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:
  - Laying – 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

Table 2. Peripheral Autonomic Disorders Commonly Associated with Orthostatic Hypotension.

Disorder	Associated Features	Comments	Diagnostic Tests
Diabetes	Usually but not always associated with generalized polyneuropathy; orthostatic hypotension may occur early in clinical course; other autonomic manifestations may include gastroparesis, diarrhea, constipation, urinary retention, and erectile dysfunction[1,2]	Most common cause of autonomic dysfunction in developed countries	Fasting blood glucose and glucose tolerance test
Hereditary amyloidosis (familial amyloid polyneuropathy)	Usually associated with generalized polyneuropathy, with predominant small-fiber (pain and temperature) abnormalities; often associated conditions include carpal tunnel syndrome (often an early manifestation), cardiomyopathy and conduction abnormalities, vitreous opacities, and increased intraocular pressure; scalloped pupils may be present; diarrhea and weight loss are common; macroglossia is not present[3,4]	Develops in the 3rd to 5th decade of life; characterized by deposition of insoluble beta-fibrillar proteins in epineurium, perineurium, and endoneurium, perineurial tissues, and neural vasculature; most common amyloid precursor is mutant transthyretin; sporadic cases may be common; mutations in genes encoding for apolipoprotein A1, fibrinogen Aα, lysozyme, and gelsolin also give rise to amyloidosis	Assessment of fat aspirate or rectal- or gingival-biopsy specimen for amyloid deposits; genetic testing
Primary amyloidosis (AL amyloidosis; immunoglobulin light chain–associated)	Usually associated with generalized polyneuropathy, with predominant small-fiber (pain and temperature) abnormalities; often associated conditions include carpal tunnel syndrome (often an early manifestation), cardiac involvement, macroglossia (with tooth indentation in about 30% of patients), periorbital purpura, easy bruising, organomegaly, weight loss, nephrotic syndrome, and edema[3,5,6]	Presents in the 6th to 7th decade of life; caused by production of amyloidogenic monoclonal immunoglobulin protein (M protein, light chains or light-chain fragments) by monoclonal population of bone marrow cells; deposition of insoluble beta-fibrillar proteins in epineurium, perineurium, and endoneurium, perineurial tissues, and neural vasculature	Assessment of fat aspirate or rectal- or gingival-biopsy specimen for amyloid deposits; immunoelectrophoresis of blood and urine
HSAN type II (also called familial dysautonomia)[7]	Insensitivity to pain and temperature stimuli but superficial cutaneal, absence of reflexes (diminished), hypoactive corneal and tendon reflexes, and absence of lingual fungiform papillae[7,8]	An autosomal recessive disorder seen primarily in Ashkenazi Jewish children	Test for a splicing mutation in the IkB kinase-associated protein gene (IKBKAP), which is present in 99.5% of patients
Idiopathic immune-mediated autonomic neuropathy	Gastrointestinal hypomotility, urinary retention, xerostomia, and xerophthalmia[9,10]	May respond to immunomodulating therapy	Test for nicotinic ganglionic acetylcholine receptor antibodies, which are present in some patients
Sjögren's syndrome	Sicca syndrome, features of dysautonomia other than orthostatic hypotension may occur[11]	Autonomic manifestations may be present with normal serologic tests	Tests for anti-Ro (SSA) and anti-La (SSB) antibodies
Paraneoplastic autonomic neuropathy	Autonomic features of underlying cancers may be first manifestation of a cancer[12]	Occurs most often in patients with small-cell lung cancer; also seen in non–small-cell lung cancer, cancers of gastrointestinal tract, prostate, breast, bladder, kidney, pancreas, testicle, and ovary	Tests for anti-Hu antibodies (type 1 anti-neuronal nuclear antibodies [ANNA-1]), which are most prevalent; type 2 Purkinje-cell antibodies (PCA-2); and collapsin response mediator protein 5 (CRMP-5), which may also be present

* HSAN denotes hereditary sensory and autonomic neuropathy.

Figure 1: Neurogenic orthostatic hypotension caused by peripheral autonomic disorders

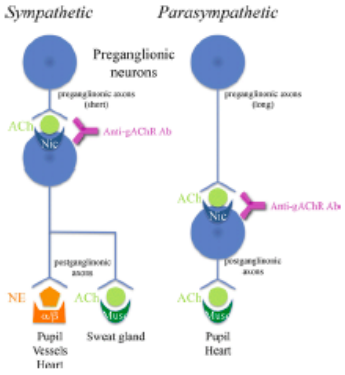

Figure 2: Mechanism of Anti-gnAChR Ab affecting sympathetic and parasympathetic nervous systems in AAG

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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 orthostasis 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)

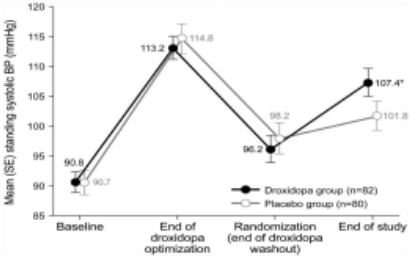

Figure 3: Mean standing systolic blood pressures in droxidopa trial

TEACHING POINTS

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