Norepinephrine in Health and Disease

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Tyrosine \rightarrow \text{TH} \quad BH_4 \quad \text{Iron} \quad O_2 \quad \text{DOPA}
DOPA + Vitamin B6 $\rightarrow$ Dopamine
DOPA + Carbidopa = Sinemet™
DBH

$O_2$

Vitamin C

VMAT

Copper

Proton Pump

Dopamine (DA)

Norepinephrine (NE)
TYR \[\rightarrow\] DOPA \[\rightarrow\] DA

DA \[\rightarrow\] NE

TH \[\rightarrow\] LAAAD

DBH

Copper

Vitamin C

O\(_2\)

VMAT

Proton Pump

Vitamin C
Sympathetic Noradrenergic System (SNS) Underactivity or Failure

**Drugs**
- Diabetes
- Parkinson disease (PD)
- Cancer (paraneoplastic)
- Multiple system atrophy (MSA)
- Spinal cord injury
- Pure autonomic failure
- Amyloidosis
- Familial dysautonomia
- Dopamine-beta-hydroxylase deficiency
- Acquired sensory and autonomic neuropathy
- Autoimmune autonomic ganglionopathy

**Common**

**Rare**
Spinal Cord

Cranial

Thoracolumbar Spinal Cord

SIGNS
- Ptosis
- Miosis
- Orthostatic hypotension
- Post-prandial dec. BP
- Dec. HR during exercise

SYMPTOMS
- Orthostatic intolerance
- Fatigue
- Exercise intolerance
- Heat intolerance
- Post-meal lightheadedness
- "Coat hanger" phenomenon
- No goosebumps
- Dec. ejaculation
- Dec. emotional intensity
Sympathetic Noradrenergic System (SNS) Failure

Orthostatic intolerance & hypotension
Post-prandial lightheadedness & hypotension
Heat intolerance & hypotension
Fatigue
Tendency to slow pulse rate during exercise
“Coat hanger” pain
Droopy eyelids (ptosis)
Decreased ability to ejaculate
Tendency to constricted pupils
No goosebumps
Heart Rate
bpm

Blood Pressure
mm Hg

VALSALVA

I  II  III  IV
Persistent, consistent?

No

If episodic & unexpected, consider autonomically mediated syncope.

Yes

Identifiable cause?

Yes

Drugs
Hypovolemia
Cardiac pump failure
Venous pooling
Periph. Neuropathy
CNS lesion

No

Neurogenic?

Yes

Beat-to-beat BP responses to Valsalva maneuver
Orthostatic plasma norepinephrine
Orthostatic vascular resistances

No

Peripheral NE denervation?

Yes

Cardiac sympathetic neuroimaging
Supine plasma catechols
Neuropharmacologic probes

No

Rule out hypovolemia, other non-neurogenic causes.

Main diagnoses:
If evidence of central neurodegeneration, MSA
If no central neurodegeneration, AAG

Yes

Main diagnoses:
If evidence of central neurodegeneration, PD+OH, LBD
If no central neurodegeneration, PAF
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<th>MSA_p</th>
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<td>Pyramidal, or</td>
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Neonatal Diagnosis and Treatment of Menkes Disease

Stephen G. Kaler, M.D., M.P.H., Courtney S. Holmes, B.S., M.T.,
David S. Goldstein, M.D., Ph.D., Jingrong Tang, M.D., Ph.D.,
Sarah C. Godwin, B.S., Anthony Donsante, Ph.D., Clarissa J. Liew, M.D.,
Susumu Sato, M.D., and Nicholas Patronas, M.D.

ABSTRACT

BACKGROUND
Menkes disease is a fatal neurodegenerative disorder of infancy caused by diverse mutations in a copper-transport gene, ATP7A. Early treatment with copper injections may prevent death and illness, but presymptomatic detection is hindered by the inadequate sensitivity and specificity of diagnostic tests. Exploiting the deficiency of a copper enzyme, dopamine-β-hydroxylase, we prospectively evaluated the diagnostic usefulness of plasma neurochemical levels, assessed the clinical effect of early detection, and investigated the molecular bases for treatment outcomes.

METHODS
Between May 1997 and July 2005, we measured plasma dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in 81 infants at risk. In 12 newborns who met the eligibility criteria and began copper-replacement therapy within 22 days after birth, we tracked survival and neurodevelopment longitudinally for 1.5 to 8 years. We characterized ATP7A mutations using yeast complementation, reverse-transcriptase–polymerase-chain-reaction analysis, and immunohistochemical analysis.

II-3, Age 32 mos
Norepinephrine \rightarrow \text{COMT} \rightarrow \text{SAMe} \rightarrow \text{Normetanephrine}
L-DOPA

LAAAD

Dopamine

L-DOPS

LAAAD

Norepinephrine
ALDH
VMAT2
DA
V
Leak
DOPA
TH
Reuptake
Protein cross-linking
H
2
O
2
Lipid peroxidation
Reactive oxygen species
DOPAC
AR
DOPAL
α-Synucleinopathy
MAO-A
Cu
+2
Fe
+2
Protein cross-linking
Lipid peroxidation
TH
DOPA
LAAAD
DAT
DA
V
Release
Pathway traffic
Principles of Autonomic Medicine

David S. Goldstein, MD PhD