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CASE REPORT

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Pandysautonomia associated with impaired ganglionic neurotransmission and circulating antibody to the neuronal nicotinic receptor

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Abstract We report the case of a patient with chronic autonomic failure who had evidence of decreased postganglionic traffic to intact sympathetic nerve terminals. The patient complained mainly of decreased salivation, constipation, dry skin, and orthostatic intolerance. There was no evidence of central neurodegeneration. Autonomic function testing showed orthostatic hypotension without tachycardia and abnormal blood pressure and pulse rate responses to the Valsalva maneuver, indicating combined sympathetic and parasympathetic neurocirculatory failure. In contrast to patients with pure autonomic failure, the patient had normal left ventricular myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity, establishing intact postganglionic sympathetic innervation; and in contrast to patients with multiple system atrophy or baroreflex failure, the patient had a low plasma norepinephrine concentration and brisk norepinephrine response to orthostasis. These findings indicated an impediment to ganglionic neurotransmission. Serologic testing demonstrated a circulating antibody to the ganglionic nicotinic acetylcholine receptor. The findings in this case support the concept that circulating antibodies to this receptor can interfere with ganglionic neurotransmission and produce autoimmune autonomic neuropathy.

Key words pandysantonica · autoimmune autonomic neuropathy

Introduction

In pure autonomic failure (PAF, Bradbury-Eggleston syndrome), the patients have neurogenic orthostatic hypotension without evidence of progressive central neurodegeneration [1]. PAF patients typically have low plasma norepinephrine levels [2], a failure to increase plasma norepinephrine levels during orthostasis [3], decreased or absent blood pressure changes in response to drugs that release or inhibit release of norepinephrine from sympathetic nerve terminals [4, 5], and decreased or absent left ventricular myocardial concentrations of 6-[^{18}F]fluorodopamine-derived radioactivity [6, 7]. Neurochemical, neuropharmacologic, and neuroimaging findings therefore have established that in such patients, the orthostatic hypotension results from sympathetic neurocirculatory failure, due to generalized loss of sympathetic postganglionic nerve terminals.

Autoimmune autonomic neuropathy (AAN) can resemble PAF. AAN patients have been thought to complain more commonly of dry mouth and constipation than do PAF patients, and the condition is more likely to develop subacutely as a post-viral or carcinoma-associated syndrome or in the setting of another autoimmune disease [8]. AAN patients often have a circulating antibody to the ganglionic nicotinic acetylcholine receptor (AChR), whereas PAF patients do not [8].

Here we report the case of a patient with chronic autonomic failure, initially diagnosed with PAF, who had evidence of decreased ganglionic neurotransmission, rather than loss of postganglionic innervation, as the basis for sympathetic neurocirculatory failure. This finding, and the discovery that the patient's plasma contained an antibody that bound to the ganglionic nicotinic AChR, led to a diagnosis of idiopathic AAN, with antibody-mediated impairment of ganglionic neurotransmission.

Case report

A 77-year-old black widow who lived alone was evaluated at the NIH Clinical Center for orthostatic hypotension, dry mouth, and constipation.

She had no health problem until middle age, when hypertension developed. High blood pressure persisted when she was lying down, but for about two years the blood pressure had normalized when she was sitting. She noted gradually progressive orthostatic intolerance. She never lost consciousness but did have two presyncopal episodes causing falls without head trauma. Salivation decreased and became absent over several months, resulting in difficulty swallowing solids but not liquids. The dry mouth and difficulty swallowing caused decreased appetite, and she lost more than 30 lbs (170 to 143) over several months. The patient also became progressively more constipated over about five months. She also noted that she had to strain to begin urination, had hot flashes and night sweats every night for about five months, frequent headaches, and difficulty sleeping associated with depression. Medications at the time of evaluation included Florinef, midodrine, lorazepam for anxiety, Tylenol No 3 for back pain, hydroxyzine for itchy dry skin and rash, and Remeron for depression. She noted that her eyelids drooped after cataract operations within the last year. She complained of increasing forgetfulness but no other symptoms attributable to central neurodegeneration.

Physical examination showed an elderly, thin, right-handed, light-skinned black woman who was alert and well-oriented, looked healthy, was chewing gum, and complaining of itchy dry skin and dry mouth. Her blood pressure supine was 166/62 mm Hg and 158/52 after standing upright 5 minutes, with supine pulse rate 69 bpm and upright 73. She had warm, noticeably dry palms but normal turgor and color. Her eyes were brown and hair black and turning gray. She had bilateral ptosis. Pupils were unreactive to light. Neck vein pressure seemed normal, and she had no thyromegaly or carotid bruit. Her pulse was regular, without detectable respiratory sinus arrhythmia. Bowel sounds were present. Her speech and gait were normal, with symmetrically decreased but present deep tendon reflexes.

Autonomic function testing

Valsalva maneuver

Non-invasive measurement of beat-to-beat blood pressure and pulse rate was done using a Colin 7000 ± device and electrocardiogram (Fig. 1). The blood pressure decreased progressively in phase II, and there was no pressure overshoot in phase IV. The heart rate remained constant. The abnormal Valsalva blood pressure and pulse rate responses indicated sympathetic and parasympathetic neurocirculatory failure.

6-[^{18}F]Fluorodopamine positron emission tomographic scanning

Thoracic 6-[^{18}F]fluorodopamine positron emission tomographic scanning demonstrated increased 6-[^{18}F]flu-

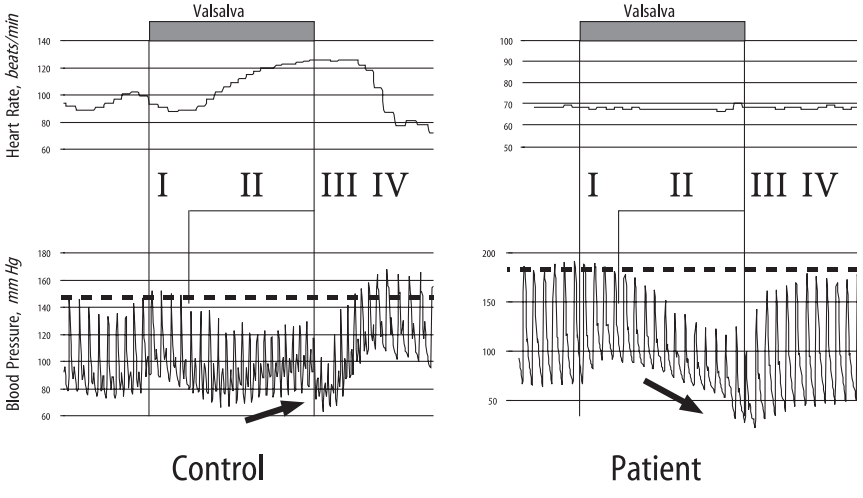

Fig. 1 Pulse rate and blood pressure responses to the Valsalva maneuver in a control subject and the patient described in this case report. The patient had evidence of parasympathetic and sympathetic failure.

orodopamine-derived radioactivity throughout the left ventricular myocardium (Fig. 2).

Plasma catechols

Blood was sampled from an antecubital vein with the patient supine and then after standing for 5 minutes. The plasma was separated and assayed for levels of catechols [9]. Plasma norepinephrine was low during supine rest (Table 1) but increased markedly during standing (normally plasma NE approximately doubles).

Trimethaphan infusion

Trimethaphan infusion at first decreased blood pressure, but as the infusion continued, the blood pressure returned to about the baseline value.

Table 1 Plasma levels of catechols

Condition	DHPG pg/ml	NE pg/ml	DOPA pg/ml	EPI pg/ml	DA pg/ml	DOPAC pg/ml
Supine	542	49	1119	5	9	2176
Upright	611	877	1070	7	28	2064
Lower limit of normal	500	80	900	4		1000
Upper limit of normal	1400	498	2500	83		3000

DHPG dihydroxyphenylglycol; *NE* norepinephrine; *DOPA* dihydroxyphenylalanine; *EPI* epinephrine; *DA* dopamine; *DOPAC* dihydroxyphenylacetic acid

Autoantibody testing

The patient's plasma was tested for circulating antibody to the ganglionic nicotinic AChR. Testing was performed at the Mayo Clinic Neuroimmunology laboratory (Rochester, MN) using a previously described and validated immunoprecipitation radioassay [10]. Four control plasma samples (from three normal volunteers and one patient with pure autonomic failure) and duplicate aliquots of the patient's plasma were sent to the assay laboratory. The samples had numerical codes that did not identify the sources of the samples. A high level of antibody binding to the ganglionic nicotinic AChR (5,420 pmol/L; normal value, less than 50 pmol/L) was detected in only the patient's plasma samples. In an in vitro blocking assay [8], the patient's plasma did not inhibit binding of agonist to isolated ganglionic AChR.

Treatment

The patient did not notice improvement by chewing nicotine gum; however, treatment with bethanechol, a muscarinic cholinergic agonist, produced a remarkable, immediate return of salivation and alleviated the patient's constipation. Treatment with midodrine, an orally acting alpha-adrenoceptor agonist, improved the patient's orthostatic tolerance.

Discussion

In this patient, the history of neurogenic orthostatic hypotension without central neurodegeneration, coupled

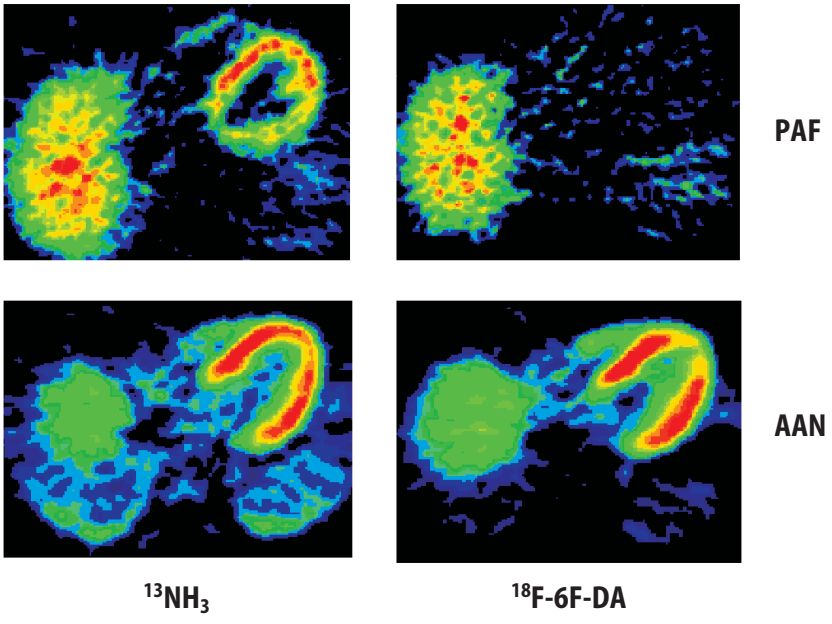

Fig. 2 Thoracic positron emission tomographic scans after i. v. administration of the perfusion imaging agent $^{13}NH_3$ and the sympathoneural imaging agent 6-(^{18}F)fluorodopamine (^{18}F-6F-DA) into (top) a patient with pure autonomic failure (PAF), and (bottom) the patient described in this case report, with autoimmune autonomic neuropathy (AAN). The patient with PAF had no detectable 6-(^{18}F)fluorodopamine-derived radioactivity in the left ventricular myocardium, in marked contrast with the patient described in this case report.

with the laboratory findings of physiological evidence for sympathetic and parasympathetic neurocirculatory failure, a low plasma norepinephrine level, and a small decrease in blood pressure during i. v. infusion of trimethaphan, led to an initial diagnosis of PAF [3, 4, 11].

In this case, however, 6-[^{18}F]fluorodopamine positron emission tomographic scanning results indicated normal sympathetic innervation [6, 12]. In fact, myocardial 6-[^{18}F]fluorodopamine-derived radioactivity exceeded normal, a finding consistent with hyperinnervation or ganglion blockade [13, 14], but not with PAF. Moreover, the patient had a marked increase in her plasma norepinephrine level during standing, whereas patients with PAF typically have a blunted norepinephrine response.

The history of inability to salivate, constipation, and urinary retention, the findings of ptosis and tonic pupils on physical examination, and the above findings questioning the diagnosis of PAF, suggested an alternative diagnosis of autoimmune autonomic neuropathy (AAN). Patients with AAN often have a circulating antibody to the neuronal nicotinic AChR, whereas patients with PAF do not. The detection of such an antibody led to a change in the diagnosis to idiopathic AAN.

The antibody in this patient did not directly interfere with binding of acetylcholine to the ganglionic AChR. Therefore, it appears that the antibody works more subtly. This more subtle influence might help explain the finding of an exaggerated increase in the plasma norepinephrine level during standing. Blockade of ganglionic neurotransmission *per se* would be expected to blunt the norepinephrine response to orthostasis. Perhaps the antibody alters the property of the AChR, such that receptor occupation by the antibody increases tonic inhibition of norepinephrine release but exaggerates phasic norepinephrine responses to sudden changes in nerve traffic.

Myasthenia gravis and other autoimmune diseases can be associated with dysautonomia [15, 16]; and acute or subacute autonomic failure, mainly detected by altered sympathetic cholinergic sweating or altered parasympathetic cholinergic regulation of heart rate, can be associated with a circulating antibody to the neuronal AChR mediating ganglionic neurotransmission [8, 10].

Such associations do not prove that ganglionic AChR antibodies actually impede ganglionic neurotransmission. The findings in the present case provide important support for such a role, since the same patient who had a high level of ganglionic AChR antibody also had a constellation of absent heart rate responses, abnormal Valsalva blood pressure, decreased salivation, constipation, tonic pupils, no response to nicotine or trimethaphan but brisk responses to a direct muscarinic cholinergic agonist and a direct alpha-adrenoceptor agonist, and neuroimaging evidence for intact postganglionic sympathetic nerves. We cannot think of any other single explanation for such a constellation besides impaired ganglionic neurotransmission. The findings in this case therefore support the view that ganglionic AChR antibodies play a pathophysiologic role in AAN.

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