

Small fiber neuropathy in Wilson's disease: literature review

Neuropatia de fibras finas na doença de Wilson: revisão de literatura

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Abstract

Introduction: Peripheral neuropathy is a very common neurological disorder and its prevalence is increasing due to the aging process of the population and the increase in comorbidities such as diabetes and obesity. Fine fiber peripheral neuropathy (NFF) is considered a syndrome that presents isolated sensory manifestations, or a combination of sensory and autonomic manifestations. Wilson's disease (WD) is an autosomal recessive disorder caused by impaired copper metabolism due to mutations in the ATP7B gene. Among the neurological alterations presented by patients with WD is peripheral neuropathy. **Objective:** To review the literature about thin fiber neuropathy in Wilson's Disease, increasing the understanding of this dysfunction about its causes and types of approaches presented in the literature. **Methods:** A literature review was carried out based on the data survey present in the Scielo and PUBMED databases from January to June 2021, using the descriptors: "Small Fiber Neuropathy", "Wilson's Disease", "Peripheral Neuropathy". **Results:** 29 articles were selected, whose For a better understanding, the results found in the literature review were divided into topics. From 29 recruited articles, 15 were excluded, as they had other underlying diseases that could justify the presence of neuropathy in addition to Wilson's disease. Of the 14 articles included in the research: 3 described the presence of fine fiber neuropathy in WD, 4 articles highlighted the presence of mild axonal sensory motor polyneuropathy in WD, 7 articles showed evidence of autonomic neuropathy, 2 with predominantly sympathetic dysfunction and 1 parasympathetic. **Conclusion:** Fine fiber

neuropathy remains a challenging diagnosis in the field. and may be present in mild forms, even in diseases with predominant involvement of the CNS. In WD there are also reports of this peripheral neurological involvement, with a predominance of involvement of thin autonomic fibers with repercussions that are not yet completely understood. The understanding of this dysfunction is still not fully clarified and there are still many things to be understood about Wilson's disease, so further study on this topic is necessary since studies addressing this issue are still scarce in the literature, even with an increase in number of cases diagnosed with Wilson's disease and presenting associated sensory complaints.

Keywords: Small fiber neuropathy, Wilson disease, Peripheral nervous system diseases, Peripheral neuropathies

Resumo

Introdução: A neuropatia periférica é um distúrbio neurológico bastante comum e vem aumentando sua prevalência devido ao processo de envelhecimento da população e aumento de comorbidades como diabetes e obesidade. A neuropatia periférica de fibras finas (NFF) é considerada uma síndrome que apresenta manifestações sensitivas isoladas, ou a combinação de manifestações sensitivas e autonômicas. A doença de Wilson (DW) é um transtorno autossômico recessivo causado por deficiência na metabolização do cobre decorrente de mutações no gene ATP7B. Entre as alterações neurológicas apresentadas pelos pacientes com DW está a neuropatia periférica. **Objetivo:** Revisar a literatura acerca da neuropatia de fibras finas na Doença de Wilson aumentando a compreensão dessa disfunção sobre suas causas e tipos de abordagens apresentadas na literatura. **Métodos:** Foi realizada uma revisão bibliográfica a partir do levantamento de dados presente nas bases de dados Scielo e PUBMED no período de janeiro a junho de 2021, utilizando os descritores: "Small Fiber Neuropathy", "Wilson's Disease", "Peripheral Neuropathy". **Resultados:** Foram selecionados 29 artigos, cujos originais foram utilizados para composição deste estudo. Para melhor compreensão, os resultados encontrados no levantamento bibliográfico foram divididos em tópicos. Dos 29 artigos recrutados 15 foram excluídos, pois apre-

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sentavam outras doenças de base que pudessem justificar a presença de neuropatia além da doença de Wilson. Dos 14 artigos incluídos na pesquisa: 3 descreveram a presença de neuropatia de fibras finas na DW, 4 artigos destacaram a presença de leve polineuropatia sensitivo motora axonal na DW, 7 artigos mostraram evidência de neuropatia autonômica, sendo 2 com disfunção predominantemente simpática e 1 parassimpática. **Conclusão:** Neuropatia de fibras finas permanece como um diagnóstico desafiador na literatura, podendo estar presente em formas leves, mesmo em doenças com envolvimento predominante do SNC. Na DW também há relatos desse acometimento neurológico periférico, com predomínio de envolvimento de fibras finas autonômicas de repercussões ainda não completamente compreendidas. A compreensão dessa disfunção ainda não está totalmente esclarecida e ainda há muitas coisas a serem compreendidas sobre a doença de Wilson, portanto faz-se necessário mais estudo sobre essa temática uma vez que ainda é escasso na literatura estudos que abordem esse assunto mesmo havendo aumento do número de casos diagnosticados com doença de Wilson e que apresentam queixas sensitivas associadas.

Palavras chave: Neuropatia de fibras finas, Doença de Wilson, Doenças do sistema nervoso periférico, Neuropatias periféricas

Introduction

Several mechanisms such as metabolic, infectious, nutritional, genetic and autoimmune disorders can damage the integrity of peripheral nerves, causing peripheral neuropathy⁽¹⁾. Peripheral neuropathy is a very common neurological disorder that has been increasing in prevalence due to the aging process of the population and the increase in comorbidities such as diabetes, glucose control disorders and obesity. This disorder is an important cause of reduced quality of life due to pain, altered gait and depressive conditions⁽²⁾.

Neuropathies can be classified as: mononeuropathies when they affect an isolated nerve; multiple mononeuropathies when there is successive involvement of several nerves; and polyneuropathies when multiple nerves are affected symmetrically and diffusely. According to the duration, they can be acute (up to one month), subacute (months) and chronic (years). Furthermore, they can be classified as sensory, motor, sensorimotor or autonomic; or even, taking into account the exclusive involvement of large fibers versus small fibers⁽³⁾.

Objective

To review the literature about small fiber neuropathy in Wilson's Disease, increasing the understanding

of this dysfunction about its causes and types of approaches presented in the literature.

Methods

This study consists in a literature review on peripheral neuropathies in Wilson's Disease. A bibliographic survey was carried out in the Scielo and PubMed databases, as well as an additional search in the references cited by the collected articles. The following descriptors were used: "Small Fiber Neuropathy", "Wilson's Disease", "Peripheral Neuropathy".

There was a scarcity of literature related to the topic, which has been the object of study by the authors for several years, in addition to the absence of studies on this subject in works published in Portuguese, thus becoming the motivation for writing this review, as it has the increasing number of cases diagnosed with Wilson's disease that present in the course of the disease the presence of peripheral neuropathy has been observed.

Titles and abstracts of articles were analyzed during the literature review. Those whose content was closest to the objective of the study were read in full and selected and those who would be excluded were determined. Articles that presented clinical cases with other underlying diseases that could be associated with the emergence of neuropathy in addition to Wilson's disease were excluded from the research.

Results

Through a literature review, 29 original articles were selected. For a better understanding of the subject covered, the results found in the bibliographic survey were divided into topics. Out of 29 articles, 14 were further evaluated, as they presented only Wilson's disease as the underlying disease that could explain the onset of peripheral neuropathy. According to the research findings, we subdivided the results in topics ranging from the explanation of the definition of small fiber neuropathy to the types of treatments proposed in the literature.

Small fiber neuropathy

The small fibers of the peripheral nervous system may be poorly myelinated or unmyelinated (majority). These fibers (C and A delta fibers) are responsible for conducting stimuli such as temperature and painful sensation, after mechanical or thermal stimulation on the skin. Due to the involvement of C fibers in the autonomic function, their degeneration can be reflected in pure autonomic dysfunctions⁽⁴⁾.

A syndrome that presents isolated sensory mani-

festations or a combination of sensory and autonomic manifestations, with neurological examination (usually) almost normal, is called small fiber peripheral neuropathy (SFN). This group of diseases usually affects the distal endings of nerves, which trigger dysfunction. The reported complaints directly interfere in the patients' quality of life⁽¹⁾.

Classification

Peripheral neuropathy can present with somatic complaints, the most common being burning feet, changes in thermal and painful sensitivity, which can follow a length-dependent pattern, that is, the distribution of neuropathy depends on the length of the nerve. It is usually symmetric, starting with distal involvement of the hands and feet (stock or glove pattern) and ascending, in the case of the lower limbs, to the ankle or knees⁽⁵⁾.

In non-length-dependent neuropathies, complaints may be focal or multifocal, and may present a bizarre topography, as in the case of burning mouth syndrome. In addition to somatic complaints, there may be autonomic impairment mediated by cholinergic and vasomotor fibers that trigger the following symptoms: pupillary dysfunction, tachycardia, exercise intolerance, orthostatic hypotension, anhidrosis, heat intolerance, dry skin, esophageal dysmotility, gastroparesis, diarrhea, constipation, erectile dysfunction, neurogenic bladder and retrograde ejaculation^(3,6).

Etiologies

Currently, several factors are related to the development of NFF, among them are:

- Metabolic dysfunctions: diabetes, glucose intolerance, hypothyroidism and vitamin B12 deficiency;
- Infectious diseases: influenza, HIV, leprosy and hepatitis C;
- Drugs and toxic substances: antiretroviral drugs, metronidazole, nitrofurantoin, chronic alcohol abuse, thallium, arsenic, statins;
- Immune-mediated diseases: celiac disease, sarcoidosis, Sjogren syndrome, systemic lupus erythematosus, rheumatoid arthritis, connective tissue disease, inflammatory bowel disease;
- Genetic diseases: Fabry disease, hemochromatosis, sodium channel mutation, Tangier disease, amyloidosis;
- Neuropathy associated with neoplasms: paraneoplastic syndrome;
- Neurodegenerative: Parkinson's disease, amyotrophic lateral sclerosis;
- Idiopathic causes

Among all these factors listed above, the most common cause of SFN is diabetes. The prevalence of this type of neuropathy in diabetes is greater than that of large fiber neuropathy^(6,4,7,1).

Clinical manifestations

Symptoms of SFN vary widely among individuals in terms of severity, distribution and progression, and may be associated with somatic, autonomic or mixed complaints. Generally, SFN is length-dependent, presenting changes initially in the extremities of the lower limbs. However, there are reports of non-length-dependent cases, with the alterations being distributed irregularly in the upper extremities, face, trunk and other focal regions, conditions which are more related to inflammatory and immune-mediated diseases⁽⁸⁾.

The symptoms reported are: burning sensation, allodynia, generalized pain, cramps, muscle pain, electric shock sensation, evoked pain, paresthesia, numbness, decreased discrimination, painful conditions related to increased temperature or physical exercise, paroxysmal neuropathic pain. There may be associated pruritus. Other symptoms also reported include headache, fatigue, irritable bowel syndrome, cognitive dysfunction, and sleep disturbance. The autonomic symptoms mentioned by these patients are: nausea, vomiting, postural hypotension, sexual dysfunction, vasomotor dysregulation with fluctuating purple or blue discoloration in hands and feet, abnormal sweating, arrhythmias, presyncope and urinary complaints⁽⁹⁻¹⁰⁾.

Small fiber peripheral neuropathy in Wilson's disease

Wilson's disease (WD) is an autosomal recessive disorder caused by impaired copper metabolism due to mutations in the ATP7B gene. This gene is responsible for decoding the ATP7B protein, the main carrier of biliary copper excretion. Deficient copper metabolism generates an accumulation of this metal in the body and subsequently causes the appearance of clinical manifestations resulting from this intoxication, among which are neurological alterations. Neurological manifestations account for 60% of the initial presentation of patients in the third and fourth decade of life with WD⁽¹¹⁻¹²⁾.

Among the neurological diseases presented by patients with WD, there is peripheral neuropathy. Descriptions of peripheral neuropathies in Wilson's disease are limited. There are rare records of large-fiber neuropathies in Wilson's disease, described in table 1. In sensory neuropathies, the complaints consist of paresthesia, tingling, burning, changes in

thermal and painful sensitivity³. Table 1 details all studies related to the literature on small fibers in WD described in the literature, as well as the rare cases of large fiber neuropathy.

Studies of small fiber neuropathies in WD are rare (Table 1). Small-fiber neuropathies can be pure sensory, pure autonomic or mixed (sensitive+autonomic). In the study by Gondim et al (2014) involving four clinical cases of patients with Wilson's disease with small fiber neuropathy, the main clinical complaints were burning and paresthesia. The alterations related to autonomic fiber dysfunction were urinary incontinence and syncope. Table 1 described below presents the studies collected in this research that described peripheral neuropathy associated with Wilson's Disease and their respective findings in a clear and detailed way.

The study carried out by Bhattacharya et al⁽¹⁵⁾ with 14 patients with WD observed that almost a

third of those surveyed had abnormalities in the autonomic tests of cardiovascular function, with greater impairment of the parasympathetic function. Because cardiovascular autonomic dysfunction was more common in patients with severe changes in the central nervous system, the authors concluded that this autonomic dysfunction is related to impairment of central autonomic neurons. However, there was no confirmation of the absence of autonomic involvement of small fibers⁽¹⁵⁾.

Another study carried out by Quick et al⁽¹⁶⁾ identified patients with more severe impairments resulting from Wilson's disease had higher NT-proBNP levels, a prognostic predictor in patients with advanced heart failure. On 24-hour Holter examination, 84% of patients had supraventricular ectopic rhythms. The authors believe that the increase in troponin, in cases with greater exacerbations, is related to toxicity

Table 1

Literature review of studies due to small fiber peripheral neuropathy in WD, large fiber and autonomic neuropathy in WD

<i>Authors</i>	<i>Type of neuropathy</i>	<i>Study findings</i>
Sturniolo et al, 2015 ⁽¹⁴⁾	Small fibers	They investigated corneal changes and evaluated the parameters of the subbasal corneal nervous plexus in patients with WD by means of corneal confocal microscopy. The analysis showed significant alterations in the subbasal corneal plexus and corneal epithelium, showing peripheral small fiber neuropathy in these patients.
Gondim et al, 2014 ⁽¹³⁾	Small fibers	Reported evidence of small fiber sensory changes in 2 patients among 4 of the individuals recruited with DW using the skin wrinkle test (TEC) and clinical evidence of autonomic dysfunction.
Jung et al, 2005 ⁽¹⁹⁾	Large fibers	Described a case report of a patient with WD who presented signs of peripheral neuropathy before undergoing treatment with penicillamine. The suspicion was confirmed by nerve biopsy and electromyography, a mixed-type neuropathy. Therefore, the study suggests that, although uncommon, peripheral neuropathy should raise the neurologist's suspicions of DW in young patients.
Miyakawa et al, 1973 ⁽²¹⁾	Large fibers	The case report described a 16-year-old boy with WD who presented with progressive worsening of neurological symptoms. He underwent a nerve biopsy. Pathological changes at the microscopic level of nerve fibers consisted of primary demyelination and secondary change in axon shape.
Leven, Fasshauer, 1978 ⁽²²⁾	Large fibers	Conducted electrodiagnostic studies with 3 patients diagnosed with WD. The studies showed a decrease in motor nerve conduction velocity, but it was not very marked. Sensory conduction velocity was also low, sensory action potentials showed low amplitudes and contained large amounts of late phases. One patient's electromyography showed denervation at the start of treatment.
Samier et al, 2009 ⁽²³⁾	Large fibers	Described the case report of a patient with WD who evidenced in an electrophysiological study the presence of length-dependent sensorimotor peripheral neuropathy.
Giesen et al, 2003 ⁽²⁰⁾	Autonomic and small fibers	Described the study with seventeen patients with WD submitted to sensory and autonomic tests. The findings were compatible with a potential impairment of unmyelinated C fibers in WD, which is independent of the predominant motor dysfunction found in the basal ganglia

Table 1

Literature review of studies due to small fiber peripheral neuropathy in WD, large fiber and autonomic neuropathy in WD

<i>Authors</i>	<i>Type of neuropathy</i>	<i>Study findings</i>
Bhattacharya et al, 2002(15)	Autonomic fibers	They performed a study using autonomic function tests in fourteen patients who had a diagnosis of WD. The study concluded that one third of patients with WD had autonomic dysfunction with greater impairment of parasympathetic function and that the involvement of central neurons is related to autonomic dysfunction of cardiac function.
Quick et al, 2019(16)	Autonomic fibers	They carried out a prospective study with 122 people, equally divided into a control group and a group of people with WD. The aim of the study was to determine whether patients with WD showed signs of cardiac impairment, structural heart disease, or autonomic dysfunction. The study demonstrated that cardiac involvement and autonomic dysfunction in WD are possible, however the underlying cause is still unknown.
Chu et al, 1997(17)	Autonomic fibers	They evaluated the involvement of the autonomic nervous system in Wilson's Disease in 25 patients through the sympathetic skin response and RR interval variation, then compared to the control group. The findings of this study suggested that autonomic dysfunction may occur in WD and that the sympathetic function is more compromised, mainly due to central involvement.
Liet al, 2017(18)	Autonomic fibers	They carried out a prospective study of patients with WD to observe whether they had autonomic dysfunctions and deficiencies after 3 years of adequate follow-up. The study revealed cardiovascular autonomic dysfunction involving the sympathetic and parasympathetic branches in patients with WD. Autonomic function is generally stable after initiation of treatment.
Soni et al, 2009(24)	Autonomic fibers	They evaluated the cardiovascular autonomic reflexes clinically and electrophysiologically in 30 patients and then compared to the control group. The authors concluded that autonomic dysfunction occurs in WD and affects parasympathetic functions more than sympathetic ones.
Meenakshi-Sundaram et al, 2002(25)	Autonomic fibers	They evaluated 50 patients with WD, who had variable disease duration and severity, using skin sympathetic response and RR interval variability in deep breathing. They concluded in this study that disautonomia, often subclinical, is common in WD and probably of central origin. It is more frequent in those with neurological manifestations. Sympathetic and parasympathetic functions are equally affected.

and inflammation resulting from the accumulation of copper in the myocardium⁽¹⁶⁾.

Chu et al⁽¹⁷⁾ recruited 25 patients with WD to verify the autonomic involvement by the sympathetic skin response and the variation in the RR interval. In this study, the most common autonomic signs and symptoms among the patients were: seborrheic dermatitis, salivation and dry mouth. Symptoms related to sweating were also relatively common: excessive sweating, decreased sweating, anhidrosis, and dry skin. Four patients had heat intolerance and another four reported cold intolerance. Half of the patients had an abnormal skin sympathetic response and three had an abnormality in the RR interval variation. These data suggest that the sympathetic nervous system is more affected in WD, however there is also involvement of the parasympathetic nervous system⁽¹⁷⁾.

Li et al⁽¹⁸⁾, in their longitudinal study on autonomic dysfunction in WD using baroreflex sensitivity and spectral analysis, obtained the following results: heart rate tended to be higher; parasympathetic parameters, especially the Valsalva ratio, were reduced; the increase in heart rate during isometric handgrip was smaller, implying sympathetic dysfunction; baroreflex sensitivity was decreased under multiple conditions; autonomic dysfunction was more severe in the subgroup with neurological dysfunctions and the UPDRS was correlated with several autonomic dysfunctions⁽¹⁸⁾.

Diagnosis

The diagnosis of small fiber neuropathy is not easy, especially in patients with other more intense neurological complaints, such as extrapyramidal

complaints in Wilson's disease with peripheral neuropathy. For this reason, neurophysiological, histological and morphological investigations of peripheral nerves should be emphasized during the process of establishing the diagnosis. The definitive diagnosis of small fiber peripheral neuropathy can only be made by confirming the involvement of the A delta and C fibers. It is noteworthy that the description of a sensory complaint compatible with impairment of nerve-dependent length in small fiber neuropathy is very common^(27, 8).

Nerve conduction studies and common electro-neuromyography are ineffective in this pathological condition to establish its diagnosis, as they cannot assess these types of nerve fibers (Fibers C and A delta). Therefore, specialized tests that were developed to assess the function of unmyelinated and autonomic sensory fibers are needed. They can be divided into tests for the assessment of somatic fine fibers and tests for the assessment of autonomic fibers. Table 2 below describes these types of tests⁽¹⁾.

The thermoregulatory sweat test allows the assessment of fine fibers, preganglionic sympathetic fibers and the autonomic pathways of the central nervous system. The sensory quantification test (QST) assesses the perception limits of sensations related to temperature, vibratory and painful sensitivity stimuli. Specific electrophysiological tests include laser evoked potentials, temperature detection threshold measurement and autonomic function tests, thus making them effective for the diagnosis of SFN. The use of laser evoked potentials allows the investigation of A fibers and possibly C fibers peripherally and the spinothalamic tract centrally. The stimulus caused by this device allows reproducible and quantifiable responses specifically from the sensory small fibers and the spinothalamic tract. Its sensitivity to SFN ranges from 70% to 80%^(1,28).

The QSART test allows the assessment of preganglionic sudomotor function by means of acetylcholine-

-induced iontophoresis in the skin. It is sensitive and reproducible, however it requires specific equipment making its availability limited. The skin wrinkling test consists of the evaluation of a sympathetic response of the small fibers present in the digital pulps from the skin contact with a stimulating substance, usually the vasoconstrictor cream EMLA is used. The skin reflex sympathetic response is evaluated based on potentials obtained in the skin from stimuli sent by electrodes placed on the hands and feet that trigger changes in the sudomotor response. The RR interval variation measurement test is widely used to assess the autonomic nerve supply to the heart, however there are other tests that simultaneously assess blood pressure and heart rate in response to dynamic maneuvers, such as Valsalva maneuver, tilt test and handgrip^(27-28,6).

Skin biopsy used to measure epidermal nerve fiber density is considered the gold standard for assessing small fiber function, and is associated with immunohistochemistry that is used to label nerve fibers, thereby increasing its diagnostic value. Corneal confocal microscopy is a non-invasive method used to assess the density of fine type C fibers originating from the trigeminal nerve present in the eye's cornea⁽⁴⁾.

The Certainty Rating Scale for the Diagnosis of Small Fiber Neuropathies is based on clinical symptoms, signs, and examination findings. Tests to confirm the etiology of small fiber neuropathies consist of screening for the cause from disease history, medical history, family history, and clinical examination. If this information is insufficient, tests and exams may be requested to help identify the cause. Among the tests requested to identify the etiology of neuropathy, the following are initially requested: fasting glucose test; VDRL; TSH; serum vitamin B12; tests for levels of total cholesterol, LDL and triglycerides. In a second moment, the following may be requested: homocysteine and methylmalonic acid levels; immunofixation electrophoresis; antinuclear antibodies; ACE levels; anti-endomysial (or anti-glutaminase) antibodies;

Table 2

Specific tests for the assessment of small fiber neuropathy

<i>Assessment tests for small somatic fibers</i>	<i>Autonomic fine fiber assessment tests</i>	<i>Test for the assessment of autonomic and somatic fibers</i>
Thermoregulatory sweat test	Quantitative sudomotor axon reflex test (QSART)	Skin biopsy
Sensitive Quantitation Test (QST)	Skin Wrinkle Test	In vivo Confocal Microscopy
Potentials evoked by heat of contact	Sympathetic Skin Responses	Certainty Rating Scale for the Diagnosis of Small Fiber Neuropathies
	Heart rate response to deep breathing and Valsalva test (cardiovascular function tests)	Tests to confirm the etiology of fine fiber neuropathies

HIV; HTLV; and screening for hepatitis B and C. Additional tests may be ordered according to gender, nutritional status, and age. If inflammatory, autoimmune or paraneoplastic disorders are suspected, a lumbar puncture should be requested^(1,5).

Treatment

It is essential in the treatment to identify the underlying cause (which is treatable), eliminate risk factors and control the painful condition. Pain is the main complaint in SFN, so treatment should have as its primary objective the control of pain. The main types of medication used to control neuropathic pain are antidepressants, anticonvulsants and opioids⁽²⁸⁾.

Literature recommends tricyclic antidepressants, serotonin reuptake inhibitors, pregabalin and gabapentin as first line of pharmacological treatment for pain control. As a second line of treatment are lidocaine patches, high capsaicin and tramadol patches; strong opioids and botulinum toxin are recommended as a third line of treatment⁽²⁷⁾.

The etiology and prevention of further damage must be considered during treatment, as well as corrections of dietary deficiencies, removal of toxic compounds or inappropriate medications, and the control of associated immune-mediated diseases⁽⁴⁾.

Neuropathic pain is a complex pathological condition that significantly interferes with the individual's quality of life, triggering mood changes, depression, sleep disorders and mild cognitive impairment. Therefore, a multidisciplinary approach should be recommended, with professionals such as physiotherapists and psychologists aiming to restore functionality and emotional control⁽²⁸⁾.

Conclusion

Neuropathy in Wilson's disease is a challenging diagnosis given the predominance of complaints due to the involvement of the central nervous system. Despite this, the presence of small-fiber neuropathy is possible, with restricted autonomic or sensory and autonomic involvement. As it is a disorder that is not so explored in the literature, this work contributes to the understanding of this theme, as well as to reinforce the importance of developing more studies related to the topic in order to clarify points that still remain unclear about the SFN in Wilson's disease.

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