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Botulinum Toxin Therapy in a Patient with HHH Syndrome with Gait Disturbance: A Case Report

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Abstract

Background : Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is a rare, autosomal recessive metabolic disorder which is caused by genetic mutations that disrupt the urea cycle. It is characterized by variable clinical presentation and the age of onset. Patients may present with gait disturbance and progressive paraplegia and muscle tightness in the lower extremities. The use of botulinum toxin in metabolic disease has rarely been discussed. We describe a case of a 14-year-old-boy with HHH syndrome, who presented with a several - month history of gait disturbance and lower extremity weakness.

Case presentation : A 14-year old male had a history of recurrent upper respiratory tract infections, occasional vomiting, loss of appetite, and general weakness, all of which started since he was 10 months old. He was diagnosed with HHH syndrome at one year of age. At the age of 14, he was referred for the assessment and treatment of his gait disturbance and aggravated weakness of the lower extremities. Brain MRI, electrodiagnostic study and blood test were performed to exclude any lesions related to neurologic dysfunction. Botulinum toxin type A were injected into muscles of adductor longus, adductor magnus, lateral and medial hamstring, and lateral and medial gastrocnemius muscle heads under needle electromyography guidance to reduce lower limb spasticity. Intensive physical therapy including gait training and stretching exercise of adductor and calf muscles were also provided. After intensive physical therapy and botulinum toxin injection to reduce lower limb spasticity, he was able to ambulate for 20 meters independently without any walking aids. There were no adverse events after the injection.

Conclusion : Botulinum toxin injection is a safe and effective therapy for patients with HHH syndrome who suffer from gait disturbance.

Key Words : botulinum toxins, gait disturbance, HHH syndrome, metabolic disorder, progressive paraplegia

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Ⅰ. Introduction

1. Research Background and Needs

Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is a rare autosomal recessive disorder caused by genetic mutations that disrupt the urea cycle through the impairment of ornithine transport across the inner mitochondrial membrane. It is characterized by the loss of appetite, recurrent vomiting, developmental delay, mental retardation, seizure, ataxia, and episodic loss of consciousness. Neurologically, this disorder can present with developmental delay, pyramidal dysfunction, myoclonic seizure, ataxia and gait disturbance. (Kim et al., 2012; Martinelli et al., 2015).

Botulinum toxin type A (BXT-A) is widely used in neurological disorders for various symptoms such as focal dystonia, spasticity, hemi-facial spasm, hyperhidrosis, and the drooling of saliva (Comella & Pullman, 2004). It is also considered safe for use in children (Lukban et al., 2009). The injections of botulinum toxin have been mainly studied and found to be useful in the treatment of spasticity in central nervous system lesions such as stroke, cerebral palsy, traumatic brain injury, spinal cord injury and multiple sclerosis (Moeini-Naghani, et al., 2016).

2. Research Purpose

The use of botulinum toxin in metabolic disease has rarely been discussed. HHH syndrome causes the accumulation of ammonia due to interruption of the urea cycle. Previous studies showed that the level of ammonia can affect the regulation of BTX-A (Patter-Curtis & Johnson, 1989). It has not yet been reported whether the use of BTX-A is safe or effective in a patient with the urea cycle disorder. We report a case of BXT-A use in a patient with HHH syndrome who suffered from gait disturbance.

Ⅱ. Case presentation

A 14-year old male presented to our clinic with a history of recurrent upper respiratory tract infections, occasional vomiting, loss of appetite, and general weakness, all of which started since he was 10 months old. He was diagnosed with HHH syndrome at one year of age at which time he had elevated transaminases, hyperammonemia, increased plasma glutamine, ornithine, and methionine levels, and increased urine ornithine and citrulline levels. His elder brother had been diagnosed with HHH syndrome at a similar age.

After the diagnosis, he was commenced on low protein diet treatment and arginine supplement. The Denver Developmental Screening Test (DDST) performed when he was 12 months old showed that there were developmental delays in personal-social (7 months, age group performance), language (9 months), gross motor (9 months), and fine motor-adaptive (10 months) skills. Motor and sensory examinations were normal; deep tendon reflexes (DTRs) were normal, and no other pathological reflexes were observed.

At the age of 14, he was referred to the department of rehabilitation for the assessment and treatment of his gait disturbance and aggravated weakness of the lower extremities. At that time, it had become difficult for him to stand for long periods of time. His height was within the reference range (169 cm, 50~75 percentile), and he was underweight (48 kg, 3rd percentile or less).

Neurological examination revealed that muscle strength of both upper extremities was intact, DTRs in upper extremities were normal, and there were no pathological reflexes. Bilateral proximal lower extremity weakness was found. Medical Research Council (MRC) grades in the proximal and distal parts of the right side were 4/5 and 3/5 respectively, and those of the left side were 3/5 and 3/5, respectively. DTRs in the lower extremities were increased, and Babinski signs and ankle clonus were observed. The

patient did not show any fasciculations, muscle cramps, bulbar symptoms, respiratory muscle weakness. He was able to maintain balance in the seated position; however, he had difficulty in maintaining static and dynamic balances of the standing position.

He could not walk without the assistance of his walker. When he tried to walk with a walker, the scissoring and tip-toe gait patterns were observed. The passive ankle dorsiflexion angle was -5' on right and 0' on left. The spasticity of both adductor muscles was measured as MAS (Modified Ashworth Scale) 2 and that of both knee flexors and ankle plantar flexor muscles was MAS 1+ to 2. Sensory examination results were normal.

Brain MRI revealed no significant abnormal findings. Serum CK levels were normal. Nerve conduction study and electromyography were performed to exclude myopathy. Nerve conduction study demonstrated a decreased amplitude of compound muscle action potential in the distal muscles (abductor hallucis, extensor digitorum brevis muscles) of both lower extremities. Electromyography revealed no abnormal insertional activities, abnormal spontaneous activities and voluntary motor unit action potentials alterations and no early recruitment pattern.

BXT-A (Botox, Allergan, BXT-A) 25 units per one point were injected into muscles of adductor longus, adductor magnus, lateral and medial hamstring, and lateral and medial gastrocnemius muscle heads under needle electromyography guidance. Four weeks of gait training and stretching exercise of adductor and calf muscles were provided.

After the injection, the patient did not report any adverse events such as edema, infection and general weakness related to it. Liver enzymes and inflammatory markers were within the reference ranges. The passive range of motion of ankle dorsiflexion was improved from -5' to 10' on the right side and from 0' to 15' on the left side. Ankle clonus was reduced. The toe gait and scissoring gait patterns disappeared during ambulation, and the patient was able to walk 20 m without the help of assistive devices.

The report of this case was approved by the Institutional Review Board (IRB No. 2020-09-028).

Ⅲ. Discussion

This is the first report to our knowledge to demonstrate the effects of using BXT-A in a patient with HHH syndrome. Botulinum toxin has been used to correct gait pattern and improve ambulatory function successfully in adults and children who have neurologic diseases (Camacho & Rioseco-Camacho, 1993; Comella & Pullman, 2004).

Progressive paraplegia is typically shown in HHH syndrome (Camacho & Rioseco-Camacho, 1993) and this is thought to be secondary to decreased mitochondrial homeostasis caused by sustained concentrations of ornithine and citrulline leading to the failure of bio-energy production in brain cells and accumulation of metabolites which cause oxidative damage (Viegas et al., 2011).

Although the present case did not reveal any abnormal findings in brain MRI, typical radiologic findings of HHH syndrome are subcortical and cortical atrophy, ischemic-like lesions in the white matter of the cortex, and the calcification of the basal ganglia (Al-Hassnan et al., 2008).

Progressive gait disturbance is one of the most uncomfortable symptoms for HHH syndrome patients (Debray et al., 2008). Progressive paraplegia accompanies gait disturbance and brings overall functional limitation and dependency on assistive devices. The conventional treatment of HHH syndrome is to normalize the concentrations of ornithine and homocitrulline in the blood with arginine injection. It was reported that the continuous use of the arginine injections would not slow down or prevent the neurological complications such as paraplegia (Debray et al., 2008). Even though neurological symptoms and signs were observed in 2/3 of patients with HHH, management for neurological dysfunction in those patients had been scarcely discussed. In addition to the conventional

treatment, multidisciplinary approach for patients with HHH syndrome was needed to maximize patients' abilities to perform activities of daily living.

Botulinum toxin is widely used for muscle stiffness caused by upper motor lesions (Snow et al., 1990). Until now, botulinum toxin has been mainly used for the treatment of cerepral palsy and congenital muscular torticollis in pediatric patients. In this study, BXT-A injection therapy was used to improve gait disturbance in HHH syndrome, and it was safe and effective without any major complications. Although further research is needed to clarify the effectiveness of botulinum toxin, BXT-A is a promising treatment method for spasticity and gait disturbance in metabolic diseases, especially HHH syndrome.

Ⅳ. Conclusion

In this study, BXT-A injection therapy was used to improve gait disturbance in HHH syndrome, and it was safe and effective without any major complications. Intensive physical therapy and botulinum toxin injection could be helpful to improve impairment related to neurological dysfunction and quality of life. Although further research is needed to clarify the effectiveness of botulinum toxin, BXT-A is a promising treatment method for spasticity and gait disturbance in metabolic diseases, especially HHH syndrome.

REFERENCES

Al-Hassnan ZN, Rashed MS, Al-Dirbashi OY, et al(2008). Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome with stroke-like imaging presentation: Clinical, biochemical and molecular analysis. J Neurol Sci 264(1-2), 187-194.

Camacho J, Rioseco-Camacho N(1993). Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. Seattle, University of Washington.

Comella CL, Pullman SP(2004). Botulinum toxins in neurological disease. Muscle Nerve, 29(5), 628–644.

Debray FG, Lambert M, Lemieux B, et al(2008). Phenotypic variability among patients with hyperornithinaemia-perammonaemia-homocitrullinuria syndrome homozygous for the delF188 mutation in SLC25A15. J Med Genet, 45(11), 759-764.

Kim SZ, Song WJ, Nyhan WL, et al(2012). Long-term follow-up of four patients affected by HHH syndrome. Clin Chim Acta, 413(13-14), 1151-1155.

Lukban MB, Rosales RL, Dressler D(2009). Effectiveness of botulinum toxin A for upper and lower limb spasticity in children with cerebral palsy: a summary of evidence. J Neural Transm, 116(3), 319-331.

Martinelli D, Diodato D, Ponzi E, et al(2015). The hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. Orphanet J Rare Dis, 10, 29.

Moeini-Naghani I, Hashemi-Zonouz T, Jabbari B(2016). Botulinum toxin treatment of spasticity in adults and children. Seminars in Neurology, 36(1), 64-72.

Snow BJ, Tsui JK, Bhatt MH, et al(1990). Treatment of spasticity with botulinum toxin: a double-blind study. Ann Neurol, 28(4), 512-515.

Viegas CM, Busanello EN, Tonin AM, et al(2011). Dual mechanism of brain damage induced in vivo by the major metabolites accumulating in hyperornithinemia-yperammonemia-homocitrullinuria syndrome. Brain Res, 1369, 235-244.