Peripheral Autoimmune Neuropathy Assessed Using Corneal In Vivo Confocal Microscopy

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Background: Corneal nerves can be examined using in vivo confocal microscopy (IVCM). This new technique permits sequential observation of the corneal subbasal nerve plexus and detects early signs of diabetic peripheral neuropathy.

Objective: To describe a patient with autoimmune peripheral neuropathy followed up using corneal IVCM.

Design: Case report.

Setting: Clinic of neurology, Geneva, Switzerland.

Patient: A 56-year-old man with peripheral neuropathy diagnosed as anti–myelin-associated glycoprotein neuropathy. His symptoms initially worsened despite the administration of intravenous immunoglobulins and plasma exchange. Evolution was eventually favorable after rituximab and corticosteroids were given. At 1-year follow-up, clinical recovery was almost complete, and the patient was stable according to the results of clinical and electrophysiologic assessments.

Main Outcome Measure: Corneal nerve measurement by IVCM.

Results: Examination of corneal nerves using IVCM at 2 different times during the patient's clinical evolution (peak disease and recovery phase) demonstrated histologic signs that correlated with the results of clinical and electrophysiologic assessments.

Conclusion: This observation supports the hypothesis that corneal IVCM could also be helpful for the early detection or follow-up of autoimmune peripheral neuropathy.

Arch Neurol. 2009;66(3):403-405

REPORT OF A CASE

Across a 2-month period, a 56-year-old man developed progressive ascending sensory loss in both legs, associated with distal weakness. On hospital admission, neurologic examination of the lower limbs revealed distal and symmetrical weakness (grade 4 on the Medical Research Council scale) associated with alteration of touch and pain sensations. Tendon jerks were absent. The remaining results of his neurologic examination were normal.

Results of routine laboratory blood tests and cerebrospinal fluid examination were normal. Immunologic tests revealed a paraproteinemia IgM kappa (monoclonal gammopathy of undetermined significance) associated with anti-MAG antibodies to 7916 arbitrary units (N < 1000). Paraneoplastic antibodies (amphiphysin, CV2/CRMP5, GAD, HU, Ri, and Yo) and anti-ganglioside antibodies (GM1, GM2, GD1a, GD1b, and GQ1b) were absent. Results of serologic testing were negative (human immunodeficiency virus, hepatitis B and C, Borrelia burgdorferi, syphilis, and Campylobacter jejuni) or were not suggestive of an acute infection (herpes virus types 1-6). Findings from spinal magnetic resonance imaging and thoracic computed tomography were normal. Bone marrow biopsy results were normal except for mild polyclonal plasmacytosis.

Despite the initiation of intravenous immunoglobulin therapy and, 1 month later,
plasma exchange, the clinical course was marked by rapid progression of distal lower limb weakness and sensory ataxia, which necessitated assistance with walking. Electroneuromyography of the lower limbs at this stage showed reduced amplitudes, increased latencies, severe temporal dispersion of distal motor responses with marked slowing of nerve conduction velocities, and disappearance of F waves.

The patient had no personal or family history of eye disease and no history of contact lens wear, ocular trauma or surgery, or systemic diseases that might have affected the cornea. Results of an ophthalmic evaluation, including visual acuity and anterior segment, fundus, and corneal sensitivity using cotton-wool stimulus all over the corneal surface, were clinically normal.

Corneal IVCM was performed using a Heidelberg Retina Tomograph II Rostock Cornea Module (Heidelberg Engineering GmbH, Dossenheim, Germany). After the application of topical anesthesia (oxybuprocaine, 0.4%) (Novartis Pharma Schweiz AG, Bern, Switzerland), Lacryvisc gel (Alcon Laboratories Inc, Hünenberg, Zug, Switzerland) was applied before aligning the

Figure. Corneal nerve examination by means of in vivo confocal microscopy (left eye; bar = 50 µm). A, Basal epithelial nerve bundles are normal in our patient (arrows). B, Stromal nerves in a control patient with typically linear morphologic features (arrow). C, Stromal nerves are thickened and tortuous during clinical worsening (arrows). D, One year after escalation of therapy, including rituximab dosage, the stromal nerves are thinner and less tortuous (arrows).
lens. Raw, full-screen images were captured throughout the cornea of both eyes at the time of the aggravation. Images are presented without further digital treatment. Examination of the density and morphologic features of the stromal nerves revealed abnormally thickened (mean diameter of nerve fibers, 10 µm) and tortuous nerves (Figure, C), whereas in the normal cornea, the stromal nerves appear as linear bundles (mean diameter of nerve fibers, <5 µm) (Figure, B). In contrast, the basal epithelial nerve bundles revealed no abnormality (Figure, A).

Treatment using rituximab (anti-CD20) associated with pulse methylprednisone and azathioprine was initiated. Rapid and dramatic improvement was observed, with diminished weakness and sensory symptoms of the lower limbs. One year later, the patient was receiving prednisone, 20 mg/d by mouth, and azathioprine. Flow cytometry demonstrated a persistent effect of rituximab on B-cell depletion (<1% CD19 B cells). Clinical recovery persisted with no new symptoms or signs, and the patient could walk for more than 1 hour without assistance. A control electroneuromyogram showed increased distal motor response amplitudes and reappearance of F waves. Follow-up of the neuropathy using corneal IVCMM revealed dramatic histologic improvement marked by decreased thickness (mean diameter of nerve fibers, 5 µm) and reduced tortuosity of the stromal nerves (Figure, D).

**COMMENT**

Anti-MAG neuropathy is an autoimmune, antibody-mediated, demyelinating neuropathy. The monoclonal anti-MAG antibodies are directed against the myelin sheath and are believed to be pathogenic. Therefore, this observation is consistent with the histologic picture observed using corneal IVCMM in the present patient with thickened and tortuous stromal nerves.

In conclusion, we believe that corneal IVCMM, a noninvasive surrogate marker of nerve fiber abnormalities, may be useful for assessing peripheral autoimmune demyelinating conditions such as anti-MAG neuropathy. This new technique might help physicians detect autoimmune neuropathy earlier and follow disease progression or response to therapeutic intervention by means of repeated assessment.

**REFERENCES**