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Investigation of Cognitive Impairment in Charcot-Marie-Tooth Disease Type 1A (CMT1A)

Epameinondas Giannopoulos

Supervisor Professor

Constantin Potagas

Three-member Committee

Constantin Potagas, Associate Professor of Neurology – Neuropsychology, Medical School, National and Kapodistrian University of Athens.

Nikolaos Smyrnis, Professor of Psychiatry, Medical School, National and Kapodistrian University of Athens.

Ioannis Zalonis, Associate Professor of Psychology – Neuropsychology, Medical School, National and Kapodistrian University of Athens.

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ABSTRACT

Background: Charcot-Marie-Tooth type 1A (CMT1A) is a hereditary peripheral neuropathy caused by mutation in the peripheral myelin protein 22 (PMP-22). Evidence indicates the possible involvement of the Central Nervous System (CNS) in CMT1A, but literature regarding cognitive function in CMT1A is very limited.

Objective: The aim of the hereby dissertation is to investigate whether patients with CMT1A present cognitive deficits.

Methods: We assessed 23 CMT1A patients, with a comprehensive neuropsychological battery, including tests of memory, language and executive functions. The patients' results were compared with these of healthy participants.

Results: Differences between the performance of patients and healthy participants were detected in specific cognitive domains while most of the cognitive functions seemed intact. Additionally, a case by case investigation revealed deficits in tests measuring cognitive flexibility and reading (decoding).

Conclusions: The data collected provide evidence for mild cognitive deficits in CMT1A patients and support the possibility of CNS involvement in CMT1A disease.

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1.Introduction

1.1.Charcot-Marie-Tooth (CMT) disease

Charcot-Marie-Tooth (CMT) disease is an inherited neuromuscular disorder that primarily affects the Peripheral Nervous System (PNS). CMT is the most common hereditary form of peripheral neuropathy with estimated prevalence approximately at 1:2500, with a worldwide distribution and no ethic predisposition (Parayeson, Saveri & Pisciotta, 2017). Population surveys show large geographical variations in the prevalence of CMT (Martyn & Hughes, 1997). CMT disease, also known as peroneal muscular atrophy, is characterized by genetic heterogeneity, i.e. it is an heterogenous group of disorders caused by different gene mutations, presenting a common clinical phenotype. More than 80 genes have been found to be associated with the disease, many of them uncovered during the last decade thanks to the next generation sequencing technology (NGS) (Pareyson et al., 2017). The related genes are implicated with pathways in myelination, radial and axonal transport, Schwann cell differentiation, signal transduction, mitochondrial function, endosome, protein translation and single-stranded DNA break repair (Szigeti & Lupski, 2009). The most prevalent genes are PMP22, GJB1, MPZ, and either MFN2 or GDAP1, depending on the geographic area, and 90% of CMT patients have a mutation in one of these genes (Pareyson et al., 2017).

Irrespective of the gene mutation, which affects myelin or axon, the common trait in the CMT is an axonal degenerative process that explains the clinical phenotype with distal predominance of limb-muscle wasting, weakness and sensory loss (Parayeson & Marchesi, 2009). Based on electrophysiological studies and specifically on measurements of the nerve conduction velocities in CMT patients, CMT could be divided into two main groups, irrespective of their genetic pattern of inheritance: a demyelinating type, characterized by slowed nerve-conduction velocities (less than 38 m/s) and eminent myelin abnormalities, like onion-bulb formations detected at nerve biopsy; and an axonal type, characterized by preserved or mildly slowed nerve-conduction velocities that surpass

the 38 m/s and pathological evidence of chronic axonal degeneration and regeneration. (Pareyson & Marchesi, 2009; Shy, Garbern & Kamholz, 2002). These data not only assist us in classifying the CMT patients in different categories, diagnosing them and providing the appropriate treatment , but also reveal that there is no unique and specific cause of CMT disease since there are at least two distinct disease processes, a demyelinating process and an axonal process, provoking similar clinical traits of neuropathy (Pareyson & Marchesi, 2009 ; Shy et al., 2002). CMT1 is classified in the first category while CMT2 is categorized in the latter. Nevertheless, while knowledge regarding the pathophysiology of CMT is increasing, an intermediate type between CMT1 and CMT2 is emerging (i.e. CMTX1).

1.2 Charcot-Marie-Tooth type 1A (CMT1A)

CMT can be further subdivided into different types according to the mutated gene and the locus of that gene in the chromosome. CMT1 type, the demyelinating type, is subdivided in CMT1A, CMT1B, CMT1C, CMT1D, CMT1E and CMT1F. CMT1A is the most common form of CMT and comprises 60-90% of CMT1 patients. Furthermore, it is the best described type, since there are many reported case series and follow-ups (Pareyson & Marchesi, 2009). In the Greek population, CMT1A has been estimated at around 25% of CMT (Karadima, Floroskufi, Koutsis, Vassilopoulos, & Panas, 2011). The inheritance pattern observed in CMT1A is the autosomal dominant. In comparison with the other subtypes of CMT, CMT1A is relatively benign and almost all patients remain ambulatory throughout their lives. Nevertheless, CMT1A is characterized by substantial disease variability. Clinical presentation varies from completely asymptomatic patients to patients, in rare cases, becoming chairbound (Pareyson & Marchesi, 2009). The first two decades of a person's life is the most common period of the disease onset; the most indicative group of symptoms and signs comprises of pes cavus (claw foot), pes planus (flat feet), lower-limb areflexia, as well as wasting and weakness of intrinsic foot muscles and, later, of peroneal and anterior tibialis muscles. Moreover, the

demyelination type of CMT in which CMT1A is classified, is characterized by the development of onion bulb formation and slowed nerve conduction velocities in both sensory and motor nerves.

1.3 Peripheral Myelin Protein 22 (PMP22)

CMT1A is attributed to a genetic defect on chromosome 17 that includes the gene encoding the Peripheral Myelin Protein 22 (PMP22). In particular, a large segmental duplication of the locus 17p11.2-p12 on chromosome 17, involving approximately 1.5 Mb of DNA, seems to cause CMT1A and it was first described in 1999 in two independent reports of Raymarkers et al. and Lupski et al. CMT1A patients, have three copies of this locus instead of the normal number of two (inherited one from each parent). This chromosomal segment harbors PMP22 which is the peripheral myelin protein, and its duplication has been proven to cause CMT1A. Duplication of PMP22 is very often in clinical practice since it represents 43% of the total CMT cases (Szigeti & Lupski, 2009). That excess gene copy number of PMP22 leads to protein overexpression and subsequently to the clinical expression of the disease. This is also observed in animals; studies with mice and rats reveal that increasing copies of PMP22 to overexpress the protein, produce pathological phenotypes resembling those of human subjects with CMT1A (Li, Parker, Martyn, Natarajan & Guo, 2012).

PMP22 is a key protein of the PNS, comprising the 2-5% of PNS myelin proteins in rodents and animals and is predominantly expressed by myelinating Schwann cells of the PNS (Snipes, Suter, Welcher & Shooter, 1992). The aforesaid protein is involved in various manifestations of cell life in the PNS, such as intercellular recognition, adhesion processes, cellular growth and division, having a prominent role in myelination of peripheral nerves. (Snipes et al., 1992; Naef & Suter, 1998). The overexpression of PMP22 produces a structurally unstable myelin sheath. Therefore, mutation in this protein is expected to cause such a type of neuropathy. Although PMP22 is a peripheral myelin protein, there are reports of detection of PMP22 in the CNS. The study of Ohsawa et al. (2006) managed to detect PMP22 mRNA in most parts of the brain and spinal cord performing northern blot

analysis. This type of evidence supports the hypothesis that PMP22 might be expressed in the CNS and therefore provoke the CNS involvement in CMT1A.

1.4 CNS Abnormalities in CMT1A

The role of the CNS in CMT in general, and especially in CMT1A, has not been fully investigated and the literature regarding the cognitive functions and possible deficits in CMT1A is quite limited. It seems unusual to observe abnormalities of the CNS in peripheral neuropathy and there are no clear findings for the CNS neuropathology in CMT1A up to date. Nevertheless, studies point out neuroimaging evidence of CNS involvement in CMT. The study of Chanson et al. (2013), that included patients with PMP22 gene mutations - patients with CMT1A and patients with Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) - is consistent with the notion that there is involvement of the CNS in the CMT disease. Their study indicated CNS abnormalities regarding the White Matter (WM). Using imaging and histological examination, they managed to detect decreased WM volume in 73% of the CMT1A patients. Furthermore, they detected a decreased Fractional Anisotropy (FA) in the right thalamus and both columns of fornix when all patients with PMP22 mutation were compared to the healthy group. Moreover, in the CNS no PMP22 protein expression was detected, although the PMP22 mRNA expression in the CNS was widespread and significant abnormalities of the CNS myelin were observed. Based on these findings the authors suggested that the myelin abnormalities may be explained by changes in the PMP22 RNA expression rather than changes in PMP22 protein. The research findings of Chanson et al. (2013) regarding the imagining data are opposed to the study of Lee et al. (2017), in which no WM abnormalities in CMT1A were detected using Diffusion Tensor Imaging (DTI). Nevertheless, the study of Lee et al. (2017), revealed significant cerebral WM abnormalities in other CMT subtypes (CMT1E, CMT2A, CMT2E, CMTX1, DI-CMT).

Anatomical abnormalities of the CNS in patients with CMT1A have also been reported in

various case studies. Indicatively, in a study of a parent-offspring pair with CMT1A disease, imaging and electrophysiological data showed evidence of CNS involvement. Specifically, Magnetic resonance imaging (MRI) of the brain revealed foci of demyelination in the daughter. Moreover, in both patients, abnormalities were detected in central motor conduction time (CMCT), brainstem auditory evoked responses (BAERs) and visual evoked potentials (VEPs) (Panas, Karadimas, Kalfakis, Floroskufi & Vassilopoulos, 2003).

Besides the above-mentioned case study, another indicative case study is related to a CMT1A patient who developed CNS involvement mimicking Multiple Sclerosis (MS). WM lesions of the brain and spinal cord, indicative for MS, were visible on MRI. All examination findings suggested an autoimmune CNS demyelination. Although the occurrence of CMT1A and MS in the patient could be coincidental, the researchers postulated that the peripheral and central pathologies may have a causal association. The authors suggest that the overexpression of PMP22 might have influenced the immunological self-tolerance to CNS proteins via molecular mimicry which in turn led to CNS demyelination (Koros, Evangelopoulos, Kilidireas & Andreadou, 2013). There are more case reports of patients with concomitant presence of CMT1A and Multiple Sclerosis (Doğan, Gül, Ceylanb & Kutsa, 2019; Almsaddi, Bertorini & Seltzer, 1998; Frasson et. al, 1998).The most possible explanations of this concomitant presence, based on researchers, are the following: there might be a common pathogenic mechanism, resulting from duplications on the protein PMP22, between the two diseases or the genetic defect of CMT can contribute to triggering the autoimmune disorder of CNS myelin, or a partial homology shared among PMP22 and CNS proteins could account for the occurrence of autoimmune disorders targeted to the CNS myelin.. In addition to that, case reports suggest the coexistence of MS with other types of CMT and more specifically, CMT1B and CMTX, supporting the idea that there might be involvement of CNS in this peripheral neuropathy (Cortese et al., 2016; Isoardo, DiVito, Nobile, Benetton, Fassio, 2005).

There is much evidence about CNS abnormalities in CMTX , another subtype of CMT disease

sharing several common features with CMT1A. Specifically, many studies through neuroimaging data, indicate subcortical WM involvement in CMTX patients, in brain areas that play a prominent role in cognition such as the splenium of the corpus callosum (Karadima et al., 2014; Koutsis et al., 2019; Lee et al., 2017; Panas, Kalfakis, Karadimas, & Vassilopoulos, 2001; Paulson et. al, 2002;), the external capsule, the cingulum, the fornix and the superior longitudinal fasciculus (Lee et al., 2017). The aforementioned fibers play a prominent role in cognition since they support interhemispheric, cortico-cortical and cortico-subcortical connections, which assist the information processing. (Kasselimis et al., 2019).

CNS abnormalities have also been reported in HNPP, a disorder with close molecular genetic affinity to CMT1A and generally interrelated with CMT. A recent study revealed decreased WM volume in 71% of the HNPP participants (Chanson et al., 2013). Another study indicated MRI abnormalities, suggesting subclinical but functionally relevant CNS myelin damage in HNPP (Tackenberg et al., 2006). There are also MRI data, arising from case and family reports with HNPP patients, presenting CNS demyelination (Amato & Barohn, 1996; Sanahuja et al., 2005) or foci of myelin lesions (Dackovic et al., 2001).

1.5 Cognitive Impairment in CMT1A

Research findings of higher cortical functions in patients with CMT are scarce, they suggest, however, the possible existence of cognitive deficits. The study of Chanson et al. (2013), is the only detailed neuropsychological study on CMT1A patients and revealed mild cognitive impairment affecting the executive functions, working memory and verbal episodic memory. In particular, 77% of CMT1A patients that were recruited for cognitive evaluation, presented abnormal results. In the same study, the cognitive deficits, even mild, are in accordance with the decrease in WM volume that was detected in all patients (CMT1A & HNPP) via neuroimaging examination. These findings combined with the CNS abnormalities that the same study revealed, shed more light on the possible

cognitive deficits of CMT1A patients and the CNS involvement in this disease. However, there are several limitations to the study of Chanson et al. (2013). Firstly, the study was not exclusively oriented to CMT1A patients. That being the case, the study also included HNNP patients, hence there was not a homogenous group of patients. Moreover, the size of the group regarding the cognitive evaluation was limited since only 13 CMT1A patients were recruited for neuropsychological assessment.

In addition to the above, evidence of cognitive deficits also emerged from studies in people with other subtypes of CMT. More precisely, a report of a family with CMT-X is a case in point, as mild cognitive impairment and deficits in episodic memory were detected in two sisters and their brother, using an unspecified neuropsychological battery (Stancanelli et al., 2012). A recent study indicates evidence of deficits in executive functions and verbal recognition and decoding in patients with CMT-X using a detailed neuropsychology battery (Kasselimis et al., 2019).

Besides, data indicate cognitive impairment in CMT2. There is a family report with molecularly confirmed CMT2, caused by Mitofusin 2 gene (MFN2) mutation, that presented cognitive impairment. The two sons of the family also presented delayed language learning and simultaneous optic nerve dysfunction. (Del Bo et al., 2008). Mild cognitive deficits, particularly in executive functions, working memory and verbal episodic memory, have also been detected in HNPP patients (Chanson et al., 2013).

The above provides indication for CNS involvement in CMT1A and raises the possibility of cognitive impairment in such patients. Literature regarding cognitive functions on CMT1A patients is limited and there is absence of a systematic research focused on the investigation of cognition in CMT1A. The only research referred to CMT1A cognitive functions lacks a sufficient cohort size in order to reach reliable conclusions (Chanson et al., 2013). Nevertheless, the limited existing data lead to the conduction of a more systematic study in order to investigate possible cognitive deficits in CMT1A.

In the present research, we endeavored to study the involvement of CNS in CMT1A through the investigation of possible cognitive deficits using a comprehensive neuropsychological battery. We postulated, based on previous data, to notice differences between patients and control group in executive functions, specifically in processing speed. We did not expect to detect focal deficits in cognitive functions involving crystallized knowledge. Therefore, based on the fact that there is evidence that suggests probable cognitive impairment and CNS involvement for CMT1A patients, we attempted to investigate whether the CMT1A patients could present cognitive deficits.

2. Methods

2.1. Design

The hereby project is an exploratory descriptive study.

2.2 Participants & Exclusion Criteria

Our sample included patients with CMT1A disease and healthy participants matched to demographic characteristics to patients. We recruited patients in collaboration with the Neurogenetics Unit at the 1st Department of Neurology of Athens Eginition Hospital. The patients have been molecularly diagnosed from the Neurogenetics Unit; hence the Unit holds a pool of patients with this neuropathy. All patients contacted by phone to request participation in the present investigation. Patients with a concomitant neurological disease, psychiatric disorder or another medical condition, such as alcohol or substance abuse, epilepsy, craniocerebral injury, autoimmune syndrome, cardiovascular disease, depression, etc. were excluded from the study. Also excluded were patients with hearing or vision deficits that could affect their cognitive functions. Healthy participants derived from the project “Investigation of cortical surface patterns and their relation with speech metrics and performance in neuropsychological assessment in healthy participants”, conducted in Eginition Hospital in Athens, School of Medicine, Greece (research protocol approval ID: ΩΟΞΛ46Ψ8Ν2-7ΠΝ, July 2017). Healthy participants had been recruited from the general population with the

convenience sampling method. Similarly, to patients, healthy controls in order to participate in the investigation should not present any neurological, psychiatric or cardiovascular disorder/disease. The study was approved by the hospital ethics committee.

In total, 23 patients with molecularly confirmed CMT1A were recruited (17 males & 6 females; mean age= 42.17 ± 13.59, range 19-69 years; mean education= 14.91± 3.47, range 6-22 years) and 34 healthy controls were included (17 males & 17 females; mean age=48.38 ± 8.34, range 35-64; mean education=15.21± 3.38, range 9-24). All participants were assessed according to the standard administration procedures described in the corresponding normative studies referring below.

2.3. Material

Since our study is exploratory, we decided to include in the neuropsychological assessment a wide array of tests that could detect possible cognitive deficits in as many cognitive functions as possible. Having as reference point the study of Chanson et al., (2013) which contained 8 neuropsychological tests, we included 10 neuropsychological tests in order to examine mainly the executive functions, speech and memory. Below, we briefly present each neuropsychological test, that was included in our study, in alphabetical order.

Auditory Verbal Learning Test (AVLT) (Geffen, G., & Geffen L.B., 2000), translated and standardized in Greek (Constantinidou, Zaganas, Papastefanakis, Kasselimis, Nidos, & Simos, 2014). AVLT is a verbal memory test in which the subject hears a list of 15 nouns (List A) and is asked to recall as many words from this list as possible. After five repetitions of free recall, which is the learning condition, a second "interference" list (List B) is presented in the same manner, and the participant is asked to recall as many words from List B as possible. Then, the examinee is immediately asked to recall the words from List A. After a 30 minutes delay, the participant is asked to recall the words from List A and a list of 51 words is presented containing all of the words from List A, as a trial of memory recognition.

Boston Naming Test (BNT) (Kaplan, Goodglass, &. Weintraub, 1983), translated and standardized in Greek (Simos, Kasselimis, & Mouzaki, 2011). BNT is a neuropsychological naming test, in which drawings are used as stimulations and the participant has to name every object. In case it is required, semantic or phonological evidence could be provided.

Comprehension of instructions in Greek (CIG) (Simos, Kasselimis, Potagas, & Evdokimidis, 2014). This test assesses the verbal (auditory) comprehension of the subject. The examiner provides the participant with a dashboard on which shapes (crosses & circles) are printed in different colors. Afterwards, the examiner reads aloud some orders like: "Show me the black circle and the third shape on the second row" and the participant is asked to carry out the instructions using the dashboard in front of him/her.

Controlled Oral Word Fluency (COWF) (Kosmidis, Vlahou, Panagiotaki, & Kiosseoglou, 2004), is a test that evaluates the access and selective retrieval of semantic and lexical representations. The subject is asked to produce as many words as s/he can within a predetermined time limit (60 seconds). During the semantic fluency task, the subject has to give examples from a specific category (Animals-Fruits-Objects) and during the phonological fluency task the subject has to produce words beginning with a specified letter (letters "Χ", "Σ", "Α" of the Greek alphabet).

Corsi Block Tapping Task (Corsi, 1972; Kessels, Van Den Berg, Ruis, & Brands, 2008) is a neuropsychological test that assesses visuo-spatial short-term and working memory. The participant is asked to reproduce moving sequences that the examiner performs based on a dashboard of nine identical spatially separated blocks. The sequence starts out simple and becomes more complex on every trial. During the first task the participant reproduces the sequence in exactly the same order it was presened and during the second task in the reverse order.

Digit Span Task (Simos, Papastefanakis, Panou & Kasselimis, 2011) is a neuropsychological assessment tool for verbal working memory, and it is based on the ability to recall a sequence of

numbers of ascending length. The examiner reads a sequence of numerical digits and the examinee is asked to recall the sequence correctly, with increasingly longer sequences being tested in each trial. During the first task the participant is asked to recall the sequence forwards and during the second backwards.

Peabody Picture Vocabulary Test- Revised (PPVT-R) (Dunn, 1981) translated and standardized in Greek (Simos, Kasselimis, & Mouzaki, 2011). The PPVT-R is a test that measures the participant's receptive vocabulary ability. A page with four (4) numbered drawings is presented to the examinee and the examiner presents orally a word to him/her describing one of the drawings. The examinee is asked to choose one between those four (4) pictures, which s/he thinks it represents the word presented. The test includes 32 words, hence, the procedure is repeated 32 times, each time for every word.

Symbol Digit Modalities Test (**SDMT)** (Smith A, 1982), translated and standardized in Greek, (Constantinidou, Christodoulou, & Prokopiou, 2012). The SDMT involves a simple substitution task aiming to assess visual perception and processing speed. Firstly, a reference key is provided including numbers from 1 to 9, corresponding to specific geometric figures and the examinee has some time to process the template. Afterwards, the examinee has 90 seconds in order to pair numbers with figures as fast as s/he can, filling up in writing the provided empty board and using the template board, if needed.

Trail Making Test (TMT) (Spreen, O., & Strauss, E., 1991), translated and standardized in Greek, (Zalonis, Kararizou, Triantafyllou, Kapaki, Papageorgiou, Sgouropoulos, & Vassilopoulos, 2007). The TMT is a neuropsychological test of cognitive flexibility and visual perception and consists of two parts. The first task (TMT-A) includes a set of 25 dots numbered from 1 to 25 allocated on a piece of paper, and the subject is asked to connect the dots with numerical order as fast as possible while maintaining accuracy. The second task (TMT-B) consists of a set of 25 dots, which includes

digits from 1 to 13 or letters of the Greek alphabet from A to M and the participant has to switch numbers with letters of ascending sequencing (i.e. 1-A, 2-B etc). In order to prevent the confounding action of movement deficits, additional scores (TMT B – A and TMT B/A) are calculated for each patient (Christidi, Kararizou, Triantafyllou, Anagnostouli, & Zalonis, 2015).

Word and Pseudoword reading Fluency measures (Simos, Sideridis, Kasselimis, & Mouzaki, 2013), is a task of verbal recognition and decoding which evaluates the reading speed of the participant. The reading fluency task consists of a list of 112 high-frequency words in an order of increasing length. The pseudoword fluency task consists of a list of 70 pseudowords in an order of increasing length. For both tasks, the patient is asked to read items aloud as fast as possible within a time limit of 45 seconds.

2.4. Procedures

The neuropsychological testing took place in the Neuropsychology and Language Disorders Unit of the 1st Department of Neurology of the Eginition Hospital. Participants were provided with an information letter describing the aims of the research and the procedure, and consent was obtained from all participants. Before the examination, a short medical record was obtained (demographics, medical history, education history, work history, smoking and alcohol consumption). Before each neuropsychological test, clear instructions and examples were given to participants to ensure that their understanding for the tasks. The tests were administered in the following order: 1.Controlled Oral Word Fluency Test, 2.Boston Naming Test, 3.Peabody Picture Vocabulary Test- Revised, 4.Auditory Verbal Learning Test, 5.Trail Making Test, 6.SDMT, 7.Digit Span Test, 8.Corsi Block Tapping Task, 9. AVLT-delayed recall & delayed recognition, 10.CIG, 11.Word and Pseudoword reading Fluency measures. Participants had the option for a short break in the middle of the procedure. The entire procedure lasted approximately 1 hour and 20.

Participation in research was completely voluntary and the participants had the right to

withdraw the procedure at any time. The participants' anonymity is ensured, and the results of the examinations are managed exclusively by the Department of Neuropsychology & Language Disorders of the 1st' Department of Neurology of Eginition Hospital.

2.5 Statistical analysis

Statistical analysis was performed on IBM SPSS software version 23, with the statistical significance level set to a=0.05. Descriptive analysis was performed to explore the distribution of age, education and gender within the sample. Normality test was applied to decide if parametric or non-parametric statistics will be conducted. Independent Samples t - test and Mann-Whitney (U) Test were performed in order to compare the performance in the neuropsychological testing between patients and healthy controls. Further analysis was performed in order to examine differences between performance of patients on different neuropsychological tests.

3. Results

Descriptive analyses were performed in order to explore the distribution of age, education and gender for all 23 patients and 34 healthy participants. Demographic data for all participants are presented in Table 1.

Table 1
Descriptive Statistics for Demographic Variables

	CMT1A PATIENTS N=23	HEALTHY CONTROLS N=34	*p*
AGE (in years; M, SD)	42.17 ± 13.59 (MIN: 19; MAX: 69)	48.38 ± 8.43 (MIN: 35; MAX: 64)	.059
EDUCATION (in years; M, SD)	14.91 ± 3.37 (MIN: 6; MAX: 22)	15.21 ± 3.38 (MIN: 9; MAX: 24)	.752
GENDER	MALES: 17 (73.9%) FEMALES: 6 (26.1%)	MALES: 17 (50%) FEMALES: 17 (50%)	.071

Note. N= Number; M= Mean; SD= Standard Deviation; Min= Minimum; Max= Maximum
p value: Significant at the $p < 0.05$ level

In order to decide if parametric statistics could be performed, we applied a test of normality

for each dependent variable, for every group separately. Normality tests indicated that all variables were normally distributed except from: the Recognition pA (AVLT) index, the Trail Making Test B (TMT-B), the Trail Making Test B – A (TMT B – A) index, the Peabody Picture Vocabulary Test-Revised (PPVT-R) and the Boston Naming Test (BNT). For the variables that followed the normal distribution, we applied parametric statistics and specifically Independent Samples T-test; for the rest we applied Mann-Whitney U Test.

Independent Samples T-test and Mann-Whitney (U) Test were performed to compare the performance of CMT1A patients with that of healthy controls in different neuropsychological tests. No statistically significant difference was detected between the performance of CMT1A patients and healthy controls in the following tests. In the Auditory Verbal Learning Test there was no difference in performance for none of the sub-indices. Specifically, no difference detected in the subscales measuring Episodic Memory Encoding (AVLT – 1-5), t(55) = -0.256, p = .799, Episodic Memory-Learning Curve (AVLT - LC), t(55) = -1.09, p = .280, Immediate Recall in Interference Trial (AVLT - B), t(55) = 0.281, p = .780 Short Delay Recall (AVLT - 6), t(55) = 0.258, p = .797, Episodic Memory- Long Delayed Recall (AVLT - 7), t(54) = -0.045, p = .964, Retention (AVLT - R), t(54) = 0.456, p = .651 and Recognition (AVLT - pA), U(23, 34) = 336.00, p = .468. Similarly, the comparison between the performance of patients and that of healthy participants did not reveal statistically significant difference in the Phonemic Fluency Test, t(55) = -0.859, p = .394, and in the Semantic Fluency Test, t(55) = -0.439, p = .662. Equally, the analysis indicated no statistically significant results for the Trail Making Test A (TMT – A), t(55) = 0.856, p = .396, for the Trail Making Test B (TMT – B), U(23, 34) = 876.00, p = .073 and for the index of Trail Making Test B by A (TMT B/A) t(55) =1,89, p = .064. Moreover, no difference was detected in the performance of patients in comparison to the performance of healthy participants in the Symbol Digit Modalities Test (SDMT), t(55) = -0.885, p = .380, in the Peabody Picture Vocabulary Test-Revisited (PPVT-R), U(23, 34) = 329.500, p = .313, in the Boston Naming Test (BNT), U(23, 34) = 318.500, p = .296 and

in the Reading Words Fluency Task, t(55) = -1.814, p = .075. Finally, no statistically significant difference was found in the performance of patients in comparison with the performance of healthy participants at none of the sub-indices of the Digit Span Test or the Corsi Block Tapping Test : Digit Span Forward score (DS-F-score), t(55) = 0.112, p = .911, Digit Span Forward span (DS-F-span), t(55) = 0.415, p = .679, Digit Span Backwards score (DS-B-score), t(55) = -0.618, p = .539, Digit Span Backwards span (DS-B-span), t(55) = -0.046, p = .963, Corsi Block Tapping Test Forward score (Corsi-F-score), t(55) = -0.699, p = .487, Corsi Block Tapping Test Forward span (Corsi-F-span), t(55) = -1.075, p = .287, Corsi Block Tapping Test Backwards score (Corsi-B-score), t(54) = 1.158, p = .252, Corsi Block Tapping Test Backwards span (Corsi-B-span), t(54) = 0.464, p = .645.

Parametric and nonparametric statistics indicated statistically significant difference between the two groups in the following neuropsychological tests. The Mann-Whitney U Test conducted to compare the score of patients relatively to the scores of healthy participants for the index of Trail Making Test B minus A (TMT B-A) revealed a statistically significant difference between the two groups, U(23, 34) = 262.00, p = .036. These results suggest that there might be a deficit in the executive control process for the patients. Furthermore, the Independent Samples T -test that was performed indicated that there is a significant difference between the performance of patients and healthy participants in the Reading Pseudowords Task, t(54) = -2.231, p = .030. This difference could suggest a deficit in decoding written stimuli. Finally, the analysis revealed a statistically significant difference between the scores of patients and healthy participants in the Comprehension of Instructions in Greek Test, t(55) = -2.12, p = .039. Our results show a probable deficit in the function of verbal comprehension of patients. The data of the comparison (Mean score, Standard deviation and Median for the two groups, t, U and p values for neuropsychological tests and Cohen's d & r) are summarized in Tables 2 and 3.

Table 2
t & *p* values for Independent Samples t-tests

Tasks	CMT1A Mean ± Std. Dev	CONTROLS Mean ± Std. Dev	t	*p*	d^a
AVLT- 1 - 5	44.6 ± 0.37	45.29 ± 9.61	-0.256	.799	0.101
AVLT - LC	5.78 ± 1.88	6.38 ± 2.13	-1.09	.280	0.298
AVLT - B	6.04 ± 2.32	5.88 ± 1.98	0.281	.780	0.074
AVLT - 6	9.21 ± 2.39	9.0 ± 3.51	0.258	.797	0.069
AVLT - 7	8.95 ± 3.45	9.0 ± 3.62	-0.045	.964	0.014
AVLT - R	0.77 ± 0.19	0.74 ± 0.22	0.456	.651	0.145
FL - PH	33.73 ± 11.76	35.97 ± 8.07	-0.859	.394	0.222
FL - SEM	53.52 ± 11.99	55.02 ± 13.18	-0.439	.662	0.119
TMT - A	30.73 ± 11.23	28.50 ± 8.50	0.856	.396	0.223
TMT B/A	3.39 ± 1.38	2.78 ± 1.06	1,89	.064	0.495
CIG	11.26 ± 1.93	12.20 ± 1.43	-2.12	< **.039***	0.553
SDMT	45.75 ± 12.70	48.44 ± 8.52	-0.885	.380	0.248
RW	83.52 ± 17.96	90.61 ± 11.60	-1.814	.075	0.468
RpsW	36.78 ± 11.77	43.27 ± 9.91	-2.231	< **.030***	0.596
DS -F - score	16.69 ± 3.79	16.58 ± 3.35	0.112	.911	0.030
DS -F - span	6.39 ± 1.15	6.26 ± 1.10	0.415	.679	0.115
DS - B - score	13.95 ± 3.73	14.61 ± 4.10	-0.618	.539	0.168
DS - B - span	13.95 ± 1.14	5.05 ± 1.27	-0.046	.963	7.375
C - F - score	9.26 ± 1.71	9.64 ± 2.24	-0.699	.487	0.190
C - F - span	6.13 ± 1.17	6.50 ± 1.33	-1.075	.287	0.295
C - B - score	9.08 ± 1.78	8.54 ± 1.67	-1.158	.252	0.312

C - B - span	5.91 ± 1.08	5.78 ± 0.92	0.464	.645	0.129

Notes: M= Mean; SD= Standard Deviation
AVLT 1-5, Auditory Verbal Learning Test (Encoding); AVLT – LC, Auditory Verbal Learning Test (Learning Curve); AVLT – B, Auditory Verbal Learning Test (Immediate Recall in Interference Trial); AVLT – 6, Auditory Verbal Learning Test (Short Delay Recall); AVLT – 7, Auditory Verbal Learning Test (Delayed Recall); AVLT – R, Auditory Verbal Learning Test (Retention); FL – PH, Control Oral Word Fluency Phonemic subscale; FL – SEM, Control Oral Word Fluency Semantic subscale; TMT – A, Trail Making Test A; TMT – B/A, Trail Making Test B/A index; CIG, Comprehension of Instructions in Greek; SDTM, Symbol Digit Modality Test; RW, Word Reading fluency task; RpsW, Pseudoword Reading fluency task; DS- F, Digit Span Forward; DS – B, Digit Span Backward; C – F, Corsi Block-Tapping task Forward; C – B, Corsi Block-Tapping task Backward.
[a] *d* represents Cohen's *d* effect size calculations.
*$p < .05$

Table 3
U & *p* values for Mann-Whitney U test

	CMT1A	CONTROLS			
	Median	Median	U	*p*	r^a
AVLT - pA	30.39	27.18	336.00	.468	0.118
TMT - B	33.78	25.76	281.00	.073	0.237
TMT B-A	34.61	25.21	262.00	**< .036***	0.278
PPVT-R	23.33	30.81	329.50	.313	0.132
BNT	31.15	26.65	318.50	.296	0.156

Note. AVLT - pA, Auditory Verbal Learning Test (Recognition); TMT – B, Trail Making Test B; TMT B-A, Trail Making Test B – A index; PPVT-R, Peabody Picture Vocabulary Test-Revised; BNT, Boston Naming Test.
[a]*r* represents the effect size for Mann- Whitney U Test
*$p < .05$

Due to the conduction of multiple comparisons we applied Bonferroni and False Discovery Rate (FDR) corrections in order to prevent data that were statistically insignificant appear among the results. None of the results survived a Bonferroni or FDR correction. Nevertheless, we decided to conduct further analysis in order to examine in depth the possibility of detected cognitive deficits. We transformed raw scores to Z scores/ percentiles, based on the corresponding norms of each test, for those tests where a statistically significant difference was detected before correction, namely:

TMT B – A, Reading Pseudowords and CIG. A case by case analysis revealed that there were no patients presenting low scores for CIG but there were several patients displaying low scores for TMT B – A and Reading Pseudowords. Afterwards we recoded the z scores for the two tests, by dividing participants into two categories: those that exhibited apparent deficit (score < -1.50 sd) and those that had normal performance (score > -1.50 sd) and we conducted crosstabs analysis to explore possible concomitant existence of deficits in both tests. The analysis indicated that there were 10 patients presenting deficits in the Reading Pseudoword test and seven (7) patients presenting deficits in the Trail Making Test B – A. Three (3) patients displayed deficits in both tests while nine (9) did not display any deficit. The crosstabs analysis did not provide any statistically significant result, $\chi 2(2) = 0.002$, $p = .968$ (Table 4).

Table 4
Crosstabulation for TMT B – A & Reading Pseudowords

		Trail Making Test B - A		
		Deficit	No Deficit	Total
Reading Pseudowords	Deficit	3	7	10
	No Deficit	4	9	13
	Total	7	16	23

After we transformed raw scores to Z scores/ percentiles, based on the corresponding norms for the Reading Words test, we conducted a Paired Samples t-test, in order to compare the performance of patients in Reading Pseudowords and Reading Words. There was no significant difference in the scores of patients on Reading (M= -0.244 SD= 1.14) and of patients on Reading Pseudowords (M= -0.7830, SD= 1.86), t(2) = 1.356, $p = .189$. These results suggest that performance in both tests was equivalent among the same participant, i.e. if a person does well in the Reading Words test then s/he performs equally well in the Pseudowords test. Nevertheless, in order to explore

the exact number of patients that present deficits in both tests we conducted a Crosstabs analysis. We recoded the z-scores for Reading Words with the same way we did for Reading Pseudowords, like mentioned above and we performed a crosstabs analysis. There were three (3) patients presenting deficit in Reading Word task and 10 patients presenting deficit in Reading Pseudowords Task. Crosstabs analysis did not indicate any statistically significant result, $\chi 2$ (2) = 0.755, p = .385. These data suggest that there was no concomitant appearance of deficit in the two tests. Crosstabs analysis is presented in Table 5.

Table 5.
Crosstabulation for Reading Pseudowords & Words

		Reading Words		
		Deficit	No Deficit	Total
Reading Pseudowords	Deficit	2	8	10
	No Deficit	1	12	13
	Total	3	20	23

4.Discussion

Despite the evidence of possible CNS involvement that have been observed in CMT1A, cognition has not been fully investigated, and the available literature is limited to a study including patients with PMP22 mutations (CMT1A & HNPP) (Chanson et al., 2013). The purpose of the hereby study was to deeply explore and analyze the cognitive function of patients with CMT1A. A detailed neuropsychological examination indicated mild cognitive deficits in specific domains, while cognitive function was detected normal for the majority of the neuropsychological measures. In particular, the performance of patients in specific neuropsychological tasks was deficient compared to the performance of healthy controls. A case by case analysis revealed that CMT1A patients had low scores in TMT B minus A (TMT B – A) index and in the Pseudoword Reading Fluency Measure.

Trail Making Test is generally considered as an executive test, sensitive to detect frontal

dysfunction. The TMT B – A index is thought to be a reliable measure of cognitive flexibility and executive dysfunction (Christidi, et al., 2015), since it removes the speed component from TMT assessment (Lezak et al., 2004). Thus, B – A index provides a purer indicator of executive control processes by minimizing visuoperceptual and motor demands (Christidi, et al., 2015). Our findings indicate low performance of CMT1A on TMT B – A suggesting a probable mild executive dysfunction. This comes in accordance with the findings of Chanson et al. (2013), as far as cognitive impairment in CMT1A is concerned, mainly in executive functions supported by anatomical data of decreased WM volume. In addition, our data regarding TMT corroborate recent findings in patients with CMTX, another type of CMT that shares common features with CMT1A. This study points out deficits in performance of TMT B/A index which is also indicative for cognitive flexibility as TMT B – A (Kasselimis et al., 2019). As mentioned above, we could speculate that the low TMT B – A score in some CMT1A patients is an indicator for underlying frontal dysfunction. Nevertheless, recent findings suggest that TMT performance could not be relied exclusively on prefrontal activation. Studies, based on neuroimaging data, suggest that TMT performance activates both anterior and posterior regions, such as prefrontal & frontal areas, temporal areas, the cingulate, the insula and the paracentral lobule (Chan et al., 2015; Zakzanis, Mraz & Graham, 2005) and relies on a distributed network involving frontal and non-frontal regions (Chan et al., 2015). Given that, TMT probably reflects more general cognitive ability and not only executive function. Actually, the small number of our cohort is restrictive for the extraction of reliable conclusions about the executive functions of CMT1A patients but shed more light on the area of cognition of CMT disease.

Another intriguing finding that emerged from the hereby study was the low score of CMT1A patients on the Reading Pseudowords Fluency Task. Specifically, there were differences in the performance of patients in comparison with the group of healthy participants in the Reading Pseudowords task. A further analysis indicated that a low score on the Reading Pseudowords task was not accompanied by low performance on Reading (meaningful) Words Task. According to the

widely accepted Dual-Route Model (Coltheart, Curtis, Atkins & Haller, 1993) there are two independent mechanisms involved in reading. The first is the lexical mechanism, corresponding to the lexical route, and is engaged in the recognition and production of words. Lexical route mediates the conversion of visual input to a whole phonological representation by means of access to a lexical/semantic representation (Simos et al., 2002). This mechanism is considered to be activated while reading meaningful words. Imaging data indicate that the above-mentioned mechanism depends on the activity of the left posterior middle temporal gyrus and mesial temporal lobe areas (Simos et al., 2002). The second mechanism is the sublexical one, or the sublexical route, and it is involved in the phonological decoding, namely the mapping of individual orthographic segments into the appropriate phonological element to arrive at a complete phonological representation (Simos et al., 2002). The sublexical route seems to be activated while the subject carries out the reading of pseudowords task and imaging data suggest the involvement of left temporoparietal region in phonological decoding (Simos et al., 2002). Therefore, we could speculate that there is a possible subcortical dysfunction provoking that mild deficit in our cohort. Our data supports the recent findings of Kasselimis et al. 2019, regarding low scores of CMTX patients on the Reading Pseudowords task.

Verbal memory, encoding and learning, short-term retention, consolidation of verbal information, verbal and visuospatial working memory, confrontation naming, receptive vocabulary, auditory comprehension, processing speed and visual attention seem intact and not affected by the disease. This is a fact that raises more questions about the involvement of CNS in CMT disease. If there is a CNS involvement in CMT1A then the questions arising are the following: Which are the anatomical abnormalities of the central nervous system that induce the appearance of cognitive deficits? And why are they so “selective” provoking deficits to one function and not to another? Which are the neural networks that might be affected by the disease? Our study did not provide evidence on whether there is a clear involvement or not of CNS in CMT1A, since we managed to

detect mild cognitive deficits in a small number of patients, and one might object that these deficits are coincidental. Future extensions of this study are needed in order to clarify if CNS is involved in CMT1A.

It is important to clearly state several limitations in the present study. The most crucial one, is the size of the CMT1A group. The size of our cohort was limited by the relatively low prevalence of disease and the inclusion criteria. Despite the fact that the number of our CMT1A patients (N=23) was not sufficient in order to reach reliable conclusions, it was higher than the number of patients (N=13) included in the only existing neuropsychological study with CMT1A patients (Chanson et al., 2013). Another limitation could be considered the fact that the control group of healthy participants is not exactly matched with the patients in terms of age, gender and years of education. Based on our methodology, we extracted our data for the control group from the specified database of another study mentioned above (see Methods, Page 14). However, the database did not contain subjects with totally the same demographic characteristics with the patients, and due to the Covid-19 sanitary crisis and time constraints for the completion of the present study, the enrichment of the database was not attainable. Nevertheless, the statistical analysis demonstrated that there is no statistically significant difference (p = .059) between the two groups as far as the above-said characteristics are concerned. At this point it would be noticeable to mention that the ideal scenario would have been to include a control group with a comparable hereditary neuropathy, as mentioned in the studies of Chanson et al. (2013) and Kasselimis et al. (2019). Due to the specific time limitation for the completion of our study, it was not feasible to recruit two groups of patients with rare neuropathies.

A further limitation is the fact that the number of male (N=17) and female (N=6) patients is unequal, hence we could not compare the two groups in order to see if there is gender effect in the performance of patients. Finally, another limitation pertaining to this study, is the absence of concomitant neuroimaging data, such as DTI, that could be correlated to the cognitive deficits detected. It would be of paramount importance to know if any kind of cognitive dysfunction is an

expression of a possible grey or white matter abnormality.

Future extensions of this study should take into account the aforementioned limitations. More specifically, we suggest that future research regarding the cognitive functions in CMT1A patients should involve a larger cohort of patients which would enhance the credibility of the results. Besides, neuroimaging techniques should be applied for the detection of possible CNS abnormalities which could provoke cognitive impairment. Furthermore, we propose that future studies should include an equal number of male and female patients with the aim of shedding light on the gender effect.

In conclusion, our results suggest the existence of mild cognitive deficits in the cognitive functions of cognitive flexibility and decoding, and support the possibility of CNS involvement in CMT1A. One might object that the presenting data have little clinical significance since the detected cognitive deficits are mild. However, these could have an impact on patient's employment and overall quality of life. Thus, further research would be of great significance in order to confirm the presenting data and precisely describe cognition in CMT1A.

References

Almsaddia, M., Bertorini, T.E., & Seltzerb, W.K. (1998). Demyelinating neuropathy in a patient with multiple sclerosis and genotypical HMSN-1. Neuromuscular Disorders, 8(2), 87-9.

Amato, AA., & Barohn, RJ. (1996). Hereditary neuropathy with liability to pressure palsies: association with central nervous system demyelination. Muscle & Nerve, 19, 770–3.

Chan, E., MacPherson, S.E., Robinson, G., Turner, M., Lecce, F., Shallice,T., & Cipolotti ,L. (2015). Limitations of the trail making test part-B in assessing frontal executive dysfunction. Journal of the International Neuropsychological Society, 21(2), 169–174.

Chanson, J., Echaniz-Laguna, A., Blanc, F., Lacour, A., Ballonzoli, L., Kremer, S., Namer, I.J., Lannes, B., Tranchant, C., Vermersch, P., & de Seze, J. (2013). Central nervous system abnormalities in patients with PMP22 gene mutations: a prospective study. Journal of Neurology, Neurosurgery & Psychiatry, 84(4), 392–397.

Christidi, F., Kararizou, E., Triantafyllou, N., Anagnostouli, M., & Zalonis, I. (2015). Derived Trail Making Test indices: demographics and cognitive background variables across the adult life span. Aging, Neuropsychology, and Cognition, 22(6), 667–678.

Coltheart, M., Curtis, B., Atkins, P., & Haller, M. (1993). Models of reading aloud: dual-route and parallel-distributed-processing approaches. Psychological Review, 100(4), 589–608.

Constantinidou, F., Christodoulou, M., & Prokopiou, J. (2012). The effects of age and education on executive functioning and oral naming performance in Greek Cypriot adults: the neurocognitive study for the aging. Folia Phoniatrica et Logopaedica, 64(4), 187–198.

Constantinidou, F., Zaganas, I., Papastefanakis, E., Kasselimis, D., Nidos, A., & Simos, P.G. (2014). Age-related decline in verbal learning is moderated by demographic factors, working memory capacity, and presence of amnestic mild cognitive impairment. Journal of the International Neuropsychological Society, 20(8), 822–835.

Corsi,P.M.(1972).Human memory and the medial temporal region of the brain. Unpublished doctoral dissertation. McGill University, Montreal, Canada.

Cortese, R., Zoccolella, S., Muglia, M., Patitucci, A., Scarafino, A., Paolicelli, D., & Simone, I.L. (2016). A rare association between multiple sclerosis and Charcot-Marie-Tooth type 1B. Brain and Behaviour, 6, 00580.

Dackovic, J., Rakocevic-Stojanovic, V., Pavlovic, S., Zamurovic, N., Dragasevic, N., Romac, S., & Apostolski, S. (2001). Hereditary neuropathy with liability to pressure palsies associated with central nervous system myelin lesions. European Journal of Neurology, 8, 689–692.

Del Bo, R., Moggio, M., Rango, M., Bonato, S., D'Angelo, M.G., Ghezzi, S., Airoldi, G., Bassi, M.T., Guglieri, M., Napoli, D L., Lamperti, C., Corti, S., Federico, A., Bresolin, N., & Comi, G.P.

(2008). Mutated mitofusin 2 presents with intrafamilial variability and brain mitochondrial dysfunction. Neurology, 71, 1959-1966.

Doğana, Y., Güla, S., Ceylanb, A.C., & Kutsala, G. (2019). A special association between Charcot-Marie-Tooth type 1A disease and relapsing remitting multiple sclerosis. Multiple Sclerosis and Related Disorders, 35, 83–85.

Dunn, L.M. (1981). Manual for the Peabody picture vocabulary test-revised. Circle Pines: American Guidance Service.

Frasson, E., Polo, A., Di Summa, A., Fabrizi, G., Taioli, F., Fiaschi, A., Rizzuto, N., Moretto, G. (1997). Multiple sclerosis associated with duplicate CMT1A: a report of two cases. Journal of Neurology, Neurosurgery, and Psychiatry, 63(3), 413–414.

Geffen, G., & Geffen, L.B., (Laurence Basil), 1937- & Australian Council for Educational Research (2000). Auditory Verbal Learning Test (AVLT) computerized scoring program and population norms. Melbourne: ACER Press.

Isoardo, G., DiVito, N., Nobile, M., Benetton, G., & Fassio, F. (2005). X linked Charcot-Marie-Tooth disease and progressive-relapsing central demyelinating disease. Neurology, 65 (10), 1672–1673.

Kaplan, E.F., Goodglass, H., & Weintraub, S. (1983). The Boston naming test, 2nd ed. Philadelphia: Lea & Febiger.

Karadima, G., Floroskufi, P., Koutsis, G., Vassilopoulos, D., & Panas, M. (2011). Mutational analysis of PMP22, GJB1 and MPZ in Greek Charcot-Marie-Tooth type 1 neuropathy patients. Clinical Genetics, 80(5), 497–499.

Karadima, G., Koutsis, G., Raftopoulou, M., Floroskufi, P., Karletidi, K.M., & Panas, M. (2014). Four novel connexin 32 mutations in X-linked Charcot–Marie–Tooth disease. Phenotypic variability and central nervous system involvement. Journal of the Neurological Sciences, 341(1), 158–161.

Kasselimis, D., Karadima, G., Angelopoulou, G., Breza, M., Tsolakopoulos, D., Potagas, C., Panas, M., & Koutsis, G. (2019). Evidence for cognitive deficits in X-linked Charcot-Marie-Tooth disease. Journal of the International Neuropsychological Society, 2019, 1–9.

Kessels, R. P., van den Berg, E., Ruis, C., & Brands, A. M. (2008). The Backward Span of the Corsi Block-Tapping Task and Its Association with the WAIS-III Digit Span. Assessment, 15, 426-434.

Koros, C., Evangelopoulos, M.E., Kilidireas, C., & Andreadou, E. (2013). Central nervous system demyelination in a Charcot-Marie-Tooth type 1A patient. Case Reports in Neurological Medicine, 2013:243652.

Kosmidis, M.H., Vlahou, C.H., Panagiotaki, P., & Kiosseoglou, G. (2004). The verbal fluency task in the Greek population: normative data, and clustering and switching strategies. Journal of the International Neuropsychological Society, 10(2), 164–172.

Koutsis, G., Breza, M., Velonakis, G., Tzartos, J., Kasselimis, D., Kartanou, C., Karavasilis, E., Tzanetakos, D., Anagnostouli, M., Andreadou, E., Evangelopoulos, M.E., Kilidireas, C., Potagas, C.,

Panas, M., & Karadima, G. (2019). X linked Charcot-Marie-Tooth disease and multiple sclerosis: emerging evidence for an association. Journal of Neurology Neurosurgery and Psychiatry, 90(2), 187–194.

Lee, M., Park, C.H., Chung, H.K., Kim, H.J., Choi, Y., Yoo, J.H., Yoon, Y.C., Hong, Y.B., Chung, K.W., Choi, B.O., & Lee, H.W. (2017). Cerebral white matter abnormalities in patients with charcot-marie-tooth disease. Annals of Neurology, 81(1), 147–151.

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). Neuropsychological assessment (4th ed.). New York, NY: Oxford University Press.

Li. J., Parker, B., Martyn, C., Natarajan, C., & Guo, J. (2012). The PMP22 Gene and Its Related Diseases. Molecular Neurobiology, 47, 673-698.

Lupski, J.R., Montes de Oca-Luna, R., Slaugenhaupt, S., Pentao, L., Guzzetta, V., Trask, B.J., Saucedo-Carclenas, O., Barker, D.F., Killian, J.M., Garcia, C.A., Chakravarti, A., & Patel, P.I. (1991). DNA Duplication Associated with Charcot-Marie-Tooth Disease Type 1 A. Cell, 66(2), 219-232.

Martyn, C.N., & Hughes, R.A. (1997). Epidemiology of peripheral neuropathy. Journal of Neurology, Neurosurgery, and Psychiatry, 62(4), 310-8.

Naef, R, & Suter, U. (1998). Many facets of the peripheral myelin protein PMP22 in myelination and disease. Microscopy Research and Technique, 41, 359–371.

Ohsawa, Y., Murakami, T., Miyazaki, Y., Shirabe, T., & Sunada, Y. (2006). Peripheral myelin protein 22 is expressed in human central nervous system. Journal of Neurological Sciences, 247, 11–15.

Panas, M., Kalfakis, N., Karadimas, C., & Vassilopoulos, D. (2001). Episodes of generalized weakness in two sibs with the C164T mutation of the connexin 32 gene. Neurology, 57(10), 1906–1908.

Panas, M., Karadima, G., Kalfakis, N., Floroskufi, P., & Vasilopoulos, D. (2004). Charcot-Marie-Tooth disease type 1A with central nervous system involvement in two generations. Journal of Neurology, 251(4), 484-485.

Pareyson, D. & Marchesi, C. (2009). Diagnosis, natural history, and management of Charcot-Marie-Tooth disease. Lancet Neurology, 8(7), 654–667.

Pareyson, D., Saveri, P., & Pisciotta, C. (2017). New developments in Charcot-Marie-Tooth neuropathy and related diseases. Current Opinion in Neurology, 30(5), 471-480.

Paulson, H.L., Garbern, J.Y., Hoban, T.F., Krajewski, K.M., Lewis, R.A., Fischbeck, K.H., Grossman, R.I., Lenkinski, R., Kamholz, J.A., & Shy, M.E. (2002), Transient central nervous system white matter abnormality in X-linked Charcot-Marie-Tooth disease. Annals of Neurology, 52(4), 429–434.

Raeymarkers, P., Timmerman, V., Nelis, E., De Jonghe, P., Hoogendijk, J.E., Baas, F., Barker, D.F., Martin, J.J., De Visser, M., Bolhuis, P.A., & Van Broeckhoven, C., and the HMSN Collaborative

Research Group (1991). Duplication in chromosome 17p11.2 in Charcot-Marie-Tooth neuropathy type 1a (CMT 1A). Neuromuscular Disorders, 1(2), 93-7.

Sanahuja J, Franco E, Rojas-García R, Gallardo, E., Combarros, O., Begué, R., Granés, P., & Illa, I. (2005). Central nervous system involvement in hereditary neuropathy with liability to pressure palsies: description of a large family with this association. Archives of Neurology, 62, 1911–14.

Shy, M.E., Garbern, J.Y., & Kamholz, J. (2002) Hereditary motor and sensory neuropathies: a biological perspective. The Lancet Neurology, 1, 110-118.

Simos, P.G., Breier, J.I., Fletcher, J.M., Foorman, B.R., Castillo, E.M., & Papanicolaou, A.C. (2002). Brain mechanisms for reading words and pseudowords: an integrated approach. Cerebral Cortex, 12(3), 297–305.

Simos, P.G., Kasselimis, D., & Mouzaki, A. (2011a). Age, gender, and education effects on vocabulary measures in Greek. Aphasiology, 25(4), 475–491.

Simos, P.G., Kasselimis, D., & Mouzaki, A. (2011b). Effects of demographic variables and health status on brief vocabulary measures in Greek. Aphasiology, 25(4), 492–504.

Simos, P.G., Kasselimis, D., Potagas, C., & Evdokimidis, I. (2014). Verbal comprehension ability in aphasia: demographic and lexical knowledge effects. Behavioural Neurology, 258303.

Simos, P.G., Papastefanakis, E., Panou, T., & Kasselimis,D. (2011). The Greek memory scale. Rethymno: Laboratory of Applied Psychology, University of Crete.

Simos, P.G., Sideridis, G.D., Kasselimis, D., & Mouzaki, A. (2013). Reading fluency estimates of current intellectual function: demographic factors and effects of type of stimuli. Journal of the International Neuropsychological Society, 19(3), 355–361.

Smith A: Symbol Digit Modalities Test (SDMT). Manual (Revised). Los Angeles, Western Psychological Services, 1982.

Snipes, GJ., Suter, U., Welcher, A.A., & Shooter, E.M. (1992). Characterization of a novel peripheral nervous system myelin protein (PMP-22/SR13). Journal of Cell Biology, 117, 225–238.

Spreen, O., & Strauss, E. (1991). A compendium of neuropsychological tests: Administration, norms, and commentary (2nd ed.). New York: Oxford University Press.

Stancanelli, C., Taioli, F., Testi, S., Fabrizi, G.M., Arena, M.G., Granata, F., Russo, M., Gentile, L., Vita, G., & Mazzeo, A. (2012). Unusual features of central nervous system involvement in CMTX associated with a novel mutation of GJB1 gene. Journal of the Peripheral Nervous System, 17(4), 407–411.

Szigeti, K., & Lupski, J.R. (2009). Charcot-Marie-Tooth disease. European Journal of Human Genetics, 17, 703-710.

Tackenberg, B., Moller, J.C., Rindock, H., Bien, S., Sommer, N., Oertel, W.H., Rosenow, F., Schepelmann, K., Hamer, H.M., & Bandmann, O. (2006). CNS involvement in hereditary neuropathy

with pressure palsies (HNPP). Neurology, 67, 2250–2.

Zakzanis, K. K., Mraz, R., & Graham, S. J. (2005). An fMRI study of the trail making test. Neuropsychologia, 43(13), 1878–1886.

Zalonis, I., Kararizou, E., Triantafyllou, N.I., Kapaki, E., Papageorgiou, S., Sgouropoulos, P., & Vassilopoulos, D. (2007). A normative study of the trail making test A and B in Greek adults. Clinical Neuropsychologist, 22(5), 842–850.