Published in final edited form as:

Mov Disord. 2013 June ; 28(6): 823–827. doi:10.1002/mds.25482.

RELATIONSHIP BETWEEN PROPRIOCEPTION AT THE KNEE JOINT AND GAIT ATAXIA IN HSAN III

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Abstract

Hereditary sensory and autonomic neuropathy type III features a marked ataxic gait that progressively worsens over time. We assessed whether proprioceptive disturbances can explain the ataxia. Proprioception at the knee joint was assessed using passive joint angle matching in 18 patients and 14 age-matched controls; 5 patients with cerebellar ataxia were also studied. Ataxia was quantified using the Brief Ataxia Rating Score, which ranged from 7 to 26/30. Neuropathy patients performed poorly in judging joint position: mean absolute error was $8.7 \pm 1.0^\circ$ and the range was very wide (2.8 – 18.1°); conversely, absolute error was only $2.7 \pm 0.3^\circ$ (1.6 – 5.5°) in the controls and $3.0 \pm 0.2^\circ$ (2.1 – 3.4°) in the cerebellar patients. This error was positively correlated to the degree of ataxia in the neuropathy patients but not the cerebellar patients, suggesting that poor proprioceptive acuity at the knee joint is a major contributor to the ataxic gait associated with hereditary sensory and autonomic neuropathy type III.

Keywords

congenital insensitivity to pain; familial dysautonomia; joint sense; hereditary sensory & autonomic neuropathy; muscle spindles; proprioception; Riley-Day syndrome

INTRODUCTION

A characteristic feature of patients with hereditary sensory and autonomic neuropathy type III (Riley-Day syndrome, familial dysautonomia) is their markedly ataxic gait, which progressively worsens over time. They also have absent tendon and H-reflexes, perform poorly in the finger-to-nose pointing task and exhibit a positive Romberg sign.^{1,2} Based upon clinical examination, an early neurological study stated that “touch, vibration and position sense are all intact,”² whereas a more recent study showed that vibratory thresholds are elevated in the majority of HSAN III patients.³ The purpose of the current study was to

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Authors' roles

VGM, LNK and HK were responsible for the overall design of the experiment. VGM and LNK conducted the primary data acquisition and data analysis. VGM drafted the manuscript. FA and HK were responsible for patient recruitment. HK was responsible for neurological assessments. All authors contributed to and approved the final manuscript.

Financial disclosures

The authors report no financial disclosures. This work was supported by the National Institutes of Health [U54NS065736 to HK & LNK] and the Dysautonomia Foundation, Inc (to FBA & HK).

measure proprioceptive acuity quantitatively and to determine whether proprioceptive disturbances can explain the ataxia.

METHODS

We studied 20 patients with molecular confirmation of a diagnosis of HSAN III (n=18) or HSAN IV (n=2). All patients were recruited from the Dysautonomia Center at New York University Langone Medical Center and gave informed consent to the procedures. In addition, we studied five patients with severe cerebellar ataxia, four with the cerebellar type of multiple system atrophy (MSA c) and one with adult onset sporadic spinocerebellar ataxia. Recordings from 14 control subjects were obtained in the laboratory of the corresponding author. The participants were seated with their back supported and their knees pendent at 90°. Digital inclinometers (Angle Cube; QUINT Graphics, USA) were taped to the lateral aspect of each leg, such that the angle was 0.00° in the vertical (knee suspended) position. The reference (right) knee was passively rotated by one experimenter into one of six angles, each commencing from 0°: 7°, 14° or 21° in flexion or extension. Each block of angles was presented in a quasi-random fashion eight times. The indicator (left) knee was then passively moved, either in the same or opposite direction to which the reference knee was placed, by another experimenter at a rate of ~2°/s until the subject reported that its perceived angle matched that of the reference knee. The indicator angles, and actual reference angles, were recorded and absolute differences calculated. After each trial both knees were passively moved into extension and allowed to fall back under gravity into their natural vertical position. Participants were then rated on the 5-item Brief Ataxia Rating Score (BARS)⁴; by the neurologist (HK) who was blind to each patient's proprioceptive data. All data were analysed using Prism 5 (GraphPad Software Inc, USA).

RESULTS

Ataxia

Except for the youngest patient, all HSAN III patients had an ataxic, broad-based gait and had difficulty turning. Eight patients could walk independently but 10 required assistance. All patients had absent deep tendon reflexes. The two HSAN IV patients were not ataxic, and their tendon reflexes were present. The Brief Ataxia Rating Score (BARS) revealed wide differences across the HSAN III patients, with values ranging from 7 to 26 out of a maximum of 30. The mean ($\pm$ SE) total BARS value was 16 ± 1 , comparable to that of the patients with cerebellar ataxia (13 ± 3). Composite and component scores for all patients are shown in Table I in the Appendix.

Proprioception

Although the HSAN III patients could detect the direction in which the knee was being rotated, they generally performed poorly in judging position. Figure 1 shows X-Y plots between the reference and indicator joint angles for two patients with HSAN III, two patients with cerebellar ataxia, the two patients with HSAN IV and two control subjects. The spread of absolute errors (differences between the indicator and reference joint angles) for all patients and controls is shown in Fig. 2. The range of errors in the control subjects was narrow, whereas for the HSAN III patients it was very wide. There was no significant relationship between mean error and age across all 18 HSAN III patients ($r=0.26$).

With the exception of three patients with low matching errors, all of the HSAN III patients had higher matching errors than the controls, but errors were within the normal range for the cerebellar and HSAN IV patients. On average, the absolute error was only $2.7 \pm 0.3^\circ$ in the controls and $3.0 \pm 0.2^\circ$ in the cerebellar patients, but $8.7 \pm 1.0^\circ$ in the HSAN III patients

($p < 0.0001$ vs controls). Similar differences were seen in the slope of the relationship between the angle of the indicator and reference joints, and the correlation coefficient between the two angles (see Table I in the Appendix).

Correlations between ataxia and proprioception

Matching error was positively correlated to the total ataxia score, while the slope and correlation coefficients were *inversely* correlated, with significant relationships being found between the gait, finger-to-nose, knee-to-tibia and oculomotor components of the BARS assessment (see Table II in the Appendix). There were no significant correlations between any of the proprioceptive parameters and the BARS score for dysarthria. Nor were there any significant correlations between the proprioceptive parameters and the ataxia scores for the cerebellar patients, despite the similar degrees of ataxia.

DISCUSSION

We have shown that proprioceptive performance in the HSAN III patients correlates significantly with certain measures of the Brief Ataxia Rating Score: gait, the finger-to-nose pointing test, the eye tracking test and the knee-tibia test. Successful performance in each of these assessments relies on intact proprioceptive inputs, as well as adequate sensorimotor integration and motor control. We have shown that those HSAN III patients exhibiting the poorest proprioceptive acuity had the highest ataxia scores. Conversely, proprioception was essentially normal in the two HSAN IV patients we examined. Proprioceptive acuity was also normal in the cerebellar patients; by definition, their ataxia was centrally mediated, but it would appear from our data that proprioceptive afferents do gain sufficient access to perceptual levels to allow these patients to judge the positions of their limbs in space. It is known that the inferior olive receives proprioceptive information from the periphery as well as corollary information from the cerebellum⁵, so one might expect that cerebellar damage could compromise the information capacity of proprioceptive inputs. However, there are no changes in proprioceptive feedback provided by muscle spindles in cats with experimentally-induced cerebellar ataxia⁶ or in patients with cerebellar degeneration.⁷ Given that the proprioceptive and cerebellar systems both play important roles in sensorimotor feedback, it is clear that damage to one or other component will result in similar motor deficits, expressed as ataxia.⁸

We recently used intraneural microelectrodes to record from the common peroneal nerve in HSAN patients and showed that HSAN III patients are devoid of muscle spindle afferents, though they are still present in HSAN type IV patients.⁹ Conversely, patients with HSAN III and HSAN IV do have apparently normal cutaneous sensibility - they can feel light touch on the skin. Our recent study confirmed the presence of apparently normal tactile afferents in HSAN III,⁹ and histological studies have identified normal Meissner and Pacinian corpuscles in the skin.¹⁰⁻¹¹ Although muscle spindles provide the central nervous system with its most important source of proprioceptive information,¹² we know that certain types of cutaneous afferent can encode joint movements¹³⁻¹⁵ and that proprioceptive signals can be obtained from cutaneous afferents in the absence of changes in muscle afferent input.¹⁶ It is interesting that some HSAN III patients were not as bad as others in matching angular position, and given the loss of functional muscle spindles this suggests that certain individuals are better able to utilise proprioceptive signals provided by stretch receptors in the skin.

While this study has shown that the marked gait ataxia in HSAN III can largely be explained by loss of proprioceptive acuity, attributable to the loss of functional muscle spindles, we cannot rule out disturbed function in other systems. Indeed, while there is little evidence of gross cerebellar atrophy in these patients,¹⁷ there is some MRI evidence of white matter loss

in the middle cerebellar peduncle.¹⁸ Histological data is rare in HSAN III, but one case study showed that the diameters of α motoneurons and ventral root axons are not changed, but that the diameters of the dorsal roots and cell bodies in the dorsal root ganglia are reduced.¹⁹ Moreover, there is evidence of demyelination of the dorsal columns,²⁰ again supporting the conclusion that HSAN III primarily affects sensory, rather than motor, systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Proprioceptive acuity, assessed by passive joint angle matching at the knee in two control subjects (**A**, **B**), two patients with HSAN III (**C**, **D**), two patients with cerebellar ataxia (**E**, **F**) and two patients with HSAN IV (**G**, **H**). The angle of the reference knee is shown on the abscissa and the angle of the indicator knee is shown on the ordinate; all numbers are in degrees. Positive angles (relative the knee at 90°) indicate a dorsiflexed position of the knee and negative angles indicate a plantarflexed position. Lines of best fit (linear correlations) are shown superimposed on the data. Note that the slope of the relationship between the reference and indicator angles is lower than control values for the two patients with HSAN III but not those with HSAN IV or cerebellar ataxia.

Figure 2.

Joint matching errors (absolute difference between reference and indicator joints) for the 15 HSAN III patients, 14 control subjects, 5 cerebellar patients and 2 HSAN IV patients. Values (in degrees) are presented as mean error $\pm$ SD, calculated from all 48 matching trials conducted in each subject (6 angles $\times$ 8 trials), and sorted in ascending order for each group. The broken horizontal line indicates the magnitude of the highest error recorded in a control subject. All but three of the HSAN III patients had higher matching errors than the controls, while the matching errors of the cerebellar patients (cereb) and the HSAN IV patients were within the normal control range. Variability of error was also higher for the HSAN III patients.