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REVERSIBLE SMALL FIBER NEUROPATHY DUE TO VITAMIN B12 DEFICIENCY

NEUROPATIA DE PEQUENAS FIBRAS REVERSÍVEL DEVIDO À DEFICIÊNCIA DE VITAMINA B12

NEUROPATÍA DE FIBRAS PEQUEÑAS REVERSIBLE DEBIDO A LA DEFICIENCIA DE VITAMINA B12

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ABSTRACT

Small fiber neuropathy (SFN) involves dysfunction of thinly myelinated Aδ fibers and unmyelinated C fibers. Vitamin B12 deficiency is an uncommon but potentially reversible etiology. To describe a patient with SFN secondary to vitamin B12 deficiency with clinical and neurophysiological reversibility after replacement therapy, and to highlight the role of pain-related evoked potentials (PREP). A 63-year-old woman with no family history of neurological disease presented with hand paresthesia and burning pain in the lower limbs for one year. PREP obtained were absent. Serum vitamin B12 level was 111 pg/mL. A diagnosis of SFN due to vitamin B12 deficiency was established and replacement therapy was initiated. At follow-up, vitamin B12 level increased to 304 pg/mL, and PREP responses normalized, indicating successful treatment. This case underscores the importance of identifying the underlying etiology in patients with SFN symptoms. Recognition and treatment of vitamin B12 deficiency led to resolution of clinical and neurophysiological abnormalities. PREP represent a non-invasive, reliable, and cost-effective electrophysiological technique for evaluating Aδ-fiber function and may aid in both diagnosis and follow-up of small fiber dysfunction in systemic neuropathies.

Keywords: Small Fiber Neuropathy. Polyneuropathy. Pain-Related Evoked Potentials.

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RESUMO
A neuropatia de pequenas fibras (NPF) envolve disfunção das fibras Aδ finamente mielinizadas e das fibras C não mielinizadas. A deficiência de vitamina B12 é uma etiologia incomum, porém potencialmente reversível. Descrever uma paciente com NPF secundária à deficiência de vitamina B12, apresentando reversibilidade clínica e neurofisiológica após terapia de reposição, além de destacar o papel dos potenciais evocados relacionados à dor (PREP). Uma mulher de 63 anos, sem histórico familiar de doença neurológica, apresentou parestesia nas mãos e dor em queimação nos membros inferiores durante um ano. Os PREP obtidos estavam ausentes. O nível sérico de vitamina B12 foi de 111 pg/mL. Estabeleceu-se o diagnóstico de NPF devido à deficiência de vitamina B12, sendo iniciada terapia de reposição. No acompanhamento, o nível de vitamina B12 aumentou para 304 pg/mL e as respostas dos PREP normalizaram-se, indicando tratamento bem-sucedido. Este caso ressalta a importância de identificar a etiologia subjacente em pacientes com sintomas de NPF. O reconhecimento e o tratamento da deficiência de vitamina B12 levaram à resolução das alterações clínicas e neurofisiológicas. Os PREP representam uma técnica eletrofisiológica não invasiva, confiável e de baixo custo para avaliação da função das fibras Aδ, podendo auxiliar tanto no diagnóstico quanto no acompanhamento da disfunção de pequenas fibras em neuropatias sistêmicas.

Palavras-chave: Neuropatia de Pequenas Fibras. Polineuropatia. Potenciais Evocados Relacionados à Dor.

RESUMEN
La neuropatía de fibras pequeñas (NFP) implica disfunción de las fibras Aδ finamente mielinizadas y de las fibras C no mielinizadas. La deficiencia de vitamina B12 es una etiología poco frecuente, aunque potencialmente reversible. Describir una paciente con NFP secundaria a deficiencia de vitamina B12, con reversibilidad clínica y neurofisiológica tras terapia de reemplazo, y destacar el papel de los potenciales evocados relacionados con el dolor (PREP). Una mujer de 63 años, sin antecedentes familiares de enfermedad neurológica, presentó parestesias en las manos y dolor urente en los miembros inferiores durante un año. Los PREP obtenidos estaban ausentes. El nivel sérico de vitamina B12 fue de 111 pg/mL. Se estableció el diagnóstico de NFP debido a deficiencia de vitamina B12 y se inició terapia de reemplazo. En el seguimiento, el nivel de vitamina B12 aumentó a 304 pg/mL y las respuestas de los PREP se normalizaron, indicando un tratamiento exitoso. Este caso resalta la importancia de identificar la etiología subyacente en pacientes con síntomas de NFP. El reconocimiento y tratamiento de la deficiencia de vitamina B12 condujeron a la resolución de las alteraciones clínicas y neurofisiológicas. Los PREP representan una técnica electrofisiológica no invasiva, confiable y de bajo costo para evaluar la función de las fibras Aδ, y pueden ayudar tanto en el diagnóstico como en el seguimiento de la disfunción de fibras pequeñas en neuropatías sistémicas.

Palabras clave: Neuropatía de Fibras Pequeñas. Polineuropatía. Potenciales Evocados Relacionados con el Dolor.

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1 INTRODUCTION

Small fiber neuropathy (SFN) is characterized by structural or functional impairment of thinly myelinated Aδ fibers and unmyelinated C fibers, which mediate thermal sensation, nociception, and autonomic regulation. Clinically, SFN manifests with burning pain, dysesthesias, allodynia, and autonomic symptoms, while routine nerve conduction studies typically remain normal due to sparing of large myelinated fibers [1,2]. Among the diverse etiologies of SFN, vitamin B12 deficiency is an uncommon but reversible cause, and timely recognition is essential to prevent permanent neurological damage [3,4].

Several neurophysiological methods are available to assess small-fiber function, including quantitative sensory testing (QST), quantitative sudomotor axon reflex testing (QSART), sympathetic skin response (SSR), cardiovascular autonomic testing, and laser-evoked potentials (LEPs). These techniques differ in sensitivity and specificity and often require specialized equipment, trained personnel, or substantial time and cost, limiting their routine clinical use [5–7]. In recent years, pain-related evoked potentials (PREP) have emerged as a minimally invasive, reproducible, and accessible method for evaluating Aδ-fiber function, complementing other diagnostic approaches in SFN [8–10].

The aim of this report is to describe a patient with SFN secondary to reversible vitamin B12 deficiency, emphasizing clinical recovery after vitamin replacement and highlighting the diagnostic and follow-up utility of PREP.

Case Report

A 63-year-old woman with no family history of neurological disease presented with hand paresthesia and burning pain in the lower limbs that had progressively worsened over one year. Neurological examination was normal. Electromyography and nerve conduction studies showed no abnormalities. Laboratory investigations, including thyroid and liver function tests, as well as serology for HIV, syphilis, and hepatitis B and C, were negative.

PREP recorded using concentric planar electrode stimulation on the dorsum of the hands and feet were absent. Serum vitamin B12 level was 111 pg/mL (normal >200 pg/mL). Based on clinical presentation, laboratory findings, and neurophysiological assessment, the patient was diagnosed with SFN secondary to vitamin B12 deficiency, and replacement therapy was initiated.

At follow-up, serum vitamin B12 level increased to 304 pg/mL. PREP responses normalized, indicating recovery of Aδ-fiber function and confirming the effectiveness of vitamin B12 replacement therapy (Figure 1).

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2 DISCUSSION

This report highlights the importance of systematically investigating the underlying etiology in patients presenting with symptoms suggestive of SFN. Given the wide range of metabolic, immune-mediated, toxic, hereditary, and nutritional causes associated with SFN, accurate diagnosis requires careful clinical evaluation supported by targeted laboratory and neurophysiological testing. Among reversible etiologies, vitamin B12 deficiency deserves particular attention. Although less frequent than diabetes mellitus or autoimmune disorders, vitamin B12 deficiency can cause progressive sensory symptoms, neuropathic pain, and autonomic dysfunction that closely mimic primary small fiber disorders. Early diagnosis is crucial, as timely supplementation may lead to substantial recovery and prevent irreversible axonal degeneration [3,4].

In the present case, correction of vitamin B12 deficiency resulted in marked symptomatic and neurophysiological improvement. This reinforces the need to consider nutritional deficiencies in the differential diagnosis of SFN, particularly in patients with risk factors such as gastrointestinal disease, malabsorption, pernicious anemia, dietary restrictions, or chronic use of medications including metformin and proton pump inhibitors [11,12]. Importantly, neurological manifestations of vitamin B12 deficiency may precede hematological abnormalities, potentially delaying diagnosis if clinicians rely solely on anemia or macrocytosis as diagnostic clues [3,13].

Diagnosing SFN remains challenging because standard nerve conduction studies assess large myelinated fibers and are typically normal. Skin biopsy with quantification of intraepidermal nerve fiber density is considered a diagnostic gold standard, but it is invasive, costly, and not universally available [2]. Other tools, such as QST, SSR, sudomotor testing, and autonomic cardiovascular evaluation, provide valuable information but may be limited by variability, patient cooperation, or restricted access to specialized equipment [5,6].

In this context, PREP represent a valuable adjunctive technique. PREP evaluate Aδ-fiber function by recording cortical responses to controlled painful electrical stimuli. Their main advantages include non-invasiveness, reproducibility, relative affordability, and feasibility in centers without access to advanced neurophysiological resources [12,13]. PREP offer objective assessment of nociceptive pathway integrity and have demonstrated diagnostic utility in various systemic disorders associated with small fiber dysfunction, such as diabetes mellitus, Sjögren syndrome, fibromyalgia, and chemotherapy-induced neuropathy [14,15]. In this patient, abnormal PREP supported the diagnosis of SFN, and

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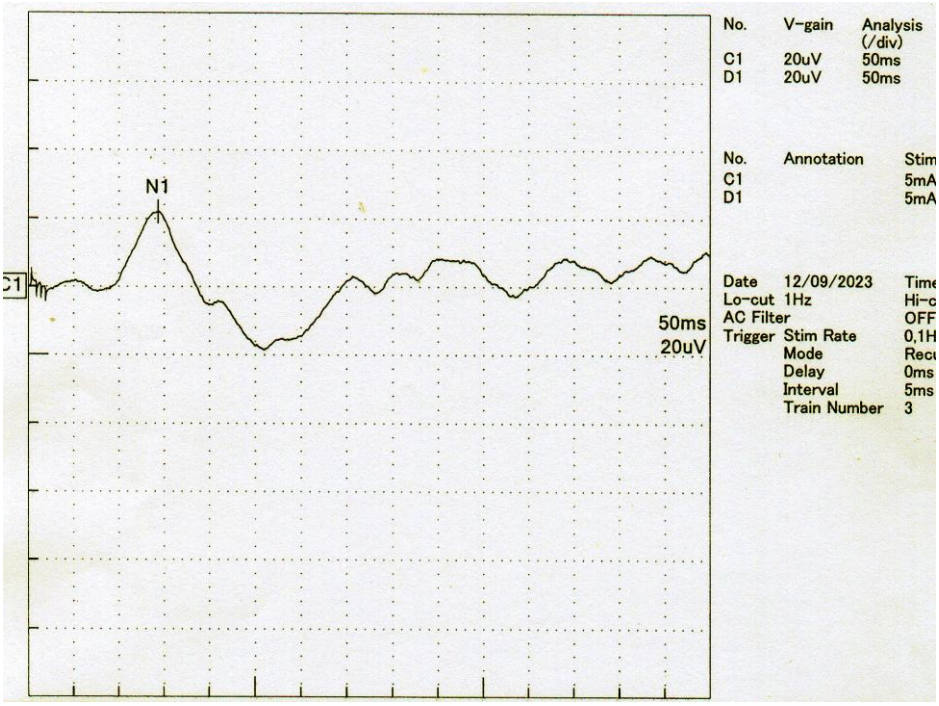
normalization after vitamin B12 replacement suggested their usefulness in monitoring therapeutic response.

Overall, this case adds to growing evidence supporting PREP as a practical, accessible, and reliable component of the diagnostic workup for SFN. While PREP do not replace structural assessment techniques such as skin biopsy or comprehensive autonomic testing, they may fill an important gap when repeated evaluations are required or when other methods are unavailable. Further studies are needed to refine normative values, standardize protocols, and define sensitivity and specificity across different SFN etiologies. Nevertheless, this report illustrates how etiological investigation combined with appropriate neurophysiological testing can improve diagnostic accuracy and patient outcomes.

Figure 1

Normal pain-related evoked potentials (PREP) recorded from the hand after vitamin B12 replacement therapy



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