

# Efeito da Toxina Botulínica Tipo A na Espasticidade e Qualidade de Vida: um Caso Clínico de Síndrome de Leigh

## *Effect of Botulinum Toxin Type A on Spasticity and Quality of Life: a Leigh Syndrome Case Report*

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### Resumo

O objetivo deste caso clínico é destacar o papel da toxina botulínica tipo A no tratamento da espasticidade e os seus benefícios na melhoria da qualidade de vida, tendo em conta a evolução clínica de um doente com síndrome de Leigh.

A síndrome de Leigh é uma encefalomiopatia subaguda necrotizante, doença neurológica progressiva com início geralmente antes dos 12 meses de idade e que não tem nenhum tratamento específico. A espasticidade é um dos possíveis sintomas que pode precipitar várias complicações.

Este caso clínico mostra os efeitos da toxina botulínica tipo A no controlo da espasticidade focal severa durante o crescimento de um doente na tentativa de combater a dor e minimizar as deformidades ortopédicas. Apesar de não existir nenhuma medida objetiva disponível, a evolução clínica e as informações dadas pelo doente e pela sua família confirmam uma melhoria na qualidade de vida.

**Palavras-chave:** Toxina Botulínica Tipo A; Doença de Leigh; Espasticidade Muscular; Qualidade de Vida.

### Abstract

*The purpose of this case report is to highlight the role of botulinum toxin type A in the treatment of spasticity and its benefits improving quality of life, taking into account the clinical evolution of a patient with Leigh syndrome.*

*Leigh syndrome is a subacute necrotizing encephalomyelopathy, a progressive neurodegenerative disorder with onset usually before 12 months of age and with no specific treatment. Spasticity is one of the possible symptoms that can precipitate several complications.*

*This case report shows the effects of botulinum toxin type A in controlling severe focal spasticity during patient's growth in an attempt to manage pain and minimize orthopedic deformities. Although there was no objective measure available, the clinical evolution and the information given by the patient and his family confirm an improvement in quality of life.*

**Keywords:** Botulinum Toxins Type A; Leigh Disease; Muscle Spasticity; Quality of Life.

### Introduction

The purpose of this case report is to highlight the role of botulinum toxin type A in the treatment of spasticity and its benefits improving quality of life, taking into

account the clinical evolution of a patient with Leigh syndrome. This rare clinical case is, as many others, an example of success in the Physical and Rehabilitation Medicine where the patient survives to the worst prognosis.

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## Case Report

23-year-old male, born full-term (39 weeks; June 1990) by forceps delivery and out of a non-consanguineous marriage. At birth his weight and length was 4 kg and 54 cm, respectively; his head perimeter was 36 cm. Previously asymptomatic and apparently healthy until the age of four when he presented to a Neurology consultation due to a three-month evolution of progressive spastic tetraparesis, dysarthria, gait disturbance and dystonic posture. The dystonia started on his left lower extremity progressing to both upper limbs, making it impossible to stand up or sit. Regarding previous history, he was a healthy child and growth was normal. There were no past significant medical illnesses, such as birth trauma, drugs related sickness, carbon monoxide poisoning, skeletal deformities or delayed development. There were no specific family histories that resembled the patient's symptoms.

During hospitalization on Pediatric Neurology Unit, a magnetic resonance imaging scan of the head performed demonstrated symmetrical areas of hipodensity in basal ganglia, predominantly the caudate nucleus and the putamen. These findings were highly suggestive of Leigh syndrome. Serum pyruvate, serum lactic acid and serum ceruloplasmin were in the normal range. There was no oculomotricity impairment. He was discharged with the diagnosis of neurometabolic disease – suspected Leigh syndrome – and his life expectancy was considered of about one year.

In the following weeks, he was brought to the Physical and Rehabilitation Medicine consultation. He had a scoliotic attitude, a severe spastic tetraparesis (grade 4 of the Modified Ashworth Scale), a marked dysarthria and nasal voice, dysphagia, and a dystonic posture characterized by flexion of the left limbs and extension of the right ones. He could not walk or sit by itself, but he was able to turn. His fine and gross motor ability all lagged behind. There were no cranial nerve dysfunctions and cerebellar function seemed to be normal. Reflexes in the upper limbs were diminished. Deep tendon reflexes were hyperactive in both lower limbs and ankle clonus was present. Sphincters control was preserved. A wheelchair was prescribed and the patient began a rehabilitation program (physical therapy and occupational therapy), being regularly reassessed.

In December 1995, a muscle biopsy was performed in the right deltoid muscle and did not reveal mitochondrial respiratory

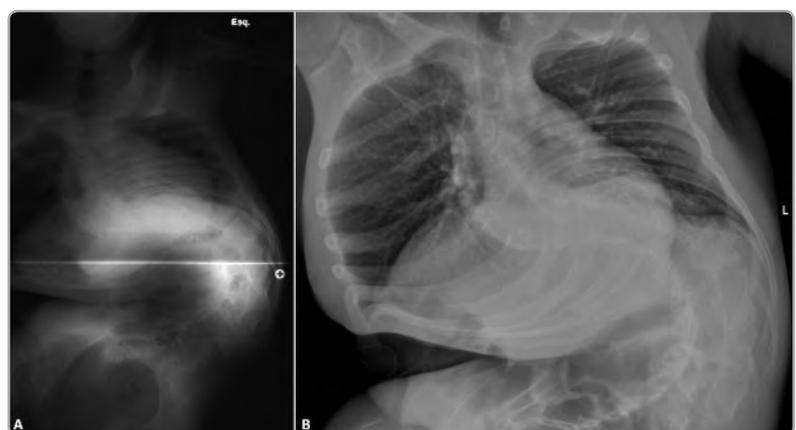
chain deficiency. Over time, there was a progressive worsening of the patient's clinical status, especially neurological, motor and respiratory. Despite being treated with baclofen (50 mg per day) and diazepam (40 mg per day) *per os*, spasticity was not controlled (Fig. 1).



**Figure 1** - Patient in the bed with scoliotic attitude and lower limb flexion because severe spasticity (1996).

In 2002, a spine radiograph revealed a severe dorso-lumbar kyphoscoliosis (Fig. 2) that compromised his pulmonary function and was the cause of some respiratory infections which motivated a few hospital admissions. The family refused the orthopaedic surgery. In September, the patient was submitted to a percutaneous endoscopic gastrostomy, but seven months later he was re-hospitalized due to rejection related to latex allergy. Since then, he was accompanied by a nutritionist.

The clinical course was of gradual deterioration. The patient was so spastic and dystonia was so severe that he could not be dressed, staying in bed all day only covered by sheets and/or blankets. Due to this situation, as an adjunct to the rehabilitation program already instituted, the patient began treatment with botulinum toxin type A (Botox®) in August 2004. The injected muscles were left gastrocnemius, left and right adductors, left and right hamstrings, and left biceps (total dose of 375 units). When he was reassessed two months later it was noticed that botulinum toxin type



**Figure 2** - Anterior-posterior extra-long spine radiography revealing a severe dorso-lumbar scoliosis (A - 2002; B - 2008).

A had produced a significant reduction in focal spasticity (not quantified on the Modified Ashworth Scale) and pain, and, indirectly, a significant improvement in dystonia. This positive evolution on global function allowed him to sit, dress, assume a more correct posture and receive a better basic care (Fig. 3). These improvements allowed him to leave home and return to school with caregivers help.



**Figure 3** - Patient sited in his wheelchair; note the fingers hyperextension (2010).

The patient continued being regularly reassessed and injected with botulinum toxin type A (14 sessions since 2005, total dose between 415 and 540 units of Botox® in each one). The combination of muscles injected in each session was variable according to the contribution of each one in the postural disturbance and the objectives set after observation and dialogue with his mother. The optimal dose of botulinum toxin type A injected into each affected muscle was based upon the extent to which it appeared to be involved. At one

moment, there was a possibility of placing a baclofen pump, but the decision was not taken due to anatomical limitations of the patient (Fig. 4). He is also regularly followed by physical and rehabilitation medicine, neurology, surgery, pneumology and orthopedics specialists.

## Discussion

Leigh syndrome (also called subacute necrotising encephalomyelopathy) is a progressive neurodegenerative disorder with a general onset in infancy or childhood, but can also occur in teenagers and adults.<sup>1-5</sup> It was first reported by Denis Leigh in 1951 in a 7 month old infant.<sup>1,2</sup> The estimated incidence of Leigh syndrome is 1:40.000 births, despite this may be underestimated since mitochondrial diseases tend to be under-diagnosed and misdiagnosed.<sup>3,4</sup>

Leigh syndrome is characterized by almost identical brain changes, but with considerable genetic, clinical and biochemistry heterogeneity.<sup>3,5</sup> This syndrome can be caused by mutations in nuclear DNA or mitochondrial DNA – Leigh syndrome is the most common clinical phenotype of mitochondrial disorders in childhood.<sup>2</sup> The mutations can arise sporadically or be inherited by autosomal recessive transmission, X linked transmission or by maternal transmission (maternal inheritance accounts for 20% of the cases).<sup>1,2,4</sup> There is more than one defect that causes Leigh syndrome, moreover it is the mitochondrial disorder with the largest genetic heterogeneity.<sup>5</sup>

Clinically, Leigh syndrome is characterized by a wide variety of abnormalities, from severe neurologic problems to a near absence of abnormalities, which may difficult the diagnosis.<sup>2</sup> Most often, the central nervous system is affected, resulting in developmental delay and regression, seizures, strabismus, nystagmus, optic atrophy, swallowing difficulties, ataxia, muscular hypotonia, spasticity, breathing abnormalities, lactate acidemia and acute deterioration after common infections.<sup>1-5</sup>



**Figure 4** - Posterior view of patient's spine deformation (2010).

The diagnostic criteria are progressive neurological disease with motor and intellectual developmental delay; signs and symptoms of brainstem and/or basal ganglia disease; raised lactate levels in blood and/or cerebrospinal fluid; and characteristic symmetric necrotic lesions in the basal ganglia and/or brainstem.<sup>3</sup> Neuroimaging plays an important role in diagnosis as well as follow up of patients with Leigh syndrome.<sup>1,3</sup> The most characteristic neuroradiological findings in Leigh syndrome are bilateral, symmetric and focal necrotic lesions associated with demyelination, vascular proliferation and gliosis in the basal ganglia, thalamus, substantia nigra, and brainstem.<sup>1-3</sup> Often, the basal ganglia are affected before the brainstem and the involvement of the upper brainstem followed by lower brainstem indicates advanced stage of the disease which can cause respiratory failure and sudden death.<sup>3</sup> In most patients, the cerebral white matter is generally only involved in late stages of the disease.<sup>3</sup>

There is currently no cure for Leigh syndrome.<sup>1,2,4</sup> Treatments generally involve palliative measures, control of endocrine dysfunction, dietary control and surgical procedures if necessary, and are only partially effective.<sup>1,2,4</sup> Efforts for prevention and prenatal diagnosis are still in the early stage.<sup>1</sup> The prognosis for Leigh syndrome is poor.<sup>4</sup> Life expectancy is usually about a year within the onset of symptoms although both acute fulminating illness of a few days and prolonged survival have been reported.<sup>2,4</sup> With accurate diagnosis and prompt institution of adequate supportive therapy, symptomatic amelioration can be achieved, thereby adding life to the limited years of survival of these patients.<sup>1</sup> Multidisciplinary follow-up in pediatrics, neurology, cardiology, physical and rehabilitation medicine, ophthalmology consultations to evaluate the changes severity and their development is of paramount importance in order to be sure whether the disease is under control.<sup>2</sup>

Spasticity is one of the possible symptoms of Leigh syndrome. Spasticity is a motor disorder characterized by an involuntary, velocity-dependent increase in tonic stretch reflexes and exaggerated tendon jerks resulting from hyperexcitability of the stretch reflex.<sup>6,7</sup> The patients present resistance to movement and an increased muscle tone. There are multiple methods to quantify spasticity; the modified Ashworth scale is an example.

Spasticity causes pain, insomnia and can precipitate several complications; when persistent, it leads to deformities, contractures, bony torsion, joint instability, pressure sores and retarded limb growth.<sup>8,9</sup> Although the exact incidence of spasticity is unknown, it is likely that it affects more than 12 million people worldwide.<sup>10</sup> This condition may be secondary to a disorder or trauma and, although spasticity can be severely debilitating, there are many therapeutic and medical

interventions that can attenuate its effects.<sup>7</sup> The available treatments include: preventive measures (positioning), physical therapy (cryotherapy, electrical stimulation), pharmacological agents (oral, intrathecal or local – injection of botulinum toxin or phenol) and surgical treatments such as neurotomy, cordotomy and rhizotomy.<sup>9-11</sup>

Spasticity is a major challenge for the rehabilitation team and can interfere with return of function, nursing care and physiotherapy/occupational therapy.<sup>8</sup> The main goals of spasticity management are to improve function related to the activities of daily living, mobility, the ease of care by caregivers, sleep, and overall functional independence; to prevent orthopedic deformity, the development of pressure areas, and the need for corrective surgery; to reduce pain; to allow the stretching of shortened muscles, the strengthening of antagonistic muscles, and the appropriate orthotic fit.<sup>7</sup>

Botulinum toxin is a potent neurotoxin produced by the bacterium *Clostridium botulinum* and works by binding to the presynaptic acetylcholine vesicles at the neuromuscular junction of skeletal muscles, preventing the release of the excitatory neurotransmitter.<sup>10</sup> Two types of botulinum toxin are available: type A and type B.<sup>10</sup> Chemodenervation by local injections of botulinum toxin type A is a relatively new pharmacotherapeutic option approved in 1989 in the USA.<sup>9</sup> Botulinum toxin type A is an effective treatment for children with spasticity as it causes a temporary weakening of spastic muscles and decreases the signals coming from the muscle stretch receptors, thereby directly reducing the signals that result in spasticity. There are several contraindications to the use of botulinum toxin type A in children and it has relatively few frequent side effects.<sup>12</sup>

An age limit for the use of botulinum toxin type A has not been established; its use is approved for children over 2-years-old, but the product has been used safely in infants as young as one month.<sup>12</sup> Botulinum toxin type A is most effective for focal spasticity, when only a small number of muscles are involved. More commonly injected muscles include the gastrocnemius and the hamstrings in the lower extremities.<sup>12</sup> Botulinum toxin type A is injected directly into the muscle; in large muscles, the injection is often done “blindly”.<sup>12</sup> The number of injections depends on the muscle size and, for Botox®, the maximum dose may vary from 3 to 6 units/kg for large muscles and 1 to 2 units/kg for small muscles in children.<sup>12</sup> The maximum total dose (for all muscles; Botox®) given at one time should not exceed 16 units/kg or 400 units, however some physicians use as much as 30 units/kg or up to 800 units.<sup>12</sup>

Clinical effects can be seen early as to 15 days after injection and these effects typically last for 3 to 6 months depending on the degree of spasticity, injected

doses and on compliance with the subsequent therapy program.<sup>10,12</sup> A child may appear to worsen transiently following botulinum toxin type A injections because as spasticity decreases, muscle weakness previously masked by spasticity may prevail.<sup>12</sup> The temporary decrease in muscle tone permits physical and occupational therapy interventions, such as muscle strengthening and facilitation, increasing range of motion, retraining of ambulation and gait, improving function in activities of daily living and the fit and tolerance of orthoses.<sup>9</sup> It is critical that following injection of the selected muscles, the patient continues physical and occupational therapies to achieve the goals of treatment.<sup>12</sup> Botulinum toxin type A can be re-administered when effects wane, but to minimize the potential for the development of neutralizing antibodies, should be used the smallest possible effective dose and inject it no sooner than every 3 months.<sup>12</sup>

Botulinum toxin type A has been tested as a treatment for spasticity and has proven to be an effective measure for reduction of focal spasticity, whatever the cause.<sup>13,14</sup> Improvements have been documented in tone reduction, range of motion, hygiene, gait pattern, positioning, and other criteria.<sup>13</sup> This patient experienced most of this changes after beginning botulinum toxin type A treatments.

Severe, uncontrolled spasticity can have a profound effect on the patient's ability to function and thus, their quality of life.<sup>15</sup> That is the reason why the spasticity treatment with botulinum toxin type A improves quality of life. Moreover, the treatment of patients with facial paralysis, spasmodic dysphonia, oromandibular dystonia, essential blepharospasm or focal hyperhidrosis with botulinum toxin type A has proved to be effective on the basis of quality of life criteria.<sup>16-21</sup> Although there is no objective measure, the clinical evolution and the information given by the patient and his family confirm the improvement in his quality of life.

## Conclusion

This is a successful case in which the integration into a comprehensive rehabilitation program, including spasticity management with botulinum toxin type A, physiotherapy and occupational therapy, had an important role in improving the quality of life of a patient with Leigh syndrome, which prognosis was initially very poor. Although treatment with botulinum toxin did not cure the disease, at least, reducing the spasticity, it allowed him a much better quality of life and probably increased his lifetime expectancy too.

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