STĘPIEŃ, Jakub & PASTUSZAK, Żanna. Problems with classification of polineuropaties severity in case of hereditary ones – review of literature. Journal of Education, Health and Sport. 2023;13(4):292-296. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2023.13.04.034
https://apcz.umk.pl/JEHS/article/view/42439
https://zenodo.org/record/7688443

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343.
Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159.
Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 06.02.2023. Revised: 22.02.2023. Accepted: 01.03.2023.

PROBLEMS WITH CLASSIFICATION OF POLINEUROPATIES SEVERITY IN CASE OF HEREDITARY ONES – REVIEW OF LITERATURE

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ABSTRACT
Evaluation of neuropathy severity is still a challenge for a modern medicine. Many scales were made to resolve this problem but each of them has limitations. It is known that in case of many patients there is no relation between clinical status and nerve conduction studies (NCS) results. Severe disabled patients with neuropathies can have nerve conduction study result mild impaired and conversely relation is also often observed. Many screening instruments with numerous composite scores are used to evaluate neuropathy. Most of them involved sensory perception, motor functions and reflexes like Neuropathy Disability Score (NDS), Neuropathy Impairment Score (NIS), Thoronto Clinical Neuropathy Scoring System. Electrophysiological parameters are also useful in classification of disease types especially in Charcot-Marie-Tooth one. There were many attempts of discovering new scores especially in diabetic neuropathies, involving mainly clinical features. There is lack of easy, reliable and precise scores that could improve neuropathy classification and monitoring disease progression especially in case of hereditary polyneuropathy.

Key words: polyneuropathy, Charcot-Marie-Tooth neuropathy, nerve conduction studies

PROBLEMY ZWIĄZANE Z KLASYFIKACJĄ STOPNIA CIĘŻKOŚCI POLINEUROPATII GENETYCZNIE UWARUNKOWANYCH – PRZEGLĄD PIŚMIENNICTWA

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STRESZCZENIE
Klasyfikacja zaawansowania polineuropatii stanowi wciąż wyzwanie dla współczesnej medycyny. Utworzono wiele skal, na podstawie których próbowano dokonywać tych klasyfikacji ale w przypadku każdej z nich stwierdzono różne ograniczenia. Zaobserwowano, że w wielu przypadkach wyniki badania elektroneurograficznego nie korelują ze stopniem niepełnosprawności. Chorzy ze znacznymi nieprawidłowościami w badaniu neurologicznym i dużym stopniem niepełnosprawności mogą mieć dość dobre parametry przewodzenia w badaniu neurograficznym. Opracowano wiele skal stosowanych w diagnostyce neuropatii oraz monitorowaniu jej postępu. Większość z nich obejmuje ocenę zaburzeń czucia, funkcji motorycznych oraz odruchów głębokich tak jak w przypadku NDS (Neuropathy Disability Score), NIS (Neuropathy Impairment Score) lub TCNSS (Thoronto Clinical Neuropathy Scoring System). Parametry elektrofizjologiczne maja także zastosowanie w wyodrębnieniu podtypów choroby tak jak w przypadku neuropatii Charcot-Marie-Tooth. Podjęto wiele prób utworzenia nowych systemów klasyfikacji stopnia zaawansowania choroby szczególnie w przypadku plineuropatii cukrzycowych, które obejmowały głównie elementy oceny klinicznej w badaniu przedmiotowym. Wciąż brakuje łatwej, wiarygodnej oraz dokładnej skali która mogłaby usprawnić diagnostykę oraz monitowanie przebiegu choroby.

Słowa kluczowe: polineuropatia, neuropatia Charcot-Marie-Tooth, badanie elektroneurograficzne

Evaluation of neuropathy severity is still a challenge for a modern medicine. Many scales were made to resolve this problem but each of them has limitations. It is known that in case of many patients there is no relation between clinical status and nerve conduction studies (NCS) results. Severe disabled patients with neuropathies can have nerve conduction study result mild impaired and conversely relation is also often observed.

Many screening instruments with numerous composite scores are used to evaluate neuropathy. Neuropathy Disability Score (NDS) is one of the most often used. It contains examination of temperature, vibration perception and presence of reflexes [1]. Another scale is Neuropathy Impairment Score (NIS) that contains examination of sensory functions and reflexes but also evaluation of motor functions impairment [2]. Another one, Thoronto Clinical Neuropathy Scoring System includes disease symptoms, reflexes and sensory symptoms [3]. Using presenting systems of classification, it is possible to assign patients to different disease levels but it is important to notice that one patient may have clinical features that cannot be compared directly to those of another one, even if both of them were diagnosed with the same degree of neuropathy. Explanation of this observation may be connected to the fact that symptoms of neuropathy may vary from patient to patient. Foot deformation often seen in neuropathies especially hereditary ones and asymmetric motor and sensory symptoms can make evaluation more difficult [4]. Many scores were worked out to evaluate disease severity or sole for screening in concrete type of neuropathy. As an example Michigan Neuropathy Screening Instrument questionnaire (MNSIq) contains symptoms, sensory and reflexes disturbances and is used in screening for diabetic neuropathy similar to Clinical Neuropathy Examination (CNE) [5,6]. Indubitable advantage of those scales is that they don't require specific knowledge or appropriate professional training, and can be performed not only by neurologist.

There was many attempts of creating new classification systems but none of them is widely used in medical practice. Interesting attempt of creating a scale, includes only electrophysiological features that could help in polyneuropathy severity classification was presented by Stalberg during conference in Uppsala, in May 2015 (table 1) [24].

Polyneuropathy classification	
Very mild	➢ 2 abnormal leg nerves, normal sural nerve sensory
Mild	➢ 2 abnormal findings in legs, sural nerve sensory response present but reduced amplitude
Moderate	< 4 abnormal nerves, sural sensory absent, radial sensory present, radial sensory present
Severe	➢ 6 abnormal findings, no sensory responses

Table 1. Polyneuropathy classification by Stalberg.

Electrophysiological findings are extremely important in classification of hereditary neuropathies especially Charcot-Marie-Toot (CMT) one. Taking into account results of genetic studies, many subtypes of disease can be distincted based on the type of gene mutation. Based on nerve-conduction studies CMT is subdivided into two main groups: a demyelinating form characterized by slowed nerve-conduction velocities (<38 m/s in upper-limb motor nerves) and an axonal form (CMT2), with preserved or only mildly slowed nerve-conduction velocities (>38 m/s) [7]. Electrophysiological abnormalities are present in childhood. Prolongation of distal motor latencies and decrease of nerve conduction velocities are the first observed abnormalities. These velocities are slower than normal from the age of 2 years, but do not substantially change after childhood and do not correlate with disease severity [8,9,10]. In CMT generalized Schwann cell myelin dysfunction is observed and conduction velocity slowing is observed in all body nerves including the facial and acoustic nerves even if they seem to be clinically unaffected [22].

The degree of axonal damage and loss of fibers is reflected in a reduction in amplitude of action potential for both motor and sensory nerves in axonal and demyelinating subtype of disease [20]. Those abnormalities in amplitudes can reflect clinical progression of disability [11,12,13]. Clinical impairment and disability correlate with secondary axonal loss, as shown by decreased amplitude of compound muscle action potential and changes in estimation of motor unit numbers [11]. Many controversies are related to patients with nerve conduction velocity between 30 – 40 ms in whom both demyelinating and axonal changes are observed. In that group disease symptoms progress more rapidly and relationship between nerve conduction velocity and severe of disease was the most evident [14]. In another study on group of 42 patients with Charcot-Marie-Tooth disease type 1A (CMT1A) authors proved that muscle weakness, CMAP amplitudes and motor unit number estimates correlated with clinical disability. There were no correlation between motor and sensory nerves conduction velocities and disability progression [15].

Nerve conduction velocities (NCVs) in CMT patients tend to remain constant over time and are typically symmetrical in both motor and sensory nerves in the upper and lower extremities. The amplitude changes seem to be better index of disease progression. On the other hand CMT3 – also called Dejerine Sottas syndrome (DSS) is a disease subtype connected with severe disability and early onset. Mean NCV in those patients is below 10 m/s [16]. In CTM 1A disease progress slowly and only 7% people need a wheel chair during their lives although 76 % had speeds between 15 and 35 m/s, while 24 % were below 15 m/s [17]. In CTM functional disability increases with disease duration [18]. Nerve conduction velocity is getting slower with age also in healthy people and that fact should be taken into account creating scores evaluating hereditary polyneuropathies severity [22]. Andresen revealed in his study that minimal F-wave latency is the most sensitive

parameter for detection of nerve pathology in polyneuropathy [23]. That data was related to diabetic patients and indicator with similar sensitivity should be performed for hereditary ones.

Creating scale useful in CMT neuropathy severity is also difficult because of variability of disease expression for CMT caused by the same gene mutation. Garcia presented two different CMT1A phenotype in twins. Factors that can modify disease phenotype remain elusive [19]. Signs of chronic denervation in muscles like increased amplitude and duration of unit potential are observed in needle EMG examination. Signs of ongoing denervation (i.e., fibrillation potentials and positive sharp waves) are characteristic for the most severe and rapidly progressive forms [21].

Shy worked out the CMT Neuropathy Score (CMTNS) to measure disease progression [25]. That score is used to evaluate impairment in patients with CMT1A and CMT1X and involves sensory perception, symptoms evaluation, motor function and reflexes [26]. Pareyson revealed in his trial that CMTNS is not sensitive enough to detect change in clinical trials that ran for less than two years. There were attempts of modifying that scale, but that new scores need to be tested on large group of patients [27].

Proper polyneuropathy system is extremely necessary in routine neurological practice. It could improve organization of medical researches, monitoring disease progress and treatment effects. Majority of scores involve sensory perception, motor functions, reflexes and disease symptoms. In some cases that symptomatology may be subtle and sometimes doesn't reflect disease severity. Electromyographic study is very sensitive in diagnosis of polyneuropathy and can also useful in evaluation of disease progression. It can be extremely useful in slowly progressing forms of disease like hereditary ones for example CMT. There were many attempts of creating new scores but none of them is widely used in clinical practice.

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