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Contribution of muscle pathological studies in the diagnosis of muscular diseases

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Abstract

Introduction: Muscle biopsy is a diagnostic procedure used in the diagnosis of patients with suspicion of neuromuscular diseases. Clinical findings suggestive of muscle disorder like muscle weakness, cramps, muscle pain and fatigue, and elevated serum CK levels, abnormal electromyography (EMG) or muscle imaging alterations, can justify muscle biopsy when the diagnosis can not be met by other means.

Objective: The main purpose of this study was to evaluate the role of muscle biopsy in the diagnosis of a group of patients from CHUC Neuromuscular Outpatient Clinic, suspected of having a muscle disease, and to describe the most common pathologic findings.

Material and Methods: The medical files and muscle biopsy reports of patients with suspected myopathy, who performed muscle biopsy in the year 2011 and 2012, were analysed. Clinical, laboratory, EMG, pathological and molecular data were recorded

Results: Thirty-six patients were identified (twenty-one female and fifteen male). The actual mean age was 50.78 (±15.97) and the mean age of onset was 37.89 years. A familiar history was identified in six patients. Parental consanguinity was reported in two patients. Muscle weakness was reported as first symptom in nineteen patients, five refer the association of muscle weakness and myalgia, and seven myalgia. Two patients presented with high CK serum levels and one was asymptomatic. The mean CK level was high (1885.3 UI/L). EMG showed signs of muscle lesion in seven patients. The most common pathologic abnormalities were increased variability of fibres (39%), necrotic fibres (16%), internal nuclei (55.5%) and inflammatory infiltrates (38.8%). Granulomas were identified in two muscle biopsies and red-ragged-fibres (RRF) in seven. Abnormal

immunohistochemical data were present in fifteen muscle biopsies. Molecular studies were performed in fifteen patients, with six positive results.

Muscle biopsy allowed the specific diagnosis of a muscular disease in twenty-two patients. A change in clinical diagnosis, following muscle biopsy, occurred in sixteen patients.

Conclusion: Muscle biopsy plays an important role in the diagnosis of patients with muscular disorders. In this study it allowed a specific diagnosis in twenty-two patients (61.11%) and to change the pre-biopsy diagnosis in sixteen (44.44%). Muscle biopsy was considered useful in thirty-two patients (88.89 %), since it allowed a change in diagnosis or/and a specific diagnosis in this patients.

Introdução: A biópsia muscular é um procedimento diagnóstico utilizado no estudo de doentes com suspeita de patologia neuromuscular. Essa suspeita assenta na existência de um quadro clínico (fraqueza muscular, cãibras, mialgias e fadiga) e exames complementares (elevação dos valores séricos de CK, e alterações do electromiograma e de estudos de imagem) sugestivos de doença muscular. Nestas circunstâncias há indicação para realização da biópsia muscular tendo em vista o completo esclarecimento do diagnóstico.

Objetivos: Avaliar a importância da biópsia muscular no diagnóstico etiológico de um grupo de doentes da Consulta de Neuromusculares do CHUC, com suspeita de miopatia, e descrever os achados mais comuns nas biópsias musculares.

Material e métodos: Análise dos processos clínicos e relatórios das biópsias musculares de doentes com suspeita de miopatia, que realizaram biópsia muscular em 2011 e 2012,

e registo dos dados clínicos, laboratoriais, resultados da EMG, do estudo patológico e molecular de cada doente.

Resultados: Foram identificados trinta e seis doentes que cumpriam os critérios de inclusão no estudo, vinte e um do sexo feminino e quinze do sexo masculino. A média de idade actual foi de 50,78 (±15.97) anos e a idade média de aparecimento de primeiros sintomas foi de 37,89 anos. Uma história familiar positiva foi identificada em seis casos e consanguinidade parental em dois. Dezanove doentes tiveram como primeiro sintoma fraqueza muscular, cinco fraqueza e mialgias associadas, sete mialgias isoladas, dois aumento da CK sérica e um último assintomático. O valor médio da CK sérica era elevado (1885,3 UI/L). O EMG revelou sinais de lesão de fibra muscular em sete doentes. A biópsia muscular mostrou aumento de variabilidade do diâmetro de fibras em trinta e três doentes (39%), fibras em necrose em dezasseis (16%), ~~a~~ presença de núcleos centrais em vinte (55,5%), infiltrados inflamatórios em catorze (38,8%), granulomas em dois e red-ragged-fibres em sete (RRF).

A biópsia muscular permitiu estabelecer o diagnóstico definitivo em vinte e dois doentes. A mudança da hipótese de diagnóstico inicial com a realização de biópsia muscular ocorreu em dezasseis doentes.

Conclusão: A biópsia muscular tem um papel importante no diagnóstico e posterior orientação de doentes com doença muscular. Este estudo permitiu o diagnóstico específico em vinte e dois doentes (61.11%) e a alteração do diagnóstico pré-biópsia em dezasseis casos (44.44%). A biópsia muscular foi, assim, considerada útil em trinta e dois doentes (88.89%), uma vez que permitiu a modificação da hipótese de diagnóstico e/ou um diagnóstico especifico nestes doentes,

Introduction

Open muscle biopsy is a valuable procedure in the evaluation of neuromuscular disorders. It was first performed by Duchenne in 1860, on a patient with generalized weakness of infancy onset, suggestive of myopathy. In 1962, the percutaneous needle was introduced by Bergstrom. Victor Dubowitz introduced enzyme histochemical methods in 1970, as well as immunohistochemical methods in the 1980s. These techniques allowed the diagnosis of various muscle diseases and contributed to the development of molecular methods of diagnosis in the XX century[1-3].

Muscle biopsy is performed when a patient presents signs or symptoms suggestive of muscle disease, unexplained high CK levels or myopathic signs on a routine electromyography and a final diagnosis is not possible [1]. Muscle selection for biopsy should be based on the distribution and severity of the weakness. A severely weak muscle should not be selected, since it may be mostly replaced by adipose and connective tissue, nor a muscle without weakness which may not reveal sufficient abnormalities to help in the diagnosis of the underlying disease[1,4].

Muscle biopsies can be performed through open or closed technique (needle), both performed under local anaesthesia[1]. Open biopsy is the technique used at CHUC and it allows a direct visualization of the muscle, provides a larger sample and the opportunity to sample peripheral nerves if necessary. It has disadvantages since it is a more invasive procedure with possible complications like muscle herniation, hematoma, infection and wound dehiscence. Needle biopsy is less invasive and safer but this procedure has the disadvantage of being blindly performed, providing a smaller sample sometimes inadequate for histochemical analysis[4,5]. The muscle sample must be frozen or fixed and taken promptly to the pathology laboratory and its quality should be immediately analysed under a dissecting microscope[1]. The histochemical studies evaluate tissue

organization and cellular structure, and the most common stains are hematoxylin and eosin (H&E) and the modified Gomori trichrome stain. The last one is also important for the diagnosis of mitochondrial disorders, inclusion body myositis and nemaline myopathies. ATPase stains demonstrate the various muscle fibre types, which may be altered in different ways by several muscle diseases. Periodic acid-Schiff (PAS) reaction stains glycogen and other polysaccharides and is valuable in the diagnosis of glycogen storage diseases. Oil-red-U or Sudan Black stain fat and detect abnormal deposition of lipids. NADH-TR is used to demonstrate the activity of a group of enzymes present in mitochondria and endoplasmic reticulum. Besides the histological and histochemical studies, there is the possibility of identifying abnormal expression of some proteins and enzymes through immunohistochemistry[2,4,5].

With this study we intend to evaluate the role and contribution of muscle biopsy in the diagnostic workup of suspected myopathy on a group of patients from the Neuromuscular Outpatient Clinic of CHUC and to describe the most common findings on biopsies.

Material and Methods

Patients

The patients included in this study (thirty-six) were selected from the list of health users who underwent muscle biopsy in the CHUC Neurology Department, between January 2011 and December 2012. We identified a group of patients to whom this procedure was ordered at the Neuromuscular Outpatient Clinic.

Clinical Evaluation

The clinical data were obtained from the medical files of each patient and include: current age, gender, consanguinity, family history concerning neuromuscular disorders, age and nature of first symptoms, disease progression, neurological examination, current medical diseases and medication. Laboratory studies (serum CK), date and results of the electromyography (EMG) and of muscle biopsies, and final diagnosis were also reviewed.

Muscle Biopsy Evaluation

The muscle biopsies were routinely processed, the sample was frozen in isopentane chilled in liquid nitrogen and kept at -70ºC. The transverse and longitudinal cryostat sections were cut 8 µm thick, for histochemical studies, stained with H/E, PAS, Oil-red-O and Modified Gomori Trichrome, and for histoenzymatic routine methods, such as Nicotinamide Adenine Dinucleotide-Tetrazolium Redutase (NADH-TR), Succinic Dehydrogenase (SDH), Adenosine triphosphatase (ATPase) pH 4.35 and pH 9.4; and cut 4 µm thick for immunochemistry study with antibodies against dystrophin (dys 1, dys 2, dys 3), α, β,γ and δ sarcoglycans, dysferlin, merosin, α-dystroglycan and emerin. Control of human skeletal muscle was included on each glass slide immunostained in the study.

The reports of the muscle biopsies were analysed and the following features were recorded: variability of fibre diameter (normal, increased), internal nuclei (normal; increased), necrotic fibres (absent, present, rare or frequent), inflammatory infiltrates (absent, present-localization), granulomas (present), Red-Ragged-Fibres (RRF) (absent; present), specific histological features and immunohistochemical results were also analysed.

Results

Clinical evaluation:

Thirty-six patients aged 20 to 82 years (50.8±15.97) were included in the study: fifteen were male (41.7%) with ages between 30 and 77 (50.67±13.97) and twenty-one female (58.3%) aged 20 to 80 (50.86±17.59) years.

A family history for similar symptoms was positive in six patients (16.67%), negative in twenty-one patients (58.3%) and unknown in nine patients (25%). Parental consanguinity was identified in two patients (5.55%). (Table 1).

Table 1- Demographic data

	Gender (n)	Gender (%)	Age	Family history (n)	Family history (% of total cases)	Consanguinity (n)	Consanguinity (% of total)
Female	21	58.33	[20-80] (50.86±17.59)	3	8.33	1	2.78
Male	15	41.67	[30-77] (50.67±13.97)	3	8.33	1	2.78
Total	36	100	[20-80] (50.8±15.97)	6	16.67	2	5.55

Thirty-one patients (86%) came from the central region of Portugal: twelve (33.3%) from Coimbra district, seven (19.4%) from Aveiro, seven (19.4%) from Viseu and five (13.9%) from Leiria. Five came from north and south regions.

The mean age at first symptom was 37.89±22.13 years (range: [1-77] years). These data were unknown in eleven patients (23%).

The reasons leading to muscle biopsy are illustrated at Table 2: muscle weakness was the most common indication for biopsy, twenty patients (55.56%) complained with this symptom; other frequent indications were a combination of proximal weakness and

myalgia in five patients (13.9%) and myalgia in seven patients (19.4%). Other reasons to perform muscle biopsy were high CK serum and family history of muscle disease.

Table 2- First symptoms of patients with muscle disorders

First symptoms	N	Percentage (%)
Weakness	20	55.56
Proximal weakness	10	50
Distal weakness	3	15
Ptosis	2	10
Facial weakness	1	5
Proximal and distal weakness	1	5
Generalized weakness and ptosis	1	5
Proximal weakness and ptosis	1	5
Proximal and facial weakness	1	5
Proximal weakness and myalgia	5	13,89
Myalgia	7	19,44
High CK level	2	5,56
Asymptomatic	1	2,78
No data	1	2.78
Total	36	100

The progression of symptoms (Table 3) was known in twenty-nine patients (80.5%): it was progressive in twenty-one (58.33%) and stable in eight (22.22%).

Table 3-Evolutions of symptoms

Evolution of symptoms	N	Percentage (%)
Progressive	21	58.33
Stable	8	22.22
No data	7	19,44

The individual CK values at presentation were available for twenty-four patients (66.7%). Nineteen patients (79.2%) had high CK levels at presentation (mean 1885.3 UI/L).

EMG data are presented at Table 4: EMG was performed in twenty-five patients (69.4%) and seven revealed myopathic alterations (28%). (Table 4).

Table 4 - EMG results

	N	Percentage (%)
No EMG	11	22.91
EMG	25	69.4
normal	16	64
signs of muscle lesion	7	28
other alterations	2	8

The following diagnosis was suspected in thirty-four patients (94.4%) before performing biopsy: metabolic myopathy in eight (22.22%), inflammatory myopathy in eight (22.22%), muscular dystrophy in seven (19.44%), mitochondrial myopathy in three (8.33%) and congenital myopathy in three patients (8.3%). A non-specified myopathy was considered for five patients (13.89%). (Table 5).

Table 5- Pre-biopsy diagnosis

Suspected diagnosis pre-biopsy	N	Percentage (%)
Metabolic myopathy	8	22.22
Inflammatory myopathy	8	22.22
Muscular dystrophy	7	19.44
Mitochondrial myopathy	3	8.33
Congenital myopathy	3	8.33
Myopathy	5	13.89
No pre-biopsy diagnosis	2	5.56

There was no known medical history, medications or toxins responsible for the symptoms.

Muscle Biopsy Evaluation:

The mean time from first symptoms to muscle biopsy was 10.33 years (range: [0-56] years old). Fifteen biopsies were performed in 2011 (41.7%) and twenty-one in 2012

(58.3%). The muscles selected for biopsy were the deltoid muscle in thirty-two patients (88.9%), the vastus lateralis muscle in two patients (5.6%), the extensor digitorum longus muscle (2.7%) in one from and the gastrocnemius medialis in another one (2.7%).

Muscle patothological findings, shown in Table 6, identified two patients with no signs of muscular disease (5.5%) (both with signs of neurogenic atrophy). Five patients registered non-specific muscle alterations (13.9%). Four had myopathic changes without a specific ethology (11.1%). Twenty-five (69.4%) recorded a result suggestive of a specific diagnosis. Eleven patients (44%) with inflammatory changes, eight (32%) compatible with inflammatory myopathy, of these eight, three with polymyositis, one with dermatomyositis, one with inclusion body myositis, one with sarcoidosis and one with necrotizing myopathy; and four (16%) with macrophagic myophasciitis lesions. Three patients (12%) had a mitochondrial myopathy. Two biopsies (10%) were characteristic of metabolic myopathy (both suggestive of glycogenolysis V). One biopsy (4%) showed alterations of centronuclear myopathy (congenital myopathy). Eight patients (32%) presented muscular dystrophy, of these, six presented reduced dysferlin expression, and two reduced gamma-sarcoglycan expression (table 6).

Table 6- Muscle biopsy pathological findings

Biopsy pathological findings	N	Percentage (%)
Normal	0	0
Signs of neurogenic atrophy	2	5.56
Unspecific alterations	5	13.89
Myopathic changes	4	11.11
Alterations sugestive of specific diagnosis	25	69.44
Inflammatory myopathy	11	44
Muscular distrophy	8	32
Mitocondrial myopathy	3	12
Metabolic myopathy	2	8
Congenital myopathy	1	4

The variability of fibres was increased in thirty-three patients (91.7%) and normal in the other cases (8.3%). Necrotic fibres were present in sixteen (44.4%), of these sixteen, seven patients presented rare necrotic fibres (43.75%) and nine patients showing frequent necrotic fibres (56.25%). Internal nuclei were absent in sixteen (44.4%) and increased in twenty (55.6%). Inflammatory infiltrates occurred in fourteen patients (38.9%). Two patients with granulomas (5.5%) and seven with RRF (19.4%) were identified. (See table 7).

Immunohistochemical results were available concerning thirty-two patients (88.9%). Fifteen patients showed alterations concerning the immunohistochemical studies (46.7 %); five revealed absent or reduced expression of dysferlin (33.3%); four patients registered irregular or absent expression of gamma-sarcoglycans (26.7%) – one of these patients also recorded absent dysferlin and beta-sarcoglycan expression; five patients presented MHC I sarcolemma expression (13.9%), two also had MCH I expressed at sarcoplasm and two patient registered no myophosphorylase activity (5.5%). (Table 7).

Molecular studies:

Molecular studies were performed in sixteen patients (50%), being positive in seven patients (43.75%). The mutations detected were: mtDNA alteration 3310 C>T, associated with NonInsulin-Dependent Diabetes Mellitus/Hypertrophic Cardiomyopathy (NIDDM/HCM); mtDNA alteration 4336T>C, associated with Alzheimer´s disease and Parkinson´s disease (ADPD); *PYGM* gene: homozygous mutation c.148C>T (p.R50X);, in exon 7; compound heterozygous mutations c.148C>T (p.R50X) and c.2392T>C (p.W798R); *DMD* gene: deletion of exons 45 and 47; *SGCG* gene: compound heterozygous mutations c.525delT (p.Phe175LeufsX20) in exon 6 and c.629A>G

(p.His210Arg) in exon 7; *RYR1* gene: compound heterozygous mutations c.648C>T, c.14129+80A>T and c.14130-80C>G.

Besides the mutations previously mentioned, molecular studies were requested concerning the *CAPN3* gene, *TTN* gene, *TCAP* gene, *CHRNE* gene, *FSHD* gene, *DYSF* gene, *ANO5* gene, *FKRP* gene; DMD gene and *SGCA* gene.

Table 7- Muscle biopsy findings

Biopsy findings	n	Percentage (%)
Variability of diameter fibres	33	91.67
Necrotic fibres	16	44.44
frequent necrotic fibres	8	53.33
rare necrotic fibres	7	47.67
Internal nuclei	20	55.56
Inflammatory infiltrate	14	38.85
lymphocytic and macrophagic	4	28.57
macrophagic PAS positive	2	14.29
mononuclear	4	28.57
mononuclear and lymphocytic	1	7.14
lynphoplasmocitic	2	14.29
Non-specified	1	7.14
Granulomas	2	5.56
RRF	4	19.44
Immunohistochemistry study	32	88.89
with alterations:	15	46.88
Absent or reduced expression of dysferlin	5	33.33
Irregular or absent expression of gamma-sarcoglycans	4	26.67
MHC I expression	5	46.88
No myophosphorylase activity	2	5.55

Muscle biopsy allowed the specific diagnosis of a muscular disease in twenty-two patients (61.11%): dermatomyositis (three cases), polimyositis (one case), inclusion body myositis (one case), sarcoidosis (one case), axial myopathy (one case); mitochondrial myopathy (two specific mitochondrial myopathies after molecular tests and two); metabolic myopathy (two cases); muscular dystrophies (eight cases); congenital myopathy (one case). Seventeen of muscle biopsies results were concordant with the

primary clinical diagnosis (47.22%). A change in clinical diagnosis following muscle biopsy occurred in seventeen patients (47.22%).

Molecular tests were performed in sixteen patients and confirmed the post-biopsy diagnosis in six patients (37.5%) and in one case (6.25%), allowed the diagnosis after a unspecific biopsy result.

Table 8- Case number of pre-biopsy diagnosis and number of changes in diagnosis

Pre-biopsy diagnosis	N	n of change diagnosis	Percentage of change in diagnosis (%)	n of same diagnostic category	Percentage of same diagnostic category (%)
Metabolic myopathy	8	7	87.5	1	12.5
Inflammatory myopathy	8	1	12.5	7	87.5
Muscular dystrophy	7	1	14.28	6	85.71
Mitochondrial myopathy	3	1	33.33	2	66.67
Congenital myopathy	3	2	66.67	1	33.33
Myopathy	5	3	60	1	20
No pre-biopsy diagnosis	2	2	100	0	0
Total	36	17	47.22	17	47.22

Discussion

Muscle biopsy is a diagnostic tool in the evaluation of patients suspected of having muscular diseases and it has been considered the gold-standard for the diagnosis of myopathies[6].

The clinical utility of the muscle biopsy has been questioned since it is an invasive and costly procedure, and there are major advances in molecular procedures to diagnosis muscle disorders[7].

With this study we intend to investigate the importance of muscle biopsy in the diagnosis of these disorders. Thirty-six patients were included, all of them with suspected myopathy, followed at the CHUC Neuromuscular Outpatient Clinic.

The main indications for performing muscle biopsy were weakness in twenty patients (55.56%), myalgia in seven cases (19.44%) and a combination of weakness and myalgia in five patients (13.89%).

Biopsy as a valuable diagnostic procedure was studied based on the number of total specific diagnosis made possible, and the change in the suspected pre-biopsy diagnosis including new diagnosis. It was also evaluated the number of concordant diagnosis (pre-biopsy diagnosis similar to post-biopsy diagnosis), the number of non-specific diagnosis made by muscle biopsy and the most common pathological findings on muscle biopsy.

Concerning the utility of the muscle biopsy, a change in the diagnosis occurred in seventeen patients (47.22%), allowing a specific muscle disease diagnosis in seven cases (41.17%). The other nine, one had signs of chronic denervation (possible motor neuron disease), six had nonspecific abnormalities and two had no alterations. The total specific diagnosis were twenty-two (61.11%).

The results of muscle biopsy confirmed the suspected pre-biopsy diagnosis in seventeen cases (47.22%).

Muscle biopsy was considered useful in thirty of the cases (88.89%).

The most common pathological findings were characteristic of inflammatory myopathy (30.05%) and muscular dystrophies (22.22%); other specific diagnosis were mitochondrial myopathy (8.33%), metabolic myopathy (5.56%), congenital myopathy (2.78%) and neurogenic atrophy (5.56%).

Similar studies, about the utility of muscle biopsy have been made. C.-H. Lai *et al.*[8], studied a group of two hundred and fifty-eight patients in a time frame of three years; the most common first symptom found that led to muscle biopsy were weakness in 78% of the cases; a muscle biopsy was defined as clinically useful when the results changed clinical diagnosis, treatment or resulted in a specific diagnosis. This study revealed a change in diagnosis in 47% of the cases, a specific diagnosis in 43% of the patients and a change in treatment in 33% of the subjects; 74% of muscle biopsies were considered useful in the diagnosis and management of patients with muscular diseases. The most common pathological findings were inflammatory myopathies (22.5%) and metabolic myopathies (including mitochondrial myopathies) (14.2%).

In a pediatric study by Chang XZ *et al.*[9], that included eighty-two children suspected of having muscle disease, with a time frame of five years; muscle biopsy confirmed the diagnosis, giving specific diagnosis in 37.5% of the cases; of these 39.4% were muscular dystrophies, 12.12% inflammatory myopathies, 6% congenital myopathy, 1% mitochondrial myopathy and 6% metabolic myopathy (one glycogenosis and one lipid storage myopathy); 30.5% of the patients had unspecific alterations at muscle biopsy and 29.2% revealed a normal muscle biopsy.

In another pediatric study from Cuisset JM *et al*[10], four hundred and nineteen biopsies were analyzed; one hundred and ninety-three were compatible with congenital myopathies (39.38%), ninety-two revealed muscle dystrophy (18.77%), nineteen mitochondrial myopathies, thirteen metabolic myopathies and eleven inflammatory myopathies; in sixteen cases, muscle biopsy revealed alterations compatible with non-muscular disease and sixteen showed unspecific alterations. Muscle biopsy provided a specific diagnosis in one hundred and eighty-four patients (44%). When studying children

with suspected muscular disease, muscle biopsy were indispensable to establish the etiological diagnosis and allowed a specific orientations in 45% of the patients.

Comparing the present study with the results of the cited articles, the main indications for muscle biopsy are similar (C-H. Lai *et al.*[8]), with weakness being the most frequent first symptom (55.56% vs 78%).

When comparing the number of specific diagnosis, results contrast between the present thesis and the other studies. The present study provided a specific diagnosis in 61.11% of the cases against 43% in C.-H. Lai *et a.l*[8], 37.5% in Chan XZ *et a.l*[9] study and 44% in Cuisset JM *et a.l*[10] study. This difference could be related to criteria used to perform a muscle biopsy and the criteria used to define a specific diagnosis.

The utility of biopsy was higher in the present study when compared to C.-H. Lai *et al.*[8] (83.33% vs 74%), this difference can be explained by the difference in specific diagnosis and by the criteria used to define a biopsy as useful (in our study excluded diagnosis were also considered to define the utility of the biopsy).

The most common pathological findings in the pediatric studies[8,9] were suggestive of muscular dystrophy, accounting for almost 40% in both reports; in the present study, considering the cases with first symptoms reported before the age of 18 (five cases), 40% of these also had a muscle biopsy compatible with a muscular dystrophy.

When compared with the C.-H. Lai *et al.*[8] report , our study also revealed inflammatory myopathy as the most frequent pathological finding (30.5 vs 22.5%), preceding the muscular dystrophies group (22.22%), contrasting with the results of C.-H Lai *et al*[8], where metabolic and mitochondrial myopathies are the second most frequent alterations found on muscle biopsy (14.3%).

This paper confirms that muscle biopsy has an important role on the diagnosis of muscular disorders such as inflammatory myopathies, muscular dystrophies, metabolic myopathies and congenital myopathies.

Muscle biopsy should not be considered as a diagnostic method alone, but should be interpreted together with clinical and family history, neurological examination and other complementary investigations.

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