The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

CASE REPORT Open Access

Usefulness of the skin-wrinkling test in a patient with probable small fiber neuropathy and Gaucher disease

Renata Dal-Prá Ducci[1*], Michelle Zonkowski Ribas[2], Enzo Oku Martinazzo[3], Otto Jesus Hernandez Fustes[1], Paulo José Lorenzoni[1], Claudia Suemi Kamoi Kay[1] and Rosana Hermínia Scola[1]

Abstract

Background Gaucher disease (GD) is an autosomal recessive disease characterized by an inborn metabolic error. Although pain attributed to skeletal involvement is one of the most frequent symptoms of this condition, some patients may have neuropathic pain. Therefore, recent studies have analyzed the occurrence of peripheral polyneuropathy in patients with GD. In these studies, in cases when normal neurological examination and electroneuromyography were found, small fiber neuropathy (SFN) was investigated, mainly using skin biopsy and quantitative sensory testing.

Case presentation We demonstrate the usefulness of the skin-wrinkling test performed by immersion in water for the evaluation of SFN in a 27-year-old woman with GD who presented with neuropathic pain. After excluding other causes, the main hypothesis was an association between SFN and GD, which was recently described in the literature and possibly underdiagnosed.

Conclusions Although only skin biopsy can confirm the diagnosis of SFN, the skin-wrinkling test can be useful for the complimentary assessment of pain in patients with GD, owing to its easy application and wide availability.

Keywords Gaucher disease, Small fiber neuropathy, Peripheral nervous system diseases, Skin wrinkling, Neuropathic pain

Background

Gaucher disease (GD) is an autosomal recessive disorder with a mutation in the glucosylceramidase beta 1 (*GBA1*) gene, which encodes the lysosomal enzyme glucocerebrosidase [1]. GD is considered the most common lysosomal storage disorder [2].

Pain is one of the most frequent symptoms and is generally attributed to skeletal involvement. However, it may present with neuropathic characteristics in some patients [3]. In this context, recent studies have evaluated the occurrence of peripheral polyneuropathy in GD [1, 3, 4]. Due to normal neurological examination and electroneuromyography (ENMG), some cases were further investigated for small fiber neuropathy (SFN). The methods used to assess SFN in these studies were mainly skin biopsy and quantitative sensory testing [1, 3].

The skin wrinkling test can also be used to assess the involvement of small fibers [5, 6] and has been correlated with fiber density in skin biopsy [7]. The test can be performed by prolonged immersion in water, consisting of keeping the hands in water at a temperature of 40 °C

*Correspondence:
Renata Dal-Prá Ducci
renata.ducci@hc.ufpr.br
[1] Service of Neuromuscular Disorders, Division of Neurology, Department of Internal Medicine Clinics Hospital Complex, Federal University of Paraná (CHC-UFPR), General Carneiro, 181, Curitiba, PR 80060-900, Brazil
[2] Federal University of Paraná (UFPR), Curitiba, Brazil
[3] Pontifical Catholic University of Paraná (PUCPR), Curitiba, Brazil

for 30 min and observing the presence or absence of skin wrinkling [5].

In this case report, we describe a case of SFN attributed to GD after excluding other etiologies, that was treated at the Clinics Hospital Complex of the Federal University of Paraná (CHC–UFPR). We also demonstrate the usefulness of the skin wrinkling test performed by immersion in water in the evaluation of SFN. The patient signed an informed consent form and the study was approved by the Ethics Committee of the CHC–UFPR.

Case presentation

A 27-year-old woman was diagnosed with GD at 5 years of age and received imiglucerase infusions every 15 days. She worked in the telemarketing business and had no history of dermatitis. At 24 years of age, she developed paresthesia and intense burning pain in her lower limbs. The Douleur Neuropathique 4 Questions (DN4) questionnaire score was 7 out of 10, indicating the presence of neuropathic pain (score ≥ 4) [8]. General physical examination revealed hepatosplenomegaly with no other alterations. Neurological examination revealed no abnormalities. In the complementary investigation, ENMG was performed, with results within normal limits, thus excluding large fiber neuropathy (LFN).

The skin-wrinkling test recorded by photographs was performed, in which the palms of the hands were photographed at time 0 to verify basal changes in the fingers and 30 min after immersion in water for comparison [5, 9]. The patient kept her hands immersed in water at 40°C, controlled by a thermometer, for 30 min. The wrinkling of each finger after 30 min, except for the first digit, was graded into three categories: 0.0, no wrinkling; 0.5, slight wrinkling; and 1.0, clear wrinkling. The patient had a mean wrinkling of 0 and, therefore, abnormal wrinkling (Fig. 1).

Given the compatible clinic, neurological examination with minimal alterations, and ENMG within normal limits, a diagnosis of probable SFN was made. Metabolic/nutritional, infectious, neurotoxic, immune-mediated, hereditary, and other possible etiologies described for SFN were excluded by clinical clinical assessment and laboratory investigations. Thus, the etiological hypothesis of SFN in this case was GD. The patient maintained the enzyme replacement for GD, and the treatment for the neuropathic pain was optimized.

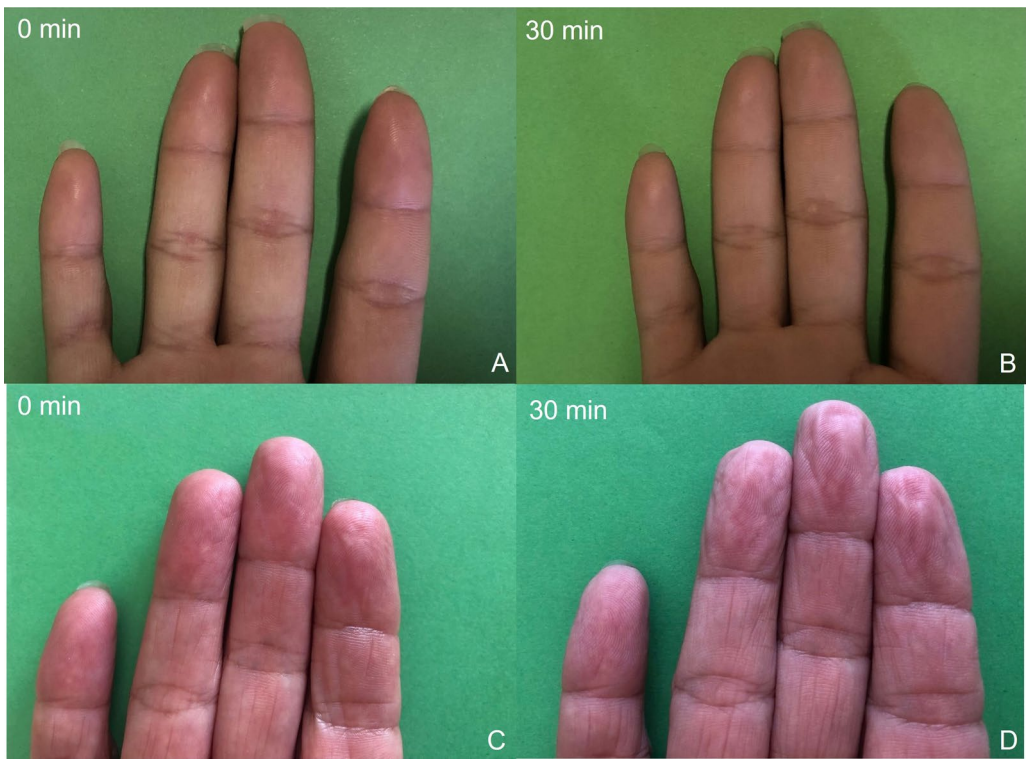

Fig. 1 Skin-wrinkling test. **A** Patient's hands at 0 min. **B** Lack of wrinkling on patient's hands at 30 min. **C** Expected wrinkling at 0 min in a healthy subject. **D** Expected wrinkling in 30 min in a healthy subject

Discussion

SFN is a group of neuropathies that involve sensory and autonomic fibers [6]. The main etiologies are metabolic, infectious, neurotoxic exposure, immune-mediated, and hereditary. However, up to 50% of patients have an undefined etiology [6, 10]. Among the idiopathic causes, new etiological possibilities are constantly emerging. GD was recently described, as shown in this case.

GD involves the progressive lysosomal storage of glucocerebroside in macrophages in the bones, bone marrow, liver, spleen, lungs, and nervous tissue [4, 11]. Although little described, the association between GD and polyneuropathies was observed in studies that found SFN in 21.4% and LFN in 10.7% of patients with GD [4].

The sensitivity of the skin wrinkling test ranges from 66% to 80% [5, 12]. One of the main reasons for this sensitivity is the fact that it is done on the hands and the condition usually starts in the feet [5]. However, the skin wrinkling test is a simple, inexpensive, and readily available examination that can be used for the characterization of small fiber involvement [7, 9, 12]. Studies have shown that the skin wrinkling test can be correlated with skin biopsy findings [6, 7], thus, proving to be a useful test mainly in the evaluation of SFN symptoms by general practitioners. The patient in this case, with absent wrinkling, presents probable SFN, corroborating the findings reported by Devigli et al. [3].

Another important point in the identification of SFN in patients with GD is the treatment, given that GD treatment usually includes enzyme replacement therapies [11], but the treatment of neuropathic pain differs from skeletal or inflammatory pain. Thus, an individual approach to each type of pain becomes essential [1].

Conclusions

This case report describes a patient with GD who was investigated for peripheral polyneuropathies after new pain developed with neuropathic characteristics. After excluding LFN and investigating other etiological possibilities described for SFN, we hypothesized an association between SFN and GD, which was recently described in the literature and possibly underdiagnosed. Although only skin biopsy can confirm the diagnosis of SFN, the skin-wrinkling test can be useful for the complimentary assessment of pain in patients with GD, owing to its easy application and wide availability.

Abbreviations

CHC–UFPR	Clinics Hospital Complex of the Federal University of Paraná
DN4	Douleur Neuropathique 4 Questions
ENMG	Electroneuromyography
GBA1	Glucosylceramidase beta 1
GD	Gaucher disease
LFN	Large fiber neuropathy
SFN	Small fiber neuropathy

Acknowledgements

Not applicable

Author contributions

All authors contributed to the study conception and design. Material preparation and data collection by RDPD, MZR, EOM, OJHF, PJL, CSKK, RHS. The first draft of the manuscript was written by RDPD, MZR, EOM, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This report did not receive any specifc grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Clinics Hospital Complex of the Federal University of Paraná (CHC–UFPR) in Curitiba, Paraná, Brazil. CAAE 89776718.1.0000.0096.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

Received: 10 February 2023 Accepted: 20 October 2023
Published online: 16 November 2023

References

1. Andréasson M, Solders G, Björkvall CK, et al. polyneuropathy in Gaucher disease type 1 and 3—a descriptive case series. Sci Rep. 2019;9(1):1–6. https://doi.org/10.1038/s41598-019-51976-2.
2. Halperin A, Elstein D, Zimran A. Are symptoms of peripheral neuropathy more prevalent in patients with Gaucher disease? Acta Neurol Scand. 2007;115(4):275–8. https://doi.org/10.1111/j.1600-0404.2006.00774.x.
3. Devigli G, De Filippo M, Ciana G, et al. Chronic pain in Gaucher disease: skeletal or neuropathic origin? Orphanet J Rare Dis. 2017;12(1):1. https://doi.org/10.1186/s13023-017-0700-7.
4. Biegstraaten M, Mengel E, Marodi L, et al. Peripheral neuropathy in adult type 1 Gaucher disease: a 2-year prospective observational study. Brain. 2010;133(10):2909–19. https://doi.org/10.1093/brain/awq198.
5. Datema M, Van-Dijk JG, Hoitsma E. The diagnostic value of water immersion skin wrinkling and Neuropads® in small fiber neuropathy. Clin Neurophysiol. 2012;123:2074–9. https://doi.org/10.1016/j.clinph.2012.01.026.
6. Gondim FAA, Barreira AA, Claudino R, et al. Definition and diagnosis of small fiber neuropathy: consensus from the Peripheral Neuropathy Scientific Department of the Brazilian Academy of Neurology. Arq Neuropsiquiatr. 2018;76(3):189–97. https://doi.org/10.1590/0004-282x20180015.
7. Wilder-Smith EP, Guo Y, Chow A. Stimulated skin wrinkling for predicting intraepidermal nerve fibre density. Clin Neurophysiol. 2009;120:953–8. https://doi.org/10.1016/j.clinph.2009.03.011.
8. Santos JG, Brito JO, de Andrade DC, et al. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. J Pain. 2010;11(5):484–90.

9. Fustes OJ, Kay CS, Lorenzoni PJ, et al. Pain-related Nociceptive Evoked Potential and Skin Wrinkle Test in Small Fiber Neuropathy. Arq Neuropsiquiatr. 2022;80(5):545–545. https://doi.org/10.1590/0004-282X-ANP-2021-0327.
10. Terkelsen AJ, Karlsson P, Lauria G, et al. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. Lancet Neurol. 2017;16(11):934–44.
11. Rosenbloom BE, Weinreb NJ. Gaucher disease: a comprehensive review. Crit Rev Oncogen. 2013;18(3).
12. Teoh HL, Chow A, Wilder-Smith EP. Skin wrinkling for diagnosing small fibre neuropathy: comparison with epidermal nerve density and sympathetic skin response. J Neurol Neurosurg Psychiatry. 2008;79: 835837.

Publisher's Note