Corticomotoneuronal Integrity and Adaptation in Spinal Muscular Atrophy

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Objective: To gain further insight into disease pathophysiologic process and potential adaptations through investigating whether cortical dysfunction or plasticity is a feature of spinal muscle atrophy (SMA).

Design: Prospective, double-center study.

Setting: Outpatient clinics and research institute.

Participants: Clinical assessments, combined with threshold-tracking transcranial magnetic stimulation techniques, were completed in 11 genetically characterized patients with SMA.

Main Outcome Measures: Clinical, functional, and neurophysiologic variables were compared between the 11 patients with SMA types 2 and 3, 24 healthy control participants, and 81 patients with amyotrophic lateral sclerosis (ALS) serving as disease controls.

Results: Maximal motor-evoked potential amplitude as a percentage of the compound muscle action potential was significantly increased in patients with SMA compared with the healthy controls but was similar to that in ALS (SMA, mean [SE], 39.7% [4.0%]; ALS, 38.8% [2.8%]; controls, 20.3% [2.5%]; F=10.1; P<.001). In contrast, short-interval intracortical inhibition (SMA, 14.4% [1.6%]; ALS, 4.3% [1.8%]; controls, 17.0% [2.3%]; F=11.4; P<.001) and cortical silent-period duration (SMA, 204.4 [9.8] milliseconds; ALS, 182.7 [5.2] milliseconds; controls, 208.8 [3.7] milliseconds; F=4.8; P=.01), similar between SMA patients and healthy controls, were significantly larger when compared with the findings in ALS. Of relevance, peripheral disease burden as measured by the compound muscle action potential amplitude (SMA, 6.3 [0.8] mV; ALS, 5.9 [0.4] mV; controls, 11.8 [0.5] mV; F=35.5; P<.001) and Neurophysiologic Index (SMA, 0.7 [0.2]; ALS, 0.7 [0.1]; controls, 3.1 [0.2]; F=108.2; P<.001), were significantly reduced in both SMA and ALS patients when compared with healthy controls.

Conclusions: Taken together, findings from the present study suggest that despite spinal motoneuron degeneration there remains preservation of corticomotoneuronal function in SMA. The greater corticomotoneuronal projections to surviving spinal motoneurons likely represent an adaptive response to spinal motoneuron degeneration in SMA.

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PINAL MUSCULAR ATROPHY (SMA) is a neurodegenerative disorder of spinal motoneurons characterized clinically by muscle weakness and atrophy secondary to mutations in the survival motor neuron 1 gene (SMN1 (OMIM *600354; GenBank U18423).1 Although SMA presents as a pure lower motoneuron disorder, the survival motor neuron (SMN) protein, encoded by the SMN1 and SMN2 (OMIM *601627; GenBank NM_022875) genes, is expressed in the spinal cord and brain. Alterations in spinal circuitry, specifically, deafferentation of motoneurons,2 has been demonstrated to be an early pathophysiologic event in SMA and may contribute to motor dysfunction. There has been a general paucity of studies assessing the functional integrity of corticomotoneurons in SMA. Whether corticomotoneuronal dysfunction occurs in SMA has not been elucidated and remains of clear significance in developing a better understanding of disease pathophysiologic characteristics.

It is accepted that cortical plasticity may develop following lower motoneuron injury due to poliomyelitis3 and, for example, with spinal cord injury, and it appears to be a dynamic process.3-8 Specifically, abnormalities of cortical activation, with downregulation of intracortical interneuronal circuits, have been well documented following spinal cord injury. In contrast, the potential reorganization of the structure, function, and connections of the corticomotoneuron in response to peripheral neurodegeneration, or neuroplasticity,9 has also not been determined in SMA. Resolution of this issue may be of therapeutic significance for patients with SMA given that rehabilitation programs aimed at optimizing neuronal processing may improve motor function and thereby quality of life.
Cortical function may be clinically assessed using threshold-tracking transcranial magnetic stimulation (TMS) techniques.\textsuperscript{10} Separately, cortical dysfunction in the form of cortical hyperexcitability has been reported\textsuperscript{11,12} as part of the process of neurodegeneration in amyotrophic lateral sclerosis (ALS), an adult-onset disorder of motoneurons that in part resembles SMA.\textsuperscript{13} The development of cortical hyperexcitability in ALS was linked to neurodegeneration. In addition, cortical hyperexcitability appeared as a primary change before onset of clinical weakness in asymptomatic familial carriers of mutations involving the copper/zinc superoxide dismutase 1 (SOD1) gene.\textsuperscript{14} Consequently, the present study used novel threshold-tracking TMS techniques to assess whether cortical plasticity was evident in SMA and whether the reduced expression of the SMN protein in the central nervous system of patients with SMA was associated with the development of cortical hyperexcitability or, alternatively, reduced excitability.

**METHODS**

**PARTICIPANTS**

Prospective studies were undertaken in 11 adolescent and adult patients with SMA types 2 and 3. Diagnosis was confirmed by genetic testing with homozygous deletions of exons 7 and 8 in the SMN1 gene. By definition, patients with SMA type 2 manifested weakness after 6 months of age and the maximum motor milestone was the ability to sit. Those with SMA type 3 had symptomatic onset after 18 months of age and attained the ability to walk unaided.\textsuperscript{15} No patient was taking medications with central nervous system activity, for example, benzodiazepines or antidepressants, which are known to affect cortical excitability.\textsuperscript{16} All patients gave informed consent or assent to the procedures, which were approved by the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee.

Patients with SMA underwent clinical assessments of muscle strength using the Medical Research Council (MRC) sum score\textsuperscript{17} that incorporates 7 muscles on both sides (4 from the upper limbs and 3 from the lower limbs), with normal strength indicated by a total score of 70. The Spinal Muscular Atrophy Functional Rating Scale (SMAFRS)\textsuperscript{18} was used to assess the functional status of patients, with a maximum score of 50 indicating normal function. Hand function was evaluated using the Triggs hand function score,\textsuperscript{19} graded as follows: 0, normal; 1, mild to moderate hand weakness without impairment of dexterity; 2, weakness with significant impairment of dexterity (ie, difficulty with handwriting and buttoning clothes); and 3, marked weakness (major disability and loss of fine motor control). Muscle strength was clinically assessed using the MRC for the abductor pollicis brevis (APB) because this muscle was used for excitability testing.

**PERIPHERAL NERVE STUDIES**

Amplitude of the compound muscle action potential (CMAP) (peak to peak) was recorded from the APB muscle, as were distal motor and F-wave latencies, and the number of F-responses recorded in 20 trials was expressed as F-wave frequency. The CMAP provided an index of motor activation capacity against which cortically evoked motor responses could be compared. The Neurophysiological index (NI) was calculated according to an established formula\textsuperscript{20}: NI = CMAP amplitude (in millivolts) \times [F-wave frequency/distal motor latency (in milliseconds)].

**CORTICAL EXCITABILITY AND TMS THRESHOLD TRACKING**

Cortical excitability studies were performed using reported threshold-tracking TMS techniques.\textsuperscript{10} Briefly, a 90-mm circular coil was applied over the motor cortex and oriented to induce current flow in a posterior-anterior direction. The coil was adjusted until the optimal position for a motor-evoked potential (MEP) was obtained from the APB muscle. The site was marked to ensure constant placement of the coil, the coil position was fixed with a brace, and the patient's head was stabilized with cushioning. The setup was constantly monitored for movement throughout the experiment.

Magnetic currents were generated by 2 high-power magnetic stimulators that were connected to a device (BiStim; Magstim Company Ltd) that allowed conditioning and test stimuli to be independently set and delivered through one coil. The MEP was measured from peak to peak, and the threshold-tracking target was set to 0.2 mV,\textsuperscript{10} which is the midpoint of the steepest portion of the logarithmic stimulus-response curve. All neurophysiologic variables were recorded with the target muscle at rest. The target muscle was closely observed for the presence of voluntary activity as recorded by surface electrodes and also was viewed on a monitor; the participants were asked to relax the target muscle if the examiner noted the appearance of any voluntary activity.

Cortical excitability testing incorporated several measurements, from which various data could be extracted for analysis.

1. Resting motor threshold (RMT) was defined as the stimulus intensity required to produce and maintain the target MEP of 0.2 mV.
2. The stimulus-response curve was determined by increasing the intensity of the magnetic stimulus to the following levels: 60%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, and 150% RMT. Three stimuli were delivered at each level of stimulus intensity and MEP amplitudes were averaged. The absolute MEP reflects the sum and interaction of upper and lower motoneuron activity. To determine the corticometeroneuronal contribution, the peak-to-peak amplitude of the maximum MEP was expressed as a percentage of the peak-to-peak maximal CMAP amplitude obtained with supramaximal stimulation of the median nerve (millivolts) and reflected the density of the upper motoneuron projections on the anterior horn cell. Although the stimulus-response curve was recorded in all patients, the maximum MEP amplitude (as a percentage) and minimum MEP onset latency (milliseconds), were used for group comparisons.
3. Central motor conduction time (in milliseconds) was calculated according to the F-wave method.\textsuperscript{21}
4. Cortical silent period was induced by a single-pulse TMS while the patients performed a weak voluntary contraction. The duration of the silent period was measured from the beginning of the MEP to the return of electromyographic activity.\textsuperscript{22}
5. The function of intracortical inhibitory and excitatory circuits was assessed by applying subthreshold-conditioning stimuli set to 70% RMT at increasing interstimulus intervals, similar to previously devised paired-pulse TMS threshold-tracking protocols.\textsuperscript{10,23} Short-interval intracortical inhibition (SICI) was determined using sequential interstimulus intervals including 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, and 7.0 milliseconds. The SICI was measured as the increase in the test stimulus intensity required to evoke the target MEP and calculated off-line as follows:\textsuperscript{10,23,24} SICI = [(conditioned test stimulus intensity – RMT)/RMT] \times 100.
Intracortical facilitation was measured during interstimulus intervals of 10, 15, 20, and 30 milliseconds. Facilitation was measured as the decrease in the conditioned test stimulus intensity required to evoke the target MEP.

Recordings of CMAP and MEP were amplified and filtered (3 Hz to 3 kHz) using an alternating current amplifier (Grass ICP511; Grass-Telefactor, Astro-Med, Inc) and sampled at 10 kHz using a 12-bit data acquisition card (PCI-MIO-16E-4; National Instruments). Data acquisition and stimulation delivery (both electrical and magnetic) were controlled by QTRACS software (Institute of Neurology, Queen Square, London, England).

DATA ANALYSIS

Cortical excitability in patients with SMA was compared with that in 24 age-matched healthy individuals serving as controls (12 males; age range, 12-36 years; mean, 26.4 years) and, as disease controls, 81 patients with clinically probable or definite ALS with limb-onset disease (56 males; age range, 25-78 years; mean [SE], 56.6 [1.4] years; disease duration, 1.5 [0.2] years; mean [SE], 17.9 [2.0] years) as defined by the revised El Escorial criteria.24 Clinical staging of ALS was performed in all patients using the ALS-Francis Functional Rating Scale–Revised (ALSFRS-R; maximum score is 48 when there is no disability),25 MRC scores for assessment of disease severity were analyzed using the Spearman rank correlation test.

RESULTS

Clinical features for the patients with SMA are summarized in the Table. Clinical severity varied, ranging from mild to profound weakness, as did functional impairment, as reflected by the broad spectrum in MRC score (range, 0-49; median, 41). At the time of the study, 5 patients (45% of the total cohort) were independently ambulant. All patients with SMA reported infrequent (less than twice a month) or no muscle cramps or fasciculations. Clinical examination of the hand revealed generalized muscle wasting in patients with SMA in contrast to preferential split-hand wasting involving the APB and first dorsal interosseous muscles that is characteristic in patients with ALS. Of further relevance, as expected, there were no upper motoneuron clinical features in patients with SMA in contrast to those with ALS. In patients with ALS, the mean score on the ALSFRS-R was 39.3 (0.8), the MRC evaluation using the APB was 4.3 (0.1), and the Triggs hand score was 1 (0.2).

Table. Clinical Details for 11 Patients With SMA Types 2 and 3a

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Abbreviations: APB, abductor pollicis brevis; MRC, Medical Research Council; SMA, spinal muscular atrophy; SMAFRS, SMA Functional Rating Scale.

aMuscle strength was clinically assessed using the MRC score for the sum of deltoid, biceps, wrist extensors, APB, iliofemoral, quadriceps femoris, and tibialis anterior on both sides (normal strength scores 70). The patients had a mean (SE) age of 21.9 (1.3) years, SMAFRS score of 36.3 (4.1), total MRC score of 51.5, MRC APB score of 4.4 (0.1), age at presentation of 4.5 (1.3) years, disease duration of 17.9 (2.0) years, and Triggs hand score of 1.0 (0.2).

The CMAP amplitude (SMA, 6.3 [0.8] mV; ALS, 5.9 [0.4] mV; controls, 11.8 [0.5] mV; F = 35.5; P < .001) and NI (SMA, 0.7 [0.2]; ALS, 0.7 [0.1]; controls, 3.1 [0.2]; F = 108.2; P < .001) were significantly reduced in both SMA and ALS patients when compared with healthy controls (Figure 1) and confirmed a similar degree of peripheral disease burden across patients with SMA and ALS.

PERIPHERAL NERVE STUDIES

Reproducible MEPs were obtained in all patients with SMA. The central motor conduction time was similar across all groups (SMA, 6.0 [0.3] milliseconds; controls, 6.0 [0.3] milliseconds; ALS, 5.1 [0.2] milliseconds; F = 2.6; P = .08). The RMT, defined as the TMS intensity required to produce and maintain the target MEP response, was also similar between the groups (SMA, 54.0% [2.9%]; controls, 55.6% [1.6%]; ALS, 57.2% [1.1%]; F = 0.3; P = .60) and remained stable throughout the testing period, supporting minimal head or stimulator movement during the study.

The magnetic stimulus-response curve was nonlinear in patients with SMA and healthy controls. There was no significant difference between single-pulse maximal MEP amplitude (SMA, 2.5 [0.4] mV; controls, 2.4 [0.3] mV; ALS, 2.1 [0.2] mV; F = 0.8; P = .4). The MEP:CMAP ratio, which
between conditioning and stimulus intensity were the same. Additionally, the paired-pulse TMS threshold-tracking protocol ensured that the interaction between groups. The SICI, defined as an increase in the test stimulus intensity required to track a constant target MEP of 0.2 mV, was similar in the SMA and healthy control groups (9.9% [1.9%] vs 10.7% [1.4%]; *P = .36) but markedly greater when compared with that in the ALS group (1.5% [1.4%]; *P < .001; Figure 3A). In addition, peak SICI at 1 millisecond (SMA, 6.6% [3.3%]; controls, 6.7% [1.2%]; *P = .49) and 3 milliseconds (SMA, 14.4% [1.6%]; controls, 17.0% [2.3%]; *P = .20) was also similar in the SMA and healthy control groups but was significantly greater when compared with the ALS group (SICI of 1 millisecond: ALS, 1.6% [1.2%]; *F = 4.9; *P = .009; SICI of 3 milliseconds: ALS, 4.3% [1.8%]; *F = 11.4; *P < .001; Figure 3B).

Following SICI, a period of intracortical facilitation developed between interstimulus intervals of 10 to 30 milliseconds. Intracortical facilitation was similar between the SMA and healthy control groups (0.7% [1%] vs –0.1% [1%]; *P = .43) but was significantly greater in the SMA group when compared with the ALS group (–2.9% [1.3%]; *P = .02; Figure 3C). Taken together, these findings suggest that cortical excitability was preserved in patients with SMA and have reaffirmed the presence of cortical hyperexcitability in ALS.

The duration of the cortical silent period increased from 0 to 204.4 (9.8) milliseconds in patients with SMA as stimulus intensity increased from 60% to 150% RMT and was similar to that of healthy controls (from 0 to 208.8 [3.7] milliseconds). The cortical silent period duration was significantly longer in patients with SMA vs those with ALS (ALS, 0 to 182.7 [5.2] milliseconds; *F = 4.8; *P = .01).

**CORRELATION WITH CLINICAL MEASURES**

Combining clinical assessments of disease severity with neurophysiologic characteristics, the CMAP amplitude in SMA correlated with clinical measures of disease burden (Figure 4), including MRC sum score (*R = 0.88; *P = .008), MRC score from the target APB muscle (R = 0.88; *P = .009), and the SMAFRS score (R = 0.87; *P = .01). In contrast, clinical assessments of disease severity, disease duration, or age at onset did not significantly correlate with cortical excitability measures, including MEP and peak SICI in participants with SMA. As such, the correlation of clinical measures of disease severity with reduced CMAP in patients with SMA highlights the predominance of peripheral abnormalities in the pathophysiologic processes of SMA and the development of the clinical phenotype.

**COMMENT**

Using clinical and functional measures combined with threshold-tracking TMS techniques, the present study has identified degeneration of the lower motoneuron axis in SMA. Despite this process, there remained preservation of corticomotoneuronal function in patients with SMA, refuting any significant physiologic effects of reduced SMN protein expression within the central nervous system. These findings suggest that a unique pathophysiologic process underlies lower motoneuron degeneration in SMA, particularly when compared with ALS. Specifically, measures of cortical excitability, including resting motor threshold, SICI, intracortical facilitation, and cortical silent-period duration, were normal in SMA. Further-
more, the descending corticomotoneuronal output remains preserved in SMA; consequently, it is proposed that the greater contribution and projections onto the surviving spinal motoneurons likely represent adaptive neuroplasticity rather than the cortical hyperexcitability that develops in ALS.

NEUROPLASTICITY IN SMA

Adaptive changes involving motor pathways have been documented across a range of childhood neurologic disorders.\(^25\)-\(^28\) Potential mechanisms of this enhanced plasticity include low levels of \(\gamma\)-aminobutyric acid (GABA) \(\lambda\)-mediated intracortical inhibition\(^29\) and a prolonged period of synaptic reorganization in addition to potential responses to disease or therapy. Given that subthreshold conditioning stimuli do not excite the spinal motoneuron, the changes in threshold observed during the paired-pulse threshold-tracking TMS paradigm may be regarded as solely intracortical in origin and reflect excitatory and inhibitory function.\(^30\) Specifically, SICI is linked to the function of GABAergic intracortical interneurons.\(^31\) Findings from the present study argue against ongoing enhanced intracortical plasticity in adolescents and adults with chronic SMA and reflect the clinical course, in which the greatest loss of strength occurs at disease onset, suggesting a considerable early loss of motoneurons followed by increasing stability of the surviving neurons with slow or no clinical deterioration.\(^32\)

The absolute MEP amplitude depends on the sum of complex interactions between the corticomotoneuron and spinal motoneuron. Accordingly, the MEP:CMAP ratio may be applied to determine the corticomotoneuronal contribution onto surviving spinal motoneurons.\(^33\) Findings from the present study have established an increase in the MEP:CMAP ratio that in turn may suggest the presence of adaptive central plasticity in SMA; this is a novel finding. The finding of preserved corticomotoneuronal function in SMA may refute the development of cortical hyperexcitability, as occurs in the various phenotypes of ALS,\(^11\) including the progressive muscular atrophy variant,\(^12\) as a possible basis. A potential mechanism underlying this increase in the MEP:CMAP ratio may relate to an increased density of corticomotoneuronal projections onto the anterior horn cells, resulting in greater summation of excitatory postsynaptic potentials on the motoneuron and ultimately increased efficiency of motor output and thereby muscle strength.\(^34\)-\(^37\) Furthermore, the “up front” course of SMA, in which the most rapid decline appears initially, appears to coincide with the period of enhanced synaptic reorganization and plasticity during development.

The absence of a significant correlation between MEP with disease duration or age at onset may further support the hypothesis that the timing of neurodegeneration is early and followed by increasing stability. Of further relevance, larger MEPs have been observed in affected muscles in adults who had developed poliomyelitis in early life, when the ability of the developing cortex to reorganize might be quite different from that of the adult cortex.\(^3\) In further contrast, corticomotoneuronal plasticity has not been demonstrated in previous studies of distinct pure lower motoneuronal disorders in which neurodegeneration is initially clinically apparent in maturity, including studies in patients with spinobulbar muscular atrophy (Kennedy disease).\(^36\)

Neuromodulation of corticospinal axons by local neural circuits originating at either the level of the brainstem or spinal cord, as suggested by observations that anterior horn cell activity in SMA is less suppressed by exposure to GABA,\(^39\) may also contribute to any observed plasticity. While this latter mechanism cannot be discounted, the finding of normal cortical silent-period duration, in part mediated by local spinal inhibitory circuits acting via GABA_{\text{A}} receptors,\(^16\) would seem to argue against this mechanism in patients with SMA, at least in the present cohort. Alterations in spinal circuitry, specifically, deafferentation of motoneurons,\(^2\) has been demonstrated as an early pathophysiologic event in SMA and may contribute to motor dysfunction.

Figure 3. Short-interval intracortical inhibition (SICI). In healthy control participants, SICI occurs between interstimulus intervals (ISIs) of 1 to 7 milliseconds. This is followed by intracortical facilitation (ICF), as indicated by a decrease in the test stimulus intensity. A, The SICI was comparable between patients with spinal muscular atrophy (SMA) and the healthy controls and significantly reduced in patients with amyotrophic lateral sclerosis (ALS) (*P = .001). B, The mean SICI, between ISIs 1 to 7 milliseconds, in patients with SMA was similar to that of controls but significantly greater vs patients with ALS (P = .001). C, The ICF was similar between patients with SMA and healthy controls but significantly smaller compared with patients with ALS (†P = .02). Limit lines indicate standard error.
dependent from glutamate excitotoxicity, in keeping with studies that have established preservation of glial and neuronal glutamate transporters in SMA. This notion is supported by the clinical observation that the “split hand,” which refers to preferential atrophy of thenar and first dorsal interosseous muscles and is mediated by cortical mechanisms related to glutamate excitotoxicity, appears to be specific to ALS, contrasting with generalized atrophy of intrinsic hand muscles observed in SMA.

In addition, the possibility of alterations in descending corticomotoneuronal pathways in SMA may be of therapeutic significance. Specifically, physical therapies commenced at an early age in individuals with SMA may enhance central adaptive processes, thereby potentially promoting stabilization and improvement of motor function. As such, pharmacologic therapies aimed at enhancing central plasticity, in particular the corticomotoneuronal pathway, may further complement physical therapies to improve motor function in SMA.

Perhaps of further relevance, alterations in the intrinsic excitability of spinal motoneurons, thereby resulting in greater spinal motoneuron drive for a given input, may also have contributed to the increased MEP:CMAP ratio. Supportive evidence of such a hypothesis is suggested by upregulation of persistent sodium conductances in SMA axons and spinal motoneurons, resulting in greater intrinsic motoneuronal excitability.

Technical factors in the form of aberrant muscle activity may have inadvertently contributed to an increase in MEP amplitude. Of note, muscle contraction results in an increase in MEP amplitude and shortening of MEP latency. However, this seems an unlikely explanation for an increased MEP amplitude in the present cohort of SMA patients because muscle activity was monitored during the testing procedure and the MEP latency was not significantly different from that of healthy and ALS controls.

**CLINICAL IMPLICATIONS**

When taken in total, findings from the present series may tend to argue against any significant physiologic effects of reduced SMN protein expression within the central nervous system. These findings may further suggest that motoneuron degeneration in SMA is a process that is

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**REFERENCES**


17. Medical Research Council. *Aid to the Examination of the Peripheral Nervous System.*


