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

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ABSTRACT

Background: Muscle and skin biopsies are commonly used diagnostic procedures in the evaluation of pediatric 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.
Results: 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.

Muscle and skin biopsies are two of the most frequently used diagnostic procedures in the evaluation of neuromuscular and genetic disorders in children. However, few modern reports have documented the diagnostic yield and clinical utility of skeletal muscle biopsy. Those reports published to date state the diagnostic yield to be very low indeed (36%) [1]. Furthermore, it is an invasive and costly procedure. Therefore, the need for muscle biopsy in children in the modern era should be evaluated; we performed the current study with this aim. We also evaluated the use of electromyography (EMG) in our patients who underwent muscle biopsy.

1. Methods

This study was approved by the Mayo Clinic Institutional Review Board. We retrospectively searched our patient database for the medical records of consecutive pediatric patients (age ≤18 years) who underwent diagnostic skeletal muscle biopsy at Mayo Clinic, Rochester, Minnesota, between January 2008 and April 2012. No patients who underwent a muscle biopsy were excluded on any basis. Study data were collected and managed using REDCap electronic data capture tools hosted at our institution [2].

From the medical records of included patients, we collected data on age, sex, presenting symptoms, preoperative EMG results, site of muscle biopsied, concomitant performance of skin biopsy, intraoperative or postoperative complications, histologic diagnosis of the muscle biopsy, electron microscopy result of the skin biopsy, and the resultant diagnosis and treatment given.

All biopsies were performed in the operating room under general anesthesia by pediatric surgeons according to a previously specified protocol (see Appendix A). This includes specification by the referring physician of the muscle to undergo biopsy and the need for skin biopsy. On our electronic surgical listing, a specific marker exists for all muscle biopsies; once checked, this automatically alerts the muscle laboratory in advance to anticipate a specimen. All muscle specimens are checked for adequate size (length, width, depth) according to a predetermined checklist designed specifically for pediatric muscle biopsies. The specimen should be received in the muscle laboratory within 30 min.

We categorized the pathologic diagnosis into 3 categories: normal pathology, minimal change not sufficient to make a definitive

Abbreviations: EMG, electromyography; MH, malignant hyperthermia.
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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 (eg, 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

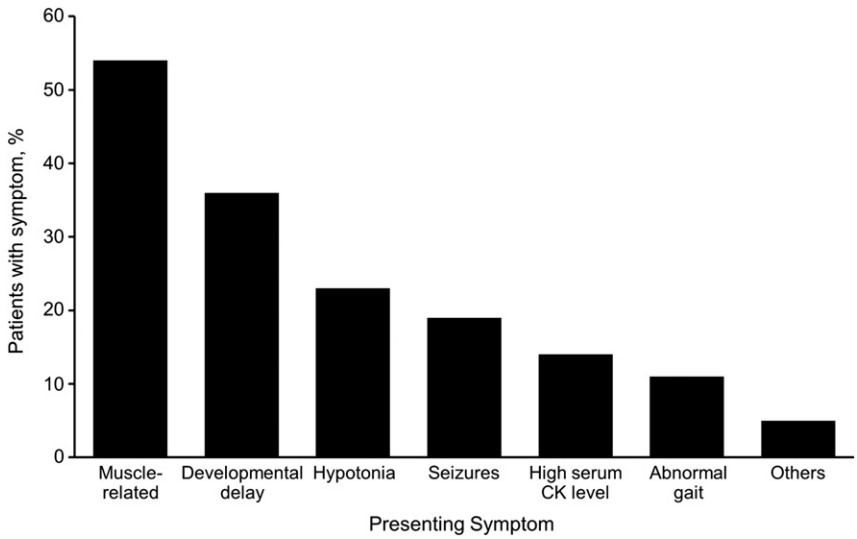

Fig. 1. Presenting Symptoms in Study Patients (N = 169). CK indicates creatine kinase.