

Autoimmune Autonomic Ganglionopathy

A Possible Postganglionic Neuropathy

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Objective: To evaluate postganglionic autonomic and somatic nerve fiber involvement in a patient with chronic autoimmune autonomic ganglionopathy.

Design: Case report.

Setting: Department of Neurological Sciences, University Federico II of Naples.

Patient: A patient with a 16-year history of severe autonomic failure and a high nicotinic acetylcholine receptor antibody titer underwent an extensive laboratory evaluation.

Main Outcome Measures: Evaluation of sympathetic and parasympathetic functions and sural nerve and skin biopsies.

Results: Clinical and laboratory evaluations showed the involvement of cardiovascular, pupillary, sudomotor, gastrointestinal, and bladder functions. Sudomotor function study and skin biopsy findings revealed postganglionic autonomic damage. Moreover, sural nerve and skin biopsy specimens provided clear evidence of somatic nerve fiber involvement.

Conclusions: We demonstrated postganglionic autonomic damage that could be related to a prolonged and severe impaired synaptic transmission and we report, for the first time to our knowledge, a somatic nerve fiber involvement in autoimmune autonomic ganglionopathy.

Arch Neurol. 2011;68(4):504-507

AUTOIMMUNE AUTONOMIC ganglionopathy (AAG) is a form of acquired autonomic failure affecting parasympathetic, sympathetic, and enteric functions. There is much evidence to support that AAG is a disorder of synaptic transmission caused by specific antibodies against the $\alpha 3$ subunit of the nicotinic acetylcholine receptor (nAChR) at the autonomic ganglia level.¹ However, authors of sudomotor function studies have hypothesized that there is a postganglionic autonomic neuropathy,² which has been recently demonstrated on sural nerve biopsy findings.³ Herein, we report a case of chronic AAG showing postganglionic autonomic and somatic nerve fiber involvement.

REPORT OF A CASE

CLINICAL FEATURES

A 55-year-old man complained of a slowly progressive widespread autonomic dysfunction over a 16-year period. At 39 years of age, he started to have a bowel disorder

characterized by diarrhea alternating with constipation. Over the years, he developed a progressive and marked orthostatic hypotension with frequent episodes of loss of consciousness, blurred vision, urinary retention requiring squatting and pressing over his bladder, erectile failure, decreased sweating with heat intolerance, and reduced salivation resulting in difficulty swallowing solids and gradual tooth loss. Moreover, he reported early satiety and postprandial abdominal bloating with a marked weight loss, about 40 kg, over a few years. There was no history of an acute illness preceding this disorder, and there was no family history of autonomic dysfunction. Neurological examination revealed dilated pupils unresponsive to light, dry eyes and mouth, and generalized dry skin. Strength, sensation, and deep tendon reflexes were normal.

LABORATORY FINDINGS

Routine blood cell count, blood chemistry findings, and urine analysis results were normal. A biopsy specimen from periumbilical fat revealed no amyloid deposi-

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tion. Lumbar puncture showed a slight hyperproteinorachia (50 mg/dL; normal, <45 mg/dL). Ganglionic nAChR antibody levels were markedly increased (24.14 nmol/L; normal, <0.05 nmol/L) and diminished after 2 weeks and 1 month from the first intravenous immunoglobulin administration (19.55 and 14.17 nmol/L, respectively). The supine plasma norepinephrine concentration was reduced (41 pg/mL; normal, >70 pg/mL) and failed to increase on standing. The tonic pupil responded to pilocarpine, 0.125%, administration (right and left pupil diameter: before, 7 and 6 mm; after, 2 and 2 mm), establishing parasympathetic denervation hypersensitivity. The head-up tilt test (60°) documented a significant drop of both systolic and diastolic blood pressure (from basal values of 146/89 mm Hg to 71/52 mm Hg) without a relevant increase of heart rate, consistent with a severe sympathetic dysfunction. Twenty-four-hour Holter arterial pressure showed an inverse circadian blood pressure profile. Analysis of time-domain and frequency-domain heart rate variability on a 24-hour electrocardiography-Holter recording showed a marked reduction of heart rate variability values, indicating a striking impairment of parasympathetic cardiac autonomic function. Myocardial scintigraphy revealed a normal heart to mediastinum ratio of iodine 123-labeled metaiodobenzylguanidine (early, 2.23; late, 2.59; normal, >1.83) consistent with an intact sympathetic innervation to the heart. Neurographic findings were within the normal limits with the exception of reduced sensory action potential amplitude in the right sural nerve (4.4 μ V; normal, \geq 5 μ V). Quantitative sensory testing⁴ revealed mild abnormalities of tactile thresholds and mechanical pain perception. Sympathetic skin response showed the absence of response to pain and acoustic stimuli in the lower limbs. A thermoregulatory sweat test revealed a generalized anhidrosis and results of a dynamic sweat test⁵ supported a postganglionic sudomotor dysfunction. The dynamic sweat test results showed a reduced sweat drop density (84/cm²; normal, >104/cm²) after stimulation with pilocarpine, 1%, at the right forearm and both sweat drop density (50/cm²; normal, >75/cm²) and sweat output (0.229 μ L/cm²/min; normal, >0.260 μ L/cm²/min) of the right leg. Skin samples taken from the third fingertip, thigh, and distal leg, and processed according to published procedures,⁴ showed a marked loss of epidermal nerve fibers (ENFs) and a poor subepidermal neural plexus. The ENF density, regardless of biopsy site, was lower than the 5% cutoff: third fingertip, 1.5 ENF/mm (5% cutoff=6 ENF/mm); thigh, 4.7 ENF/mm (5% cutoff=18.2 ENF/mm); and distal leg, 2.7 ENF/mm (5% cutoff=10.2 ENF/mm). A severe loss of Meissner corpuscles (3.6/mm²; 5% cutoff=19.7/mm²) and their myelinated endings (13.1/mm²; 5% cutoff=32.6/mm²) was present in glabrous skin. In all skin samples, few calcitonin gene-related peptide and substance P-immunoreactive fibers were found. Innervation of dermal annexes (erector pilorum muscle, sweat glands, and vessels) appeared poor and deranged with sparse occurrence of vasoactive intestinal peptide cholinergic and dopamine β -hydroxylase noradrenergic immunoreactive fibers (**Figure**, A-F). Left sural nerve biopsy, performed when he was 41 years old and before the diag-

nosis was assessed, showed a moderate loss of large myelinated fibers on light microscopy (**Figure**, G and H).

TREATMENT

The patient was previously treated with fludrocortisone acetate and a low dose of prednisone without any benefit. A slight beneficial effect on orthostatic hypotension was associated with the use of midodrine hydrochloride. During the last year, he underwent 2 cycles of intravenous immunoglobulin treatment (400 mg/kg/d for 5 days) with transitory positive effects on sudomotor and gastrointestinal functions that lasted only few weeks. Afterward, the patient refused to undergo plasma exchange and start long-term immunosuppression therapy.

COMMENT

We report a case of chronic AAG associated with a high nAChR antibody titer and widespread sympathetic and parasympathetic dysfunction. Moreover, we provide evidence of postganglionic autonomic and somatic nerve fiber involvement in AAG.

Typically, patients with chronic AAG with mild or restricted autonomic failure present with low antibody titers whereas high levels of antibodies are associated with severe acute/subacute AAG subtypes. However, high antibody titers, such as in this case, can be associated with chronic AAG and severe autonomic dysfunction.⁶

Whether AAG is due to impaired synaptic transmission alone or is also due to postganglionic fiber loss is still up for debate. Experimental evidence has shown that neurons in the autonomic ganglia are intact, arguing against neuronal/axonal loss,⁷ while other authors have reported the reduction of unmyelinated fibers on sural nerve biopsy findings.³ In our patient, metaiodobenzylguanidine imaging supported a normal cardiac sympathetic innervation while sudomotor function study results suggested postganglionic damage, as already described.^{2,8}

Thus, even though AAG is considered to be an immune-mediated reversible defect in autonomic ganglionic synaptic transmission,⁹ a long-standing immune attack to autonomic ganglia may cause the loss of neuronal cells.³ In our patient, skin biopsy findings provided clear evidence of postganglionic nerve damage. Along with the loss of autonomic nerve fibers, skin biopsy findings disclosed, for the first time to our knowledge, a widespread involvement of somatic nerve fibers. In fact, besides the reduction of autonomic innervation, there was a marked loss of Meissner corpuscles and their myelinated afferent fibers in glabrous skin and a widespread loss of small somatic myelinated and unmyelinated fibers in hairy skin. Moreover, sural nerve biopsy findings, consistent with electrophysiological findings, confirmed the somatic nerve fiber involvement.

If autonomic fiber loss is not surprising, the involvement of somatic nerve fibers is unexpected and, to our knowledge, not reported before, although minor sensory symptoms can be present in AAG.¹⁰ A possible explanation of the discrepancy between our pathological

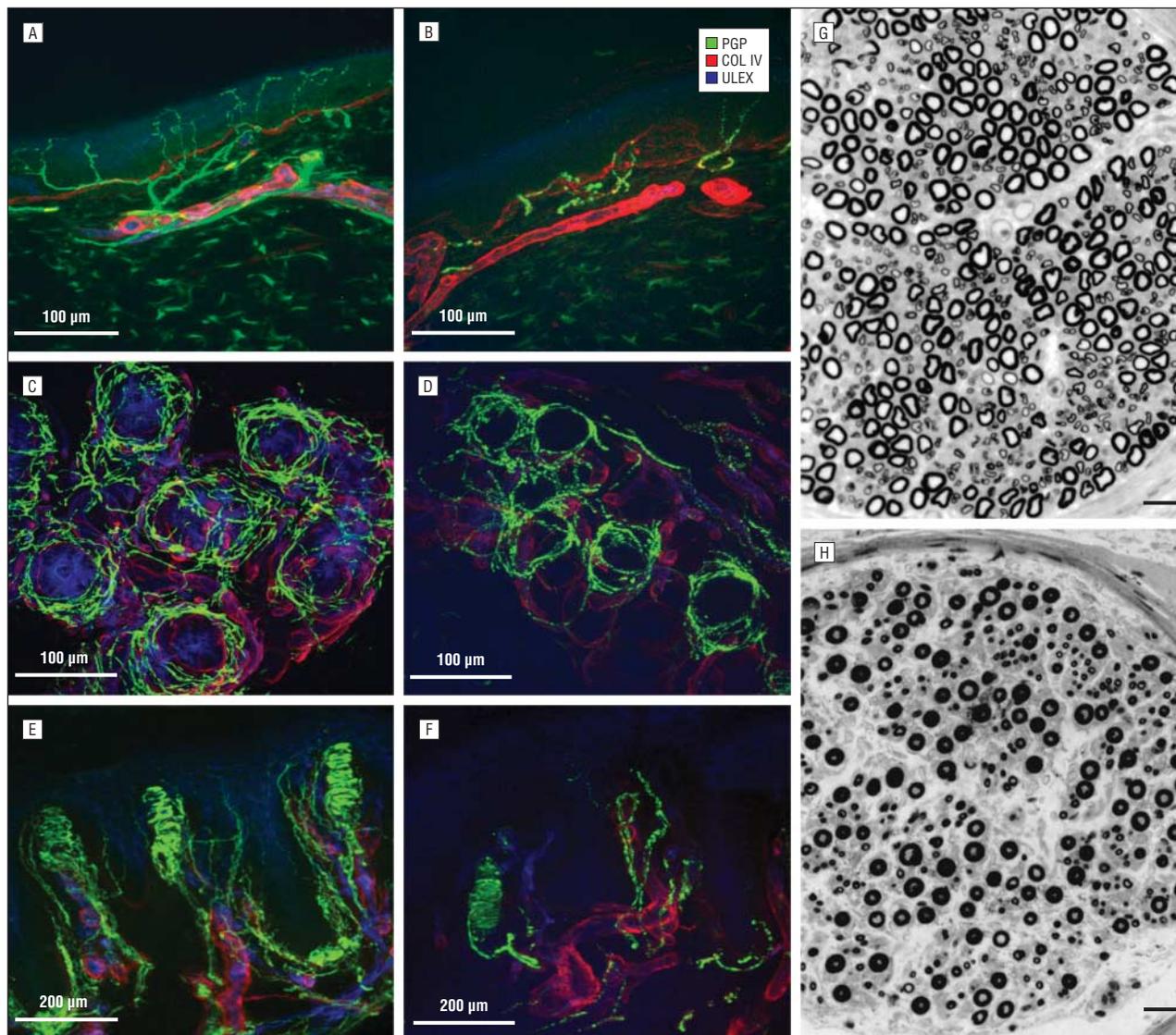


Figure. Skin and sural nerve biopsy findings. A-F, Skin biopsy findings. Confocal digital images showing a severe sensory and autonomic cutaneous denervation in a patient with autoimmune autonomic ganglionopathy. There is a marked loss of epidermal nerve fibers in hairy (B compared with A) and glabrous (F compared with E) skin with a very poor subepidermal neural plexus. The density of Meissner corpuscles is also reduced with evident morphological abnormalities of the surviving receptors (F compared with E). Sudomotor innervation appears poor and deranged (D compared with C). Nerves (in green) are marked with protein gene product 9.5 (PGP), blood vessels and the basement membrane (in red) are marked with collagen IV (COL IV), and endothelia (in blue) are marked with *Ulex europaeus* (ULEX). G and H, Sural nerve biopsy findings. Semithin section from epoxy resin-embedded sural nerve biopsy specimen showing a moderate loss of large myelinated fibers (H) compared with an age-matched control (G) (toluidine blue stain; scale bar=20 μ m).

findings and those observed by Koike et al³ on sural biopsy could be related to the higher nAChR antibody titer in our patient. In fact, an intense autoimmune attack against the α 3 nAChR may not be restricted to the autonomic ganglia but may also involve dorsal root ganglia neurons. Dorsal root ganglia neurons express multiple nicotinic acetylcholine receptor subtypes, and α 3 nAChRs have been described in a minority of mammalian dorsal root ganglia neurons.^{11,12} Another possible explanation for our findings is that α 3 nAChRs, previously believed to be expressed uniquely by neurons of human autonomic ganglia, are also present on the keratinocyte surface and are involved in modulating their adhesion and migration.¹³ Keratinocytes participate in the skin surface perception through interactions with nerve fibers^{14,15} and have trophic effects on the axonal devel-

opment and survival of sensory neurons.¹⁶ Thus, the blockage of nAChRs, causing paralysis of keratinocyte locomotion and cell-cell detachment, could affect the neuroepidermal junction and the survival of nerve endings. However, the pathogenetic role of the long-standing action of nAChR autoantibodies on somatic nerve fibers remains a hypothesis because we are dealing with a single case. On the other hand, the chronic autonomic denervation of skin could imply a derangement of the vascular dermal bed with secondary damage of cutaneous nerve fibers, as hypothesized in other chronic pathological conditions.¹⁷ However, this mechanism seems unlikely in our patient, because we did not observe abnormalities of his dermal vascular structures.

In conclusion, our study supports that, at least in chronic AAG, a prolonged and severe impaired synaptic

transmission may lead to a postganglionic autonomic neuropathy. Additionally, we demonstrate for the first time, to our knowledge, widespread and subclinical somatic nerve fiber involvement in AAG.

Accepted for Publication: November 29, 2010.

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