Safety and yield of muscle biopsy in pediatric patients in the modern era

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Muscle and skin biopsies are commonly used diagnostic procedures in the evaluation of neuromuscular and genetic disorders. However, few modern reports have documented their diagnostic yield and clinical utility. We reviewed our experience at a tertiary care center.

Methods: We retrospectively studied consecutive pediatric patients who underwent muscle biopsy at our institution between January 2008 and April 2012. Of 169 patients, 97 (57%) were male, and the median (range) age was 7 years (9 days to 18 years). In 101 patients (60%), a pathologic diagnosis was made. Histologic results of biopsy were completely normal in 45 patients (27%). Minimal abnormalities not sufficient to make a definitive pathologic diagnosis were reported in 23 patients (14%). Sensitivity and specificity of preoperative electromyography in detecting muscle pathology were 58% and 56%, respectively. No complications occurred from the use of general anesthesia. The only complication was a right femoral vein laceration when the right vastus medialis muscle was chosen as a biopsy site.

Conclusion: Muscle biopsy in children is safe and useful in establishing the best management plan for patients with suspected neuromuscular disorders. This finding contradicts those of previous studies.

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pathologic diagnosis, and pathologic changes sufficient to make a pathologic diagnosis. These categories were based on the neuromuscular pathologist’s description of the muscle histology. We avoided using the terms specific and nonspecific to report the histologic results, because a nonspecific pathologic diagnosis may still be enough to make a specific clinical diagnosis.

We defined the clinical diagnosis as a specific clinical diagnosis made by the clinician (e.g., neurologist or geneticist) on the basis of the findings of the muscle histologic analysis and clinical findings. Suggested diagnoses based on the muscle histologic results were made by the clinician when the results were not enough to make a specific clinical diagnosis but raised the possibility of other clinical entities that warranted more detailed investigations; these suggested diagnoses were not included under the definition of the specific clinical diagnosis. Therefore, it is possible to have a pathologic diagnosis but not a clinical diagnosis. In this study, we included inborn errors of glycogen and lipids and lysosomal storage disease under the category of metabolic myopathies. Mitochondrial myopathies were considered a different category.

Safety was assessed by documenting the development of intraoperative or postoperative complications, with specific attention to the development of malignant hyperthermia (MH) or rhabdomyolysis and the use of volatile agents for anesthesia. Sensitivity, specificity, and positive and negative predictive values of EMG were calculated by comparing the results of EMG with those of the histologic diagnosis from muscle biopsy, which was considered the diagnostic standard. When measuring these parameters, the result of EMG, designated as normal or abnormal, was compared with the result of muscle pathology, designated as normal or abnormal. Statistical analysis was performed using JMP statistical software version 9.0.1 (SAS Institute, Inc).

2. Results

Our search identified 169 pediatric patients, 97 (57%) of whom were male. The median age of our study population was 7 years (range, 9 days to 18 years). The main presenting symptoms were neuromuscular-related symptoms— including weakness, muscle cramps, muscle stiffness, and rhabdomyolysis—in 54% of patients (n = 91) (Fig. 1). Other presentations included developmental delay (36%), hypotonia (23%), seizures (19%), high serum creatinine kinase level (14%), and abnormal gait (11%). Five percent of patients had other symptoms, such as hypoglycemia, positive autoantibody test, failure to thrive, progressive neurologic deterioration, and unexplained lactic acidosis. Some patients had multiple symptoms; the most common combination was hypotonia and developmental delay, which was reported in 27 patients (16%).

The neurologist was the referring physician for 89% of patients (n = 151); the rest were from the rheumatology and medical genetics departments (8 and 10 patients, respectively). Mitochondrial disorders represented the most commonly made preoperative diagnosis (n = 50), followed by metabolic myopathies (n = 36). Other preoperative diagnoses were muscular dystrophy, myasthenia gravis, other neuromuscular junction abnormalities, and inflammatory myopathies.

EMG was performed before muscle biopsy in 68 patients (40%); 71% of the EMG procedures were performed in the right upper and lower extremity muscle groups. Results of EMG were abnormal in 36 patients (including neuropathic pattern, myopathic pattern, and nonspecific abnormality). Comparing results of EMG with those of skeletal muscle biopsy, EMG showed a sensitivity of 58%, specificity of 56%, positive predictive value of 69%, and negative predictive value of 44% in detecting some type of muscle pathology.

In most cases, the site of the muscle biopsy was on the contralateral site of the EMG. The left side was chosen in 139 cases (82%), with 105 (62%) of all biopsies taken from the left vastus lateralis muscle (Table 1). The left and right vastus lateralis muscle together made up 73% of all biopsied muscles.

The only reported intraoperative complication was a femoral vein laceration, which occurred when the biopsy was obtained from the left vastus medialis muscle. The surgeon fainted as the muscle was being cut and the change in direction of the scissors caused the femoral vein laceration. The laceration was repaired primarily without postoperative bleeding or thrombosis; duplex ultrasonography on postoperative day 1 and at 12 months was used to confirm patency, and physical examination revealed no swelling, fibrosis, or other significant findings. No cases of MH or rhabdomyolysis occurred, even when EMG showed myopathic patterns and when volatile agents were used during general anesthesia. No postoperative complications occurred, such as wound infection, hematoma, or reoperation.

All 169 specimens contained adequate tissue for pathologic evaluation, as determined by the muscle laboratory. In 101 patients (60%) the pathologist was successful in reaching a pathologic diagnosis. Type 2 fiber atrophy (n = 16) and type 1 fiber atrophy (n = 13) were the most commonly identified entities (29% of the

![Fig. 1. Presenting Symptoms in Study Patients (N = 169). CK indicates creatine kinase.](image-url)
Discussion

DNA analysis.

suspicion for a mitochondrial disease. Twenty of these biopsies
muscle biopsy.

enzymatic analysis of the frozen muscle tissue, genetic studies, and
diagnoses that were subsequently investigated, including further
diagnosis, the muscle biopsy was helpful in suggesting other clinical
finding was also evident on the pathologic examination of the
muscle biopsy.

The pathologic diagnosis was helpful in making a specific clinical
diagnosis in 55 patients (33%). In the patients without a clinical
diagnosis, the muscle biopsy was helpful in suggesting other clinical
diagnoses that were subsequently investigated, including further
enzymatic analysis of the frozen muscle tissue, genetic studies, and
fibroblast cultures.

In 50 patients, the muscle biopsy was obtained because of clinical
suspicion for a mitochondrial disease. Twenty of these biopsies
showed no features suggesting mitochondrial myopathy. In 13 of the
patients, the frozen muscle tissue was used for further studies of
mitochondrial cytopathy, such as respiratory chain and mitochondrial
DNA analysis.

3. Discussion

Muscle biopsy in children is relatively common, and we aimed to
review our institution’s experience with this procedure to determine
the benefit to our patients. Evaluation of a child with a neuromuscular
or genetic disorder can be extensive and invasive because of the
ambiguity of the presenting symptoms and the broad differential
diagnosis. In a study by Reynolds et al. [1], the results of muscle biopsy
in patients with suspected neuromuscular diseases were normal or
showed nonspecific abnormality in more than 64% of the patients. A
disease-specific therapeutic treatment plan based on the results of the
muscle biopsy was recommended in only 19% of patients, 50% of
whom had an inflammatory myopathy [1]. A later study showed an
even lower diagnostic yield of 8% [3].

In contrast, we found muscle biopsy to be beneficial on several
levels. A definitive pathologic diagnosis can be made on the basis of
the biopsy findings, and the pathologic finding often contributes
substantially to the disease-management strategy. The muscle biopsy
carried favorably to diagnosis in most of our patients. The
pathologic diagnosis was definite in most cases (60%); 14%
showed some pathologic changes in the muscle that were not
enough to make a pathologic diagnosis, and biopsy results were
normal in 27%. The pathologic diagnosis was helpful in making a
specific clinical diagnosis in 55 patients (33%). In 114 patients, the
histologic results – even normal and inconclusive results – helped
in suggesting alternative clinical diagnoses and directing further
investigations. Even if no clinical diagnosis is made based on the
results of muscle biopsy, certain pathologic findings are extremely
helpful for the physician both in ruling in or out other diagnostic
possibilities and from a management standpoint. This finding
contradicts the pediatric surgical literature in which changes in
therapy after muscle biopsy were considerably lower; in a recent
study, 8% of patients had changes in therapy, and authors
concluded that muscle biopsy is inconsistently useful [3]. Another
advantage is that the harvested muscle tissue can be stored and
used at a later time, if need arises, for enzyme-level analysis or
detailed genetic studies.

In addition to its utility, skeletal muscle biopsy performed under
general anesthesia was safe in our study, with no reported
complications related to anesthesia, even when volatile agents
were appropriately used in those patients. At our institution,
pediatric anesthesiologists are available at all times for patients
aged 18 years or younger. It is presumed that patients undergoing
muscle biopsy for neuromuscular disorders are at risk for MH,
rhabdomyolysis, or both, when volatile agents are used as general
anesthetic. In a previous study from our institution, among 271
patients who underwent muscle biopsy for suspected neuromuscu-
lar disorder, with volatile anesthetic agents used as the general
anesthetic, no patients exhibited signs or symptoms of MH or
rhabdomyolysis [4]. Only 1 patient had histologic evidence of
rhabdomyolysis, which occurred before the use of the volatile
agent. The estimated risk of MH developing in a patient with
suspected neuromuscular disorder as a result of exposure to volatile
anesthetic agents during muscle biopsy is approximately 1% or less
[4]. Therefore, we continue our recommendation that general
anesthesia using volatile agents can be safe when obtaining muscle
biopsy in children with suspected neuromuscular disorder.

Overall, we had no sampling issues. All of the obtained biopsy
specimens were adequate for histologic examination, as determined
by the neuromuscular pathologist and the muscle laboratory. The
vastus lateralis muscle was the most common muscle biopsied
because most of the muscle symptoms involve the proximal
musculature and the muscle itself does not have a major vessel or
nerve nearby. We encountered only 1 intraoperative complication,
which was a right femoral vein laceration that was primarily repaired
when the right vastus medialis muscle was biopsied. Although the
complication had no sequelae, postoperative duplex ultrasonography
was necessary to ensure vein patency the day after biopsy and 1 year
later. For future prevention of such a complication, we do not
recommend biopsy of the vastus medialis muscle because of its

Table 1
Location of Muscle Biopsies (N = 169).

<table>
<thead>
<tr>
<th>Biopsy Site</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vastus lateralis</td>
<td>123 (73)</td>
</tr>
<tr>
<td>Deltoid</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Triceps</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Vastus medialis</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Biceps femoris</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Others*</td>
<td>8 (5)</td>
</tr>
</tbody>
</table>

* Rectus abdominis, gastrocnemius, or gluteus medius.

total pathologic diagnoses). Other diagnoses are shown in Table 2.
Pathologic analysis of the muscle biopsy suggested dystroglycano-
pathy in 5 patients, 3 of whom harbored a mutation in the FKRP
(fukutin-related protein) gene.

Biopsy results were histologically normal in 45 patients (27%). In
23 patients (14%), biopsy results showed minimal abnormalities not
sufficient to make a diagnosis. These abnormalities include small
grouping of type 1 fibers, overreaction of a small group of fibers to
nonspecific esterase, abnormal distribution or decreased activity of
oxidative enzymes, and scant inflammatory cell infiltrate.

Concomitant skin biopsy from the incision edge was obtained in
71 patients. Skin biopsy electron microscopic examination confirmed
the presence of lysosomal storage disease in 1 patient. Interestingly,
this finding was also evident on the pathologic examination of the
muscle biopsy.

The pathologic diagnosis was helpful in making a specific clinical
diagnosis in 55 patients (33%). In the patients without a clinical
diagnosis, the muscle biopsy was helpful in suggesting other clinical
diagnoses that were subsequently investigated, including further
enzymatic analysis of the frozen muscle tissue, genetic studies, and
fibroblast cultures.

In 50 patients, the muscle biopsy was obtained because of clinical
suspicion for a mitochondrial disease. Twenty of these biopsies
showed no features suggesting mitochondrial myopathy. In 13 of the
patients, the frozen muscle tissue was used for further studies of
mitochondrial cytopathy, such as respiratory chain and mitochondrial
DNA analysis.

Table 1
Location of Muscle Biopsies (N = 101).

<table>
<thead>
<tr>
<th>Specific Diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 fiber atrophy</td>
<td>16</td>
</tr>
<tr>
<td>Type 1 fiber atrophy</td>
<td>13</td>
</tr>
<tr>
<td>Denervation pattern</td>
<td>11</td>
</tr>
<tr>
<td>Reinnervation</td>
<td>9</td>
</tr>
<tr>
<td>Deinnervation and reinnervation</td>
<td>8</td>
</tr>
<tr>
<td>Myopathy (nonspecified)</td>
<td>7</td>
</tr>
<tr>
<td>Inflammatory myopathy</td>
<td>6</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>6</td>
</tr>
<tr>
<td>Increased fat content of the muscle fibers</td>
<td>5</td>
</tr>
<tr>
<td>Alphadystroglycanopathy</td>
<td>5</td>
</tr>
<tr>
<td>Type 1 fiber predominance</td>
<td>3</td>
</tr>
<tr>
<td>Chronic myopathy (muscular dystrophy)</td>
<td>3</td>
</tr>
<tr>
<td>Glycogen storage disease (McArdle and type 1B)</td>
<td>2</td>
</tr>
<tr>
<td>Centronuclear myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Minocore disease</td>
<td>1</td>
</tr>
<tr>
<td>Becker muscular dystrophy</td>
<td>1</td>
</tr>
<tr>
<td>Lysosomal storage disease (ceroid lipofuscinos)</td>
<td>1</td>
</tr>
<tr>
<td>Myotubular myopathy; congenital myasthenia gravis</td>
<td>1</td>
</tr>
<tr>
<td>Congenital myopathy</td>
<td>1</td>
</tr>
<tr>
<td>Dysferlinopathy</td>
<td>1</td>
</tr>
</tbody>
</table>
proximity to major vessels and nerves in the femoral triangle, if other muscles can be used.

EMG is another tool in the evaluation of muscle disorders. However, although EMG can be used to diagnose a peripheral neuropathy or myopathy in infants with hypotonia, normal EMG results are fairly common in the setting of confirmed muscle disorders. Therefore, muscle biopsy is often needed to help diagnose myogenic alterations. Early-onset myopathies sometimes may show a neurogenic EMG pattern, but this should not invalidate a clinical diagnosis of myopathy; this result may also indicate the need for muscle biopsy [5]. Therefore, we are not surprised by our findings of sensitivity, specificity, and positive and negative predictive values for EMG compared with biopsy in detecting evidence of myopathy in the pediatric population; other reports have shown similar EMG findings [5]. We routinely perform EMG on the contralateral side of the muscle biopsy to avoid any possibility of needle myopathy, which could give false-positive results. Although, ideally, the correlation should be done in the same muscle, this would not be optimal for the just-mentioned reason.

Skin biopsy, which is often requested at the same time as muscle biopsy, is easy to obtain while performing muscle biopsy. The skin biopsy specimen can be used for electron microscopy, which in the current study confirmed the diagnosis of lysosomal storage disease for one of the patients. Interestingly, the diagnosis was also confirmed by muscle biopsy. In most cases, electron microscopy reveals normal cellular ultrastructure, so it is not always helpful, but having the sample means that the obtained skin tissue can be used subsequently for fibroblast culture.

This study had several limitations. It is a retrospective study with the associated patient-selection bias. Our institution is a tertiary referral center with a dedicated muscle laboratory and pediatric anesthesiologists. Therefore, our results and the safety of the muscle biopsy procedure may be different from those at other centers with different expertise.

4. Conclusion

We find that muscle biopsy is consistently useful in helping our pediatric patients. The surgeon’s viewpoint of the muscle biopsy result is different from the pediatric neurologist’s or rheumatologist’s. What may be nonspecific or inconclusive on a pathology report may actually be considered conclusive and specific from the primary caregiver’s perspective. In this matter, we disagree with most of the reported literature about the diagnostic yield of muscle biopsy; these previous studies reported limited usefulness of muscle biopsy, but we consider the results of the muscle biopsy to contribute substantially to disease management for the patient. Even if a definitive pathologic or clinical diagnosis is not made, the suggestion and/or exclusion of other possibilities is invaluable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jpedsurg.2014.02.079.

References