Consensus clinical management guideline for beta-propeller protein-associated neurodegeneration

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ABBREVIATIONS

BPAN	Beta-propeller protein-associated neurodegeneration
NBIA	Neurodegeneration with brain iron accumulation

This review provides recommendations for the evaluation and management of individuals with beta-propeller protein-associated neurodegeneration (BPAN). BPAN is one of several neurodegenerative disorders with brain iron accumulation along with pantothenate kinase-associated neurodegeneration, PLA2G6-associated neurodegeneration, mitochondrial membrane protein-associated neurodegeneration, fatty acid hydroxylase-associated neurodegeneration, and COASY protein-associated neurodegeneration. BPAN typically presents with global developmental delay and epilepsy in childhood, which is followed by the onset of dystonia and parkinsonism in mid-adolescence or adulthood. BPAN is an X-linked dominant disorder caused by pathogenic variants in *WDR45*, resulting in a broad clinical phenotype and imaging spectrum. This review, informed by an evaluation of the literature and expert opinion, discusses the clinical phenotype and progression of the disease, imaging findings, epilepsy features, and genetics, and proposes an approach to the initial evaluation and management of disease manifestations across the life span in individuals with BPAN.

Beta-propeller protein-associated neurodegeneration (BPAN, OMIM no. 300894) is an X-linked dominant neurodegeneration with brain iron accumulation (NBIA) disorder. Mutations in *WDR45* were identified in a group of adults with brain iron accumulation and similar clinical features.[1] BPAN is the most common NBIA disorder, with an estimated prevalence of 2 to 3 per million individuals (Table 1). BPAN was initially characterized by global developmental delay and epilepsy in childhood with the development of dystonia, parkinsonism, and dementia in young adulthood. With increasing numbers of individuals identified with BPAN and recognition of a more expansive clinical phenotype, the purpose of this review is to provide recommendations for best practice in caring for individuals with BPAN.

METHOD

This review results from an evaluation of the literature and consensus of clinicians with experience treating individuals with BPAN. PubMed was searched from July to August 2019 using the exact search terms 'BPAN', 'beta-propeller protein-associated neurodegeneration', 'SENDA', and 'WDR45'. Clinical management information was extracted from published case reports. One author reviewed and compiled all the articles retrieved by this search (JLW), while a second author also reviewed the articles related to epilepsy (IB). English language case series, case reports, and reviews were included. The full texts of the articles were obtained and reviewed. The references of the articles were reviewed to determine if any additional articles should be included that did not appear in the original PubMed search. Data relevant to the clinical presentation and management were extracted from each article and compiled into a spreadsheet (e.g. imaging findings, endocrinological features, etc.). The findings related to each clinical feature, in addition to experience of the authors, informed the descriptions and consensus of the group in formulating recommendations. Expert opinion was sought in an approach similar to that used in the development of the pantothenate kinase-associated neurodegeneration clinical management guideline.[2] Specifically, a draft was circulated to clinical experts in BPAN for review and subsequent revision. The revised draft was then shared with families affected by BPAN for review.

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DIAGNOSIS AND INITIAL ASSESSMENT AND CARE

Presenting features in childhood

BPAN is more common in females and typically presents with global developmental delay particularly impacting expressive language, abnormal gait, epilepsy, sleep disturbance, and autistic features, including hand stereotypies and repetitive behaviors. A rounded face with coarse features, mild telecanthus, and a diastema may be present in early childhood. Bruxism and hyperpnea are common, as seen in Pitt–Hopkins syndrome and Rett syndrome. Since the clinical features are non-specific and imaging may not demonstrate classic findings at a young age, the diagnosis is often made when a gene panel or exome sequencing reveals a mutation in *WDR45*.

Presenting features in adulthood

BPAN should be considered in adults with intellectual disability who develop early-onset parkinsonism, dystonia, and dementia. Adults with BPAN typically have moderate-to-severe intellectual disability and manifest neurodegeneration in early or mid-adulthood that is characterized by dystonia, parkinsonism, and dementia, often with behavioral changes. The deterioration often prompts imaging showing a characteristic pattern of iron deposition suggestive of NBIA.

Phenotypic spectrum of BPAN

The BPAN phenotypic spectrum is broad, at least in part due to complex genetic mechanisms. Children may present with an infantile-onset epileptic encephalopathy and severe developmental disability, or with a Rett-like or Angelman-like phenotype, including midline or flapping hand stereotypies. However, females with mild intellectual disability and typical motor function have been observed.[3–5] An individual with a pathogenic *WDR45* mutation may even be asymptomatic.[6] A number of males with BPAN have been described[7–10] and the phenotype is broad for males and females alike.

What this paper adds

- The complex epilepsy profile of beta-propeller protein-associated neurodegeneration (BPAN) often resolves in adolescence.
- The treatment for an individual with BPAN is supportive, with attention to sleep disorders, complex epilepsy, and behavioral problems.
- Individuals with BPAN have shifting needs throughout their life span requiring multidisciplinary care.

Diagnostic imaging

Brain magnetic resonance imaging (MRI) including iron-sensitive sequences demonstrates an evolution of changes that are specific to BPAN (Fig. 1). The appearance of increased iron does not necessarily coincide with or predict clinical deterioration. Early imaging findings include mild white matter volume loss, delayed myelination, and a thin corpus callosum. However, a normal brain MRI does not exclude the diagnosis of BPAN in a young child. A hypointense signal in the globus pallidus and substantia nigra on iron-sensitive sequences usually appears after 2 to 4 years of age, followed by similar changes on T2 sequences. A symptomatic adolescent or adult may also have generalized volume loss and a 'halo' of T1 hyperintensity around a hypointense band in the cerebral peduncles, which is pathognomonic for BPAN. A transient T2 hyperintense signal in the deep cerebellar nuclei has been described; this is a finding not seen in other NBIA disorders.[11,12]

Genetic testing

When BPAN is suspected, genetic testing is recommended to confirm the diagnosis. Sequencing and deletion/duplication testing of the *WDR45* gene can be made as a single gene test or as part of a gene panel. Rare cases have been associated with microdeletions encompassing *WDR45*. Parental testing is recommended to determine whether the pathogenic variant is de novo or inherited.

Somatic mosaicism and X inactivation

The phenotypic spectrum in BPAN is impacted by somatic mosaicism and, in females, X inactivation.[1] Somatic

Table 1: Estimated incidence, inheritance pattern, and clinical features of NBIA disorders

Disorder	Estimated prevalence per million	Inheritance	Clinical features
BPAN	2–3	X-linked dominant	Global developmental delay, epilepsy, dystonia, parkinsonism in adulthood
PKAN	2	Autosomal recessive	Classic: severe, progressive dystonia, retinal degeneration Atypical: speech disorders, dystonia, psychiatric symptoms
PLAN	1	Autosomal recessive	INAD: psychomotor regression, ataxia, dystonia, spasticity, optic atrophy aNAD: speech delay, developmental regression, dystonia, spasticity, optic atrophy PLA2G6-related dystonia-parkinsonism: parkinsonism, dystonia, cognitive decline, psychiatric changes
MPAN	1	Autosomal recessive	Impaired gait, spasticity, weakness, dystonia, psychiatric changes, optic atrophy, parkinsonism
FAHN	<1	Autosomal recessive	Spasticity, dysarthria, optic atrophy, intellectual impairment
CoPAN	<1	Autosomal recessive	Spasticity, oromandibular dystonia, dysarthria, neuropathy, parkinsonism

NBIA, neurodegeneration with brain iron accumulation; BPAN, beta-propeller protein-associated neurodegeneration; PKAN, pantothenate kinase-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration; INAD, infantile neuroaxonal dystrophy; aNAD, atypical neuraxonal dystrophy; MPAN, mitochondrial membrane protein-associated neurodegeneration; FAHN, fatty acid hydroxylase-associated neurodegeneration; CoPAN, COASY protein-associated neurodegeneration.

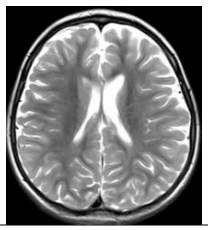
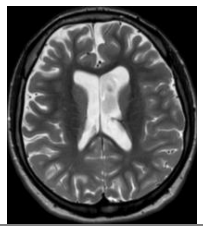
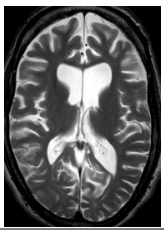
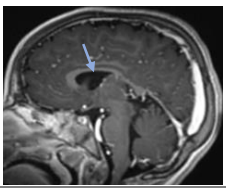
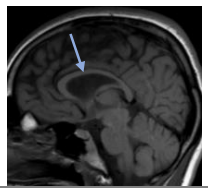
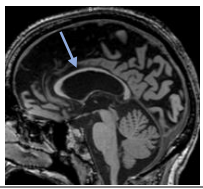
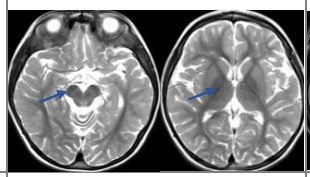
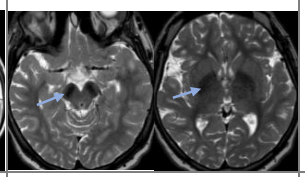
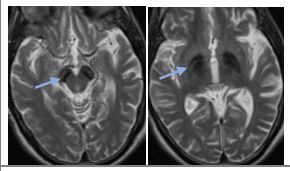
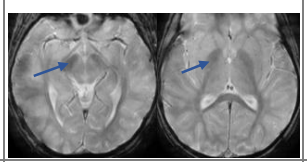
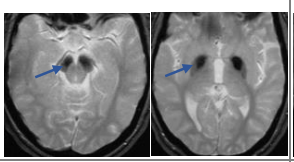
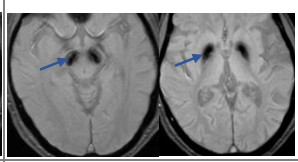
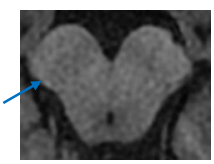
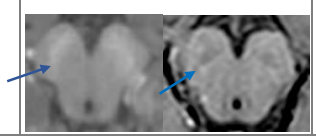
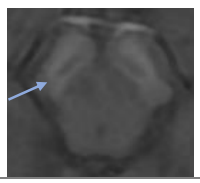
	Age		
MRI feature	Childhood	Adolescence	Adulthood
(a) White matter	Delayed myelination	Normal myelination	Normal myelination
(b) Cerebral and cerebellar volume T2	Mild volume loss or normal 	Mild to moderate volume loss 	Severe volume loss 
(c) Corpus callosum T1	Normal or thinned 	Normal or thinned 	Normal or thinned 
(d) Substantia nigra and globus pallidus T2	Normal or mild hypointensity 	Hypointensity 	Hypointensity 
(e) Substantia nigra and globus pallidus T2*/GRE/SWI	Normal or mild hypointensity 	Hypointensity 	Hypointensity 
(f) Substantia nigra T1 halo'	Absent or T1 hyperintensity without dark central band 	T1 hyperintensity with or without subtle central dark band 	More prominent 'halo' 

Figure 1: Progression of common imaging features seen in beta-propeller protein-associated neurodegeneration (BPAN): (a) delayed evolution of imaging in BPAN (myelination may be present in childhood); (b) generalized volume loss appearing in childhood or adolescence and progressing into adulthood; (c) thinning of the corpus callosum; (d,e) hypointense signal appearing in childhood or adolescence in the globus pallidus and substantia nigra on iron-sensitive sequences, increasing in hypointensity with age; (f) 'halo' of T1 hyperintense signal around a hypointense signal band in the cerebral peduncles becoming apparent in adolescence and more prominent in adulthood. GRE, gradient echo; SWI, susceptibility-weighted imaging.

mosaicism describes the presence of two sets of cells in an individual, one with a mutation in *WDR45* and one without. Single gene and panel testing can detect mosaicism. Gonadal mosaicism also occurs in BPAN.[7] Genotype alone is not a strong predictor of phenotype, which is also influenced by: (1) the developmental timing and tissue distribution of somatic mutation, (2) the presence of a second X chromosome, and (3) the pattern of X inactivation. Typically, one

X chromosome is randomly 'turned off' in each cell. In BPAN, the pattern of X inactivation may be non-random thereby influencing phenotype.[1,13,14] One can speculate that female outliers who are asymptomatic or have mild phenotypes have favorable X inactivation or somatic mosaicism. Males with somatic mosaicism tend to have a phenotype ranging from mild to classic BPAN, while those without mosaicism tend to be more severe than classic female cases.[7,9]

Genetic counseling, recurrence risk, and mosaicism in population norm parents

BPAN is inherited in an X-linked dominant manner. There are more affected females than males, possibly due to early loss of male conceptuses. Most cases are de novo and simplex, meaning they are the only affected individual in the family. Still, parental testing is recommended since recurrence has been reported. If neither parent has the variant, then recurrence is slightly greater than the population risk but still less than 1% due to possible gonadal mosaicism.[7] When a parent has the same *WDR45* variant and evidence for mosaicism, then the recurrence chance could increase to 50%.

Most individuals with BPAN do not reproduce. However, mildly affected females should have genetic counseling once they near child-bearing age. The chance to pass on a *WDR45* pathogenic variant is as great as 50%. Since their unusually mild phenotypes are attributed to mosaicism and/or skewed X inactivation, their children would be more likely to have a classic BPAN phenotype. Finally, many families worry that a typically developing sibling could have a child with BPAN. Monozygotic co-twins may have low-level mosaicism for a *WDR45* pathogenic variant that occurred before the splitting of the zygote and would have an increased recurrence risk.[6] Similarly, if a female sibling inherits a mutation from a parent with gonadal mosaicism and happens to have favorable X inactivation, the increased recurrence risk would be difficult to identify. While rare, these scenarios have occurred and warrant discussion, genetic counseling, and possibly genetic testing.

Disease progression in BPAN

Individuals with typical BPAN have seizures in childhood, which tend to resolve in late childhood or adolescence. Although delayed, they continue to make developmental gains in childhood, with most walking and able to say a single word by 3 years of age.[15] In late childhood, behavioral problems and sleep disturbances can be significant, although typically seizures have resolved and there is a period of stability. Then, ranging from later in childhood to mid-adulthood, most individuals experience disabling parkinsonism, dystonia, and dementia (Table 2). The timing of neurological deterioration varies and the age range is not yet fully understood. In a review of 64 cases, the mean age of deterioration was 27 years 2 months (range 13–39y);[16] however, ascertainment bias for a disorder only recently described may have skewed that mean to a later age. There are no confirmed predictors of neurological deterioration nor is it certain that all individuals with BPAN experience regression. A prospective natural history study of BPAN currently underway may elucidate predictors of regression (http://nbiacure.org/our-research/in-the-clinic/bpanready/).

EVALUATION, MANAGEMENT, AND SURVEILLANCE

The care of the individual with BPAN requires anticipatory guidance for the individual affected and their family and a focus on managing the features that most impact quality of life: seizures, behavioral problems, communication deficits, sleep disorders, and neurological regression. Given the limited published literature, most of the recommendations are based on the consensus agreement of expert clinicians with experience in the care of individuals with BPAN.

Therapeutic targets

The specific function of *WDR45* seems to be in formation of the autophagosome. Mutations in *WDR45* result in impaired autophagy, which underlies the pathological abnormalities seen in BPAN.[17] Iron metabolism is affected in the fibroblasts of patients with BPAN, suggesting a mechanism for brain iron accumulation.[18] As with other NBIA disorders, the accumulation of iron is likely a secondary phenomenon in BPAN,

Table 2: Clinical progression of individuals with beta-propeller protein-associated neurodegeneration[a]

	Age		
Clinical feature	Childhood	Adolescence	Adulthood
Seizures	Mild to intractable, often multiform, may occur with fever	Decrease in seizures	Seizures uncommon
Language/cognitive	Expressive>receptive delay; may have speech regression with onset of seizures or autism	Minimal spoken language, may use signs or augmentative communication	Dementia with loss of communication skills
Motor	Gross motor delay, most eventually walk, ataxic, hunched or crouched gait, hand stereotypies	Static function	Development of dystonia, parkinsonism, loss of ambulation
Behavioral	Autistic features, behavioral challenges		
Endocrinological	Precocious adrenarche	–	–
Other	Sleep disruption	Sleep disruption	Sleep disruption, incontinence

[a]Note that the spectrum of the disease is broad and progression will vary.

raising questions of whether removing iron should be a therapeutic goal. Mouse models of BPAN have been published[19] and these may serve as critical resources for early feasibility studies of rational therapeutics for the disease.

Iron chelating agents

With the unifying feature of iron accumulation, there has been interest in iron chelation as a therapeutic approach in the NBIA disorders. In a randomized controlled trial of deferiprone in individuals with pantothenate kinase-associated neurodegeneration, there was no significant difference between placebo and treatment groups regarding change in dystonia measurement after 18 months.[20] The two reported adults with BPAN treated with deferiprone did not benefit; one had worsening parkinsonism that improved on discontinuation and the other had no improvement in clinical symptoms, although they tolerated only a low dose.[5,21] These data do not support the use of iron chelating agents in BPAN outside of a clinical trial setting.

Recommended evaluation and care at the time of diagnosis

Neurology and development

Neurologists play an important role in childhood, managing epilepsy that may be refractory, and again in adulthood, when movement disorder expertise may be needed to treat rapidly progressive and complex parkinsonism. Children with BPAN should have an initial developmental evaluation to assess and guide interventions.

Ophthalmology

Since treatable eye findings are common in BPAN, an eye examination is recommended.

Brain MRI

A brain MRI may help solidify an uncertain genetic diagnosis; however, once the diagnosis is established, repeat imaging is not recommended if solely to document the MRI changes associated with BPAN.

Laboratory testing

Although there have been reports of abnormalities in some laboratory tests in individuals with BPAN (aspartate aminotransferase, creatine kinase, lactate dehydrogenase, neuron-specific enolase),[8,9] these abnormalities are of uncertain significance. We do not recommend routinely doing these tests without clinical indication.

Medical genetics and genetic counseling

Due to the complex genetics of the disorder, medical genetics evaluation and genetic counseling are recommended. Annual re-evaluation helps keep families informed of genetic advances.

Rehabilitation therapy

Children with BPAN may benefit from early involvement of physical, occupational, and speech therapy to maximize developmental potential.

Family support

Sharing resources for advocacy and support organizations with families can provide much needed support after diagnosis.

Symptom-based interventions

Seizures

Seizures occur in about two-thirds of children with BPAN.[22] Similar to Rett syndrome, individuals with BPAN can have a complex epilepsy, which is refractory to treatment, and spells on awakening from sleep that are eventually proven to be seizures. While there is no BPAN-specific approach, the neurologist must be attentive and reassure that despite their complexity, seizures usually cease in adolescence, at which time antiseizure medication should be tapered.

Infantile/epileptic spasms. Children with BPAN may have an early (3mo[10,23]) or late (3y[24]) onset of spasms.[9,10,12,23,24] Children with BPAN should undergo standard evaluation and treatment of infantile/epileptic spasms.[22]

Episodes on wakening. In our experience, children with BPAN may have stereotyped events on wakening that can be epileptic. Electroencephalography (EEG) monitoring may be helpful, although a negative surface EEG does not exclude the possibility of seizure.

Initiation of an antiseizure medication. An antiseizure medication should be considered in children with recurrent, unprovoked seizures. No single antiseizure medication has proven more effective in BPAN. Cannabidiol may be used on-label if children meet the criteria for Lennox–Gastaut syndrome, although there are no BPAN-specific data for cannabidiol. A ketogenic diet or vagal nerve stimulator may be considered in children refractory to medication.

EEG. Diffuse, continuous fast (beta) activity may be an early, non-specific feature of the BPAN EEG.[25] Children with BPAN can have a variety of other EEG abnormalities including diffuse slowing, generalized spike wave or polyspike wave discharges, and focal or multifocal spikes. Hypsarrhythmia is commonly seen in children with epileptic spasms. An EEG is recommended after a first seizure and subsequently if expected to impact management.

Discontinuation of antiseizure medications. Many children with BPAN outgrow their seizures in adolescence. Children with BPAN who demonstrate 2 years of seizure freedom should be offered a trial period off antiseizure medications.

Speech, language, and communication

Most individuals with BPAN develop no more than a few spoken words. Communication challenges may compound behavioral issues as children get older. Practitioners should set realistic expectations for spoken language, framing recommendations for early evaluation by a speech therapist with expertise in augmentative and alternative communication. Children with autism spectrum disorder should receive a comprehensive treatment model, which may include applied behavior analysis and developmental

approaches to support communication. All children with BPAN should have a formal audiological evaluation.

Motor skills

Most children with BPAN achieve independent ambulation, although it may occur significantly later than is developmentally typical.[15] In childhood, physical therapy is recommended to support motor development. We encourage therapists and families to develop short-term, realistic goals and re-evaluate these periodically. Involvement of physical therapy in adolescence is encouraged to maintain skills.

Behavior and psychiatric care

Behavioral problems can be a source of significant difficulty in individuals with BPAN. We suggest establishing care with a psychologist or psychiatrist experienced in managing behavioral problems in individuals with intellectual disability. A behavioral management program, such as applied behavior analysis, may be beneficial.

Sleep

Sleep disruption has a major impact on the quality of life of individuals with BPAN and their families. Clinicians should inquire about the context of sleep disruption, which can be multifactorial (e.g. dysregulation of the sleep cycle, sleep-disordered breathing, seizures, reflux, spasticity). The suspected etiologies will drive diagnostic investigations and interventions. While data are lacking, providers may shape their approach using the following suggestions.[26]

Diagnostics. The following diagnostics are suggested: sleep study to evaluate sleep-disordered breathing; EEG if seizures are suspected to be disrupting sleep; serum ferritin in individuals with restless sleep.

Treatment. Non-pharmacological treatment may include a bedtime routine, limited napping, white noise, a weighted blanket, and graduated extinction. The sleep environment should also be evaluated for safety. Regarding pharmacological treatment, data are limited and there are no medications approved by the US Food and Drug Administration or the European Medicines Agency to treat insomnia in children. First-line medications include melatonin. Second-line medications include alpha agonists (clonidine). Third-line medications include antihistamines (hydroxyzine, diphenhydramine; may lower seizure threshold), antidepressants (trazodone, mirtazapine), benzodiazepines, gabapentin, zolpidem, and atypical antipsychotics (risperidone; may exacerbate parkinsonism).

Precocious adrenarche

Some children with BPAN have been noted to have precocious adrenarche as young as 1 to 2 years of age.[4,12] Early puberty with menarche at age 6 years was observed in one individual. If a young child develops pubic hair, axillary hair, acne, or adult-type body odor without breast development, menarche, or testicular/penile enlargement, no further evaluation or intervention is typically indicated. In rare cases of early puberty, further evaluation is recommended.

Vision

Individuals with BPAN frequently have ophthalmological abnormalities, such as strabismus, amblyopia, astigmatism, and myopia, although numerous other findings have been reported.[8–10,13,16,21,22,27] Regular care with ophthalmology is recommended. Individuals with visual impairment should seek early evaluation with a low-vision specialist.

Nutrition, diet, and supplements

There is no evidence of clinical benefit from any specific dietary modifications or nutritional supplements in BPAN. We recommend against a low-iron diet since it leads to systemic iron deficiency without impacting brain iron levels or disease course. There has been interest in cannabidiol to treat mood disorders, autism, insomnia, and behavioral problems, based on very limited data. Practitioners should inquire about the use of these products and partner with patients and families in their decisions about the use of these products.

Some children present with hyperphagia requiring behavioral management, but increased childhood body mass index does not typically persist into adulthood. Later in the disease, dysphagia and weight loss may become a problem when dystonia and parkinsonism appear. Clinicians should ask about dysphagia at every visit and refer for further evaluation if present. A gastrostomy tube may be needed.

Regression, dystonia, and parkinsonism

The final evolution in BPAN is a period of neurodegeneration characterized by parkinsonism, often with dystonia, developing in adolescence to adulthood, sometimes over the course of months. The movement disorder is accompanied by cognitive deterioration that may manifest initially with subtle behavioral changes, including apathy or aggression, progressing over time to overt dementia. Families naturally struggle with anxiety with these changes; stress and renewed grief are common. Treatment with dopaminergic medication is appropriate since individuals with BPAN typically show a robust response; however, the development of brittle motor fluctuations and dyskinesias, sometimes with painful dystonia, creates challenges in medication management that are best managed by a neurologist with movement disorder expertise.[13,28,29] Children with BPAN do not typically develop parkinsonism and rarely need treatment for movement disorders. There are no data on the use of deep brain stimulation for the treatment of parkinsonism in BPAN; however, the potential for deep brain stimulation to worsen cognitive function mandates a cautious approach.

Palliative and end-of-life care

The life expectancy of individuals with BPAN varies depending on the individual clinical presentation. As adults develop progressive dystonia, they are at increased risk of dying, with deaths reported in young to middle adulthood (30–50y) from complications of parkinsonism and

aspiration.[13] Palliative care may be of particular utility for adults who begin to demonstrate decline and in severely disabled individuals, to support a focus on quality of life and help with decisions around end-of-life care.

Transition

As a child with BPAN transitions toward adulthood, an ongoing conversation between families and healthcare providers, educators, social workers, and care coordinators can provide support. Guidelines[30] and tools[31] are readily available.

Emergency care plan for individuals with BPAN

Individuals with BPAN should have an emergency care plan, which is a concise overview of their condition and treatment recommendations. The care plan may include recommended seizure management, behavioral approaches, and how to reach the individual's physician. The American Academy of Pediatrics has developed an emergency information form for children with special needs that would be suitable for children and adults with BPAN.[32]

Immunization

Individuals with BPAN should undergo a standard approach to immunization.

Education

Children with BPAN should have an individualized education plan to support their particular needs, which should be re-evaluated at least annually.

Psychosocial challenges and support

Families affected by BPAN benefit from strong support systems. Most families of younger children, having adjusted to the reality of having a disabled child, experience new anxiety and grief when they learn that their child will likely have regression with parkinsonism and cognitive decline. Some families may become hypervigilant, worrying that any new symptom in their young child with BPAN represents the onset of regression. Reassurance may help alleviate this worry. For families of adult patients, clinical confirmation of the onset of parkinsonism and cognitive decline may be a source of new grief.

THE ROLE OF NBIA ADVOCACY GROUPS

The growing number of cases identified and increasing social media presence have led to the formation of several advocacy groups. Participation in these can be a rich source of support and information but may be overwhelming for some newly diagnosed families. Clinicians should discuss these resources with appropriate balance and cautions. More formal activities are carried out through the NBIA Alliance (http://www.nbiaalliance.org/), an international federation of family advocacy organizations offering additional opportunities for families and care providers to interact and learn from one another through forums and family conferences.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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