

Prevalence of somatic small fiber neuropathy in elderly: a review

Prevalência de neuropatia somática de pequenas fibras em idosos: uma revisão

Prevalencia de la neuropatía somática de fibras pequeñas en ancianos: una revisión

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Abstract

Somatic small fiber neuropathy (SSFN) is a neuromuscular disease that affects peripheral nerves and leads to structural and functional changes involving small myelinated (A δ) and unmyelinated (C) fibers, and whose pathophysiological mechanisms are not well elucidated, but depend on the underlying etiology. Due to the lack of studies on this pathology, it is likely to be underdiagnosed, which is a problem, since this disease in elderly people can lead to multiple negative effects on daily life due to neuropathic pain, paresthesia, and dysautonomia of various systems. The clinical diagnosis of this pathology is based on data from the clinical history and physical examination, as well as some complementary examinations and tests, such as the quantitative sudomotor axon reflex test (QSART). Moreover, the treatment of the disease is still limited and most approaches focus on the control of symptoms, such as neuropathic pain. The present study consists of a narrative review of the literature conducted in Medline databases from 2010 to 2022 on small-fiber neuropathy, the elderly, and neuralgia, using the terminology indicated by the Health Sciences Descriptor System (DeCS), and aims to highlight the relevance of the association of senile comorbidities and the aging process with somatic small-fiber neuropathy. Thus, future studies investigating the pathophysiological mechanisms of SSFN are of utmost importance, as well as studies aimed at developing more effective diagnostic methods.

Keywords: Small fiber neuropathy; Elderly; Neuralgia.

Resumo

A neuropatia somática de pequenas fibras (NSPF) é uma doença neuromuscular que afeta os nervos periféricos e leva a alterações estruturais e funcionais envolvendo pequenas fibras mielinizadas (A δ) e não mielinizadas (C), e cujos mecanismos fisiopatológicos não estão bem elucidados, mas dependem da etiologia subjacente. Devido à falta de estudos sobre esta patologia, é provável que seja subdiagnosticada, o que constitui um problema, uma vez que esta doença em pessoas idosas pode levar a múltiplos efeitos negativos na vida cotidiana devido a dor neuropática, parestesia e disautonomia de vários sistemas. O diagnóstico clínico desta patologia baseia-se nos dados da história clínica e no exame físico, bem como em alguns exames e testes complementares, como o teste quantitativo do reflexo axonal sudomotor (QSART). Além disso, o tratamento da doença ainda é limitado e a maioria das abordagens concentra-se no controle dos sintomas, como a dor neuropática. O presente estudo consiste em uma revisão narrativa da literatura realizada nas bases de dados Medline, no período de 2010 a 2022, sobre neuropatia de pequenas fibras, idosos e neuralgia, utilizando a terminologia indicada pelo Sistema de Descritores em Ciências da Saúde (DeCS), e objetiva destacar a relevância da associação das comorbidades senis e do processo de envelhecimento com a neuropatia somática de pequenas fibras. Assim, estudos futuros que investiguem os mecanismos fisiopatológicos da NSPF são de extrema importância, bem como estudos que visem o desenvolvimento de métodos diagnósticos mais eficazes.

Palavras-chave: Neuropatia de pequenas fibras; Idosos; Neuralgia.

Resumen

La neuropatía somática de fibras pequeñas (NSFP) es una enfermedad neuromuscular que afecta a los nervios periféricos y provoca cambios estructurales y funcionales que afectan a las fibras pequeñas mielinizadas (A δ) y no mielinizadas (C), y cuyos mecanismos fisiopatológicos no están bien dilucidados, sino que dependen de la etiología subyacente. Debido a la falta de estudios sobre esta patología, es probable que esté infradiagnosticada, lo cual es un problema, ya que esta enfermedad en las personas mayores puede provocar múltiples efectos negativos en la vida diaria debido al dolor neuropático, las parestesias y la disautonomía de varios sistemas. El diagnóstico clínico de esta patología se basa en los datos de la historia clínica y la exploración física, así como en algunas exploraciones y pruebas complementarias, como el test de reflejo axonal sudomotor cuantitativo (QSART). Además, el tratamiento de la enfermedad sigue siendo limitado y la mayoría de los enfoques se centran en el control de los síntomas, como el dolor neuropático. El presente estudio consiste en una revisión narrativa de la literatura realizada en las bases de datos Medline, en el período de 2010 a 2022, sobre neuropatía de fibra pequeña, anciano y neuralgia, utilizando la terminología indicada por el Sistema Descriptor de Ciencias de la Salud (DeCS), y tiene como objetivo destacar la relevancia de la asociación de las comorbilidades seniles y el proceso de envejecimiento con la neuropatía somática de fibra pequeña. Así pues, son de suma importancia los estudios futuros que investiguen los mecanismos fisiopatológicos de la NSFP, así como los estudios dirigidos al desarrollo de métodos de diagnóstico más eficaces.

Palabras clave: Neuropatía de fibras pequeñas; Ancianos; Neuralgia.

1. Introduction

Somatic small fiber neuropathy (SSFN) is a neuromuscular disorder that affects peripheral nerves and courses with structural and functional changes involving small myelinated fibers (A δ) and unmyelinated fibers (C) (Ghasemi et al., 2020; de Greef et al., 2018). A δ fibers transmit thermal and painful sensations, and C fibers, in addition to pain and temperature, are also related to autonomic function (Hovaguimian et al., 2011; Basantsova et al., 2019; Pál et al., 2020; Eijkenboom et al., 2018), innervating mainly the musculature of the heart, the wall of blood vessels and the gastrointestinal and genitourinary tracts, as well as some glands, such as salivary, sweat and tear (Zhou et al., 2019). The precise pathophysiological mechanisms, in turn, are still not very well elucidated, but it is known that they depend on the underlying etiology and include oxidative stress, ischemia, direct neurotoxic effect, hypoxia and inflammatory mediators (Medici et al., 2013; Devigili et al., 2016).

Due to the scarcity of studies, readily available diagnostic methods, and knowledge of the disease, SSFN is likely to be underdiagnosed (Raasing et al., 2021). An American study reported an increasing incidence of 1.3/100,000/year and a prevalence of 13.3/100,000, with a mean age of onset of 54 years (Johnson et al., 2021). In this scenario, the SSFN indices are notoriously more relevant in the elderly community compared to the young population, with a prevalence of 53 per 100,000 inhabitants (Peters et al., 2013). In addition, based on all diagnoses made, it was observed that approximately 19.6% were in individuals over 65 years old (Brouwer et al., 2015; Treister et al., 2017). Indeed, the increase in the number of elderly people in the population has been evidenced not only in developed nations, but also in developing countries, such as Brazil (Veras et

al., 2018). According to the WHO (World Health Organization), in 2025 there will be 1.2 billion people in this age group in the world, an estimate that may contribute to the increase in the prevalence of SSFN.

At this point, small fiber neuropathy in the elderly population has a significant negative impact on the individual's routine and quality of life (Brouwer et al., 2015), especially due to neuropathic pain, paresthesia and dysautonomia of various systems (Saperstein et al., 2020; Brouwer et al., 2019), which are difficult to manage due to their pathological origin (Güneş et al., 2018). Furthermore, the fact that these complaints that strongly indicate SSFN are undervalued or treated as unspecific is certainly another issue that also favors the probable underdiagnosis of this pathology (Guimarães-Costa et al., 2018).

In this context, many health conditions are associated with the development of this pathology, such as obesity, diabetes mellitus (DM), dyslipidemia (DLP), systemic arterial hypertension (SAH), thyroid diseases, use of some medications, leprosy, obstructive sleep apnea, among others (Kraychete et al., 2011; Khan et al., 2018; Dalla Bella et al., 2016; Hong et al., 2013). Thus, given the risk factors for the development of this disease, its prevalence in the elderly population stands out, as 56.4% have SAH, 20.5% DM and 33.3% DLP (Leite-Cavalcanti et al., 2009), with a clear correlation between target population and predisposing comorbidities in the age group described (Pál et al., 2020; de Greef et al., 2018).

Regarding the clinical diagnosis, the suspicion of involvement of fine fibers is based on clinical history data and the physical examination performed (Güneş et al., 2018; de Greef et al., 2018). A detailed report of symptoms, rate of progression and complaints suggestive of involvement of autonomic fibers is necessary, since SSFN can be, in addition to the aforementioned comorbidities, accompanied by various conditions that can mask the diagnosis, such as vitamin deficiency B12, connective tissue diseases, sarcoidosis, HIV and hepatitis C infection, Fabry disease, among others (Saperstein et al., 2020; Truini et al., 2018; Üçeyler et al., 2011). In most cases, the clinical examination is sufficient to diagnose that disease, however, for situations in which the diagnosis is doubtful, auxiliary tests are performed (Raasing et al., 2021).

Amongst the complementary exams to confirm the diagnosis, some tests are more relevant. Quantitative sensory testing can provide a threshold for detecting thermal, vibratory, and painful sensation, despite having some limitations (Peltier et al., 2009). The quantitative sudomotor axon reflex test (QSART) analyzes postganglionic sympathetic cholinergic function (Low et al., 2006). Skin biopsy, in turn, is widely used in this investigation, as it is capable of measuring the cutaneous density of nerve fibers with a sensitivity of 78-92% and specificity of 65-90% (Gibbons et al., 2006; Piscoquito et al., 2021; Nolano et al., 2017). Finally, the skin wrinkle test is also an evaluation of sympathetic nerve fibers, using a scale in which the arithmetic mean of the degrees of wrinkling of fingers 2, 3, 4 and 5 is made (Teoh et al., 2008).

With regard to treatment, evidence is still limited, especially for disease-modifying, preventive, and etiology-specific treatments. Thus, most approaches focus on symptom management. There are several symptoms that can be experienced by patients, one of the most frequent being neuropathic pain. This symptom responds better to the use of drugs from the antidepressant class, such as tricyclics and serotonin and noradrenaline reuptake inhibitors, as well as some anticonvulsants, such as pregabalin and gabapentin (Sène et al., 2018).

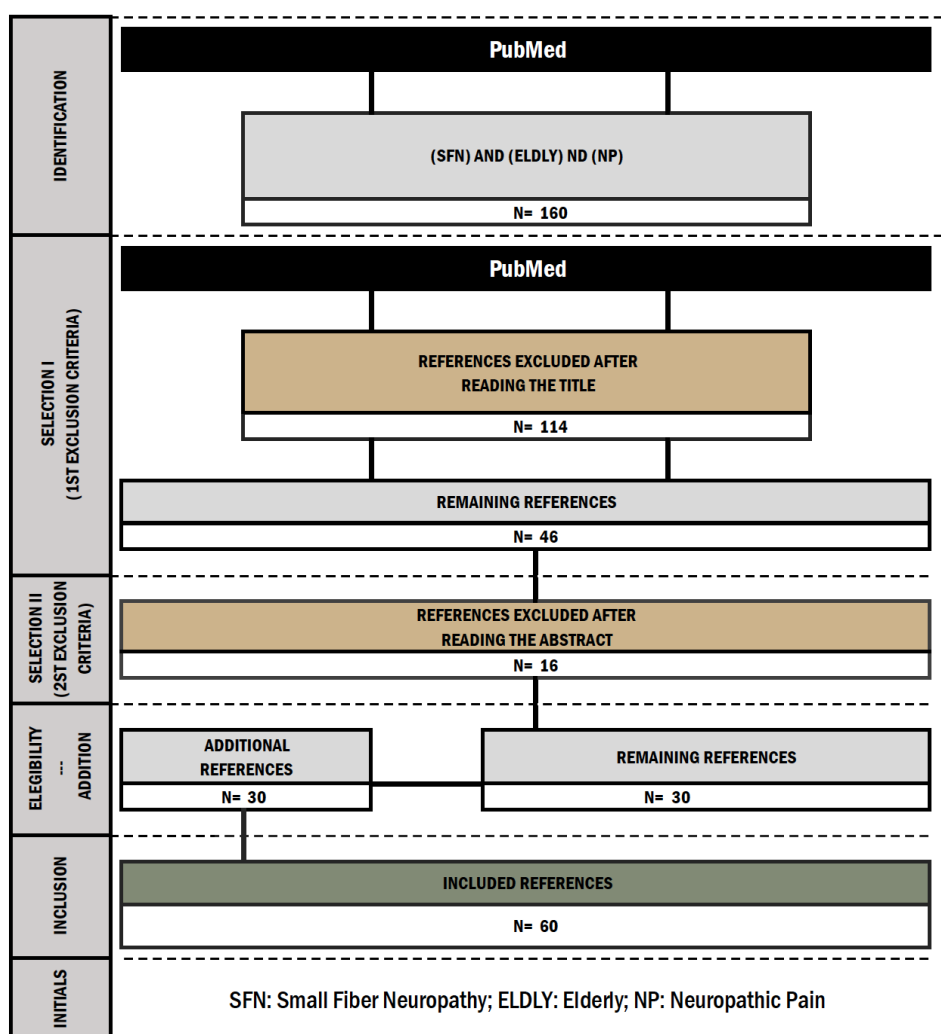
Thus, the present study seeks to highlight the relevance of the association of senile comorbidities and the aging process with somatic small fiber neuropathy, in order to, through the data, analyze the best context about the pathology and provide evidence that can support conducts individual and precise for each affected elderly person.

2. Methodology

A narrative literature review was conducted in the Medline Databases, from 2010 to 2022, on small fiber neuropathy, elderly and neuropathic pain. In the Medline, 160 articles were found by the Mesh descriptor “(small fiber neuropathy) AND (elderly) AND (neuropathic pain)”, of which 46 were selected, after the first set of criteria — exclusion of titles not addressing

to the topic “small fiber neuropathy and/or elderly”, articles not included in the search period 2010-2022, as well as non-English articles. The second set of criteria — exclusion of the abstracts not addressed to small fiber neuropathy or elderly, as well as articles with animal models— was applied, by which 16 articles were excluded. Moreover, although not being the focus of the population study, some articles with younger individuals (age < 60) were also included when addressing to small fiber neuropathy and other pathologies associations. Other articles that did not contemplate these conditions were excluded. To ensure content saturation, the authors checked the included research references and related reviews on topics to identify missing publications. Furthermore, 30 articles from the Medline Database were manually screened and added according to their relevance in the qualitative evidence synthesis. Of the total, 60 original articles remained (Figure 1).

Figure 1 – Flowchart of the article selection.



Source: Authors.

3. Results and Discussion

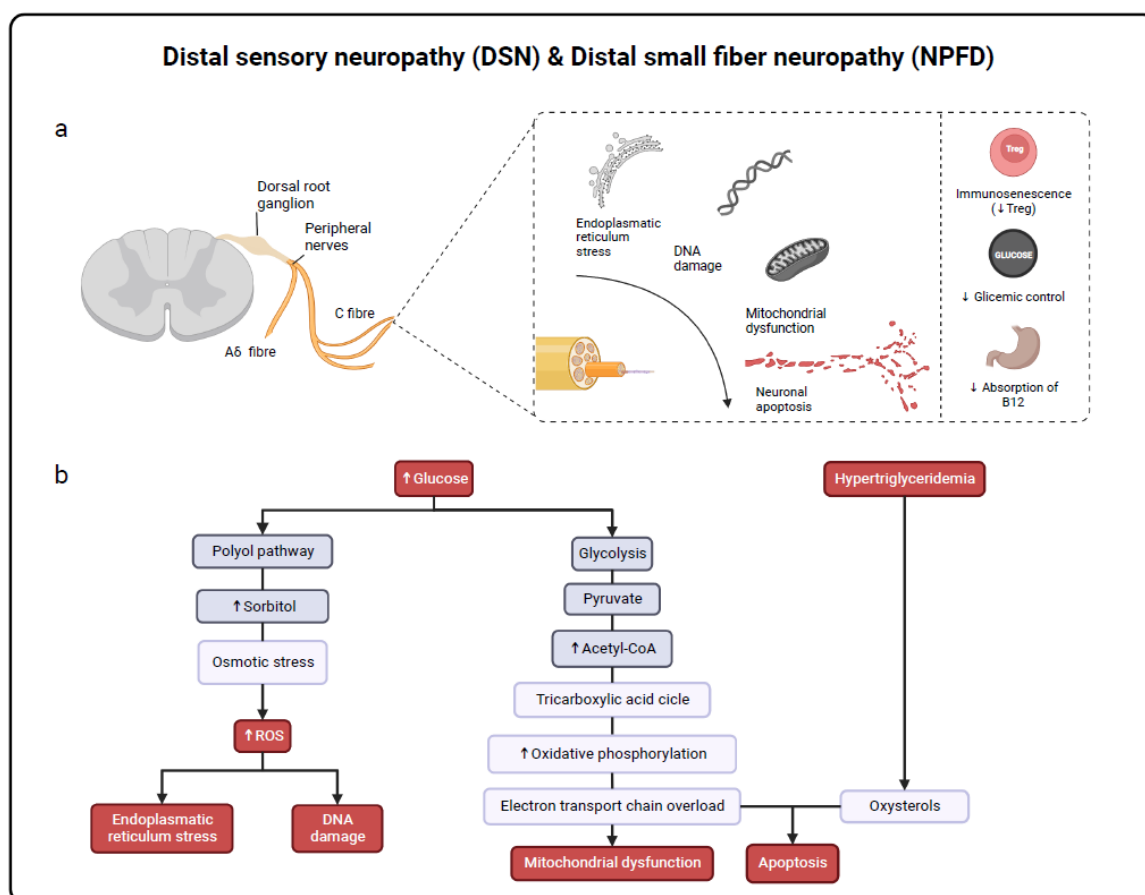
3.1 Pathophysiology of small fiber neuropathy

Regarding the pathophysiology of SSFN, its mechanisms are still unclear. However, it is understood that there is a close correlation with the pathogenesis of the underlying etiology (Uceyler et al., 2010). Several pathologies may be associated with SSFN, which would lead to oxidative stress, ischemia, direct neurotoxic effects, hypoxia and inflammation (Ghasemi et al., 2020). Thus, the mechanisms of several metabolic disorders have been studied, such as diabetes, a disease that can interfere

with the polyol pathway and result in higher levels of sorbitol, generating more reactive oxygen species (ROS), ischemia and nerve damage (Hoeijmakers et al., 2012; Thaisetthawatkul et al., 2020). It is worth noting that the main mechanism causing neuropathy is hyperglycemia, although microvascular involvement, hypertriglyceridemia, as well as genetic and immunological mechanisms may contribute. There is a growing spectrum of types of diabetic neuropathies that differ based on the type of fibers involved (eg, myelinated, unmyelinated, autonomic, somatic), distribution of involved nerves, and neuropathy mechanisms. The most common type is distal sensory neuropathy (DSN), which affects the distal ends of large myelinated fibers, more often sensory than motor, and is often asymptomatic. The next most common is distal small fiber neuropathy (NPF), which largely affects unmyelinated fibers and carries the burning feet syndrome phenotype (Ghasemi et al., 2020) (Figure 2).

From the histopathological point of view, SSFN is characterized by the degeneration of the distal endings of small-diameter sensory fibers (Hoeijmakers et al., 2012). In a prospective study, in which the gene expression of local and systemic inflammatory cytokines in patients with SSFN was evaluated, a significant increase in the local expression of IL-6 and IL-8 in the skin of people affected by the disease was evidenced. However, unlike generalized pain syndromes, in which the levels of systemic cytokines are increased, only a slight elevation of IL-2 and the anti-inflammatory cytokines IL-10 and TGF-1 was found in the participants' blood (Uceyler et al., 2010).

Figure 2 - Pathophysiology of DSN and NPF. (a) Degeneration of peripheral A δ fibre and C fiber in small fiber neuropathy due to hyperglycemia and hypertriglyceridemia. (b) Molecular mechanism by which hyperglycemia and hypertriglyceridemia causes chronic inflammation, inducing reactive oxygen species (ROS), endoplasmic reticulum stress, DNA damage, mitochondrial dysfunction and apoptosis.



Source: Authors.

3.2 Aging and small fiber neuropathy

Small fiber neuropathy is common and prevalent in the elderly. The disease can be associated with many medical conditions. It often has a negative impact on quality of life due to painful paresthesia, dizziness, and sedative side effects of pain medications. In addition, screening for associated conditions is important because etiology-specific treatment can slow disease progression and improve symptoms. The aging process involves changes in the peripheral nervous system, with emphasis on the reduction of myelin in the sensory nerves, which leads to vibratory, tactile and painful loss, often accompanied by a decrease in cardiac and peripheral vascular control, which may also be related to changes in the neurotransmitters and in the control of blood glucose levels (Saperstein et al., 2020; Pál et al., 2020; Bitzi et al., 2021; McArthur et al., 2012). Thus, the pathological disorders of comorbidities add deterioration and worsening of the peripheral functioning of small fibers, for example, diabetes mellitus, chronic renal failure, B12 deficiency, autoimmune diseases, oncological diseases, smoking history, among others (Galosi et al., 2021; Chao et al., 2010; Kopf et al., 2018).

World epidemiology shows that there is an increase in the prevalence of comorbidities, especially in the older population, promoting the risk for this age group that represents most of the diagnoses of the pathology (Saperstein et al., 2020; Brouwer et al., 2015). Furthermore, aging processes are already sufficient for the development of impairments in the functioning of small fibers, for example, the decrease in the glycemic control threshold allows irregular glycemic rates to impair neuronal functioning (Truini et al., 2018; Galosi et al., 2020), the physiological increase in gastric pH and its absorptive capacity decreases the absorption of B12, which preponderates a deficiency (Güneş et al., 2018; de Greef et al., 2018), senescence decreases the amount of regulatory T Lymphocytes (Tregs) that associated with the rate of chronic inflammation in the elderly allows, which can be intensified by the metabolic syndrome, causes inflammatory infiltrative lesions of small fiber transmission (Thaisetthawatkul et al., 2020) and, finally, a history of high smoking, oncological diseases and kidney disease tends to dysregulation of electrolytes and plasma proteins that are essential for synaptic functioning and prevention of small fiber neuropathy (Kuo et al., 2020).

Despite the evidence of all the pathophysiological correlations between the SSFN comorbidities and the aging process, the mechanisms and the chronification of the disease remain poorly understood and individual, since pain involves a complex of psychological, neurophysiological, socioeconomic and cultural factors, increasing the prevalence of other comorbidities, for example, depression, anxiety, sleep deprivation, among others (Saperstein et al., 2020; Pál et al., 2020). In summary, SSFN pain has biopsychosocial relationships in the elderly that involves an individual and early diagnostic approach to optimize the patient's symptomatic relief (Brouwer et al., 2015; Bitzi et al., 2021).

3.3 Clinical features

Although small fiber neuropathy is not, in most cases, debilitating, since motor function and proprioception are preserved (Zhou et al., 2019), it is known that such pathology leads to a significant reduction in the general quality of life, mainly due to the various signs and symptoms that patients may experience during the course of the disease (Bakkers et al., 2014).

The symptomatology encompasses both somatic involvement and autonomic dysfunction (Bitzi et al., 2021; Heij et al., 2012), which can be explained by the fact that the small fibers are responsible for transmitting part of the impulses related to the skin and smooth muscles (Saperstein et al., 2020). First, chronic pain is often the first somatic symptom to suggest SSFN (Sène et al., 2018), being characterized as burning, stabbing and pricking or similar to electric shocks (Zouari et al., 2019; Giannoccaro et al., 2014). A Swiss cohort reported that these pains were neuropathic in origin in at least 48% of cases (Bitzi et al., 2021). In addition, paresthesia, dysesthesia - including itching, numbness, and sensation of crushing and cold - and,

especially, allodynia, are also conditions that are commonly present in SSFN (Sène et al., 2018; Schaefer et al., 2014).

When present, muscular weakness restricts itself to the territory of the affected nerve, with diminished or suppressed osteotendinous reflexes local in the nerve location. Alterations in the superficial (thermal, pain and protopathic tact) and profound sensibilities (vibration sensitivity, postural sensitivity, conscious proprioception, discriminating two points, topognosia) can or can not be present during neuropathic pain (Zouari et al., 2019).

According to a Dutch study, autonomic manifestations are present in approximately half of patients (Peters et al., 2013). These symptoms of dysautonomia depend on the affected structure, whether exocrine glands or smooth muscles of internal organs (Sène et al., 2018), and are quite varied, including xerostomia, hypohidrosis, hyperhidrosis, palpitations, orthostatic hypotension, diarrhea or constipation, urinary retention, among others (Zhou et al., 2019; Gibbons et al., 2014) (Figure 3). Such impairment of autonomic fibers is seen more frequently in patients with SSFN associated with amyloidosis, diabetes mellitus, sarcoidosis and Sjögren's Syndrome, in addition to rarely manifesting in the absence of somatic symptoms (Gibbons et al., 2014).

Figure 3 - Clinical features of somatic small fiber neuropathy. Dysautonomia of the disease depends on the affected structure.

| Clinical features of somatic small fiber neuropathy | |
|---|---|
| Committed organs | Symptoms |
| Exocrine glands | <ul style="list-style-type: none"> • Xerostomia • Hypohidrosis • Hyperhidrosis |
| Heart | <ul style="list-style-type: none"> • Palpitations • Orthostatic hypotension |
| Gastrointestinal | <ul style="list-style-type: none"> • Diarrhea • Constipation |
| Genitourinary | <ul style="list-style-type: none"> • Urinary retention |
| Muscular | <ul style="list-style-type: none"> • Supressed osteotendinous reflexes |
| Nerves | <ul style="list-style-type: none"> • Chronic pain |

Source: Authors.

3.4 Clinical trials

According to a dutch study, trustable diagnosis tests that examine every part of the fiber system still do not exist. Therefore, the most exact SSFN diagnosis in clinical practice is through the combination of tests based on the structural and sensorial function of the small fiber nerves (Raasing et al., 2021; Birnbaum et al., 2014). However, other studies show that skin

biopsy with the evaluation of Intraepidermal Nerve Fiber Density (IENFD) is the diagnosis gold standard (Zhou et al., 2019), because it is an evidence of denervation in the skin of SSFN patients (Birnbaum et al., 2019; Provitera et al., 2018; Wu et al., 2017; Casanova-Molla et al., 2012; Lauria et al., 2015). According to a study done by neurologists, epidemiologists and other specialists in the area, it was concluded that a diminished IENFD detection utilizing skin biopsy can be sensible and specific for clinically defined syndromes consistent with small fiber neuropathy (Devigili et al., 2019). Besides, the skin biopsy seems to have greater diagnostic utility than the neurologic examination and the qualitative sensorial tests, which depend a lot on the subjective perception of the patient. Thus, prospective studies that evaluate the quantitative methodology (instead of modalities that depend on the patient's report) and that do not include the reference standard diagnostic tests are necessary.

Other methods can help to diagnose SSFN such as the Quantitative Sensory Testing (QST) and the Quantitative Sudomotor Axon Reflex Test (QSART) (Parambil et al., 2011). QST is a diagnostic method for diseases of the peripheral nervous system and provides a threshold for the detection of thermal, pain and vibration sensitivity. However, it represents some limitations, for example, not permitting the differentiation of individuals that simulate sensory loss, with normal responses and peripheral neuropathy (Hovaguimian et al., 2011; Freeman et al., 2003). Regarding the QSART, it measures the postganglionic sympathetic cholinergic function (Illigens et al., 2009), which facilitates peripheral neuropathy diagnosis through the morphological evaluation of the sweat gland's innervation (Hovaguimian et al., 2011). Furthermore, the skin wrinkle test for the SSFN diagnosis has been studied, the test evaluates the small fibers' viability through the individual's right hand submersion in a solution of NaCl 0,5 mmol/l for 30 to 40 minutes (Teoh et al., 2008). However, until this moment, few controlled prospective studies have evaluated the capacity of this test to diagnose SSFN.

4. Conclusion

In summary, although the SSFN prevalence in the elderly is still not totally established, it is a fact that this pathology causes a negative impact in the routine, functionality and quality of life of these individuals. Thus, the aging process and the comorbidities associated with it, such as diabetes, lead to nervous disorders with mechanisms that are still not clear, but are linked with oxidative stress, ischemia, hypoxia and inflammation. Finally, there are many barriers in what concerns the SSFN diagnosis, since few tests are proven to be efficient in the confirmation of this neuropathy.

In this perspective, future studies to investigate the pathophysiologic mechanisms of SSFN profoundly are important, as well as studies aiming the development of more effective diagnostic methods. Besides, new evidence of more efficient treatments through randomized clinical trials in the population that carries this condition has become important.

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