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Clinical/Scientific Notes

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α-SYNUCLEIN ACCUMULATION IN SKIN NERVE FIBERS REVEALED BY SKIN BIOPSY IN PURE AUTONOMIC FAILURE

Pure autonomic failure (PAF), a rare clinical manifestation of Lewy body (LB) disorders, is characterized by fibrillary aggregates of α-synuclein in the cytoplasm of a select population of neurons and glia. It is a sporadic, idiopathic, neurodegenerative disorder with orthostatic hypotension as the cardinal symptom. Patients may also present with decreased sweating, urinary dysfunction, constipation, and sexual dysfunction. Postmortem studies[1-3] have disclosed prominent LB pathology in sympathetic and parasympathetic nervous systems, as well as the substantia nigra and locus ceruleus. Here, we show for the first time α-synuclein accumulation in nerve fibers in the dermis of a patient with PAF.

The patient is a 73-year-old man with a 13-year history of severe orthostatic hypotension with recurrent syncope, urinary dysfunction (hesitancy and prolongation), erectile failure, and decreased sweating with heat intolerance. Supine blood pressure was 163/84 mm Hg. After 1 minute of a 60° head-up tilt test, the patient's blood pressure fell to 62/33 mm Hg and he fainted. The patient's pulse was 60 beats/minute before tilting and 65 beats/minute after 1 minute of tilting, and his plasma noradrenaline was 40 and 36 pg/mL before and after tilting, respectively (normal: >100 pg/mL). The coefficient of variation of R-R intervals was 0.81% (normal: >1.5%). Denervation supersensitivity to noradrenaline was detected with infusion testing. A thermoregulatory sweat test revealed a patchy lack of sweating in the legs. The heart-to-mediastinum (H/M) ratio of ^{131}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy was reduced (early: 1.30, late: 1.25, normal: >1.85).

After the patient provided informed consent, skin samples, 5 mm in diameter and including the dermis, were obtained from around his ankles, directly fixed in 10% buffered formalin for 24 hours, and cut into 6-μm-thick serial paraffin sections. The sections were stained with hematoxylin and eosin and also stained immunohistochemically with an autoimmunostainer (20NX, Ventana, Tucson, AZ) and antiphosphorylated α-synuclein (psyn) antibodies (psyn#64 monoclonal and PSer129 polyclonal, gifts from Dr T. Iwatsubo, University of Tokyo). We also stained alternating serial sections with polyclonal anti-psyn and antiphosphorylated neurofilament antibodies (SMI31 monoclonal, Sternberger Immunochemicals, Bethesda, MD) to show the axons. Additional sections were immunostained with anti–tyrosine hydroxylase (TH) antibodies (Calbichem-Novabiochem Corporation, Darmstadt, Germany).

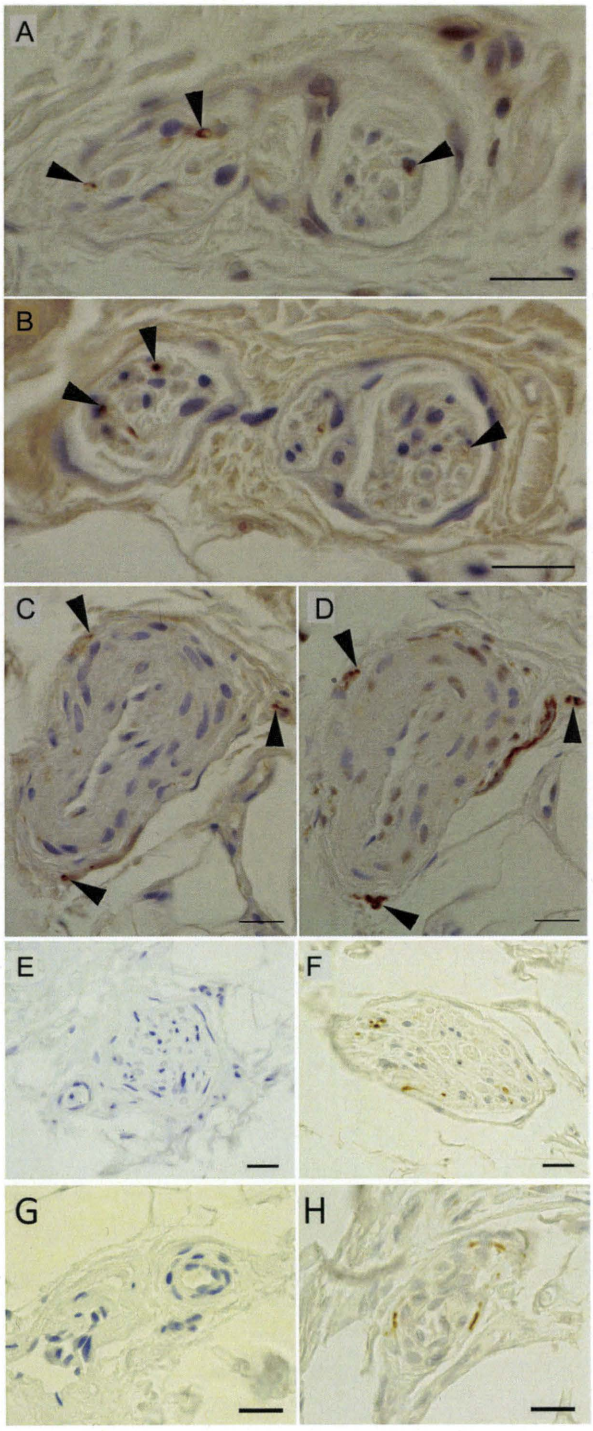
Anti-psyn immunohistochemistry showed positive neurites and dots in unmyelinated nerve fascicles of the dermis and subcutaneous tissue (figure, A and B). Small psyn-positive dots or thin linear structures were also found around blood vessels and were coincident with SMI31-immunoreactive axons (figure, C and D). TH immunostaining showed no immunoreactivity in the patient's nerve fascicles and blood vessel walls (figure, E and G), although sections from control subjects were TH-positive (figure, F and H).

Our patient fulfilled the criteria of the consensus statement on the definition of PAF.[4] Autonomic function tests indicated both sympathetic and parasympathetic involvement.

Skin α-synuclein has been detected by immunoblotting in some patients with Parkinson disease (PD),[5] and we have reported psyn-positive unmyelinated nerve fascicles in the skin of patients with PD and dementia with Lewy bodies (DLB), including aggregates within TH-immunoreactive axons and nonreactive axons.[6] Therefore, we biopsied the skin areas that showed no sweating in the thermoregulatory sweat test, because cutaneous sudomotor nerves contain unmyelinated adrenergic and cholinergic sympathetic nerve fibers that innervate blood vessels and sweat glands. The cutaneous unmyelinated nerve fascicles were immunoreactive for α-synuclein, and some extended into the walls of blood vessels. With absent TH immunoreactivity in nerve fascicles and blood vessel walls, dysfunction of sympathetic nerve fibers

Editorial, page 536

Figure Immunostaining for α-synuclein and tyrosine hydroxylase in the skin



Immunohistochemical study of nerve fascicles and vascular walls in the skin around the patient's left ankle with antiphosphorylated α-synuclein (psyn) antibodies (A: psyn#64, monoclonal; B, C: PSer129, polyclonal), antiphosphorylated neurofilament antibodies (D: SMI31 monoclonal), and anti-tyrosine hydroxylase (TH) antibodies (E–H). A–H: bars = 20 μm. C and D are serial sections. (A, B) Dot-like psyn immunoreactivity (arrowheads) was present in a cross-section of a nerve fascicle. (C, D) Psyn immunoreactivity revealed dots and a thin linear structure (C, arrowheads), which was determined with SMI31 to be the wall of a blood vessel extending from a nerve fascicle (D, arrowheads). (E, F) TH immunoreactivity was absent in a cross-section of a nerve fascicle in this patient (E). In contrast, TH immunoreactivity was observed in a control subject (79-year-old man; F). (G, H) TH immunoreactivity was absent in a cross-section of a blood vessel wall in this patient (G). In contrast, TH immunoreactivity was detected in a control subject (89-year-old man; H). No erector pili muscle was observed in the skin of this patient.

may underlie this patient's hypohidrosis and could be caused by the α-synuclein aggregation.

In PD and DLB, α-synuclein aggregates in the distal axons of the cardiac sympathetic nerves provoke the degeneration of these nerves.[7] MIBG myocardial scintigraphy enables the quantification of postganglionic sympathetic cardiac innervation; the H/M ratio was reduced in our patient, suggesting that α-synuclein aggregation may also be the pathologic cause of cardiac sympathetic nervous system degeneration in PAF.

We have shown that LB-related pathology in the skin is always accompanied by LB-related pathology in the CNS and adrenal glands of patients with PD and DLB.[6] Thus, synuclein accumulation in cutaneous nerve fibers may indicate that this patient without parkinsonism also has LB–related pathology in the adrenal glands and brain. Indeed, varying amounts of LBs and neuronal loss occur in the substantia nigra, locus ceruleus, and adrenomedullary cells in patients with PAF.[1-3]

α-Synuclein pathology in cutaneous nerves in this patient provides additional evidence that PAF is an α-synucleinopathy. Examining biopsies of hypohidrotic skin for α-synuclein-positive cutaneous nerve fibers in a series of patients with PAF should be performed in the future.

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LESIONAL REFLEX EPILEPSY ASSOCIATED WITH THE THOUGHT OF FOOD

A 44-year-old right-handed woman was walking in the Scottish highlands. Upon unwrapping her lunch, she had a focal seizure with witnessed onset on the right side of the face and secondary generalization. Postictally, she was aphasic with a right hemiparesis. She was airlifted to hospital. Sodium valproate was commenced, increasing to 700 mg twice daily, and she was discharged home. Three weeks later, the smell of food triggered another seizure and she was admitted to the neurology unit where carbamazepine was introduced (200 mg twice daily).

The next morning, the patient had a simple partial seizure after eating a spoonful of porridge and 3 more when eating lunch, a snack, and dinner. Thereafter, most meals triggered seizures, as did other food-related stimuli such as being offered a piece of cake, seeing her visitors pass around food at her bedside, and smelling the hospital dinner trolley. Fifty-four seizures occurred over the next 14 days and 50 were related to food. The episodes typically lasted 80 seconds and were characterized by a tingling sensation in the tongue and right-sided facial and tongue movements. Consciousness was unimpaired.

Thirty-four seizures occurred during the act of eating, always early on in the meal while the patient still felt hungry. Fifteen were precipitated by the sight or smell of food alone, 1 while browsing a recipe book, and 3 when she could smell her pet dog's food. One seizure was provoked by discussing cooking and another was triggered by the mint flavor of toothpaste. A single nocturnal seizure was accompanied by a strong feeling of nausea. The 2 other seizures associated with nonfood stimuli were related to stressful situations such as discussing a call from the doctor. Neither chewing movements nor speaking induced seizures.

Interictal EEG was normal. MRI revealed a nonenhancing lesion in the left premotor strip (figure).

The seizures were refractory to medical therapy. An awake frontoparietal craniotomy was performed with electrocorticography. Epileptiform activity was identified in the left frontal operculum, anterior and inferior to the lesion (figure). A subtotal resection was performed. Histopathology revealed a WHO grade IV glioblastoma. No reflex seizures occurred after surgery.

Discussion. We present a case of symptomatic reflex seizures triggered by food-related stimuli, with detailed neuroimaging and electrophysiologic localization of the epileptic focus. Reflex epilepsies are characterized by seizures consistently induced by a specific stimulus. Typically, they are idiopathic and generalized. Recognized stimuli include flashing lights, music, reading, toothbrushing, and eating. Over 200 cases of idiopathic eating epilepsy have been reported, many from South Asia, with a male preponderance and onset typically in the second decade of life.[1] In all cases, the act of eating was required to provoke seizures, which were focal or generalized. Of 128 cases in which treatment response is described, 48 (37.5%) became seizure-free, 64 (50%) achieved partial control of seizures, and 16 (12.5%) showed no benefit.[1,2]

There are far fewer reported cases of symptomatic eating epilepsy. The associated pathologies include congenital malformations, vascular abnormalities, postinfective lesions, and 1 neoplasm: an astrocytoma. Lesions involved the opercula, amygdalae, and temporoparietal lobes.[3,4] Most cases were refractory to medical therapy.

Rarer still are cases of reflex epilepsy triggered by the thought of a specific stimulus. One report described a man with temporal lobe seizures induced by thinking of his childhood home.[5] Another patient with a left temporal focus on EEG had seizures when brushing his teeth but also on thinking of a toothbrush.[6] To our knowledge, there have been no reports of seizures precipitated by the thought of food or hunger alone.[1,3]

Several mechanisms have been postulated for eating epilepsy, from somatosensory and motor stimulation to gastric distension.[2,3] Primary taste areas in the anterior insula and frontal operculum are activated by taste and olfactory stimuli but also the anticipation of food.[3] Taste processing is refined in the secondary taste areas of the amygdala and orbitofrontal cortex where a greater number of neurons receive multimodal inputs.[3] Functional MRI has demon-