



CLINICAL CASE

Polyglandular Syndrome Type III and Severe Peripheral Neuropathy: An Unusual Association



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Abstract

Introduction: Polyglandular syndrome is characterized by the association of autoimmune, organ-specific, endocrine and non-endocrine diseases.

Objective: To present a case of polyglandular syndrome type III (b) accompanied by pernicious anemia and autoimmune thyroiditis.

Method: Report the clinical case of a young patient that developed progressive and disabling peripheral neuropathy framework, triggered by vitamin B12 deficiency.

Discussion: It was proven that atrophic gastritis with positive intrinsic anti-factor was responsible for the framework of pernicious anemia, which in turn dangerously reduced the serum levels of vitamin B12, leading to myelopathy. There was a progressive neurological improvement after parenteral cyanocobalamin replacement, keeping the patient at ambulatory, under maintenance therapy.

Conclusion: The importance of suspecting on polyglandular syndrome in the presence of autoimmune frameworks is important, especially those involving diabetes, thyroiditis, atrophic gastritis, pernicious anemia, vitiligo, among others.

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PALAVRAS-CHAVE

Anemia Perniciosa;
Deficiência de
Vitamina B 12;
Doenças da Medula
Espinal;
Gastrite Atrófica;
Tiroidite Autoimune

Síndrome Poliglandular Tipo III e Neuropatia Periférica Grave: Uma Associação Incomum**Resumo**

Introdução: A Síndrome Poliglandular é caracterizada pela associação de doenças autoimune órgão-específicas, endócrinas e não endócrinas.

Objetivo: Apresentar um caso de Síndrome Poliglandular do tipo III (b) acompanhada de anemia perniciosa e tireoidite auto-imune.

Método: Relata-se o caso clínico de uma paciente jovem que desenvolveu quadro de neuropatia periférica progressiva e incapacitante, desencadeada pela deficiência de vitamina B12.

Discussão: Ficou comprovado que a gastrite atrófica com anticorpo anti-fator intrínseco positivo foi responsável pelo quadro de anemia perniciosa, que por sua vez reduziu perigosamente os níveis séricos da vitamina B12. Houve melhora progressiva do quadro neurológico após reposição parenteral da cianocobalamina, mantendo-se a paciente, em seguimento ambulatorial, sob terapia de manutenção.

Conclusão: Ressalta-se a importância de se suspeitar da síndrome poliglandular na vigência de quadros auto-ímmunes, especialmente aqueles envolvendo diabetes, tireoidites, gastrite atrófica, anemia perniciosa, vitiligo, entre outros.

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1. Introduction

Autoimmune polyglandular syndrome (APS) was first described in 1926 by Schmidt, through necropsies on patients with adrenal insufficiency, in which destructive and non-specific lymphocyte infiltration was found both in the thyroid gland as in the cortex of adrenal glands.¹

The APS is characterized by the association of organ-specific autoimmune diseases, endocrine and non-endocrine.² It is divided into four types: (a) APS I, characterized by the presence of at least two of the following situations, Addison's disease, chronic hypoparathyroidism and chronic candidiasis; (b) APS II, characterized by the presence of Addison's disease associated with autoimmune thyroiditis disease and/or diabetes mellitus 1; (c) APS III, characterized by the presence of autoimmune thyroid disease with other autoimmune disease (such as diabetes mellitus 1, atrophic gastritis and pernicious anemia, vitiligo, alopecia and myasthenia gravis), except for Addison's disease and/or hypoparathyroidism; (d) APS IV, characterized by the combination of autoimmune diseases that do not fall into the categories already mentioned.³

The APS I and II are rare, with a prevalence of 1:9.000–1:200,000 inhabitants and 1.4–4.5 cases per 100,000 inhabitants, respectively. However, the epidemiological aspects of the SPA III and IV are not fully known.⁴

The polyglandular syndrome type III, in turn, can be subdivided according to the autoimmune disease associated: SPA III (a), when the patient has diabetes mellitus 1; SPA III (b), characterized by the presence of atrophic gastritis and pernicious anemia; SPA III (c) when there is vitiligo, severe alopecia or myasthenia.¹

This article reports a case of a young woman with polyglandular syndrome type III (b), which developed a progressive and disabling peripheral neuropathy with

myelopathy, triggered by vitamin B12 deficiency. It was proven that atrophic gastritis with positive intrinsic anti factor antibody lead to pernicious anemia that regressed after cyanocobalamin administration.

2. Clinical case

Female patient 34 years old, was referred from neurologist to gastroenterologist after six months of symptoms. She had initiated the neurological symptoms with paresthesia in the lower limbs, ascending and progressive, in the hallux region which advanced gradually to the thoracic region. After 4 months when she could no longer walk, having dizziness, loss of proprioceptive sensitivity and ataxia. There was no history of alcoholism, hypertension, diabetes mellitus, hepatitis, use of illicit drugs and tattoos. There is reference to a blood transfusion 3 years ago due to a miscarriage. Reported swimming in the river in childhood. At clinical examination, with regular condition, conscious, color, eutrophic, with paraesthesia and motor deficit in the lower limbs, impaired gait, using wheelchair for mobility. The research conducted by the neurologist had already discarded the hypothesis of Guillain-Barré syndrome and multiple sclerosis.

The cerebrospinal fluid examination revealed no alterations. The MRI of the spine in its thoracic and lumbar regions showed multiple cold areas and modification of signal involving the cord at various levels, showing hyperintense signal on T2 at its periphery. This finding is more pronounced near the tenth thoracic vertebra region, predominantly in the anterior-medial region of the medulla. Electromyography showed polyneuropathy with pattern of axonal impairment in the lower limbs.

The patient had no gastrointestinal symptoms, but as the blood count showed anemia with hemoglobin of 11.2 g/dL (12–15 d/dL), hematocrit of 32.9% (36–48%) and high VGM

$128 \mu^3$ ($81-101 \mu^3$), the upper digestive endoscopy was indicated, which identified an appearance suggestive of body atrophic gastritis, enanthematous/mild erosive of antrum gastritis, with a negative urease test. Pathologic result of antral biopsy revealed it to be a mild chronic atrophic gastritis in antrum with incomplete interstitial metaplasia. The intrinsic anti-factor antibody was positive and the anti-parietal cell antibody negative; the total abdominal ultrasonography revealed no alterations.

Serology for HIV, HTLV 1, VDRL, hepatitis B and hepatitis C virus, cytomegalovirus, toxoplasmosis and schistosomiasis were negative. Anti-core factor, anti-Sm antibody, anti-DNA, anti-cardiolipin, anti-Ro were also non-reactive. Amino-transferases, PCR and ESR were within normal limits, but serum TSH was at $8:34 \text{ mIU/mL}$ ($0.35-5.5 \text{ mIU/mL}$). The rheumatoid factor was negative and anti-thyroglobulin (anti-TG), anti-tpo antibodies were positive. The dosage of vitamin B6 was 6.5 pg/mL ($5.0-30.0 \mu\text{g/L}$) and vitamin B12 $< 50 \text{ pg/mL}$ ($210-980 \text{ pg/mL}$) showing that this is a serious deficiency.

The serum vitamin B12 levels normalized after parenteral administration, with progressive neurological improvement.

3. Discussion

This article reports the case of a previously healthy young patient, who starts with neurological manifestations, evolving progressively to neuropathy with myelopathy. Following, it was detected the presence of autoimmune diseases such as pernicious anemia with vitamin B12 deficiency (positive intrinsic anti-factor antibody) and thyroiditis (with anti-thyroglobulin antibody), which led to the diagnosis of autoimmune polyglandular syndrome type III (b).

A deficiency of vitamin B12 can lead to hematological changes, neurological, psychiatric and/or gastrointestinal impairment.⁵ The most frequent cause of this deficiency is pernicious anemia, which is the lack of intrinsic factor (a protein secreted by the parietal cells necessary for the absorption of vitamin B12), consequent to autoimmune gastritis.¹⁷ The autoimmune atrophic gastritis is characterized by atrophy of the gastric body and and/or by the presence of circulating autoantibodies against parietal cells and their secretory products, as intrinsic factor.⁶

Chronic autoimmune destruction of proton pump H^+/K^+ ATPase results in decreased gastric acid secretion, hypergastrinemia and iron deficiency. In a more advanced stage of the disease, pernicious anemia may occur as a result of vitamin B12 deficiency.⁶ Deficiency of this vitamin can cause demyelination of peripheral nerves and the central nervous system, being associated with peripheral neuropathy.⁷

Myelopathy due to vitamin B12 deficiency is manifested initially by paresthesia and weakness, affecting all four limbs in a symmetrical pattern. In advanced stages, there are paraplegia and varying degrees of spasticity, associated with hyper- or hyporeflexia, ataxia, paresthesia, alterations of deep sensitivity, cognitive dysfunction, pelvic floor disorders, decreased visual acuity. The occurrence of sensory level is rarely observed.⁹ Initial laboratory diagnosis

is based on the serum vitamin B12, which is reduced in most cases.¹⁰ Treatment consists of parenteral replacement of vitamin B12. Response to treatment is related to the severity and time between onset of symptoms and treatment.⁹

In this case the neurological manifestations presented were consequence of pernicious anemia based on the good response to cyanocobalamin and the histological demonstration of atrophic gastritis and the presence of the intrinsic anti-factor antibody.¹¹

Few reports in the literature have described the transverse myelitis by cyanocobalamin deficiency, with well-defined sensory level, as in our case. Kosik et al.¹² reported the framework of a young patient with a diagnosis of pernicious anemia with acute transverse myelitis and level at T10 due to vitamin B12 deficiency. Vasconcellos et al.¹³ in turn, described a severe and fatal reports of transverse myelitis with sensory level, which did not respond to replacement therapy. According to Vasconcellos, the presence of sensory level denotes severe case of vitamin B12 deficiency and may be considered a finding associated with a bad prognosis. In the case presented here, the patient had flaccid and areflex paraplegia with sensory level at T10; however, contrary evidence, it evolved with a favorable prognosis after replacement of cyanocobalamin.

The electroneuromyography in cases of polyneuropathy reveals, in general, decreased or absent sensory nerve action potentials and normal conduction velocity.¹⁶ Nuclear magnetic resonance in turn may show areas of demyelination in the brain or spinal cord corresponding to areas of hyperintensity in the sequence weighted in T2. This finding is most commonly found in the posterior cord of the marrow. The radiological changes may take up to 12 months to disappear.^{5,13}

In the blood count is observed anemia and less commonly leukopenia, besides thrombocytopenia. Megaloblastic anemia is present in most cases and in 1/3 of the cases may be absent.¹³ Heaton et al.¹⁰ in a study on 143 patients, who had a vitamin B12 deficiency, observed that 27.4% had normal hematocrit and 23% had a normal MCV. A bone marrow biopsy is usually hyperplastic, with a predominance of red cell precursors.¹⁶ The patient in this case had anemia with high MCV, which is the most frequent finding according to the literature. In the present case there was normalization of the MCV with treatment. The dosage of the intrinsic anti-factor antibody is positive in cases of pernicious anemia.

Stabler et al.¹⁷ have shown that vitamin B12 deficiency causes reversible megaloblastic anemia, demyelinating disease, or both, and that parenteral replacement or high dose of vitamin B12 orally is an effective therapy.

Laboratory diagnosis of vitamin B12 deficiency can be accomplished through the dosage of cyanocobalamin or homocysteine and methylmalonic acid in the urine.¹³ However, the dosage of homocysteine and methylmalonic acid have better sensitivity and specificity than cyanocobalamin, which has limited sensitivity and specificity.¹⁴ Though infrequent, deficiency of vitamin B12 may present with normal or even increased serum level.¹⁵ Liver disease, for example, can increase the levels of the transport proteins (transcobalamins I and III) with a consequent increase in serum cyanocobalamin.¹⁶

The detection of antibodies is sufficient for the diagnosis of autoimmune disease of the thyroid. Positive anti-peroxidase antibodies (anti-TPO) are strongly indicative markers of autoimmune thyroiditis and are present in 90% of disease cases and currently used to define the existence of an autoimmune thyroiditis. Anti-Tg antibodies are present in 20–50% of patients.⁸ The presence of positive anti-tpo and anti-tg, associated with high levels of TSH were enough for diagnosis of autoimmune thyroiditis in the case presented.

The treatment is based on the parenteral replacement of cyanocobalamin.¹⁶ Some schemes are proposed, for example 1000 mg IM twice a week for two weeks, followed by a weekly dose for 3 months and a monthly dose thereafter. The recovery becomes evident after 3–6 months of treatment; after this period the recovery is slow and can last up to years.⁹

In conclusion, spinal presentation of vitamin B12 deficiency in the form of transverse myelitis, as synchronous manifestation of polyglandular syndrome type III (b) is a rare condition, one should suspect the vit B12 deficiency when certain neurological changes are evident. The presence of sensory level is explained by the spinothalamic tract impairment as observed in the present case reported. The most commonly cause implicated in this deficiency, according to the literature, is pernicious anemia. It is a treatable disease, if diagnosed early, have a good prognosis. Our patient showed with severe disabilities and neurological symptoms for 6 months which could explain the reversal of the neurological status. Still, the patient had sensory level, considered a poor prognostic factor in cases of myelopathy due to vitamin B12 deficiency, but that progressed well after replacement therapy.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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