Neurología 36 (2021) 388—401

NEUROLOGÍA

www.elsevier.es/neurologia

LETTER TO THE EDITOR

Chronic autoimmune autonomic ganglionopathy. A rare case of dysautonomia☆

Ganglionopatía autonómica autoinmune crónica. Una causa rara de disautonomía

Dear Editor,

Autoimmune autonomic ganglionopathy (AAG) is an acquired immune-mediated disorder.[1] It was initially described in 1974 as pure pandysautonomia, and considered a variant of Guillain-Barré syndrome.[2] In 1994, patients with the condition were found to present antibodies specific for the alpha-3 subunit of the ganglionic acetylcholine (ACh) receptor.[3] Most cases are acute or subacute and occur in the context of recent history of respiratory tract infection.[2] We present the case of a patient with slowly progressive dysautonomia and provide data from a small fibre study.

Our patient was a 43-year-old man with no relevant medical history. Approximately a year before the initial assessment, he began to present slowly progressive symptoms of orthostatic intolerance, with dizziness, blurred vision upon standing, and leg weakness when walking. Symptoms improved in the decubitus position. He subsequently began to present frequent syncopes. A cardiological evaluation ruled out heart disease, and the tilt test revealed orthostatic hypotension. The patient underwent an autonomic function study. He reported nocturia, erectile dysfunction, eye and mouth dryness, lack of sweating during exercise, and photophobia. A neurological examination revealed normal cognitive function. The cranial nerve examination showed bilateral fixed mydriasis, normal ocular motility, normal fifth and twelfth cranial nerve function, and normal motor and sensory function. The autonomic function study revealed alterations in cardiac sympathetic, cardiovagal, sudomotor, and pupillary function (Table 1). A blood test did not detect anaemia or leukocytosis, and showed normal erythrocyte sedimentation rate and normal levels of glucose, creatinine, vitamin B_{12}, and folic acid. The patient tested negative for HIV infection and presented normal levels of serum gamma globulins. An immunity study revealed no anti-Ro, anti-La, or antinuclear antibodies. Imaging studies revealed no signs of tumour. Motor and sensory nerve conduction studies yielded normal results. A skin biopsy revealed normal density of unmyelinated fibres in the epidermis and dermis (sweat glands).

Table 1 Autonomic function study results.

Test	Results	Normal values[a]
Cardiac sympathetic function		
Blood pressure (mm Hg)		
Decubitus	122/60	
Standing	80/37	
Blood pressure drop after postural change	42/23	<20/10
Plasma NE in decubitus (pg/mL)	10	95—446
Valsalva manoeuvre, phase IV	Absent	
Isometric exercise		
Baseline DBP (mm Hg)	61	
Increase in DBP during exercise	3	≥10
Sympathetic sudomotor function		
SSR (μV)		
Palms	Absent	≥200
Soles	Absent	≥100
Cardiovagal function		
Deep breathing (bpm)	2	≥10
Valsalva ratio	1.0	≥1.3
30:15 ratio	1.0	≥1.3
Cholinergic pupillary function		
0.001% pilocarpine		
Baseline pupil diameter (mm)	6	
Pupil diameter after instillation (mm)	3	No change

DBP: diastolic blood pressure; NE: norepinephrine; SSR: sympathetic skin response.
[a] Reference values used in our laboratory.

Differential diagnosis of this progressive sympathetic and parasympathetic dysautonomia without sensory or motor involvement included Sjögren syndrome, which may present as dysautonomia associated with small or large sensory fibre involvement[4]; our patient did not present antibodies specific for this condition or sensory neuropathy. Amyloidosis may also present in the form of dysautonomia associated with peripheral axonal polyneuropathy.[5] However, our patient

☆ Please cite this article as: Idiáquez Cabezas J, Riquelme Alcázar J, Calvo Bascuñán M, Casar Leturia JC. Ganglionopatía autonómica autoinmune crónica. Una causa rara de disautonomía. Neurología. 2021;36:388—390.

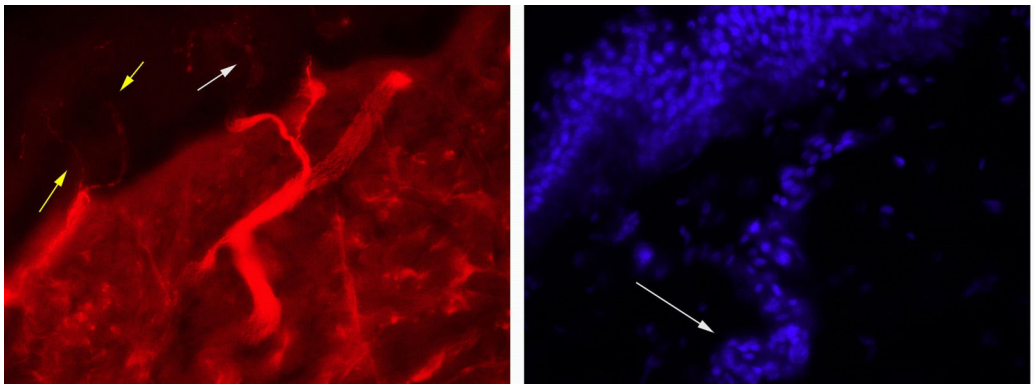

Figure 1 Skin biopsy. Left (PGP 9.5 pan-neuronal marker): normal density of epidermal nerve fibres (10.1 fibres per mm, that is 0.9 standard deviations below the mean for the patient's age and sex). Right (DAPI fluorescent stain): the arrow points to a normally innervated sebaceous gland.

did not present heart, kidney, or peripheral nerve involvement. We also considered paraneoplastic dysautonomia, which presents as acute or subacute symptoms of gastrointestinal pseudo-obstruction either in isolation or in association with encephalitis or sensory ganglionopathy.[6] However, our patient did not present brain or peripheral nerve involvement, and no alterations were found in a chest, abdomen, and prostate examination. Another possible diagnosis was pure autonomic failure (PAF), which manifests as slowly progressive sympathetic and parasympathetic dysfunction without motor or sensory involvement, secondary to a chronic neurodegenerative process (synucleinopathy).[7]

The patient presented bilateral fixed mydriasis secondary to cholinergic denervation of the pupils, a frequent finding in cases of AAG with high antibody titres but rare in patients with PAF,[8] which led us to request a study of ganglionic anti-ACh receptor antibodies. The patient tested positive for antibodies against the alpha-3 subunit of the ganglionic ACh receptor, at a concentration above 3.6 nmol/L (normal level, <0.05 nmol/L; Southwestern University, TX, USA). Orthostatic hypotension was treated with midodrine and fludrocortisone. Our patient received immunosuppressive therapy with prednisone and azathioprine; in subsequent months, orthostatic intolerance improved moderately, with occasional episodes of syncope. At a 4-year follow-up consultation, the patient reported no further episodes of syncope and no additional symptoms.

The main manifestations of AAG include orthostatic hypotension, constipation, severe pupillary cholinergic symptoms, urinary symptoms, dry eyes and mouth, and intolerance to heat due to anhidrosis.[1,2] Antibodies block ganglionic transmission, causing dysautonomia.[1] Treatment of acute AAG is based on intravenous immunoglobulins or plasmapheresis; long-term treatment includes prednisone, mycophenolate, azathioprine, and rituximab, in monotherapy or in combination.[1,2] As our patient showed slow symptom progression, we administered prednisone and azathioprine, achieving good results. Patients with symptoms of AAG may test negative for anti—ACh receptor antibodies and mainly present symptoms of sympathetic dysfunction, with no pupillary symptoms, and respond better to corticosteroids.[9]

In this case, a morphological study revealed preserved innervation of the sweat glands, which supports the hypothesis of impaired transmission without associated neuronal or axonal injury (Fig. 1). However, prolonged ganglionic transmission blockade may have caused small fibre loss.[10] Slowly progressive AAG may initially be misdiagnosed as PAF[11]; immunosuppresive therapy helps identify patients with AAG, who will respond to treatment, unlike those with PAF, a neurodegenerative disease.

Acknowledgements

We would like to thank Dr Steven Vernino of University of Texas Southwestern Medical Center for his advice and for the antibody study.

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https://doi.org/10.1016/j.nrleng.2020.06.011
2173-5808/

Camptocormia as the main manifestation of a mutation in the *POLG* gene☆

Camptocormia como principal manifestación de mutación en el gen *POLG*

Dear Editor:

The term camptocormia refers to marked flexion of the thoracolumbar spine, which resolves with supine positions, in the absence of fixed deformity.[1] This symptom may have multiple aetiologies, including parkinsonian syndromes, paraspinal myopathies, dystonia, motor neuron diseases, and functional disorders.[1–3] In exceptional cases, it can also be associated with *POLG* mutations.

We present the case of a 52-year-old man with history of mild psychomotor retardation since childhood; his father had late-onset Parkinson's disease and his mother had essential tremor. His 2 older siblings were asymptomatic. The patient was referred to our department due to progressive anteroflexion of the trunk of 4 years' progression, which hindered walking and was associated with poor coordination and slow movement, mainly affecting the right side; these symptoms were highly disabling. He displayed no signs of dysautonomia, with the exception of constipation.

Neurological examination revealed hypomimia, moderate bilateral bradykinesia, mainly affecting the right side, and low-amplitude right-sided resting tremor. Eye movement was not restricted. When standing, the patient displayed forced anteroflexion of the trunk, with the waist at an angle of approximately 70° (Fig. 1). In the decubitus position, he was able to correct his posture, lying flat on the bed.

A complete blood analysis including copper metabolism, muscle enzymes, and lactate detected no abnormalities; serology results for syphilis and HIV were negative. A brain MRI study detected no relevant alterations. A DaTSCAN study revealed dopamine transporter inactivity in both putamina and reduced uptake in the left caudate nucleus.

In the light of these findings, treatment was started with levodopa at increasing doses of up to 250 mg/6 hours, with a suboptimal response. After a 350 mg loading dose, he presented an improvement of over 30% on the UPDRS part III motor examination, with his posture improving and stabilising. The extreme anteroflexion of the trunk (Fig. 1) resolved, and he was able to carefully walk over 20 metres unassisted.

Given the history of psychomotor delay and the atypical parkinsonian symptoms, we requested an exome sequencing study, which identified a heterozygous missense mutation in exon 20 of the *POLG* gene (C.3218c > T; p [Pro1073Leu]), located on chromosome 15. The mutation is listed on the ClinVar and HGMD databases as a pathogenic variant. Functional studies have shown that this variant also affects mitochondrial DNA replication.[4]

Despite the lack of clear symptoms, we performed further diagnostic testing. An electromyoneurography study yielded normal results, and a multidisciplinary evaluation identified mild bilateral cataracts and predominantly sensorineural mixed hearing loss.

The *POLG* gene encodes the catalytic subunit of DNA polymerase gamma, which is responsible for the replication of the mitochondrial genome.[5] Mutations of the gene are associated with a broad spectrum of neurological syndromes, with age of onset ranging from infancy to adulthood; manifestations include epilepsy, psychiatric disorders, polyneuropathy, myopathy, ataxia, and progressive external ophthalmoplegia, and may be associated with such non-neurological conditions as cataracts, sensorineural hearing loss, and premature ovarian failure.[5,6]

More rarely, *POLG* mutations may be associated with parkinsonism,[7] often preceded for several years by classical

☆ Please cite this article as: Sancho Saldaña A, et al. Camptocormia como principal manifestación de mutación en el gen *POLG*. Neurología. 2021;36:390—392.