Electromyography (EMG) Accuracy Compared to Muscle Biopsy in Childhood

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Reports show wide variability of electromyography (EMG) in detecting pediatric neuromuscular disorders. The study’s aim was to determine EMG/nerve conduction study accuracy compared to muscle biopsy and final clinical diagnosis, and sensitivity for myopathic motor unit potential detection in childhood. Of 550 EMG/nerve conduction studies performed by the same examiner from a pediatric neuromuscular service, 27 children (ages 6 days to 16 years [10 boys; M:F, 1:1.7]) with muscle biopsies and final clinical diagnoses were compared retrospectively. Final clinical diagnoses were congenital myopathies (5 of 27, 18%), nonspecific myopathies (biopsy myopathic, final diagnosis uncertain; 6 of 27, 22%), congenital myasthenic syndrome (3 of 27, 11%), juvenile myasthenia gravis (1 of 27, 4%), arthrogryposis multiplex congenita (2 of 27, 7%), hereditary motor and sensory neuropathy (1 of 27, 4%), bilateral peroneal neuropathies (1 of 27, 4%), and normal (8 of 27, 30%). There were no muscular dystrophy or spinal muscular atrophy patients. EMG/nerve conduction studies had a 74% agreement with final clinical diagnoses and 100% agreement in neurogenic, neuromuscular junction, and normal categories. Muscle biopsies concurred with final diagnoses in 87%, and 100% in myopathic and normal categories. In congenital myasthenic syndrome, muscle biopsies showed mild variation in fiber size in 2 of 3 children and were normal in 1 of 3. EMG sensitivity for detecting myopathic motor unit potentials in myopathies was 4 of 11 (36%), greater over 2 years of age (3 of 4, 75%), compared to infants less than 2 years (1 of 7, 14%), not statistically significant (P = .0879). EMGs false-negative for myopathy in infants < 2 years of age were frequently neurogenic (3 of 6, 50%). In congenital myopathies EMG detected myopathic motor unit potentials in 40%, with false-negative results neurogenic (20%) or normal (40%). Because our study has no additional tests for active myopathies, for example Duchenne muscular dystrophy genetic testing, our sensitivity for myopathies is lower than if we used a more global view. In conclusion, EMG detection rate of myopathic motor unit potentials at a young age was low, improving in children over 2 years of age. In neurogenic and neuromuscular junction disorders, the EMG has a very high detection rate. In children with mild to moderate neurogenic EMG findings and normal nerve conduction, a myopathy should always be considered.

Keywords: electromyography; muscle biopsy; neuromuscular disorders

E valuation of a neuromuscular disorder begins with the clinical history and examination and is supplemented by electromyography (EMG; nerve conduction studies, neuromuscular junction studies, and concentric needle electromyography), muscle biopsy, and other laboratory tests. The EMG and muscle biopsy are complementary investigations. EMG evaluates peripheral motor unit physiology from different areas, disease severity and distribution, and the best muscle for biopsy.1,2 It assists categorizing neuromuscular disorders into neuropathic (anterior horn cell or peripheral nerve), neuromuscular junction, or myopathic, and localizes peripheral nerve pathology. Muscle biopsy examines morphology, histopathology, and biochemistry in a small area.

Although electromyography is useful in floppy infants,3,4 accuracy in children varies between 10 and 98%,4,5 lower in myopathic processes at an early age (10-64%) than neuropathic ones (65-100%).5-8 This finding reflects subjectivity in EMG reporting6 technical issues in children4 and patchy distribution of some myopathies.2,9 Shorter duration, smaller amplitude motor unit action potentials,1-12 and irregular contraction13 are typical technical problems at a young age.

We retrospectively reviewed a pediatric EMG database, selecting only EMG/nerve conduction studies with concomitant muscle biopsies plus complete hospital clinical records. EMG/nerve conduction studies and muscle biopsy were correlated, and accuracy of both was confirmed by agreement with the final clinical diagnosis. EMG accuracy
in detecting myopathic motor unit potentials at an early age was determined.

Methods

Subjects

Five hundred fifty EMGs performed over 5 years between 1999 and 2005 were reviewed from pediatric neuromuscular services at the Tel-Aviv Sourasky Medical Center, Tel Aviv, and the Hadassah Hebrew University Hospital, Mount Scopus, Jerusalem. EMG/nerve conduction studies were included only if they had (1) muscle biopsies and (2) hospital records with final clinical diagnoses, follow-up visits, and laboratory data. The clinical history and examination was used as the benchmark for a reliable final diagnosis and reviewed by a pediatric neurologist. Supplementary investigations were performed to confirm the clinical diagnosis. The cohort was grouped into final clinical diagnostic categories, and data were compared. Age-appropriate reference ranges for the electrodiagnostic studies were used.

Clinical Data

Final diagnoses were obtained from medical records and determined by history, serial physical examinations, and clinical course. Electromyographic findings contributed to final diagnoses only if they were unambiguous and consistent with the clinical history, examination, and other results. Final diagnoses were categorized into 4 groups: myopathic, neurogenic (anterior horn cell/peripheral nerve), neuromuscular junction disorder, and normal (no peripheral motor unit disorder).

Electrophysiology

All EMGs were performed by the same examiner, aware only of the general clinical problem without access to biopsies or other laboratory data. In most patients, nerve conduction studies included 1 sensory and 2 motor in the lower limbs and 1 sensory and 1 motor in the upper limbs. Distal and proximal supramaximal compound muscle action potentials, distal sensory nerve action potentials, distal latencies, distal segment motor velocities, and late responses were recorded using surface electrodes.

Concentric needle electromyography was performed in 2 lower and 2 upper limb proximal and distal muscles on the right side in most patients. Quantitative motor unit potential analysis was not performed due to technical difficulties at a young age. EMG studies were performed using Dantec keypoint 4 (Medtronic A/S, Skovlunde, Denmark).

EMGs were classified as (1) Myopathic—needle study showing: short-duration, polyphasic, low-amplitude motor unit potentials, usually with early appearance of maximum interference pattern in weak muscles and normal or abnormal spontaneous activity. (2) Neurogenic—nerve conduction study: normal, demyelinating (focal or diffuse), or axonal; needle EMG: abnormal spontaneous activity, increased duration large amplitude motor unit potentials with or without polyphasia, and reduced recruitment. (3) Neuromuscular junction disorder—repetitive stimulation of ulnar (abductor digiti minimi), spinal accessory (upper trapezius), or facial (nasalis) nerves showing >10% decrement or >50% increment in compound muscle action potential amplitudes at 3 Hz and 30 Hz stimulation, respectively, and postactivation exhaustion. A stimulated single-fiber EMG from obicularis occuli or frontalis muscles was diagnostic if increased jitter occurred in >2 of 20 potentials (each with a mean consecutive difference >55 microseconds) or average mean consecutive difference of 20 potentials >40 microseconds. (4) Nonspecific—not specific for either neurogenic or myopathic disease; nerve conduction study: low-amplitude compound muscle action potentials with normal sensory amplitudes, isolated abnormal late responses; needle EMG: isolated scattered abnormal spontaneous activity. (5) Normal.

Pathology

Open muscle biopsies performed from the left vastus lateralis muscle in all patients were reported by the same pathologist, except 1 with normal findings and diagnosis. Histochemical stains included hematoxylin and eosin, Gomori trichrome, periodic acid–Schiff, Oil Red O, nicotinamide adenine dinucleotide tetrazolium reductase, and ATPase at preincubations of pH 4.3, 4.6, 9.4. Respiratory chain enzyme studies were performed on children with suspected mitochondrial disorders. Pathologic findings were grouped according to categories modified from Kang et al. These groupings are in 3 categories. (1) Myopathic definite: with features such as necrosis, regeneration, fibrosis, fiber atrophy or hypertrophy, fiber splitting, centrinucleation, or specific structural changes typical of congenital myopathies. (2) Myopathic probable: mild myopathic features such as a few regenerating fibers, mild to moderate variation in fiber size, mildly increased central nuclei, scattered atrophic fibers, or fibrosis. (3) Neurogenic: small angular fibers or fiber type grouping and atrophy without myopathic changes; or Normal.

Results

A total of 27 patients were identified (10 boys and 17 girls; M:F, 1:1.7). Final clinical diagnoses were congenital myopathies (5, 18%), nonspecific myopathies (biopsy myopathic, final diagnosis uncertain; 6, 22%), congenital myasthenic syndrome (3, 11%), juvenile myasthenia gravis...
(1, 4%), arthrogryposis multiplex congenita (2, 7%), hereditary motor and sensory neuropathy (1, 4%), bilateral peroneal motor neuropathies (1, 4%) and normal (8, 30%). Age range at the time of the EMG was 6 days to 16 years (average, 4 years 7 months, ± SD 4 years 7 months; and median, 3 years 6 months. Of 27 children, 17 were < 5 years old, 7 of 27 were 5 to <10 years, and 3 of 27 were 10-16 years of age.

Main Referral Causes
The main referral causes were hypotonia (20 of 27, 74%), developmental delay (9 of 27, 33%), muscle weakness (7 of 27, 26%), severe motor clumsiness (5 of 27, 19%), orthopedic problems (4 of 27, 15%), other (failure to thrive, central apnea or ataxia; 4 of 27, 15%), and contractures (2 of 27, 7%).

Referral Causes by Category
There are 4 categories of referral causes. (1) Myopathic: hypotonia (10 of 11, 91%), developmental delay (7 of 11, 64%), muscle weakness (6 of 11, 55%), dislocated hips and club feet (3 of 11, 27%), and failure to thrive or central apnea (2 of 11, 18%). (2) Neuromyotonic: arthrogryposis and club feet (3 of 4, 75%); cataract, ataxia, ptosis, and dwarfism (1 of 4, 25%). (3) Neuromuscular junction disorder: 3 of 4 with congenital myasthenic syndrome had a chronic history of tiredness on effort and proximal muscle weakness without diplopia, and 1 of 4 with juvenile myasthenia gravis had progressive external ophthalmoplegia and ptosis. (4) Normal: hypotonia (8 of 8, 100%), severe motor clumsiness (3 of 8, 38%), developmental delay (2 of 8, 25%), and dislocated hips (1 of 8, 13%).

Myopathic category. All 11 children with myopathic muscle biopsies were diagnosed clinically as having myopathy (Table 1). There were no muscular dystrophy patients. Biopsies showed 5 congenital myopathies (myotubular, multi-minicores, actinopathy, and 2 with fiber type disproportion), and 6 myopathic biopsies with final diagnosis uncertain. The EMG detected myopathy in 4 of 11 children (sensitivity, 36%): 2 congenital myopathies (actinopathy,19 multi-minicores, and 2 with myopathies of unknown etiology.

False-negative EMG findings in myopathy were normal in 3 of 11 children (27%); 2 congenital myopathies [both fiber type disproportion], and 1 myopathy of unknown cause) and mild to moderate neurogenic in 4 of 11 children (36%; 1 with congenital myopathy [myotubular] and 3 with myopathy of uncertain etiology).

Age at EMG in this category ranged from 6 days to 9 years (mean, 2 years 1 month). Infants <2 years showed a low EMG detection rate for myopathic motor unit potentials 1 of 7 (14%), increasing to 3 of 4 (75%) over 2 years of age.

Neurogenic category. These children had a diagnosis of a neurogenic disorder based on their clinical findings of arthrogryposis, areflexia, or muscle atrophy. EMGs were concordant with this final diagnosis in 4 of 4 children (100%). Muscle biopsy was neurogenic in 1 of 4 with arthrogryposis multiplex congenita and normal in 3 of
Juvenile myasthenia gravis

In 8 children, EMGs and muscle biopsies were increased jitter and blocking, and a normal muscle biopsy. One child (9 years of age) with juvenile myasthenia gravis (MuSK antibody-negative) had scattered myopathic motor unit potentials on EMG. In 1 of 3, the biopsy was normal. Single-fiber EMG in 1 showed increased jitter with blocking. One child (9 years, boy, progressive external muscle weakness since infancy; Gowers sign, facial weakness, kyphoscoliosis, hyperlordosis, F1) with decreased muscle action potential to a single stimulus. Repetitive stimulation confirmed the diagnosis in all 4 with a 44-73% decrement. Supramaximal compound muscle action potential amplitudes were normal at rest, 25-41% decrement at 3 Hz. Supramaximal compound nerve stimulation confirmed the diagnosis in all 4 with a 44-73% decrement.

Table 2. Neuromuscular Junction Disorders: Clinical, Electrophysiologic, and Biopsy Features

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Antibody</th>
<th>RNS</th>
<th>EMG</th>
<th>Single-Fiber EMG</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital myasthenic syndrome</td>
<td>Acetylcholine receptor antibody-neg (Rapsyn N88K mutation neg.)</td>
<td>PTD 17% (abductor digitii minimi), 25% (trapezius)</td>
<td>Normal</td>
<td>+ VFS</td>
<td></td>
</tr>
<tr>
<td>9 y, girl, ++ progressive prox. weakness since infancy; Gowers sign, + facial weakness, kyphoscoliosis, hyperlordosis, F1</td>
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<tr>
<td>14 y, girl, + prox. weakness, motor delay, F1</td>
<td>Acetylcholine receptor antibody-neg.</td>
<td>PTD 29% (trapezius). + M</td>
<td>Normal</td>
<td>+ VFS</td>
<td></td>
</tr>
<tr>
<td>13 y, girl, mainly upper limb prox. weakness, + facial weakness, tiredness on effort, F1</td>
<td>Acetylcholine receptor antibody-neg.</td>
<td>PTD 41% (trapezius). Normal</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile myasthenia gravis</td>
<td>Acetylcholine receptor antibody-neg. MuSK pos.</td>
<td>PTD 28% (nasalis) 30 Hz = 44% decr.</td>
<td>Normal</td>
<td>+ VFS</td>
<td></td>
</tr>
<tr>
<td>9 y, boy, progressive external ophthalmoplegia, dysphagia</td>
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NOTE: RNS = repetitive nerve stimulation (right side); prox. = proximal; + = mild; ++, marked; FI = familial inheritance; MuSK = anti–muscle-specific tyrosine kinase antibodies; PTD = pre-tetanic decrement with 3 Hz stimulation; M = myopathic; decr. = decrement; J = increased jitter; B = blocking; MCD = mean consecutive difference; VFS = variation in fiber size.

4 children (75%) with hereditary motor and sensory neuropathy, bilateral peroneal neuropathies, and arthrogryposis multiplex congenita.

Neuromuscular junction disorder category. The 4 children in this group had muscle biopsies as part of an initial evaluation for myopathy (Table 2). Later a neuromuscular transmission disorder was suspected. This diagnosis was confirmed by a positive response to edrophonium (tensilon test) and pyridostigmine (Mestinon®). Repetitive nerve stimulation confirmed the diagnosis in all 4 with a 25-41% decrement at 3 Hz. Supramaximal compound muscle action potential amplitudes were normal at rest, and none had a stimulus-linked repetitive compound muscle action potential to a single stimulus. Repetitive stimulation at 30 Hz showed a 44-73% decrement.

Three children had congenital myasthenic syndrome (aged 8-14 years; acetylcholine receptor antibody-negative). None had ophthalmoplegia or dysphagia. In 2 of 3, the muscle biopsy showed mild variation in fiber size (1 with scattered myopathic motor unit potentials on EMG). In 1 of 3, the biopsy was normal. Single-fiber EMG in 1 showed increased jitter with blocking. One child (9 years of age) with juvenile myasthenia gravis (MuSK antibody-positive; acetylcholine receptor antibody-negative) had increased jitter and blocking, and a normal muscle biopsy. Normal. In 8 children, EMGs and muscle biopsies were concordant with a normal final diagnosis (no peripheral motor unit disorder).

Correlation of Findings

EMG accurately concurred with final diagnoses in 20 of 27 (74%) and was discordant in 7 children (26%). All patients with discordant EMGs (false-negatives) had diagnoses of myopathy. In these 7 children, the EMGs findings were normal (3 of 7; 43%) or neurogenic (4 of 7; 57%).

Biopsies agreed with final diagnoses in 20 of 23 (87%): myopathies, 11 of 11; normal, 8 of 8; and neurogenic, 1 of 4. Muscle biopsies show mild to severe variation of fiber size in congenital myasthenic syndrome, but because they are not used to diagnose neurotransmission disorders they were excluded from this analysis.

EMG detection rate of myopathic motor unit potentials in infants with myopathic muscle biopsies below 2 years of age was low 1 of 7 (14%), increasing to 3 of 4 (75%) in children over 2 years of age. Statistical significance was not attained due to the low number of children. EMG sensitivity for detecting mild-to-moderate neurogenic EMG findings occurred frequently in the myopathy category (8 of 11, 73%). In young children < 2 years of age with myopathy, 3 of 6 (50%) of the false-negative EMGs were neurogenic.

Discussion

The study showed that EMG had a very high diagnostic yield in neurogenic and neuromuscular junction disorders with a low detection rate for myopathies in young children. The EMG was very reliable (100%) in excluding pathology in normal children, also noted in other infant studies (67-100%). The 74% EMG concordance with clinical diagnoses in our study lies between the 55% of an arthrogryposis multiplex congenita study, and 82-98% of other childhood studies. EMG sensitivity for detecting
myopathy at an early age in this series was 36%, similar to the 40% concordance in 1 hypotonic infant study, and between the 10-91% concordance in other childhood studies. We found the EMG detection rate of myopathy in infants < 2 years of age to be low (14%), increasing to 75% in children 2 to 9 years of age, confirming reports of lower EMG sensitivity for myopathy at an early age. A study of 498 children and adolescents by Hellmann et al also showed low (50%) EMG myopathic detection rates under 1 year of age, increasing to 64% by 1-5 years, and 91% by 5-16 years. Because our study has no additional tests for active myopathies, for example Duchenne muscular dystrophy genetic testing, our sensitivity for myopathy is lower than if we used a more global view. However, our study was specifically to show EMG sensitivity for myopathies in infants and children at a young age (10 of 11 children were < 5 years of age). We confirmed the view that congenital myopathies often have false-negative EMG findings at an early age.

False-negative EMGs in myopathies may be due to (1) technical issues at an early age, (2) patchy distribution of some myopathies, and (3) neurogenic EMG findings. Mild-to-moderate neurogenic EMG findings as the only EMG change in myopathy occurred in 36% of children (Table 1) and the pathophysiology of this has been described. Therefore, if the EMG shows only mild to moderate neurogenic findings in children with normal nerve conduction studies, a myopathy should always be considered.

The 100% EMG detection rate of neurogenic disorders in this study is similar to that found in other childhood studies (90-100%). In contrast, muscle biopsies were normal in most children in the neurogenic group because they were obtained at an early age and from proximal muscle (vastus lateralis), while early neurogenic pathology was distal in these children with peripheral neuropathy or distal arthrogryposis.

Repetitive nerve stimulation and single fiber EMG are often the only diagnostic studies in childhood neuromuscular junction disorders, particularly in congenital myasthenic syndromes (Table 2). Thus, false-negative (normal) studies in these patients may result in underdiagnosis. The high detection rate of neuromuscular junction disorders in this study reflects the older age of our patients as equivocal or false-negative results occur more commonly in young children. We found mild variation of fiber size in 2 of 3 congenital myasthenic syndrome patients, confirming the findings of Gurnett et al of mild to severe variation of fiber size.

We conclude that the electrodiagnostic test is useful in the correct indication. In neurogenic and neuromuscular junction disorders, the EMG has a very high detection rate in childhood and is accurate as a screening test in excluding motor unit pathology in hypotonic children. EMG detection of myopathic motor unit potentials compared to muscle biopsy at a young age (< 2 years) was low, improving in children > 2 years of age.

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References
