



# HALLMARK CHARACTERISTICS OF NEURODEGENERATIVE DISORDERS

DIFFERENCES AND SIMILARITIES FOR THE BRAIN DISORDERS:  
SEVERE BPAN, RETT SYNDROME, PARKINSON'S AND ALZHEIMER'S.

7/17/2025

MARC W. FARISS, PH.D.

**PROPOSED RESEARCH PROJECT TITLE:** Dietary supplementation with safe, high-dose biotin (vitamin B7) improves neurodevelopment and reduces neurodegeneration in young children with severe BPAN Disorder and Rett Syndrome.

**HYPOTHESIS:** The absence of available essential micronutrients in the brain, such as biotin, plays an important role in delayed neurodevelopment and in neurodegeneration.

**BPAN DISORDER FEATURES:** Beta-propeller associated neurodegeneration (BPAN) disorder is caused by a spontaneous, single mutation to the x chromosome gene, *WDR45*. This mutation results in a functional loss in *WIPI4* activity, a protein important in autophagy. Young children with BPAN suffer from Rett Syndrome, characterized by delayed neurodevelopment resulting in delayed or absence of speech, standing/walking, and cognitive abilities. This delayed neurodevelopment can quickly lead to neurodegeneration before the age of five.

As described in a letter from Dr. Joseph Vithayathil, MD, PhD, Isabella Elaine Lazzara's attending physician at Children's Hospital of Philadelphia,

*"This disorder manifests as early global developmental delay, with most prominent delays in language and speech development. Epilepsy is also a common feature. These developmental features are also accompanied by delayed myelination in the brain on MRI. As patients age, this disorder progresses to include regression and loss of skills due to progressive neurodegeneration with subsequent development of parkinsonism symptoms (dystonia/movement disorders, bradykinesia, cognitive decline). Patients also show progressive accumulation of iron within basal ganglia and substantia nigra on MRI. Given this imaging finding, BPAN is one of a group of disorders called Neurodegeneration with Brain Iron Accumulation (NBIA). Regarding Isabella specifically, her current manifestations of this disorder include developmental delays and epilepsy. She also has imaging findings consistent with young children with BPAN."*

**OVERALL CONCLUSIONS:** Though the initial insults that cause Severe BPAN, Rett Syndrome, Parkinson's and Alzheimer's may be different, the cascade of toxic events that follow and result in neurodegeneration appears to be identical (common final pathway to neurodegeneration). High-dose biotin supplementation has been reported to reduce neurodegeneration in clinical and experimental models of these disorders. Presumably through a protective effect on oxidative stress, mitochondrial dysfunction and possibly the reactivation of a silenced x chromosome (in females).



Disorder Characteristics of Neurodegeneration

Severe BPAN

Rett Syndrome

Parkinson's

Alzheimer's

D I F F E R E N C E S

1. Known Initial Insult (cause)	Yes (single mutation, x chromosome)	Yes (single mutation, x chromosome)	No	No
2. Onset Age (yrs)	1+	1+	60+	60+
3. Gender Bias	Often Lethal In Males	Often Lethal In Males	Male (2x)	Female (2x)
4. Seizures	Common	Common	Rare	Uncommon
5. Delayed Neurodevelopment	Common	Common	Uncommon	Uncommon

S I M I L A R I T I E S

1. Brain Location	Substantia Nigra /Cerebrum	Substantia Nigra /Cerebrum	Substantia Nigra /Cerebrum	Cerebrum
-------------------	-------------------------------	-------------------------------	-------------------------------	----------

S I M I L A R I T I E S

2. Sequence of Pathology - Events in the Brain

a. Endoplasmic Reticulum (ER) oxidative damage (↑cell debris, ↓protein & lipid synthesis).	Yes	Yes	Yes	Yes
b. Mitochondrial oxidative damage (↓energy production, ↑cell debris).	Yes	Yes	Yes	Yes
c. Autophagy dysfunction (↓removal of cell debris).	Yes	Yes	Yes	Yes
d. Iron accumulation (inside and outside brain cells).	Yes	Yes	Yes	Yes
e. Tangles of protein and lipid (inside and outside brain cells).	Yes	Yes	Yes	Yes



Disorder Characteristics of Neurodegeneration	Severe BPAN	Rett Syndrome	Parkinson's	Alzheimer's
S I M I L A R I T I E S				
f. Neuronal cell injury & death (↓in cognitive ability, language & motor skills).	Yes	Yes	Yes	Yes
g. Oligodendrocyte injury & death (↑demyelination).	Yes	Yes	Yes	Yes
h. Microglial cells and astrocytes injury & death (↑brain inflammation).	Yes	Yes	Yes	Yes
i. Neurodegeneration accelerates.	Yes	Yes	Yes	Yes
S I M I L A R I T I E S				
3. High-Dose Biotin Supplementation				
a. Reduces Neurodegeneration (Clinical and Experimental Models)	Yes	Yes	Yes	Yes