Spinal Cord MT Imaging Correlates with Somatosensory Evoked Potentials in Adrenomyeloneuropathy

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Introduction

Adrenomyeloneuropathy (AMN) is the adult form of X-linked Adrenoleukodystrophy (X-ALD) and is the most common phenotype (~ 40% of all patients). It is a non-inflammatory, distal axonopathy that severely involves the ascending dorsal columns in the cervical region and the descending corticospinal tracts in the lower thoracic and lumbosacral regions. Somatosensory evoked potentials (SSEP) show utility in evaluating progressive disorders of the CNS and locating regions of demyelination. It has been shown that AMN and symptomatic heterozygotes have abnormal median and tibial nerve SSEP which mainly involve the central pathways[1]. Magnetization transfer-weighted (MTw) imaging of the cervical spinal cord corroborates the histopathology of demyelination in the dorsal column and conventional MRI (T1w and T2w) shows no presence of inflammation[3]. Recently, CSF normalized MTw imaging (MTCSF) showed sensitivity to neurological disability and quantitative sensory-motor tests in AMN[2]. The purpose of this study was to determine the association between the central abnormalities detected by SSEP of upper and lower limbs and MTCSF.

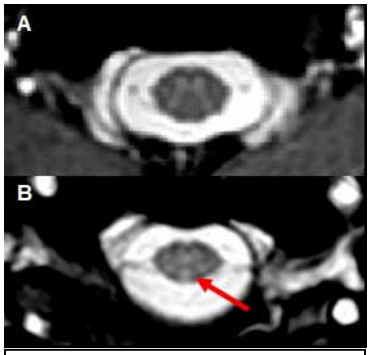

Figure 1: MTCSF images (C2) in healthy volulnteer (A) and AMN patient (B) with decreased SSEP measures. Note: DC hyperintensity in (B, arrow).

Methods

Thirty-two subjects clinically diagnosed with AMN under went SSEP and MRI evaluation after informed written consent. MRI studies were performed on a 1.5 T Intera, Philips Medical Systems, Best, The Netherlands) using the quadrature body coil transmission, and a two-element phased array coil for reception. MTw data sets were obtained using a 3D-gradient echo (TR/TE/α = 50 ms/13 ms/7°), with a 15-ms MT prepulse, and 4 RF offsets logarithmically sampled between 10 and 32 kHz. Other parameters were: FOV = 225 x 225 mm, nominal resolution = 0.9 x 0.9 mm, 32 slices at 1.5 mm slice thickness. The highest slice was acquired at the level of the foramen magnum and covered the cervical cord from C1 to C3; total scan time was 12 minutes. MTw images for each offset frequency were normalized by the in-slice signal within the CSF of the 10 kHz scan and called MTCSF[3]. SNR was improved by calculating the $MTCSF_{int}$: the integral of the CSF-normalized MTw images as a function of offset (in kHz). $MTCSF_{int}$ was quantified by selecting ROIs from within the dorsal column (DC) of each slice. Neck lengths differ, and thus the $MTCSF_{int}$ signal intensities from C1 to C3 were spline interpolated to fit 25 slices. Higher $MTCSF_{int}$ area reflects greater degree of demyelination[2]. Three sets of short latency SSEPs were recorded. The first set was obtained after electrical stimulation of the left median nerve at wrist level while the second and third sets was recorded following stimulation of the posterior tibial nerve in the left foot and right foot, respectively, below ankle level. For each set, 2,000 responses were collected with high-pass and low-pass filters at 100 and 2,000 Hz, respectively and a pulse interval of 212.9ms and averaged. For the median nerve stimulation set, the N9 (Erb's point potential), N/P13 (craniocervical junction potential) and N19/20 (central) latencies were recorded and the N/P13-N20 interpeak interval computed For the tibial nerve stimulation set, , SSEPs were recorded the third lumbar to iliac crest (L3S-iliac) and CPz referenced at Fz. We measured L3 or LP (conus medullaris potential), and P37 (central potential) absolute latencies and computed P37-LP interpeak latency. Delayed interpeak latencies (N/P13-N19/20; P37-LP) or delayed or absent central responses (N19/20; P37) with normal N/P13 or LP latencies were interpreted as evidence of delay along CNS pathways only. In the case of absent or delayed peripheral potentials (EP, PF, N/P13, L3), the status of the cortical responses (absent) was neither counted as normal nor abnormal. T-test and simple linear regression were used to evaluate the association between dorsal column MTCSF signal intensities and SSEP variables.

Results and Discussion

Figure 1 shows a comparison between healthy (A) and severe AMN patient (B). The definition of MTCSF is such that highly myelinated white matter is dark, gray matter horns are less dark and CSF bright. The hyperintensity seen in the dorsal column (DC) (fig 1, arrow) is the principle site of insult in AMN as reported by Powers et al[4] and Fatemi et al[2]. The mean central absolute (N19/20) latencies in the upper limb of the normal vs delayed groups were 20.9± 0.81 vs 25.2± 3.6 ($p<0.001$), and mean prolongation of N/P13-N20 interpeak interval in these groups were 6.4± 0.19 vs 8.1± 3.0 ($p<0.04$). In subjects with the delayed central latencies the mean dorsal column $MTCSF_{int}$ is significantly greater (17.9± 1.7 vs 19.2± 1.2, $p<0.03$) than the normal latency group (Fig. 2). There is a significant positive correlation between each subject's mean dorsal column $MTCSF_{int}$ value and SSEP of central latency (N19/20) and interpeak latency (N/P13-N20) (Fig. 3) of the upper limb ($p<0.033$ and $p<0.043$ respectively). The greater the delay in the transmission of SSEP in the median nerve the higher the $MTCSF_{int}$ indicating the sensitivity of MT based imaging on the myelination status of the spinal cord. Delay in right limb interpeak latency (P37-LP) was greater than the left limb and $MTCSF_{int}$ values increased as the right limb's interpeak lantency increased ($p<0.001$). Signal hyperintensity in the MTCSF images is due to myelin injury[2] and has been shown to be sensitive to disease status in AMN. A conclusion of this work is that abnormalities seen by conventional SSEP of care are corroborated by imaging findings and thus corroborate each other in the in vivo detection of non-inflammatory demyelinating pathology. Unfortunately, the absence of evoked potentials limits the range over which demyelination may be measured and its utility in monitoring disease progression in AMN may be restricted. Further study will determine if SSEP and correlation with $MTCSF_{int}$ are maintained over time.

References: 1) Kaplan PW et al. Neurology. 1997;48(6):1662-7 2) Fatemi A et al. Neurology. 2005;64(10):1739-45 3) Smith SA et al. MRM. 2005;54(1):201-6 4) Powers JM et al. J Neuropathol Exp Neurol. 2000;59(2):89-102.

Figure 2: Comparison of $MTCSF_{int}$ Values Between Normal and Delayed Central SSEP Latencies in Upper Limb

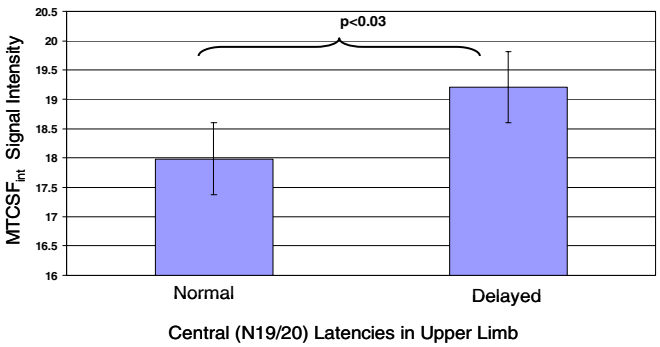

Figure 3: Linear Relationship between $MTCSF_{int}$ values and N/P13-N20 Interpeak Interval of Upper Limb