Monthly Mito
EXPERT SERIES
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Friday, October 9th
12:00pm EST / 9:00am PST

WELCOME

Overlap Between
Mitochondrial Disorders
and Disorders of
Neurotransmitter
Metabolism

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Director of the Mitochondrial Program
Co-Director of the Neurometabolic Program
Boston Children's Hospital
Neurotransmitters: Body’s Chemical Messengers

- Molecules used by the nervous system to transmit messages between neurons, or from neurons to muscles

- Dopamine, serotonin, glutamate, GABA, acetylcholine convey information from one neuron (message sender) to another "target" neuron (message recipient)

https://qbi.uq.edu.au/brain/brain-physiology/what-are-neurotransmitters
• Molecules used by the nervous system to transmit messages between neurons, or from neurons to muscles

• **Dopamine, serotonin, glutamate, GABA, acetylcholine** convey information from one neuron (message sender) to another "target" neuron (message recipient)

• The small space between the two is called a synapse

• Communication between two neurons happens in the synaptic cleft

https://www.google.com/search?q=neurotransmitters
Dopamine and Serotonin

Dopamine Pathways

- Frontal cortex
- Nucleus accumbens
- VTA
- Striatum

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Serotonin Pathways

- Substantia nigra
- Striatum
- Raphe nuclei
- Hippocampus

Functions
- Mood
- Memory processing
- Sleep
- Cognition
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**Functions**
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- Cognition
Aromatic Amino Acid Decarboxylase (AADC) Deficiency

Tyrosine

Tyrosine hydroxylase

L-Dopa

Tryptophan

Tryptophan hydroxylase

5-HTP

AADC

Dopamine

Serotonin

Norepinephrine

Melatonin

Epinephrine

Courtesy of K. Hyland
Effect of AADC Deficiency on Dopamine, Serotonin, Epinephrine, and Norepinephrine Metabolism

Tyrosine hydroxylase

Tyrosine → L-Dopa → Dopamine → Norepinephrine → Epinephrine

Tryptophan hydroxylase

Tryptophan → 5-HTP → Serotonin → Melatonin

AADC

Courtesy of K. Hyland
Effect of AADC deficiency on dopamine, serotonin, epinephrine and norepinephrine metabolism

Tyrosine hydroxylase

Tyrosine → L-Dopa

Tryptophan hydroxylase

Tryptophan → 5-HTP

AADC

Dopamine

Serotonin

Norepinephrine

Epinephrine

Axial hypotonia
Limbo hypertonia

Movement disorders

Dystonia
Rigidity
Hypokinesia
Tremor
Parkinsonism

Oculogyric crises

Courtesy of K. Hyland
Effect of AADC deficiency on dopamine, serotonin, epinephrine and norepinephrine metabolism

Autonomic instability:

- Ptosis, frequently severe
- Excessive sweating
- Nasal congestion
- Arterial hypotension, bradycardia
- Temperature instability, especially hypothermia

Tyrosine hydroxylase

L-Dopa

AADC

5-HTP

Tryptophan hydroxylase

Dopamine

Serotonin

Norepinephrine

Epinephrine

Melatonin

Courtesy of K. Hyland
Effect of AADC deficiency on dopamine, serotonin, epinephrine and norepinephrine metabolism

Autonomic instability:
- Ptosis, frequently severe
- Excessive sweating
- Nasal congestion
- Arterial hypotension
- Temperature instability, especially hypothermia
- Mood instability, irritability
- Sleep problems

Tyrosine hydroxylase
Tyrosine → L-Dopa
L-Dopa → Dopamine
Dopamine → Norepinephrine
Norepinephrine → Epinephrine

Tryptophan hydroxylase
Tryptophan → 5-HTP
5-HTP → Serotonin
Serotonin → Melatonin

AADC enzyme is missing.
Patients with AADC deficiency present very early.

Symptoms start in the first months of life, yet many of them are not diagnosed until much later.

One of the key symptoms of AADC deficiency is developmental delay.

Most children do not reach any motor milestones.

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Healthy AADC Deficiency

<table>
<thead>
<tr>
<th>Healthy</th>
<th>AADC Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hold Head Upright</td>
<td>3-4 months$^a$</td>
</tr>
<tr>
<td>Sitting</td>
<td>9 months$^a$</td>
</tr>
<tr>
<td>Standing</td>
<td>12 months$^a$</td>
</tr>
<tr>
<td>Walking</td>
<td>15 months$^a$</td>
</tr>
</tbody>
</table>

$^a$Based on Denver II Developmental Milestone chart.

4 old boy from Saudi Arabia

At 6 weeks of age --- episodes suggestive of seizures --- noted to be hypoglycemic

At 7 months --- tonic episodes with eye deviation that were felt to be seizures. Treated with antiepileptics

At 9 months, evaluation for disorders of glucose metabolism
Several admissions with video EEG telemetry: episodes are not seizures

Episodes appear to represent dystonia in combination with oculogyric crises

Exome sequencing revealed homozygous mutation in *DDC* gene

Neurotransmitter metabolite testing on CSF consistent with AADC deficiency
Consensus Guidelines Recommendation: Core Diagnostic Test to Confirm AADC Deficiency

2 out of 3 core diagnostic tests should be positive to confirm AADC deficiency:

- **CSF Neurotransmitter Metabolites Panel**
  - 5-HIAA
  - HVA
  - MHPG

- **Single Gene or Genetic Panel Testing**
  - Mutation of the DDC gene

- **Plasma Enzyme Assay**
  - Low levels of AADC enzyme activity in plasma

MHPG, 3-methoxy-4-hydroxyphenylglycol.

*The appendix includes the pathway for production and metabolism for serotonin, dopamine, and other catecholamines.

AADC Deficiency Has Been Documented Worldwide

AADC deficiency can affect patients of varying populations\(^3\):
- Asian
- Caucasian
- Arabic
- Iranian
- Jewish

Disease first described in 1990
More prevalent in Asian population

**Prevalence of AADC deficiency**

- **Predicted birth rates**
  - US 1/42,000 - 1/90,000
  - EU 1/118,000
  - Japan 1/182,000
  
 Mean age of symptom onset **2.7 months**

 Mean age at diagnosis **3.5 years**

 (median 13 months; range: 2 months–23 years)

- **Prevalence**
  - Worldwide ~ 1800
  - US 840
  - EU 853
  - Japan 125

Mitochondrial Disorders

Image by Mariana Ruiz Villarreal

http://cmapspublic.ihmc.us/rid=1102536487930_333741980_4083/ATPanim.gif
http://www.mammag.uci.edu/foswiki/bin/view/MAMMAG/PhilosophicalPremiseOfMAMMAG
Mitochondrial Disorders

- Arise as a result of dysfunction of the mitochondrial respiratory chain
- Disorders impacting the structure or function of the mitochondria
- Tissues and organs that are highly dependent on aerobic metabolism are affected the most

Source: Mitochondria Research Society
Mitochondrial Disorders

“Any symptom, any organ, any age, any mode of inheritance”

• Hundreds of different diseases
• Different combination of symptoms
• Many genes causing the same disease
• The same gene can cause many different types of MDs
• Neurological symptoms are very common, especially in children with MDs
"If organelles could talk," available at: www.beatricebiologist.com
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Prevalence of Mitochondrial Disorders

• At least 1 in 4,300 of adults will develop mitochondrial disease

Source: The Mariani Foundation Center for the Study of Pediatric Mitochondrial Diseases, hosted by the Molecular Neurogenetics Unit of the IRCCS Foundation Neurological Institute "C. Besta" at Bicocca http://www.mitopedia.org/eng/img/mitocondri2_z.jpg

Source: U.S. National Library of Medicine
Why are patients with disorders of NT metabolism diagnosed with MDs?

- Many common features
- Lack of awareness
- Problems with obtaining genetic testing
Disorders of NT metabolism

• developmental delay
• abnormal muscle tone
• dysautonomia
• oculogyric crises can look like seizures
• difficult to diagnose

• Present early
• No newborn screening at the moment, but it is possible

Mitochondrial Disorders

• developmental delay
• abnormal muscle tone
• dysautonomia
• seizures
• difficult to diagnose

• Can present early
• No newborn screening, hardly possible
<table>
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<tr>
<th>Disorders of NT metabolism</th>
<th>Mitochondrial disorders</th>
</tr>
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<tbody>
<tr>
<td>• Affect primarily CNS</td>
<td>• Affect multiple organs</td>
</tr>
<tr>
<td>• Diagnosis can be made by metabolic CSF analysis</td>
<td>• Metabolic screening can suggest, but is never fully diagnostic of a MD</td>
</tr>
<tr>
<td>• Brain MRI normal or nonspecific</td>
<td>• Brain MRI frequently abnormal, esp. in children, but can be normal</td>
</tr>
<tr>
<td>• Metabolically stable</td>
<td>• Metabolically unstable</td>
</tr>
<tr>
<td>• Can be diagnosed by gene panels</td>
<td>• Can be diagnosed by gene panels, but frequently requires whole exome sequencing and mtDNA sequencing</td>
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Invitae and PTC Therapeutics have partnered to offer the PTC Pinpoint sponsored testing program, which provides no-charge genetic testing and counseling for individuals in the US suspected of having a neurotransmitter disorder such as AADC deficiency.

The panel analyzes up to 37 genes that are associated with disorders of monoamine metabolism, GABA metabolism, and neurotransmitter receptors and transporters utilizing either blood or saliva samples.

Individuals tested through the PTC Pinpoint Program are eligible for no charge post-test genetic counseling to help interpret their test results.

No age limit as to whom can be tested.

www.invitae.com/PTC-pinpoint
Diagnosis of Mitochondrial Disorders

Sequence analysis of the entire mitochondrial genome with quantification of heteroplasmy levels

Detection of deletions with breakpoints and heteroplasmy

Next generation (NGS) panels (up to 1100 genes)

Whole genome (exome) sequencing

Around 1400+ nuclear genes are involved in proper mitochondrial function

Science, VOL 349 ISSUE 6255
Disorders of NT metabolism

- Specific treatments: Dopamine and serotonin agonists, Melatonin
- Gene therapy for AADC is available

Mitochondrial disorders

- No specific therapies with rare exceptions
- Gene therapies not available
Treatment of AADC Deficiency
Several companies around the world developed gene therapy in which virus carrying the deficient enzyme (aromatic amino acid decarboxylase) is injected directly in the brain.
Summary

• Disorders of Neurotransmitter Metabolism and Mitochondrial Disorders are underdiagnosed, but diagnosis of NTs is less complicated.

• In spite of being very different conditions, they may have similar clinical presentations.

• Gene therapy is on the horizon for NTs, but not yet for MDs.
Thank you for your attention