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PHENOTYPIC VARIABILITY AND DIAGNOSTIC CHARACTERISTICS IN INHERITED PERIPHERAL NEUROPATHY IN LATVIA

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Inherited peripheral neuropathies (IPN) are a clinically and genetically heterogeneous group of disorders. The most common IPN is Charcot-Marie-Tooth (CMT) disease. Here we describe IPN clinical variability and diagnostic characteristics in the Latvian population. A total of 101 patients were enrolled in the study. Genetic testing consisted of PMP22 *copy number analysis and whole-exome sequencing (WES). Clinical assessment comprised CMT Neuropathy Score version 2 (CMTNSv2), CMT Examination Score, pain, anxiety and memory/cognitive ability testing. The diagnostic yields for* PMP22 *copy number detection and WES were 45.8% and 77.8%, respectively. Disease severity assessment indicated high clinical heterogeneity, with CMTNSv2 scores ranging between 0 and 33. More than one-third of patients reported pain, and it was found to be significantly more common in patients with at least a mild anxiety level. From the initial development of symptoms, on average, it took more than 13 years for a diagnosis of IPN to be confirmed. This study updates the IPN genetic and clinical profile of the Latvian population and demonstrates the presence of a high level of heterogeneity. The time to diagnosis for IPN patients needs to be improved by employing multiplex ligation-dependent probe amplification initially followed by WES.*

Keywords: *genetic, Charcot-Marie-Tooth disease, phenotype, diagnosis.*

INTRODUCTION

Inherited peripheral neuropathies (IPN) are a clinically and genetically heterogeneous group of disorders. The majority of IPN are Charcot-Marie-Tooth (CMT) disease, while hereditary sensory and autonomic neuropathy, distal hereditary motor neuropathy and hereditary neuropathy with pressure palsies (characterised by a relapsing-remitting disease course) occur less frequently (Ramchandren, 2017; Bacquet *et al*., 2018).

CMT is not only the most common IPN but it is also the most common hereditary neuromuscular disorder with an approximate prevalence of 1 in 2500–3000. CMT is classified based on neurophysiological findings: CMT type 1 is demyelinating neuropathy, CMT type 2 is axonal neuropathy and CMT intermediate type is characterised by both demyelinating and axonal damage. CMT1A is the most common CMT subtype, followed by CMTX1 (Jeong *et al*., 2013; Bacquet *et al*., 2018; Bird, 2019).

Currently, there are more than 100 gene variants associated with CMT disease. Therefore, in this article, CMT types

will be defined according to the gene in which the disease-causative variant was identified. As the gene count causing CMT continues to rise, molecular disease confirmation can be challenging. There is still a substantial proportion of patients without an identified causative gene variant for the disease. Due to a high prevalence of *PMP22* duplication causing CMT1A in more than a half of CMT patients, the first diagnostic step is usually multiplex ligation-dependent probe amplification to determine *PMP22* copy number. Further, next-generation sequencing panels may be utilised, followed by whole-exome sequencing (WES) and even whole-genome sequencing (Bacquet *et al*., 2018).

CMT is not only genetically heterogeneous but also clinically heterogeneous. Patients with CMT show variance in the age of onset of symptoms, rate of progression and severity of symptoms, as well as nerve damage. The most frequent features are distal motor deficit, sensory loss and foot deformations (Bacquet *et al*., 2018; Bird, 2019). A high prevalence of neuropathic pain in CMT patients has recently been reported, especially in the *PMP22* dup (CMT1A) type (Azevedo *et al*., 2018; Bjelica *et al*., 2020). Interestingly, there is high clinical intrafamilial and interfamilial variability, even for families with the same disease-causing gene variant (Bacquet *et al*., 2018).

CMTX1 is caused by mutations in the *GJB1* gene that encodes connexin 32 protein (Cx32). Cx32 is expressed not only in the peripheral nervous system but also in the central nervous system (CNS). CMTX1 patients can exhibit CNS involvement with relapsing-remitting neurologic symptoms. There are controversial data pertaining to evidence of cognitive impairment prevalence and decreased volume of white matter in patients with CMTX1 (Chanson et al., 2013; Daniel *et al*., 2019; Tian *et al*., 2021).

There are several proposed biomarkers for disease progression (Rossor *et al*., 2020; Millere *et al*., 2021). However, due to slow disease progression and clinical variability, there are still no specific pharmacotherapies available for CMT. Regular rehabilitation — such as usage of orthoses, walking aids, surgery for deformations, regular physiotherapy and occupational therapy — is crucial to decrease functional disabilities and increase quality of life (Jeong *et al*., 2013; Johnson *et al*., 2014; Bird, 2019).

Here we describe the clinical variability, including the presence of neuropathic pain, and characterise the diagnosis of IPN in the Latvian population. For a small subgroup, we determine and compare memory impairment in patients with different CMT types and controls.

MATERIALS AND METHODS

Study participants were enrolled from geneticists', neurologists' and paediatric neurologists' clinical practices in an outpatient setting. Hereditary neuropathy was diagnosed based on either symptoms and clinical/neurophysiological examination and/or a confirmative genetic testing result. Patients responded to a sociodemographic questionnaire.

Patients were clinically and neurophysiologically evaluated with standardised tests. Neurography was conducted to characterise neurophysiological parameters; it was performed by a certified specialist according to the standard polyneuropathy protocol. Clinical characteristics were based on symptoms and objective neurologic examination findings, as well as using CMT Neuropathy Score version 2 (CMTNSv2) (Murphy *et al*., 2011) and the corresponding CMT Examination Score (CMTES) with exclusion of neurophysiologic findings. To assess the presence of neuropathic pain, the Douleur Neuropathique 4 (DN4) scale was employed. Furthermore, to evaluate the association of pain with anxiety, the General Anxiety Disorder-7 (GAD-7) scale was applied. Objective assessment of memory/cognitive ability was performed using a computerised neuropsychological test battery, CNS Vital Signs (CNSVS), which provides age-adjusted standard scores for verbal memory (i.e. recognition memory for words) and visual memory (i.e. recognition memory for designs).

An adapted phenol-chloroform method was used to isolate DNA from peripheral blood collected from patients and, if possible, their family members. The first step of our genetic analysis was determination of *PMP22* copy number using a multiplex ligation-dependent probe amplification kit P405 (MRC Holland, Netherlands) according to the manufacturer's protocol. For patients indicating CMTX type, *GJB1* was analysed by bidirectional sequencing with a BigDye Terminator Kit (ThermoFisher Scientific, USA) following an adapted manufacturer's protocol using primers published previously (Kovale *et al*., 2021). For patients with negative findings, WES was performed using a Twist Bioscience's Exome Library Preparation Kit produced by the biotechnology company CeGaT (Germany). We conducted the bioinformatics analysis using an in-house bioinformatics pipeline following best practice guidelines. Genetic variants were classified according to criteria recommended by the American College of Medical Genetics (Richards *et al*., 2015).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Central Medical Ethics Committee of Latvia (No. 3/18-03-21). Informed consent was obtained from all subjects involved in the study.

RESULTS

There were 101 patients from 72 families enrolled in this study. The mean age was 37.9 ± 18.4 years and the gender distribution was 46 male and 55 female patients. There were 18 children in our study group. The mean age in this subgroup was 12.6 ± 3.7 years and there were nine boys and nine girls.

The genetic analysis of our study group participants revealed that *PMP22* duplication occurred the most frequently (n = 44; index patients n = 33), followed by gene disease-causative variants in *GJB1* (n = 13; index patients n = 6) and *HINT1* (n = 6; index patients n = 3; causing neuromyo-

tonia and axonal neuropathy). Several patients displayed the *PMP22* deletion (n = 3; index patients n = 2; causing hereditary neuropathy with pressure palsies) and gene disease-causative variants in *MFN2* (n = 2; index patients n = 1; causing CMT2A), *HSPB1* (n = 2; causing distal hereditary motor neuropathy), *MPZ* (n = 1; causing CMT1B), *BSCL2* (n = 1; causing distal hereditary motor neuropathy) and *MORC2* (n = 1; causing CMT2Z). There were eight patients and six index patients with variants of unknown significance and 20 patients and 16 index patients still remained genetically undiagnosed following WES (Fig. 1). The diagnostic yields in our study group for *PMP22* copy number detection and WES were 45.8% and 77.8%, respectively.

Neurophysiological examination revealed that most of the patients (n = 78) had demyelinating neuropathy (CMT1). There were 16 patients with axonal neuropathy (CMT2) and five patients had the intermediate form with mixed demyelinating and axonal damage. Two study participants had no data regarding neuropathy in nerve conduction studies. When comparing the genetic characteristics of CMT1 and CMT2, we found that a higher proportion of CMT2 patients remained genetically undiagnosed following WES; 31.3% (n = 5) of CMT2 patients versus 19.2% (n = 15) of CMT1 patients.

The study group underwent a thorough clinical characterisation (Fig. 2). The majority of our patient group had typical inherited polyneuropathy symptoms, such as *pes cavus*, hammer toe and changed gait pattern. *Pes cavus* was found to be the most common feature (79.2%), followed by reduced deep tendon reflexes (76.2%) and difficulties in running (74.3%). The same symptom dominance was found in the paediatric subgroup. A minority of patients reported difficulties in hand manipulation (33.7%), foot callosities (21.8%) and acrocyanosis (18.8%).

Disease severity was assessed using the scoring systems of CMTNSv2 and CMTES (Table 1). A significant association was found between patient age and disease severity parameters (CMTNSv2, CMTES) ($p < 0.05$). The *GJB1* (CMTX1) group was the most severely affected according to CMTNSv2 and CMTES scores; however, the difference was not statistically significant ($p > 0.05$). Evaluating gender differences in the *GJB1* group, male patients (n = 6) had higher neuropathy severity scores (CMTNSv2 18.2 ± 9.9, CMTES 12.7 ± 6.8) compared with female patients (n = 7;

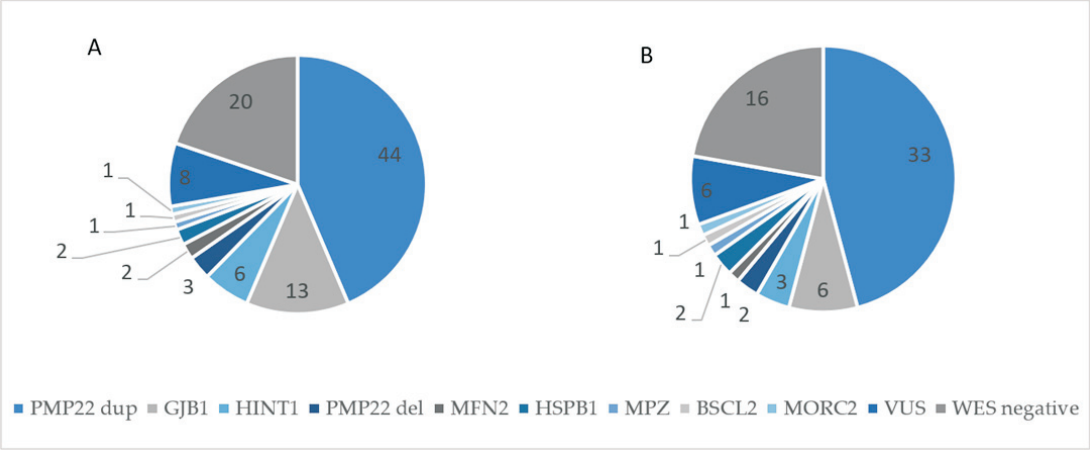

Fig. 1. Genetic characteristics of the study group (A; n = 101) and index patient group (B; n = 72) according to the gene in which the disease-causative variant was identified. VUS, variant of unknown significance; WES, whole- exome sequencing.

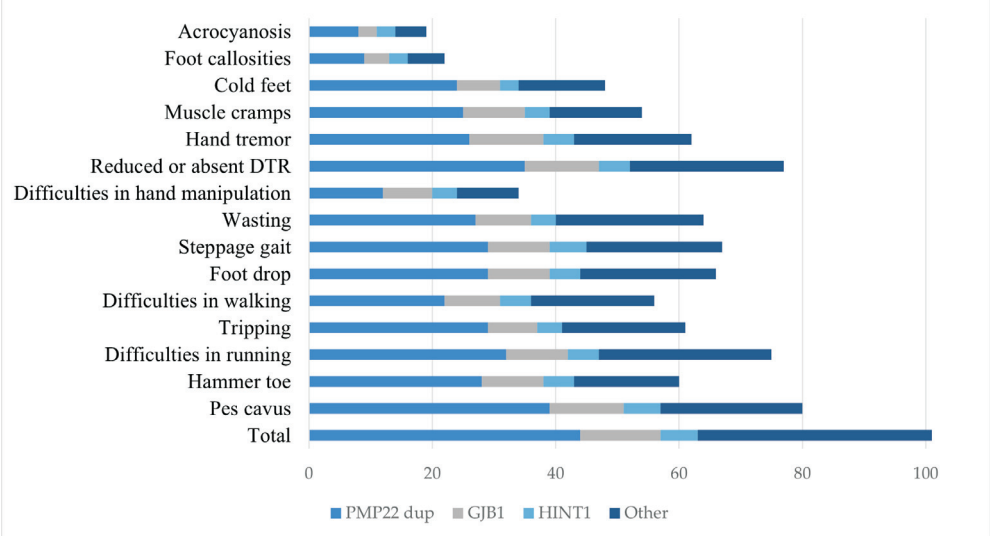

Fig. 2. Clinical variability of the patient group as a whole and according to the gene in which the disease-causative variant was identified. DTR, deep tendon reflexes.

Table 1. Disease severity characteristics of the patient group as a whole and according to the gene in which the disease-causative variant was identified

	Total n = 101	*PMP22* dup n = 44	*GJB1* n = 13	*HINT1* n = 6	Other n = 38
CMTNSv2 (SD), range	10.7 (7.6), 0–33	11.9 (6.5), 0–29	15.2 (9.9), 2–30	10.2 (5.1), 2–15	7.9 (7.5), 0–33
CMTES (SD), range	7.2 (5.7), 0–25	7.0 (5.2), 0–22	10.8 (7.2), 2–24	8.2 (4.2), 2–12	6.1 (5.6), 0–25

SD, standard deviation; CMT, Charcot-Marie-Tooth disease; CMTNSv2, CMT Neuropathy Score version 2; CMTES, CMT Examination Score

Table 2. Pain characteristics of adult patients as a whole and according to the gene in which the disease-causative variant was identified

	Total n = 83	*PMP22* dup n = 37	*GJB1* n = 11	*HINT1* n = 4	Other n = 31
Musculoskeletal pain	34 (41.0%)	15 (40.5%)	7 (63.6%)	1 (25.0%)	11 (35.5%)
Neuropathic pain (DN4)	23 (27.7%)	9 (24.3%)	5 (45.5%)	0 (NA)	9 (29.0%)

DN4, Douleur Neuropathique 4; NA, not applicable

Table 3. Anxiety characteristics of adult patients as a whole and according to the gene in which the disease-causative variant was identified

	Total n = 82	*PMP22* dup n n = 36	*GJB1* n = 11	*HINT1* n = 4	Other n = 31
GAD-7 score ≥ 5	17 (20.7%)	9 (25.0%)	4 (36.4%)	0 (NA)	4 (12.9%)
GAD-7 score ≥ 10	11 (13.4%)	5 (13.9%)	3 (27.3%)	0 (NA)	3 (9.7%)
GAD-7 score ≥ 15	3 (3.7%)	2 (5.4%)	0 (NA)	0 (NA)	1 (3.2%)

GAD-7, General Anxiety Disorder-7; NA; not applicable

CMTNSv2 12.7 ± 9.8, CMTES 9.3 ± 7.6). Interestingly, according to CMTES, 13 patients were clinically asymptomatic. The age range of these patients was 8 to 52 years (mean 25.8 ± 15.2 years), the gender distribution was balanced (7 males and 6 females) and most of them were either WES negative (n = 5) or *PMP22* dup (n = 5).

More than one-third (41.0%) of the adult patients reported musculoskeletal pain. Furthermore, DN4 assessment revealed 27.7% experienced neuropathic pain (Table 2). Approximately one in every four *PMP22* dup patients (CMT1A) and one in every two *GJB1* patients (CMTX1) had neuropathic pain. These patients with neuropathic pain had higher neuropathy severity scores than patients in the same genetic group without neuropathic pain — *PMP22* dup group: CMTNSv2 14.0 ± 7.4 versus 11.4 ± 6.5 and CMTES 9.7 ± 5.2 versus 6.5 ± 4.9; *GJB1* group: CMTNSv2 20.0 ± 8.3 versus 15.2 ± 9.9 and CMTES 14.2 ± 7.2 versus 10.5 ± 6.9 — however, the difference was not statistically significant ($p > 0.05$).

GAD-7 was used to determine the presence of underlying anxiety in the adult patient group (n = 82, one patient was missing data) (Table 3). Scores of 5, 10, and 15 were taken as the cut-off points for mild, moderate and severe anxiety, respectively. At least a mild anxiety level was present in 20.7% of all adult patients. Furthermore, it was even more prevalent in the *GJB1* group (36.4%) and *PMP22* dup group (25.0%). A moderate or severe anxiety level was present in 13.4% of all adult patients. Again, it was more common in the *GJB1* group (27.3%). Patients with at least a mild anxiety level had higher CMTNSv2 (15.7 ± 7.6 versus 10.7 ± 7.4) and CMTES (10.8 ± 6.1 versus 7.4 ± 5.3) scores than patients without increased anxiety level; however, the difference was not statistically significant**.** Moreover, patients with an increased GAD-7 score had a significantly higher prevalence of musculoskeletal pain (70.6% versus 33.8%, $p > 0.05$). Their prevalence of neuropathic pain was also higher, but the difference did not reach statistical significance (35.3% versus 26.2%, $p > 0.05$). Gait disturbances such as tripping (76.5% versus 63.1%, $p > 0.05$) and difficulties in walking (64.7% versus 61.5%, $p > 0.05$) tended to be more common in patients with an increased anxiety level.

A proportion of our patients (n = 21; 9 *PMP22* dup patients, five *GJB1* patients and seven other CMT patients; mean age 37.3 ± 12.5 years) were assessed for memory/cognitive ability by undergoing CNSVS memory tests. No abnormalities regarding CNSVS memory domain scores in verbal and visual memory were identified. All patients had mean scores that were within the average range and no differences were found among the various genetic groups.

Table 4. Clinical and disease severity of patients with and without rehabilitation

	CMTNSv2 (SD)	CMTES (SD)	Musculoskeletal pain	Neuropathic pain	Difficulties in walking
With rehabilitation n = 13	12.8 (7.8)	9.4 (6.7)	5/13 (38.5%)	3/13 (23.1%)	9/13 (69.2%)
Without rehabilitation n = 88	10.4 (7.6)	6.9 (5.5)	32/88 (36.4%)	23/88 (26.1%)	47/88 (53.4%)

SD, standard deviation; CMT, Charcot-Marie-Tooth disease; CMTNSv2, CMT Neuropathy Score version 2; CMTES, CMT Examination Score

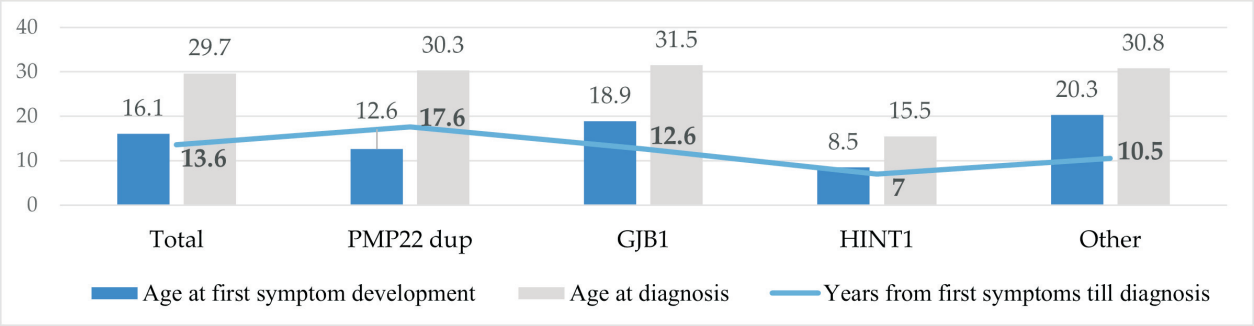

Fig. 3. Mean diagnostic characteristics in years of the various hereditary neuropathy groups.

Most of our patients reported having no regular rehabilitation. Indeed, only 12.9% (n = 13) indicated having regular rehabilitation activities such as physiotherapy. Furthermore, only 6.9% of all patients (i.e. 7 of the 13 having regular rehabilitation) were using orthoses despite foot drop being present in almost two out of every three patients (65.3%). Table 4 compares the clinical and disease severity of patients with and without rehabilitation. Patients with regular rehabilitation had higher disease severity scores according to CMTNSv2 and CMTES, as well as a higher prevalence of difficulties performing daily activities, such as walking. The frequencies of musculoskeletal pain and neuropathic pain in the two groups were similar.

The mean age at onset of first symptoms was 16.1 ± 14.0 years and the mean time to diagnosis was more than 13 years. Despite the relatively small sample sizes of the various genetic groups, our data indicate that *PMP22* dup patients had the longest time to diagnosis (17.6 years; Fig. 3).

DISCUSSION

This study characterises the clinical features and diagnostic peculiarities of 101 IPN patients from the Latvian population.

A proportion of our study group received a genetic diagnosis after performing *PMP22* copy number analysis. Further genetic confirmation was achieved as a result of WES. Indeed, 77.8% of patients received a diagnosis of a pathogenic variant or variant of unknown significance following WES. High WES diagnostic yields have previously been reported in paediatric patients (78%) and patients with primarily neurologic conditions (65%) (Reuter *et al*., 2019). The WES diagnostic yield in our paediatric group reached 76.5%. This is slightly lower than in the study group as a whole; however, our paediatric sample size was small (n = 18). Genetic diagnostic precision in paediatric populations is very important as the most common neuropathy cause in children is genetic, and potential treatments for specific IPN types are currently under development (Attarian *et al*., 2014; E. Millere *et al*., 2020). We found that the diagnostic yield was higher in patients with demyelinating neuropathy forms (CMT1; 80.8%) than in patients with axonal neuropathy forms (CMT2; 68.7%). This finding is in line with other reports, albeit in higher proportions (Rudnik-Schöneborn *et al*., 2016; Bacquet *et al*., 2018; Padilha *et al*., 2020).

The neuropathy severity scores of our patient group were lower than those reported in the Inherited Neuropathies Consortium natural history study, a cross-sectional analysis of 1652 CMT patients from 13 centres (Fridman *et al*., 2015). Regardless of gender, we found that the CMTX1 patient group had higher neuropathy severity scores than the other genetic groups. The difference, which was not statistically significant, was more pronounced in males, typical of an X chromosome-associated disorder.

Our assessment of disease severity in the study group as a whole and in the various genetic groups indicated a wide range of disability levels from no symptoms and absent neurophysiological changes to severe disability, even within a single genetic group. Clinical heterogeneity is common and is still not fully understood in IPN. Various influencing factors could be involved — environmental as well as genetic (Cornett *et al*., 2016; Tao *et al*., 2019).

More than one-third of our patients complained about musculoskeletal pain. Furthermore, patients with an increased anxiety level (as assessed by GAD-7) had a significantly higher prevalence of musculoskeletal pain. Anxiety is a common psychological disorder in chronic pain patients. Anxiety as well as emotional distress can be experienced after painful events, consequently leading to avoidance be-

haviour in patients based on a fear of repeating painful stimuli. Anxiety also has a significant impact on the exacerbation of pain perception. The presence of anxiety can increase functional disability in the long term and delay rehabilitation with personalised physiotherapy (Woo, 2010; A. Millere *et al*., 2020).

A proportion of our patients also had neuropathic pain, indicating probable small nerve fibre damage. In an earlier pilot study, we observed a significantly higher prevalence of neuropathic pain in *PMP22* dup patients and an association with neuropathy severity (E. Millere *et al*., 2019). However, studying a larger sample size, these findings were not confirmed. Nevertheless, neuropathic pain is a symptom reported by CMT patients and as such should be addressed accordingly (Jeong *et al*., 2013; Bjelica *et al*., 2020).

A subgroup of our CMT patients underwent an assessment of their memory/cognitive ability. No memory impairments were observed in any of the CMT genetic groups as assessed by CNSVS. However, other studies evaluating CNS involvement in patients with CMT have reported contrasting data. For example, a prospective study with 30 patients showed that 70% of patients with *PMP22* dup and *PMP22* del had cognitive impairment and a decreased volume of white matter (Chanson *et al*., 2013; Daniel *et al*., 2019) At present, it is unclear whether these data are a coincidental finding or whether the two processes share a common pathogenetic mechanism. Therefore, magnetic resonance imaging studies of larger patient cohorts are needed to more fully investigate cognitive functioning in CMT patients, especially *GJB1* patients (CMTX1) due to CNS involvement during their disease course.

Rehabilitation with physiotherapy and technical aids (especially orthoses) for CMT patients is crucial to reduce symptoms, maintain daily activities and improve quality of life (Corrado *et al*., 2016; Kenis-Coskun and Matthews, 2016). Unfortunately, just 12.9% of our patient group reported having regular rehabilitation and only around a half of these patients used orthoses**.**

Our study data highlight that timely diagnosis and appropriate treatment are important issues requiring action for CMT patients in Latvia. The time to diagnosis was more than 13 years for the patient group as a whole and it was even longer (more than 17 years) for the most common CMT type, i.e. *PMP22* dup. The estimated prevalence of CMT in different countries varies greatly, e.g., 9.7 per 100 000 in Serbia and 82.3 per 100 000 in Norway. Based on the average estimated prevalence of CMT (14.5 per 100 000) (Theadom *et al*., 2019), we believe that IPN in Latvia is underdiagnosed and that substantially reducing the time to diagnosis should be an important future objective**.**

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IEDZIMTU PERIFĒRU NEIROPĀTIJU KLĪNISKĀ DAŽĀDĪBA UN DIAGNOSTIKAS RAKSTUROJUMS LATVIJĀ

Iedzimtas perifēras neiropātijas (IPN) ir klīniski un ģenētiski heterogēna slimību grupa. Biežākā IPN ir Šarko–Marī–Tūta (ŠMT) slimība. Šajā rakstā raksturota IPN klīniskā dažādība un diagnostika Latvijas populācijā. Pētījumā piedalījās 101 IPN pacients. Ģenētiskā testēšana ietvēra *PMP22* kopiju skaita noteikšanu un pilna eksoma sekvenēšanu (*whole-exome sequencing, WES*). Klīniskā izvērtēšanā izmantoja ŠMT Neiropātijas skalas otro versiju (ŠMTNSv2), ŠMT klīniskās atrades skalu, veikta sāpju, trauksmes un atmiņas/kognitīvo spēju testēšana. Pēc *PMP22* kopiju skaita noteikšanas diagnozi apstiprināja 45,8% gadījumu, savukārt pēc *WES* — 77,8%. Slimības smaguma izvērtēšana norādīja augstu klīnisko dažādību, ŠMTNSv2 atradās vērtību robežās no 0 līdz 33. Vairāk nekā trešdaļa pacientu atzīmēja sāpes, un to ticami biežāk novēroja pacientiem ar zemu trauksmes līmeni. Laiks no pirmo simptomu parādīšanās līdz IPN diagnozes noteikšanai bija vairāk kā 13 gadi. Pētījums aktualizē IPN klīnisko un ģenētisko profilu Latvijas populācijā, kā arī apliecina augstu slimības klīnisko dažādību. Laiks līdz diagnozes noteikšanai jāuzlabo, sākotnēji pielietojot multipleksa ligācijas atkarīgu proves pavairošanu ar sekojošu *WES*.