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Case Report

Erythromelalgia presenting with posterior reversible encephalopathy syndrome: A pediatric case report

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ABSTRACT

Background: Erythromelalgia is a rare disorder characterized by erythema, warmth, and burning pain in the extremities. We report a pediatric case of erythromelalgia in a patient who developed posterior reversible encephalopathy syndrome (PRES), without any cutaneous signs.
Case presentation: A previously healthy 12-year-old girl presented to our pediatric clinic with burning extremity pain that had persisted for 6 weeks. The patient was treated with analgesics; however, the pain was refractory to these agents. Seven days after the first visit, she developed afebrile seizures and was transferred to our hospital. Her initial blood pressure was 139/105 mmHg (+2.0 SD), and brain magnetic resonance imaging revealed high intensity areas in the bilateral parietal and occipital lobes, leading to a diagnosis of PRES. Her blood pressure was difficult to control with anti-hypertensive agents. Burning pain in her extremities was relieved by cooling and worsened by warming. Although erythema was not observed in her hands or legs, erythromelalgia was suspected based on the characteristic nature of her pain. Intravenous lidocaine was administered for diagnosis, which was dramatically effective. After initiating mexiletine, the burning pain in her extremities disappeared, and hypertension improved. A final diagnosis of erythromelalgia with PRES was made.
Conclusion: A history of temperature-dependent pain relief and deterioration are important indicators of disease diagnosis, even if patients indicate a lack of erythema or warmth. Physicians should be aware that persistent pain due to erythromelalgia can lead to refractory hypertension and development of PRES.

1. Introduction

Erythromelalgia is a rare condition characterized by redness, warmth, and severe burning pain in the distal extremities. Cutaneous erythema, heat intolerance, and relief with cooling are the characteristic features of this condition [1,2]. Diagnosis is based on these clinical findings along with the exclusion of other diseases such as vasculitis or Fabry disease [1,2]. Erythromelalgia can be classified as primary or secondary. Primary erythromelalgia is an inherited or sporadic disorder, while secondary erythromelalgia is associated with other underlying conditions including myeloproliferative, collagen vascular, musculoskeletal, and neurological disorders or reaction to certain drugs [1,2]. Primary erythromelalgia can be diagnosed based on the presence of *SCN9A* and *SCN10A* mutations, encoding the voltage-gated sodium channels, $Na_v1.7$, and $Na_v1.8$ [1–4]. This channel is expressed in the dorsal root ganglion neurons and sympathetic ganglion neurons [4–6]. Gain-of-function mutations cause neuronal sodium channels to open easily and remain open, resulting in prolonged activation of sensory neurons [4,7]. This pathogenesis is postulated to lead to its characteristic symptoms.

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Hypertension has been a known comorbidity of erythromelalgia [7,8], however, posterior reversible encephalopathy syndrome (PRES) has not been reported to date. Herein, we report a first case of erythromelalgia in a pediatric patient who developed PRES.

2. Case presentation

A previously healthy 12-year-old girl presented to our pediatric clinic with pain. Six weeks before the initial visit, she had experienced severe burning pain in both the hands and feet, which worsened with warming, resolved with cooling, and persisted throughout the day. Physical examination revealed no sign of arthritis or redness of the extremities. Neurological examination was difficult because of severe pain. Laboratory examination revealed no elevation in the level of inflammatory markers. Although she was administered ibuprofen and acetaminophen, her pain worsened and could not be ameliorated using these agents. Seven days after her first visit, she experienced afebrile seizures following a headache and was transferred to our hospital. Her vital signs were as follows: body temperature: 37.4C; heart rate: 124 beats per minute; blood pressure: 139/105 mmHg (>+2.0 SD) [9]; SpO_2: 99 % on room air. The level of consciousness was E3V5M6. Physical examination revealed pain in the hands and feet, without edema, redness, or other skin features of the extremities. Deep tendon reflexes and other neurological examination results were within the normal range. Blood and cerebral fluid analyses revealed no significant findings (Supplementary Table 1). Brain magnetic resonance imaging (MRI) showed a high-intensity area in the cerebral cortex and subcortical white matter in the parietal and occipital lobes in fluid-attenuated inversion recovery (FLAIR) images (Fig. 1A–C), suggesting the development of PRES. No abnormal findings were observed in the diffusion-weighted images and apparent diffusion coefficient (ADC) map (Supplementary Fig. S1). She was admitted to the intensive care unit and anti-hypertensive treatment was initiated with continuous intravenous nicardipine. Secondary hypertension was evaluated using blood, urine, and imaging for pheochromocytoma, hyperthyroidism, and renovascular hypertension (Supplementary Table 2); however, no specific findings were observed. Spinal MRI, hand radiography, carotid artery ultrasound, ankle-brachial index, nerve conduction velocity study, and serum vitamin B1 and B12 concentrations, were performed for evaluation of extremity pain, which was within the normal range. Genetic testing for Fabry disease did not detect the pathogenic variant. Although her extremities showed no redness, erythromelalgia was suspected based on the nature of the pain. Intravenous lidocaine was administered on day 18, and the pain dramatically resolved within 20 min; the pain scale became 1/10 from 8/10. Therefore, the patient was tentatively diagnosed with erythromelalgia, and her extremity pain gradually improved after administering mexiletine. The abnormal signals in the cerebral cortex and subcortical white matter lesions disappeared in the follow-up MRI on day 17 (Fig. 1D–F), consistent with the natural course of PRES. She was comprehensively diagnosed with erythromelalgia and had developed PRES due to severe pain-induced hypertension. A detailed timeline of the investigation and treatment after admission is shown in Fig. 2. During the six-month follow-up visit, her pain was still well-controlled with mexiletine.

We performed genetic analysis of *SCN9A* and *SCN10A* for the diagnosis of hereditary erythromelalgia. Written informed consent for this genetic analysis was obtained from the patient's parents. Because the genetic analysis of this patient and her parents was for clinical diagnostic purposes only, approval by our institution's ethics committee was not required. Genomic investigation of primary erythromelalgia did not identify any clear pathogenic variants in *SCN9A* and *SCN10A*. Sequence analysis of *SCN9A* revealed a heterozygous missense variant c.3335G>A (p.Ser1112Asn) in exon 18, while analysis of *SCN10A* identified two heterozygous missense variants: c.5536C>A (p.Leu1846Ile) in exon 28 and c.860C>T (p.Thr287Ile) in exon 7. In silico analysis suggested that *SCN9A* (p.Ser1112Asn) and *SCN10A* (p.Leu1846Ile) may have pathogenic potential (Supplementary Table 3). However, the familial genetic analysis revealed that her father (36-year-old) carried the same *SCN9A* variant, while her mother (35-year-old) carried the same *SCN10A* variants. Based on these findings, the identified variants of *SCN9* and *SCN10* were classified as being of "uncertain significance" (Supplementary Table 3) [10]. The possibility of pathogenic variants with incomplete penetrance remained. Furthermore, the potential for digenic inheritance involving *SCN9A* and *SCN10A* could not be excluded, although no reports had described such a mechanism regarding erythromelalgia. Functional profiling could not be performed.

3. Discussion

To the best of our knowledge, this is the first case report of a patient with erythromelalgia who subsequently developed PRES. Since the patient did not have skin erythema during the initial presentation, prompt diagnosis was challenging.

The typical clinical symptoms of erythromelalgia include episodic erythema, warmth, and burning pain in the extremities. Although our patient did not show any cutaneous manifestations, the characteristic pain history of deterioration with warmth and relief with cooling led us to perform a diagnostic test using lidocaine administration [7,11]. Moreover, erythema of the extremities is found in 66–83 % of patients with erythromelalgia [12,13]. A lack of pertinent history or physical examination for erythema should not exclude the diagnosis of erythromelalgia, which necessitates accurate recording of the nature of pain reported by the patients having this disease.

Our patient presented with an afebrile seizure due to PRES, which was diagnosed based on the history of hypertension and typical MRI findings. Hypertension in patients with erythromelalgia has been reported in a systematic review, in which three patients with *SCN9A* mutation required management of hypertension [7]. Although other reports also demonstrated that hypertension was observed in 6 % (2/32)-46 % (6/13) of patients [8,14], it was not well described in these publications whether it was pain-induced or a lifestyle-related disease. Some *SCN9A* mutations are also associated with sympathetic ganglion neurons [6]. Although hypertension in this patient was refractory to anti-hypertensive agents, it resolved with mexiletine. The patient may have developed persistent or episodic hypertension due to prolonged pain or autonomic abnormalities, which finally led to the development of PRES.

A good response to mexiletine treatment has been reported previously [11,15], although some cases of erythromelalgia can be difficult to control [1,8]. Pathogenesis of inherited erythromelalgia (e.g. I848T, L858H, and L858F mutations in Nav.17) is thought to increase the excitability of dorsal root ganglion neurons by hyperpolarizing voltage-dependence of Nav1.7 channels and slowing channel deactivation [7]. Mexiletine is a class IB sodium channel blocker, which is particularly effective in neuropathic pain by reducing action potential duration and is effective in some cases of erythromelalgia with *SCN9A* mutation [1,16].

A recent report recommended genetic screening for patients with neuropathic pain [17]. In the present case, interpretation of the genetic variants is difficult due to the lack of functional evaluation of her genetic variants and the possibility of incomplete penetration of *SCN9A* and *SCN10A*. The detection rate of pathogenic variants was relatively low in previous reports: 11 % (132/1139) of *SCN9A*, *SCN10A*, and *SCN11A* in patients with neuropathic pain [17], and 7 % (3/42) of *SCN9A* mutation detection in pediatric erythromelalgia [18]. Although our case has a limitation concerning genetic evaluation, we believe that erythromelalgia was accurately diagnosed based on the characteristic clinical symptoms and treatment response to mexiletine.

4. Conclusion

Herein, we report a pediatric case of erythromelalgia in a patient

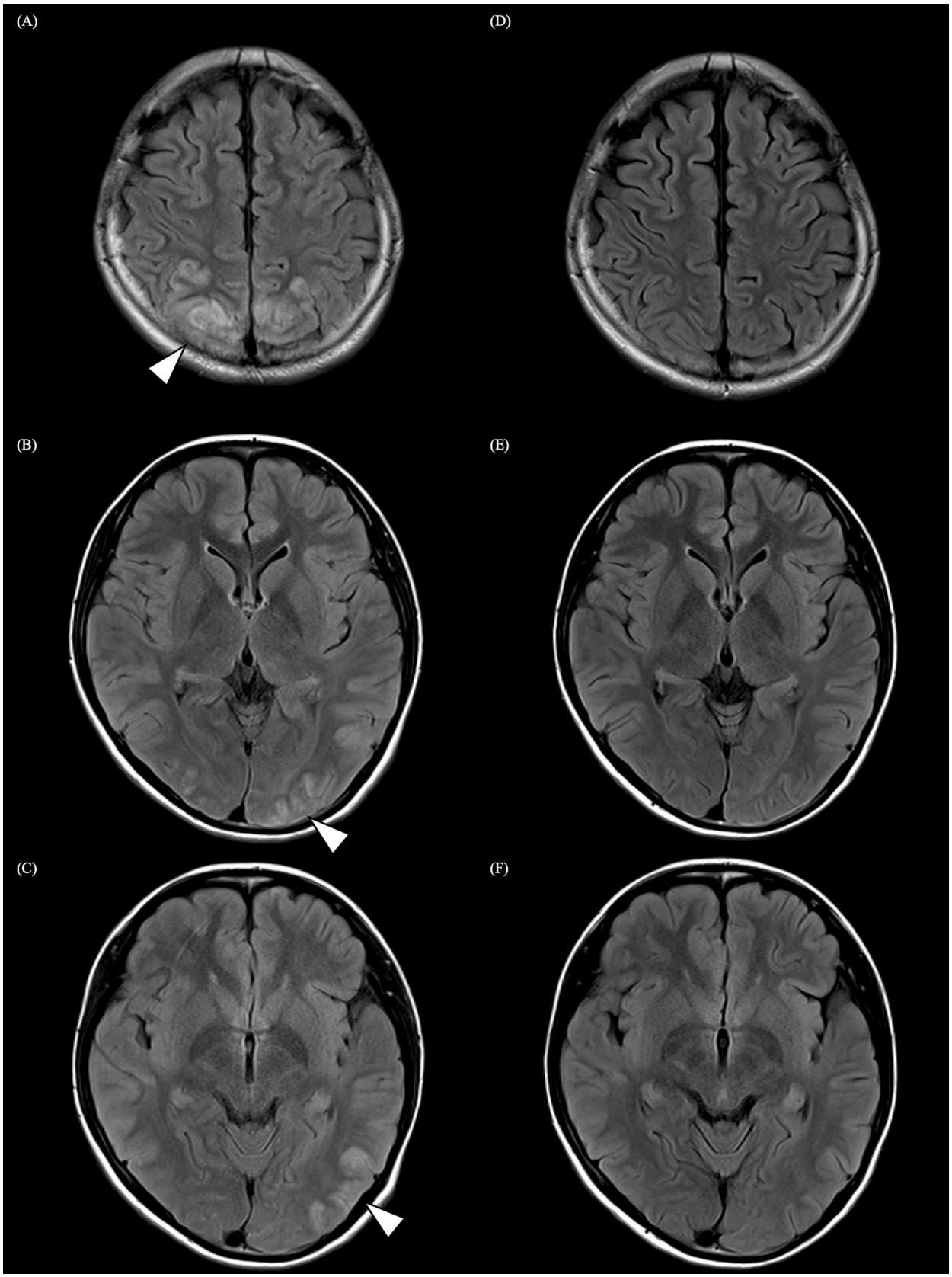

Fig. 1. Brain magnetic resonance imaging of fluid-attenuated inversion recovery. High-intensity areas in the cerebral cortex and subcortical white matter in bilateral parietal and occipital lobes were observed on the day of admission (A–C). These high-intensity areas disappeared on day 17 day after admission (D–F).

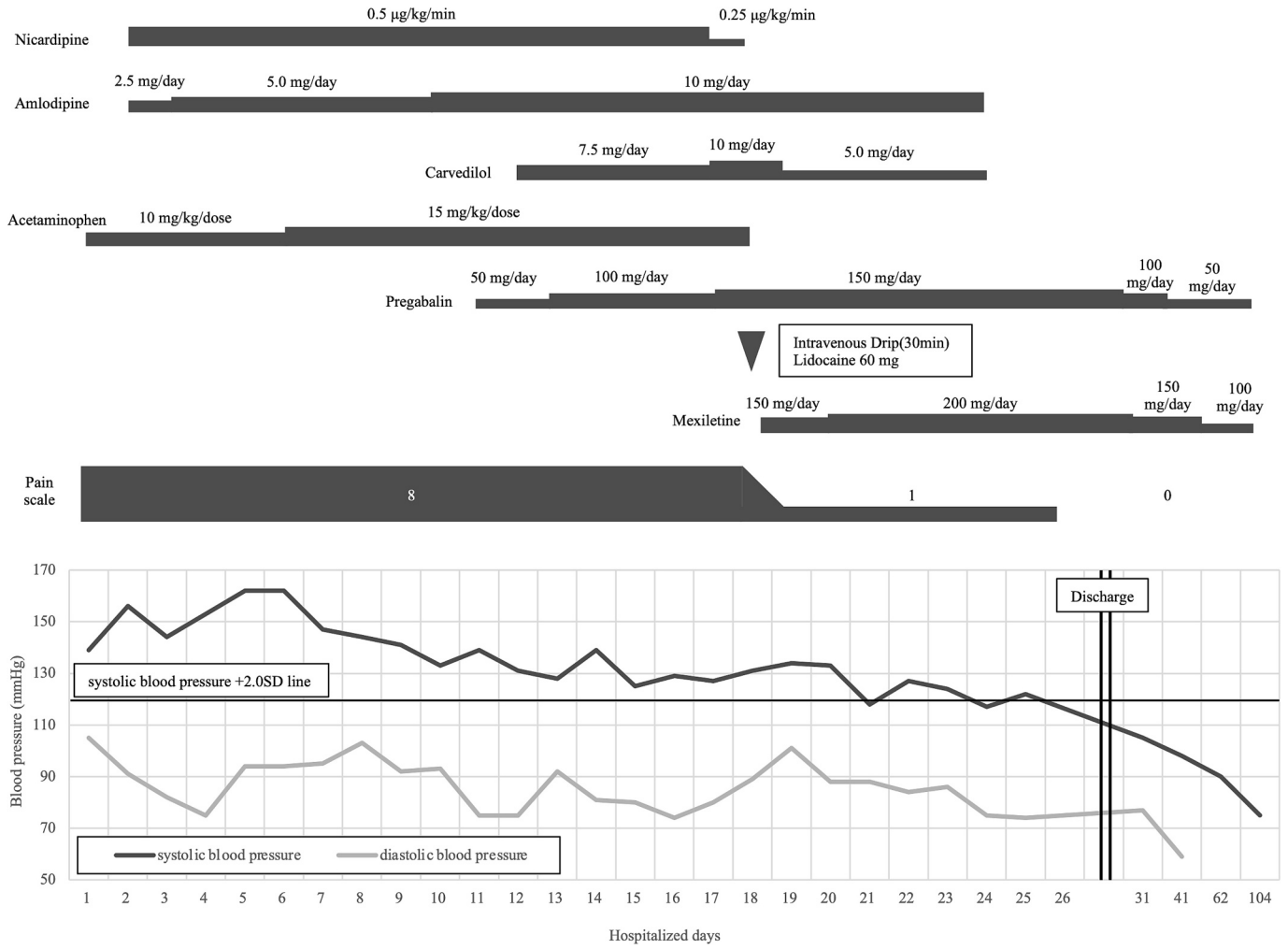

Fig. 2. Clinical timeline after admission. Anti-hypertensive drugs (nicardipine, amlodipine, and carvedilol) were administered; however, they were ineffective. Acetaminophen and pregabalin were ineffective for pain control. Intravenous lidocaine led to a dramatic response, and subsequent oral mexiletine improved the patient's condition. Her blood pressure returned to normal after pain control. She was discharged on day 26 and remains pain-free to date.

who developed PRES, without any cutaneous signs. A history of temperature-dependent pain relief and deterioration is an important indicator for diagnosing the disease, even in cases lacking erythema or warmth. Physicians should be aware that persistent pain due to erythromelalgia can lead to refractory hypertension and the development of PRES.

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Author contribution

Drs. Suzuki and Uda conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs. Tsuge, Arakawa, Shigehara, Obara, and Prof. Tsukahara contributed to clinical data interpretation, and critically reviewed and revised the manuscript for important intellectual content. Dr. Hasegawa contributed to genetic data interpretation, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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