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Autonomic neuropathy associated with anti Gad antibodies

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Introduction

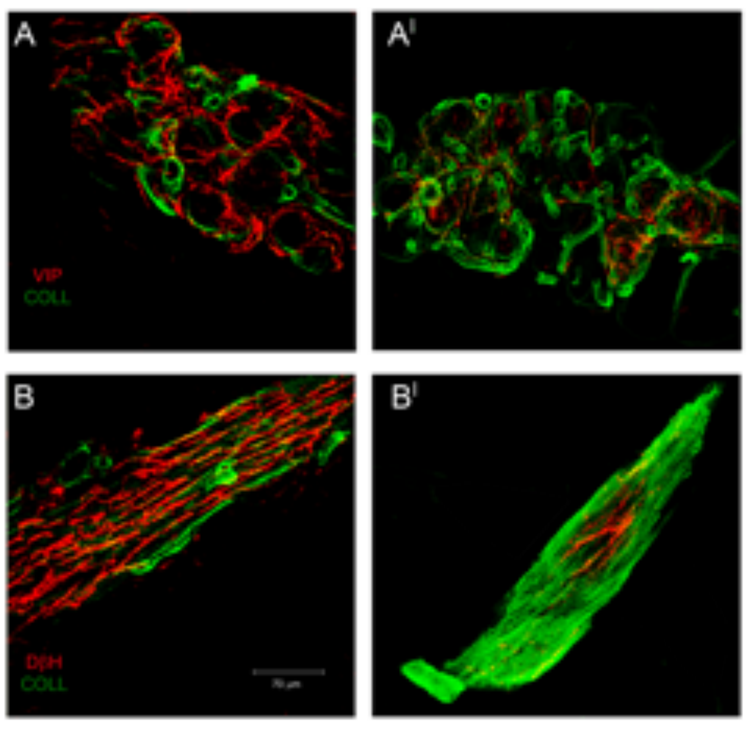
Anti Gad antibodies have been associated with several neurological and non neurological affections such as limbic encephalitis (LE), stiff person syndrome (SPS) and type 1 diabete mellitus (T1DM) (1). Recently the number of the diseases where Anti Gad antibodies can be found is increased and their presence has been described in Chronic intestinal pseudo obstruction and a supposed autonomic neuropathy (AN) which was not histologically demonstrated. Herein we describe two cases with CSF and serum Anti Gad antibodies positivity associated to AN demonstrated by skin biopsy.

Patients and methods

We reported two patients: a 50-year-old male who acutely developed severe bowel dysmotility, erectile dysfunction, distal skin dysfunctions and highly fluctuant blood pressure; he had a previous diagnosis of autoimmune hypothyroidism and chronic gastritis. When admitted to our department he was under thyroid hormone replacement therapy and reported normal values of FT3 and FT4 blood levels. The latter is a 47-year-old patient who subacutely started to complain of genitourinary dysfunctions, burning paresthesias and progressive constipation. Both patients underwent:
1) an extensive serum and CSF screening to explore possible AN causes; 2) skin biopsy from thigh and leg to ascertain the possible presence of somatic and autonomic small fiber neuropathy; 3) EMG to evaluate peripheral large nerve fiber.

Results

Plasma glucose, glycated hemoglobin levels, complete blood count, serum protein electrophoresis, screening for vitamins deficiency and microbiological conditions were normal in both patients. Serum autoimmune tests were normal except for significantly elevated Anti Gad antibodies levels in both patients. Anti Gad antibodies levels resulted also highly elevated in the CSF in both patients. Skin biopsy disclosed a prevalent autonomic small fiber neuropathy whereas EMG excluded a large nerve fiber involvement. Both patients underwent a cycle of high-dose corticosteroids with good recovery of the autonomic dysfunctions.



LEGEND FOR FIGURE
A confocal study of autonomic patterns of innervation in a control subject (A,B) and in the first patient (A^I,B^I).
Leg autonomic innervation disclosed by confocal microscope x40 for sweat gland (A, A^I) and muscle arrector pilorum (B,B^I) in an age-matched control subject and the first patient. Nerve fibers are marked in red by specific autonomic markers for sweat gland and muscle arrector pilorum (VIP and DBH, respectively) whereas the collagen staining is shown in green.
The muscle arrector pilorum showed a rich density of fibers running in a longitudinal and wavy pattern in the control subject but these fibers were poor with a deranged pattern of innervation in the patient. The innervation of the sweat gland appeared reduced in the patient when compared to the control subject.

Discussion

It is unclear whether GAD antibodies have a pathogenic role or not. The former hypothesis is supported by a work (2) which demonstrated that experimental administration in rats of human Ig anti GAD, extracted by patients affected by SPS, provoke similar symptoms in the test animals. Conversely, recently a study failed to prove that GAD-ab binding to live neurons is followed by internalization and by the reaching of intracellular GAD isoforms (3). Although we can not define whether Anti Gad antibodies have a pathogenic role or not, our suggestion is that their detection in serum and CSF could be an useful biochemical tool in patients affected by autonomic neuropathy to clarify autoimmune etiology and hence to perform immune modulation based treatment.

Conclusion

Anti Gad antibodies positivity should be searched in patients with AN when no acquired causes are evident. This positivity may help to address the patient to a possible immunomodulatory treatment although the pathogenic role of Anti Gad antibodies has not been demonstrated yet.

References

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