

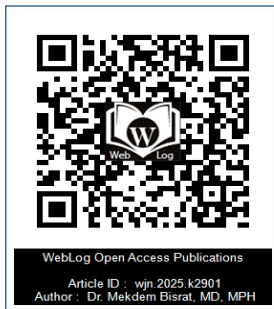


Exploring the Incidence of Cognitive Dysfunction and Sleep Disorders in Charcot-Marie-Tooth

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Abstract

Background: Charcot-Marie-Tooth disease (CMT) is a genetically heterogeneous peripheral neuropathy traditionally considered to spare the central nervous system (CNS). However, recent reports suggest possible CNS involvement, including cognitive impairment and sleep disturbances. The true prevalence of these manifestations remains unclear due to limited large-scale data.

Methods: We conducted a retrospective cohort study using data from 141 healthcare organizations within the Global Collaborative Network. Patients aged ≤50 years with a diagnosis of hereditary motor and sensory neuropathy (ICD-10: G60.0) were included. Exclusion criteria comprised conditions that independently contribute to cognitive or sleep disorders. Diagnoses of cognitive impairment and sleep disorders were identified using standardized ICD-10 codes.

Results: Among 11,795 patients, 466 (3.95%) were diagnosed with cognitive impairment and 791 (6.71%) with sleep disorders. Cognitive impairment was more common in females (4.34%) than males (3.56%), with peak incidence in the 25–29 age group (6.2%). Sleep disorders also showed higher prevalence in females (7.51%) versus males (5.91%), peaking similarly in the 25–29 age group (11.9%). Striking racial disparities were noted: Native Hawaiian/Pacific Islander and American Indian/Alaska Native patients had the highest prevalence of both conditions (41.7% and 25.6%, respectively). These patterns suggest underrecognized CNS involvement in CMT across diverse subgroups.

Conclusion: Cognitive dysfunction and sleep disorders occur at clinically significant rates in patients with CMT, particularly among younger adults and racially minoritized populations. These findings highlight the need for expanded clinical screening and further mechanistic studies to understand CNS involvement in CMT.

Keywords: Charcot-Marie-Tooth; Cognitive Dysfunction; Sleep Disorder

Introduction

Charcot-Marie-Tooth disease (CMT), also known as Hereditary Sensory Motor Neuropathy, is a group of inherited neurological disorders characterized by progressive dysfunction of the peripheral nerves, leading to distal muscle weakness, atrophy, and sensory loss. With a prevalence of approximately 1 in 2,500 individuals, CMT affects an estimated 125,000 people in the United States, making it the most common inherited neurological disorder [1, 2].

Although CMT has traditionally been viewed as a disease limited to the peripheral nervous system, emerging evidence suggests that the central nervous system (CNS) and cognitive function may also be affected in certain subtypes. This challenges the long-held belief that CMT is exclusively a peripheral neuropathy [3-6].

CMT is classified into subtypes based on inheritance pattern, genetic mutation, and the type of nerve damage. The most common forms are CMT1 (demyelinating) and CMT2 (axonal), with rarer variants such as CMT4 (autosomal recessive) and CMTX (X-linked). The most prevalent subtype, CMT1A, is caused by duplication of the *PMP22* gene, which plays a critical role in myelin synthesis and maintenance. CMT1B results from mutations in the *MPZ* gene, involved in myelin compaction. CMT2A is associated with mutations in the *MFN2* gene, which affects mitochondrial structure and function. CMTX1, the most common X-linked form, is caused by mutations in *GJB1*, which encodes the protein connexin 32. Notably, connexin 32 is expressed not only in Schwann cells

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but also in oligodendrocytes, suggesting a possible mechanistic link to CNS involvement. Additionally, rare autosomal recessive forms such as CMT4C (*SH3TC2*) and CMT4A (*GDAP1*) have also been linked to central or cognitive abnormalities [7, 8].

While case reports and small cohort studies have described CNS findings—such as white matter lesions, cerebellar dysfunction, and cognitive deficits—in certain CMT subtypes, these features remain poorly understood and their clinical significance unclear [4-6]. For instance, patients with *GJB1* mutations have shown transient CNS symptoms, abnormal brain MRI findings, and subtle impairments in executive function, attention, and processing speed [9, 10]. However, no large-scale population-based studies have systematically assessed the incidence or prevalence of CNS or cognitive involvement in CMT, limiting our understanding of the full spectrum and burden of these manifestations.

In addition to motor and sensory impairments, many individuals with CMT report sleep disturbances, which can further affect quality of life. These include insomnia, poor sleep quality, excessive daytime sleepiness, and symptoms suggestive of restless legs syndrome or sleep-disordered breathing [11]. Such disturbances may arise from chronic neuropathic pain, muscle cramps, nocturnal fasciculations, and reduced mobility. Yet, systematic research into the prevalence and underlying mechanisms of sleep disorders in CMT remains limited, with current knowledge primarily derived from small studies and self-reported symptoms [11-14].

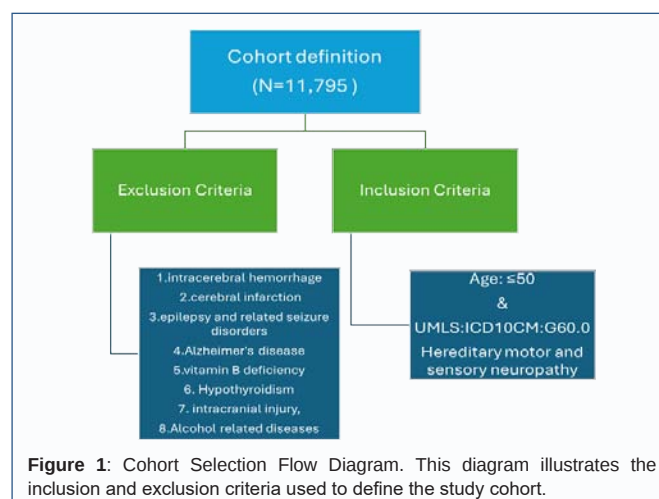
Most prior research has been confined to small cohorts and has primarily focused on the peripheral nerve features of CMT. In contrast, this study aims to examine the incidence and spectrum of cognitive dysfunction and sleep disorders in individuals with CMT, two underexplored domains that may significantly impact patient outcomes. Addressing these gaps has important implications for diagnosis, clinical management, and patient counseling, especially as genetic testing and neuroimaging become increasingly integrated into routine care.

Methods

We conducted a retrospective cohort study to obtain the incidence of cognitive deficits and sleep disorders in patients with Charcot-Marie-Tooth disease. The study recruited patients with a diagnosis of hereditary motor and sensory neuropathy. The analysis was carried out in two main stages: first, defining the patient cohort through a structured query, and second, executing the analysis based on that cohort. This process was designed to ensure consistency and reproducibility across all data-contributing healthcare organizations (HCOs).

The cohort was defined using a standardized query executed on the Global Collaborative Network, which included 141 participating HCOs. All 141 HCOs responded, with 125 providers contributing relevant patient data. The final cohort consisted of 11,795 patients who met the inclusion and exclusion criteria outlined in the query.

To be included in the cohort, patients had to be 50 years old or younger at the time of their most recent demographic record. Additionally, patients were required to have a diagnosis of hereditary motor and sensory neuropathy (UMLS:ICD10CM:G60.0), which could occur at any time in their medical history. However, patients were excluded from the cohort if they had any diagnoses from a predefined list of conditions within five years before or any time



after the qualifying neuropathy diagnosis. These exclusion diagnoses included intracerebral hemorrhage, cerebral infarction, epilepsy and related seizure disorders, Alzheimer's disease, vitamin B deficiency, hypothyroidism, intracranial injury, and a range of alcohol-related and psychiatric disorders (Figure 1).

The analysis window spanned from January 1, 2004, through December 31, 2024. A lookback period was applied to distinguish between incident and prevalent cases by reviewing all historical records up to one day before each patient's analysis window. Descriptive statistics were used to summarize demographics and calculate the prevalence of cognitive impairment and sleep disorders. To explore subgroup patterns, the analysis was stratified by age, sex, and race; ethnicity was not included as a stratification variable. Events of interest were identified using standardized diagnostic codes: cognitive impairment included R41, G31.84, and R41.844, while sleep disorders included G47.0, G47.27, Z72.821, and G47.9. Patients were flagged as positive for an event if they met at least one qualifying diagnosis. All analyses were conducted using the built-in tools of the Global Collaborative Network platform, ensuring consistency across contributing healthcare organizations.

This study was conducted in accordance with the Declaration of Helsinki. Only de-identified data were used, and institutional review board (IRB) approval was not required for this secondary data analysis.

Results

Cohort Characteristics

A total of 11,795 patients diagnosed with hereditary motor and sensory neuropathy (ICD-10: G60.0) were included in the final cohort after applying inclusion and exclusion criteria. All patients were ≤50 years old at the time of their most recent demographic record. The cohort was approximately balanced by sex (Female: 53.1%, Male: 46.9%) and represented a diverse racial background (White: 61.1%, Black/African American: 25.0%, Asian: 2.9%, Other/Unknown: 11.0%).

Outcome 1: Cognitive Impairment

Among the 11,795 patients included in the cohort, 466 (3.95%) were diagnosed with cognitive impairment based on qualifying ICD-10 codes. Female patients demonstrated a higher incidence (4.34%) than male patients (3.56%). Age-stratified analysis revealed that the

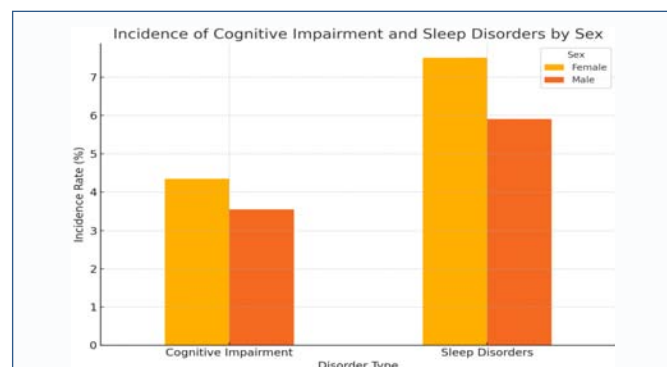


Figure 2: Sex-Based Incidence. This graph illustrates the rates of cognitive and sleep disorders by sex.

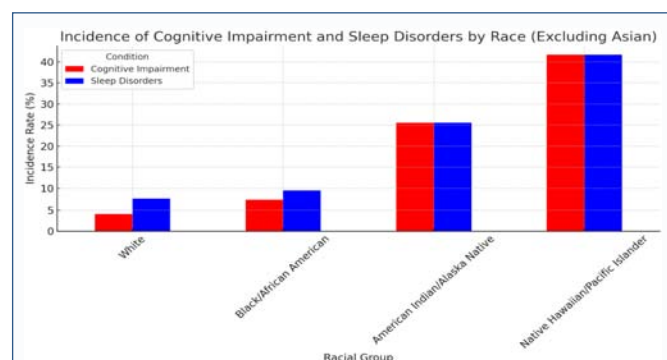


Figure 3: Racial Disparities. This graph illustrates the incidence of cognitive and sleep disorders across racial subgroups.

highest incidence occurred in the 25–29 age group (6.2%), with rates in other pediatric and young adult brackets generally ranging from 3.1% to 4.8%. When stratified by race, the burden of cognitive impairment was disproportionately higher among certain minority groups. Native Hawaiian or Pacific Islander patients had the highest incidence at 41.7%, followed by American Indian or Alaska Native patients at 25.6%. Black or African American patients had an incidence of 7.3%, while White patients had a rate of 4.1%. These findings suggest that cognitive dysfunction may be an underrecognized manifestation of Charcot-Marie-Tooth disease, particularly among young adults and racially minoritized populations.

Outcome 2: Sleep Disorders

Sleep disorders were diagnosed in 791 patients, representing 6.71% of the total cohort. Similar to the cognitive impairment findings, sleep disturbances were more common among female patients (7.51%) compared to males (5.91%). The highest incidence was again observed in the 25–29 age group, where the rate reached 11.9%, mirroring the age pattern seen with cognitive impairment. Racial disparities were also evident in the distribution of sleep disorder diagnoses. Native Hawaiian or Pacific Islander patients exhibited the highest incidence (41.7%), followed by American Indian or Alaska Native patients (25.6%), Black or African American patients (9.5%), and White patients (7.6%). These patterns reinforce the emerging evidence that central nervous system–related symptoms, such as sleep and cognitive dysfunction, may be more prevalent in individuals with CMT than previously understood, particularly among certain subgroups.

Figure 2-4 shows the stratified data by age, race and sex for both cognitive and sleep disorders.

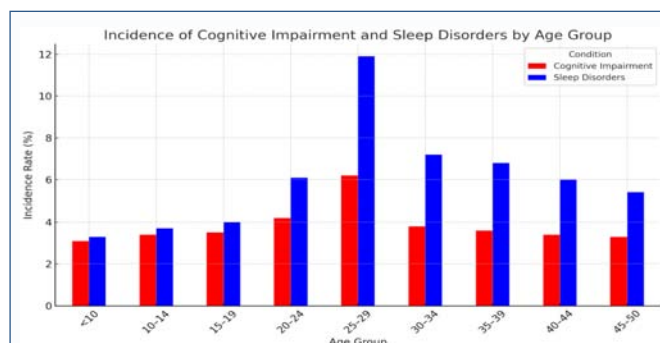


Figure 4: Age-Based Incidence. This graph illustrates the prevalence of cognitive and sleep disorders by age group.

Discussion

Our study reveals that a significant proportion of individuals with Charcot-Marie-Tooth disease (CMT) experience central nervous system (CNS)-related symptoms, with 3.95% of the cohort diagnosed with cognitive impairment. These findings align with prior studies that suggest CNS involvement in specific CMT subtypes, particularly CMTX1, which is linked to mutations in the *GJB1* gene encoding connexin 32. This protein is expressed not only in Schwann cells but also in oligodendrocytes, providing a plausible biological basis for CNS effects [15]. Kasselimis et al. reported cognitive dysfunction and executive deficits in CMTX patients, correlating with MRI findings of transient or persistent white matter lesions, especially in the splenium of the corpus callosum [15]. As the corpus callosum plays a vital role in interhemispheric integration, especially for higher-order cognitive tasks such as visuospatial processing and executive functioning, structural abnormalities in this area may underlie the observed impairments [16].

Interestingly, our findings suggest that the burden of cognitive impairment in CMT may extend beyond CMTX subtypes. Emerging studies have identified white matter abnormalities in other genetic forms of CMT, including CMT1A and CMT2A, raising the possibility that CNS involvement may be more widespread than previously assumed [17, 18]. White matter lesions in these patients have been linked to disruptions in corticospinal and cerebellar pathways, potentially contributing to not only motor dysfunction but also subtle deficits in cognition. These associations warrant further exploration, particularly using neuroimaging and neuropsychological assessments to determine whether anatomical changes correlate with measurable cognitive dysfunction [18]. Our study provides early epidemiologic evidence to support this expanded view.

In terms of demographic patterns, our results did not show significant differences in cognitive impairment rates between men and women. This aligns with a growing body of literature showing no sex-based differences in cognitive outcomes among patients with inherited neuropathies, including CMT [19, 20]. However, this lack of disparity may obscure more nuanced sex-specific phenotypes that could emerge with larger sample sizes or more granular cognitive testing. Additionally, the role of X-linked inheritance in CMTX1 may confound sex-based analyses, as male patients typically experience more severe phenotypes, while female carriers may remain asymptomatic or have milder presentations [20]. Thus, while sex differences were not observed in our cohort, further stratification by genotype may help clarify the relationship.

Sleep disorders were present in 6.71% of our cohort, a notable finding given that sleep dysfunction is often underreported in CMT. Prior studies suggest that pain, fasciculations, and reduced mobility contribute significantly to insomnia and sleep fragmentation in this population [21]. Additionally, symptoms such as restless legs syndrome and sleep-disordered breathing have been observed with greater frequency in individuals with peripheral neuropathies [22]. Our findings support this, with sleep disturbances disproportionately affecting women and peaking in young adulthood. The high prevalence of sleep disorders in the 25–29 age group may reflect a confluence of neuropathic symptoms and stressors related to life-stage demands. This intersection deserves greater attention in both clinical care and research.

Racial disparities were also apparent in both cognitive impairment and sleep disorder rates, with Native Hawaiian/Pacific Islander and American Indian/Alaska Native patients experiencing the highest burden. This trend mirrors broader disparities in neurological care access and outcomes among historically marginalized communities [23]. Socioeconomic stress, environmental risk exposures, and structural healthcare inequities may all contribute to higher diagnostic rates or underrecognized disease severity in these populations. Notably, these disparities were consistent across both CNS domains studied, suggesting systemic differences in either biological risk, diagnostic capture, or both [24]. Further investigations are needed to disentangle genetic, environmental, and social determinants of these disparities in CMT.

Our study has several strengths, including the use of a large, multicenter dataset spanning 141 healthcare organizations, which enhances the generalizability of our findings. Additionally, we employed strict inclusion and exclusion criteria to reduce diagnostic misclassification, focusing on clearly defined cognitive and sleep-related ICD-10 codes. However, our study is limited by the use of the TriNetX database which is unable to stratify the patients with Charcot Marie Tooth disease into which sub-types they have. Additionally, the database relies on administrative coding, which may underestimate the true prevalence of subclinical or undiagnosed CNS involvement. Moreover, there is an absence of genotypic data precludes precise correlations between genetic subtype and neurologic outcomes. Future research should incorporate prospective neurocognitive testing and sleep studies across genetically defined CMT cohorts to better understand the full scope of CNS manifestations and their underlying mechanisms.

Conclusion

This large-scale, multicenter analysis reveals that cognitive dysfunction and sleep disorders are underrecognized yet clinically significant comorbidities in patients with Charcot-Marie-Tooth disease, particularly among younger adults and racially minority populations. The findings challenge the traditional notion of CMT as a purely peripheral neuropathy and support emerging evidence of central nervous system involvement across various genetic subtypes. Given the potential impact of these symptoms on quality of life, routine screening for cognitive and sleep disturbances should be considered in the clinical management of CMT. Further research incorporating genetic, neuroimaging, and neuropsychological data is essential to clarify the underlying mechanisms and guide targeted interventions.

Conflicts of Interest

The authors declare that there are no financial, personal, or professional conflicts of interest that could have influenced the content, results, or conclusions of this study.

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