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Abstract

BACKGROUND: Unsteadiness during standing and walking is a frequent complaint of patients with polyneuropathy (PNP). OBJECTIVE: To determine whether balance disorders in patients with PNP may be caused by reduced proprioceptive input from the feet alone or whether impaired vestibular input, resulting from involvement of the vestibular nerve, can be an additional factor. METHODS: A total of 37 patients (mean age 65 years +/- 12 SD; 12 women) with electrodiagnostically confirmed PNP (predominantly axonal: 18; predominantly demyelinating: 19) underwent horizontal search-coil head-impulse testing, which assesses the high-acceleration vestibulo-ocular reflex (VOR). RESULTS: Relative to a healthy comparison group, the gains (eye velocity divided by head velocity) of the horizontal VOR were reduced in 27 of 37 patients (unilateral: 13; bilateral: 14). The percentages of patients with unilateral or bilateral VOR deficits were not significantly different between patients with axonal or demyelinating PNP. CONCLUSIONS: Two thirds of patients with axonal or demyelinating polyneuropathy (PNP) showed unilateral (approximately 50%) or bilateral (approximately 50%) gain reductions of the horizontal high-acceleration vestibulo-ocular reflex. This finding suggests that, in many patients with PNP, the neuropathic process includes the vestibular nerve. Such information is highly relevant for subsequent physical therapy, since vestibular exercise improves balance control and reduces disability.
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ABSTRACT

Background: Unsteadiness during standing and walking is a frequent complaint of patients with polyneuropathy (PNP).

Objective: To determine whether balance disorders in patients with PNP may be caused by reduced proprioceptive input from the feet alone or whether impaired vestibular input, resulting from involvement of the vestibular nerve, can be an additional factor.

Methods: A total of 37 patients (mean age 65 years ± 12 SD; 12 women) with electrodiagnostically confirmed PNP (predominantly axonal: 18; predominantly demyelinating: 19) underwent horizontal search-coil head-impulse testing, which assesses the high-acceleration vestibulo-ocular reflex (VOR).

Results: Relative to a healthy comparison group, the gains (eye velocity divided by head velocity) of the horizontal VOR were reduced in 27 of 37 patients (unilateral: 13; bilateral: 14). The percentages of patients with unilateral or bilateral VOR deficits were not significantly different between patients with axonal or demyelinating PNP.

Conclusions: Two thirds of patients with axonal or demyelinating polyneuropathy (PNP) showed unilateral (≈50%) or bilateral (≈50%) gain reductions of the horizontal high-acceleration vestibulo-ocular reflex. This finding suggests that, in many patients with PNP, the neuropathic process includes the vestibular nerve. Such information is highly relevant for subsequent physical therapy, since vestibular exercise improves balance control and reduces disability.


GLOSSARY

CIDP = chronic inflammatory demyelinating polyneuropathy; hVOR = horizontal vestibulo-ocular reflex; PNP = polyneuropathy; qHIT = quantitative head-impulse test; VOR = vestibulo-ocular reflex.

It is generally assumed that postural imbalance and unsteadiness in patients with polyneuropathy (PNP) result from reduced somatosensory input to the brain from the distal part of the legs.1 Additional vestibular impairment, however, could also play a role, i.e., imbalance in patients with PNP may be multisensory.2 From a therapeutic perspective, the recognition of such an additional vestibular impairment is pivotal, because therapeutic strategies focusing on vestibular rehabilitation are able to improve postural stability.3,5

So far, a concomitance of peripheral neuropathy and vestibular impairment as determined by caloric irrigation has been described in two populations of patients with PNP. 1) Half of patients with auditory neuropathy and associated PNP showed reduced caloric vestibular responses.6 The positive family history in many of these patients hints at a possible hereditary vestibulo-cochlear syndrome associated with PNP. 2) Similarly, in half of patients with PNP with dizziness as the predominant symptom, caloric responses were unilaterally or bilaterally reduced.7 Limits for normal caloric responses used in this study, however, did not conform to a

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generally accepted standard. Overall, the inclusion criteria in both cited studies prevent drawing any conclusions about the prevalence of vestibular impairment in a general population of patients with PNP. Moreover, caloric testing, used in these studies to quantify vestibular function, assesses the vestibular system at a frequency range well below the frequencies relevant during daily life.9

To clarify the prevalence of vestibular impairment in unselected patients with predominantly axonal or predominantly demyelinating PNP, we conducted a prospective study using search-coil head-impulse testing, which assesses vestibular function at natural stimulus frequencies.9,10

METHODS Participants were selected from patients referred to our academic neurologic center for further evaluation of polyneuropathic symptoms. Detailed history taking and complete neurologic examination were performed. Patients were specifically assessed for spontaneous and gaze-evoked nystagmus, correcting saccades following Halmagyi-Curthoys head impulses,11 positional and positioning nystagmus, muscle atrophy and weakness, hyporeflexia and areflexia, as well as stand, gait, and limb ataxia. Sensory examinations included touch, pain, temperature, vibration, and position sense. Vibration sense was tested with a 128 Hz tuning fork at the ankles, knees, and index fingers and considered reduced at 4/8 or below. Patients were examined by two of the authors (A.S. and A.S.-P.).

All patients underwent both electroneurographic and electromyographic investigations. Independent of the clinical severity of symptoms, a consecutive 37 patients (65 ± 12 years; 12 women) with electrophysiologic signs of PNP, but no cerebellar impairment and no extraordinary muscle palsy, were included in the study. Standard nerve conduction studies (motor and sensory) included the median, ulnar, sural, and peroneal nerves on both sides. If peroneal nerve conduction velocities ranged within normal limits or if distal peroneal compound muscle action potentials were not detectable, tibial nerves were also investigated. Electromyography was performed in the abductor digiti minimi, intersosseus dorsalis I, and in the tibialis anterior muscles on both sides. If tibialis anterior muscle activity was normal, extensor digitorum brevis and abductor hallucis were additionally investigated. Axonal PNP was diagnosed in the presence of 1) marked amplitude reduction of compound sensory action potentials, 2) marked slowing of motor and sensory nerve conduction velocities, 3) no or only mild reduction in nerve conduction velocities, and 4) electromyographic signs of denervation. Conversely, demyelinating PNP was diagnosed in the presence of 1) marked prolonged distal motor latency of the compound muscle action potentials, 2) marked slowing of motor and sensory nerve conduction velocities, 3) abnormal temporal dispersion or motor conduction blocks, 4) relative preserved amplitudes of compound muscle action potentials upon distal stimulation, 5) marked prolonged latencies of F-waves, and 6) absence of electromyographic signs of denervation. If both axonal and demyelinating electrophysiologic signs were present, the classification of the patient (predominantly axonal or predominantly demyelinating) was based on the predominance of criteria. Age-related normative values were taken from Ludin.12 Additional tests in all patients included serum protein electrophoresis, immunoelectrophoresis, and vasculitis screening. Independent of the clinical severity of PNP, CSF analysis was performed in all patients, which is standard procedure in our academic neurology department, unless the exact cause of the PNP is unambiguous after the clinical, electrophysiologic, and serologic assessments. Ten of 37 patients further underwent nerve and muscle biopsy, 10 of 37 patients cranial MRI, and 13 of 37 patients MRI or CT of the spine.

All patients were evaluated with the quantitative head-impulse test (qHIT). qHIT was performed by a technician who was unaware of the results of the electrophysiologic examinations. In all patients, qHIT was performed within 2 weeks of the electrophysiologic investigations. Eye and head movements were recorded in a magnetic frame (Remmel type system, modified by A. Lasker, Baltimore, MA) using search-coils, which were calibrated before each session.13 Horizontal head impulses (amplitude: 20–40; duration: 150–200 msec; peak velocity: 300 °/s; peak acceleration: 10,000 °/s2) were applied by an investigator standing behind the subject who was visually fixing upon a target light 1.24 m straight ahead. The directions of the head impulses were pseudorandomly intermingled and four to six impulses were performed in each direction. The gain of the horizontal vestibulo-ocular reflex (hVOR) was determined by computing the coefficient eye-in-space displacement divided by head-in-space displacement as head-in-space moved from 3° to 7° eccentricity from straight ahead.14 As the representative gain during head impulses to either side, the median value was computed. Median gain values were considered pathologic, if they were below two standard deviations of the average gain determined in a healthy control group. This group consisted of 14 healthy subjects (7 women; 25–75 y; 55 ± 15 y), who were selected by age frequency matching from a previously published population of 28 healthy subjects (15 women; 18–75 y; 44 ± 15 y).15 By this procedure we ensured that the average ages of patients and control subjects were not significantly different.

All subjects gave informed consent to participate in the study. The protocol was approved by a local ethics committee and was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS The average age of patients with PNP (12 women) was 65 ± 12 years (range 25–83) at the time of study enrollment. Average ages of patients with predominantly axonal (66 ± 10 y; n = 18, 8 women) and patients with predominantly demyelinating PNP (65 ± 13 y; n = 19, 4 women) were similar. Average duration of symptoms, as recorded in the medical histories, was 6.7 ± 5.5 years (range 1–20). Abnormal clinical findings on patients with PNP included the following: 1) unilaterally (n = 12) or bilaterally (n = 10) abnormal bedside head-impulse tests; 2) stand and gait ataxia (n = 29); 3) sensory deficits (touch: n = 37; pain: n = 33; temperature: n = 33; position: n = 19; vibration: n = 25); and 4) abnormal motor signs (muscle atrophy: n = 20; muscle weakness: n = 19; hyporeflexia or areflexia: n = 33 patients). The following etiologic factors for PNP were identified: diabetes mellitus (n = 5, 4 axonal), Waldenström macroglobulinemia (n = 3, none axonal), small-cell lung cancer paraneo-
plastic disorder with positive anti-Hu antibodies (n = 1, axonal), cancer chemotherapy (n = 2, 1 axonal), hereditary disorders (hereditary motor and sensory neuropathy type II: n = 2), and chronic inflammatory demyelinating polyneuropathy (CIDP) (n = 9). In 15 patients (10 axonal), PNP was idiopathic.

Compared to healthy subjects, the average gain (eye velocity divided by head velocity) of the high-acceleration hVOR was reduced in patients with PNP (figure 1). Although many individual gain values recorded from patients with PNP during qHIT to either side (two data points per subject) were in the normal range (above dashed line), the average gain value was below the average gain value of the healthy comparison group (comparison group: 0.85 ± 0.07 SD; patients with PNP: 0.67 ± 0.14 SD; unpaired two-tailed t test: p < 0.01). Overall, 27 patients (73%; 56 ± 24 y; 10 women) showed deficient hVOR gain values in one or both directions (unilateral: 13; bilateral: 14), while hVOR gain values to both sides were normal in 10 patients. Figure 2 depicts three typical examples of horizontal eye and head position traces during horizontal qHIT to both sides (A: normal hVOR gains in a patient with CIDP; B: unilaterally reduced hVOR gain in a patient with predominantly axonal PNP of unknown etiology; C: bilaterally reduced hVOR gains in a patient with CIDP).

Average gain values during qHIT to either side were not significantly different between patients with predominantly axonal (0.66 ± 0.16 SD; n = 18) and patients with predominantly demyelinating (0.68 ± 0.13 SD; n = 19) PNP. Vestibular hypofunction was found in 81% of patients with predominantly axonal and in 63% of patients with predominantly demyelinating PNP (figure 3). The numbers of patients with bilateral normal gains, unilateral gain reduction, or bilateral gain reduction showed a distribution that was not different between both PNP groups (χ² test: p = 0.69, Fisher exact probability test: p = 0.77). When hVOR gains to both sides were averaged in each patient, values were abnormal in about half of the patients (predominantly axonal: 50%; predominantly demyelinating: 58%). The distribution of normal and abnormal average hVOR gains was not different between the two PNP groups (χ² test: p = 0.63, Fisher exact probabil-
normally ranges around 7–15 msec. With standard deviation, one would expect that demyelinating PNP. In contrast to a process of axonal neuropathy, vestibular nerve is comparable in both classes of PNP. In this prospective study, more than two thirds of patients with clinical and electrophysiologic signs of PNP showed an additional impairment of the hVOR. Thus, in many patients with PNP, the neuropathic process seems to involve the vestibular nerve. To assess the hVOR, we applied qHIT, which probes the vestibular system at frequencies that are relevant during locomotion and natural head movements. We therefore conjecture that imbalance, if present in patients with PNP, is frequently due to both proprioceptive and vestibular deficits, i.e., represents a multisensory balance disorder.

The percentages of unilateral and bilateral vestibular deficits were similar in patients with predominantly axonal and in patients with predominantly demyelinating PNP. This suggests that the vulnerability of the vestibular nerve is comparable in both classes of PNP. In contrast to a process of axonal damage, however, one would expect that demyelination would prolong the latency of the VOR, which normally ranges around 7–15 msec.16 With standard methods of latency measurements we could not find significant differences between the two groups of patients with PNP. More sophisticated methods of time series analysis and higher recording sample rates (in this study: 1,000 Hz) might differentiate ocular responses from head impulses between the two PNP groups. Alternatively, brainstem auditory evoked responses may be more sensitive in detecting latency changes of the vestibulo-cochlear nerve.17

The strong association of PNP with vestibular dysfunction found in our study suggests a common pathomechanism. This impression is supported by a recent study in which 22% of patients with bilateral vestibulopathy were also diagnosed with PNP.18,19 Among the patients with bilateral vestibulopathy and PNP, about one third had additional cerebellar signs, which led the authors to speculate that the combination of vestibular, polyneuropathic, and cerebellar deficits may be due to a common neurodegenerative or autoimmune pathomechanism. The patients with PNP in our study lacked cerebellar signs; nevertheless, the association of vestibular and polyneuropathic deficits was evident. Possibly, there is a continuum between different combinations of polyneuropathic, vestibular, and cerebellar signs and symptoms, depending on the etiology and duration of the underlying disease.

The aim of our study was to detect an additional vestibular impairment in patients with PNP. The fact that patients with PNP were referred to an academic neurology department may represent a bias factor in neuropathic etiology and disease severity and consequently also in vestibular involvement. The surprisingly high percentage of deficient high-acceleration hVOR found in this study, however, should prompt more comprehensive neuro-otologic studies on patients with PNP, including turntable testing, caloric irrigation, vestibular evoked myogenic potentials, posturography, and auditory testing. Moreover, we advise clinicians to perform the bedside head-impulse test, which allows a reliable estimation of vestibular function outside the vestibular laboratory.11,20

The detection of an additional vestibular deficit impacts physical therapy, which then should include vestibular exercises to improve balance control. Physical therapy has been shown to enhance vestibular function and to improve compensatory proprioceptive and visual sensory strategies.4,5

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