Neurogenic Syncope

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Neurology and Sleep Medicine
Neurogenic Syncope

- Anatomy of Autonomic Nervous System
- Physiology of sympathetic and parasympathetic system
- Etiology of syncope
- Differential diagnosis of syncope
- Syncope associated with Neurodegenerative disorders
The Parasympathetic Division

Parasympathetic division (craniosacral)
Sympathetic Responses

- Stress ↑ sympathetic system ↑ fight-or-flight response.
- ↑ production of ATP.
- Dilation of the pupils.
- ↑ heart rate and blood pressure.
- Dilation of the airways.
- Constriction of blood vessels that supply the kidneys and gastrointestinal tract.
Sympathetic Responses continued..

• ↑ blood supply to the skeletal muscles, cardiac muscle, liver and adipose tissue
• ↑ glycogenolysis ↑ blood glucose.
• ↑ lipolysis.
Parasympathetic Responses

• Rest-and-digest response.
• Conserve and restore body energy.
• ↑ digestive and urinary function.
• ↓ body functions that support physical activity.
Integration and Control of Autonomic Functions

• Direct innervation- brain stem and spinal cord.
• Hypothalamus is the major control and integration center of the ANS.
• It receives input from the limbic system.
### Causes of Syncope

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence (Mean) %</th>
<th>Prevalence (Range) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflex-mediated:</td>
<td></td>
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<tr>
<td>• Vasovagal</td>
<td>18</td>
<td>8-37</td>
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<tr>
<td>• Situational</td>
<td>5</td>
<td>1-8</td>
</tr>
<tr>
<td>Carotid Sinus</td>
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<tr>
<td>Orthostatic hypotension</td>
<td>8</td>
<td>4-10</td>
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<tr>
<td>Medications</td>
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<td>1-7</td>
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<tr>
<td>Psychiatric</td>
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<td>1-7</td>
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<tr>
<td>Neurological</td>
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<td>3-32</td>
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<tr>
<td>Organic Heart Disease</td>
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<td>1-8</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
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<td>4-38</td>
</tr>
<tr>
<td>Unknown</td>
<td>34</td>
<td>13-41</td>
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</tbody>
</table>

Syncope: Etiology

1. Neurally-Mediated
   - Vasovagal
   - Carotid Sinus
   - Situational
     - Cough
     - Post-micturition
   24%

2. Orthostatic
   - Drug Induced
   - ANS Failure
     - Primary
     - Secondary
   11%

3. Cardiac Arrhythmia
   - Brady
     - Sick sinus
     - AV block
   - Tachy
     - VT
     - SVT
   - Long QT Syndrome
   14%

4. Structural Cardio-Pulmonary
   - Aortic Stenosis
   - HOCM
   - Pulmonary Hypertension
   4%

5. Non-Cardiovascular
   - Psychogenic
   - Metabolic e.g. hyperventilation
   - Neurological
   12%

Unknown Cause = 34%

DG Benditt, UM Cardiac Arrhythmia Center
Neurally Mediated Syncopal Syndromes

- Vasovagal, Vasodepressor, Reflex syncope
- Most common with prolonged standing or dehydration or both
- Most common neurally mediated syncope syndrome are triggered with the mechanism such as emotional faint, carotid sinus syncope, micturition or gastrointestinal syncope, glossopharyngeal or trigeminal syncope, exercise syncope commonly seen in patients with aortic stenosis
- Mainly caused by acute hemodynamic reaction produced by sudden change in autonomic nervous system activity
Physiology of NMS

• Abnormality in afferent pathway
  1. The normal pattern of autonomic outflow that maintains BP in standing position is acutely reversed
  2. Parasympathetic outflow to the sinus node of heart is increased causing bradycardia while sympathetic outflow to the blood vessels is reduced causing profound vasodilation
  3. Syncope can be triggered with pain or fear procedure by descending signal from cortical, limbic or hypothalamic structure to autonomic control centers in the medulla
Physiology of NMS

1. This can also be triggered by peripherally stimulation of sensory receptor that response to pressure or mechanical deformation caused by vagus and glossopharyngeal nerve

2. Can occur with compression of the carotid baroreceptor in the neck or rapid emptying of distended bladder or distention of the gastrointestinal tract

• Abnormality in efferent pathway

1. Increase in parasympathetic efferent activity to sinus note producing bradycardia or even a sinus arrest
Disorders of Orthostatic Tolerance

- With significant fall in systemic arterial pressure
  - **Orthostatic hypotension**
    1. Drugs: Anti-hypertensives, dopamine agonist
    2. Chronic autonomic failure syndrome
    3. NMS (vasovagal, vasodepressor or reflex syncope; carotid sinus syncope; micturition of GI syncope, glossopharyngeal/trigeminal syncope; ventricular, neurocardiogenic syncope; exercise syncope in aortic stenosis)

- **Acute decrease in cardiac output**
  1. Cardiac arrhythmia
  2. Pulmonary embolism
Disorders Orthostatic Intolerance

- Without significant fall in systemic arterial pressure

1. Acute increase in cerebral vascular resistance
   - Hyperventilation/panic attack
   - Cough syncope, trumpet player syncope
2. Postural tachycardia syndrome
3. Cerebrovascular deconditioning due to prolonged bedrest
Mechanism of Action

- Orthostatic hypotension
- Definition: Persistent decrease in systolic blood pressure of 20 mm Hg and in diastolic pressure of 10 mm Hg
- In standing position, arterial pressure and brain level is 20 mm Hg lower than arterial pressure at the level of aortic arch
- Auto-regulatory mechanisms keep cerebral blood flow fairly constant despite of the change of cerebral arterial pressure
- If cerebral arterial pressure falls below 40 mmHg, cerebral auto-regulation cannot prevent a significant decrease in cerebral blood flow
Mechanism of Action

• In erect position, gravitational force produce a downward translocation of approximately 800 mL of blood from thorax to legs and pelvis
• 70% of intravascular volume is below the level of heart
• Blood in the leg veins—venous return to heart is reduced—cardiac output falls—autonomic reflexes to increase heart rate and peripheral vascular resistant to maintain systemic arterial pressure and adjust blood flow to target organs
Medication Induced Orthostatic Hypotension

- This is mainly common in elderly due to impaired reflux
- Antihypertensive drug, Dopaminergic agonist, neuroleptics, antidepressant, alpha receptor blockers
- Post prandial orthostatic hypotension—mainly seen in elderly
- Believed due to impaired baroreflex–mediated vasoconstriction
- Chronic autonomic failure; Impaired baroreflex–mediated norepinephrine release from postganglionic sympathetic nerve terminal leading to low circulatory levels of angiotensin II caused by impaired secretion of renin—leading to impaired vasoconstriction and reduced invascular volume
Orthostatic Intolerance Without Significant Hypotension

• Cerebral perfusion pressure equals cerebral arterial pressure minus intracranial pressure

• **Causes for increased ICP**
  1. Panic attacks: Hyperventilation contributing to hypercapnia
  2. Repetitive coughing: Increased intra-thoracic and intra-abdominal pressure transmitted via the great veins of cranial vault causing transient elevation of ICP
  3. Playing a wind instrument
  4. Straining to defecate
Orthostatic Intolerance Without Significant Hypotension

• Causes to reduced cerebral arterial pressure
• Hypocapnia caused by hyperventilation
• Other causes
  1. Subclavian steal syndrome
  2. Postural tachycardia syndrome
  3. Cardiovascular deconditioning due to prolonged bedrest
Clinical Differentiation

• Orthostatic hypotension with normal autonomic reflexes
  while standing position drop in systolic pressure with marked reflex tachycardia

• Orthostatic hypotension with sympathetic failure
  while standing position drop in both systolic and diastolic pressure with minimal or little increase in the heart rate
Clinical Symptoms

• Orthostatic hypotension without autonomic failure
  Loss of consciousness associated with following:
  1. Sympathetic hyperactivity- Palpitation
  2. Piloerection (goosebumps)
  3. Pallor due to cutaneous vasodilation and diaphoresis
  4. Cold sweats (combination of cutaneous vasodilation and diaphoresis produces the peculiar phenomena)
  5. Flushed (Thermoregulatory sweating occurs along the skin vasodilation to dissipate heat and the person appear red or flushed)
  6. Blurred vision (caused by pupillary dilation)
Clinical Symptoms

• Orthostatic hypotension with autonomic failure will not experience above mentioned sympathetic response
Symptoms of Orthostatic Hypotension

• Visual disturbances such as blurring, tunneling, darkening of vision, or seeing stars called scotomata caused by ischemia of optic nerve and occipital cortices and sensation of dizziness, lightheadedness, giddiness, faint feeling and occasionally yawning
Causes of Syncope-like States

- Migraine*
- Acute hypoxemia*
- Hyperventilation*
- Somatization disorder (psychogenic syncope)
- Acute Intoxication (e.g., alcohol)
- Seizures
- Hypoglycemia
- Sleep disorders

* may cause ‘true’ syncope
Differential Diagnosis of Syncope

- Seizure disorder
- Narcolepsy with cataplexy
- Syncope associated with neurodegenerative disorder
- Psychogenic disorder
## Conventional Diagnostic Methods/Yield

<table>
<thead>
<tr>
<th>Test/Procedure</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td><strong>(based on mean time to diagnosis of 5.1 months)</strong></td>
<td></td>
</tr>
<tr>
<td>History and Physical (including carotid sinus massage)</td>
<td><strong>49-85%</strong> ¹, ²</td>
</tr>
<tr>
<td>ECG</td>
<td><strong>2-11%</strong> ²</td>
</tr>
<tr>
<td>Electrophysiology Study without SHD*</td>
<td><strong>11%</strong> ³</td>
</tr>
<tr>
<td>Electrophysiology Study with SHD</td>
<td><strong>49%</strong> ³</td>
</tr>
<tr>
<td>Tilt Table Test (without SHD)</td>
<td><strong>11-87%</strong> ⁴, ⁵</td>
</tr>
<tr>
<td>Ambulatory ECG Monitors:</td>
<td></td>
</tr>
<tr>
<td>• Holter</td>
<td><strong>2%</strong> ⁷</td>
</tr>
<tr>
<td>• External Loop Recorder (2-3 weeks duration)</td>
<td><strong>20%</strong> ⁷</td>
</tr>
<tr>
<td>• Insertable Loop Recorder (up to 14 months duration)</td>
<td><strong>65-88%</strong> ⁶, ⁷</td>
</tr>
<tr>
<td>Neurological †</td>
<td><strong>0-4%</strong> ⁴, ⁵, ⁸, ⁹, ¹⁰</td>
</tr>
</tbody>
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⁵ Kapoor, *JAMA*, 1992  
⁶ Krahn, *Circulation*, 1995  
* Structural Heart Disease  
† MRI not studied
Seizure

- Typically aura associated with complex partial seizure but not with generalized tonic clonic seizure
- Usually associated with tonic or myoclonic activity
- Prolonged post-ictal phase
- Can be associated with tongue biting or urinary/bowel incontinence
- Post-confusion episodes
Narcolepsy with Cataplexy

• Abrupt onset of REM sleep leading to cataplexy
• Abrupt atonia of muscle associated with REM sleep
• Usually associated with clinical history of excessive daytime sleepiness
• Can be triggered with sudden stimulation
• Last for few seconds to minutes
• No post-ictal state
• No other prodromal aura
Syncope Associated with Neurodegenerative Disorder

• Synucleinopathies
  1. Multiple system atrophy
  2. Parkinson’s disease
  3. Pure autonomic failure
  4. Dementia of Lewy body

• Tauopathies
  1. Alzheimer’s disorder
  2. Frontotemporal dementia
  3. Progressive supranuclear palsy
  4. Inherited and sporadic ataxias
  5. Prion disorder
Patho-physiology

• Lewy body formation in autonomic ganglion
• Pure autonomic failure: Lewy body formation and neurodegeneration of postganglionic autonomic neurons
• Parkinson’s disease: neuronal degeneration in substantia nigra associated with Lewy body formation and postganglionic autonomic neuron
• Multisystem atrophy: Neuronal degeneration in basal ganglia, brain stem, spinal cord and cerebellum without lewy body formation
Parkinson’s Disease

• Typical symptoms of autonomic failure in PD include constipation, urinary urgency or incontinence, orthostatic or postprandial lightheadedness, heat or cold intolerance, and erectile dysfunction.
• Characteristic signs include difficulty swallowing, decreased bowel sounds, and orthostatic hypotension (OH).
• 40% of Parkinson patient suffered with orthostatic hypotension
• Sympathetically mediated vasoconstriction is impaired leading to drop in blood pressure upon standing
Parkinson’s Disease

- Due to neuronal degeneration there is a reduction of neurotransmitters norepinephrine and precursor of norepinephrine
- Reduced cardiac sympathetic denervation
- Reduced intensity of postganglionic noradrenergic nerve fiber to heart
- Dopamine in periphery act as a diuretic and leads to vaso-dilation
- Patients with Parkinson’s disease who suffered with autonomic failure and reduced cardiac sympathetic denervation are increase risk of syncope associated with levodopa treatment
Dementia of Lewy Body

- Fluctuations in alertness
- Cognition, and visual hallucinations are core features of DLB.
- Cognitive or psychiatric manifestations at initial presentation, but they may also present with parkinsonian features alone.
- Autonomic features typically occur after the development of cognitive changes, but DLB may also present with parkinsonism or autonomic dysfunction, or both, without significant cognitive or psychiatric abnormalities.
- Chronic autonomic failure is virtually universal in DLB. Urinary incontinence and constipation are very common (Horimoto et al, 2003). Neurogenic OH also is common and can precede cognitive and motor deficits by several years
Multiple System Atrophy

• MSA–C, MSA–p
• Progressive disorder with life expectancy of 6-9 years
• Cerebellar type: significant gait and limb ataxia
• Parkinson type: Resting tremor, bradykinesia, stooging, reduced arm swing
• Other symptoms includes dysarthria, dystonia, stridor of voice, pseudobulbar affect, postural instability, myoclonus, rapid decline in motor activity
Alzheimer’s Disease

- Sympathetic noradrenergic neurons are intact
- normal plasma norepinephrine level
Fronto-temporal Dementia

- Cortical atrophy in frontal and temporal region
- Dementia associated with aphasia, personality disorder
- Mild autonomic dysfunction include sialorrhea, hyperhidrosis, urinary frequency or incontinence, heat intolerance, erectile dysfunction, or dry eyes or mouth, but there are no reports of OH, suggesting that sympathetic noradrenergic outflow to blood vessels is intact. Impaired cardiac vagal control, abnormal pupillary accommodation, and sudomotor dysfunction have been noted
Conclusion

• Detailed clinical history
• Conventional diagnostic testing helpful in Cardiogenic syncope
• Neurologic examination to help differentiate Neurodegenerative disorder
• Treatment of underlying neurologic disorder and supportive measures