Case Report

Synergistic Effects of Incobotulinum Toxin and Physiotherapy in a Rare Case of Paraparesis in a 7-Years-Old Affected by Klippel-Feil Syndrome Related to MYH3 Gene Mutation: A Case Report

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Synergistic Effects of Incobotulinum Toxin and Physiotherapy in a Rare Case of Paraparesis in a 7-Years-Old Affected by Klippel-Feil Syndrome Related to MYH3 Gene Mutation: A Case Report

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Abstract: Klippel-Feil disease is a condition characterized by a defect in the spine, consisting in the fusion or non-separation of two or more vertebrae of the cervical tract. It usually affects 1 every 50.000 newborns, and the pathogenesis remains unknown to date, although the role of certain genes deputed in segmentation processes is being studied. A single case of gene Myosin Heavy Chain 3 (MYH3) mutation is described by researchers. Affected patients are often characterized by a relatively short neck and, therefore, poor mobility, a low hairline and obesity and may have other health problems of different nature. The frequent presence of comorbidities worsens the quality of life of these young patients. The following case describes the synergistic effect of Incobotulinum toxin type A and physiotherapy in a small patient with MYH3 mutation-related Klippel-Feil Syndrome (KFS) complicated by bilateral paraplegia, to improve the spasticity condition of the lower limbs. To assess improvements over time, the patient underwent rating scales to determine spasticity (Modified Ashworth Scale: MAS), the neck's range of motion (ROM), and muscle tone by using MyotonPro®. Specifically, measurements were taken on the day of the first medical examination (T0), the month after the injection and the startup of therapeutic exercise (T1), at three months (T2), and then once a month for a total of 6 months (T3, T4 and T5). This therapeutic approach led to entirely satisfactory results with the child's well-being, prolonged until the sixth month and with a total absence of any side effects.

Keywords: Klippel-Feil Syndrome; Myosin Heavy Chain 3 mutation; MYH3 mutation; spine defects; spasticity; botulinum toxin type A; incobotulinum; therapeutic exercise; physiotherapy

1. Introduction

Klippel-Feil disease is a condition characterized by a defect in the spine, consisting in the fusion or non-separation of two or more vertebrae of the cervical tract which generally occurs between the third and the eighth week of gestation [1]. Although the incidence is not clarified with certainty, one study defines it as about 0.2 cases per 1000 people [2]. The prevalence is about 1 every 50.000 new infants worldwide, mainly affecting the female sex (60%) [3]. Most cases are sporadic, with diagnosis found on radiographs made for other reasons [4]. Typically, patients present a very short and minimally mobile neck, given precisely by vertebral fusion, a visibly low hairline, and obesity. To worsen the quality of life of these young patients, these physical clinical features indicative of the disease can possibly be associated with several malformations and/or other pathologies of various kinds. Among the most frequent reported in the literature there are scoliosis, in 60% of cases, and spina bifida occulta, in the 45%, but some cardiological, nephrological and unfortunately also neurological pathologies are, as well, not difficult to encounter [5].

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As can easily be guessed, the most problematic association is with neurological disorders that can, moreover, range from seizures to paraplegic conditions. Although it appears that neurological issues can be found in the 15-20% of KFS patients, the treatment and resolution of these symptoms is worthy of attention by doctors and researchers to enable children to conduct a life as similar as possible to that of healthy peers. From the numerous studies reported in the literature, it seems that the major cause of these problems is due to abnormalities of the occipitocervical tract and from the spinal cord compression both intrinsically, such as in canal stenosis, and extrinsically [6,7]. An example of the latter case is a patient with KFS who manifested bilateral paraplegia as result of cervico-dorsal neuroenteric cyst [8].

Although KFS has been thoroughly investigated in the literature, the pathogenesis remains unclear to date. From what emerges, it appears to be a congenital condition related to specific mutations in particular genes responsible for bone formation, development, and segmentation [9]. Among those analyzed in more detail, there are growth differentiation factor 6 (GDF6) and 3 (GDF3), mesenchyme homeobox 1 (MEOX1), and the one involved in our case report which is myosin heavy chain 3 (MYH3) gene, responsible for the formation of the sarcomeric unit and thus the contractile apparatus of skeletal and cardiac muscle [10]. While monoallelic variants of the gene in focus are a cause of distal arthrogryposis [11–13], heterozygous variants can be cause of contractures, pterygia, and the spondylocarpotarsal fusion syndrome, a condition characterized by contractures and fusion of the vertebrae of the spine, carpal and tarsal bones [14]. In any case, it appears that the pathogenetic mechanism caused by MYH3 gene variants consists in an inhibition of TGF-β signaling, which is critical in the osteoblastic and bone differentiation process [15].

Even though KFS turns out to be asymptomatic in most cases, it can prove to be a major problem for young patients with neurological complications. Thus, our specific study treats the case of a young girl with KFS associated with MYH3 gene abnormalities with an accompanying major spastic paraparesis. The aim, therefore, is to demonstrate how, even in such a complex syndrome, the synergistic treatment with Incobotulinum toxin and physiotherapy can be very helpful in the objective improvement of the patient's lifestyle.

2. Case Report

A little patient diagnosed with KFS due to MYH3 gene mutation and paraparesis since 2019, presented to the Bari "General Hospital". Firstborn, born at term from spontaneous birth, from a pregnancy carried out physiologically. Early stages of psychomotor development were referred in the norm. The parents reported that the onset of walking occurred at 14 months with anserine characteristics in the initial phase. In 2019, in response to the rigidity of the passive mobilization of the lower limbs, the girl was subjected to evaluation at the pediatric Metabolic Diseases and Genetics Unit at "Giovanni XXIII" Hospital, Bari where, after careful analysis, hyposomy, left convex dorso-lumbar syndromic scoliosis derived from the posterior fusion of the dorsal vertebrae 9, 10 and 11 (D9-D10-D11) arches, abnormalities of the epistrofeo and probable posterior fusion of the arches of D4-D5 and D2-D3 were observed. In this occasion, the little girl has been diagnosed with a rare case of KFS. At the genetic analysis, a genomic variant c.800-1G>A in conditions of heterozygosis of the gene MYH3 was found. The segregation analysis revealed the paternal origin of the variant. The patient underwent orthopedic evaluations for the management of scoliosis, for which surgical indication was excluded, and was followed by the neuropsychiatry and territorial rehabilitation service and by the endocrinology service for the treatment of hyposomia (currently treated with growth hormone, GH). Due to the finding of a knee flexion attitude, with functional limitation of walking and, consequently, recreational abilities, therapeutic exercise was started, without any benefit. Since pediatric treatment with anti-spastic drugs is not recommended and there was no indication to undertake intrathecal baclofen therapy, the patient was referred to our clinic for a careful evaluation. Considering injection treatment with botulinum toxin type A and specifically, Incobotulinum (Xeomin®, Merz Pharma), indicated, the patient was appropriately treated and discharged with an indication for physiotherapy to begin immediately. The patient was evaluated before the combined therapy of BTX-A and therapeutic exercise (T0) and in subsequent follow-ups respectively 30 days (T1), 90 days (T2), 120

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days (T3), 150 days (T4) and 180 days after the beginning of the treatment, for a total of 6 months of observation.

The parameters we considered as benchmarks to study the progress of improvements over time were three, and specifically: range of motion (ROM), which is able to quantify the passive and active joint mobilization in degrees; the Modified Ashworth Scale (MAS), to study spasticity and muscular tone; Biceps Femoris (BF) dynamic stiffness by using MyotonPRO®, which we have already used in other studies and with very precise results [16–19].

At T0, a neurological visit showed normal mental status, speech, cranial nerve examination and no sign of meningeal irritation. The physical examination showed walking possible for medium-long distances with bilaterally slight flexion of the knees at 20° and hyporetropedal support (left>right). Resistance to passive mobilization was appreciated starting from the medium degrees in knee extension with a minus of 15° on the left and 10° on the right, as for hypertonicity of the BF muscle, bilaterally (MAS=3). Achilleus Clonus cannot be summoned. Absent hyperextension of the big toe and claws of the fingers. During the first evaluation, after collecting the written informed consent from the parents, we treated the girl BF with incobotulinum toxin type A (Xeomin®, Merz Pharma), diluted in 1 cc of physiological solution, with 7 Units (U) for left BF and 5U for right BF, via ultrasound-guided injection. Three days after the botulinum toxin injection, the patient undertook a specific physiotherapy program with the aim of promoting the diffusion of the toxin and enhancing its effects, with a frequency of 2 times a week.

3. Results

One month after the infiltrative and physiokinesitherapy treatment (T1), the patient was re-evaluated. At walking, knee flexion, peristence of retropodal hyposupport on the left. In the supine position, the left knee was 15° and the right one 10° flexed, reducible to passive mobilization without bilaterally deficits. 3 months later (T2), further evaluation was carried out. At walking, knee flexion attitude, retropodal hyposupport on the left. In the supine position, the right knee was 5° flexed and completely reducible to passive mobilization, on the left the knee was flexed at 10° and was completely reducible to passive mobilization. Given the persistent benefit of the infiltration, further treatment with BTX-A was postponed and further check-up after 1 month (T3). Even at T3 and T4, clinical and myometric improvements persisted and, therefore, the second infiltration was not performed. However, at T5 clinical and myometric data had no longer improved and therefore we carried out a new infiltrative treatment (7U on the left and 5U on the right). Results are summarized in tables 1, 2 and 3 **(Table 1, 2, 3)**.

Table 1. ROM assessment of Right and Left Biceps Femoris during the study; data demonstrated improvement until 6 months after injection. () indicates minus.

	T0	**T1**	**T2**	**T3**	**T4**	**T5**
Right Biceps Femoris	20° (10°)	5° (0°)	5° (0°)	5° (0°)	7° (0°)	10 (5°)
Left Biceps Femoris	20° (15°)	10° (0°)	10° (0°)	10° (0°)	10° (0°)	15° (7°)

Table 2. this table shows MAS assessment of Right and Left Biceps Femoris during the study; data demonstrated improvement until 6 months after injection. () indicates minus.

	T0	**T1**	**T2**	**T3**	**T4**	**T5**

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Right Biceps Femoris	3	1+	1+	1+	1+	3
Left Biceps Femoris	3	1+	1+	1+	2	3

Table 3. this table shows miometric tone assessment of Right and Left Biceps Femoris during the study; data demonstrated improvement until 6 months after injection. () indicates minus.

	T0	**T1**	**T2**	**T3**	**T4**	**T5**
Right Biceps Femoris	18,9	16,4	17,0	17,1	16,8	17,9
Left Biceps Femoris	20,4	17,0	17,3	17,5	18,6	19,6

Patient is currently being followed by our clinic and no side effects have been reported.

4. Discussion

Botulinum toxin (BoNT) is a potent neurotoxin produced by gram-positive spore-forming bacteria: *Clostridium botulinum* [20]. Its use is well established for conditions as varied as dystonia, spasticity and sialorrhea, but its application is also spreading in the aesthetic field [21]. Seven types of BoNTs are reported in the literature, differing from each other in serological typing [22]. Among these, several subtypes have been identified, that differ in certain amino acid sequences and, as a result, have distinct toxo-pharmacological properties, denoted by an alpha numeric code [23]. Among the products normally used in the medical field there are *onaBoNT*, *aboBoNT* and *incoBoNT*, which are serotype A, and *rimaBoN* which consists in serotype B [24]. Generally, the toxin comes in vacuum dried or lyophilized form, which is why dilution with saline is always necessary for its use. After that, the resulting solution can be injected into muscle or specific sites, such as the salivary glands, a technique widely used in Parkinsonian patients suffering from sialorrhea. The mechanism of action of BoNT consists in the inhibition of the release of Acetylcholine (Ach) from the motor terminals, and thus, the inhibition of skeletal muscles contraction even when the action potential exceeds a certain threshold [23]. The effects tend to be seen in the first few weeks with maximum effect at thirty days from the injection. Any ineffectiveness of the product, although in very rare cases, may be due to the formation of antibodies to the toxin itself. In addition, it seems that human serum albumin (HSA), which is normally used to stably the toxin, might induce the destruction of the toxin itself [26]. According to the US Food and Drugs Administration (FDA), among the named toxin, *incoBoNT* is the one with the lowest concentration of HSA [25].

In treating spasticity, the first approach is to administer oral antispasmodic drugs, but resistance is unfortunately not so uncommon. Moreover, in addition to the classic problem of resistance, for young patients with KFS, taking pills is difficult to manage. Our case turns out to be unique.

As previously pointed out, the association of KFS with neurological symptoms is not so common: only 15-20% of affected patients may have concomitant mild disorders, such as paresthesia or synkinesis, but also more important and disabling pathologies such as frequent seizures, gait alteration with ataxic walking or even para, hemi or quadriplegia. Neurological sequelae can also depend on bone abnormalities. Specifically, all movements involving the neck should always be well controlled, if not completely avoided. In this specific case, it is also a good idea to perform physiotherapy treatments exclusively with experienced personnel, as traumatic injuries even of minor nature could prove to be very disabling. A study conducted in 1987 reports the occurrence of signs of spinal cord compression and quadriplegia after a low-intensity trauma [26]. It appears, moreover, that inherent in the disease is a predisposition to easier spinal cord injuries. Indeed,

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vertebral fusion seems to lead to a certain hypermobility of the immediately above and below segments. In addition to the direct possibility of spinal cord damage given precisely by this hypermobility itself, there is also the possibility of indirect damage, with the formation of osteophytes over time that can lead to major neurological sequelae even with minor trauma [27]. In addition, nerve root compression can lead to upper and lower neuron injury resulting in spasticity, hyperreflexia, and ataxia [28]. Treatment is usually symptomatic, and surgical intervention tends to occur only in very rare cases with disabling symptoms that do not regress with specific medical therapy.

Since our patient was not experiencing any problems at the level of the cord and had not suffered of any kind of trauma, we hypothesized that the associated paraparesis might somehow result from the very rare mutation found in the patient, of which we found no further cases in the literature. As already pointed out, the patient had no issues that could in any way hinder her in a lifestyle as similar as possible to that of a person of her own age, except paraparesis. Therefore, we considered botulinum toxin treatment hoping it could leave the patient free of this symptom for as long as possible and enhance the effect and duration by associating it with specific therapeutic exercise.

5. Conclusions

KFS is often an asymptomatic condition, but it can be associated with a lot of different anomalies. Those that are certainly most disabling turn out to be the neurological issues that, although infrequent, can impair the lifestyle and normal growth of affected patients. Treatment of this condition is symptomatic. Specifically, our case report deals with a very rare and peculiar case of KFS in a child with a mutated MYH3 gene and neurological manifestations such as paraparesis. In this case, it was shown how the combined treatment of therapeutic exercise and BTX-A injection into the BF muscles can bring benefit in the absence of side effects, resulting in a child with a lifestyle as similar as possible to that of her peers.

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