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Efferent and afferent evoked potentials in patients with adrenomyeloneuropathy

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ABSTRACT

Objective: This paper investigates efferent and afferent conductions of the central nervous system by various evoked potentials in patients with adrenomyeloneuropathy (AMN).
Patients and methods: Ten pure AMN patients without cerebral involvement were studied. Motor evoked potentials (MEPs), somatosensory evoked potentials (SEPs), auditory brainstem response (ABR), and pattern reversal full-field visual evoked potentials (VEPs) were recorded. For MEP recording, single-pulse or double-pulse magnetic brainstem stimulation (BST) was also performed.
Results: Abnormal MEP was observed in all ten patients, abnormal SEP in all ten, abnormal ABR in nine, and abnormal VEP in only one. Brainstem latency was measured in three of the seven patients with central motor conduction time (CMCT) prolongation. The cortical–brainstem conduction time was severely prolonged along the normal or mildly delayed brainstem–cervical conduction time in those three patients.
Conclusions: The pattern of normal VEP and abnormal MEP, SEP, ABR is a clinically useful electrophysiological feature for the diagnosis. BST techniques are helpful to detect, functionally, intracranial corticospinal tract involvement, probably demyelination, in pure AMN patients.

1. Introduction

X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder caused by mutation of the ABCD1 gene [1] whose biochemical abnormality is characterized by the accumulation of very long chain saturated fatty acids (VLCFA) [2–5]. The highly varied phenotype of X-linked ALD is classified into subtypes such as childhood cerebral ALD, adolescent cerebral ALD, adrenomyeloneuropathy (AMN), adult cerebral ALD, olivo-ponto-cerebellar ALD and Addison's disease-only ALD [6–8]. No correlation exists between phenotypes and genotypes [9]. The central nervous system pathology comprises two apparently disparate types of cerebral form (cerebral ALD) and AMN. The cerebral ALD is characterized by a severe inflammatory demyelinating lesion in the cerebrum (myelinopathy) [10]. The AMN is characterized by distal axonopathy: degeneration of spinal tracts distributed in a 'dying-back' pattern [11]. These two major forms of the disease differ fundamentally with respect to their prognoses. Although rapidly progressive cerebral ALD engenders total disability during the first decade, some patients with AMN survive to the eighth decade [6]. However, about half of the AMN patients clinically develop cerebral involvement within 10 years after onset [7,8]. The patients without cerebral involvement are referred to as "pure" AMN, whereas the patients with cerebral involvement are referred to as "cerebral" AMN. The magnetic resonance image (MRI) in pure AMN is often normal but may show changes up to the internal capsule [12,13], and the corticospinal tract lesions in pure AMN are considered to be axonal pathology [12,14,15]. On the other hand, the pathological mechanism in cerebral AMN is proposed to be the cerebral demyelination in addition to the distal axonopathy [12]. Therefore, the assessment of brain function using neurophysiological methods is very important in considering prognosis and possible treatment in AMN patients [6].

Central efferent function is physiologically examined using motor evoked potential (MEP). In fact, MEP studies have revealed frequent abnormal central motor conduction in AMN patients [16–18]. The central motor conduction time (CMCT) mainly reflects the overall function of the motor tract of the central nervous system. However, it does not indicate the level of motor tract involvement: whether it is intracranial, extracranial, or both. We previously developed methods to activate the descending motor tracts at the level of the pyramidal decussation (foramen magnum) using electrical stimulation [19] and magnetic stimulation [20]. The methods [brainstem stimulation (BST)] have been shown to be clinically useful for localizing corticospinal tract lesions in patients with various neurological disorders [21–25]. For this investigation, we applied this stimulation along with cortical and spinal stimulations to show

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Table 1
Background of patients.

Case	Age	ABCD1 mutation	Disease duration (years)	Main symptom(s)	Brain MRI	Loes score	Spinal MRI
1	32	Missense (H667N)	1	Spastic gait, pigmentation	Normal	0	Normal
2	44	Nonsense (W595X)	1	Spastic gait, sensory disturbance (leg)	Normal	0	Atrophy
3	61	N.E.	4	Spastic gait, muscular weakness (leg), sensory disturbance (leg)	Normal	0	Normal
4	30	Missense (S290W)	5	Spastic gait, sensory disturbance (leg), dysuria, dyschezia, impotence	P, V	2.5	Normal
5	31	Missense (F540S)	5	Spastic gait	V	0.5	Normal
6	24	Missense (A616D)	6	Spastic gait, sensory disturbance (leg), dysuria, impotence	Normal	0	Normal
7	31	Frameshift (Y281)	8	Spastic gait, sensory disturbance (leg), dyschezia	C	0.5	Normal
8	33	Missense (G277R)	8	Spastic gait, dysuria, dyschezia impotence	P	2	Atrophy
9	58	N.E.	18	Spastic gait, dysuria	Normal	0	Atrophy
10	58	N.E.	19	Spastic gait, impotence	Normal	0	Normal

MRI: magnetic resonance image, P: pyramidal system, V: visual pathway, C: cerebellum, N.E.: not examined.

which part of the descending tract was affected. We also adopted a recently reported powerful stimulation method to evoke clear MEPs in patients without any MEPs to single-pulse BST: double-pulse magnetic BST [26].

The central afferent functions are usually studied with various evoked potentials such as somatosensory evoked potential (SEP), auditory brainstem response (ABR), and visual evoked potential (VEP). These three evoked potentials also have shown afferent system conduction abnormalities in AMN patients [16,17,27–32].

The aim of this study is to investigate efferent and afferent conductions of the central nervous system in pure AMN patients using the four types of evoked potentials including magnetic BST. Some results of MEPs in this study were described in a previous report [26].

2. Methods

2.1. Patients

We studied ten male patients with AMN. Based on the course of the disease and clinical symptoms, they were diagnosed as AMN. Plasma VLCFA was abnormally increased in all of them. The ABCD1 gene mutation was analyzed in seven patients (cases 1, 2, 4-8) after receiving their informed consent [33,34]. Their patient characteristics and clinical features are presented in Table 1. Their ages were 24–61 years (mean ± SD, 40.2 ± 13.9 years). Their body heights were 165–175 cm (169.1 ± 3.2 cm). The durations of illness at the time of our experiment were 1–19 years (7.5 ± 6.3 years). All patients presented with spastic paraplegia with positive Babinski signs. Five patients presented with diminished superficial and deep sensation in the lower extremities (cases 2–4, 6, and 7). On the other hand, all patients presented no symptoms of motor and sensory systems in the upper extremities. They all also had no auditory and visual complaints. Brain and spinal MRIs were also taken. The lesions observed on brain MRI were described according to a previous paper [35]. Because all patients had no clinical or radiological cerebral involvement, all of them were classified into pure AMN [12,13]. Both MEP and SEP were recorded on the more affected side of motor symptom; ABR and VEP were recorded on both sides. We compared the latencies of these evoked potentials with the normal values in our institution.

Informed consent to participate in this study was obtained from all patients. The protocol was approved by the Ethics Committee of the University of Tokyo. It was conducted in accordance with the ethical standards of the Declaration of Helsinki.

2.2. MEP recording

Patients were seated comfortably on a reclining chair. MEPs were recorded from the first dorsal interosseous (FDI) and tibialis anterior (TA) muscles with pairs of Ag/AgCl surface cup electrodes placed in a belly tendon montage. Signals were fed to an amplifier (Biotop; GE Marquette Medical System, Japan) with filters set at 100 Hz and 3 kHz; the signals were recorded using software (TMS bistim tester; Medical Try System, Japan) for later off-line analyses.

Magnetic stimulation was conducted using a monophasic stimulator (Magstim 200; The Magstim Co. Ltd., UK) for transcranial magnetic stimulation (TMS), magnetic spinal motor root stimulation, and single-pulse BST. Double-pulse BST was given by connecting the two magnetic stimulators linked with a Bistim module (The Magstim Co. Ltd., UK).

For both muscles, CMCT was measured in each patient. For FDI, the onset latency of MEP elicited by TMS over the contralateral hand motor area using a round coil (10 cm diameter; The Magstim Co. Ltd., UK) was measured in the active condition (cortical latency). Induced current flowed in the posterior to the anterior direction over the hand motor area [36,37]. For TA, cortical latency was measured placing a double-cone-coil (The Magstim Co. Ltd., UK) [38] over the Cz (international 10–20 system), with induced current flowing mediolaterally over the leg motor area [39]. The onset latency of MEP to magnetic spinal motor root stimulation was also measured by activating cervical and lumbar spinal nerves with a round coil (10 cm diameter) placed over the spinal enlargement (spinal latency) [40,41]. The CMCT was calculated by subtracting the spinal latency from the cortical latency [37].

For FDI, single-pulse BST was also performed in active and relaxed conditions [20]. For BST, a double-cone-coil was placed with the center of the junction region over the inion. The coil current flowed downward at the junction of the coil so that the maximal current induced in the head flowed upward because this current direction has the lowest threshold for evoking MEPs [23]. The onset latency of MEP to single-pulse BST was measured (brainstem latency). When a single-pulse BST with maximal stimulator output was insufficient to evoke any MEP, double-pulse BST at an interstimulus interval of 2 ms was tried in a relaxed condition [26]. The stimulus intensities of double-pulse BST were set at the maximal stimulator output. The onset latency of MEP to double-pulse BST was measured from the time of the second pulse, which was identical to that of single-pulse BST (brainstem latency) [26]. The cortical–brainstem and brainstem–cervical conduction times were obtained, respectively, by subtracting the brainstem latency from the cortical latency and the spinal latency from the brainstem latency.

2.3. SEP recording

For this study, the SEPs were elicited after electrical stimulation (a constant current square wave pulse with duration of 0.2 ms) of the median nerve at the wrist or posterior tibial nerve at the ankle, as described in previous reports [16]. For recording N13 and