

Botulinum toxin injection to improve functional independence and to alleviate parenting stress in a child with advanced pantothenate kinase-associated neurodegeneration

A case report and literature review

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Abstract

Rationale: Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disease. Progressive motor symptoms such as dystonia and spasticity begin in childhood and relentlessly become incapacitating later in life. Treatments including anticholinergics and iron chelation are usually ineffective. Botulinum toxin type A (BoNT-A) is effective for adult patients with dystonia or spasticity.

Patient concerns: We reported a 10-year-old female patient with advanced PKAN, manifesting as generalized dystonia and spasticity.

Diagnosis: The patient was diagnosed with PKAN by a pediatric neurologist.

Interventions: The patient received BoNT-A injection.

Outcomes: The effect was obvious at four weeks after the injection, with an improvement of 25% in Barry-Albright Dystonia Scale and 4% in Functional Independence Measure for Children score. Furthermore, there was a 3.8% reduction in Parenting Stress Index Short Form score and 8.3% improvement in Pain and Impact of Disability domain in the score of Cerebral Palsy Quality of Life for Children.

Lessons: BoNT-A injection was effective to improve functional independence and to alleviate stress of caregivers in the patient with advanced PKAN.

Abbreviations: ADL = activities of daily living, BADS = Barry-Albright dystonia scale, BoNT-A = botulinum toxin type A, CP QOL-Child = cerebral palsy quality of life for children, ITB = intrathecal baclofen, PKAN = pantothenate kinase-associated neurodegeneration, PSI-SF = parenting stress index short form, WeeFIM = functional independence measure for children.

Keywords: botulinum toxin injection, dystonia, functional independence, pantothenate kinase-associated neurodegeneration, stress of caregivers

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1. Introduction

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive disease caused by mutations in the PANK2 gene.^[1] The gene encodes pantothenate kinase 2, and plays an important role in fatty acid metabolism.^[1] The disease can lead to abnormal iron deposition in the basal ganglia of the brain, which may show hypointensed globus pallidus with a surrounded region of hyperintensity in T2-weighted sequences of brain magnetic resonance imaging, the so-called “eye of the tiger” sign.^[1]

In classic PKAN, the children present with symptoms early and has a progressive course.^[1,2] Motor symptoms usually develop before the age of 6, with an initial change in gait leading to frequent falls. Involuntary control of muscle tones such as dystonia and spasticity begin in early childhood and can cause the patient to become incapacitated later in life.^[2]

Several treatments for PKAN have been proposed. Iron-chelation therapy which lead to signal reduction in globus pallidus iron content has inconclusive clinical benefit.^[3] Oral anticholinergics, benzodiazepines, and other anti-spastic agents

Table 1**Botox dosage for each injected muscle.**

Side	Injected muscles	Unit of Botox
Right	Sternocleidomastoid	30
	Splenius capitis	30
	Semispinalis capitis	20
	Levator scapulae	20
Left	Teres major	30
	Biceps brachii	30
	Flexor pollicis longus	20

such as baclofen, were widely used for decades with only mild to moderate improvements.^[2] Deep brain stimulation might be a promising option, but there are currently limited case reports in literature.^[2]

Botulinum toxin type A (BoNT-A) injection, which blocks acetylcholine release at the neuromuscular junctions, has been widely used in managing dystonia and spasticity in a variety of diseases. It had been proposed to be safe and effective in controlling the jaw-opening dystonia in a case of PKAN.^[4] However, its impact on quality of life and the stress for caregivers have not been addressed.

We evaluated the effect of BoNT-A injection therapy for a patient with advanced PKAN with emphasis on the functional and societal domains.

2. Case report

The patient is a 10-year-old Taiwanese female patient who was diagnosed with PKAN by a pediatric neurologist. Her initial presentation was unsteady gait since 2 years old. Dystonia over head and neck developed subsequently at age of 5. Spasticity and dystonia of 4 extremities appeared gradually and exacerbated her function a lot. She had been treated with oral baclofen, clonazepam, and carbidopa/levodopa for 6 months with mild improvement. Therefore, she was referred to our clinic for feasibility of BoNT-A injection. Upon presenting to our clinic, she had been wheelchair-dependent for 1 year and had severely impaired activities of daily living (ADL). On physical examination, we noted severe, generalized dystonia and spasticity involving head, neck, trunk, and 4 extremities with the following chief manifestations: head tilt to right side, left shoulder retraction, bilateral elbow flexion, left thumb-in-palm posture with wound, bilateral thighs adduction, bilateral ankle plantar flexion with contracture, episodic respiratory distress. After explaining the details to her and her parents, we performed single 180 units of Botox (onabotulinumtoxin A, Allergan Inc., Irvine, CA) injection for her smoothly. The injected muscles and dosage for each muscle are described in Table 1.

We evaluated the patient before and 4 weeks after Botox injection through 4 domains. Outcome measures include dystonia pattern by Barry-Albright dystonia scale (BADs), quality of life by primary caregiver proxy-report form of cerebral palsy quality of life for children (CP QOL-Child), ADL by the functional independence measure for children (WeeFIM), and parenting stress of caregivers by parenting stress index short form (PSI-SF). After 4 weeks post injection, we continued evaluating her condition clinically every 4 weeks.

The therapeutic effect was the most apparent 4 weeks after BoNT-A injection. We noticed improved active range of motion in the neck, and she could turn her head to right side. She was able to have voluntary extension of the left elbow and left thumb.

Table 2**Outcome measures before and after Botox injection.**

Parameter	Time	
	Before injection	4 weeks after injection
BADS	24	18
WeeFIM	25	26
PSI-SF	115	111
CP QoL-Pain and Impact of Disability	48	44

BADS = Barry-Albright dystonia scale, CP QOL-Child = cerebral palsy quality of life for children, PSI-SF = parenting stress index short form, WeeFIM = functional independence measure for children.

Moreover, the frequency and the duration of respiratory distress also decreased.

The improvement in each domains are as follows: BADs improved for 25%, from 24 to 18; CP QoL-Pain and Impact of Disability decreased for 8.3%, from 48 to 44; WeeFIM improved for 4%, from 25 to 26; PSI-SF decreased for 3.5%, from 115 to 111 (Table 2). There were no side effects throughout the follow-up period.

Informed consent was obtained from the patient and her guardians for publication of the case details. The ethical approval was not necessary for this case report under the regulations of institutional review board of the National Cheng Kung University Hospital.

3. Discussion

Although PKAN was first described in 1922, few choices of management exist for this progressively disabling disease.^[1,2] The current treatment options for PKAN can be classified into 2 categories. First, disease-modifying agents, such as deferiprone, aims to remove the intracellular iron accumulated in the basal ganglion. The second group is used for symptomatic treatment of involuntary muscle control, including oral anticholinergics, benzodiazepines, and anti-spastic agents.

Deferiprone is an iron-chelating agents originally used to treat iron overload in thalassemia major. Previous study^[3] revealed deferiprone caused significant signal reduction in globus pallidus iron content assessed by magnetic resonance imaging. None of the patients, however, demonstrated a significant change on Burke-Fahn-Marsden dystonia rating scale and quality-of-life scale. It suggests that deferiprone should not be used as a monotherapy.

Pratini et al^[5] reported combined therapy with intrathecal baclofen (ITB) and oral deferiprone in a patient with classic PKAN. The patient had improved spasticity in Ashworth Scale scores in upper and lower extremities. Furthermore, the range of motion for lower extremity muscles also improved after deferiprone was given concomitantly. His mother reported greater ease of care, and was satisfied with the treatment. However, the authors did not discuss the patient's quantitative functional outcome.

BoNT-A is now recommended as a first-line treatment for focal dystonia in adults due to its favorable efficacy and minimal side effects.^[6,7] But there is limited studies supporting its use in pediatric population with dystonia.^[8] We found no clinical trials but only 2 case reports in the literature for application of BoNT-A to control abnormal muscle tone in children with PKAN.^[4,9] Dressler injected 400 units of Dysport (AbobotulinumtoxinA, Ipsen Ltd., Paris, France) into the pterygoid and mylohyoid muscles to successfully control jaw opening dystonia in a 20-year-old man with PKAN.^[4] In the other report,^[9] a girl with PKAN

complicated with gait disturbance secondary to progressive hypertonia of muscles in lower extremities. She received 400 units of Dysport injection into the tibialis posterior and medial part of gastrocnemius. The author stated that the patient was able to achieve a stable stance and gait after the treatment. Her quality of life and social relationships also improved.

Management for our case of PKAN with generalized dystonia and spasticity is more complicated as compared with previous 2 case reports with focal dystonia. Regarding the safety with high dose of BoNT-A injection in pediatric population, we only injected the muscles of neck causing torticollis and muscles of left upper extremity with residual function. The dosage of BoNT-A was determined according to the recommendation in the previous literature.^[10] We aimed to alleviate her pain due to torticollis and to facilitate her use of left upper extremity for some simple tasks such as itch-scratching. We also hoped to lessen the tremendous burden of her caregivers.

Timmermann et al^[11] used bilateral pallidal stimulation for patients with neurodegeneration disease that had brain iron accumulation. Of note, 60.9% of them were diagnosed as PKAN.^[7] Their results revealed similar improvement in severity of dystonia (25.7%) as our study. However, stress levels of caregivers were not assessed and several adverse events associated with bilateral pallidal stimulation were reported in the study.

To our knowledge, this is the first report to describe the therapeutic effect of BoNT-A injection for generalized dystonia and spasticity associated with PKAN. Four weeks after BoNT-A injection, the patient was able to turn her neck to the directions of right side, and to extend her left elbow and left thumb voluntarily for some simple ADL such as itch scratching. Most importantly, there was marked decrease in the frequency and duration of respiratory distress, which could be life-threatening for the patient. The parents and the patient were satisfied with the results, and were willing to receive additional injection.

In summary, the improved functional independence in patient and reduced parenting stress of caregivers suggest that BONT-A injection may be a good and safe option for patients with PKAN.

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