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ARTICLE

Clinical aspects of patients with sarcoglycanopathies under steroids therapy

Aspectos clínicos de pacientes com sarcoglicanopatias sob efeito de corticoterapia

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ABSTRACT

Patients with sarcoglycanopathies, which comprise four subtypes of autosomal recessive limb-girdle muscular dystrophies, usually present with progressive weakness leading to early loss of ambulation and premature death, and no effective treatment is currently available. **Objective:** To present clinical aspects and outcomes of six children with sarcoglycanopathies treated with steroids for at least one year. **Method:** Patient files were retrospectively analyzed for steroid use. **Results:** Stabilization of muscle strength was noted in one patient, a slight improvement in two, and a slight worsening in three. In addition, variable responses of forced vital capacity and cardiac function were observed. **Conclusions:** No overt clinical improvement was observed in patients with sarcoglycanopathies under steroid therapy. Prospective controlled studies including a larger number of patients are necessary to determine the effects of steroids for sarcoglycanopathies.

Keywords: steroids, limb-girdle muscular dystrophy, sarcoglycan proteins, myopathy.

RESUMO

Pacientes com sarcoglicanopatias, que compreendem quatro subtipos de distrofias musculares de cinturas autossômicas recessivas, geralmente apresentam fraqueza progressiva, levando à perda precoce da deambulação e morte prematura, e não há tratamento eficaz disponível até o momento. **Objetivo:** Descrever os aspectos clínicos e a evolução de seis crianças com sarcoglicanopatias tratados com corticosteróides por pelo menos um ano. **Método:** Prontuários dos pacientes foram analisados retrospectivamente. **Resultados:** Estabilização da força muscular foi observada em um paciente, uma ligeira melhora em dois, e um ligeiro agravamento em três. Além disso, foram observadas respostas variáveis de capacidade vital forçada e da função cardíaca. **Conclusões:** Não houve melhora clínica evidente em pacientes com sarcoglicanopatias sob terapia com corticosteróides. Estudos prospectivos controlados incluindo maior número de pacientes são necessários para determinar os efeitos dos corticosteróides para sarcoglicanopatias.

Palavras-chave: corticosteróides, distrofia muscular de cinturas, proteínas sarcoglicanas, miopatia.

Sarcoglycanopathies (SG) comprise four subtypes of autosomal recessive limb-girdle muscular dystrophies (LGMD), which are caused by mutations in sarcoglycan protein complex, and involve four distinct trans membrane proteins: α-sarcoglycan (LGMD2D), ß-sarcoglycan (LGMD2E), γ-sarcoglycan (LGMD2C) and δ-sarcoglycan (LGMD2F)[1]. The sarcoglycan complex is integrated in the muscle membrane as a part of the dystrophin-glycoprotein associated complex[2]. A wide range of mutations in any of these proteins destabilize the whole sarcoglycan complex, resulting in the different types of LGMDs[1]. In the Brazilian population, sarcoglycanopathies account for about one third of the classified forms of AR-LGMD[3]. LGMD2D is the most frequent sarcoglycanopathy, followed by LGMD2E and LGMD2C, while LGMD2F is the most rare[4]. The clinical phenotype of sarcoglycanopathies is very heterogeneous regarding age of onset and rate of progression, and severity can vary even among members of the same family[4]. In general, the different forms of the disease are characterized by progressive weakness and degeneration of skeletal muscle, leading to loss of ambulation, difficulties in breathing and often premature death, associated to an elevated serum creatine kinase (CK) level[4]. Cardiac involvement is frequently reported[5,6]. Besides a rehabilitation program, there is currently no effective treatment for these patients[6,7].

Steroid treatment with prednisone or deflazacort has been shown to slow disease progression in Duchenne muscular dystrophy (DMD)[8-11]. The treatment is also potentially

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effective to delay restrictive respiratory insufficiency, scoliosis and in a lesser extent cardiac involvement in patients with this disease[8,12-14]. The mechanisms of this improvement are not completely clear but steroids may have the potential benefits of inhibiting muscle proteolysis, stabilizing fiber membrane, reducing intracellular calcium concentration, and stimulating myoblast proliferation[15-17].

Albeit controversial, steroid therapy has also been sporadically used to treat other forms of muscular dystrophy. There have been reports of positive results in isolated cases of sarcoglycanopathy treated with steroids, especially in those with a rapid progression[18-20]. Mainly due to these reports, steroid therapy is often empirically tried in sarcoglycanopathy patients in an individual basis. In this work, we retrospectively analyze clinical aspects and outcomes of six such patients, which have been submitted to steroid therapy for at least one year.

METHOD

We retrospectively analyzed medical records of patients of the Neuromuscular Disorders Section of the Hospital das Clínicas of FMUSP with a clinical and histological diagnosis of SG, and selected those that received steroid therapy for at least one year (Table 1).

RESULTS

In our records we found six children with SG, all female, that had been treated with steroids for at least one year. The age at onset of the disease ranged from 4 to 10 years. Chief complaints in the first clinical consultation were frequent falls (3 patients), difficulty in climbing stairs (2 patients) and inability to rise from the floor (1 patient). All patients had normal cognitive function. The main clinical signs on physical examination were winging of the scapula, scoliosis and calf hypertrophy (Table 1). In all patients the CK level was increased. In three patients (cases 2, 3 and 4) the CK level was markedly increased (40X normal value), and in others (cases 1, 5 e 6) the value ranged from 10 to 20X the normal value.

Muscle biopsies (performed in the biceps brachialis muscle) of four patients showed a dystrophic pattern, classified as severe (cases 2 e 4) or moderate (cases 1 and 5). No inflammatory changes were found. No muscle biopsy was done for cases 3 and 6 because their siblings (patients not included in this report) already had a histological diagnosis of SG, confirmed by the absence of at least one SG protein expression. According to the immunohistochemical staining pattern, the patients were classified as having either a deficiency of α-SG (cases 2, 5 and 6), or a deficiency of γ-SG (case 1).

Analyses of the genes responsible for production of α-, β-, γ- and δ-SG (SGCA, SGCB, SGCG and SGCD, respectively) were done using exon-specific PCR amplification and sequencing for the most frequently mutated exons in our population[3]. A heterozygous frameshift mutation in exon 8 of the SGCG gene (c.657delC) was detected in case 3, and case 4 harbored a mutation in exon 3 of the SGCB gene, which leads to an exchange of methionine to lysine at position 100 (c.299T>A, p.M100K).

In all cases, treatment with steroids, either prednisolone (case 3) or deflazacort (cases 1, 2, 4, 5 and 6), was initiated when the clinician first noticed a rapid and marked decrease of muscle strength. This was characterized by either an increase in the frequency of falls, greater inability to rise from the floor or worsening of walking capacity. The decision of introducing steroid therapy for patients with SG was made based in an attempt to obtain similar results to those obtained for patients with DMD and other forms of muscular dystrophies, the latter based on a few reports in the literature describing positive effects of this therapy[18-20]. Prednisolone was used on an intermittent regimen (10 days on and 10 days off) at a dose of 1 mg/kg/day, whereas deflazacort was used daily at a dose of 0.9 mg/kg/day.

Table 1. Clinical features of 6 unrelated patients with sarcoglycanopathy.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	F	F	F	F	F	F
Consanguinity	No	No	No	No	No	No
Family history	No	No	Yes	No	No	Yes
Age at onset	5y	6y	9y	4y	10y	5y
First symptoms	Frequent falls	Frequent falls	Difficulty climbing stairs	Frequent falls	Difficulty climbing stairs	Difficulty rising from the floor
Calf hypertrophy	Yes	No	Yes	No	No	No
Scoliosis	Yes	Yes	No	No	No	No
Joint contractures	+	-	+	+	-	+
Scapula winging	+	+	+	+	+	+
Molecular study	-	-	c.657delC *SGCD*	c.299T>A *SGCB*	-	-

Y: years; mo: months.

Patients received steroids for one year (cases 3, 4 and 5), two years (cases 2 and 6) or four years (case 1). There was stabilization of muscle strength in case 6, a slight improvement in cases 1 and 2, and a slight worsening in cases 3, 4 and 5. No patient lost ambulation during the treatment period (Table 2). In addition, forced vital capacity (FVC) was rendered stable in three children (cases 2, 3 and 6), as shown in repeated pulmonary function tests, had a mild improvement in two (cases 1 and 4), and in only one child there was a mild reduction of FVC from 58% to 52% (case 5). On cardiac tests, two children had a mild improvement of the ventricular ejection fraction (cases 1 and 5) and one child (case 3) had a mild deterioration. In the other patients, the cardiac function remained stable during follow-up (Table 2). No adverse effects were observed in these cases, except a mild increase in body weight in two patients (cases 5 and 6).

DISCUSSION

Patients with SG typically present the first symptoms in the first decade of life with progressive weakness leading to early loss of ambulation and premature death due to cardiomyopathy or respiratory insufficiency. For this reason, as for DMD, the identification of therapies capable of alleviating the progression of the disease is imperative.

In this retrospective study we have analyzed the clinical aspects and outcomes of ambulant children with SG that have been treated with steroids. Despite an absence of inflammatory changes in muscle biopsies in all of them, the indication of steroids for these patients was based in: 1) rapid progression of the disease, especially for walking function; 2) a few reports from the literature describing positive response of SG patients to steroid therapy[18-20]; and 3) the demonstrated beneficial effects of steroids for DMD, considering that the clinical progression and histopathology of SG are quite similar to those observed in DMD, and in both situations the basic mechanism of the disease is related to the disintegration of a complex of proteins located to the sarcolemma of the muscle fibers[1-2]. However, we did not observe overt clinical improvement in this group of SG patients treated for different periods of time (one to 4 years); indeed, three patients worsened and three showed a more stable course. This might indicate that the response to steroid therapy can vary individually, e.g., according to the specific mutation. A variable response was also observed for pulmonary and cardiac functions.

In the literature, an effective positive action of steroids in patients with SG has been rarely reported[18-20]. Angelini et al. described improvement in both muscle strength and functional performance after five months of therapy with deflazacort in a 39 years-old patient with mild muscular dystrophy caused by α-SG deficiency[18]. Connoly et al. reported maintenance of the proximal muscle strength on quantitative testing after two years of treatment with prednisone and azathioprine in an 8 year-old girl with α-SG deficiency[19]. Wong-Kisielet et al. described stabilization and improvement of muscle strength in two siblings with β-SG after 30 months of deflazacort therapy[20].

In other forms of muscular dystrophies there have also been reports of a positive response to corticosteroids[21-22]. Godfrey et al. described three children with an LGMD phenotype and pathogenic *fukutin* mutation that had a remarkable steroid responsiveness[21]. These patients were ambulant and had marked elevation of serum CK and muscle biopsy with inflammatory changes. Darin et al. described two patients with FKRP deficiency (LGMD2I) and a Duchenne-like phenotype that showed a good clinical response to treatment with prednisolone[22]. Similarly, both patients had muscle biopsies with dystrophic patterns in association with inflammatory changes, suggesting that patients with inflammatory reaction in the muscle biopsy might present a better response to corticosteroids. In contrast, Walter et al. randomized 25 patients with genetically defined dysferlinopathy (LGMD2B) to receive deflazacort or placebo for six months and demonstrated that deflazacort

Table 2. Treatment response to steroid in 6 unrelated patients with sarcoglycanopathy.

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Proximal upper extremity strength	2	3	2	3	4	3	4	4	3	3	4	4
Distal upper extremity strength	4	4	3	4	5	3	4	4	4	4	4	4
Proximal lower extremity strength	2	3	2	2	4	3	4	3	2	2	3	3
Distal lower extremity strength	3	3	3	3	5	3	4	4	4	3	4	4
FVC (% predicted)	68%	97%	73%	68%	70%	77%	40%	67,7%	57%	52%	77%	80%
Echo (FE)	69%	71%	44%	57%	69%	61%	65%	65%	55%	61%	65%	67%
Treatment onset (y)	13		13		14		10		11		11	
Treatment duration (mo)	48		24		12		12		12		24	
Loss of ambulation	No		No		No		No		No		No	

Y: Years; mo: Months; pre: Pretreatment; post: Post treatment; FVC: Forced vital capacity; Extremity strength graded on Medical Research Council (MRC) scale.

did not improve muscle strength[23]. Furthermore, there was a trend of worsening muscle strength in the group under deflazacort treatment, which recovered after discontinuation of the study drug. In addition, patients showed a broad spectrum of steroid side effects[23].

Regarding the response to corticosteroids of the cardiac function, our study showed a mild improvement of the ventricular ejection fraction in two patients and in three patients the cardiac function remained stable. In another way, Bauer et al. demonstrated that prednisolone led to a decompensation of cardiac hemodynamics and induced additional cardiac damage in the delta-sarcoglycan-deficient mouse[24].

Despite the fact that our study has shown an apparent benefit of the medication to some of our cases, the evaluation period of the effects of steroids was still too short, especially when evaluating the ability to walk. More specific tests, such as 6M walking test, for a longer period of observation, may be used in the future to better assess the effects of steroids on the gait of these cases. Moreover, results of this retrospective analysis are preliminary, thus prospective studies including larger number of patients, with defined subgroups, and inclusion of control groups, will certainly bring more definitive information regarding the real benefits of steroids for SG.

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