Acta Neuropathol Commun* 2014; 2: 52.

4. Broderick L, Gandhi C, Mueller JL, Putnam CD, Shayan K, Giclas PC, *et al*. Mutations of complement factor I and potential mechanisms of neuroinflammation in acute hemorrhagic leukoencephalitis. *J Clin Immunol* 2013; 33: 162-71.

5. Takanashi J, Oba H, Barkovich AJ, Tada H, Tanabe Y, Yamanouchi H, *et al*. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. *Neurology* 2006; 66: 1304-9.

6. Ito Y, Natsume J, Kidokoro H, Ishihara N, Azuma Y, Tsuji T, *et al*. Seizure characteristics of epilepsy in childhood after acute encephalopathy with biphasic seizures and late reduced diffusion. *Epilepsia* 2015; 56: 1286-93.

7. Ferrari TP, Hamad AP, Caboclo LO, Centeno RS, Zaninotto AL, Scattolin M, *et al*. Atypical presentation in Rasmussen encephalitis: delayed late-onset periodic epileptic spasms. *Epileptic Disord* 2011; 13: 321-5.

8. Iimura Y, Jones K, Hattori K, Okazawa Y, Noda A, Hoashi K, *et al*. Epileptogenic high-frequency oscillations skip the motor area in children with multilobar drug-resistant epilepsy. *Clin Neurophyisiol* 2017; 128: 1197-205.

9. O'Connor KC, McLaughlin KA, De Jager PL, Chitnis T, Bettelli E, Xu C, *et al*. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. *Nat Med* 2007; 13: 211-7.

10. Ramanathan S, Mohammad S, Tantsis E, Nguyen TK, Merheb V, Fung VSC, *et al*. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. *J Neurol Neurosurg Psychiatry* 2018; 89: 127-37.

TEST YOURSELF

(1) What are the possible causes of AHLE?

(2) In which paediatric cases were anti-MOG antibody first reported?

(3) What are the possible mechanisms of development of ES following AHLE and AESD?

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