Consensus Clinical Management Guidelines for Pantothenate Kinase-Associated Neurodegeneration (PKAN)

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Introduction

Pantothenate kinase-associated neurodegeneration (PKAN, formerly Hallervorden–Spatz syndrome, OMIM #234200) is the most common neurodegeneration with brain iron accumulation (NBIA) disorder, with an estimated incidence of 1-3 per million[1] and accounting for about half of NBIA cases.[2] As is the case for most rare disorders, evidence-based guidance for the clinical management of PKAN is limited, often relying instead on anecdotal evidence, case reports and small series studies. Despite the small number of geographically dispersed people with PKAN, clinicians with concentrated experience have developed opinions and expertise about their optimal care. Moreover, family members and affected individuals themselves develop substantial personal experience in meeting their needs. In this document we have amalgamated such professional expertise, lay experiences and published data into a consensus guideline. This guideline summarizes what we believe are current best practices and therapeutic approaches for the care of people with PKAN and their families.

Methods

This guideline largely reflects the consensus opinion of clinical experts in PKAN. In addition, peer-reviewed publications were systematically searched for, evaluated, and their conclusions incorporated into this document when applicable. PubMed (http://www.ncbi.nlm.nih.gov/pubmed) was searched January - February 2016 using the following search terms: 'PKAN', 'pantothenate kinase-associated neurodegeneration', 'HSS', 'Hallervorden-Spatz syndrome', 'NBIA', and

'neurodegeneration with brain iron accumulation.' Limited consideration was made of publications utilizing aggregated data from multiple NBIA disorders or in which a diagnosis of PKAN could not be confirmed based on the information provided.

A draft guideline was developed and submitted for review in four phases (approved by the OHSU IRB as protocol e8165). The first was to an international group of clinical experts, each with more than 10 years of experience with PKAN. Based on their recommendations, revisions were made and a second phase of review was sought by leaders of international patient advocacy groups. After further revisions were incorporated, a draft was shared with people with PKAN and their family members from nine affected families who commented further. Finally, an open call to the NBIA community was made via the NBIAcure.org website for final reviews and comments.

Role of the funding source

Leaders and members of the non-profit lay advocacy organizations that funded this work reviewed and edited this manuscript but had no other role in this work.

Diagnosis and initial care

The diagnosis of PKAN is usually considered on the basis of clinical suspicion and radiological data. Often, the clinical features are suggestive, and the diagnosis becomes strongly suspected after the characteristic brain MRI pattern is revealed. Since the *PANK2* gene discovery[3], the phenotypic spectrum of PKAN has broadened,

and with it, the range of presenting features. Greater access to early neuroimaging using MRI sequences that are sensitive to iron and to clinical whole exome sequencing can significantly reduce the time to diagnosis of people with early clinical manifestations.

Classic PKAN: presenting features

Classic PKAN defines the group of people with the youngest age at onset and most rapid rate of disease progression. The natural history of classic PKAN is relatively homogeneous. Onset in classic PKAN occurs before 6 years of age in 90% (range: 6 months-12 years, mean: 3 years 4 months).[2] The main presenting features are limb dystonia and spasticity, clumsiness with frequent falls. While retinopathy is common, clinically significant visual impairment usually lags behind the neurological manifestations. Earlier histories of developmental delay, ADHD, or toe-walking also are common.

Atypical PKAN: presenting features

Atypical PKAN is an inclusive term for all non-classic PKAN phenotypes. The spectrum of atypical PKAN is broad and more accurately encompasses a continuum from classic disease. Disease onset is in later childhood, adolescence or adulthood (age range: 1–28 years, mean age: 13 years 8 months),[2,4] and the rate of progression is slower. Atypical PKAN often presents with neuropsychiatric or speech problems followed later by the development of dystonia or parkinsonism, sometimes superimposed on a history of attention deficit hyperactivity disorder (ADHD). Action-induced jaw dystonia occurring with eating or speaking is an unusual clinical feature that should always prompt consideration of the diagnosis of PKAN. Similarly,

truncal opisthotonus is common in both classic and atypical disease and is highly suggestive of PKAN.

Diagnostic MRI

People suspected to have PKAN based on clinical features should undergo brain MRI using iron sensitive sequences such as SWI, GRE, T2 as a first line diagnostic investigation to identify the characteristic changes.*[2] The MRI abnormality, called the 'eye-of-the-tiger' sign, is observed on T_2-weighted imaging and consists of hypointense signal in the globus pallidus surrounding a region of hyperintense signal (Figure 1).[5] This pattern is found in both classic and atypical disease, though occasionally people with PKAN will lack this finding.[6-8] MRI changes are usually evident by 3-4 years of age in classic disease if iron-sensitive sequences are employed and may be present much earlier. By the time clear neurologic features are present, the brain MRI almost always shows characteristic changes. If the brain MRI is not typical for PKAN in a person strongly suspected to have this disorder, genetic testing is indicated.

Genetic testing

When PKAN is suspected, genetic testing is recommended in order to confirm the diagnosis. Sequencing and deletion/duplication analyses of the *PANK2* gene, which is mutated in PKAN, are needed for a complete analysis. Genetic information is valuable for predicting prognosis, facilitating prenatal or pre-implantation genetic diagnosis in future pregnancies, and identifying other carriers in the family. Clinical genetic testing laboratories may be found worldwide through local medical genetics or neurology professionals. NBIA gene panels are now available at select labs and

may be a more efficient and cost-effective option in some situations. For people for whom genetic testing is not possible, reasonable confidence in the diagnosis can often be established when characteristic clinical and radiographic changes are documented. In cases where only one *PANK2* mutation is identified, experts can help establish a confident diagnosis based on clinical and MRI data.

Other recommended care at the time of diagnosis

- Neurology – Establishing care with a neurologist is important to document the individual's baseline at the time of diagnosis and facilitate subsequent interventions as needed, such as initiating treatment with medication or referral to physical or other therapies. Given the progressive nature of the disease, a good relationship with open communication between the neurologist and family is key. A child neurologist is appropriate for children; a movement disorders neurologist is a good choice to manage adults and some older children with PKAN. Co-management with a rehabilitation medicine physician is optimal in countries where this specialty expertise is available.
- Ophthalmology – Clinical eye examination is recommended to assess visual function since retinopathy is common, especially in children with classic PKAN. Electroretinography (ERG) is not needed to guide clinical management in most people.
- Brain MRI - If a diagnosis of PKAN is confidently established on the basis of genetic data prior to obtaining a brain MRI (*e.g*. by whole exome sequencing), we suggest performing a brain MRI only if the results will impact medical decision-making. Conversely, imaging may confirm or exclude a diagnosis of PKAN when

clinical and genetic data are equivocal.

- Genetic counseling - Genetic counseling is important in the early care of families with a new diagnosis of PKAN and can identify other family members at risk of being affected or being *PANK2* mutation carriers. Since PKAN is an autosomal recessive disorder, each full sibling has a 1-in-4, or 25%, chance of being affected. Discussion about diagnostic evaluation in siblings of a proband is a priority, especially when they are younger or share abnormal features with their affected sister or brother. In this instance, assessment by neurological exam, MRI or diagnostic genetic testing should be considered. Healthy, unaffected siblings have a 2-in-3 chance of being carriers and can consider carrier testing when they become adults. Genetic testing is recommended only for symptomatic siblings. Genetic counselors can also connect families to the PKAN family community and to the lay advocacy network, the NBIA Alliance.
- Other testing – Other manifestations of PKAN include acanthocytosis and abnormal spermatogenesis, neither of which warrants investigation in most individuals at the time of diagnosis. Acanthocytosis is difficult to confidently establish in the clinical lab, and its presence does not guide further care.
- Rehabilitation therapy – Disabling physical, occupational or speech problems should be addressed as early as possible after diagnosis in order to preserve function.
- Family support – Psychosocial care and counseling should be offered to families and to affected persons as soon as possible after diagnosis. Social counseling and guidance can provide families with important information about benefits

available for disabled persons that may help to prepare them for any adaptations needed for daily activities.

Disease progression in PKAN

PKAN is a progressive neurodegenerative disorder affecting movement, balance, speech, vision, cognition, affect and behavior. In classic PKAN, most children lose the ability to ambulate independently and safely by age 10 years. The pattern of progression is saltatory, with step-wise decline occurring over a few days or weeks, followed by plateauing that may be sustained for weeks or months. In general, motor skills that have been lost are not regained. The overall trajectory of change is that of relentless progression, and no clear exacerbating factors have been identified to account for the periods of more precipitous decline. This pace continues until the child loses all independent function, typically during the second decade. Despite the severe degree of motor impairment, children with PKAN retain the cognitive abilities that they attain during development. Some children, especially those with very young onset of disease, do have significant intellectual and developmental disabilities, but they do not lose cognitive skills in tandem with motor function.

In classic PKAN, severe dystonia and postural instability leading to frequent falls cause the most disability, complications and pain. Dystonia leads to stridor, extreme opisthotonic posturing, bone fractures, joint dislocation and recurrent tongue-biting. The resulting pain and distress can precipitate a vicious cycle and lead to status dystonicus. Other secondary complications include airway obstruction,

orthopedic deformity and infection.

Atypical PKAN progresses more slowly, and some individuals experience plateauing of symptoms for many months, years or even decades. Static disease or minimal progression over 5-10 years is not uncommon for people with atypical PKAN. One study of 9 individuals with atypical PKAN suggested that the majority of significant symptoms developed during the first 5 years, followed by a relatively stable phase of slower progression[9] —a pattern that has also been observed by the authors. Although dystonia is also prominent in atypical PKAN, parkinsonism usually contributes more significantly to the disability as disease advances, and dysarthria has a significant impact on quality of life. Unlike dystonia in the disease, the parkinsonism of PKAN is relatively symmetric, usually with significant postural instability, little tremor, and variable bradykinesia and rigidity.

Variability is observed within families; however, most affected siblings are phenotypically concordant and their disease typically advances at a similar rate. Adults with PKAN have graduated from college, served in the armed forces, married and raised children. The range and spectrum of disability is very wide.

The clinical exam is most useful in gauging progression and in guiding ongoing management. Moreover, MRI in children requires sedation and is not without risk. *We recommend against regular brain MRI in PKAN unless the results would guide specific medical decision-making*.

Treatment and ongoing management and surveillance

Rational therapeutics

Although there currently is no disease-modifying therapy for PKAN, rational therapeutics that target the primary biochemical defect are in development.[3,10] For now, medication management is primarily symptomatic, and ongoing care follows general recommendations developed for people with a chronic progressive disease.

Vitamin B5 (pantothenate) and related compounds

PKAN is an inborn error of coenzyme A biosynthesis. Pantothenate forms the chemical backbone of coenzyme A, which is essential for hundreds of biochemical reactions essential for health. Pantothenate was hypothesized to be a potential therapeutic for PKAN based on the concept of enzymatic substrate overload.[3] This idea presumes at least partial PANK2 enzyme function, which is predicted to occur in people with atypical PKAN but not in those with classic disease. However, because of its low toxicity, pantothenate has been tried by many people with classic and atypical PKAN to determine if it might have benefit. No clinical trial has been performed to evaluate the efficacy of pantothenate.

Regardless of phenotype, we recommend consideration of a trial of high dose pantothenate for at least 3 months for all people with PKAN, starting at a dose of 250 mg orally and increasing weekly by 500mg until a daily dose of 2-5 grams is reached or side effects become evident. Based on anecdotal experience, pantothenate is well-tolerated with few side effects. Some adults with atypical PKAN

perceive benefit from pantothenate to their gait, speech and clarity of thinking. For most children with classic PKAN, pantothenate seems to offer little or no benefit, and the volume of the compound may be challenging to administer to a child. *For those perceiving no benefit, we recommend discontinuing the vitamin supplement.*

Compounds that bypass the defective PANK2 enzyme, including pantetheine, phosphopanthetheine, and coenzyme A and their derivatives, have shown promise in ameliorating various manifestations of defective pantothenate kinase 2 in disease models investigated in the research laboratory.[10-12] Anecdotal reports of oral pantetheine supplementation have suggested possible improvement in attention in some people with PKAN while others have observed no benefit. Studies are underway to assess the safety and therapeutic efficacy of several intermediary compounds.

Iron-chelating agents, including deferiprone

The role that iron plays in PKAN pathogenesis is still unclear because iron dyshomeostasis is a secondary phenomenon in this disorder. Nevertheless, high iron levels develop in globus pallidus and probably contribute to cell and tissue damage. The utility of iron chelators has been limited by systemic iron depletion.[13] Newer agents more readily cross the blood-brain barrier yet have a lower affinity for iron, thereby minimizing systemic iron loss. Deferiprone is one agent under study in PKAN, and preliminary data support its effectiveness in lowering brain iron levels as measured by MRI; however, convincing evidence of clinical benefit is lacking.[14,15] An international randomized, double-blind, placebo-controlled study to

assess the safety, tolerability and efficacy of deferiprone in PKAN is underway (clinicaltrials.gov/ct2/show/NCT01741532). Results of this trial will be known in early 2017.

Symptom-based interventions

Medications

Dystonia is the most disabling motor symptom for the majority of people with PKAN. Over time, dystonia affects more body regions and typically worsens in those regions affected. Motor symptoms in PKAN are often mixed, manifesting with dystonia, spasticity and parkinsonism. Therefore the main treatment goal is relief of the most disabling symptoms with the aim to minimize both disability and off-target effects as much as possible.

Dystonia and spasticity are usually managed with anticholinergics, benzodiazepines and other anti-spasticity agents, alone or in combination, as symptoms dictate. For focal dystonia, botulinum toxin [1] injections can also provide targeted relief of dystonia and spasticity. *The first-line drugs that are most commonly effective in PKAN are trihexyphenidyl, clonazepam, and baclofen*. If dystonia dominates the phenotype, we recommend starting treatment with trihexyphenidyl; if spasticity is prominent, with baclofen. Clonazepam may be added for troublesome breakthrough spasticity or dystonia that is not relieved with the first two medications. Second-line drugs for

[1] Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the treatment of upper limb spasticity, in patients under 16 years of age for the treatment of cervical dystonia, and in patients under 12 years of age for the treatment of blepharospasm and strabismus.

PKAN include clonidine, gabapentin, tetrabenazine, and pregabalin. Where symptoms are not adequately controlled with first-line drugs, we recommend a trial of these medications with taper and discontinuation if no benefit is observed after two weeks at the target dose.

We recommend that, where feasible, drugs be introduced one at a time at a low starting dose and increased gradually to an efficacious dose or to tolerability, whichever occurs first. If a specific medication provides no clear benefit by 4-6 weeks after achieving the target dose, the drug may be withdrawn gradually. Children generally tolerate significantly higher doses of these drugs than adults and may require same to achieve relief of symptoms. A corollary is that a previously well-tolerated drug regimen may cause adverse effects as the child with PKAN moves into adolescence and adulthood; this is especially true of anticholinergics. *Therefore we recommend a critical review of an established drug regimen annually, with directed questions regarding adverse effects predicted from the specific drugs included in the regimen.*

PKAN-associated dystonia and even the parkinsonism observed in older individuals with PKAN are rarely responsive to dopaminergic medications. Most people with PKAN have had a trial of levodopa at some point in their disease and very few report any benefit. Similarly, dopamine agonists seem to be of limited utility in the disease. Interestingly, some adults with PKAN do report improvements in postural instability with amantadine. *We do not recommend dopaminergic drugs as first line*

agents for symptom management in PKAN; however, a trial of amantadine should be considered in adults with postural instability.

Agents to avoid

Anecdotal reports of three siblings with atypical PKAN treated with alpha-tocopherol (vitamin E), selenium, and idebenone indicated precipitous worsening of symptoms, with subsequent improvement once these compounds were stopped.[16] Therefore we recommend avoiding these compounds, including as nutritional supplements, unless there is a specific medical indication for their use in a person with PKAN.

Surgical procedures, sedation and anesthesia

Anesthesia for procedures in individuals with PKAN should be undertaken only when absolutely necessary and with close collaboration between the primary provider and anesthesia and surgical teams. Adequate post-operative pain and dystonia management are critical. Pre-existing neck and oromandibular dystonia may complicate both awake and sedated intubation, and for reasons that are unclear, procedures with anesthesia may precipitate an acute exacerbation of dystonia in people with PKAN. This phenomenon has been observed even with light anesthesia and with a variety of anesthetic agents; however, it is difficult to attribute changes specifically to the anesthesia rather than to the indication for a procedure.

Acute dystonic reactions to anesthetic agents such as propofol have been reported in previously healthy adults and therefore this drug tends to be avoided in people

with movement disorders;[17] however, there is no evidence that people with PKAN are more vulnerable to this anesthetic complication than the general population and in fact, propofol has been used successfully in PKAN in case reports.[18-20]

Intrathecal and intraventricular baclofen therapy

The administration of baclofen into the central nervous system for dystonia and spasticity may provide greater efficacy and cause fewer systemic side effects than oral dosing. *We recommend starting with oral baclofen, increasing the dose as symptoms require. Once the maximum oral dose fails to control symptoms or causes unacceptable adverse effects, central dosing should be considered.* Better outcomes have been observed in those with lower extremity symptoms who are still ambulatory; the gravity-dependence of drug delivered into the intrathecal space may preserve ambulation for longer in this situation. The approach seems to have less robust effects on opisthotonus in non-ambulatory people than might be expected. Usually a test intrathecal dose is administered in the outpatient setting to judge response before committing to implantation of the pump. Standard procedures for test dosing and for catheter and reservoir placement should be used. Over time, trials of continuous infusion with or without added bolus dosing may be considered to optimize function and minimize discomfort. As with all medications, dosing needs are likely to change over time. Skin breakdown around an indwelling device is a risk for those whose dystonia causes pressure and abrasion to the overlying skin, but problems of frequent catheter kinking and life-threatening drug withdrawal in the setting of opisthotonus have not been observed. Among the most important considerations for any surgical procedure, including pump placement, is

the experience and record of success of the performing surgeon. Therefore, we strongly encourage families to request this information to enable them to make an informed decision.

Intraventricular administration of baclofen is reported to be as safe as intrathecal dosing[21-23] and requires even lower doses;[21] however, experience with this approach is limited in PKAN. In theory, intraventricular dosing may offer advantages over intrathecal administration to those with head, neck and upper body dystonia, but this has not been specifically studied.

Deep brain stimulation (DBS)

Dystonia relief from DBS has been mixed in PKAN, similar to the experience in other secondary dystonias. Numerous case reports and series that include mixed NBIA etiologies report benefit for many people in the first year or years with placement in the globus pallidus interna; however, benefit usually is not sustained as disease advances, and cases with little or no clinical benefit are less likely to be published,[24-29] Adolescents and adults with atypical PKAN are more likely to benefit from DBS; we are unaware of children with classic PKAN who have had significant sustained benefit beyond a few months. While DBS is considered to be part of the current management arsenal for PKAN, there is no consensus about the efficacy of DBS in relieving dystonia in PKAN nor of the optimal candidate, timing in disease progression or stimulator settings. When DBS is considered, we recommend referral to an experienced DBS center for evaluation. A discussion of risks, benefits,

alternatives and realistic outcome goals is essential. Indwelling medical devices increase the risk for infections that can be difficult to treat. Other considerations that should guide decision-making include the person's general health and the likelihood of their gaining relief from their most disabling symptoms.

Recommendations for DBS electrode settings are guided by dystonia rather than the specific diagnosis of PKAN. A delay between settings changes and clinical response that may be as long as weeks to months is common in dystonia. Risk from DBS is not significantly different in children and adults with PKAN compared with what has been reported in other disorders.

Thalamotomy and pallidotomy

For severe disabling dystonia that is refractory to medical management, thalamotomy[30] and pallidotomy[18,31,32] have been performed in PKAN, sometimes with good symptomatic relief. Concerns have been raised about the irreversible nature of these procedures, especially in children and adolescents, and these ablative procedures have been largely replaced by deep brain stimulation. Despite this, in certain cases of refractory painful dystonia, this approach may provide relief to the person with PKAN.

<u>Rare movement disorders in PKAN</u>

Tics, chorea and myoclonus have been reported in PKAN[33,34]. A diagnosis of a tic disorder or Tourette syndrome may precede that of PKAN, especially in children and adolescents. Treatment approaches, when indicated, should generally follow

standard medical management for such symptoms;[35] however, *we recommend that noradrenergic agents such as clonidine, guanfacine, and atomoxetine be considered as first-line agents for treatment of tic disorders over antipsychotics* due to the latter class of drugs' risk of inducing acute and tardive dystonia in a population where this would be hard to detect in the setting of dystonia due to PKAN.

Status dystonicus

The development of increasingly frequent or continuous severe episodes of dystonic spasms, referred to as "status dystonicus" or "dystonic storm", is common in PKAN and demands urgent medical attention often requiring hospitalization. Most children and young adults with severe PKAN experience an episode of status dystonicus at least once during the course of their disease. *Anytime there is a worsening of dystonia, aggressively assessing for and treating the common precipitants specific to PKAN is the highest priority*. These include bone fracture (often atraumatic or minimally traumatic), occult bleeding or infection, and recurrent soft tissue trauma (tongue, lips, cheek biting). Early recognition of worsening of symptoms is key to averting progression to status dystonicus and to realizing a better outcome. The triggers, management and complications of status dystonicus in PKAN are similar to those in other disorders. *Therefore, we recommend following the detailed general guidelines that have evolved over the past few years[36], with exceptions described below for PKAN and detailed in figure 2*.

Use of a simplified dystonia severity action plan is recommend for all people with PKAN.[28] A scale to assess risk of status dystonicus can help determine the level of

care required for management at any given stage, and management recommendations should be tailored to the individual. Common triggers in PKAN include rib, skull and long bone fractures (often occult), gastrointestinal bleeding, infection, joint injury or dislocation, fecal impaction, tongue-biting and respiratory compromise from stridor. Aggressively assessing for and treating these conditions is the first priority anytime there is a worsening of dystonia. Other common triggers include abrupt initiation or cessation of a medication, and anesthesia or surgery. No specific medications or anesthetic agents are contraindicated in PKAN based on rigorous data.

Management of status dystonicus in PKAN must be guided by the individual's underlying disease state. The first-line therapy is to start or increase antidystonic drugs, especially benzodiazepines. Intubation with deep sedation and surgical interventions, including DBS placement and ablative procedures such as pallidotomy, may be appropriate in a minority of people.[37] L-dopa has little or no efficacy in relieving symptoms in most people with PKAN, and therefore is not recommended despite its use in management of status dystonicus associated with other etiologies. In addition, *drugs with D2 antagonist activity, including high-potency neuroleptics such as haloperidol and atypical antipsychotics such as risperidol, should be used with caution and for as short a period as possible because of their propensity to cause acute and tardive dystonia.*[38]

Laryngeal dystonia and stridor

Inspiratory stridor caused by adductor laryngeal breathing dystonia is a worrisome manifestation of PKAN in both children and adults.[39] It may occur in isolation, but more often an underlying precipitant that is causing pain can be identified. Agitation from stridor can further exacerbate laryngeal dystonia and cause a cycle of increasing distress that can be difficult to interrupt and may precipitate generalized status dystonicus. Careful evaluation to systematically exclude a treatable cause for agitation is essential. Respiratory function must be monitored closely and is a critical factor in guiding the need for and type of intervention. *Stridor may be tolerated in PKAN and may not necessitate intervention; however, if respiratory function is compromised or if agitation accompanies the stridor, then aggressive management is indicated to ease the dystonia and support respiration*. For persistent laryngeal dystonia that interferes with respiration and oxygenation, botulinum toxin injections to bilateral thyroarytenoid muscles may provide relief but can take several days to manifest. Rarely, tracheostomy may need to be considered in consultation with an otolaryngologist.[40,41] Once the stridor is relieved, respiratory function usually returns to normal. In PKAN, stridor often recurs.

Multidisciplinary Management of PKAN

Optimum symptomatic management of PKAN requires a multidisciplinary approach that focuses on anticipatory and preventive measures as well as active interventions to address secondary complications from the disorder. Implementing a comprehensive management plan can improve quality of life and function.

Standardizing care can also facilitate planning for multicenter trials and reveal aspects of care that require attention.

Care of the person with PKAN requires anticipatory guidance for the person affected and their family, monitoring for complications and management of the neurological symptoms. In this guideline, we have focused more on PKAN-specific problems and their management. Many of the non-specific problems that are associated with chronic neurological diseases can occur in PKAN as well. Routine monitoring and proactive prevention efforts are important to initiate in order to minimize these risks.

The following are guidelines for the symptomatic management of PKAN, namely orthopedic, respiratory, gastrointestinal, nutritional, pain and palliative care issues, as well as treatment strategies for commonly encountered medical problems and emergencies. Given the limited published literature in this area, the majority of recommendations are based on the expert opinion of clinicians with experience in the care of people with PKAN. We have not included standard approaches to addressing common problems where recommendations are not specific to PKAN.

Feeding

Difficulty with eating is almost universal in PKAN. In the child with classic disease, this typically manifests with progressive difficulty with mastication and swallowing that can initially be managed with diet modification, but which eventually compromises nutritional status in almost all cases. Many older individuals with

atypical PKAN exhibit eating dystonia, an unusual action-induced dystonia in which the tongue or jaw freezes during the act of mastication, requiring sensory tricks or manual manipulation of the food in the mouth to overcome. These techniques, along with diet modification, are often sufficient to maintain nutritional status in individuals with atypical disease. Speech, feeding and swallowing therapy may also help with specific issues. However, *if a person can no longer maintain an adequate diet orally due to dysphagia or respiratory complications, insertion of a gastrostomy tube is recommended.* Placement should precede the occurrence of significant weight loss (10% of normal body weight) or complications from aspiration. Most people still can enjoy food by mouth, but tube feeding can be utilized for the majority of their nutrition to provide adequate caloric intake. In our experience, some families may resist gastrostomy tube insertion because emotionally they relate it to a sign of disease progression, failure or simply "giving up." *We recommend setting expectations early in disease that a feeding tube may be necessary at some point* as a useful measure to optimize quality of life by allowing time for activities other than oral feeds (which can be slow, ineffective, and tiring). Emphasizing G-tube placement as a routine disease management strategy rather than an end-of-life intervention may help alleviate such stress and anxiety. In our experience, many families who initially resisted the implementation of a feeding tube have later shared that they felt significant relief after gastrostomy placement, reporting that they could be more certain of adequate nutrition, that it was safer than oral feeding in people who were at risk of aspiration, and that quality of life was improved both for the person with PKAN and the caregivers.

Severely abnormal posturing may lead to difficulty in maintenance of g-tube placement and in re-insertion. Careful attention to proper re-insertion and monitoring of placement are important.

Nutrition, diet and supplements

Several factors can impact nutrition in PKAN including feeding problems, gastro-intestinal dysmotility and chronic gastro-esophageal reflux. In addition, people with PKAN have increased energy expenditure and many require 5-10% more calories to maintain a healthy weight than calculated based solely on age and gender.[42]

Nutritional requirements are otherwise based on age and general health. There is no evidence of clinical benefit from any specific dietary modifications or nutritional supplements in PKAN. *We recommend against a low iron diet as it leads to systemic iron deficiency without significantly impacting brain iron levels. A healthy nutritionally complete diet is recommended*.

A ketogenic diet has been tried by a few families, but only mixed anecdotal reports are available. There is no convincing evidence of any effect, good or bad, in people with PKAN based on very limited information. In mice with defective pantothenate kinase 2, a ketogenic diet significantly worsened their general health and function as predicted based on increased demand for coenzyme A for mitochondrial fatty acid oxidation.[11] As a result, *we recommend against a ketogenic diet for all people with PKAN.* We support families in their desire to try experimental nutritional

supplements as long as the risks are predicted to be low and they understand the uncertainty of those predictions.

Dental and oral health

Trauma to the mouth, tongue, jaw and teeth is very common in PKAN, resulting from orobuccolingual dystonia, tongue-biting, and direct impact as a result of falls. Jaw-opening and jaw–closing dystonia can be disabling and very painful, with attendant risks of temporomandibular joint damage or dislocation, severe tongue-biting and biting injuries to the hands and lips with risk for secondary infection. When sensory tricks are ineffective, botulinum toxin can be effective in managing oral dystonia and is a first-line treatment to consider; otolaryngologists may be most experienced with the injection techniques needed for a good outcome, especially for jaw-opening dystonia, which is especially challenging to treat without increasing dysphagia and the risk of aspiration. Bite blocks affixed to the teeth or a bite-guard may be effective in preventing tongue-biting as long as the block does not become a choking hazard. In extreme circumstances, full-mouth dental extraction has provided relief from tongue- or lip-biting when jaw-closing dystonia is difficult to control. However, because dental procedures, like other medical procedures, carry some risk of precipitating a dystonic crisis in the person with PKAN, *we recommend a generally conservative approach to dental care. In addition to attention to daily oral hygiene practice and regular dental care, we recommend consultation with otolaryngology and oral surgery experts when indicated.*

Drooling

Drooling (sialorrhea) is common in PKAN as a result of jaw-opening dystonia, which interferes with swallowing. Most people manage the problem with bibs in children or a towel on hand to wipe saliva. This simple approach is often sufficient to manage drooling. Anticholinergic agents, including trihexyphenidyl, commonly used to treat dystonia in PKAN, may decrease saliva production as a side effect that can lessen drooling. Glycopyrrolate, hyoscine patch, or botulinum toxin injections into the parotid and submandibular glands may be considered if absolutely necessary, but *we do not routinely recommend medical or surgical interventions for drooling unless there is significant morbidity arising from this symptom.*

Vision

Visual impairment is common in PKAN but disability from this feature lags behind that from the neurological disease for most people. There are adults with PKAN for whom the retinopathy seems to dominate the clinical phenotype for many years however. Ocular features include pigmentary retinopathy, abnormalities of eye movements and pupillary function, and blepharospasm.[43] Most children and some adults will manifest poor vision in low-light conditions and constricted visual fields; these features may contribute to falls. While electrophysiologic abnormalities are commonly detected by electroretinogram (ERG), the results are of no clear clinical utility for most people with PKAN, and *we do not recommend ERG except in rare cases where it is clinically indicated. Regular clinical ophthalmologic examinations are*

recommended. Where blepharospasm is disabling, botulinum toxin injections should be employed as a first-line treatment.

Respiratory care

The respiratory complications of PKAN are similar to those associated with other chronic diseases that cause severe motor dysfunction. These include aspiration pneumonia and restricted pulmonary function from skeletal deformities. Stridor caused by laryngeal dystonia may compromise respiratory function; therefore this complication warrants close monitoring. Its management has been discussed in a prior section. Close attention to and regular monitoring of respiratory function is indicated for all people with PKAN. *We recommend a pulmonary hygiene regimen if the person with PKAN has difficulty handling secretions or is otherwise considered to be at risk for aspiration.*

Rehabilitation and mobility

People with PKAN develop abnormal tone to varying degrees, depending on the course and severity of their disease. Dystonia, spasticity, reduced joint mobility and contractures can all develop. Maintenance of range of motion in all joints is fundamental to care in order to facilitate optimal function, maintain good posture, promote ambulation for as long as possible, and minimize the development of fixed deformities and secondary complications of contractures. Physical therapists, occupational therapists, speech therapists and physicians with expertise in rehabilitation are all crucial to the multidisciplinary model of care. *Regular*

evaluation by individuals with expertise in rehabilitation medicine is crucial to maintaining functional abilities in PKAN.

Durable medical equipment is often beneficial and must be tailored to each individual's needs and goals. Regular review of equipment for fit and function is essential to meet changing needs. Many people with PKAN need devices to aid safe general mobility required for daily activities including orthotics, walkers, adapted strollers, manual and electric wheelchairs, standers and gait trainers. Assessment of the local environment at home, school and work is essential to allow adaptations where needed.

Exercise

Although there are no data to support a specific type of exercise program for people with PKAN, *we recommend implementing an exercise program early in the disease course that can be adjusted as functional abilities change.* There are no data to support a need for exercise restriction in PKAN. The main aims are to provide regular effective stretching and strengthening routines that are individualized for each person's needs. Fluctuations in dystonia should guide therapy day-to-day. Sustaining weight-bearing activities for as long as possible in the disease (for example with standers and gait trainers) may help to preserve bone mass and reduce the risk of fractures.

Management of skeletal complications

People with PKAN are at greater risk of skeletal complications secondary to abnormal limb tone (dystonia, spasticity), reduced mobility and osteopenia. They should therefore be monitored by clinical examination for spinal deformity, hip subluxation and dislocation, spinal cord lesions, and fractures. Baclofen pump placement, commonly used for dystonia management in PKAN, may accelerate the rate of scoliotic change, as in other disorders,[44] although not all studies support this.[45,46] The approach to monitoring and management follows general guidelines for people with similar disabilities. Despite concerns that the extreme opisthotonic posturing observed in children with PKAN could increase the risk of catheter kinking and subsequent baclofen withdrawal syndrome, the authors have not observed this.

Fractures are common in PKAN, and *an increase in dystonia or distress should always prompt a systematic assessment for occult fracture*. Although there are no studies documenting decreased bone mass or increased fracture risk in people with PKAN, osteopenia is common in other non-ambulatory populations, and our experience indicates that pathologic/fragility fractures in PKAN are commonly associated with minor trauma or severe dystonia. This observation suggests that bone mass is decreased despite the significant stress from dystonia. For baseline bone health assessment, a dual energy x-ray absorptiometry (DEXA) scan is useful. Encouraging optimal weight-bearing activities in addition to appropriate intake of calcium and vitamin D are recommended. Many examples of children with acute worsening of their dystonia have ultimately been attributed to an occult fracture that was missed for many days. Attention to this risk is therefore of paramount importance. Use of

soft casts rather than plaster casts for fracture management will lessen complications from the specific device.

Speech, Language and Communication

The very young child with classic PKAN may have delayed speech and language development as part of a larger picture of intellectual and developmental disability. Even with intensive therapy, some children do not catch up to their peers in language abilities. Additionally, intellectual and motor dysfunction may make alternative methods of communication challenging in classic disease. In older children and adults with PKAN, language ability is not usually affected but dysarthria, palilalia, tachyphemia and hypophonia are common speech disabilities. In these individuals, speech therapy and the use of augmentative communication devices are valuable tools for preserving communication. Motor dysfunction may interfere with the utility of some devices, but the drive to communicate usually allows people to overcome their increasing limitations and find effective ways to make their needs and wants known to others. Pacing speech with either hand tapping or a delayed feedback device can improve palilalia and tachyphemia and preserve intelligible speech. *Speech therapy consultation early in disease, including with an augmentative communication specialist if available, can help to preserve the widest range of means for communication.*

Pain management

Although many people with PKAN are reported by family members to have a high pain tolerance, dystonia often causes pain and agitation. Pain can, in turn, worsen dystonia and lead to a cycle that can be difficult to break. The prominence of dystonia in PKAN, in conjunction with impaired communication, complicates assessment and management. For these reasons *it is especially important to carefully and systematically assess for treatable causes of pain with every exacerbation of dystonia.* Pathologic fractures, occult gastrointestinal bleeding, occult infection, pressures sores, and joint subluxation or dislocation are recognized risks in PKAN that must be excluded. Once treatable causes have been considered and dystonia management optimized, controlling pain for comfort becomes the central goal. The choice of medications to manage pain is not specific to PKAN and should consider age, other medications, and respiratory and general state of health. Early involvement of pain specialists, including pediatric and adult palliative care teams, can ease suffering.

Sleep

A good sleeping pattern is fundamental to optimizing quality of life and mood and to reducing fatigue, pain and anxiety. Sleep disturbance is not normally an issue early in the disease course of PKAN nor is it a significant issue for most children. In adults later in their course of disease, reduced sleep time and lower efficacy of sleep have been reported,[47] as have been periods of difficulty with arousal from sleep. As neurological symptoms progress, healthy sleep may be compromised by medications or pain. Although dystonia disappears in sleep, the person with PKAN

may have difficulty getting comfortable at sleep onset and changing position during the night, and thus may have poor quality sleep. Identifying and addressing any issues interfering with sleep in addition to developing a good sleep regimen and environment will be beneficial. When adjunctive therapies are needed, melatonin or chloral hydrate may improve sleep induction. Adding clonazepam or another benzodiazepine at night or changing the timing of an existing dose to bedtime may serve to both sedate the person with PKAN and lessen dystonia and spasticity.

Seizures

Since seizures are not a specific feature of PKAN,[16] their occurrence should be presumed to be unrelated to the primary disease process, and their management should follow a standard approach.

Sexual health and reproduction

Adults with PKAN are able to have sexually fulfilling relationships. Reproductive capabilities seem to differ between men and women with PKAN. Women with PKAN have conceived and delivered healthy children without complications. Men with PKAN have fathered children; however, data suggest that men with PKAN may have defects in sperm motility, shape and number, all factors likely to decrease fertility (Hayflick, unpublished). Despite this, *contraception is recommended for both men and women with PKAN who do not wish to conceive.* Recommendations for specific types of contraception are the same as for people without PKAN.

Psychiatric and behavioral care

Psychiatric disabilities affect most adolescents and adults with atypical PKAN. These problems often manifest before a diagnosis is established and may complicate the diagnostic odyssey. Common symptoms include impulsivity, obsessive-compulsive disorder, emotional lability, anxiety and depression.[2,48] Attention deficit hyperactivity disorder (ADHD) is a common phenotypic feature of PKAN in children,[1,33,49] and some children may benefit from treatment. Rarely, psychosis may manifest prior to or after onset of neurological symptoms.[49-52] The inclusion of a psychiatrist in the medical team can help address these issues in a timely manner. Cognitive behavioral therapy may benefit people with PKAN. Although atypical neuroleptics may sometimes be indicated for management of behavioral and psychiatric complications of PKAN, their propensity to precipitate or aggravate parkinsonism and induce acute and tardive dystonia mandates caution in their use in this population.

Emergency Care Plan for people with PKAN

An emergency plan is a comprehensive set of instructions for families that outlines when, where, who, and how to contact emergency personnel should the person with PKAN need emergent care. This plan also provides critical information for emergency providers. The plan should list the person's diagnoses with baseline findings, current medications, known drug allergies, immunization status, common presenting problems with specific suggested management strategies, and contact information for subspecialty providers. If any medical devices have been implanted

(*e.g.*, DBS electrode, intrathecal baclofen pump), then include emergency contact information for each care team as well as the manufacturer's contact information, and be sure to inform first-responders of the presence of these devices. *Setting up an emergency care plan and maintaining a current emergency information form for the person with PKAN is recommended.* Including a link to or copy of this Guideline may also be helpful to the medical team providing emergent care to an individual with PKAN.

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 PKAN (http://www.acep.org/Clinical---Practice-Management/Emergency-Information-Form-for-Children-With-Special-Health-Care-Needs/). Maintaining a current emergency information form will ensure that a person's complicated medical history is concisely summarized and available when it is needed most. This form should be completed with the treating physician and should be reviewed and updated at least annually.

Immunization

For children and adults with PKAN, the standard approach to immunization for people with similar disabilities should be followed. There are no known immunologic effects from PKAN that would alter response to or contraindicate immunization.

Education

For all people with PKAN, *addressing ongoing and changing educational needs is a high priority.* School provides valuable educational and social opportunities. Therefore *every effort to accommodate special needs should be made with the goal of maximizing function*. Educational resources must be assessed frequently and adjusted as the disease progresses. Interval assessments should include neuropsychological evaluation that takes into account motor difficulties.[53,54] Many people with PKAN will qualify for tailored educational programs that ensure a child with disability is attending a primary or secondary educational institution that is able to meet their specific needs and optimize their learning environment. Tailored education programs should also include physical, occupational and speech therapy when appropriate.

Other issues that need attention in a school setting include: adaptations for gait difficulty and wheelchair use; management of attention deficit hyperactivity disorder and other neuropsychiatric symptoms; limitations from impairment of vision and speech; need for augmentative communication resources; and assistance with feeding and toileting.

People with milder forms of PKAN may graduate from college, join training programs, or enter the work force. Maximizing opportunities for intellectual and social engagement is an important goal. Because academic success can be impacted by neuropsychiatric disabilities, attention to their management will contribute to success in school and at the workplace.

Psychosocial Support

Providing adequate support for families at the time of diagnosis is important, and ongoing input is also necessary as families cope with this chronic, progressive disease. Isolation is a frequent challenge in older teenagers and young adults with PKAN, who have progressive limitations with independent communication and mobility. Support systems in place for such people vary between countries but can include daytime activity or work programs and young adult respite programs. Such programs have additional benefit in providing respite for caregivers, usually family members. Connecting with other teenagers and young adults through the NBIA Alliance can also be very useful. Caregivers can also find support through this network from others facing similar challenges and share ideas and experiences through family meetings, listservs, and other forums (see Key Resources below). Finally, as PKAN progresses, some people will be referred for hospice or palliative care with a focus on pain management and quality of life. The modern model of pediatric palliative care can be an excellent resource for both medical and psychosocial support.

Palliative and end-of-life care

Palliative care for people with PKAN can ease suffering as their disabilities worsen. *Early involvement of the palliative care team is encouraged and can be sought anytime after diagnosis.* Care is focused on improving quality of life through relief of symptoms and provision of psychological, social, and spiritual care, a consideration

sometimes overlooked for children and young adults. Palliative medicine can be provided in conjunction with routine medical care (including ongoing treatment) at any stage in an illness. When appropriate, the palliative care team is also responsible for formulating a personalized end-of–life plan expressing the will of the person and family, as well as how to plan the end of life in a critical or emergency situation. The plan is likely to change over time, requiring different considerations as disease progresses. An advanced directive can be prepared with the help of palliative care professionals, which conveys preferences, wishes, beliefs and values for end-of-life decisions, including brain and tissue donation for research. Such statements will greatly assist clinicians in caring for people with limited communicative or decision-making capacity.[55-58]

The role of NBIA lay advocacy organizations

In our experience, most families eventually seek contact with other PKAN families and become part of this community, but many are not ready to do so initially following the diagnosis. The NBIA Alliance is an international federation of family advocacy organizations for NBIA disorders. As of 2016, the Alliance included organizations from eight countries including Canada, France, Germany, Italy, the Netherlands, Spain, Switzerland and the United States of America. Sharing a common vision, the Alliance members work together to raise awareness of NBIA disorders and to promote and support research. They offer opportunities for families to connect and share their experiences. Email forums, restricted-access Facebook groups, networking programs, and an international meeting place on

RareConnect (https://www.rareconnect.org/en/community/neurodegeneration-with-brain-iron-accumulation-nbia) facilitate discussions among individuals and families from around the world. Family meetings, held at regular intervals and in varying locations, provide updates to families on the latest research and treatments and promote networking and support through speakers, workshops and social gatherings for both adults and children. Contact with these organizations can be made via their websites, telephone, mail, or email. See the Key Resources section for more information.

Concluding remarks

As we learn more about the natural history of PKAN and enter the era of disease-modifying therapeutics, our recommendations will change to reflect these advances. This guideline is intended to be a living document that will benefit from continual review and revision. We look forward to a time when our interventions fundamentally change the course of this devastating disease.

Figure legends:

Figure 1: Characteristic brain MRI changes in PKAN. A) Normal brain T2-weighted axial section showing normal signal in globus pallidus. B) PKAN brain showing a central hyperintense signal region surrounded by a region of signal hypointensity in the globus pallidus.

Figure 2: Overview of the management of status dystonicus in PKAN. DSAP, dystonia severity action plan; GPi, Globus pallidus internus; ITB, intrathecal baclofen; DBS, deep brain stimulation; CK, creatine kinase; ICU, intensive care unit; HDU, high dependency unit; IV, intravenous.

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Key Resources

NBIAcure.org	Information for families, physicians and scientists
NBIAdisorders.org	Information, support, research opportunities
NBIAalliance.org	International alliance of NBIA patient advocacy groups
TIRCON.eu	Information for physicians and scientists on the work of the TIRCON consortium (Treat Iron-Related Childhood-Onset Neurodegeneration)

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Figure 1.

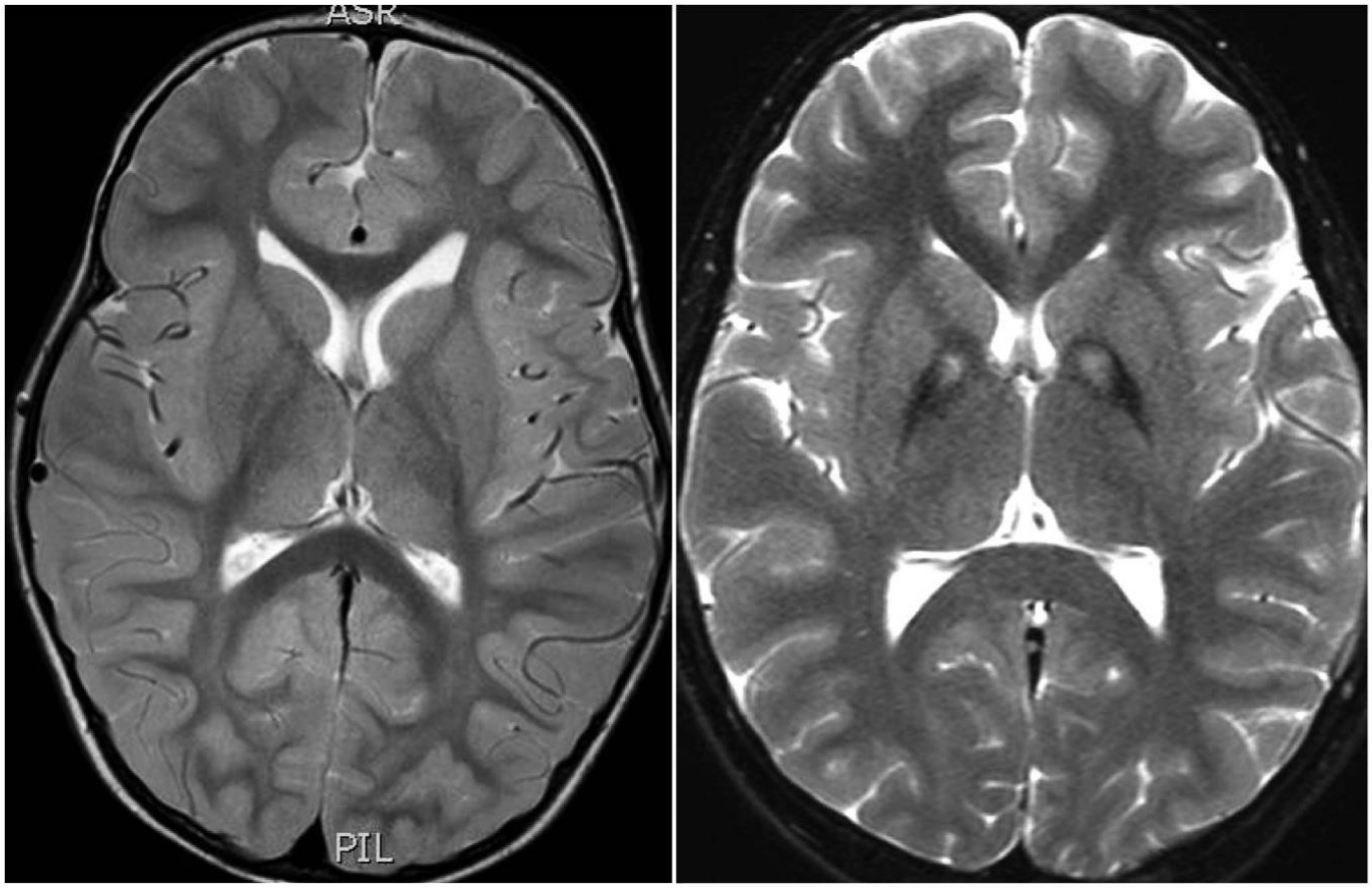
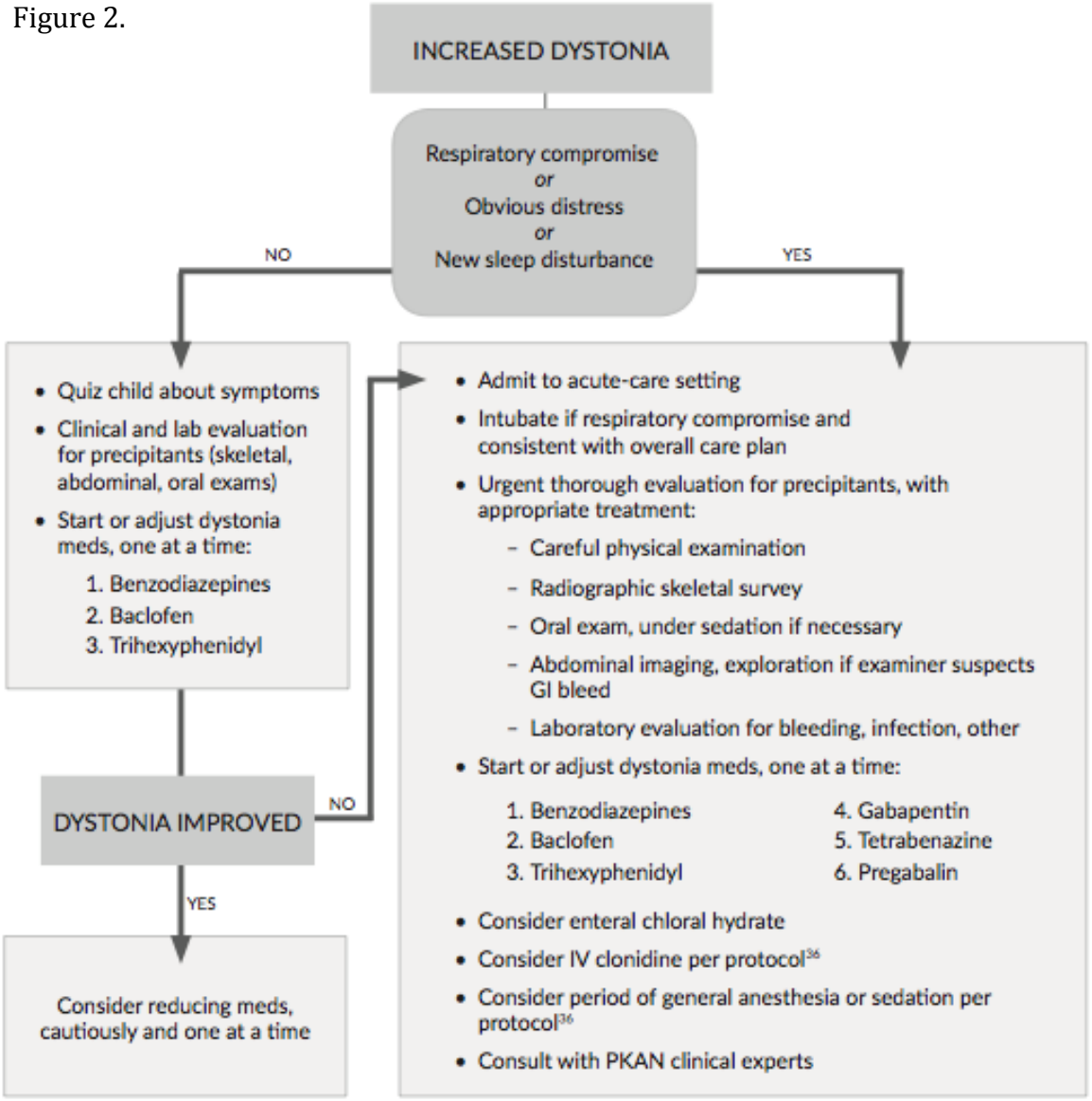


Figure 2.


INCREASED DYSTONIA
Respiratory compromise
or
Obvious distress
or
New sleep disturbance
NO
YES
• Quiz child about symptoms
• Clinical and lab evaluation for precipitants (skeletal, abdominal, oral exams)
• Start or adjust dystonia meds, one at a time:
1. Benzodiazepines
2. Baclofen
3. Trihexyphenidyl
DYSTONIA IMPROVED
NO
YES
Consider reducing meds, cautiously and one at a time
• Admit to acute-care setting
• Intubate if respiratory compromise and consistent with overall care plan
• Urgent thorough evaluation for precipitants, with appropriate treatment:
– Careful physical examination
– Radiographic skeletal survey
– Oral exam, under sedation if necessary
– Abdominal imaging, exploration if examiner suspects GI bleed
– Laboratory evaluation for bleeding, infection, other
• Start or adjust dystonia meds, one at a time:
1. Benzodiazepines
2. Baclofen
3. Trihexyphenidyl
4. Gabapentin
5. Tetrabenazine
6. Pregabalin
• Consider enteral chloral hydrate
• Consider IV clonidine per protocol[36]
• Consider period of general anesthesia or sedation per protocol[36]
• Consult with PKAN clinical experts