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.

Arch Neurrol. 2007;64:731-733
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, 30-35 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 × 10^3/µL, a total protein level of 1.18 × 10^-1 g/dL (normal level, <0.4 × 10^-1 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 451 glutamic acid of C1INH, which had not yet been reported on an online register that lists all pub-
lished mutations of the C1INH 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 C1INH gene have never been reported in those with hereditary C1INH deficiency. The C1INH deficiency might cause SLE-like illness,6 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 C1INH deficiency was directly involved in the development of vasculitic neuropathy in our patient. The relation of a new mutation in the C1INH 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 of hereditary C1INH deficiency1-4 and because only our patient developed neurological symptoms among family members having the same C1INH gene mutation.

C1INH is a serine protease inhibitor possessing a variety of biological functions.2-4 C1INH regulates the activation of the complement and contact systems. Following the activation of C1 by an immune complex, C1INH controls activation of the classic complement pathway via the inactivation of 2 proteases (C1r and C1s).1-4 C1INH 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.1-3,7 In addition, C1INH was shown to inhibit selectin-mediated leukocyte-endothelial cell adhesion.8 In our patient, the serum complement profiles and the pathological symptoms 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 C1INH deficiency caused hypersensitivity vasculitic neuropathy.

Our patient presented only with symptoms of neuropathy on 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 C1INH deficiency might involve the nervous system without systemic manifesta-

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**Figure 3.** Mutation analysis of the C1 inhibitor (C1INH) gene, showing a heterozygous 2-base pair deletion (17925_17926 del GA in exon 8 of the C1INH gene: the sequence of exon 8 in a normal allele is shown (the dotted line reveals 17925_17926 GA) (A) and the sequence of exon 8 in a mutated allele is shown (the arrow reveals 17925_17926 del GA) (B).

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**REFERENCES**


Accepted for Publication: November 9, 2006.

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Financial Disclosure: None reported.