SIBLINGS WITH HEREDITARY SPASTIC PARAPLEGIA: EFFECTIVENESS OF BOTULINUM TOXIN INJECTIONS AND REHABILITATION PROGRAM

Afitap İçağasıoğlu,[1] Meltem Esenyel,[1] Raife Şirin Atlığ,[2] Selin Turan Turgut[3]

[1] Istanbul Medeniyet University Göztepe Training and Research Hospital Physical Med. and Rehabilitation Dept., Istanbul
[2] Istanbul Avicenna Kartal Umut Hospital Physical Medicine and Rehabilitation Department, Istanbul
[3] Karaman Public Hospital Physical Medicine and Rehabilitation Department, Karaman

ABSTRACT

There is a little evidence in the literature regarding the effectiveness of Botulinum Toxin type A injections as an adjuvant therapy to customised rehabilitation programs in pediatric patients with hereditary spastic paraplegia. This is a report on two siblings aged 4 and 6, who underwent 3 sessions of botulinum toxin A injections to the hip adductors and ankle plantar flexor muscles. Additionaly, patients were given a home exercise program consisted of stretching the agonist muscles and strengthening of the antagonist muscles. Dynamic ankle foot orthoses were also prescribed and used regularly. Both patients showed remarkable improvements in muscle tone and gross motor function measurements. The effects of Botulinum toxin A injections lasted for a mean of 5- 6 months in both children.

Key Words: *Spasticity, botulinum toxin A, rehabilitation.* ***Nobel Med 2014; 10(2): 96-99***

HEREDİTER SPASTİK PARAPLEJİLİ KARDEŞLER: BOTULİNUM TOKSİN ENJEKSİYONU VE REHABİLİTASYON PROGRAMININ ETKİNLİĞİ

ÖZET

Literatürde, herediter spastik paraplejili pediatrik hastaların rehabilitasyon programlarına destekleyici tedavi olarak uygulanan botulinum toksin A enjeksiyonlarının etkililiği ile ilgili çok az kanıt bulunmaktadır. Bu olgu sunumunda; 4 ve 6 yaşlarında iki çocuğun kalça adduktör ve ayak bileği plantar fleksör kaslarına yapılan 3 seans botulinum toksin A enjeksiyonu anlatıldı. Ek olarak hastalara agonist kasları germe ve antagonist kasları güçlendirmeye yönelik ev egzersiz programı da verildi.Aynı zamanda dinamik ayak bileği ortezleri de düzenli kullandırıldı. Her iki hastada da kas tonusunda ve kaba motor fonksiyon ölçümlerinde dikkat çekici iyileşme saptandı. Her iki çocukta da botulinum toksin A enjeksiyonunun etkileri ortalama 5-6 ay boyunca devam etti.

Anahtar Kelimeler: Spastisite, botulinum toksin A, rehabilitasyon. **Nobel Med 2014; 10(2): 96-99**

INTRODUCTION

Hereditary spastic paraplegia (HSP) is a genetically heterogeneous group of neurodegenerative disorders characterized by progressive lower extremity weakness, spasticity and pyramidal signs, with little or no involvement of the upper limbs.[1,2] HSP pathology involves axonal degeneration that is most pronounced in the terminal segments of the longest descending (pyramidal) and ascending (dorsal columns) tracts.[3] The most common inheritance pattern of HSP is autosomal dominant; but autosomal recessive and X-linked patterns are also seen. The disease has a wide genetic variation with more than 30 genes have been localised to date.[4] However, spastin gene (SPG4), is the single most common gene involved.[5] Although SPG3A typically begins in early childhood, some SPG3A HSP patients have symptom onset in late childhood, adolescence, or adulthood.[6] HSP is classified as "pure" when no additional features exists besides pyramidal signs. It is termed "complex" HSP, when accompanied by other neurological signs such as ataxia, mental retardation, extrapyramidal signs, epilepsy, polyneuropathy, optic atrophy, deaffenss and ichthyosis.[2,7] Different central nervous system structures such as cerebral cortex, cerebellum, basal ganglia and corpus callosum might be involved in complicated cases.

Gait disturbances and stiffness of the legs are the presenting signs in the patients. As an interesting feature of HSP, spasticity is much more pronounced than the paresis. Ankle plantar flexors and hip adductors are affected more prominently when compared with the ankle invertors and hip flexors.[1,2] Unfortunately, no spesific treatment exists, treatment is only symptomatic. It is a progressive disorder as a nature, therefore rehabilitation is a very important part of the treatment to preserve the function. However, patients may require mobility aids such as a cane, a walker, or a wheelchair with advancement of the disease. Medical treatment of spasticity may begin with oral baclofen or tizanidine but efficacy is weak.[8] Intratechal baclofen should be reserved for patients with severe diffuse and disabling spasticity.[1]

Botulinum toxin type A is effective in the treatment of chronic focal spasticity, by inducing paralysis in the injected muscles. It is a potent neurotoxin that inhibits exocytosis of synaptic vesicles containig acetylcholine to the neuromuscular junction. The resultant paralysis provides relaxation lasting for a few months and enables the muscle to stretch and lengthen, provides a better range of motion of the joints, therefore it helps to prevent limb deformity. However, in order to maintain these good results for a longer time and to improve the function, customised exercise programs should be administered together with the application of appropriate orthosis when necessary.

Table 1. Spasticity as determined by Modified Ashworth scale and functional level as determined by GMFC(88) in Case 1.

	Before Botulinum Toxin A injection	1 month after Botulinum Toxin A injection
Modified Ashworth Scale	August 2010: Gastrosoleus: (R): 2 (L):2 Adductors: (R): 1 (L):1 February 2011 Gastrosoleus: (R): 2 (L):2 Adductors: (R): 1 (L):1 June 2011 Gastrosoleus: (R): 2 (L):2 Adductors: (R): 1 (L):1 November 2011 Gastrosoleus: (R): 2 (L):1 Adductors: (R): 1 (L):1 (injection was not needed)	Gastrosoleus: (R): 1 (L):1 Adductors : (R) :0 (L):0 Gastrosoleus: (R): 1 (L):1 Adductors : (R) :0 (L):0 Gastrosoleus: (R): 1 (L):1 Adductors : (R) :0 (L):0
GMFC (88)	August 2010 : 223 February 2011 : 223 June 2011 : 240 November 2011 : 249	240 241 245

There is a very limited information regarding the efficacy of botulinum toxin type A injection in HSP.[1,9,10] We report our experience with botulinum toxin type A in two siblings as an adjuvant therapy to the rehabilitation program.

CASE

4 year-old brother and 6 year old sister applied to the Physical Medicine and Rehabilitation Outpatient Department in August 2010 with the complaints of tip toe walking. The perinatal background was unremarkable. They had genetic analysis which revealed heterozygot mutation in SPG3A location. A positive family history was established with 14 family members, and two generations were affected. Both children had "pure" HSP. The cognitive levels were normal. There were no need for brain imaging.

Locomotor system and neurological examinations were performed. Muscle tone was assessed by the modified Ashworth scale, motor function by the Gross motor function classification (GMFC-88). These evaluations were made at baseline and 1 month after the each botulinum toxin injections.

Parents of the patients were informed about the procedure and consents were taken. The injection preparation consisted of botulinum toxin type A (Botox, Allergan, Irvine, California) in a final concentration of 5 U/0.1 mL of saline (0.9% sodium chloride solution) with the dose not exceeding 6 U/kg weight per muscle →

Table 2. Spasticity as determined by Modified Ashworth scale and functional level as determined by GMFC (88) in Case 2.

	Before Botulinum Toxin A injection	1 month after Botulinum Toxin A injection
Modified Ashworth Scale	August 2010: Gastrosoleus: (R): 2 (L):2 Adductors: (R): 1 (L):1 February 2011 Gastrosoleus: (R): 2 (L):2 Adductors: (R): 1 (L):1 June 2011 Gastrosoleus: (R): 2 (L):2 Adductors: (R): 1 (L):1 November 2011 Gastrosoleus: (R): 1 (L):1 Adductors: (R): 1 (L):1 (injection was not needed)	Gastrosoleus: (R): 1 (L):1 Adductors : (R) :0 (L):0 Gastrosoleus: (R): 1 (L):1 Adductors : (R) :0 (L):0 Gastrosoleus: (R): 1 (L):1 Adductors : (R) :0 (L):0
GMFC (88)	August 2010 : 245 February 2011 : 255 June 2011 : 258 November 2011 : 263	255 258 260

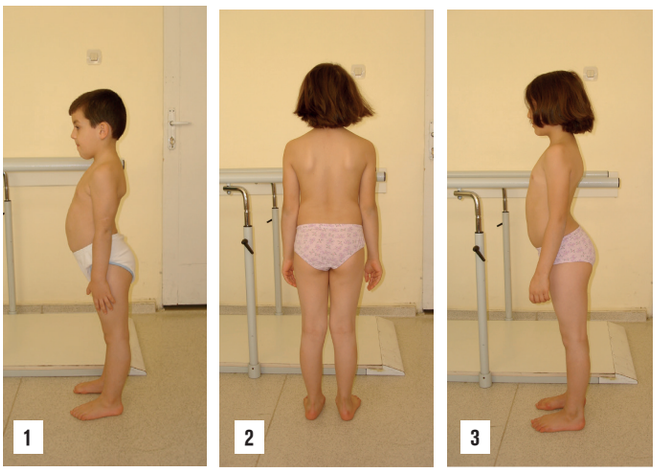

Figure 1: Pes planovalgus in case 1 **Figure 2:** Pes planovalgus in case 2.
Figure 3: Lomber lordosis and genu recurvatum in case 2.

or a maximal total dose of 12 U/kg body weight. The dose was determined by the weight of the children, number of muscles injected and degree of spasticity. 8 U/kg Botulinum toxin A injected to the adductors and gastrocnemius muscles. The muscles were identified by palpation using known anatomical landmarks. Lidocaine 25 mg, prilocaine 25 mg/g cream was applied to achieve local anesthesia 1 hour prior to the injections. After completion of the injections, children were kept under observation for half an hour. No complications were observed during and after the injection.

A home exercise program consisted of stretching the agonist muscles and strengthening of antagonist muscles was given. The parents and caregivers were trained on the exercise program. Dynamic Ankle foot orthosis were prescribed and used regularly.

Case 1: 4 year old boy applied to our clinic with the complaints of tiptoe walking, difficulty assending stairs, running, and playing with the ball which started a year ago. He was not able to keep up with his friends of the same age. He was diagnosed as having HSP and told that there was no spesific treatment and advised to be brought to a Rehabilitation Department. Physical examination of the lower extremity revealed pes planovalgus with equinus deformity due to spasticity (Figure 1).

He had mildly spastic gait. Marked hyperreflexia was detected in the lower extremities. Babinsky sign was present. Cutaneous reflexes and joint position perception were well preserved. Values for spasticity and functional status before and 1 month after the Botulinum Toxin A injections are presented in Table 1.

Case 2: 6 year-old girl presented with complaints of difficulty in walking and tiptoe walking. She walked at the age of two and complaints started soon afterwards. She always had difficulty keeping up with her friends of the same age. Physical examination of the lower extremity revealed pes planovalgus with equinus deformity due to spasticity (Figure 2,3).

She had mildly spastic gait with hyperreflexia that was detected in the lower extremities. Babinsky sign was present. Cutaneous reflexes and joint position perception were well preserved. Values for spasticity and functional status before and 1 month after the Botulinum Toxin A injections are presented in Table 2.

DISCUSSION

Although, hereditary spastic paraplegia is a rare disease, it should be remembered in children presenting with spasticity and related symptoms. Spasticity and paraparesia result in equinovarus in distal and adduction in proximal part of the lower limbs. Increased lumbar lordosis also contribute. Difficulties maintaining upright positioning and walking occur as a consequence. In order to achieve a better alignment with improved muscle strength and function, we decieded to give botulinum toxin A injections. Botulinum toxin A injections are considered safe for the pediatric population and it is effective for treating chronic focal spasticity.[11] In a recent study on pediatric patients with HSP, significant reduction in the Ashworth scale and improvement in Gross Motor Function Measure Score were reported when each injection was evaluated seperately (pre-and postinjection).[1] The first injection had the greatest impact on the Gross Motor Function Measure Score. Authors had two explanations for this observation. First explanation is the progressive nature of the HSP →

with deteriorating of the symptoms and spasticity with time, and eventually insufficiency of botulinum toxin to overcome the spasticity. Another explanation they made is the possible formation of antibodies interfering with botulinum toxin action that are formed when receiving consecutive injections.[12]

In our cases, changes in Modified Ashworth Scale and Gross Motor Function Measure Score were quite remarkable. Both children improved functionally, although the disease is progressive. Parents of the children reported functional gain by decreasing the degree of effort needed for actions. Although the effect of botulinum toxin A on muscle relaxation is temporary, it provides better conditions to strengthen the muscle and to obtain a better alignment, therefore it provides a very good base for rehabilitation.

In the literature, two other studies were evaluated the effect of botulinum toxin injections in patients with HSP, but their study population included adults.[9,10] They reported similar improvements as we have observed in our cases.

In conclusion, botulinum toxin A therapy has high cost and transient effect, but its benefits outweight these disadvantages. It is effective, easy to use and safe for reducing focal spasticity in pediatric HSP patients.

* The authors declare that there are no conflicts of interest.

C **CORRESPONDING AUTHOR:** Afitap İçağasıoğlu İstanbul Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi, Fizik Tedavi ve Rehabilitasyon AD, İstanbul afitapi@gmail.com

✓ **DELIVERING DATE:** 18 / 07 / 2013 • **ACCEPTED DATE:** 11 / 03 / 2014

REFERENCES

1. Geva-Dayan K, Domenievitz D, Zahalka R, fattal-Valevski A. Botulinum Toxin Injections for Pediatric Patients with Hereditary Spastic Paraparesis. J Child Neurol 2010; 25: 969-975.
2. Depienne C, Stevanin G, Brice A, Durr A. Hereditary spastic paraplegias :an update. Curr Opin Neurol 2007; 20: 674-680.
3. Hedera P, Eldevik OP, Maly P, Rainier S, Fink JK. Spinal cord magnetic imaging in autosomal dominant hereditary spastic paraplegia. Neroradiology 2005; 47: 730-734.
4. Stevanin G, Ruberg M, Brice A. Recent advances in the genetics of spastic paraplegias. Curr Nuerol Neurosci Rep 2008; 8: 198-210.
5. McDermottCJ, Burness CE, Kirby J, et al. Clinical features of hereditary spastic paraplegia due to spastin mutation. Neurology 2006; 67: 45-51.
6. Sauter SM, Engel W, Neumann LM, et al. Novel mutations in the Atlastin gene (SPG3A) in families with autosomal dominant hereditary spastic paraplegia and evidence for late onset forms of HSP linked to the SPG3A locus. Hum Mutat 2004; 23: 98.
7. Appleton RE, Farrell K, Dunn HG. Pure and Complicated forms of hereditary spastic paraplegia presenting in childhood. Dev Med Child Neurol 1991; 33: 304-312.
8. Lambrecq V, Muller F, Joseph PA, et al. Intrathecal baclofen in hereditary spastic paraparesis: benefits and limitations. Ann Readapt Med Phys 2007; 50: 577-581.
9. Rousseaux M, Launay MJ, Kozlowski O, Daveluy W. Botulinum toxin injection in patients with hereditary spastic paraparesis. Eur J Neurol 2007; 14: 206-212.
10. Hecht MJ, Stolze H, Auf dem Brinke, et al. Botulinum neurotoxin type A injections reduce spasticity in mild to moderate hereditary spastic paraplegia: report of 19 cases. Mov Disord 2008; 23: 228-233.
11. Goldstein EM. Safety of high-dose botulinum toxin type A therapy for the treatment of pediatric spasticity. J Child Neurol 2006; 21: 189-192.
12. Herrman J, Geth K, Mall V, et al. Clinical impact of antibody formation to botulinum toxin A in children. Ann Neurol 2004; 55: 732-735.

• *Yazarlardan Sn. Doç. Dr. Meltem Esenyel vefat etmiştir. Kendisine Allah'tan rahmet dileriz. Nobel Medicus ailesi*