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Rare Association Between Neuroimmunological Diseases: A Possible Autoimmune Polyglandular Syndrome Type IV

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Abstract

Autoimmune polyglandular syndromes (APS) are a diverse group of clinical conditions characterized by loss of immune tolerance in various tissues. This condition can be diagnosed in childhood or adulthood, with changes in the components of the disease throughout life. Here, an unusual case of association between immune-mediated diseases will be addressed: Myasthenia Gravis, Systemic Lupus Erythematosus, and Celiac Disease. In this patient, each disease was expressed over time. Finally, we assume that this is a clinical form of APS type IV, due to the lack of thyroid involvement to date.

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Introduction

Autoimmune conditions are easily transposable. The common genetic origin among proteins that control the antigen recognition and production system is the main cause [1, 2]. Autoimmune polyglandular syndromes (APS) are a diverse group of clinical conditions characterized by loss of immune tolerance in various tissues. APS represents the association of different autoimmune diseases, frequently endocrine disorders [1]. Signs and symptoms include alopecia, vitiligo, celiac disease, myasthenia gravis, autoimmune gastritis with vitamin B12 deficiency.

This condition can be diagnosed in childhood or adulthood, with changes in the components of the disease throughout life [1]. In accordance with the advancement of DNA sequencing techniques, new forms of polyendocrinopathy were discovered [1]. The clinical manifestations can overlap, as is the case of the weakness present both in Celiac Disease and Myasthenia Gravis, for example [3].

In the present study, an unusual case of association between immune-mediated diseases will be addressed: Myasthenia Gravis, Systemic Lupus Erythematosus, and Celiac Disease. In this patient, each disease was expressed over time. Therefore, we assume that this is a clinical form of APS type IV, due to the lack of thyroid involvement to date.

Case Report

L.B, 40-year-old woman, a medical doctor. The patient had a previous medical history with various morbidities. Menstrual irregularity in adolescence and adulthood. Severe abdominal pain at the age of 9 without a clarified diagnosis, even after hospitalization. At the age of 16, she underwent orthopedic correction surgery and there was a need for bone graft in the right humerus.

In 2005, at the age of 25, the patient was diagnosed with myasthenia gravis, with a 6-month evolution of weakness in the lower limbs, tiredness, and fluctuating symptoms. Pyridostigmine Bromide 60mg twice a day was prescribed, and the patient reported improvement in symptoms. After 3 months, she underwent thymectomy, with no improvement after surgery. 2 years after diagnosis, she gave birth to her first child. No signs of worsening during pregnancy, however with worsening of symptoms in the postpartum and puerperium. Since this episode, she started Azathioprine 3 mg/kg/day and maintained it for 3 years, until 2011.

In 2017, the patient complained of a malar rash, alopecia, arthralgia, and numbness. Laboratory tests revealed Antinuclear Antibodies (ANA) Test positive - titer of 1: 640 and coarse speckle pattern. Therefore, based on clinical symptoms and laboratory findings, the patient fulfilled the American College of Rheumatology's 1997 criteria for Systemic Lupus Erythematosus [4]. At the moment, no specific medication was used, and the symptoms were controlled separately.

Soon after, the patient gave birth to her second child. During pregnancy, she used Hydroxychloroquine Sulfate (3mg/kg/day) to prevent the increased activity or cause worsening of Lupus disease. Even so, her symptoms worsened in the puerperium again. Thus, until today, the patient is using Acetylsalicylic Acid (ASA) 100mg/day (prophylaxis of Antiphospholipid Factor Syndrome), Azathioprine 3 mg/kg/day, Pyridostigmine Bromide 60mg twice a day, Deflazacort 6mg/day, as well as an antidepressant medication due to Postpartum Depression.

Recently, the patient's older child was diagnosed with celiac disease. 2 months ago (Feb. 2020), due to the hereditary nature of the disease, the patient underwent serological tests for detection. There was no IgA deficiency; count of 53,51 Tissue Transglutaminase Antibodies (tTG-IgA) (normal for adults is < 19 mg/dl and IgA Endomysial antibody (EMA-IgA) was non-reactive. Consequently, the investigation for celiac disease was positive, and the patient received guidance on the importance of a gluten-free diet.

In the last month, other routine blood tests were performed: Vitamin B9/Folic acid and vitamin B12/ Cobalamin were within normal limits. Creatinine and CPK levels were 0,63 and 31, respectively. Normal thyroid functions - TSH 0,53 and Thyroid Peroxidase Antibody (TPO) negative. Acetylcholine receptor (AChR) antibody levels were 1,47 (normal for an adult is Less than 0.25 nmol / L), confirming the Myasthenia Gravis diagnosis.

Currently, she is under outpatient follow-up treatment of Lupus, Myasthenia Gravis, and Celiac

Disease. Daily, she controls the diseases by taking all the drugs already mentioned above. Due to the clinical presentation of the patient with 3 organ-specific autoimmune diseases, which does not fit the criteria for polyglandular syndrome type I, II, or III, we believe it is a clinical form of Autoimmune Polyglandular Syndrome type IV.

Discussion

Polyendocrine disorders, also known as Autoimmune Polyglandular Syndrome (APS), are classified into 4 types so far [1]. Autoimmune polyendocrine syndrome type 1 is a rare autosomal recessive disease caused by mutations in the AIRE gene, which is one of the autoimmune regulators. Clinical triad is composed of mucocutaneous candidiasis, hypoparathyroidism, and adrenal failure (Addison's disease). Other typical components include patterns of chronic constipation or diarrhea [5]. Ovarian failure affects 60% of women with type 1 APS before the 30 age [1].

APS 2 is associated with at least two of these three endocrinopathies: type 1 diabetes, autoimmune thyroiditis, or Addison's disease [1, 6]. Like most autoimmune diseases, those affected are often female. Many of these patients may develop other clinical conditions, such as celiac disease, alopecia, vitiligo, ovarian failure, and pernicious anemia [1]. The development of genetic studies of APS showed that the same genes and single-nucleotide polymorphisms are associated with several organ-specific autoimmune diseases. Patients with APC 2 and celiac disease generally have variations in CR3-DQ2 and DR4-DQ8, and these haplotypes pose a risk for type 1 Diabetes Mellitus, thyroid disease, and Addison's disease; this explains why patients develop illnesses simultaneously [1]. Treatment requires hormonal therapy and management of complications.

Celiac disease (CD) is defined as a chronic gluten intolerance that results in intestinal inflammation, villous atrophy, crypt hyperplasia, and malabsorption [3]. Classic symptoms include abdominal discomfort, fatigue, impaired bone mineralization, and hypocalcemia. In the case presented above, the patient's first manifestation of celiac disease may have been the unexplained abdominal pain at age of 9. One-third of CD patients suffer from one or more associated autoimmune diseases, as well as nutritional and mineral deficiencies are commonly found [1,2]. Therefore, we recommend seeking and clarifying these differential diagnoses, especially other autoimmune disorders with similar symptoms, such as myasthenia gravis [3]. The diagnosis of Celiac Disease is clinical, endoscopic, and histological. For confirmation, the measurement of circulating autoantibodies, such as tTG-IgA and EMA-IgA, is performed. In the case of IgA deficiency, IgG autoantibodies can be measured.

Type 3 autoimmune polyendocrine syndrome (APS-3) is defined by the presence of autoimmune thyroid disease (TAD) and another autoimmune illness, excluding Addison's disease, hypoparathyroidism or chronic candidiasis [7]. The most common associations with TAD are with chronic atrophic gastritis (39 % of the cases) or with Diabetes Mellitus type 1 [2, 7]. APS type 4 is represented by the association between other endocrine disorders or autoimmune diseases [6], as was the case of the patient previously reported in this article, who presented myasthenia gravis, systemic lupus erythematosus, and celiac disease. Therefore, it is a heterogeneous disease, involving disorders that do not fall into type I, II, or III [2, 8].

Myasthenia Gravis is a disease caused by defects in the neuromuscular junction, with antibodies against local receptors (3). The main clinical manifestation includes fluctuating symptoms, which usually worsen at the end of the day, as well as with heat or stress [9]. The treatment is primarily clinical, and some patients may benefit from surgical treatment, such as thymectomy, or even acupuncture [10,11].

By contrast, the other symptoms presented by the patient during her clinical evolution were compatible with Systemic Lupus Erythematosus and later confirmed by the laboratory exams. SLE has the characteristic of having a pathology shared with other diseases, mainly due to chronic inflammation with clinical and serological heterogeneity [6, 12]. Among these characteristics, there are different manifestations of SLE in relation to the central nervous system (CNS) and peripheral nervous system (PNS), in addition to psychiatric disorders [12]. Interestingly, in this report, the patient presented postpartum depression, probably facilitated by

the immune response.

Conclusion

The presence of an endocrine disease increases the risk of developing others. Celiac disease is a predictor of polyglandular syndromes, especially in adults and females. Polyglandular Syndromes are heterogeneous and also vary in presentation depending on the period of life in which the patient is. For this reason, we recommend that clinical physicians investigate further when they encounter patients with two or more associated immunological diseases, ensuring a better quality of life for these patients.

In the reported case, there was an interaction of Myasthenia Gravis, a rare immune-mediated disease, involving the neuromuscular junction, Systemic Lupus, and Celiac Disease. The answers to such interactions lie in embryological, genetic, and environmental research, each one as pieces of the autoimmune puzzle.

Disclosures

Funding Sources and Conflict of Interestt

No specific funding was received for this work and the authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months

The authors declare that there are no additional disclosures to report.

Ethical Compliance Statement

The authors confirm that the approval of an institutional review board was not required for this work. Even so, the patient signed a statement of consent (in Brazilian Portuguese - Termo de Consentimento Livre e Esclarecido) for the use of the information contained in the patient's medical record. We also confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

Abbreviations

APS - Autoimmune Polyglandular Syndrome

MS – Myasthenia Gravis

CD – Celiac Disease

SLE - Systemic Lupus Erythematosus

References

1. Lahner E, Conti L, Cicone F, Capriello S, Cazzato M, Centanni M et al. Thyro-entero-gastric autoimmunity: Pathophysiology and implications for patient management. Best Practice & Research Clinical Endocrinology & Metabolism. 2019;33 (6):101373.
2. Kahaly G, Frommer L, Schuppan D. Celiac Disease and Glandular Autoimmunity. Nutrients. 2018;10 (7):814.
3. Thawani S, Brannagan T, Lebwohl B, Green P, Ludvigsson J. Celiac disease and risk of myasthenia gravis – nationwide population-based study. BMC Neurology. 2018;18(1):28.
4. Feletar, M., Ibañez, D., Urowitz, M., & Gladman, D. The impact of the 1997 update of the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus: What has been changed?. Arthritis & Rheumatism. 2003;48(7): 2067-2069. https://doi.org/10.1002/art.11167
5. Högenauer C, Meyer R, Netto G, Bell D, Little K, Ferries L et al. Malabsorption Due to Cholecystokinin Deficiency in a Patient with Autoimmune Polyglandular Syndrome Type I. New England Journal of Medicine. 2001;344(4):270-274.
6. Bliddal S, Nielsen C, Feldt-Rasmussen U. Recent advances in understanding autoimmune thyroid disease: the tallest tree in the forest of polyautoimmunity. F1000Research. 2017;6:1776.
7. Betterle C, Garelli S, Coco G, Burra P. A rare combination of type 3 autoimmune polyendocrine syndrome (APS-3) or multiple autoimmune syndrome (MAS-3). Autoimmunity Highlights. 2014;5 (1):27-31.
8. Mihalache L. A Rare Case of Severe Type 4 Polyglandular Autoimmune Syndrome in a Young Adult. Acta Endocrinologica (Bucharest). 2016;12 (1):104-110.
9. Gilhus N, Tzartos S, Evoli A, Palace J, Burns T, Verschuuren J. Myasthenia gravis. Nature Reviews Disease Primers. 2019;5(1).
10. Taioli E, Paschal P, Liu B, Kaufman A, Flores R.

Comparison of Conservative Treatment and Thymectomy on Myasthenia Gravis Outcome. The Annals of Thoracic Surgery. 2016;102(6):1805-1813.

11. Shi S, Ji X, Wang Y, Liu B, Zhang H, Lu C. Acupuncture for patients with myasthenia gravis. 2020.
12. Di Battista M, Marcucci E, Elefante E, et al. One year in review 2018: systemic lupus erythematosus. Clin Exp Rheumatol. 2018;36(5):763-777.