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ORIGINAL ARTICLE

The reversible effect of neck flexion on the somatosensory evoked potentials in patients with Hirayama disease: a preliminary study

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Abstract

The aim of this study was to examine and characterize the reversibility of the cervical somatosensory electrophysiological pathways during neutral and flexed neck positions. The parameters of somatosensory evoked potentials (SEPs) during neutral and flexed neck positions (N9, N13, and N20 SEP latencies; N9–N13 and N13–N20 inter-peak latencies; and the changes in N9–N13 and N13–N20 inter-peak latency during neutral and flexed neck positions) were measured in the patients with Hirayama disease (HD) and also in the healthy controls. In patients with HD, there was a significant difference in the mean value of N13–N20 inter-peak latency during the flexed neck position compared to that of the healthy controls ($p < 0.05$). In a multivariate logistic regression analysis, N13–N20 inter-peak latency during the flexed neck position significantly correlated with the presence of HD ($p < 0.05$). Collectively, in this cohort of patients with HD, the neck flexion of patients with HD showed a reversible effect on the SEP parameter, especially in N13–N20 inter-peak latency. Conventional diagnosis of HD is based on nerve conduction studies and electromyography along with a cervical flexion MRI, and our study suggests the possibility of an additional and cost-effective electrophysiological marker that may be helpful in the diagnosis of HD.

Keywords Hirayama · Sensory evoked potentials · Neck flexion · MRI · Motor neuron disease

Introduction

Hirayama disease (HD) is a rare but localized disorder of the anterior horn cell, predominantly affecting young men [1, 2]. Clinically, HD is characterized by distal upper limb weakness involving the C7–T1 myotomes that present with weakness and wasting, but the brachioradialis muscle is usually spared [2]. Weakness usually occurs in both the extensor and flexor muscles, but the finger extensors and wrist flexors are predominantly involved. Although increased deep tendon reflex of the lower extremities may be present, there is usually no involvement of cranial nerves and sphincter function [3]. Additionally, most patients with HD manifest unilateral weakness and atrophy, and it is rarely asymmetric [2, 3]. Although there have been significant advances in the imaging of HD, the characteristic findings of neurophysiological studies in patients with HD remain controversial. The aim of this study was to elucidate the electrophysiological characteristics of the somatosensory pathways via somatosensory evoked potential (SEP) studies.

Methods

Patients and controls

Somatosensory evoked potential (SEP) studies in a neutral position and with the neck fully flexed were performed in 12 male patients with HD. All of them had typical clinical features of juvenile muscular atrophy of the distal upper extremity, without sensory deficit or sphincter involvement.

All patients underwent a comprehensive neurological examination to differentiate other diseases. None of our patients had lower limb symptoms or signs (such as fasciculation, muscle atrophy, and weakness). Patients with a history of neck trauma or surgery were excluded. All patients underwent routine nerve

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conduction studies (NCS) and electromyography (EMG) of the symptomatic upper limb that showed chronic denervation and reinnervation process in C7- to T1-innervated muscles (Fig. 1). Furthermore, all patients included in this study were also diagnosed by a flexion cervical MRI that showed typical findings: anterior displacement of the spinal cord with compression of the posterior dural sac (Fig. 2). Clinical factors including age at disease onset, the duration of disease, height (cm), bodyweight (kg), and body mass index (BMI) were also retrieved from the medical records. In addition, 11 age-matched healthy male controls, without any history of cervical injury and with normal neurological examination, underwent SEP studies in both neutral and flexed neck positions. The study was approved by the Investigational Review Board at Kyungpook National University Chilgok hospital.

Somatosensory evoked potentials

Upper extremity SEP studies were performed bilaterally by electrical stimulation of the median nerves at the wrist. Stimulation was performed with pulses of 0.2-ms duration delivered at a rate of 4 Hz via a surface electrode. The intensity was increased until a constant thumb movement was observed. At each site, a total of 200 epochs were twice averaged at 2 μv/div, sweep time 40 ms, and filter setting 30–3000 Hz [3]. The responses for the upper extremity were recorded with surface electrodes placed at [1] Erb's point ipsilateral to stimulation for the N9 brachial plexus component; [2] the spinous process of the 7th cervical spine for the N13 cervical components; and [3] the contralateral parietal cortex for the N20 cortical component. Response latencies were measured to the wave peak. Considering that the previous report suggested that the latency interval between N13 and N20 (inter-peak latency) was significantly increased in patients with HD during neck flexion, we also evaluated the N13–N20 inter-peak latency in neutral and flexed neck positions. In addition, we also evaluated the changes in N9–N13 and N13–N20 inter-peak latencies during neutral and flexed neck positions. The N9–N13 inter-peak latency was calculated to evaluate conduction between the brachial plexus and the dorsal column of the spinal cord dorsal horn. The N13–N20 inter-peak latency was calculated to evaluate conduction between the dorsal column of the spinal cord dorsal horn and the sensory cortex. For stimulation and recording, a standard EMG machine and software were used (Medelec Synergy, USA).

Statistical analysis

Descriptive and frequency analyses of the data were presented as the mean with standard deviation. The parameters of SEP were compared between neutral and flexed neck positions in patients with HD as well as in the healthy controls. Group comparisons between patients with HD and healthy controls were performed using the Wilcoxon rank-sum test or the Mann-Whitney *U* test and the Pearson's chi-squared test where applicable. Multivariate logistic regression analysis with forward stepwise selection was performed to evaluate the meaningful clinical factors and SEP parameters during neutral and flexed neck positions (N9, N13, and N20 SEP latencies; N9–N13 and N13–N20 inter-peak latencies; and the changes in

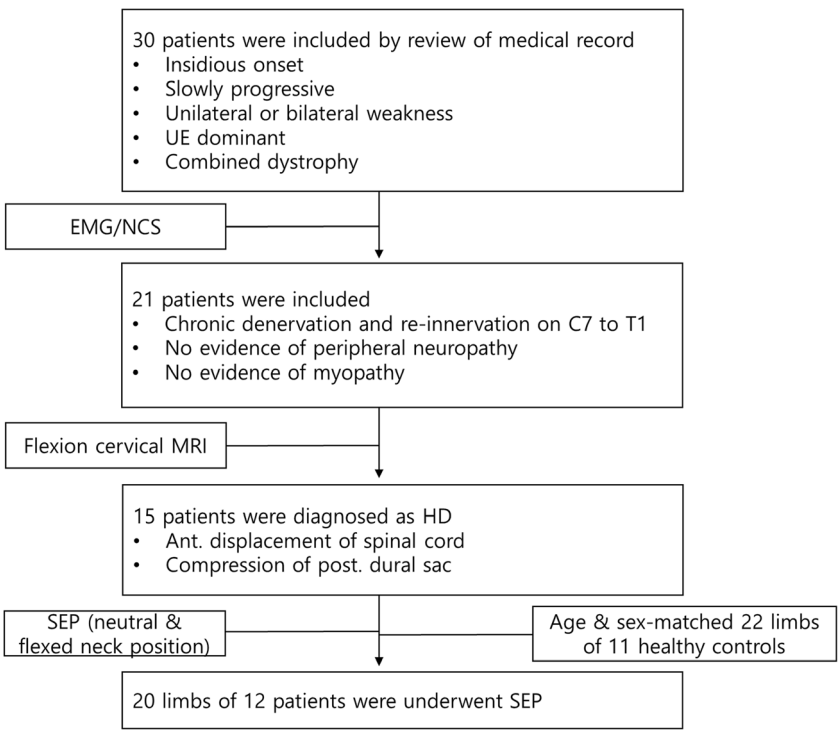

Fig. 1 The flowchart of this study

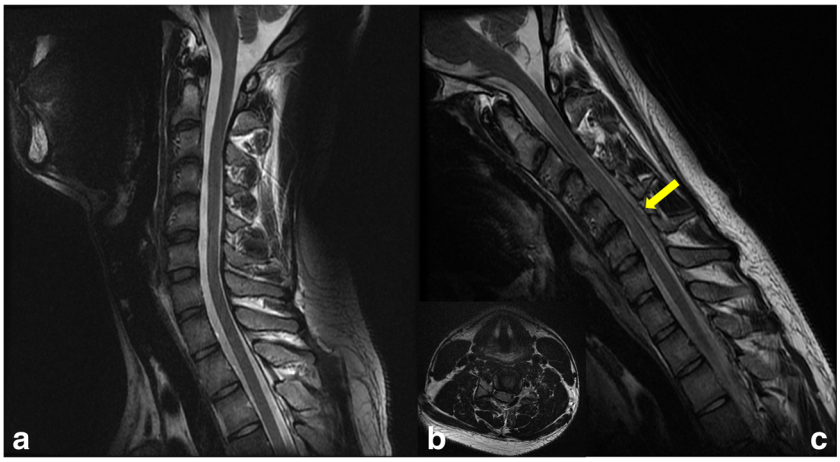

Fig. 2 **a** The supine cervical magnetic resonance imaging (MRI) is unremarkable, while flexion MRI illustrates anterior effacement of the posterior dural sac leading to ischemic compression of the dorsal lemniscus (arrow) (**b**, **c**)

N9–N13 and N13–N20 inter-peak latency during neutral and flexed neck positions) for patients with HD. The area under the curve (AUC) was calculated from the receiver operating characteristic (ROC) curve to assess the accuracy of the predictive factor for HD (Fig. 3). *P* values less than 0.05 were considered to denote statistical significance. Statistical analyses were performed using SPSS software, version 22.0 (SPSS, Chicago IL, USA), and the MedCalc program for Windows.

Results

Patient characteristics

Mean age of the patients at the time of examination was 18.9 ± 2.92 years (range 14–26 years). The mean age at the onset of symptoms was 17.0 ± 2.33 years (range 13–20 years). The controls had a mean age of 17.91 ± 1.54 years (range 15–20 years). The height, body weight, and BMI of the patients at the time of examination were 170.7 ± 3.95 cm (range 168–175.7 cm), 61.9 ± 4.88 kg (range 54–69 kg), and 21.2 ± 1.69 (range 19.3–23.7), respectively. The height, body weight, and BMI of the healthy controls at the time of examination were 167.9 ± 4.53 cm (range 167.8–174 cm), 60.3 ± 6.43 kg (range 46.6–67.6 kg), and 21.3 ± 1.69 (range 17.8–23.3), respectively (Table 1).

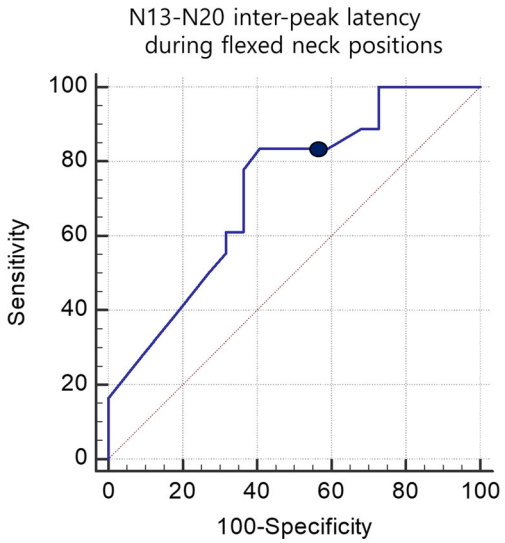

Fig. 3 The area under the ROC curve (AUC) for the N13–N20 inter-peak latency during flexed neck position as a continuous variable was 0.722. For the optimal cut-off value, a N13–N20 inter-peak latency during flexed neck position of 5.8 ms showed the highest Youden's index (sensitivity 83.33%, specificity 59.09%)

Nerve conduction study

In patients with HD, the parameters—latencies and amplitude of the median and ulnar sensory NCS—were within normal limits. Additionally, there were no statistical differences in the mean values of the terminal latencies and amplitude of the median and ulnar sensory NCS between patients with HD and the healthy controls ($p \geq 0.05$). In the motor NCS, however, compound motor action potential (CMAP) amplitude of the median and ulnar NCS in patients with HD were lower than those of the healthy controls, but failed to show a statistically significant difference. However, there was a statistically significant difference in the mean value of ulnar CMAP amplitude between patients with HD and healthy controls ($p < 0.05$) (Table 1).

Somatosensory evoked potentials

In patients with HD, median N9, N13, and N20 latencies were within normal limits, and there were no differences in the mean values of the median N9, N13, N20 latencies and N9–N13 and N13–20 inter-peak latencies of either neutral or flexed neck positions between patients with HD and the healthy controls ($p \geq 0.05$). In patients with HD, there were no significant differences in the mean values of the median N9, N13, and N20 latencies between recordings in the neutral and flexed neck positions in healthy controls. However, our data showed a significant difference in the mean value of the

Table 1 Characteristics of the patients and healthy controls in this study

	Patients with HD	Healthy Control	*P* value
Number (limbs)	12 (20)	11 (22)	N/A
Age	18.95 ± 2.91	17.91 ± 15.40	0.171
Sex (M:F)	12:0	11:0	0.925
Duration (months)	22.22 ± 22.03	N/A	
Height (cm)	170.63 ± 3.86	167.94 ± 4.53	*0.046*
Body weight (kg)	61.71 ± 4.74	60.31 ± 6.42	0.381
BMI	21.21 ± 1.70	21.34 ± 1.69	0.874
MMT finger flexor	4.45 ± 0.43	5.00 ± 0.00	*<0.001*
MMT finger extensor	4.40 ± 0.50	5.00 ± 0.00	*<0.001*
MMT wrist extensor	4.80 ± 0.30	5.00 ± 0.00	*0.008*
MMT wrist flexor	4.68 ± 0.37	5.00 ± 0.00	*0.001*
Onset latency of median sensory nerve	2.06 ± 0.24	2.21 ± 0.43	0.058
Onset latency of ulnar sensory nerve	1.99 ± 0.16	2.01 ± 0.34	0.318
SNAP amplitude of median nerve	29.27 ± 8.45	24.39 ± 8.50	0.117
SNAP amplitude of ulnar nerve	26.40 ± 4.98	23.69 ± 7.50	0.229
Onset latency of median motor nerve	2.88 ± 0.34	3.34 ± 0.88	0.081
Onset latency of ulnar motor nerve	2.45 ± 0.29	2.32 ± 0.26	0.196
CMAP amplitude of median nerve	9.53 ± 2.67	10.92 ± 1.22	0.061
CMAP amplitude of ulnar nerve	7.33 ± 4.01	10.14 ± 1.10	*0.010*

BMI, body mass index; *CMAP*, compound motor action potential; *MMT*, manual muscle test; *SNAP*, sensory nerve action potential. Italicized values mean significance at the $P < 0.05$

N13–N20 inter-peak latency during flexed neck position compared to that of the healthy controls ($p < 0.05$). Moreover, in patients with HD, there was a significant difference in the mean value of the N13–N20 inter-peak latency between neutral and flexed neck positions ($p < 0.05$) (Table 2).

We used multivariate logistic regression analysis with forward stepwise selection to evaluate the meaningful clinical factors and SEP parameters during neutral and flexed neck positions for patients with HD; the N13–N20 inter-peak latency during a flexed neck position significantly correlated with the presence of HD ($p < 0.05$) (Table 3). In the ROC curve analysis, the areas under the ROC curves for the diagnosis of HD was 0.722 (95% CI, 0.558–0.852; $p = 0.0061$). The optimal cut-off values obtained from the maximal Youden's index were more than 5.8 on the N13–N20 inter-peak latency during flexed neck positions (sensitivity 83.33%, specificity 59.09%) for the diagnosis of HD disease (Fig. 2).

Discussion

The pathophysiology of HD is not well understood, and more data are needed to extrapolate it. Currently, the most widely accepted hypothesis regarding microcirculation-related ischemia is supported by the typical MRI findings observed in HD, in which frequent spinal cord compression is observed during

Table 2 Results of somatosensory evoked potentials studies in patients with HD and healthy control during neutral and flexed neck position

	SEP parameters	Neutral position	Flexed neck position	*P* value
Healthy control	N9 latency	8.96 ± 0.73	8.99 ± 0.69	0.457
	N13 latency	12.39 ± 1.09	12.39 ± 0.096	0.935
	N20 latency	18.02 ± 1.02	18.10 ± 1.00	0.124
	N9-N13 inter-peak latency	3.44 ± 0.56	3.40 ± 0.49	0.620
	N13-N20 inter-peak latency	5.63 ± 0.53	5.71 ± 0.62	0.197
Patients with HD	N9 latency	9.10 ± 0.32	9.08 ± 0.35	0.570
	N13 latency	12.52 ± 0.36	12.20 ± 0.83	0.093
	N20 latency	18.38 ± 0.41	18.49 ± 0.49	0.138
	N9-N13 inter-peak latency	3.42 ± 0.24	3.11 ± 0.78	0.109
	N13-N20 inter-peak latency	5.87 ± 0.38	6.29 ± 0.61	*0.024*

HD, Hirayama disease. The italicized value means significant at the $P < 0.05$

Table 3 Multivariate logistic regression analysis with forward stepwise method of SEP parameters associated with the presence of Hirayama disease

Parameter	Beta coefficient	Standard error	OR (95% CI)	*P* value
N13–N20 inter-peak latency during neck flexion	− 1.629	0.661	0.196 (0.054–0.716)	*0.014*

OR, odds ratio; *CI*, confidence interval. The italicized value means significance at the $P < 0.05$

neck flexion [4–6]. According to this hypothesis of "flexion myelopathy," the microcirculatory disturbances in the anterior spinal artery are a result of segmental anterior horn neuronal loss [7]. Another hypothesis is related to disproportionate growth of the vertebral bone and the contents of the spinal canal, especially the dural sac, during adolescent growth, partly explaining the high prevalence of HD in adolescent males and the fact that the probability of onset decreases after age 20 [8].

The diagnosis of HD is based on the history and clinical symptoms that reveal unilateral or asymmetric distal dominant weakness, with an age of onset between 10 to 20 years without sensory disturbances, and that stop progressing after a few years. (Tashiro K, Kikuchi S, Itoyama Y, Tokumaru Y, Sobue G, Mukai E et al. Nationwide survey of juvenile muscular atrophy of distal upper extremity (Hirayama disease) in Japan. Amyotro lateral sclera 2006;7:38–45). These clinical findings are supported by nerve conduction studies and electromyography where the muscles innervated by C7–T1 are usually affected. With the advancement of imaging technology, recent reports of HD show the importance of a cervical MRI on neck flexion, which shows typical findings of HD. There have been reports on additional electrophysiological markers such as usage of evoked potentials. However, studies of SEP during neck flexion of patients with HD have shown conflicting results. Few prior studies showed an amplitude decrease of the N13 cervical response of SEP in patients with HD during neck flexion as opposed to neutral position [9–11]. In contrast, other studies failed to show electrophysiological abnormalities during neck flexion [12, 13]. Recently, Abraham et al. [3] compared SEPs (median and ulnar N9, N13, N20 latencies and amplitudes) between patients with HD with neutral and flexed neck positions, but they reported that neck flexion had no effect on measured SEP parameters while motor evoked potentials showed a statistically significant change. This is probably due to the fact that only parameters such as N9, N13, and N20 absolute latencies were simply compared in neutral and flexed neck position without considering the inter-peak latencies [3]. Moreover, the motor evoked potentials that were of significance in the previous literature have limitations in explaining the forward effacement of the posterior dural sac, because according to this hypothesis, the corticospinal tract is less affected than the dorsal column. Therefore, the strength of our study is that additional parameters such as N9–N13 and N13–20 inter-peak latencies were considered, which changes the values of N9–N13 and N13–N20 inter-peak latencies between neutral and flexed neck positions during the analysis. As expected, the N13–N20 inter-peak latency during flexed neck positions in patients with HD showed a statistically significant result in the multivariate model when compared with that of normal subjects. Considering that the N13–N20 inter-peak latency reflects the somatosensory pathway in the dorsal column of the spinal cord dorsal horn and the sensory cortex, delayed inter-peak latency of N13–N20 is thought to be caused by the direct compression of the dorsal column of the lower cervical spinal cord by the posterior dura sac during neck flexion. Conversely, when compared using only standard SEP parameters (e.g., N9, N13, and N20 latencies), delayed SEP latency effects due to local compression of the spinal cord dorsal horn caused by neck flexion can be masked because of the long pathway of the SEP. However, this needs to be elucidated by a study including a larger number of HD patients.

Our study is not without limitations. First, the number of patients with HD enrolled was small, reducing the power of explanation. Second, although we performed the flexion SEP with the maximum effort of the patient, there is no standardized and uniform method of flexion, and that may have influenced our results. Third, this was a retrospective study with varied disease duration; lastly, the statistically significant difference between the height of the patients with HD and the height of the normal controls limits the significance of our results.

Conclusion

Collectively, in this cohort of patients with HD, neck flexion seems to have a direct and reversible influence on SEP, especially in the N13–N20 inter-peak latency. Conventional diagnosis of HD is based on nerve conduction studies and electromyography along with a cervical flexion MRI, and our study suggests the possibility of an additional and cost-effective electrophysiological marker that may be helpful in the diagnosis of HD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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