Pathophysiology of Acute Hepatic Porphyria (AHP)
Introduction to the Pathophysiology of AHP

- Acute exacerbations are precipitated by events that either directly induce the enzyme aminolevulinic acid synthase 1 (ALAS1) or increase the demand for heme synthesis in the liver, and subsequently disinhibit ALAS1.

- Upregulation of ALAS1 is the key contributor to elevated levels of the neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG).

- Elevated levels of ALA and PBG are thought to be responsible for the neuropathologic effects in AHP and accompanying signs and symptoms.

- AHP exacerbations and, for some patients, chronic symptoms are associated with widespread neurologic lesions, leading to dysfunction across the:
  - Autonomic nervous system
  - Central nervous system
  - Peripheral nervous system

Mechanisms for the Increase in ALA and PBG by Key Regulating Enzyme ALAS1

AHP: characterized by defects in genes encoding heme biosynthesis pathway enzymes in the liver\(^1\)-\(^3\)

Deficiency in enzyme activity leads to decreased metabolism of the neurotoxic intermediates ALA and PBG\(^2,4\)

Disease precipitating factors can increase the demand for heme, which through feedback regulation increases ALAS1\(^5\)

Upregulation of ALAS1 leads to overproduction of ALA and PBG, which can enter the circulatory system and are thought to be the cause of AHP exacerbations\(^2,5,6\)

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Induction of ALAS1 by Precipitating Factors is the Key Factor Involved in AHP Exacerbations

• AHP is a disease of low penetrance\(^1\)
  – Although the proportion of patients who develop overt clinical disease is <20%, manifest disease can be associated with debilitating and even life-threatening exacerbations\(^1\)
  – Because penetrance is relatively low, not all family members with a mutation for the disease will develop clinical disease\(^2\)

• Low penetrance suggests the key role of environmental factors and possibly genetic modifiers in precipitating exacerbations\(^3\)

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Proposed Pathophysiologic Mechanisms for Neurotoxicity by ALA Based on Existing Publications

- **Inhibition of peripheral myelin formation**

- **Decrease in Na+/K+ pump function, leading to axonal depolarization**

- **Oxygen free radical formation causing oxidative stress**

**Axonal dysfunction**

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Clinical Evidence for the Role of ALA and PBG in AIP-Associated Exacerbations

Background

- A retrospective analysis of 23 consecutive patients with porphyria-like symptoms from Taiwan
- AIP documented in 12 patients based on history of past exacerbations, clinical manifestations, precipitating factors, elevated urinary ALA and PBG levels, and molecular genetic defects

Results

- All 12 patients with AIP-associated neuropathies had motor paresis during or after a severe attack with CNS manifestations
- Urinary ALA and PBG levels were elevated during or after the exacerbation in all 12 patients with AIP

Electrophysiological Findings and 24-Hour Urine ALA and PBG Levels in 12 Patients with AIP

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Motor Nerve Conduction Velocity and Electromyography</th>
<th>ALA Level (mg/day)*</th>
<th>PBG Level (mg/day)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP patients with motor nerve abnormalities (n=7)</td>
<td>Motor axonal polynueropathy involving upper extremities</td>
<td>38.6</td>
<td>136.9</td>
</tr>
<tr>
<td></td>
<td>Asymmetric motor neuropathy prominently involving both radial and left peroneal nerve</td>
<td>34.3</td>
<td>78.9</td>
</tr>
<tr>
<td></td>
<td>Axonal motor polynueropathy</td>
<td>63.9</td>
<td>52.1</td>
</tr>
<tr>
<td></td>
<td>Absence of all sensory and motor action potentials</td>
<td>20.8</td>
<td>70.0</td>
</tr>
<tr>
<td></td>
<td>Axonal motor neuropathy</td>
<td>87.3</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Bilateral radial neuropathy</td>
<td>198.1</td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td>Bilateral radial motor neuropathy</td>
<td>38.0</td>
<td>38.0</td>
</tr>
<tr>
<td>AIP patients with normal findings (n=5)</td>
<td>Normal</td>
<td>7.7-318.6</td>
<td>11.4-154.7</td>
</tr>
</tbody>
</table>

*Reference range for 24-hour urinary ALA=0.3-7.4 mg/day and PBG=0-2 mg/day.

Summary

Pathophysiology of AHP

- Exacerbations and, for some patients, chronic symptoms are associated with widespread neurologic lesions, leading to dysfunction across the autonomic, central, and peripheral nervous systems.\(^1,2\)
- Elevated levels of the neurotoxic intermediates ALA and PBG are thought to be responsible for the neuropathologic effects.\(^2,3\)

Mechanisms of ALA neurotoxicity

- ALA is especially thought to be neurotoxic, with various proposed mechanisms leading to axonal dysfunction.\(^4-6\)
  - Inhibition of myelin formation.\(^4\)
  - Decrease in Na+/K+ pump function, leading to axonal depolarization.\(^5\)
  - Oxygen free radical formation causing oxidative stress.\(^6\)

Clinical evidence for the role of ALA and PBG in AHP exacerbations

- In 12 patients retrospectively diagnosed with AIP, urinary ALA and PBG levels were elevated during or after exacerbations in all patients.\(^7\)
- Other studies have shown that PBG and ALA are elevated during and after AHP exacerbations.\(^8,9\)