Muscle Disorders in Pediatric Patients in King Chulalongkorn Memorial Hospital

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The authors retrospectively studied histopathologic findings and diagnoses of muscle specimens taken from 188 pediatric patients presenting with clinical neuromuscular disorders in King Chulalongkorn Memorial Hospital between August 1991 and December 2003. Eighty patients (67.8%) established the definite diagnosis by histopathological findings of muscle specimens. About 18.6, 17.7, 7.6, 5.9, 5.0, 3.4, 2.5 and 1.7 percent of the total number of patients were diagnosed as Duchenne muscular dystrophy, Spinal muscular atrophy, Congenital myopathies, Mitochondrial disease, Inflammatory myopathies, Becker muscular dystrophy, Congenital muscular dystrophy and Vacuolar myopathies respectively. Since the histopathological findings in muscle helped to establish the definite diagnosis in most pediatric patients in the present study, thus muscle biopsy is essential for establishing a definite diagnosis in any patient with a suspected neuromuscular disorder.

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Muscle disorders can be broadly subdivided into myopathies, in which the pathology is confined to the muscle itself and neuropathies or neurogenic atrophies, in which muscle weakness is secondary to an abnormality along the course of the peripheral nerve, from the anterior horn cell to the neuromuscular junction. The myopathies have included muscular dystrophies, congenital myopathies, metabolic myopathies, inflammatory myopathies and a few disorders affecting predominantly muscle. Accurate diagnosis in muscle disorders is dependent on a careful clinical assessment and followed by the appropriate investigation including serum enzymes analysis, electrodiagnosis, ultrasound and magnetic resonance imaging, muscle biopsy, electron microscopy and molecular genetics. However, the diagnosis of specific neuromuscular diseases in infants and children is often confirmed histologically by muscle biopsy. The present study reports the histopathological diagnosis and findings of muscle specimens taken from 118 pediatric patients in King Chulalongkorn Memorial Hospital between August 1991 and December 2003.

Material and Method

The authors retrospectively studied histopathologic findings and diagnoses of muscle specimens taken from pediatric patients presenting with clinical neuromuscular disorders in King Chulalongkorn Memorial Hospital between August 1991 and December 2003. All infants and children presenting with clinical neuromuscular disorders and paternal permission were investigated to make a definite diagnosis by creatine kinase level analysis, electrophysiologic studies and muscle biopsy. Electron microscopy and appropriate molecular technology were selectively performed according to their diagnostic utility and cost. Almost all of the muscle biopsies had been taken from the quadriceps (vastus lateralis) by pediatric surgeons using the open procedure under general anesthesia. The muscle specimens were prepared and histochemically stained using standard techniques described elsewhere [(1)]. Histopathological findings and diagnoses were verified by either one or two of the investigators (SJ and SS). Finally, the definite diagnosis of patients was made by using the standard criteria which was dependent on clinical assessment, electrodiagnosis, muscle biopsy findings, electron microscopy and molecular genetics study [(2)].

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Results

One hundred and eightheen pediatric patients presenting with clinical neuromuscular disorders were muscle biopsied during the study

period. Fifty seven percent were boys and forty three percent were girls. The mean age of patients at the time of biopsies was 5.4 years, ranging from 1 month to 14 years. The result of histopathological findings and diagnoses of all muscle biopsies are summarized in Table 1.

Eighty patients (67.8%) of 118 patients had a definite diagnosis, whereas 38 patients (32.2%) had no definite diagnosis. Thirty three patients (27.8%) had muscular dystrophies (22 Duchenne, 4 Becker, 1 Fascioscapulohumeral, 2 Limb girdle, 3 congenital and 1 non-specific). One of 3 congenital muscular dystrophy had absent merosin staining in muscle fibres and abnormal MRI brain imaging in the cerebral white matter. Nine patients (7.6%) had congenital myopathies (2 Central core disease, 3 Nemaline and 4 Congenital fibre type disproportion). Twenty one patients (17.7%) had spinal muscular atrophies (10 type I or severe, 6 type 2 or intermediate, 3 type III or mild and 2 undetermined severity). Six patients (5%) had inflammatory myopathies (2 polymyositis, 1 dermatomyositis and 2 unknown etiology). Seven patients (5.9%) had mitochondrial diseases and 3 of 7 patients were diagnosed as Leigh syndrome. Immunohistochemical staining for cytochrome oxidase (COX) activity, 2 of 7 patients with mitochondrial disease had COX - negative fibres. On electron microscopy the mitochondrial abnormality was confirmed in all patients with mitochondrial diseases. Two patients were diagnosed as vacuolar myopathies due to muscle biopsies demonstrated vacuoles in muscle fibres on light microscopsy. However, PAS staining for glycogen were normal, thus the vacuolar content could not be identified.

Table 1. Histopathological findings and diagnoses of pediatric patients

Histopathological findings/diagnoses	no. (%)
Muscular dystrophies	
Duchenne	22 (18.6)
Becker	4 (3.4)
Fascioscapulohumerral	1 (0.8)
Limb girdle	2 (1.7)
Congenital	3 (2.5)
Non-specific	1 (0.8)
Congenital myopathies	
Central core disease	2 (1.7)
Nemaline	3 (2.5)
Congenital fibre type disproportion	4 (3.4)
Spinal muscular atrophies	
Type I	10 (8.5)
Type II	6 (5.0)
Type III	3 (2.5)
Undetermined type	2 (1.7)
Charcot-Marie-Tooth disease	1 (0.8)
Inflammatory myopathies	
Polymyositis	2 (1.7)
Dermatomyositis	1 (0.8)
Unknown etiology	3 (2.5)
Metabolic myopathies	
Mitochondrial diseases	7 (5.9)
Vacuolar myopathies	2 (1.7)
Stiff baby syndrome	1 (0.8)
Miscellaneous	
Myopathic changes	2 (1.7)
Neurogenic changes	1 (0.8)
Atrophic muscles	3 (2.5)
Type II fibre atrophy	9 (7.6)
Type I fibre predominance	3 (2.5)
Type II fibre predominance	1 (0.8)
Non-specific findings	19 (16.1)
Total	118 (100)

Discussion

The most common muscle disease in children in the present study was Duchenne Muscular Dystrophy (DMD). DMD is the most common X-linked disorder affecting approximately 1 in 3500 male births [3]. It is an x-linked recessive muscle wasting disorder caused by mutation in the dystrophin gene, located on the short arm of the x-chromosome at XP 21.2 [4]. The patient usually presents with severe muscle degeneration, calf pseudohypertrophy, progressive muscle weakness leading to loss of ambulation before 13 years of age and death by the third decade. Although molecular techniques, direct detection of mutation and linkage analysis is sufficient comfirmation of an XP 21 myopathy[5-7], muscle biopsy remains the definite means of confirming the tissue diagnosis. The second common muscle disease in the present study was Spinal muscular atrophy (SMA). SMA is one of the most common autosomal recessive diseases (incidence 1 in 6,000 livebirths). The locus of the gene responsible for SMA has been mapped to chromosome 5 q 13.3 [8,9]. SMA is characterized by degeneration of the anterior horn cell of the spinal cord leading to symmetrical muscle weakness. The SMAs are classified depending on the age of onset, the maximum muscular activity achieved and age of survival. Type I (Werdnig-Hofmann disease) is the most severe form with onset at birth or within 6 months of age, unable to sit unaided and death before 2 years of age. Type II (intermediate form) with onset between 3 and 15 months of age, able to sit but unable to stand or walk unaided and survival beyond 2 years. Type III (Kugelberg-Welander disease) is the mildest form with onset after 2 years, able to stand alone and a more benign course [10]. Atrophic fibres are a consistent feature of muscle biopsy in SMA, and involved

both type I and type II muscle fibres. The atrophic fibres tend to be rounded in outline, are usually clustered in large groups (large group atrophy), often whole bundles, and are interspersed with fasicles containing clusters of large type I fibres. Congenital myopathies refer to a group of primary muscle diseases that is present from birth or in the neonatal period with weakness and hypotonia of a nonprogressive or only slowly progressive nature and subdivided further according to the findings on pathologic study of the muscle[11]. Since the congenital myopathies share a number of common clinical features, it is not usually possible to determine the precise variety of myopathy on the basis of clinical feature alone. The muscle biopsy with histochemistry staining and electronmicroscopy serves as the most discriminating diagnostic study. The first clue to diagnosis of mitochondrial myopathy is usually the finding in biopsy sections of ragged - red fibres on Gomori trichrome, or of intensively reactive fibres with oxidative enzymes, or of COX - negative fibres on staining for COX activity [12] or of ultrastructural abnormalities of mitochondria in muscle biopsy specimens from patients with myopathies or multi-system disorders. For a practical approach, all children presenting with a suspected clinical neuromuscular disorder should have their history and physical examination taken inorder to come to a provisional diagnosis or restricted differential diagnosis. Laboratory investigations are then selected according to their diagnostic utility, cost, and associated risks. Measurement of serum creatine kinase is a useful but non specific test. It should be measured before doing an electromyogram, because this procedure might elevate the creatine kinase value. Serum creatine kinase is elevated in children with active primary muscle disease. With chronic myopathies, the creatine kinase value is related to the stage of illness. As with serum creatine kinase, the increment of the serum aspartate transaminase, alanine aminotransferase, and lactate dehydrogenase concentration also reflects the egress of the protein through defective muscle fiber membranes in active primary muscle disease. Electrophysiological studies such as electromyogram and measurement of nerve conduction velocity may help to determine 1) the level of the lesion (nerve, neuromuscular junction, or muscle) 2) What muscles and nerves are involved ? and 3) How active is the disease process? The gold standard of investigation in muscle disorders is the muscle biopsy. Since the histopathological findings in muscle help to establish the definite diagnosis in most pediatric patients in the present study, thus muscle biopsy is essential for establishing a definite diagnosis in any patient with a suspected neuromuscular disorder. The site of the muscle biopsy should be selected based on the distribution of muscle weakness, as assessed clinically. The muscle should not be so severely affected that it is largely replaced by connective tissue or fat with little residual evidence of the underlying muscle disorder, or so little affected that it does not reflect the changes. Electron microscopy and appropriate molecular technology should be selectively performed according to their diagnostic utility and cost.

Conclusion

Muscle disorders can be broadly subdivided into myopathies and neuropathies or neurogenic atrophies. Accurate diagnosis in this wide array of disorders is dependent on a careful clinical assessment followed by the appropriate investigations, i.e. serum creatine kinase analysis, imaging of muscle, electrophysiological studies, muscle biopsy and molecular genetics. The present study demonstrated that muscle biopsy and histopathological findings of muscle specimens could establish the definite diagnosis in 67.8 percent of pediatric patients with suspected neuromuscular disorders. Muscle biopsy is, thus, essential for establishing a definite diagnosis in any patient with a suspected neuromuscular disorder.

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โรคกล้ามเนื้อในผู้ป่วยเด็ก โรงพยาบาลจุฬาลงกรณ์

สังคม จงพิพัฒน์วณิชย์, ธีระศักดิ์ นรภักดิ์สุนทร, ชนพ ช่วงโชติ

จากการศึกษาย้อนหลังผลพยาธิสภาพของชิ้นกล้ามเนื้อผู้ป่วยเด็กที่มีอาการแสดงทางคลินิก สงสัยว่าจะเป็นโรคกล้ามเนื้อที่โรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนสิงหาคม พ.ศ.2534 ถึง เดือนธันวาคม พ.ศ.2546 จำนวน 118 ราย พบว่า ผลการตรวจพยาธิสภาพชิ้นกล้ามเนื้อสามารถช่วยวินิจฉัยโรคได้แน่นอนถึงร้อยละ 67.8 ของผู้ป่วย โดยพบผู้ป่วยเป็นโรค Duchenne muscular dystrophy, Spinal muscular atrophy, Congenital myopathies, Mitochondrial disease, Inflammatory myopathies, Becker muscular dystrophy, Congenital muscular dystrophy และ Vacuolar myopathies ร้อยละ 18.6, 17.7, 7.6, 5.9, 5.0, 3.4, 2.5 และ 1.7 ตามลำดับของจำนวนผู้ป่วยทั้งหมด ดังนั้นการตัดชิ้นกล้ามเนื้อเพื่อย้อม histochemistry และตรวจโดยกล้องจุลทรรศน์และกล้องจุลทรรศน์อิเลคตรอนจึงเป็นสิ่งจำเป็นในการช่วยวินิจฉัยโรคในผู้ป่วยที่มีอาการแสดงทางคลินิกสงสัยว่าจะเป็นโรคกล้ามเนื้อ