Hereditary Angioedema Type 1 with Recurrent Dizziness

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Abstract:
A 41-year-old woman presented with recurrent dizziness. After an attack of dizziness, she felt edematous sensations in her hands. However, according to photographs taken during the attack, the edema on the back of the patient’s hands and fingers appeared mild. Laboratory examinations revealed a low C4 and C1 inhibitor (INH) activity. A direct sequencing analysis of C1INH revealed a pathogenic gene mutation. Based on these results, she was diagnosed with hereditary angioedema (HAE) type 1. These findings indicate that HAE can cause recurrent dizziness, and it should therefore be included in the differential diagnosis in patients with recurrent neurologic symptoms, even in the absence of severe edema.

Key words: hereditary angioedema, complement, C1INH gene, dizziness

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Introduction
Hereditary angioedema (HAE) is an autosomal dominant disease that typically manifests as recurrent severe attacks of massive, localized edema in the face, extremities, and genitals (1). In severe cases, the edema may extend to the upper respiratory tract and gastrointestinal system, resulting in airway obstruction and acute abdominal pain, nausea, and diarrhea.

Although neurological involvement in either angioedema or angioneurotic edema has been described previously (2-5), little is still known about the neurological symptoms which accompany HAE, except for a few case reports on paroxysmal neurological symptoms, such as transient cerebral ischemia-like syndromes, opsoconus, and poor balance (6, 7). HAE includes heterogeneous conditions which are distinct from angioedema or angioneurotic edema.

We herein report the case of a patient with genetically confirmed HAE type 1 with recurrent dizziness.

Case Report
A 41-year-old woman presented to our department with recurrent dizziness. The patient had a medical history of paralytic ileus at 20 years of age. She was a non-smoker and non-drinker. She took vitamin B12 supplements and was allergic to shellfish. There was no family history of angioedema. Nine months prior to presentation, she experienced sudden dizziness and had difficulty in waking. Bed rest did not improve her dizziness. About 30 minutes after the start of an attack, she felt edematous sensations in her hands without urticaria. These symptoms abated spontaneously after about 1 hour. Since this first episode, similar attacks recurred several times per month, each lasting a few hours. No inducing factors, such as positional change were noted, and no other accompanying symptoms were reported, such as hearing loss, brainstem signs, headache, nausea, presyncope, respiratory distress, or abdominal pain. First, her inner ear function was evaluated in the otolaryngological department, and it was found to be normal.

On physical examination during the interictal period, no limb edema was found. Neurological examinations revealed no abnormalities of the cranial nerves, muscle strength, sensory function, tendon reflexes, or motor coordination. It was difficult to actually observe such attacks in the outpatient department owing to their infrequency, so we asked her to photograph the edema during the attacks. On such photographs, edema on the back of the patient’s hands and fingers did not appear to be severe because the veins and creases of the hands were clearly visible.
Figure. Photograph of the back of the patient’s hands and fingers during the interictal period (left) and during an attack (right).

her hands were visible (Figure). Head computed tomography, magnetic resonance imaging, and angiography revealed no abnormalities in the brainstem, cerebellum, or vertebro-basilar artery. Laboratory examination revealed low C4 (3.8 mg/dL; normal, 10-40 mg/dL), normal C3 (94 mg/dL; normal, 90-180 mg/dL), and low C1 inhibitor (INH) activity (under 25%; normal, 70-130%). Informed consent was obtained from the patient, and the approval for a genetic study was obtained from the Kyushu University Ethical Committee. Genomic DNA was extracted from the peripheral blood, and a direct sequencing analysis of the C1INH gene revealed a c.4453T>A substitution in exon 4, resulting in a Val196Asp amino acid replacement. This mutation has been reported in patients with HAE (8). Based on these results, she was diagnosed with HAE type 1.

She was treated with tranexamic acid as long-term prophylaxis. However, the attack frequency and severity of edema and dizziness did not noticeably decrease.

Discussion

The diagnosis of this patient was challenging for several reasons. First, her chief complaint was recurrent dizziness rather than edema, the typical manifestation of HAE. Moreover, she did not have a family history of HAE. However, de novo C1INH gene mutations account for at least 25% of all such cases (9), and genomic sequencing revealed a 4453T>A mutation in C1INH.

The present case has two important implications for clinical practice. First, HAE can cause recurrent dizziness. Dizziness associated with HAE has been reported (6, 10). However, these reports lacked sufficient descriptions of the symptoms to establish a link with the primary disease. In our patient, dizziness was followed by mild hand edema, a cardinal symptom of HAE, which usually lasted for a few hours. In general, the underlying etiologies of dizziness include peripheral vestibular dysfunction, functional dizziness, central vestibular dizziness, and vestibular migraine (11). In addition to these diseases, HAE is a potential diagnostic consideration in patients with recurrent dizziness. Because dizziness associated with HAE might be accompanied by hearing loss, tinnitus, and migraine as previously reported (6), the diagnosis is more difficult in complicated cases. An accurate diagnosis may be possible when the clinician detects the presence of comorbid edema during history taking. The actual pathophysiology of dizziness in HAE is unclear, but it has been suggested that increased vascular permeability and ensuing local edema due to the liberation of bradykinin explains the neurologic symptoms (6, 7).

Second, HAE can cause neurological symptoms without severe edema. The edema associated with HAE is generally described as intense, massive, and diffuse (1). However, in this patient, the edema of her hands was relatively mild according to photographs, and there were also no symptoms involving the respiratory tract and gastrointestinal system. HAE is difficult to diagnose in cases with mild edema. It is thus important to consider recurrent edema as a possible sign of HAE, regardless of its severity, and to screen for serum C4, C1 INH antigenic protein, and the C1 INH function level (12).

An antifibrinolytic agent or tranexamic acid is used for the long-term prophylaxis of HAE (8). In this case, however, it did not substantially reduce the attack frequency or severity of edema and dizziness. Recent reports have indicated that both acute treatment and long-term prophylaxis with plasma-derived C1 INH can improve angioedema as well as the associated neurological symptoms (6, 7). Although her edema was relatively mild, the use of plasma-derived C1 INH may be considered according to the severity of dizziness and its influence on the quality of life.

In conclusion, HAE can cause recurrent dizziness. Furthermore, HAE should be included in the differential diagnosis in patients with recurrent neurologic symptoms, even in the absence of severe edema.

The authors state that they have no Conflict of Interest (COI).

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