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Salbutamol benefits children with congenital myasthenic syndrome due to ALG2 mutation

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Background: We previously reported on four siblings who had congenital myasthenic syndrome (CMS) due to *ALG2* mutation. Three of them showed slowly progressive deterioration and were wheel-chair bound. Another patient, reported by others, with CMS due to *ALG2* mutation responded to pyridostigmine therapy.
Objective: To report on the beneficial effect of salbutamol in 4 patients with CMS due to *ALG2* mutation who did not respond to pyridostigmine therapy.
Patients and methods: Four siblings (one male and 3 females, age range 4.1–25.4 years) belonging to a multiplex, consanguineous Saudi family featuring CMS due to *ALG2* mutation received oral salbutamol (4 mg three times daily). Previous trial of pyridostigmine therapy was not effective. The response was assessed by QMG score at baseline and 1–3 months.
Results: An increasingly positive response, as measured by the QMG score, was noted after only one month of salbutamol, which was well tolerated in all patients. Improvement in specific subcomponents of the QMG score such as leg outstretched in 45° supine, and raising arm 90° was most marked. The youngest child could stand with support after the third month of therapy.
Conclusion: Salbutamol is an effective treatment in CMS due to *ALG2* mutation. This study provides class IV evidence that salbutamol given at a dose 12 mg/day improves function as measured by the QMG score.

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Correlation of respiratory function tests with repetitive stimulation of long thoracic nerve in myasthenia gravis

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Objective: Myasthenia gravis (MG) is an autoimmune disease characterized by blockage of neuromuscular transmission. Respiratory and bulbar weakness is the major complications and early diagnosis of these complications is very important for the planning of treatment.
Method and patients: 21 patients with myasthenia gravis and 21 healthy controls were included to this study. Repetitive nerve stimulation (RNS) with 3 Hz tests were done using facial (orbicularis oculi (OO)), ulnar (adductor digiti minimi (ADM)) and long thoracic nerves (serratus anterior (SA)). The difference between the first and fourth compound muscle action potential (CMAP) amplitudes was recorded. Respiratory functions were evaluated with forced vital capacity (FVC) and the ratio of forced expiratory volume in 1 s (FEV1) to FVC.
Results: 15 men and 6 women were included in the patient group; the mean age was 56,9 years. Although there was no difference between the values of RNS from the facial nerve in the patient and control groups, the mean decrement was higher in RNS of the long thoracic nerve of patient group. The sensitivity and specificity of long thoracic nerve according to facial nerve was 0.86 and 0.66 respectively. Strong correlation between the decrement percentage from SA recordings and FEV1/FVC ratio and medium-strong correlation between percent FEV1/FVC were obtained. There was a significant difference between the decrements recorded from SA than the other muscles in the evaluation of patient group.
Conclusions: Use the RNS of long thoracic nerve compared with the respiratory function tests might be a well-tolerated and simple way for early diagnosis of pulmonary dysfunction in MG.

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A case of Becker muscular dystrophy with rimmed vacuoles

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Objective: We describe rimmed-vacuoles as principle diagnostic pathology on muscle biopsy of a patient with genetically confirmed Becker muscular dystrophy (BMD).
Background: Rimmed vacuoles can be seen in subsets of muscle disorders such as distal myopathies and hereditary inclusion body myopathy (hIBM). They are not pathognomonic of dystrophinopathy.
Case presentation: 34 year old Persian male presented for evaluation of slowly progressive proximal muscle weakness since the age of 17, bilateral calves hypertrophy, and cardiomyopathy. He had no family history of muscle disorder. CK was 914 IU/L and EMG/NC showed myopathy with mild irritability. Skeletal muscle biopsy showed a chronic myopathy with no active regeneration/degeneration. Salient feature of the biopsy was rimmed vacuoles with confirmed autophagic nature on enzyme histochemistry and electron microscopy. Membrane

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protein immunohistochemistry (IHC) did not show any deficiency. In view of strong clinical consideration of BMD genomic sequencing analysis of the DMD gene was performed. This showed deletion of exons 45–47 confirmatory for Becker muscular dystrophy.

Discussion: Initial pathologic impression was that of a dystrophic/myopathic syndrome characterized by occasional rimmed vacuoles but without significant inflammation. The clinical phenotype did not suggest a "distal myopathy" but rather a hereditary syndrome with impression of hIBM. Pathologic differentials included variants of limb-girdle muscular dystrophies. A dystrophinopathy was not considered in view of the normal IHC.

Conclusion: Our findings broaden the differentials of vacuolar myopathies. In relevant clinical setting a dystrophinopathy should be considered in a biopsy combing vacuolar damage and normal membrane IHC.

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Clinical profile and molecular diagnosis of Chinese patients with facioscapulohumeral muscular dystrophy

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Background and objective: FSHD is a common muscular inherited disorder, caused by contraction of D4Z4 repeats on chromosome 4q35. However, the complicated genotype-phenotype relationship remains a controversial subject.

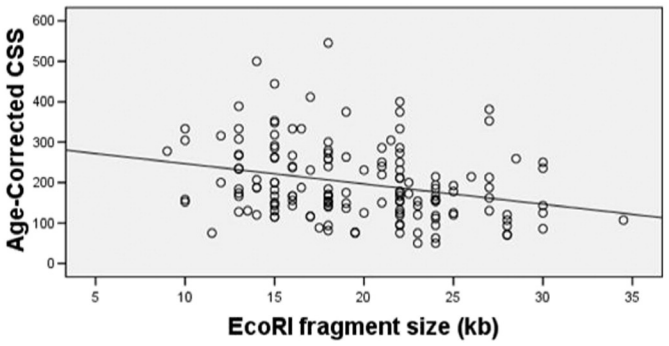
Materials and methods: 178 affected individuals from 136 unrelated Chinese families were investigated. Genetic testing was performed by PFGE separation and southern blotting. A ten-grade FSHD clinical severity scale was adopted.

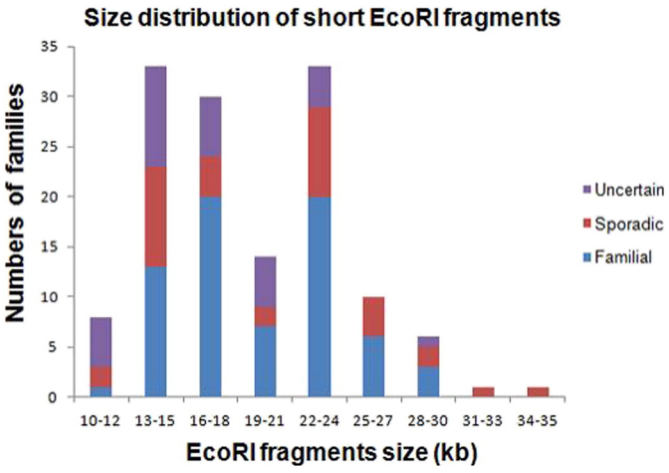
Results: A significantly inversed correlation between short EcoRI fragment size and disease severity was observed in all symptomatic patients (Fig. 1). However, in female group, either the asymptomatic carriers or severe patients showed large variation in the size of short EcoRI fragment (Table). It also showed significant difference between the sporadic and familial cases in the size distribution of short EcoRI fragments ($c^2 = 5.69$, $P < 0.05$, Fig. 2).

Conclusion: A majority of phenotypic spectrum was still incompatible with their heterozygous contraction of D4Z4 repeats, especially in female cases. Our results suggested that there are multi-factors synergistically modulating the phenotype of FSHD.

Groups[a]	Male			
	n	Age (years)[b]	EcoRI fragment (kb)	Range (kb)
I	3	40.0 ± 12.5	19.3 ± 3.8	15–22
II	22	28.2 ± 10.1	21.7 ± 6.1	12–35
III	18	25.9 ± 5.9	20.0 ± 5.6	13–30
IV	27	30.0 ± 10.7	19.2 ± 4.4	12–26
V	15	34.3 ± 13.5	18.6 ± 3.9	13–29
VI	4	28.5 ± 7.6	13.5 ± 2.7	10–15
Total	89	29.7 ± 10.5	19.6 ± 5.2	10–35

Groups[a]	Female			
	n	Age (years)[b]	EcoRI fragment (kb)	Range (kb)
I	16	35.2 ± 10.2	19.7 ± 5.8	13–30
II	14	29.7 ± 12.0	20.1 ± 4.5	10–28
III	9	30.0 ± 13.4	19.3 ± 4.1	13–24
IV	20	30.3 ± 12.1	21.2 ± 5.2	13–30
V	13	36.3 ± 13.2	16.5 ± 5.8	10–27
VI	12	33.4 ± 11.1	18.6 ± 4.3	14–27
Total	84	32.2 ± 11.9	19.4 ± 5.2	10–30





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Favorable response of botulinum toxin to the axial muscle spasms in a patient with stiff-person syndrome autoimmune: A case report

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Summary

Introduction: The stiff-person syndrome is a rare neurological disorder characterized by marked axial stiffness with severe hyperlordosis and painful muscle spasms, which can be triggered by sensory and emotional stimuli. The antibodies against glutamic acid decarboxylase (GAD) suggest an autoimmune etiology. Various treatments (benzodiazepines, baclofen, botulinum toxin, immunoglobulin and immunosuppressive therapy) have been used with varying response.

Case report: The case of a female patient of 20 years, with clinical picture of one and a half axial hypertension and left-sided, marked lumbar lordosis and very painful muscle spasms axial paroxysmal is reported; progressive course. Additional tests are performed: oligoclonal bands with pattern 2 and anti-GAD positive serum; occult tumor (total body PET normal) is discarded. Diagnosis of stiff-person syndrome autoimmune done. Management starts with benzodiazepines, baclofen and immunoglobulin for 4 cycles (2 g/

kg every 2 months); without obtaining a sustained clinical response to axial muscle spasms and the lumbar lordosis. It was decided to apply botulinum toxin type A (Dysport) 500 U distributed in lumbar, thoracic and cervical paraspinal musculature; evidencing the fifth day a resolution of muscle spasms and improvement in lumbar lordosis (pre-90° and post-76° angle), achieving improvement in the patient's pain, posture and obtaining an independent way.

Conclusion: The use of botulinum toxin can be a good therapeutic option for the management of pain and muscle spasms that do not respond to other treatments for people with stiff-person syndrome. The use of botulinum toxin is a therapeutic alternative to improve posture of these patients associated hyperlordosis.

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Dysferlinopathies in Uruguay: First four genetically confirmed cases with different phenotypes

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Background: Primary dysferlinopathies are a heterogeneous group of muscular dystrophies autosomal recessive caused by mutations in chromosome 2, which encodes the dysferlin protein. The clinical presentation is variable. Hyper-CKemia is very frequent. Affected patients may present with involvement of the posterior compartment of leg in Miyoshi myopathy (MM), proximal involvement in limb girdle muscular dystrophy type 2B (LGMD2B) or less commonly, with involvement of the anterior tibial compartment.

Objective: Describe the clinical presentation in the first cases of dysferlinopathies diagnosed in Uruguay.

Patients: Case 1: Male, 30 y. At 15 experience difficulty in sports practice, with decreased muscle mass of both calves at the beginning, with progression to proximal muscles. Serum CK: 37,000. With clinical raise of MM, confirmatory genetic study was obtained.

Case 2: Male, 35 y. Two years evolution of lower limb fatigue and gait disturbance. Bilateral, predominantly proximal and left amyotrophies with mild paresis in muscle groups of the hip and knee joint with conserved distal forces. Serum CK: 13,000. The genotype was consistent with dysferlinopathy of LGMD2B.

Case 3: Female, 32 y. Initially distal leg myopathy at 22 which has progressed to involve the proximal legs, with a slower progression than Case 1. Serum CK: 5000. The analyses of dysferlin gene detected deleterious mutation.

Case 4: Female, 69 y. Phenotype of LGMD2B. The analyses of dysferlin gene detected a recently disease-causing mutation.

Conclusion: We described the first four cases of dysferlinopathies with molecular confirmed diagnosis in Uruguay: two LGMD2B and two MM.

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Familial polyglucosan body myopathy: A clinical spectrum

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Background: Polyglucosan body myopathies are due to heterogeneous causes.

Objectives. Mutations in the newly identified RBCK1 gene have been recognized to be a rare cause of polyglucosan body myopathy. Here we report a novel family in which a form of adult-onset limb-girdle myopathy was associated with polyglucosan storage in muscle.

Methods and patients: In 3 affected relatives we investigated the clinical phenotype, the muscle morphological and ultrastructural features, the RBCK1 genotype and the role of ubiquitin-proteasome and lysosomal-autophagic degradation pathways by analysing ubiquitin, p62/SQSTM1, LC3 and MuRF-1 proteins.

Results: The phenotype in all 3 patients was characterized by limb-girdle muscular dystrophy with onset in the fifth decade, associated with autoimmune disorders in 2 cases (generalized vitiligo, chronic inflammatory demyelinating polyneuropathy), without overt cardiac impairment. Accumulation of PAS-positive, amylase-resistant polyglucosan bodies was detectable in 2 of the 4 muscle biopsies studied. Immunofluorescence analysis showed that the inclusions were strongly labelled for ubiquitin and p62/SQSTM1, and immunoblotting revealed increased levels of MuRF-1 and LC3-II proteins in muscles from patients as compared to controls.

Conclusions: As compared with cases with RBCK1-related myopathy, this family shows late-onset of limb girdle muscular dystrophy and lack of cardiac involvement, whereas muscle histopathological features are completely matching. We offered evidence supporting the role of both the ubiquitin–proteasome and the lysosomal–autophagic degradation pathways in this family, although the mechanism generating polyglucosan bodies in this family is most likely in glycogenin-1 (under investigation).

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Neuropathy in patients with confirmed antineural antibodies in the course of primary brain tumors — Case series

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Objectives: Paraneoplastic neurological syndromes are seen in the course of different types of systemic malignant diseases. There are very few case reports of paraneoplastic syndromes in the course of primary brain tumors.

Case series: In 5 patients with different types of brain tumors, we confirmed the presence of antineural antibodies (anti-neuroendothelium, anti-MAG, anti-GFAP, anti-PCNA, and anti-Ro52). We performed a wide range of the electrophysiological tests (standard electroneurography, electromyography, conduction velocity test, quantitative sensory tests, autonomic tests). The findings indicated

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changes of motor, and sensory nerves, with the tendency to small fibre impairment. The clinically obvious polyneuropathy was found only in one patients with anti-MAG antibodies.

Conclusion: The presence of the electrophysiological changes of peripheral nerves in the patients with primary brain tumors, and positive antineural antibodies, suggest the autoimmunological response in the peripheral nervous system. We considered the possibility of paraneoplastic neurological syndromes in the presented cases.

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