



Diving into Dizziness – A Diagnosis of Autoimmune Autonomic Ganglionopathy

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INTRODUCTION

Orthostatic hypotension

- A common complaint in both inpatient and outpatient settings
- Multiple etiologies incl. medication-induced, hypovolemia, diabetic dysautonomia, adrenal insufficiency, paraneoplastic, etc.

CASE DESCRIPTION

- 55 year old male presented with 2 months of severe symptomatic orthostatic hypotension, new onset constipation, progressive weakness and 50lbs unintentional weight loss
- No symptomatic improvement despite multiple fluid challenges, high doses of midodrine & fludrocortisone during recent outside admissions
- PMH:** poorly controlled T2DM, peripheral neuropathy, resected GIST tumor
- Vitals:**

- Lying – BP 165/107, HR 65
- Sitting – BP 105/62, HR 107
- Standing – BP 129/89, HR 118 (could not stand >10 seconds)

- Exam** – strength 5/5 diffusely, normal muscle tone, decreased sensation to light touch in bilateral feet, distal > proximal muscle wasting, absent lower extremity reflexes

Workup

- A1c 10%
- Normal cortisol, TSH, B12, SPEP, UPEP
- Normal TTE, telemetry
- Negative CT A/P, PET scan
- Fat pad biopsy negative for amyloid deposition
- EMG: mild-moderate diffuse axonal sensory neuropathy
- Paraneoplastic panel: **+alpha-3 gnAChR antibodies**
- Diagnosed with **autoimmune autonomic ganglionopathy (AAG)** based on autonomic symptoms and +gnAChR antibodies
- Started on IVIG 0.5 mg/kg/day with some improvement of reflexes and orthostatic blood pressures

DISCUSSION

Disorder	Associated Features	Comments	Diagnostic Tests
Diabetes	Usually first noticed associated with general autonomic dysfunction; orthostatic hypotension may occur early in clinical course after autonomic manifestations (e.g. orthostatic hypotension, diarrhea, constipation, urinary retention, and erectile dysfunction)	Other common cause of autonomic dysfunction in developed countries	Fasting blood glucose and glucose tolerance test
Hereditary angiodysplasia (familial amyloid angiopathy)	Usually associated with generalized polyneuropathy, with prominent small fiber (pain and temperature) abnormalities, often as isolated conditions. include rapid lateral spread (often after early medication), orthostatic hypotension and conduction abnormalities, chronic pain, and increased intracranial pressure. subclinical pathologic may be present. diarrhea and weight loss are common. neuroglycopenia is not present	Develops in the last 10 decades of life, characterized by deposition of amyloid fibrils (beta-2-microglobulin) in peripheral nerves, paranasal sinuses, and endocardium, pericardial tissue, and neural excitation; most common amyloid precursor in neuropathic conditions; specific cases may be common; mutation in gene encoding for apolipoprotein A2 (ApoA2) has been identified	Assessment of for apraxia or motor or gait and history questions for amyloid deposition; genetic testing
Primary amyloidosis (AL amyloidosis; immunoglobulin light chain-associated)	Usually associated with generalized polyneuropathy, with prominent small fiber (pain and temperature) abnormalities, often as isolated conditions. include rapid lateral spread (often after early medication), orthostatic hypotension and conduction abnormalities, chronic pain, and increased intracranial pressure. subclinical pathologic may be present. diarrhea and weight loss are common. neuroglycopenia is not present	Occurs in the last 10 decades of life; characterized by deposition of amyloid fibrils (immunoglobulin light chain) in peripheral nerves, paranasal sinuses, and endocardium, pericardial tissue, and neural excitation; most common amyloid precursor in neuropathic conditions; specific cases may be common; mutation in gene encoding for apolipoprotein A2 (ApoA2) has been identified	Assessment of for apraxia or motor or gait and history questions for amyloid deposition; immunoelectrophoresis of blood and urine
HSMN type II (also called hereditary spastic paraparesis)	Hereditary spastic paraparesis and temperature sensory loss; sensory loss, absence of knee (Joh) reflex, hyperactive ankle and tendon reflexes, and absence of hyperreflexia	An autosomal recessive disorder seen primarily in Ashkenazi Jewish children	Tests for a splicing mutation in the toll-like receptor-associated protein gene (TRAPPC2), which is present in 98.9% of patients
Idiopathic sensory-mediated autonomic neuropathy	Idiopathic sensory-mediated autonomic neuropathy	May respond to immunomodulating therapy	Tests for serotonergic ganglionic acetylcholine receptor antibodies, which are present in some patients
Sjögren's syndrome	Sicca syndrome, because of dysfunction of lacrimal and salivary gland secretory cells	Autonomic manifestations may be present with initial diagnosis	Tests for anti-AChR (5A) and anti-LA (5B) antibodies
Paraneoplastic autonomic neuropathy	Neurologic features of underlying cancer may be first manifestation of a cancer	Occurs most often in patients with small cell lung cancer; also seen in non-small-cell lung cancer, various forms of gastrointestinal tract, prostate, breast, bladder, kidney, pancreas, testis, and ovary	Tests for anti-α antibodies (type 1 anti-muscarinic receptor antibodies (PMSF-1), which are most prevalent; type 2: Pankcreatic cell antibodies (PCA-1), and cell surface response molecule protein 3 (CRM-1), which may also be present)

*HSMN denotes hereditary sensory and autonomic neuropathy.

Figure 1: Neurogenic orthostatic hypotension caused by peripheral autonomic disorders

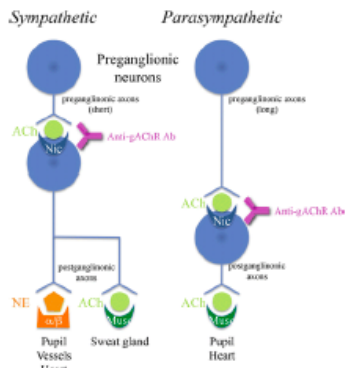


Figure 2: Mechanism of Anti-gnAChR Ab affecting sympathetic and parasympathetic nervous systems in AAG

DISCUSSION

- AAG** – rare paraneoplastic or idiopathic condition with acquired subacute dysautonomia
- 50% of patients have ganglionic nicotinic acetylcholine receptor antibodies
- Clinical manifestations
 - Sympathetic – syncope, anhidrosis, **orthostatic hypotension**
 - Parasympathetic – urinary retention, dry eyes and mouth, impaired pupillary function
 - Enteric – **constipation**, gastroparesis
- Non-pharmacologic measures for orthostatic treatment
 - Compression stockings
 - Abdominal binder
 - Slow positional changes
 - Increasing fluid/salt intake
 - Crossing legs, tip-toeing
- Treatment of AAG
 - Immunomodulatory therapies (IVIG, plasma exchange, mycophenolate mofetil, cyclophosphamide)
 - Fludrocortisone
 - Midodrine
 - Droxidopa

Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial (Neurology 2014)

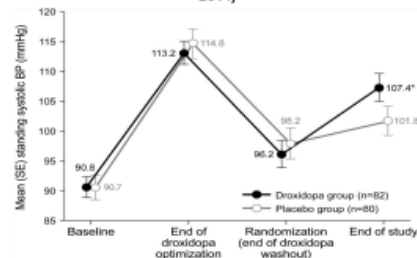


Figure 3: Mean standing systolic blood pressures in droxidopa trial

TEACHING POINTS

- Always keep a broad differential diagnosis in mind when evaluating a patient with orthostatic hypotension – try to avoid anchoring bias.
- Autoimmune autonomic ganglionopathy (AAG) is a rare cause of autonomic dysfunction associated with +gnAChR antibodies.
- Consider droxidopa for management of refractory neurogenic orthostatic hypotension.

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