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Treatment of Classic Pantothenate Kinase-Associated Neurodegeneration (PKAN) with Deferiprone and Intrathecal Baclofen

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Abstract

Neurodegeneration with brain iron accumulation (NBIA) describes a heterogeneous family of diseases characterized by high brain iron, particularly in the basal ganglia. The most common manifestation of childhood NBIA is classic Pantothenate Kinase-Associated Neurodegeneration (PKAN), a severe, progressive type of autosomal recessive neuroaxonal dystrophy characterized by early onset of symptoms (as opposed to atypical PKAN, with average onset age 14 years). There is currently no established therapy for the disease. Intrathecal baclofen has been reported to improve ease of care and dystonia in PKAN patients. Deferiprone, an iron chelator, has been shown to be safe and tolerable in PKAN patients, as well as effective in reducing brain iron accumulation as measured by MRI. This case report highlights the potency of combining ITB and oral deferiprone in a patient with classic PKAN. Although treatment with deferiprone alone was not attempted, this combination therapy appears to be more efficacious than treatment with only intrathecal baclofen.

Keywords

Neurodegeneration with Brain Iron Accumulation; Pantothenate Kinase-Associated Neurodegeneration; Baclofen; Deferiprone

Neurodegeneration with brain iron accumulation (NBIA) describes a heterogeneous family of diseases characterized by high brain iron, particularly in the basal ganglia. The most common manifestation of NBIA in childhood is the disease pantothenate kinase-associated neurodegeneration (PKAN). PKAN is a type of autosomal recessive neuroaxonal dystrophy caused by mutations in the *PANK2* gene; the PANK2 enzyme is normally responsible for the first step in coenzyme A biosynthesis¹. Classic PKAN is characterized by early onset (typically under 6 years of age) with rapid disease progression, whereas atypical PKAN has an average age of onset of 14 years and progresses more slowly. Common clinical features of classic PKAN include dystonia, dysarthria, rigidity, pigmentary degeneration of the

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retina, limb spasticity, contractures, spinal deformity, Parkinsonism, and bulbar dysfunction¹. Radiologically, classic PKAN can be characterized by an “eye-of-the-tiger pattern [on MRI] ...bilateral areas of hyperintensity within a region of hypointensity in the medial globus pallidus on T2-weighted images”². Classic PKAN patients are commonly first diagnosed with attention-deficit hyperactivity disorder (ADHD). In later stages, many patients experience gastroesophageal reflux, dysphasia, and constipation³. Management of patients with PKAN is complex, as symptoms of the disease require attention from multiple medical disciplines, including neurosurgery, pulmonology, hematology, rehabilitation, neurology, and orthopedics.

Although there is currently no established therapy for PKAN, various drugs are used to alleviate or lessen its symptoms. Baclofen, a gamma-aminobutyric acid (GABA) receptor agonist, is one of the ‘mainstay drugs’ used to treat dystonia in patients with PKAN⁴. It is often administered via an intrathecal baclofen (ITB) pump, and has been recommended as a safe and effective treatment for dystonia⁵. ITB for the treatment of dystonia was first reported in 1991⁶. It has been suggested that ITB for treatment of dystonia is more effective in patients who also have spasticity or pain⁷, both of which have been observed in PKAN. In a study of seven patients with PKAN treated with ITB, Albright et al found that although parents reported improvements in ease of care and severity of dystonia, there was no statistically significant difference in dystonia scores⁸. Woon et al found that treatment with ITB in PKAN patients improved vocalization, swallowing, drooling, fine motor skills, and ease of care⁵. More recently, intraventricular baclofen delivery has been used to treat PKAN with favorable outcomes. However, further investigation into dosage and efficacy of this technique are needed⁹.

Deferiprone (1,2-dimethyl-3-hydroxypyrid-4-one or L1) is an iron chelator that was first used in thalassemia patients receiving blood transfusions. It has been shown to cross the blood-brain barrier and to remove intracellular iron, as well as acting as a reverse siderophore by way of iron redistribution^{10,11,12,13}. Deferiprone as a treatment for NBIA was first reported in 2008 in a 61-year-old woman, with treatment resulting in reduced brain iron deposition, improved gait, and decreased incidence of choreic dyskinesias¹⁴. Subsequent pilot trials investigating deferiprone for the treatment of PKAN have found that the drug is safe and tolerable, as well as effective in reducing brain iron accumulation as measured by MRI. However, the standard dose of deferiprone used for hemocytosis may be associated with increased neurotoxicity in patients with PKAN. The link between clinical and radiological findings, however, is unclear, as only mild to moderate motor improvement was noted in some patients in one study (dosage of 30 mg/kg/day)¹⁵, and no clinical improvement noted in the other study (dosage of 25 mg/kg/day)¹⁶. Studies in thalassemia patients have shown side effects of the drug to include agranulocytosis, musculoskeletal pain, and zinc deficiency, so monitoring of blood count, iron balance, and liver and renal function has been used in patients treated with deferiprone. Both pilot trials emphasized the need for an international, placebo-controlled, long-term study to investigate the clinical efficacy of iron chelation treatment for PKAN^{15,16}.

This case report highlights the potency of combining ITB and oral deferiprone in a patient with classic PKAN. Although treatment with deferiprone alone was not attempted, this combination therapy appears to be more efficacious than treatment with only intrathecal baclofen.

CASE REPORT

This is a case of a 15-year-old male with a diagnosis of classic PKAN, severe progressive dystonia, and blindness currently being treated with deferiprone and ITB.

Born without complications and full-term, the patient was treated early in life for suspected ADHD and bipolar disorder. At age 5, he was diagnosed with retinitis pigmentosa and subsequently declared legally blind. However, since he was at the time fully functional, further investigation into the cause of his blindness and behavioral disorders was not pursued.

At age 10 (2007) an MRI of the patient's brain confirmed the presence of iron deposition in the basal ganglia (see Figure 1). Because his symptoms had begun when he was under age 6, the patient was diagnosed with classic, rather than atypical, PKAN. The disease progressed so severely that within 18 months, he went from a fully functional young boy to a severely handicapped 12-year old. By age 11 (2008), he was unable to walk; at the height of his dystonia (age 12) he tolerated only a prone position and was constantly in an opisthotonic posture supported by pillows, with upper extremities, trunk, and lower extremities in severe hyperextension. He was unable to sit in a wheelchair and therefore transported in a wagon. At age 11, bilateral deep brain stimulators (DBS) were placed in attempt to manage his dystonia based on positive published results on the use of DBS for dystonia^{17,18}. The IPG (implanted pulse generator) was placed in the patients' abdomen, rather than the more common infraclavicular location, due to his small size and poor nutritional status, to improve tissue coverage over that available in the chest. However, this treatment appeared ineffective and was subsequently disconnected eight months after implantation.

During disconnection and battery removal of the DBS, an ITB pump was implanted with the catheter tip placed at C2 (See Figure 2). This decision was made based on a very good response to an ITB trial of 100 µg. During the 3-hour trial period, noted were improved Ashworth scores (see Table 1), as well as clearer speech, the regained ability to chew without gagging or choking, decreased opisthotonic arching, the ability to open both hands upon command, and knee extension past 90 degrees. After ITB pump implantation, the patient received 1050 µg of baclofen per day, as well as oral baclofen (10 mg) and diazepam (4 mg) as needed for stiffness. Oral baclofen was given as a supplement, as it was thought that oral medication might potentiate the effects of ITB. It was noted that baclofen was helpful in managing his dystonia and spasticity, and enabled him to regain functions such as smiling, laughing, crying, and moving his arms. Physical therapy evaluation after ITB pump implantation noted that he had no spasticity in his lower extremities, and was able to relax his trunk and head in both prone and supine position for a few minutes, if requested. Occupational therapy reported increased tongue mobility and the ability to eat more easily as compared to prior to baclofen treatment, as well as the capability to communicate by nodding his head "yes" and "no". One year later, the catheter tip was moved to C6, where it remains today. The patient currently receives 1018 ug/day of baclofen, with a 40ug periodic bolus added 2-4 times/day upon worsening of symptoms.

Feeding was another complex issue in this patient. In 2009, he was seen by gastroenterology about feeding and weight loss concerns. Although at this time he was still able to take food orally, doing so was complicated by significant coughing and swallowing difficulties. He was placed on bolus nasogastric (NG) tube feeds with Nutren Junior and consulted by surgery for the placement of a gastrostomy (G) tube. However, due to his consistent opisthotonic posturing and presence of instruments within his abdomen, the surgeon felt that a G-tube would be mechanically difficult for him. His mother reported about a 20lb weight gain after NG-tube placement, but also complained that he would pull out the NG-tube at least once a week. He had two hospitalizations for aspiration pneumonia, which his mother felt were due to his repeated purposeful removal of the tube.

Although ITB appeared to cause significant improvements in this patient, his complex medical management encouraged the pursuit of other therapeutic drug options. In July of

2009, the FDA granted Compassionate Use Investigational New Drug approval for the use of deferiprone in the patient. He was administered a low dose of oral deferiprone twice daily. On check-up one month later, he presented with a 14-pound weight gain and was again able to sit in his wheelchair. Because of this regained ability, he was again consulted for G-tube placement, which was performed in December of 2010 mainly for the concern of aspiration. In a follow-up visit slightly over a year after treatment with deferiprone was started, remarkable improvement was noted, especially in the extent of his dystonia. Better head movements and the ability to lift up his leg were also noted by the physician, and the patient's mother reported that while at home, he was interactive, responded to conversation, and was able to answer 'yes' or 'no' by lifting his elbow. Range of motion measurements before and after treatment with deferiprone are reported in Table 2.

Treatment with deferiprone was interrupted only for intercurrent infections. There appeared to be no other physical side effects of the drug such as neutropenia or joint swelling. The patient's liver function has been stable with no changes in his metabolic panel. In screening for iron deficiency, decreases in ferritin and transferrin saturation were noted, and low dose iron supplementation was started (2 mg/kg/day) based on recommendation by the physician responsible for his deferiprone dosage and hematologic oversight. Since deferiprone has a tendency to chelate areas with high levels of iron, it also removes some circulating iron. We therefore started supplemental iron in order to keep the blood levels of ferritin normal, subsequently keeping RBC levels normal; the previously observed low ferritin has since been normalized. There has been no hematologic manifestation of such iron deficiency, as MCV, RDW, and hemoglobin levels actually improved (see Table 3).

The patient is currently taking, among other medications, 40 mg/day of diazepam, and 1035 µg/day of intrathecal baclofen, 1000 mg/day of deferiprone, and 6.1 mg/day of ferrous sulfate. He remains stable and further side effects of intrathecal baclofen or deferiprone have not been reported.

DISCUSSION

This currently 15-year-old boy diagnosed with classic PKAN progressed, upon treatment with ITB and oral deferiprone, from a boy in constant opisthotic posture who was carried in a wagon to being able to sit in a wheelchair. The patient was treated with a daily dosage of deferiprone just in between that used in recent pilot trials^{15,16}. However, his baclofen dose was higher than that given in previous studies on ITB as a treatment for dystonia^{5,19}. No adverse side effects of either drug was reported, aside from decreases in ferritin and transferrin saturation, which were not reflected in hematologic measurements such as MCV, RDW, or hemoglobin level. He has now been treated with ITB and oral deferiprone for three years; his mother reports greater ease of care, is happy with the treatment outcome, and wishes to continue therapy with both drugs.

This case highlights the fact that although there is no approved treatment for PKAN, drugs like baclofen and deferiprone may lead to marked improvements in quality of life, dystonia, and ease of care for these patients. Although deferiprone is only variably efficacious with regards to clinical improvements^{15,16}, some patients such as presented in this study may derive great benefit from taking the drug. ITB therapy has also been shown to decrease the extent of dystonia in patients with PKAN, as was observed in this patient. The authors recommend that patients with severe, progressive dystonia and classic PKAN be considered for dual treatment with ITB and deferiprone.

Based on this and 2 other cases of PKAN treated with deferiprone under an IND at *****, a large scale, phase-three placebo controlled trial will be pursued. This international trial will

begin enrolling patients with PKAN for treatment with deferiprone in the fall of 2012, with ***** serving as the U.S. site involved in the study. This clinical trial is supported by both the FDA and a Framework 7 European Union grant, Treat Iron Related Childhood Onset Neurodegeneration (TIRCON).

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Figure 1. Axial T2WI MR demonstrating bilateral hypointensity of the globus pallidi with central hyperintensity (“eye-of-the-tiger” pattern).

Figure 2.
Abdominal X-ray, showing placement of DBS (image left; patient's right) and intrathecal baclofen pump (image right; patient's left).

Table 1

Ashworth scale scores reported from intrathecal baclofen trial of 100 µg

	Pre-Baclofen (right/left)	Post-1 hour (right/left)	Post-2 hours (right/left)	Post-3 hours (right/left)
Wrist extension	3/2	3/1	3/2	1/1
Elbow flexion	1/3	1/1	1/1	1/1
Elbow extension	1/3	1/3	1/1	1/1
Hip abduction	5/4	3/1	1/1	1/1
Hip flexion	4/5	3/5	3/4	4/4
Knee extension	5/5	2/1	1/2	2/1
Ankle dorsiflexion	5/5	1/1	1/1	1/1
Ankle plantar flexion	1/1	1/1	1/1	1/1

Table 2

Range of motion measurements (degrees) reported before and after treatment with deferiprone. WNL=within normal limits

Range of Motion (ROM)	Right pre-treatment	Right post-treatment	Change in right ROM	Left pre-treatment	Left post-treatment	Change in left ROM
Hip flexion	-10	60	+70	15	60	+45
Hip extension	20	25	+5	15	30	+15
Hip abduction	6	20	+14	10	15	+5
Hip adduction	10	WNL		10	WNL	
Hip IR	-13	35	+48	15	42	+27
Hip ER	75	55	-20	85	42	-43
Knee flexion	150	135	-15	135	145	-10
Knee extension	-40	-40	0	-20	-35	-15
Dorsiflexion	-70	-40	+30	-80	-40	+40
Plantar flexion	80	60	-20	80	55	-25
Eversion	-40	-30	+10	-37	-50	+13
Inversion	40	50	+10	37	65	+28

Table 3

Blood count, blood iron, and body weight, reported before treatment with deferiprone and at follow-up.
MCV=mean corpuscular volume; RDW=red blood cell distribution width

	Prior to treatment with deferiprone	Follow-up at 14 months
MCV	76 fL	83 fL
RDW	15.1	13.4
Transferrin saturation	10.7%	11.3% *
Ferritin	28.7 ng/mL	9.5 ng/mL *
Hemoglobin level	11.9 g/dL	13.5 g/dL
Body weight	58.4 lb	78.0 lb

* Iron saturation and ferritin were measured at 11 months.