Misdiagnosis and diagnostic delay in non-paraneoplastic sensory neuronopathies

Erro e atraso diagnóstico nas neuronopatias sensitivas não paraneoplásicas

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ABSTRACT

Sensory neuronopathies (SN) are a group of peripheral nerve disorders characterized by multifocal non-length-dependent sensory deficits and sensory ataxia. Its recognition is essential not only for proper management but also to guide the etiological investigation. The uncommon SN clinical picture and its rarity set the conditions for the misdiagnosis and the diagnostic delay, especially in non-paraneoplastic SN. Therefore, our objectives were to characterize the diagnostic odyssey for non-paraneoplastic SN patients, as well as to identify possible associated factors. Methods: We consecutively enrolled 48 non-paraneoplastic SN patients followed in a tertiary neuromuscular clinic at the University of Campinas (Brazil). All patients were instructed to retrieve their previous medical records, and we collected the data regarding demographics, disease onset, previous incorrect diagnoses made and the recommended treatments. Results: There were 34 women, with a mean age at the diagnosis of 45.9 ± 12.2 years, and 28/48 (58%) of the patients were idiopathic. Negative sensory symptoms were the heralding symptoms in 25/48 (52%); these were asymmetric in 36/48 (75%) and followed a chronic course in 35/48 (73%). On average, it took 5.4 ± 5.3 years for SN to be diagnosed; patients had an average of 3.4 ± 1.5 incorrect diagnoses. A disease onset before the age of 40 was associated to shorter diagnosis delay (3.7 ± 3.4 vs. 7.8 ± 6.7 years, p = 0.01). Conclusions: These results suggest that diagnostic delay and misdiagnosis are frequent in non-paraneoplastic SN patients. As in other rare conditions, increased awareness in all the healthcare system levels is paramount to ensure accurate diagnosis and to improve care of these patients.

Keywords: Ganglia, sensory; ataxia; diagnostic errors; delayed diagnosis.

RESUMO

As neuronopatias sensitivas (NS) representam um grupo de doenças caracterizadas por ataxia sensitiva e déficits sensitivos multifocais e não-comprimento dependentes. O seu reconhecimento é fundamental para o tratamento apropriado e para a investigação de doenças associadas. O quadro clínico pouco frequente aliado à baixa prevalência, especialmente das formas não-paraneoplásicas (NSnp), colaboraram para o atraso e erro no diagnóstico. Os objetivos desse trabalho são descrever a odisseia diagnóstica dos pacientes com NSnp e tentar identificar possíveis fatores associados. Métodos: Foram incluídos consecutivamente 48 pacientes com NSnp acompanhados no ambulatório de doenças neuromusculares da Universidade Estadual de Campinas (Brasil). Dados demográficos e sobre o início da NS (incluindo diagnósticos que lhes foram dados e tratamentos prescritos) foram coletados. Resultados: Na coorte descrita havia 34 mulheres e a idade ao diagnóstico era de 45,9 ± 12,2 anos. Os sintomas inaugurais eram sensitivos deficitários em 25/48 (52%) dos pacientes, sendo assimétricos em 36/48 (75%) e de evolução crônica em 35/48 (73%). Para 28/48 (58%) dos pacientes a NS era idiopática. Em média, os pacientes com NSnp tiveram um atraso diagnóstico de 5,4 ± 5,3 anos com uma média de 3,4 ± 1,5 diagnósticos incorretos. Pacientes com início antes dos 40 anos tiveram diagnóstico mais precoce que aqueles com início tardio (3,7 ± 3,4 vs. 7,8 ± 6,7 anos, p = 0,01). Conclusão: Os dados ora apresentados sugerem que o erro e o atraso diagnóstico são frequentes e impactam os pacientes com NS. A importância do diagnóstico das NS deve ser constante em todos os níveis do sistema de saúde para o diagnóstico correto e a consequente melhora no cuidado a esses pacientes.

Palavras-chave: Gânglios sensitivos; ataxia; erros de diagnóstico; diagnóstico tardio.

Sensory neuronopathy (SN) is characterized by primary dorsal root ganglia damage and typically manifests as sensory ataxia with multifocal non-length-dependent sensory deficits. First described in 1948 by Dr. Derek Denny-Brown, the full phenotypic spectrum and the identification of all SN-related disorders are still pursued. In a way rarely seen...
in Neurology, a precocious SN pattern recognition may provide a window of opportunity for the proper treatment of some of the SN-associated conditions. Lung cancer-related SN, for example, may have the neoplasm prognosis significantly improved, as SN may precede a clinically-relevant tumor. This strategy, based on the SN recognition triggering a focused workup, may increase the diagnosis not only of cancer-related etiologies but also of different disorders, such as Sjögren syndrome or autoimmune hepatitis, that may benefit from a tailored treatment.

In 2009, Camdessanche et al. published a set of diagnostic criteria that take into account clinical, electrodiagnostic and neuroimaging data of SN. These criteria have been validated and are helpful in clinical practice. Despite this, the diagnosis of SN is still challenging for both specialists and non-specialists, for several reasons. This is particularly critical for non-paraneoplastic SN (npSN). Paraneoplastic SN often has an abrupt onset and a somewhat stereotyped presentation, which is not true for the remaining SN subtypes. Since npSN is considered a rare disease, health care providers may not be aware of this diagnosis. Besides this, the npSN clinical picture is highly pleomorphic, resembling other neurological and non-neurological disorders. For instance, some patients display predominant small fiber-related symptoms, while others are essentially characterized by large nerve fiber-related symptoms, such as sensory ataxia and impaired proprioception. The disease course is also highly variable, ranging from acute to chronic progression. Put together, these features increase the likelihood of misdiagnosis and diagnostic delay.

Therefore, our objective was to investigate the diagnostic odyssey of npSN patients, with particular interests in the incorrect diagnoses made, diagnostic delay intervals and eventual predictive factors for this delay.

METHODS

Patient selection and clinical evaluation

We consecutively included patients diagnosed with npSN according to the criteria published by Camdessanche et al., followed at a tertiary referral outpatient neuromuscular clinic of the University of Campinas hospital, São Paulo, Brazil between 2016 and 2017. Once npSN was diagnosed, all patients underwent a comprehensive workup focused on autoimmune, infectious, vitamin deficiency and neoplastic etiologies. If this workup had negative results, the patient’s disease was then labeled as idiopathic npSN.

One of the authors (ARMM) interviewed all patients, focusing on the disease onset, symptoms at that time, and all previous contacts with the health system (appointments and hospitalizations) until the correct diagnosis. We identified the number and the specialty of all consultant physicians as well as the suggested treatments.

Before this active inquiry, all patients were taught what the SN-related signs and symptoms were, to avoid misinterpretations regarding those appointments that were not related to the SN. The disease course was classified as the time between the disease onset and the establishment of the full clinical picture, and considered as acute (less than one month), subacute (more than one and less than six months), or chronic (more than six months). Furthermore, the patients were encouraged to retrieve all available information about their medical care since the disease onset. These included, but were not restricted to, previous disease reports, referral forms, therapeutic plans, previous prescriptions and, eventually, a copy of the medical records from their former clinics.

In order to avoid a recall bias, instead of focusing on the diagnostic delay and misdiagnoses, we justified these procedures to the patients as part of the efforts to make their medical records in our institution as complete as possible. Given the heterogeneity of the patients referred to our center, we reviewed the outside medical records to ensure accurate conclusions. It was important to clarify that a diagnosis was only considered incorrect if there were means to exclude that particular condition based on clinical history and ancillary tests. In addition to the crude description of the diagnostic odyssey, we looked for factors associated with the diagnostic delay, trying to delineate possible milestones involved in this process.

Statistical analysis

Demographic and clinical data are presented with descriptive statistics (measures of central tendency and dispersion) and the Two-sample t-test, Pearson’s χ² test or Fisher’s exact test were applied to compare groups when appropriate, with p-value < 0.05 considered significant. Groups were compared considering sex, associated etiologies, heralding symptom (negative and positive sensory complaints and ataxia), asymmetric symptoms at the onset and the evolution course. All included patients agreed with and signed an informed consent statement form. This study was approved by our local ethics committee and was carried out following the 1964 Declaration of Helsinki and its later amendments.

RESULTS

Demographics and clinical characteristics

A total of 48 npSN patients were enrolled. Mean age at evaluation was 51.0 ± 11.3 years (range 26–72) and the male:female ratio was 14:34. The age at the disease onset was 41.4 ± 10.5 years (range 20–63), and the mean age at the diagnosis was 45.9 ± 12.2 years. Considering specifically the sexes, men and women had similar ages at onset: 43.1 ± 11.1 and 40.7 ± 10.3 years, respectively (p = 0.48). The mean disease duration at the time of this evaluation was 9.0 ± 7.4 years.
Gait ataxia was the debut symptom in 11 patients (23%), whereas negative and positive sensory symptoms were the inaugurating symptoms of npSN in 25 (52%) and 12 (25%) patients, respectively. Interestingly, two patients (5%) had pruritus as the first symptom. These initial symptoms were asymmetric in 36 (75%) and symmetric in 12 (25%) of the npSN patients. Symptoms evolved in a chronic fashion in 35 patients (75%), whereas for 13 patients (27%) the disease had an acute/subacute onset.

Twenty-eight patients (58.3%) had idiopathic or primary npSN; in 11 (23%) patients, their SN was related to Sjögren syndrome; four (8.3%) had associated autoimmune hepatitis; and five (10.4%) had other associated diseases, which included one human T-cell lymphotropic virus infection, one Zika virus infection, one hepatitis C virus infection, one monoclonal gammopathy of undetermined significance and one patient with systemic lupus erythematosus. Of only those patients with an underlying SN-related condition, 12/20 (60%) of them had npSN phenotyping that enabled, through proper workup, the diagnosis of the associated disease. Table 1 summarizes the general demographics and information about the disease onset and diagnostic delay/misdiagnosis.

### Diagnostic delay and misdiagnosis

Concerning the diagnostic delay, on average, patients from this group had a 5.4 ± 5.3-year interval between the disease onset and the correct diagnosis (range 1-21). None of these patients had the first evaluation made in our clinic. Their path throughout the health system due to SN-related symptoms included appointments with a mean of 4.3 ± 2.4 (1–10) physicians, which included general practitioners, orthopedic surgeons, general and vascular surgeons, psychiatrists, neurosurgeons, neurologists, and others. Each patient received an average of 3.4 ± 1.5 incorrect diagnoses (ranging from 1–7) (Table 1). Table 2 lists the incorrect diagnoses given after an appointment for SN-related symptoms and signs. Based on the misdiagnoses, on 64 occasions a prescription was given (mean of 1.3 per patient), with non-steroidal anti-inflammatory drugs being the most-frequently recommended (23%). As well as all the distress imposed by incorrect diagnoses and treatments, more than half of these patients, 27/48 (56%), indicated that they had stopped their working activities due to SN-related symptoms.

### Factors associated with the diagnostic delay

Group comparisons were made considering different characteristics such as sex, associated etiologies, heralding symptom (negative and positive sensory complaints and ataxia), asymmetric symptoms at the onset and the evolutionary course. A disease onset before 40 years of age (n = 27) was associated with a shorter diagnostic delay when compared with those patients (n = 21) with a disease onset after 40 years of age (3.7 ± 3.4 vs. 7.8 ± 6.7 years, p = 0.01). All the remaining characteristics were not significantly associated with longer diagnostic delays or with a higher number of misdiagnoses (p > 0.05).

### DISCUSSION

To the best of our knowledge, this is the first study specifically devoted to investigate the diagnostic odyssey of npSN. Herein, we were able to show that misdiagnoses with consequent diagnostic delays were a significant issue in this cohort, especially for patients older than 40 years.
of age. Our data revealed that, on average, patients receive three incorrect diagnoses before npSN was recognized. The whole process took more than five years, and appointments with at least four physicians, to reach the proper diagnosis. Such a delay has implications that go beyond the impact on the quality of life, due to ataxia and unemployment, as these patients may be exposed to inadequate therapeutic regimens and possible postponement of the identification of associated diseases.

These numbers were similar to other rare neuromuscular disorders, where the diagnostic delay was also a problem. This was the case, for example, of hereditary transthyretin amyloid neuropathy (150 patients: 46.4 ± 25.4 months of delay) and myotonic dystrophy type I (679 patients: 7.3 ± 8.2 years of delay). It is reasonable to consider that the rarity shared by all these disorders, taken together with the above-mentioned npSN diagnosis delay data, place the lack of awareness as a cornerstone for all these conditions.

Such diagnostic delay has become even more relevant for SN, as Antoine et al. recently published an electrodiagnostic-based study that argued in favor of an eight-month window from the disease onset as the ideal period for starting therapy to achieve SN stabilization. Moreover, even retrospective data pointing to a modest treatment response in Sjögren-related SN, one should not generalize these findings to all SN-related diseases or even to the idiopathic ones that may benefit from an early diagnosis.

Paraneoplastic SN often has an acute and dramatic onset of symptoms, which leads to fast medical evaluation and presumably “early” diagnosis. We hypothesized that clinical recognition would be much worse for npSN, as its onset is often insidious and not associated with other systemic signs. There is also a scarcity of data regarding npSN. This was the reason we focused this survey on the latter subgroup. An evaluation of the list of incorrect diagnoses identifies some terms that, essentially, are not wrong, especially from a topographic perspective. This is true for “neuropathy”, which leads this list (10% of the wrong diagnoses). The main issue with this term, that led us to label it as a diagnostic mistake, is that it was not capable of triggering the additional etiologic workup needed for SN. “Polyneuropathy” was found to be one of the top diagnostic hypotheses. Even though SN and polyneuropathies share common manifestations, the former has typical multifocal asymmetric sensory deficits as opposed to the symmetric length-dependent deficits of the latter. This clinical distinction should be always looked for in an attempt to avoid this misdiagnosis.

Another possible explanation for our results is the remarkable phenotypic heterogeneity that characterizes SN. Apart from classic sensory ataxia, positive symptoms related to small fiber damage frequently play a role in the clinical picture. Additionally, some features, such as pseudoarthrosis and pseudoparesis, which emerge from the severe proprioceptive deafferentation present in SN, could be considered as inexplicable, or even resultant from a psychiatric condition, to less experienced physicians. However, since none of these distinct complaints of the SN patients were related to a shorter delay in diagnosis, or to fewer misdiagnoses, it appears that SN may not be part of the “average physicians” diagnosis list. Alternatively, we cannot exclude the possibility that a larger sample size might have been able to detect these differences.

Considering that this was a tertiary level-based study, a referral bias might have taken place. The consequences might have been the increment in the diagnosis delay related to the sequential level-referral process, as well as a possible referral process favoring more severely-affected patients. In this latter scenario, we hypothesize that estimates for diagnostic delay would be even higher when considering the general population. In our opinion, paucisymptomatic patients would suffer from longer delays, because of their mild phenotype that may easily resemble other long-standing peripheral nerve disorders.

Nevertheless, since early diagnosis is essential to improve the care of SN patients, it is imperative to increase general medical awareness about these diseases. This objective may be reached with medical education. One should focus on the prompt identification of the classical clinical pictures. For atypical presentations, the challenge becomes even bigger, but detailed nerve conduction studies/electromyography and spinal cord imaging may help physicians recognize SN in this scenario.

Considering this worrisome scenario, both patients and physicians share harmful consequences. On the one hand, an average SN patient is exposed to unnecessary treatment regimens and to a long and costly workup; on the other hand, physicians may become vulnerable to the trend of malpractice claims that is taking place in the healthcare system. To recognize those steps in the SN diagnostic process that are amenable to enhancement is paramount in improving the final outcomes. In summary, this long diagnostic odyssey is similar to what is seen in other rare neurologic diseases. Moreover, it is also highly probable that this also takes place in other geographical areas around the globe. In this end, these results should be interpreted as a call for attention to the improvement of care of these patients.

### References


