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Motor Unit Number Estimation in Infants and Children with Spinal Muscular Atrophy

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Abstract

Spinal muscular atrophy (SMA) is a disease of lower motor neurons. Motor unit number estimation (MUNE) is an electrophysiologic method to estimate the number of motor neurons innervating a muscle group. We applied the multiple point stimulation technique to the ulnar nerve–hypothenar muscle group to study lower motor neuron loss in 14 SMA subjects, including those presymptomatic, and varying from newborn through 45 years of age. Preliminary data support the value of MUNE to help understand the time course of motor neuron loss in SMA.

Keywords

motor neuron disease; motor unit number estimation (MUNE); spinal muscular atrophy (SMA)

Spinal muscular atrophy (SMA) is characterized by loss of lower motor neurons. It presents most frequently in infancy and early childhood and is divided into types based on severity of weakness.[12] The degree of lower motor neuron loss in the different types is predominantly inferential and cannot be determined from clinical assessments.[8,13,15] Clinical observations suggest an initial rapid loss followed by prolonged periods of stability in some individuals,[4,8,13,15] but subsequent rates of lower motor neuron loss are unknown. Life expectancy is markedly reduced, but varies greatly between and within types, and it is not known how survival is related to lower motor neuron loss.[15]

Motor unit number estimation (MUNE) is an electrophysiologic method to estimate the number of lower motor neurons innervating a group of muscles supplied by a nerve,[10] and is well suited to assess motor neuron loss in SMA. MUNE values are calculated from the ratio of the maximal compound muscle action potential (CMAP) to the average single motor unit potential (SMUP). MUNE principles and assumptions have been reviewed elsewhere.[2,10,14] We chose the multiple point stimulation technique and refined the procedure for use with infants and young children.

Methods

Our protocol had institutional review board approval. Patients and parents were fully informed; consent forms were signed by the parents of the ten subjects under age 6 years,

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both parental consent and subject assent forms were signed for two subjects 7 and 17 years old, and consent forms were signed by the three subjects over 18 years of age. In severely weak infants, MUNE was performed in conjunction with another clinically indicated procedure requiring sedation. Infants and children who could not cooperate with MUNE and were not undergoing other procedures were lightly sedated with intravenous doses of midazolam (0.1–0.2 mg/kg). They received blow-by oxygen, continuous electrocardiographic and pulse oximetry monitoring, and intermittent blood pressure measurement, and were observed during and after the procedure by a nurse or anesthesiologist. Some infants and children tolerated the procedure without sedation.

The multiple point stimulation technique is based on electrical activation of single motor axons in an all-or-none fashion. A sample of SMUPs was obtained by moving the stimulating electrode to multiple points along the motor nerve.[5] The ulnar nerve provided sufficient stimulation sites in infants. CMAP and SMUP responses were recorded with adhesive recording and reference electrodes over the hypothenar eminence. Nerve stimulation could usually be accomplished by bipolar surface stimulation. Needle stimulation was used when high current intensities from surface stimulation were required to achieve a maximal CMAP in infants with a high proportion of subcutaneous fat tissue, when a large stimulus artifact occurred, when inadvertent activation of the median nerve was noted, or when involuntary limb movements were problematic. A monopolar needle (cathode) was positioned close to the ulnar nerve in conjunction with a surface anode to activate the whole nerve for the CMAP and single axons with less current. Responses were considered all-or-none when they were present and stable (without fractionation) at one current level and absent at a lower level. MUNE calculations were based on negative peak areas.

Results

SMA subjects had homozygous deletions in the telomeric survival motor neuron gene (SMN1) on chromosome 5.[9] We previously studied presymptomatic subjects and patients with SMA types I, II, and III based on clinical criteria.[12] No complications occurred from sedation or MUNE testing. Infants and children tolerated the procedure with minimal or no visible discomfort, and no parent expressed undue concern. All subjects tested (or their parents) expressed willingness to return for repeat testing.

MUNE values were readily obtained except in one neonate with arthrogryposis (subject 4) in whom no CMAP or muscle twitch was elicited. Otherwise, between 5 and 13 SMUPs were collected for each subject. The same SMUP, defined as having an identical waveform, could frequently be activated from multiple sites along the nerve. When sedation was light, voluntarily activated SMUPs could frequently be recorded, and were often identical to many recorded during nerve stimulation. Low MUNE values were found in all symptomatic subjects. A 9-month-old infant (subject 2) diagnosed prenatally and studied prior to symptom onset had a normal MUNE value. Her symptomatic brother (subject 9) with SMA type II was studied at 2.5 years of age and had markedly reduced values. Subject 1, a clinically normal 16-day-old neonate diagnosed prenatally (two siblings with SMA type I died by 6 months of age) had a normal CMAP amplitude but a MUNE value less than 50%

of expected, suggesting lower motor neuron loss with compensatory collateral reinnervation in utero. Subject 11 was 45 years old and had a very low MUNE value number, supporting prolonged motor neuron survival in some cases.

Test–retest reliability was performed on subjects 2, 8, and 10 on the same or next day, and was found to show consistent values. CMAP amplitude values ranged widely and, although they correlated in a general sense with MUNE values, they did not correlate with SMA type or subject age. The CMAP and MUNE values in the control subject (subject 15) were very much higher than in symptomatic SMA subjects. SMUP values in SMA subjects varied widely. The average SMUP value for nine symptomatic SMA subjects was 0.18 mV compared with 0.04 mV in the control subject, indicating motor unit enlargement from collateral reinnervation.

Discussion

We have refined a MUNE technique to assess the number of motor units innervating a distal muscle group in infants and young subjects with SMA. The procedure is well tolerated and safe. These data cannot be obtained from CMAP amplitude or routine needle electromyography due to the effects of collateral reinnervation,[14] or from clinical observation or tests of function.[3,7] SMA has traditionally been considered to affect predominantly proximal muscle groups, but our data indicate severe involvement of distal muscles.

MUNE has only rarely been applied to SMA.[11] The multiple point stimulation technique addresses the issue of alternation, uses low stimulation intensities to collect SMUPs, and can be performed on any electromyography machine. Near-nerve stimulation, although invasive compared with surface stimulation, was better tolerated in some infants in whom higher levels of stimulation were required. MUNE determinations require approximately 20 min to perform.

We believe our results are technically sound and reflect the number of surviving lower motor neurons. Reduced numbers of voluntarily activated SMUPs supports severe lower motor neuron loss. Test–retest reproducibility was good, especially when values were low.[1,5] Our data from normal young subjects are limited, but the MUNE value is similar to adult values[10] and consistent with anatomic estimates.[6]

Our goal in refining MUNE testing in SMA infants and children is to assess the natural history of lower motor neuron loss. Preliminary data suggest that MUNE values fall to low levels early in the progression of weakness. Serial MUNE testing and correlation with functional status and other factors known to modify phenotype are pending. Informative endpoint measures for clinical trials in SMA are problematic, and MUNE may be promising, especially for presymptomatic subjects.

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Abbreviations

CMAP	compound muscle action potential
MUNE	motor unit number estimation
SMA	spinal muscle atrophy
SMN1	telomeric survival motor neuron gene
SMUP	single motor unit potential

Table 1

Demographic, clinical, and MUNE data.

Subject number	SMA type	Age	MUNE value (stimulation technique)*	CMAP NP area (mV.ms)/amplitude (mV)	Average SMUP NP area (mV.ms)/amplitude (mV)
1	Presymptomatic	16 days	87 (S)	16.9/5.9	0.18/0/0.05
2	Presymptomatic	9 months	401 (S)	16.1/6.7	0.04/0.03
			432 (S)	16.1/6.7	0.04/0.02
3	Presymptomatic	23 days	268 (S)	11.5/4.1	0.04/0.02
4	O/I	1 day	Not possible (S)	NR	
5	I	6 months	5 (NN)	1.2/0.54	0.23/0.11
		8 months	3 (S)	0.9/0.5	0.26/0.13
6	I	4 months	10 (NN)	2.4/0.9	0.24/0.12
			8 (S)	2.4/0.9	0.29/0.13
7		I3.5 months	11 (S)	1.6/0.26	0.07/0.03
		4.5 months	4 (S)	1.1/0.13	0.07/0.04
		4.5 months	6 (NN)	0.8/0.20	0.13/0.05
8	I	22 years	12 (NN)	2.6/0.70	0.22/0.08
			9 (NN)	2.9/0.73	0.31/0.10
9	II	2.5 years	16 (S)	5.3/2.0	0.33/0.13
10	II	19 years	9 (NN)	15.8/5.3	1.77/0.63
			20 (NN)	15.8/5.3	0.80/0.26
11	II	45 years	6 (S)	6.5/1.4	1.15/0.35
12	III	9 years	103 (NN)	22.2/6.8	0.22/0.12
13	III	4.5 years	50 (S)	20.4/7.5	0.41/0.13
14	III	17 years	76 (S)	9.0/3.6	0.12/0.07
15	Control	6.5 years	311 (S)	39.0/13.3	0.13/0.04

CMAP, compound muscle action potential; MUNE, motor unit number estimation; NP, negative peak; NR, not reported; NN, near-nerve stimulation; S, surface nerve stimulation; SMA, spinal muscular atrophy; SMUP, single motor unit potential.

CMAP and SMUP values expressed as negative peak area (mV.ms) and negative peak amplitude (mV) for clinical interpretation, but MUNE calculated from negative peak area values.