Diagnostic yield of muscle biopsies in pediatric population: a tertiary center experience

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Background and aim. Muscle biopsy is still an important exam on the investigation of neuromuscular diseases although data regarding its diagnostic yield can be disappointing. We aimed to analyze the diagnostic yield of muscle biopsies in the pediatric population.

Patients and methods. We retrospectively analyzed a tertiary Neuropathology laboratory database to identify patients (<18 years old), submitted to muscle biopsy between January 2015 and August 2019. Demographics, clinical presentation, diagnosis, treatment, and follow-up were evaluated. Descriptive statistical analysis was performed.

Results. One-hundred and six patients were included, 52,8% (*n* = 56) were male. Median age at biopsy was 6 years (IQR 10 years). Patients were divided into 8 groups, according to clinical diagnostic suspicion: mitochondrial myopathies (*n* = 29), congenital myopathies (*n* = 9), inflammatory myopathies (*n* = 8), muscular dystrophies (*n* = 7), raised CK values in serum (*n* = 7), metabolic myopathies (*n* = 5), weakness /other neuromuscular symptoms (*n* = 30) and multiple clinical suspicions (*n* = 11). Biopsy was normal in 50 patients. Of the remaining, 27 displayed specific diagnostic features, with 88,9% (*n* = 24) allowing a definite diagnosis: muscular dystrophies (*n* = 7), metabolic myopathies (*n* = 5), congenital myopathies (*n* = 4), inflammatory myopathies (*n* = 4), mitochondrial myopathies (*n* = 3) and spinal muscular atrophy (*n* = 1). Histology led to a change of treatment in 4 patients, all diagnosed with inflammatory myopathies. Median length of follow-up was 1 year (IQR 2 years).

Conclusion. Biopsy diagnostic yield was 22,6%, and it was useful either in diagnostic or therapeutic approaches in 35,8%. Although advances of molecular techniques led to a decrease in muscle biopsy indications, it remains an important tool on the diagnosis of neuromuscular diseases.

Key words. Muscle biopsy. Muscular dystrophy. Myopathies. Neuromuscular diseases. Spinal muscular atrophy.

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Introduction

Neuromuscular diseases are a challenging group of pathologies and diagnostic approaches frequently provide frustrating results. Evaluation includes a careful clinical history and neurological examination, followed by laboratory and neurophysiologic examination. With the advances in molecular diagnosis, genetic testing may replace the indications for muscle biopsy (MB) in a large number of muscle diseases. [1]. Also, data regarding diagnostic yield of MB can be disappointing, with a minority of procedures providing a definite diagnosis [2-4]. Nevertheless, MB remains a valuable tool for the evaluation of patients with neuromuscular diseases. With this work we aim to analyze the diagnostic yield of muscle biopsies in the pediatric population of a tertiary center.

Patients and methods

We performed a retrospective analysis from the MB database of a tertiary center neuropathology laboratory, in order to identify pediatric patients (under 18 years old) submitted to this procedure between January 2015 and August 2019. Demographics, clinical data, histologic diagnosis, treatment, and follow-up were evaluated. Data regarding diagnostic and therapeutic impact was evaluated by two neurologists, blinded for the patient, in order to identify cases where biopsies did have impact on diagnostic course or changed therapeutic approach. An impact on diagnosis was considered when MB provided a definite diagnosis and/or helped the diagnostic approach, either by providing clues for subsequent investigations or by straightening differential diagnosis. An impact on thera-

Table I. Sample characterization.

	(*n* = 106 patients)
Age, median [IQR]	6 (2-12)
Male sex, *n* (%)	56 (52,8)
Positive family history for muscle disease, *n* (%)	5
History of consanguinity, *n* (%)	5
Clinical diagnostic hypothesis	
Weakness /other neuromuscular symptoms, *n* (%)	30 (28.3)
Mitochondrial myopathies, *n* (%)	29 (27.4)
Multiple suspicions, *n* (%)	11 (10.4)
Congenital myopathies, *n* (%)	9 (8.5)
Inflammatory myopathies, *n* (%)	8 (7.5)
HyperCKemia, *n* (%)	7 (6.6)
Muscular dystrophies, *n* (%)	7 (6.6)
Metabolic myopathies, *n* (%)	5 (4.7)
Muscle biopsy	
Normal, *n* (%)	50 (47.1)
Unspecific myopathic alterations, *n* (%)	29 (27.4)
Definite diagnosis, *n* (%)	24 (22.6)
Muscular dystrophies, *n*	7
Metabolic myopathies, *n*	5
Congenital myopathies, *n*	4
Inflammatory myopathies, *n*	4
Mitochondrial myopathies, *n*	3
Spinal muscular atrophy, *n*	1
Non-definite diagnosis but helpful for diagnosis, *n* (%)	3 (2.8)

IQR = interquartile range

peutic was considered when MB led to a change on treatment. For this purpose, we considered only drugs and replacement treatments and excluded rehabilitation as this was a common procedure for most of the patients.

Statistics

Continuous variables were expressed as median and interquartile range and categorical variable were expressed as absolute numbers and percentages. Statistical Package for the Social Sciences SPSS software (version 25.0) was used for data analysis.

Results

One-hundred and six patients were included, 52,8% (*n* = 56) were male. Median age at biopsy was 6 years (IQR 10 years, range 8 days-18 years). Most common biopsy site was the deltoid muscle. Only 5 patients (4,7%) presented family history of muscle diseases and 5 patients had consanguineous parents.

The clinical diagnostic hypothesis for requesting biopsies were divided into 8 groups: mitochondrial myopathies (*n* = 29), congenital myopathies (*n* = 9), inflammatory myopathies (*n* = 8), muscular dystrophies (*n* = 7), raised CK values in serum (*n* = 7), metabolic myopathies (*n* = 5), weakness / other neuromuscular symptoms (*n* = 30) and in 11 cases the clinician presented multiple suspicions.

MB were normal in 50 patients. Figure shows distribution of clinical suspicions in histologically normal biopsies. Of the remaining (*n* = 56), 27 displayed specific diagnostic features and 29 unspecific myopathic alterations.

Regarding biopsies with specific diagnostic features, 88,9% (*n* = 24) allowed a definite diagnosis: muscular dystrophies (*n* = 7), metabolic myopathies (*n* = 5), congenital myopathies (*n* = 4), inflammatory myopathies (n=4), mitochondrial myopathies (*n* = 3) and spinal muscular atrophy (*n* = 1) (Table I). In the remaining 3 cases the differential diagnosis was straightened. As mentioned above, a definite diagnosis was obtained in 24 patients, which means a diagnostic yield of muscle biopsy of 22,6%. This diagnosis yield according to clinical suspicion is presented on table II.

At biopsy time, 25 patients had already been submitted to genetic investigation, and 69 performed it after the procedure. Of the latter group, results were in accordance with the biopsy in 10 patients, leading to a definite diagnosis. After muscle biopsy and genetic testing, definitive diagnosis was obtained in 35,5% of cases (*n* = 38). It is also important to mention that from the 50 patients in whom histology showed no alterations, 12 had already been submitted to genetic testing at biopsy time.

Regarding treatment, histology led to a change in 4 patients, all diagnosed with inflammatory myopathies, who were started on steroids. Although 5 cases corresponded to metabolic myopathies, a change in pharmacologic treatment was not obtained in any; 4 cases corresponded to McArdle disease where treatment includes avoiding extenuating exercise and 1 was a Pompe disease, with death shortly after MB.

Median length of follow-up was 1 year (IQR 2 years), ranging from zero – in cases where follow-up data could not be accessed, to 4 years. During follow-up period, 9 patients died.

We also evaluated the role of the muscle biopsy in the diagnosis and in the definition of the diagnostic strategy.

In 14 patients, final diagnosis on follow-up, after further investigations, including genetic testing, was according with biopsy results.

Fifty-six patients presented alterations on muscle biopsy, of which six patients had a change in the diagnosis: in 3 cases clinical suspicion was mitochondrial myopathy and histologic diagnosis revealed to be metabolic myopathies (n = 2) and congenital myopathy (n = 1); in the three remaining cases clinical suspicion were inflammatory myopathy, congenital myopathy and muscular dystrophy and histologic results were metabolic myopathy on the first two and congenital myopathy on the last. Of patients with isolated neuromuscular symptoms, one presented mitochondrial myopathy, three muscular dystrophies, one congenital myopathy, one inflammatory myopathy, seven unspecific myopathic alterations and 17 had normal biopsies.

Twenty-nine patients presented unspecific biopsy results; of those 10 patients had a definite diagnosis after further investigations and 19 remained with an indeterminate diagnosis. Of the patients with a normal histology (n = 50), 10 patients had, in fact, muscle disease as diagnosed by genetic testing/metabolic study (7 mitochondrial myopathies, 1 metabolic myopathy, 1 spastic paraparesis and 1 case of Charcot-Marie-Tooth Disease) and 40 patients remained without a definite diagnosis in the follow-up time.

After evaluation by two neurologists, muscle biopsy was considered to be helpful for diagnosis and/or treatment in 38 out of the 106 cases (35,8%).

Figure. Clinical suspicion in histologically normal biopsies.

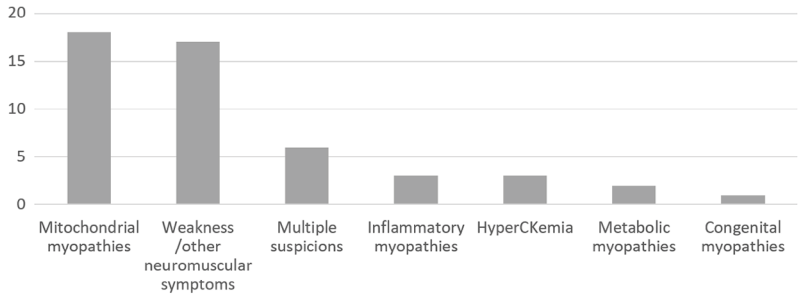

Table II. Diagnosis yield according to clinical suspicion.

	Clinical Suspicion *(n)*	Histologic diagnosis *(n)*	Diagnostic yield (%)
Inflammatory myopathy	8	3	37.5
Muscular dystrophy	7	2	28.6
Congenital myopathy	9	2	22.2
Metabolic myopathy	5	1	20
Neuromuscular symptoms	30	6	20
Multiple suspicions	11	2	18.2
HyperCKemia	7	1	14.3
Mitochondrial myopathy	29	2	6.9

Discussion

In current series, muscle biopsy showed abnormalities in 52,8% of the cases. Among these, 42,9% permitted a diagnosis and 51,8% presented unspecific alterations, that translates a diagnostic yield of 22,6%. Furthermore, in 35,8% of the patients MB was helpful in diagnosis/ treatment approach.

As mentioned above, in this cohort a definite diagnosis was obtained in 22,6%. These results show large heterogeneity in the literature, ranging from 22 to 80,4% [2-5]. Currently, given the advances brought by molecular diagnosis, MB has come to second line evaluation, being even questioned in some pathological groups [1]. For instance, looking for muscular dystrophies, the advances in Next Generation Sequencing (NGS) changed the diagnostic algorithm, with MB being performed only for confirmation of genetic findings or in cases when genetic studies are negative [1]. In our series, 9 MB were requested with clinical suspicion of muscular dystrophy; of these, 2 had already been submitted to

genetic testing which was negative, and biopsy contributed to establish a definite diagnosis.

One important biopsy indication remains metabolic myopathies where early diagnosis leads to earlier treatment and lower morbimortality. In our series, a diagnosis of metabolic myopathy was obtained in 5 cases, one Pompe disease and 4 McArdle diseases. These diagnoses are of upmost importance given the fact that they change clinical approach: for McArdle disease avoiding extenuating exercises along with some dietary measures can improve substantially quality of life; whereas for Pompe disease a treatment is available. Unfortunately, our patient with Pompe disease died soon after biopsy, before treatment could be started.

In our series, 6,6% (n = 7) of biopsies were requested for asymptomatic hyperCKemia, with a definite diagnosis being obtained in just one case. Literature shows large heterogeneity, showing that in asymptomatic patients with high CK serum values alone, the probability of muscle biopsy leading to diagnosis can range between 7 and 70% [6].

Our series showed also a large number of normal biopsies (47,2%). Previous studies have pointed to the importance of biopsy indication as the main determinant for usefulness of results [4]. Similar to what Sujka et al found, in our study inflammatory clinical suspicion presented higher diagnostic yield; indeed, the four patients in which treatment was changed after MB suffered from inflammatory myopathies. Nevertheless, it is important to acknowledge that a normal MB does not exclude neuromuscular pathology [1] and that facing a high clinical suspicion, other diagnostic approaches must be pursued. That was the case of the 10 patients in whom a diagnosis was obtained by genetic and metabolic testing after normal muscle biopsy. Also, regarding normal biopsies, 36% (n = 18) were requested for suspected mitochondrial myopathy. This data is understandable in light of the highly variable clinical expression of this group of myopathies and also because muscle biopsy allows histologic and histochemical analyses, but also biochemical analysis of the respiratory enzyme complexes and genetic testing. Moreover, 11 of these 18 patients were under 5 years old and ragged-red fibers are usually absent in muscle biopsies of children under this age [7].

The main limitation of our study is its retrospective nature, with undetailed and with lack of clinical data in several cases. Also, as a tertiary center, biopsies performed are requested from different institutions and pediatric sub-specialties, with different pre- biopsy investigations, which constitutes a limitation to reach a diagnosis.

Conclusions

Investigation of children with neuromuscular disorders is complex, challenging and often requiring a muscle biopsy. In our series diagnostic yield of muscle biopsies was 22,6%, although it was useful either in diagnostic or therapeutic approaches in 35,8%. In the future, with advances of molecular techniques, muscle biopsy indications will probably decrease although it will still be an important tool in several neuromuscular diseases, as well as in the description and confirmation of new diseases identified by genome and exome sequencing.

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Rendimiento diagnóstico de las biopsias musculares en la población pediátrica: experiencia de un centro terciario

Introducción. La biopsia muscular es un examen importante en la investigación de enfermedades neuromusculares, aunque su rendimiento diagnóstico puede ser decepcionante.

Objetivo. Analizar el rendimiento diagnóstico de las biopsias musculares en la población pediátrica.

Pacientes y métodos. Se analizó retrospectivamente una base de datos de un laboratorio terciario de neuropatología para identificar a pacientes (mayores de 18 años) sometidos a biopsia muscular entre enero de 2015 y agosto de 2019. Se evaluaron los datos demográficos, la presentación clínica, el diagnóstico, el tratamiento y el seguimiento.

Resultados. Se incluyó a 106 pacientes, de los que el 52,8% (*n* = 56) eran varones. La mediana de edad fue de 6 años (rango intercuartílico: 10 años). Los pacientes se dividieron en ocho grupos, según sospecha diagnóstica clínica: miopatías mitocondriales (*n* = 29), miopatías congénitas (*n* = 9), miopatías inflamatorias (*n* = 8), distrofias musculares (*n* = 7), valores elevados de creatincinasa en el suero (*n* = 7), miopatías metabólicas (*n* = 5), otros síntomas neuromusculares (*n* = 30) y múltiples sospechas clínicas (*n* = 11). La biopsia fue normal en 50 pacientes. De los restantes, 27 mostraron características diagnósticas específicas, y el 88,9% (*n* = 24) permitió un diagnóstico definitivo: distrofias musculares (*n* = 7), miopatías metabólicas (*n* = 5), miopatías congénitas (*n* = 4), miopatías inflamatorias (*n* = 4), miopatías mitocondriales (*n* = 3) y atrofia muscular espinal (*n* = 1). La histología llevó a un cambio de tratamiento en cuatro pacientes. La mediana de seguimiento fue de un año (rango intercuartílico: 2 años).

Conclusiones. El rendimiento diagnóstico de biopsia fue del 22,6% y fue útil en la orientación diagnóstica o terapéutica en el 35,8%. Las técnicas moleculares llevaron a una disminución de las indicaciones de biopsia muscular, pero ésta sigue siendo una herramienta importante para el diagnóstico de enfermedades neuromusculares.

Palabras clave. Atrofia muscular espinal. Biopsia muscular. Distrofia muscular. Enfermedades neuromusculares. Miopatías.