Journal of Pediatric Surgery 53 (2018) 489–492

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Impact of muscle biopsy on diagnosis and management of children with neuromuscular diseases: A 10-year retrospective critical review

Sivapol Thavorntanaburt [a], Jantima Tanboon [b,c], Surachai Likasitwattanakul [a,c], Tumtip Sangruchi [b,c], Ichizo Nishino [d], Monawat Ngerncham [e], Niramol Tantemsapya [e], Oranee Sanmaneechai [a,c,*]

[a] Division of Neurology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[b] Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[c] Neurogenetic Network, Division of Health Service Research and Development, Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[d] Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan
[e] Division of Pediatric Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 1 June 2017
Accepted 11 June 2017

Key words:
Muscle biopsy
Weakness
Myopathy
Muscular dystrophy
Complication

ABSTRACT

Background: Muscle biopsy facilitates morphologic, biochemical, and ultrastructural analysis of muscle for the purpose of making definitive neuromuscular diagnosis. However, muscle biopsy is an expensive, invasive, time-consuming, and resource-dependent procedure. The need for general anesthesia in children also increases the risks associated with this procedure. The aim of this study was to investigate the benefits of muscle biopsies performed over a 10-year period, with a focus on indications, suspected and histopathologic diagnosis, and impact on diagnosis and management decisions.
Methods: We retrospectively reviewed results of muscle biopsies performed in children at our center during the 2004 to 2014 study period. Clinical presentations, biopsy complications, pathologic results, and changes in management decision were reviewed and analyzed.
Results: Biopsies from 92 patients were included. Mean age of patients was 7.1 years, and 66.3% were male. There were no perioperative complications, and definitive diagnosis was made in 74 patients. Regardless of whether pathologic changes were found or not, information gained from muscle biopsy significantly impacted prognosis and subsequent genetic counseling.
Conclusions: Muscle biopsy is a safe and useful diagnostic tool in children suspected of having neuromuscular diseases, especially in those with muscle diseases. Definitive pathologic diagnosis helps to optimize treatment, counseling, and surveillance.
The type of study and level of evidence: Study of diagnostic test: level 1.

Evaluation for neuromuscular disease (NMD) consists of history taking and physical examination, which are supplemented, as needed, by neurophysiologic studies, other laboratory tests, muscle biopsy, and genetic testing. Muscle biopsy facilitates morphologic, biochemical, and ultrastructural analysis of muscle for the purpose of making definitive neuromuscular diagnosis. However, muscle biopsy is an expensive, invasive, time-consuming, and resource-dependent procedure. Given that healthcare-related budgets and resources are limited in Thailand, the decision whether or not to refer a patient for muscle biopsy is carefully considered. Even at a national tertiary care teaching hospital like ours, referral for muscle biopsy is made only after a careful evaluation of the risks and benefits, and after a determination has been reached that the procedure has a high probability of yielding meaningful and necessary diagnostic information. Currently, there are contradicting opinions regarding the advantages and benefits of performing muscle biopsies in pediatric patients with suspected neuromuscular diseases. Some studies have reported limited diagnostic yield and impact on therapy [1–3], with other studies reporting that muscle biopsy is a safe and useful tool for establishing definitive diagnosis in up to 70% of cases [4,5].

The aim of this study was to investigate the benefits of muscle biopsies performed over a 10-year period at our center, with a focus on indications, suspected and histopathologic diagnosis, and impact on diagnosis and management decisions. The overriding objective was to elucidate the value of this diagnostic option in a pediatric setting for the benefit of pediatric surgeons.

* Corresponding author at: Division of Neurology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand. Tel.: +66 2 419 5890; fax: +66 2 418 2238.
E-mail addresses: oranee141@gmail.com, oranee141@hotmail.com (O. Sanmaneechai).

http://dx.doi.org/10.1016/j.jpedsurg.2017.06.006
0022-3468/

1. Methods

The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University. This retrospective review was conducted in children aged ≤15 years who had muscle biopsy performed at Siriraj Hospital during the 2004–2014 study period. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. Of the pediatric muscle biopsy patients identified in our center's Department of Pathology database, only those patients referred by the Division of Neurology of the Department of Pediatrics with suspected NMD were included in the analysis. In Thailand, genetic testing for NMD is either of low yield or not available. Only 65%–75% of patients with Duchenne muscular dystrophy (DMD) can be identified with multiplex ligation-dependent probe amplification (MLPA), while 95% of patients with spinal muscular atrophy (SMA) can be identified using restriction fragment length polymorphism (RFLP) technique. As such, the pediatric neurologists at our center will request for a muscle biopsy when these tests are negative. Demographic characteristics, clinical presentations, laboratory results, muscle biopsy site(s), perioperative complications, histopathologic results, definite diagnosis, and management information were extracted, recorded, and analyzed.

All muscle biopsies were performed in the operating room under general anesthesia by a pediatric surgical team using open biopsy technique. A 2 cm longitudinal incision was made over the targeted muscle(s) and was carried down to the muscle fascia. A 1 × 1 × 1 cm muscle specimen was obtained and sent for pathologic examination. The muscle, fascia, and skin were then closed layer by layer using absorbable suture materials. In most cases, this inpatient biopsy procedure required hospital admission for 1–2 days. Muscle biopsy site(s) was(were) specified by a pediatric neurologist.

Fresh tissue muscle specimens were delivered to the Department of Pathology within 30 min of excision for freeze-fixation using isopentane and liquid nitrogen. Routine histopathologic and enzyme histochemical stains, including hematoxylin and eosin (H&E), modified Gomori trichome (mGT), reduced nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR), succinic dehydrogenase (SDH), cytochrome c oxidase (COX), acid phosphatase, alkaline phosphatase, nonspecific esterase, oil red O, periodic acid-Schiff (PAS), and myosin ATPase, were performed on all specimens. Additional stains, including Congo red, myophosphorylase, phosphofructokinase, as well as immunohistochemistry and electron microscopy were performed in selected cases. All muscle biopsies were interpreted by 1 of 2 muscle pathologists (TS, JT) at our center. In difficult cases, biopsies were reviewed with a senior pathologist (IN) from the Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan.

Pathologic diagnosis was classified into 1 of the following 3 groups: normal pathology, minimally abnormal pathology insufficient for making a pathologic diagnosis, and abnormal pathology. Abnormal pathology was classified according to the anatomic structure of the motor unit, including anterior horn cell, peripheral nerve, neuromuscular junction, and muscle. Definite diagnosis was made by pediatric neurologists based on clinical findings and muscle histopathologic results and/or genetic testing. The impact of muscle biopsy results on the case was classified into one or more of the following classifications: a change in or refinement of the diagnosis, any change(s) to current medication, initiation of genetic counseling or clinical surveillance, and/or ability to advise regarding prognosis.

Statistical analysis was performed using PASW Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used, with results being reported as either mean ± standard deviation or number and percentage.

2. Results

Ninety-two children who underwent muscle biopsy for suspected NMD were identified and enrolled. Two patients had two separate muscle biopsy operations owing to inadequate size of tissue specimen from the first operation. Mean age of patients at the time of biopsy was 7.1 years (range: 2 months to 15 years), and 66.3% of patients were male. The most common biopsy site was quadriceps femoris muscle (Table 1). No perioperative complication in any included patient was noted.

Table 1
Demographic and clinical characteristics of children with suspected neuromuscular diseases who underwent muscle biopsy.

Characteristics	(N = 92)
Age at biopsy (years), mean ± SD	7.1 ± 4.2
Male gender, n (%)	61 (66.3%)
Biopsy site, n (%)	
Quadriceps	85 (92.4%)
Biceps	1 (1.1%)
Gastrocnemius	6 (6.5%)

Clinical presentations are shown in Table 2. The most common presenting symptom was muscle weakness (90%). Other clinical presentations included gross motor developmental delay, abnormal gait, hypotonia, and high creatine kinase (CK). Some patients presented with a combination of symptoms. Infants and toddlers commonly presented with hypotonia and gross motor developmental delay, while older children more commonly presented with muscle weakness and gait abnormality. Elevated serum CK was observed in 57 patients (62%). Referring physicians were pediatric neurologists in 96% of biopsy requests, with a few exceptions from pediatric geneticists who acted as the referral physician when a pediatric neurologist was not available. Muscle diseases were the most common preoperative clinical diagnosis (89.2%) (Table 3).

There were 74 (80.3%) patients with definitive abnormal pathologic findings, including 66 (71.6%) with muscle disease and 8 (8.7%) with neurogenic disease. In the remaining 18 patients, 8 (8.7%) showed no abnormal histologic changes and 10 (11%) had only minimal changes that were not sufficient for making a definitive diagnosis. Minimal abnormalities included minimal variation in fiber size, mild type-2 muscle fiber atrophy, and minimal inflammatory cell infiltration.

Muscle biopsy results confirmed existing clinical diagnosis in 59 (64%) patients. However, in 12 (20%) patients, muscle biopsy facilitated a more specific diagnosis, especially in congenital myopathy cases. Among those 12 cases that were more specifically diagnosed, a definite diagnosis of nemaline was made in 2 cases, and a diagnosis of central core, centronuclear, myofibrillary and myotubular myopathy was made in one case each. In one patient with central core myopathy, the more specific diagnosis resulted in the issuing of a caution regarding the patient's increased risk of developing life-threatening malignant hyperthermia in response to certain anesthetic drugs. One patient with a clinical diagnosis of muscular dystrophy was more specifically diagnosed as Emery–Dreifuss muscular dystrophy. This finding led to surveillance for cardiac conduction defect, and appropriate electrophysiologic intervention was instituted.

Based on muscle biopsy results, clinical diagnosis was changed in 33 (36%) patients. In patients whose histopathologic findings facilitated a diagnosis of inflammatory myopathy, immunomodulation treatment was given, which led to their full recovery. Even in patients with normal

Table 2
Clinical presentations of 92 children with suspected neuromuscular diseases who underwent muscle biopsy.

Characteristics	n (%)
Weakness	83 (90.2%)
Gross motor developmental delay	29 (31.5%)
Abnormal gait	24 (26.1%)
Hypotonia	20 (21.7%)
Ptosis	5 (5.4%)
Respiratory failure	3 (3.3%)
Seizure	2 (2.2%)