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Brain & Development 35 (2013) 165–171

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Peripheral nerve abnormalities in pediatric patients with spinal muscular atrophy

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Received 23 November 2011; received in revised form 14 March 2012; accepted 15 March 2012

Abstract

We examined the specific nerve conduction deficits distinguishing spinal muscular atrophy (SMA) subtypes I and II. Five SMA I patients (age, 0.2–1.1 years) and 10 SMA II patients (age, 1.0–2.8 years) were examined. Patients were compared to age-matched controls for motor and sensory conduction velocity (MCV and SCV) changes, compound muscle and sensory nerve action potential amplitudes (CMAP and SNAP), and F-wave occurrence (FO). Slower MCVs were found in three of five SMA I patients; all five exhibited markedly decreased CMAP amplitudes. Tibial nerve CMAP amplitudes significantly reduced in SMA II patients ($p < 0.01$). Slower SCVs and decreased SNAP amplitudes were observed in three of five SMA I patients but not in SMA II patients. Although FOs were reduced in both extremities of SMA I patients, the reduction was prominent in the tibial nerve of SMA II patients ($p = 0.031$). Loss of motor units may be widespread in the early stage of SMA I, while specific to the legs in young SMA II patients. SMA I showed sensory nerve degeneration, especially of large myelinated fibers. SMA II showed no sensory nerve abnormalities.

Keywords: Spinal muscular atrophy; Nerve conduction study; Peripheral nerve abnormality; Sensory nerve degeneration; Wallerian degeneration

1. Introduction

Spinal muscular atrophy (SMA) is a hereditary disease characterized by degeneration and loss of motor neurons in the spinal cord and brain stem. Three clinical types (SMA I–III) are recognized [1,2]. Spinal muscular atrophy type I patients exhibit weakness before 6 months of age and are unable to sit without support, while SMA II patients usually exhibit weakness by 18 months but are able to sit unsupported at some point in their clinical course. Spinal muscular atrophy type III patients generally have a milder course and are able to walk independently. Patients with marked abnormalities in peripheral sensory nerve conduction are excluded by the diagnostic criteria for infantile SMA, but histological studies have shown loss of myelinated fibers, myelin breakdown, and axonal degeneration in sensory as well as motor nerves of SMA I patients [3–6]. For example, sural nerve biopsy in an eight-year-old SMA II patient revealed mild sensory nerve pathology, including myelin breakdown and myelin ovoids (our unpublished case).

Several studies have analyzed nerve conduction in SMA, but samples sizes were small. Furthermore, there

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http://dx.doi.org/10.1016/j.braindev.2012.03.009

was considerable variation in age at assessment, which complicates interpretation because the contribution of different axonal types changes during development. Electrophysiological studies have reported reduced motor conduction velocities (MCVs) in some SMA I patients resulting from loss of large myelinated fibers and smaller compound muscle action potential (CMAP) amplitudes in both SMA I and II patients [7,8]. Conversely, two studies found no reduction in sensory nerve conduction velocity in any type of SMA [9,10], although one reported that sural nerve responses were below detection in all SMA I patients [9].

In light of these contradictory results, the aim of the present study is to assess peripheral nerve conduction abnormalities in pediatric SMA patients in a narrow age range and characterize the nerve and axonal subtypes most affected in the different clinical types.

2. Subjects

Written informed consent was obtained from the parents of all patients in accordance with the Declaration of Helsinki for investigations involving human subjects.

Between September 2001 and January 2011, 15 patients aged 0.2–2.8 years were admitted to National Center Hospital, National Center of Neurology and Psychiatry. All were diagnosed with SMA based on clinical history and typical electromyographic patterns. Peripheral blood samples were drawn for genomic DNA analysis of survival of motor neuron 1 (*SMN1*) and neuronal apoptosis-inhibitory protein (*NAIP*). Patients were diagnosed with SMA I or SMA II according to the criteria established by the International SMA Collaboration Workshop of 1990 [1].

3. Methods

3.1. Electrophysiology

This is a retrospective investigation. On admission to our hospital, all patients are evaluated by nerve conduction study (NCS) under drug-induced sleep to confirm or exclude peripheral neuropathy, while the skin temperature is kept higher than 34 °C. Motor and sensory nerve responses were evoked and recorded using an electromyograph (Neuropack Four, Nihon Kohden Co., Tokyo, Japan).

To evoke CMAPs and the F-waves, supramaximal electrical stimuli (0.2–0.3 ms) were delivered through a two-pronged stimulator placed either over the median and ulnar nerve at the wrist and elbow, respectively, or over the posterior tibial nerve at the ankle and popliteal fossa. The F-wave with the shortest latency (F-wave minimal latency) was selected from 20 consecutive (but clearly identified) F-responses. Surface recording electrodes were placed over the main bulk of the thenar, hypothenar, and abductor hallucis muscles for recording CMAPs and F-waves from the median, ulnar, and tibial nerves, respectively. The latency of the CMAPs and F-waves were measured from the stimulus artifact to the initial negative deflection from baseline. The CMAP amplitudes were measured from the negative to the positive peak. Sensory nerve action potentials were evoked by orthodromic stimulation from a ring electrode placed on the second finger for median nerve recording, on the fifth finger for ulnar nerve recording, or by a two-pronged stimulator placed below the lateral malleolus for sural nerve recording. The SNAPs of the sural nerve were recorded by an electrode positioned at a variable surface position depending on the length of the leg. All SNAPs analyzed were the average of approximately 30 responses evoked using supramaximal stimulus intensity. The latency of sensory conduction was measured from the stimulus artifact to the positive peak of the SNAP, and the SNAP amplitude was measured from the positive to the negative peak.

The nerve conduction parameters from SMA I patients (MCV, CMAP, F-wave minimal latency, F-wave frequency, SCV, and SNAP) were compared to those recorded from non-SMA patients less than 1 year of age, while nerve conduction parameters from SMA II patients were compared to controls between 1 and 3 years of age.

3.2. Control patients

We retrospectively investigated NCSs of nine pediatric patients less than a year old (median: 0.8 years, range: 0.3–0.9 years) and 15 patients between 1 and 3 years old (median: 1.5 years, range: 1.1–2.8 years) examined for different disease conditions over the past 4 years. Neuromuscular disorders were excluded in all but two control patients (one patient aged <1 year with congenital muscular dystrophy and another with Duchenne muscular dystrophy).

3.3. Statistical analyses

The two-tailed unpaired group *t*-test was used to compare the mean MCVs, CMAP amplitudes, sensory conduction velocities (SCVs), SNAP amplitudes, and F-wave minimal latencies between SMA II patients and age-matched controls. The Mann–Whitney *U* test was used to compare the medians of F-wave occurrence (% of evoked responses) of SMA II patients and controls. Differences were considered statistically significant at $p < 0.05$. The MCV, CMAP amplitudes, F-wave latency, SCV, and SNAP amplitudes are expressed as mean ± standard deviation (SD).