**Vasculitic Neuropathy in a Patient With Hereditary C1 Inhibitor Deficiency**

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**Objective:** To report the clinical, pathological, and mutational features of hereditary C1 inhibitor (C1INH) deficiency as a cause of isolated vasculitic neuropathy.

**Patient:** A 35-year-old woman with sensorimotor mononeuritis multiplex and facial palsy.

**Results:** The sural nerve biopsy results showed a decrease of myelinated fibers with axonal degeneration and severe hypersensitivity vasculitis, with deposition of C1q on vessel walls. Mutational analysis of the C1INH gene found a new mutation, a heterozygous 2-base pair deletion in exon 8. The patient was treated with plasmapheresis and intravenous methylprednisolone, followed by oral prednisolone, which resulted in marked improvement.

**Conclusion:** Hereditary C1INH deficiency should be included in the differential diagnosis of nonsystemic vasculitis neuropathy.

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**HEREDITARY C1 INHIBITOR (C1INH) deficiency is caused by mutations of the C1INH gene and shows an autosomal dominant trait.**

The clinical manifestation, if present, is mostly angioedema and, to our knowledge, the association of neuropathy has never been reported in patients with the condition. Herein, we report a case of hereditary C1INH deficiency presenting with nonsystemic vasculitic neuropathy.

**REPORT OF A CASE**

A 35-year-old woman was referred to us for the evaluation of numbness and weakness of all 4 extremities. Two months previously, she had first noticed numbness over the lateral half of the dorsum of her left leg and foot. Two weeks later, similar paresthesia developed on the lateral half of the dorsum of her right leg and foot. She subsequently noticed weakness of both lower limbs, followed by numbness and weakness of both hands. These symptoms deteriorated rapidly during the following month. She had no systemic symptoms, such as fever, weight loss, or arthralgia. According to her medical history, she had developed a butterfly rash at the age of 17 years. She visited the section of rheumatology of our hospital at the age of 25 years for evaluation of the butterfly rash and was diagnosed as having possible systemic lupus erythematosus (SLE), because she met only 3 items of the SLE diagnostic criteria: increased antinuclear antibody titer (level, 640; normal level, $<40$), increased anti–double-stranded DNA antibody titer (level, 58.5 arbitrary units per milliliter; normal level, $<25.0$ arbitrary units per milliliter), and a butterfly rash. On this occasion, low levels of serum C4 (level, $<1$ mg/dL; normal level, 15-40 mg/dL) and total CH50 hemolytic activity (level, 2 U/mL; normal level, 30-55 U/mL) were found. She, however, remained in good health without treatment until the development of her current neurological symptoms. There was no family history of SLE or angioedema.

The results of a general physical examination were normal, except for the scar of a butterfly rash on her face. A neurological examination showed flaccid quadriparesis with distal predominance, bilateral absence of the Achilles tendon reflexes, and asymmetric impairment of all sensory modalities on the distal parts of all limbs. Her grasping power was 0 kg on the right side and 3 kg on the left side. She was unable to stand and walk. Soon after admission, left-sided facial palsy also developed.

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The results of routine laboratory studies, including urinalysis, complete blood cell counts, liver function tests, and serum electrolyte, serum urea nitrogen, fasting serum glucose, and C-reactive protein levels, were normal. Serologic test results for syphilis were negative. Her serum IgG level increased to 2780 mg/dL (normal, 850-1770 mg/dL), but her IgA and IgM levels were normal. The titers of antinuclear antibody decreased to 160 arbitrary units per milliliter, and the titer of anti–double-stranded DNA antibody also decreased to 36 arbitrary units per milliliter. Antibodies against U1RNP, Sm antigens, SS-A/Ro, SS-B/La, myeloperoxidase antineutrophil cytoplasmic antibody, proteinase 3 antineutrophil cytoplasmic antibody, single-stranded DNA, and cardiolipin were negative. Levels of complements were as follows: C1q, undetectable level; C1r, 20.1% (normal level, 40%-140%); C1s, 21.4% (normal level, 45%-130%); C2, undetectable level; C3, 70 mg/dL (normal level, 80-160 mg/dL); C4, 1 mg/dL (normal level, 15-40 mg/dL); and total CH50 hemolytic activity, 2 U/mL (normal level, 30-54 U/mL). The plasma level of C1INH was less than 2 mg/dL (normal, 10-25 mg/dL), and the C1INH activity was less than 25% (normal level, 80%-125%). The cerebrospinal fluid showed a lymphocyte count of $3.0 \times 10^3$ cells/µL, a total protein level of $1.18 \times 10^{-3}$ g/dL (normal level, <4.0 $\times 10^{-3}$ g/dL), an IgG level of 32.9 mg/dL (normal level, 1-4 mg/dL), and an IgG index of 0.75 (normal index, <0.70). The results of nerve conduction studies on 6 peripheral nerves confirmed a diagnosis of sensorimotor axonal mononeuritis multiplex. Ischemic lesions or contrast enhancement were not found on magnetic resonance images of the brain and spinal cord.

A simultaneous biopsy of the right sural nerve and adjacent peroneus brevis muscle was performed. The sural nerve was grossly enlarged. Microscopically, vasculitis consisting of a heavy extravascular infiltrate of lymphocytes associated with capillary proliferation was observed (Figure 1A). However, hypersensitivity vasculitis was not found in the adjacent muscle specimens (Figure 1B). On immunofluorescence, almost all the vessels, including proliferating capillaries, were strongly stained with anti–C1q antibody (arrows) (A), but only large arterioles were stained with anti–IgG antibody (arrowheads) (B).

Lowered serum C1INH levels and decreased C1INH activity were also found in our patient’s mother and sister. This led us to suspect hereditary C1INH deficiency. After obtaining informed consent, a mutation analysis was performed on the patient and her sister. We found a heterozygous 2-base pair deletion (17925_17926 del GA) in exon 8 of the C1INH gene (Figure 3), causing a frameshift at +51 glutamic acid of C1INH, which had not yet been reported on an online register that lists all pub-
lished mutations of the CIINH gene (available at: http://hae.enzim.hu/).

After the diagnosis, the patient was treated with plasmapheresis and intravenous methylprednisolone, 1 g/d for 3 days, followed by oral prednisolone, 60 mg/d. Her muscle strength markedly improved, and she returned to work 1 year later.

To our knowledge, the development of vasculitic neuropathy and a mutation of 17925_17926 del GA in the CIINH gene have never been reported in those with hereditary CIINH deficiency. The CIINH deficiency might cause SLE-like illness, and our patient had a history of SLE-like illness. However, vasculitic neuropathy in our patient seems not to be caused by SLE, because we could find no clinical or laboratory findings showing that the patient’s SLE had worsened during the rapid progression of her neuropathy, indicating that hereditary CIINH deficiency was directly involved in the development of vasculitic neuropathy in our patient. The relation of a new mutation in the CIINH gene with the development of vasculitic neuropathy in our patient is obscure, because little correlation has been observed between the clinical phenotype and the mutational genotype in hereditary CIINH deficiency and because only our patient developed neurological symptoms among family members having the same CIINH gene mutation.

CIINH is a serine protease inhibitor possessing a variety of biological functions. CIINH regulates the activation of the complement and contact systems. Following the activation of C1 by an immune complex, CIINH controls activation of the classic complement pathway via the inactivation of 2 proteases (C1r and C1s). CIINH suppresses the contact system via inactivation of plasma kallikrein and factor XIIa, which prevents the excessive generation of bradykinin, maintains the endothelial barrier, and modulates vascular permeability. In addition, CIINH was shown to inhibit selectin-mediated leukocyte-endothelial cell adhesion. In our patient, the serum complement profiles and the pathological features of the sural nerve showed severe hypersensitivity vasculitis and dense deposits of C1q on vessel walls, confirming that the activation of the classic complement pathway by CIINH deficiency caused hypersensitivity vasculitic neuropathy.

Our patient presented only with symptoms of neuropathy and during admission. Ischemic lesions and contrast enhancement were not observed on magnetic resonance imaging of the brain and spinal cord. A simultaneous biopsy of the sural nerve and adjacent peroneus brevis muscle showed that hypersensitivity vasculitis was present only in the peripheral nerve compartment. These findings suggest that vasculitis was confined to the peripheral nervous system in our patient. Thus, our case indicates that hereditary CIINH deficiency might involve the nervous system without systemic manifestations and, therefore, it should be included in the differential diagnosis of nonsystemic vasculitis neuropathy.

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