A Summarized Review of BPAN

Tamara Gruslova & Charlotte Zhang
Neuro Network for Youth

ABSTRACT

BPAN is a subtype of neurodegeneration with brain iron accumulation (NBIA) that results in a variety of symptoms throughout its multiple stages. The most prominent symptoms include childhood developmental delays and dementia. Moreover, BPAN is a result of mutations in the WDR45 gene which results in an ineffective WIPI4 protein and impaired autophagy. Similarly, BPAN is thought to be an X-linked condition causing a large proportion of individuals with this disorder to be female. Although several therapeutics are being investigated for their use in BPAN symptom alleviation, there continues to be no cure for this disorder. Likewise, with the cause of the disorders being discovered relatively recently, there exist many challenges in the diagnosis of BPAN. In general, there are areas that are unclear. In this paper, we compile the finding of 11 pieces of literature or online sources to discuss the major advancements regarding this disorder and the areas needing further research.

FINDINGS

General Overview

- BPAN is a subtype of neurodegeneration with brain iron accumulation (NBIA) that presents childhood developmental delays.
  - Neurodegeneration With Brain Iron Accumulation (NBIA) disorder are disorders characterized by iron accumulation in the Basal ganglia (1)
  - BPAN is 1-2%
- Iron accumulation is detected by brain MRI in the substantia nigra and globus pallidus (6)
- Previously known as static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) (6)
- BPAN displays a dominant X-linked inheritance pattern and is caused by a variety of mutations in the WDR45 gene which encodes the WD40 repeat protein interacting with phosphoinositides 4 (WIPI4) (5).
- WIPI4 is essential in autophagy (cellular recycling), iron storage, participating in autophagosome biogenesis and size control.
  - Impaired autophagy results in inefficient waste removal from cells causing them to build up and cause damage
  - Neurons even more sensitive to this (5)

Symptoms of neurodegeneration (progressive damage to nervous system) (7)

- Characterized by two phases of disease progression/manifestation:
  - First phase in childhood includes early onset global developmental delay (wide spectrum) cognitive delay, epipletic seizures, speech delay, autism, Rett-like (1,4)
  - Second phase in early adulthood entails Parkinsonism, dementia, and dystonia (8)

Genetics of BPAN

- Most individuals with this disorder are female, likely because a small number of males survive until birth
- Almost all cases of BPAN are from new mutations of the gene, although is a genetic condition (X-linked condition).

Challenges of Diagnosis

- in many cases their early brain MRI studies may not show iron accumulation in the basal ganglia [2,3]. Most of the time, brain MRI in early childhood is reported normal.
  - Commonly used clinical MRI sequences have different sensitivities for detecting brain iron accumulation (1)
  - Or: absence of iron accumulation in the globus pallidus and substantia nigra in early childhood brain MRI with its appearance later, either with standard or specialized MRI technique (1)
  - early brain MRI showed no obvious iron accumulation, but multifocal spikes, or polyspikes in electroencephalograms (EEG) were observed in four patients = diagnosis (10)
  - it becomes obvious in adulthood with hyperintense signal in T1 in substantia nigra when nervous system worsens (10)
- Limited reports of patients displaying a milder phenotype in childhood make diagnosis more challenging (1)
- In the early stage, clinical phenotypes may be nonspecific and whole exome sequencing will enable early detection of BPAN in children so that patients can be diagnosed before getting worse (10)
  - whole exome sequencing: detection of variants using WES can provide a more reliable basis for the final diagnosis. (10)
  - trio exome sequencing contributes to the early detection of BPAN(10)
- Combination of whole exome sequencing and neuroimaging: 6-year-old girl with BPAN diagnosed by whole exome sequencing & Brain iron accumulation was detected by T2-weighted MRI and T2-star weighted angiography (SWAN) after showing symptoms (11). But problem is only after showing symptoms & 6 is kinda old
- If BPAN is suspected clinically, it is essential to include certain sequences that are sensitive to iron accumulation when performing the MRI. people of different ages would have different amounts of iron accumulation that would indicate a disorder so they need to be compared to normal people of their own age's iron levels in the globus pallidus,substantia nigra, and red nucleus to determine a diagnosis, and to minimize false positive interpretation of the MRI.
- BPAN should be considered in patients with mild-to-moderate childhood-onset developmental delay ,especially if epilepsy or a Rett-like phenotype is present (1)
  - BPAN should not be excluded if patient accompanied with developmental delay or epilepsy in childhood regardless of whether he showed normal imageological examination (10)

IMAGES

(10)

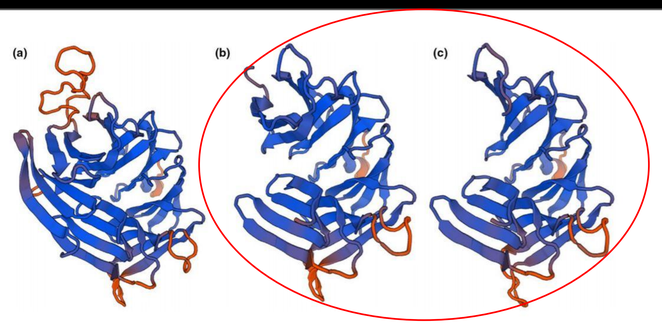
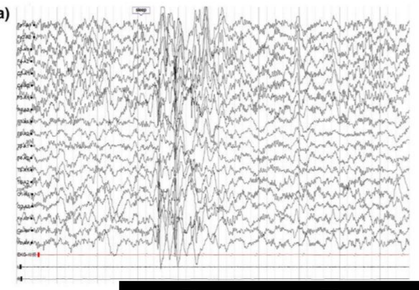


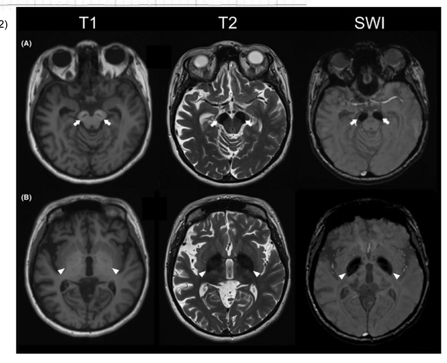
FIGURE 3 The three-dimensional structure of WDR45. (a) 3D-structure of the wild-type WDR45; (b) 3D-structure of the variant of c.806del (p.Asp269Valfs*19). (c) 3D-structure of the variant of c.726C>G (p.Tyr242*).

(a)

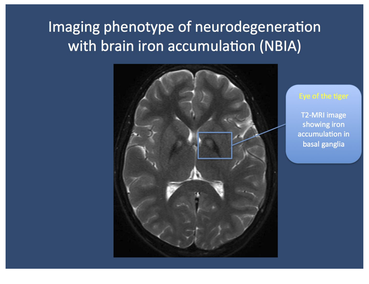


EEG showing polyspikes in age 3 patient (10)

(12)



MRI findings in BPAN. Brain MRI of the Norwegian patient at the age of 33 years, showing typical findings for BPAN. (A) Axial T1weighted image at the level of the midbrain shows symmetric hyperintense "halos" surrounding a band of central hypointensity in the substantia nigra (arrows). Axial T2-weighted and SWI image of the same area shows prominent hypointensities in the substantia nigra and cerebral peduncles (arrows). (B) Axial images at the level of the striatum show high T1 signal and low T2 and SWI signal in the globus pallidus. The low SWI signal corresponds to areas of increased iron deposition (arrowheads).



CONCLUSION

BPAN's cause was discovered relatively recently (2012) compared to other known diseases. There are limited papers on this disease due to its rarity. However, enough is known about this disorder to come up with a few conclusions: it is a X-linked disorder, caused by a mutation of the WDR45 gene that causes the resulting protein WIPI4 to be nonfunctional. This results in impaired autophagy and inefficient waste removal causing iron accumulation in the basal ganglia which in turn impairs cognitive function, leading to a variety of symptoms. Studies of Alzheimer's and other disorders involving metal ion accumulation can be applied to uncovering the mechanisms resulting in BPAN. Neuroimaging is oftentimes not sufficient in diagnosing BPAN as iron accumulation may not show in early stages, so genetic testing has to be done, with expensive trio whole exome sequencing (of the 2 parents and patient) being one of the most thorough options to detect variants (10). Thus, a likely and thorough diagnostic method is a combination of MRI (possibly T2-weighted (10)) and genetic testing early in life. Due to BPAN's variety in symptoms, it has the potential of being misdiagnosed as atypical Rett syndrome, cerebral palsy, and similar diseases, due to overlap in symptoms. This is why BPAN should not be excluded if a patient is accompanied with developmental delay or epilepsy in childhood regardless of whether he showed normal imageological examination (10). Due to overlap in the symptoms and causes of BPAN and other neurodegenerative disorders, research/therapeutic ideas and funding from related well known diseases (i.e. Alzherimer's or Parkinson's) can be utilized to study BPAN. Future studies should look into potential mechanisms through which to artificially activate autophagy in order to reverse iron accumulation and BPAN and if this is a potential treatment option.

References

1. Chard, M., Appendino, J., & Bello-Espinosa, L., et al (2019). Single-center experience with Beta-propeller protein-associated neurodegeneration (BPAN); expanding the phenotypic spectrum. *ScienceDirect, 20.* doi:https://doi.org/10.1016/j.ymgmr.2019.100483
2. Hayflick, S., Kruer, M., & Gregory, A., et. al (2013). Beta-propeller protein-associated neurodegeneration: A new X-linked dominant disorder with brain iron accumulation. *Brain, 136*(6), 1708-1717. doi:https://doi.org/10.1093/brain/awt095
3. Hoffjan, A. Ibisler, A. Tschentscher, G. Dekomien, C. Bidinost, A.L. Rosa, WDR45 mutations in Rett(−like) syndrome and developmental delay: case report and an appraisal of the literature, Mol.Cell.Probes 30(1)(2016)44–49, https://doi.org/10.1016/j.mcp.2016.01.003
4. Beta-propeller protein-associated neurodegeneration. (n.d.). Retrieved November 29, 2020, from https://www.ncbi.nlm.nih.gov/gtr/conditions/CN168656/?_ga=2.88580763.1282852205.1603550913-1400993946.1603550913
5. Hong Huan Hor, C., & Luen Tang, B. (2018). Beta-propeller protein-associated neurodegeneration (BPAN) as a genetically simple model of multifaceted neuropathology resulting from defects in autophagy. *De Gruyter, 30*(3), 2191-0200. doi:https://doi.org/10.1515/revneuro-2018-0045
6. Neurodegeneration With Brain Iron Accumulation 5; NBIA5. (2013). Retrieved November 29, 2020. https://omim.org/entry/300894
7. G. (2020, December 1). Beta-Propeller Protein-Associated Neurodegeneration. Retrieved December 05, 2020, from https://rarediseases.info.nih.gov/diseases/12570/beta-propeller-protein-associated-neurodegeneration
8. G. (2020, August 18). Beta-propeller protein-associated neurodegeneration: MedlinePlus Genetics. Retrieved December 05, 2020, from https://medlineplus.gov/genetics/condition/beta-propeller-protein-associated-neurodegeneration/
9. Zarate, Y. A., Jones, J. R., Jones, M. A., Millan, F., Juusola, J., Vertino-Bell, A., . . . Kruer, M. C. (2015). Lessons from a pair of siblings with BPAN. European Journal of Human Genetics, 24(7), 1080-1083. doi:10.1038/ejhg.2015.242
10. Tang, X., Lan, X., Song, X., Xu, W., Zhang, Y., Zhang, H., & Wu, S. (2020). De novo variants in WDR45 underlie beta-propeller protein-associated neurodegeneration in five independent families. Molecular Genetics & Genomic Medicine, 8(11). doi:10.1002/mgg3.1499
11. Okamoto, N., Ikeda, T., Hasegawa, T., Yamamoto, Y., Kawato, K., Komoto, T., & Imoto, I. (2014). Early manifestations of BPAN in a pediatric patient. American Journal of Medical Genetics Part A, 164(12), 3095-3099. doi:10.1002/ajmg.a.36779
12. Stige, K. E., Gjerde, I. O., Houge, G., Knappskog, P. M., & Tzoulis, C. (2018). Beta-propeller protein-associated neurodegeneration: A case report and review of the literature. Clinical Case Reports, 6(2), 353-362. doi:10.1002/ccr3.1358

ACKNOWLEDGEMENTS:
NNFY