Abstract

Hereditary motor and sensory neuropathy, also known as Charcot-Mari-Tooth disease (CMT), belongs to a complex and heterogeneous group of hereditary peripheral nerve diseases. The most common form of this disease is the motor and sensory neuropathy type 1A (CMT1A). The main symptoms of the disease are symmetric paresis, located initially in the distal segments of the limbs, gait and balance problems, bone deformities and altered sensation. The aim of the study is to identify and review literature on maintaining postural control in patients with hereditary motor and sensory neuropathy and to provide information on what causes balance impairment. The literature review was conducted by searching Medline, Embase and Scopus databases. The following keywords were used in the search: ‘hereditary motor sensory neuropathy’, ‘charcot marie tooth’, ‘hereditary neuropathy’, ‘balance’, ‘posture’, ‘balance control’, ‘postural control’, ‘postural organization’, ‘somatosen*’. The author took into consideration all articles that appeared in the search up to September 2020. Additionally, the bibliography of selected articles was searched. The search identified 310 articles. After the final selection 7 articles were included in the review. The conclusions are: 1. There are very few studies on postural control in patients with hereditary motor and sensory neuropathy. 2. Investigators use different methodology to assess postural control, which makes it difficult to draw clear conclusions about the cause of balance impairment. 3. There is a need for a well-designed study on a larger number of patients divided into groups according to the type of hereditary neuropathy.

Keywords: Charcot-Marie-Tooth, hereditary neuropathy, postural control

Introduction

Hereditary motor and sensory neuropathy, also named Charcot-Mari-Tooth disease (CMT) after the researchers who first reported it, belongs to a complex and heterogeneous group of hereditary peripheral nerve diseases. The most common form of this disease is the motor and sensory neuropathy type 1A (CMT1A) caused by duplication of the PMP-22 gene. The consequences of the disease are motor and sensory disorders in peripheral nerves, which are affected by demyelination and degeneration. The main symptoms of the disease are symmetric paresis, located initially in the distal segments of the limbs, gait and balance problems, bone deformities and altered sensation [1–3]. Usually vibration perception is altered first because in CMT1A demyelination occurs...
primarily in large myelinated fibres (type Ia). A correlation between a decreased ability to perceive vibration and postural instability in different groups of patients (e.g. after a stroke, with diabetic polyneuropathy) has been observed and, consequently, the importance of retaining somatosensory feedback for maintaining a stable posture was stressed [1,4,5]. A similar correlation, although with less prominent consequences, has been established between postural instability and exteroceptive sensation [1]. It has been found that sensory input from proprioceptors and skin receptors is essential for maintaining standing balance. Only as the challenges to posture increase, it is necessary to integrate the information (at the level of the central nervous system) from other organs belonging to the balance system, i.e. from the vestibular and visual systems [6]. A thesis has been formulated that impairment of postural control is mainly the result of the damage to group Ia afferent nerve fibres [7–9]. However, no correlation was found between the increase in body sway and nerve conduction velocity in large-diameter afferent fibers [4,7–9].

The aim of the study is to identify and review literature on maintaining postural control in patients with hereditary motor and sensory neuropathy.

### Materials and methods

#### Search strategy

The author reviewed literature on maintaining postural control in patients with hereditary motor and sensory neuropathy. The literature review was conducted by searching MEDLINE, EMBASE and SCOPUS databases. The following keywords were used in the search: ‘hereditary motor sensory neuropathy’, ‘charcot marie tooth’, ‘hereditary neuropathy’, ‘balance’, ‘posture’, ‘balance control’, ‘postural control’, ‘postural organization’, ‘somatosens*’.

The author took into account all articles that appeared in the search up to September 2020. In addition, the bibliography of selected articles was searched in order to identify publications that met the search criteria but were not identified during the search of electronic databases.

#### Selection

In the first selection the author took into account articles that met the following criteria: (1) the study group consisted of adults with a diagnosis of hereditary motor and sensory neuropathy; (2) the main endpoint was a standing balance assessment performed on a stabilometric platform; (3) the study used standard norms for balance measurement or there was a control group with which the study group was compared; (4) the article was in English, German or Polish.

Case reports and case series were not taken into account in the review.

#### Results

The electronic search identified a total of 310 articles (Medline – 134, Embase – 83, Scopus – 93) (Fig. 1).

![Fig. 1. Flowchart of search strategy and selection of studies for inclusion in the review](image)
### Tab. 1. Description of the studies included in the review

<table>
<thead>
<tr>
<th>Author</th>
<th>Measurement of postural stability</th>
<th>Study participants</th>
<th>Main conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geurts et al. [10]</td>
<td>Velocity of COP: (1) standing barefoot with EO, EC and in smudged glasses for 20 sec; (2) modified Stroop test 3 × 30 sec in sitting position</td>
<td>HMSN I HMSN II HS</td>
<td>Compared to the control group, patients with HMSN show decreased effectiveness of postural control as well as increased visual control of posture in standing position.</td>
</tr>
<tr>
<td>Nardone et al. [7]</td>
<td>Sway area: (1) standing with feet together, EO and EC for 51 sec; (2) standing with feet 10 cm apart, EO and EC for 51 sec</td>
<td>CMT1A HS</td>
<td>Most CMT1A patients are able to maintain a normal standing position because their Aβ fibres are only slightly altered anatomically or functionally.</td>
</tr>
<tr>
<td>Nardone et al. [8]</td>
<td>Sway area: standing with feet 10 cm apart, EO and EC for 51 sec</td>
<td>CMT1A CMT2 DN HS</td>
<td>CMT2 and DN patients are unstable when standing. CMT1A patients show only a slight deterioration of postural control (statistically insignificant) compared to healthy subjects due to the fact that their Aβ fibres are relatively spared.</td>
</tr>
<tr>
<td>van der Linden et al. [1]</td>
<td>Velocity of COP: (1) standing with EO; (2) standing with EC; (3) standing with EO on uneven surface; (4) standing with EC on uneven surface. Each task lasted 30 sec</td>
<td>CMT1A SMA (distal) HS</td>
<td>Compared to healthy subjects, postural stability is seriously weakened in both groups. Postural instability of CMT1A patients correlates significantly with a weakened vibration sensation.</td>
</tr>
<tr>
<td>Nardone et al. [11]</td>
<td>Sway area: standing with EO and EC. Each test lasted 51 sec</td>
<td>CMT1A DN HS</td>
<td>Patients with CMT1A show a normal body sway area in standing position, while in patients with diabetic neuropathy the sway area is larger compared to both healthy subjects and CMT1A patients.</td>
</tr>
<tr>
<td>Tozza et al. [12]</td>
<td>Velocity of COP and sway area: standing with EO and EC, feet 10 cm apart. Each test lasted 51 sec</td>
<td>CMT1A HS</td>
<td>Compared to healthy subjects, patients with CMT1A show weakened postural stability. Instability seems to be related to the weakening of the dorsal flexors of the foot in people with a mild course of CMT1A.</td>
</tr>
<tr>
<td>Costa et al. [13]</td>
<td>Velocity of COP: three measurements with EO and EC, each measurement lasted 15 sec.</td>
<td>CMT2G HS</td>
<td>In a mild course of the disease, postural instability of patients with CMT2G results from weakening of the dorsal and plantar flexors of the foot. In the more advanced form of the disease, weakened lower leg muscles and impaired proprioception are the cause of poorer postural control.</td>
</tr>
</tbody>
</table>
Of these, 299 items were excluded from the review. The main reasons for excluding these publications were: (1) the publication did not directly address the topic of the review; (2) the study group did not meet the inclusion criteria; (3) the endpoints did not meet the inclusion criteria.

After the pre-selection (based on the title and abstract) the author identified 11 articles. After reviewing bibliographies of the pre-selected articles, 2 more publications were added to the list. Eventually, after the final selection, 7 studies were included in the review. Table 1 presents a description of the studies included in the review and conclusions of their authors.

Discussion

The aim of this study is to provide information on organization of postural control in patients with Charcot-Marie-Tooth disease and to determine whether patients with hereditary neuropathy suffer from balance impairment and if so, what is the cause of this.

Morphometric tests have shown that in patients with CMT1A demyelination occurs mainly in large-diameter motor and sensory fibres, while thinner myelinated fibres (type II) are relatively spared by the disease [7,9]. Type Ia fibres are sensitive to changes in velocity and are stimulated even by a slight and rapid expansion of the muscle. Their loss may therefore lead to a delay in muscle response when the body has to react to a suddenly disturbed balance, but most likely it should not cause body sways while maintaining a stable standing posture. The question therefore arises as to whether large-diameter afferent fibres are actually indispensable for stabilization of the body when standing, or whether the information conducted along the fibres of a smaller diameter (group II afferent fibres) plays an essential role in optimizing postural control [7].

Research by Nardone et al. has confirmed reports by Dyck et al. that patients with CMT1A are characterized by total functional loss of Aα fibres. Large-diameter Ia afferent fibres, also known as Aα fibres, are primarily responsible for the innervation of primary endings of muscle spindles and Golgi tendon organs, which are part of the proprioceptive system [14,15]. The study by Nardone et al. found that despite the dysfunction of these fibres, postural control in patients with CMT1A was only slightly weaker in comparison to healthy subjects [7–9,16]. After dividing patients into groups according to the severity of the disease, it turned out that the balance is significantly weaker in patients with more advanced disease. The authors therefore proposed that the functional loss of Ia fibres is not in itself detrimental to the control of standing balance. Consequently, good control of standing balance in most CMT1A patients may result from the fact that type II fibres are spared by the disease, thus providing sufficient proprioceptive information to maintain a standing position [7,8,16].

In turn, the increased body sway in patients with more severe form of the disease may be linked to the fact that in these patients both types of fibres (group Ia and II) are affected by the disease [7,14]. Postural control has also been impaired in patients with CMT2, which is an axonal and more severe form of hereditary motor and sensory neuropathy. It is characterized by a severe reduction of filaments and microtubules in myelinated axons, and the damage affects both Aα and Aβ fibres [8,14]. On the basis of the results of these studies, it seems safe to propose that damage to the largest motor and sensory fibres, especially α-motoneurons and group Ia fibres, is not in itself detrimental to the control of standing balance. Only damage to a wider spectrum of sensory fibres, including afferent fibres of both larger and smaller diameter (group Ia and II), leads to a significant impairment of postural control [9]. This claim is supported also by the results provided by the studies in patients with diabetic polyneuropathy, whose balance is significantly weaker compared to healthy subjects [5,8,9]. Morphometric studies have shown that, in contrast to CMT1A patients, where demyelination concerns mainly large fibres, patients with diabetic neuropathy show a loss of both large and smaller afferent fibres, with the thin fibres being usually more affected [9]. This is in line with the results of a study by Nardone et al., in which 11 out of 22 patients with diabetic neuropathy and only 3 out of 15 patients with CMT1A had impaired sensation of prickly pain, which is conducted through small diameter fibres [9].

However, a study carried out by van der Linden et al. has produced different results. Despite reports from Nardone et al. on the key role of type II fibres in maintaining a stable standing posture, previous studies indicated that there is indeed a significant relationship between perception of vibration and postural instability in different patient groups [4]. Therefore, van der Linden et al.
al. decided that the impact of somatosensory disorders on postural control remains controversial. Apart from assessing the effect of Ia afferent fiber loss, the authors studied also a relationship between muscle weakness and balance impairment in patients with CMT1A. The results showed that in people with hereditary motor and sensory neuropathy postural control was significantly weakened in comparison to healthy people. Moreover, postural instability was significantly correlated with a weakened perception of vibration. In the discussion the authors referred to the study by Nardone et al., suggesting that differences may result from the fact that different methodology were used to perform posturography in the two studies [1]. Both Nardone et al. and van der Linden et al. used static posturography, but different parameters were used to evaluate postural control. In their measurements Van der Linden et al. used the coordinates of the centre of foot pressure (COP), from which the root mean square (RMS) amplitude of the velocity of the centre pressure (VCOP) and the sway mean amplitude in the anterior-posterior (AP) and medial-lateral (ML) direction were calculated. Based on previous studies evaluating various parameters of stabilometric measurements, the root mean square amplitude of the velocity of the centre pressure was selected as the basic parameter of body position, as it is particularly sensitive to high-frequency fluctuations in the centre of pressure (>0.4 Hz) [1]. And it is the loss of vibration that induces body sways in the high-frequency band [1,17]. Nardone et al., on the other hand, assessed the body sway area in CMT patients, which is a parameter that poorly reflects body sways in the high-frequency band [10]. Actually, studies have shown that the root mean square amplitude of the velocity of the centre pressure is indeed a reliable and validated measurement used in the assessment of standing postural control [10]. This has also been confirmed in a study by Tozza et al., where the body sway area in CMT patients did not differ from the control group, while the measurement of the velocity of the centre pressure showed significant differences between the study group and the control group [12]. Furthermore, the results of the study carried out by van der Linden et al. are in line with the study by Geurts et al., who also used the root mean square amplitude of the velocity of the centre pressure as the basic parameter for evaluation of postural control in patients with hereditary motor and sensory neuropathy. The results showed that patients with CMT present decreased effectiveness of postural control [10].

However, interpretation of this study should be approached with caution, as the study group included patients with hereditary motor and sensory neuropathy type I and type II, and the results were not divided according to the type of disease, but analysed together. Another aspect which has been taken into account in the assessment of postural control is the influence of muscle weakness on postural instability in people with CMT, which primarily concerns the lower leg muscles. In the study by van der Linden et al. no connection was found between reduced muscle strength and weakened posture control, and it is in line with the previous reports on how surprisingly little strength is needed to maintain a stable standing posture, and highlighting that this activity requires precise control by the nervous system [1,4,7,8]. However, the next two studies included in this review bring different conclusions. In the study by Tozz et al. it was noticed that CMT1A patients, even with a mild course of the disease, were characterized by weakened postural control resulting from weakened ankle dorsi-flexion muscles. There was no correlation, however, between balance impairments and weakened perception of vibration and weakened exteroceptive sensation [12]. Costa et al. evaluated patients with CMT2G. It was found that when the disease is mild, the main cause of postural control impairment is weakening of the dorsal and plantar flexor muscles of the foot. And in patients with a more advanced form of the disease impaired balance is the result of both weakened lower leg muscles and the loss of proprioception [13]. Lencioni et al. give an interesting view on the organization of postural control in patients with hereditary motor and sensory neuropathy [18,19]. It was not included in the review, however, because in their study the authors assessed the sit-to-stand movement and not the quiet standing on the stabilometric platform. They found that during the static phase (after obtaining stability following the transition to a standing position) thinner type II fibres and foot plantar flexors play the main role in maintaining a standing balance. However, the actual phase of achieving stability after getting up involves large type Ia fibres and foot dorsal flexors [18,19].

It appears that when the damage effects a wider range of afferent fibres in the lower limbs (both group Ia and group II), people with hereditary neuropathy show significant instability in standing position, as is the case with CMT2 and CMT2G patients and patients with diabetic polyneuropathy. However, in view of the reports by van der Linden et al., it is still controversial whether patients with a dysfunction of large Ia afferent fibres, whose group II fibres are spared by the disease, show postural instability when maintaining a standing position. The authors stress here the functional influence of somatosensory disorders associated with the loss of large myelinated fibres on postural control even in patients with a mild form of the disease [1].

Conclusions

Despite a small number of studies on the subject, it can be observed that authors used different methods
to assess postural control, which makes it difficult to draw clear conclusions. There is no doubt that further research is needed on larger group of patients divided according to the type and severity of hereditary neuropathy. Difficulty in maintaining a standing position is associated with an increased risk of falls and with serious limitations when performing various everyday activities. Therefore, it is important to determine whether patients with hereditary neuropathy suffer from balance impairment in terms of planning the rehabilitation process. It is also important to identify the dysfunction underlying the impaired postural control. If it is found that postural instability is closely related to the dysfunction of vibration sensation, it may be appropriate to introduce such forms of therapy as local vibration, e.g. vibrating shoe insoles [1,20].

**Funding**

This research received no external funding.

**Conflicts of interest**

The author declare no conflict of interest.

**References**

8. Nardone A, Grasso M, Schieppati M. Balance control in peripheral neuropathy. Difficulty in maintaining a standing position is associated with an increased risk of falls and with serious limitations when performing various everyday activities. Therefore, it is important to determine whether patients with hereditary neuropathy suffer from balance impairment in terms of planning the rehabilitation process. It is also important to identify the dysfunction underlying the impaired postural control. If it is found that postural instability is closely related to the dysfunction of vibration sensation, it may be appropriate to introduce such forms of therapy as local vibration, e.g. vibrating shoe insoles [1,20].