Open Journal of
Clinical & Medical
Case Reports

Volume 9 (2023)
Issue 26

Case Report ISSN: 2379-1039

Hyperexcitability to C-fiber stimulation correlates to pain with otherwise normal small fiber function

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Abstract

Small fiber neuropathy (SFN) is a disorder that affects thinly myelinated Aδ-fibers and unmyelinated C-fibers. We present the case of a 56-year-old male with paraproteinemic demyelinating neuropathy and suspected neuropathic pain. His examination revealed mechanical hyperalgesia in the feet, but quantitative sensory testing (QST) and intraepidermal nerve fiber density (IENFD) were normal. He also underwent examination with transcutaneous sinusoidal electric stimulation, a novel functional assessment of unmyelinated C-fibres, at distal arm and leg revealing extreme hyperalgesia that improved after Ig treatment in parallel to the pain. We suggest that C-fiber hyperexcitability may underlie neuropathic pain even when diagnostic criteria of SFN are not met. More studies are needed to further understand small fiber neuropathy and neuropathic pain in demyelinating polyneuropathy.

Keywords: Neuropathic pain; Small fiber; Neuropathy; C-fiber; PDN; Skin biopsy.

Introduction

Small fiber neuropathy (SFN) has been recognized as a distinct disorder that selectively or predominantly affects thinly myelinated Aδ-fibers and unmyelinated C-fibers. Common symptoms include neuropathic pain (burning, electric shock-like sensation, pins and needles), decreased sensation to temperature and pinprick and autonomic disturbances. Until recently, diagnosis was primarily based on clinical impression and many patients with SFN were underdiagnosed. The availability of skin biopsy with IENFD measurement and QST led to the development of diagnostic criteria based on abnormality of at least two clinical signs, IENFD and QST results at the distal leg [1]. SFN is present in many disorders in a length- dependent or non length-dependent pattern such as diabetic neuropathy, HIV-related neuropathy, in hematological and immune-mediated disorders, fibromyalgia etc [1,2]. It has also been reported to coexist

with demyelinating neuropathies such as CIPD and MGUS neuropathies [3-5]. Here, we describe a patient with peripheral demyelinating neuropathy and neuropathic pain with increased C-fiber excitability but normal IENFD and QST results.

Case Presentation

A 56-year-old male was referred to our laboratory with gradual onset of numbness and burning sensation in both feet and hands starting one year ago. The burning sensation was moderate and had impact on his quality of life. His examination revealed mild pin-prick hyperalgesia in the feet. Cranial nerves test, muscle strength, deep tendon reflexes, light- touch sensation, vibration and proprioception were normal. No autonomic disturbances were found. Cerebrospinal fluid (CSF) protein was elevated and nerve conduction studies (NCS) showed demyelinating polyneuropathy. Electromyogram (EMG), QST (table A and skin biopsy IENFD at distal leg (Figure 1) were also normal. Laboratory tests revealed monoclonal IgG (λ) paraprotein and bone marrow biopsy showed monoclonal IgG (λ) plasma cell dyscrasia (6-8%) and multifocal deposition of amyloid P component (+). Further tests did not reveal other amyloid-related systemic syndrome (eg. renal, liver, heart or gastrointestinal tract) except for the peripheral nerve involvement. As polyneuropathy in AL amyloidosis is usually axonal and there was no involvement of other amyloid-related systemic syndrome, the patient was not considered to suffer from AL amyloidosis and the diagnosis of paraproteinemic demyelinating neuropathy (PDN) was made [6,7]. He was treated with IVIg with clinical improvement concerning the decrease of the intensity of neuropathic pain and electrophysiological improvement of the nerve conduction velocities (NCV).

Two years later the patient relapsed mainly with symptoms of severe neuropathic pain. NCV were slower but QST and skin biopsy were normal. To investigate the neuropathic pain origin he underwent examination with sinusoidal transcutaneous electrical stimulation (intensity 0.2 mA and frequency 4 Hz for 60 seconds) at distal arm and leg. Pain intensity was assessed using numeric rating scale (NRS), with zero numeric rating scale indicating, no pain and 10 numeric rating scale indicating, maximum pain. The patient experienced intolerable pain after 15 seconds of stimulation with NRS 10 at distal leg which is exceptionally high even among neuropathic pain patients [8,9]. At the follow up examination, after treatment with IVIg, he showed clinical improvement of neuropathic pain and improvement of NRS scale after sinusoidal transcutaneous stimulation (NRS scale 8 at distal leg after 60 seconds of stimulation). Pain ratings in the hands showed as well high score at distal hand (NRS scale 10 after 15 seconds) before treatment and improvement of NRS scale after treatment (NRS scale 9 after 60 seconds) respectively.

Discussion

Dysfunction of small nerve fibers has been already reported in demyelinating neuropathies such as CIDP [4,5,10]. Although pathophysiology is not yet known, one explanation could be secondary axonal damage after chronic or severe demyelination [11]. In a study by Kokotis et al. the axon flare reaction to electrical stimulation, which is a reflex vasodilation based on activation of skin C fiber nociceptors, was decreased indicating small nerve fiber dysfunction [5]. Moreover, skin and nerve biopsies of patients with CIDP have shown decreased IENFD or unmyelinated nerve fiber degeneration, respectively [4,10]. Howe-

ver, no clear correlation between pain intensity (spontaneous pain and evoked allodynia) and IENFDwere found [4,12,13]. This indicates that hyperexcitability of nociceptors is not reflected in the current IEFN parameters, but potentially might be assessed with advanced analysis approaches including branching patterns [14].

Neuropathic pain has been lately defined as 'pain caused by a lesion or disease of the somatosensory system [15]. In painful neuropathies pain is associated to spontaneous activation and hyperexcitability of mechanoinsensitive C-nociceptors [16]. Transcutaneous electrical sinusoidal stimulation allows the selective activation of C-nociceptors and therefore, patient's pain ratings primarily reflect peripheral activation of C-nociceptors [8,9]. Our patient did not meet the current SFN criteria, but the presence of neuropathic pain, pin-prick hyperalgesia in the feet and extreme pain upon transcutaneous sinusoidal stimulation suggest a functional hyperexcitability of C nociceptors. In our opinion transcutaneous sinusoidal stimulation could be a complementary functional test for small nerve fiber dysfunction when neuropathic pain is present. Corroborating this view, our patient's symptoms and test results with sinusoidal transcutaneous stimulation improved after treatment with IVIg. IVIg is first line treatment for CIDP, Guillain Barre Syndrome and MMN. However it has been lately used for treatment of idiopathic painful SFN as patients tend to experience decreased pain severity post treatment [17]. Further studies about IVIg in idiopathic SFN even in patients with recently discovered SFN trisulfated heparin disaccharide (anti-TS-HDS) or fibroblast growth factor receptor-3 (FGFR3) autoantibodies are ongoing [18-20]. Therefore patient's improved symptoms and test results could be due to efficacy of IVIg on small nerve fibers besides large myelinated ones.

Conclusions

The past few years new diagnostic tools of SFN have been developed. In patients with neuropathic pain however, the absence of SFN according to current diagnostic criteria does not necessarily rule out hyperexcitability of Aδ and C fibers. More studies are required to further our understanding of mechanisms determining the development of neuropathic pain in small fiber neuropathy.

References

1. Devigili G, Tugnoli V, Penza P, et al. The diagnostic criteria for small fiber neuropathy: from symptoms to neuropathology. 2008; 131: 1912-1925.

2. Herrmann DN, McDermott MP, Henderson D, Chen L, Akowuah K et al. Epidermal nerve fiber density, axonal swellings and QST as predictors of HIV distal sensory neuropathy. Muscle Nerve. 2004; 29: 420-7.

3. BTA de Greef, JGJ Hoeijmakers , CML Gorissen-Brouwers , M Geerts , CG Faber , ISJ Merkies. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. Eur J Neurol. 2018; 25: 348-355.

4. Chiang MC, Lin YH, Pan CL, Tseng TJ, Lin WM, Hsieh ST. Cutaneous innervation in chronic inflammatory demyelinating polyneuropathy. Neurology. 2002; 59: 1094- 1098.

5. Kokotis P, Schmelz M, Papagianni AE, Zambelis T, Karandreas N. Decreased Axon Flare Reaction to Electrical Stimulation in Patients With Chronic Demyelinating Inflammatory. Polyneuropathy.JClinNeurophysiol. 2017; 34: 101-106.

6. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014; 15: 538.

7. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society-first revision. J Peripher Nerv Syst. 2010; 15: 185-95.

8. R.Jonas B. Namer L. Stockinger, et al. Tuning in C-Nociceptors to Reveal Mechanisms in Chronic Neuropathic Pain. Ann Neurol. 2018; 83: 945-957.

9. Rukwied R, Thomas C, Obreja O, et al. Slow depolarizing stimuli differentially activate mechanosensitive and silent C nociceptors in human and pig skin. Pain. 2020; 161: 2119-2128.

10. W M Bosboom, L H Van den Berg, H J Dieks, E Plante, H Veldman et al. Unmyelinated nerve fiber degeneration in chronic inflammatory demyelinating polyneuropathy. Acta Neuropathol. 2000; 99: 571-578.

11. Yiu EM, Burns J, Ryan MM, Ouvrier RA. Neurophysiologic abnormalities in children with Charcot-Marie-Tooth disease type 1A. J Peripher Nerv Syst. 2008; 13: 236-241.

12. Andreas C Themistocleous, Juan D Ramirez, Pallai R Shillo, et al. The Pain in Neuropathy Study (PiNS): A cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. Pain. 2016; 157: 1132-1145.

13. Cheng HT, Dauch JR, Porzio MT, et al. Increased axonal regeneration and swellings in intraepidermal nerve fibers characterize painful phenotypes of diabetic neuropathy. J Pain. 2013; 14: 941-7.

14. Wong C, Barkai O, Wang F, et al. mTORC2 mediates structural plasticity in distal nociceptive endings that contributes to pain hypersensitivity following inflammation. J Clin Invest. 2022.

15. Jensen TS, Baron R, Haanpaa M, et al. A new definition of neuropathic pain. Pain. 2011; 152: 2204-2205.

16. Kleggetveit IP, Namer B, Schmidt R, et al.: High spontaneous activity of C- nociceptors in painful polyneuropathy. Pain. 2012; 153: 2040-2047.

17. Liu X, Treister R, Lang M, et al. IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety. Therapeutic Advances in Neurological Disorders. 2018; 11: 1-12.

18. IVIg for small Fiber Neuropathy With Autoantibodies TS-HDS AND FGFR3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03401073.Accessed. (2021).

19. Levine TD, Kafaie J, Zeidman LA, et al. Cryptogenic small-fiber neuropathies: Serum autoantibody binding to trisulfatedheparan disaccharide and fibroblast growth factor receptor-3. Muscle Nerve. 2020; 61: 512-515.

20. Trevino, J. A., & Novak, P. TS-HDS and FGFR3 antibodies in small fiber neuropathy and Dysautonomia. Muscle & Nerve. 2021; 64: 70-76.

Manuscript Information: Received: June 23, 2023; Accepted: August 07, 2023; Published: August 08, 2023

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Citation: Bountziouka C, Schmelz M, Kokotis P. Hyperexcitability to C-fiber stimulation correlates to pain with otherwise normal small fiber function. Open J Clin Med Case Rep. 2023; 2089.

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