Research, Society and Development, v. 10, n. 3, e18510313094, 2021
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v10i3.13094

Type III autoimmune polyglandular syndrome: association between Type 1 *Diabetes mellitus* and *Hashimoto thyroiditis*

Síndrome poliglandular autoimune tipo III: associação entre *Diabetes Mellitus* tipo 1 e *Tireoidite de Hashimoto*

Síndrome poliglandular autoinmune tipo III: asociación entre *Diabetes Mellitus* tipo 1 y *Tiroiditis de Hashimoto*

Received: 02/18/2021 | Reviewed: 02/28/2021 | Accept: 03/04/2021 | Published: 03/11/2021

Alissa Pupin Silvério
ORCID: https://orcid.org/0000-0002-1483-2401
Universidade José do Rosário Vellano, Brazil
E-mail: alissapupin@gmail.com
Gabriela Teixeira Bazuco
ORCID: https://orcid.org/0000-0002-1908-780X
Universidade José do Rosário Vellano, Brazil
E-mail: gabriela.bazuco@gmail.com
Isabela Nicoletti Merotti
ORCID: https://orcid.org/0000-0003-1416-253X
Universidade José do Rosário Vellano, Brazil
E-mail: isabela13nm@gmail.com
Julia Dayrell Beretens
ORCID: https://orcid.org/0000-0001-5193-1305
Universidade José do Rosário Vellano, Brazil
E-mail: juliaberetens@gmail.com
Simone Caetani Machado
ORCID: https://orcid.org/0000-0002-3440-7162
Universidade José do Rosário Vellano, Brazil
E-mail: simonecaetani@uol.com.br
Alessandra Cristina Pupin Silvério
ORCID: https://orcid.org/0000 -0003-2093-2713
Universidade José do Rosário Vellano, Brazil
E-mail: alessandrapupin72@gmail.com

Abstract
Autoimmune polyglandular syndromes (APSS) are associations of two or more endocrine diseases of autoimmune origin that affect between 5-10% of the population. The grouping of these diseases depends on genetic and environmental factors, their different presentations allow the distinction of the subtypes of APS. The objective is to report the case of a patient with type III A polyglandular autoimmune syndrome, characterized by Hashimoto's thyroiditis and type 1 diabetes mellitus associated with hyperprolactinemia and Gilbert's syndrome. The patient began to show the symptoms of the syndrome at the age of 10 progressively. The treatment of each disease is being carried out, with no specific treatment for the syndrome in the literature.
Keywords: Type III autoimmune polyglandular syndrome; Type 1 Diabetes Mellitus; Hashimoto's thyroiditis; Hyperprolactinemia and Gilbert's syndrome.

Resumo
As síndromes poliglandulares autoimunes (SPAS) são caracterizadas por associações de duas ou mais doenças endócrinas de origem autoimunes que coletivamente, afetam entre 5-10% da população em geral. O agrupamento dessas doenças autoimunes depende de fatores genéticos e fatores ambientais não genéticos, e suas diferentes apresentações permitem a distinção entre dois grandes subtipos de SPA. O objetivo é relatar o caso de uma paciente portadora de síndrome autoimune poliglandular do tipo III A, caracterizada por tireoidite de Hashimoto e Diabetes Mellitus tipo 1 associada a hiperprolactinemia e Síndrome de Gilbert. A paciente começou a apresentar as manifestações da síndrome com 10 anos de idade de forma progressiva. A paciente encontra-se sendo tratada para cada doença de forma separada não sendo encontrado na literatura um tratamento específico para a síndrome.
Palavras-chave: Síndrome poliglandular autoimune tipo III; Diabetes Mellitus tipo 1; Tireoidite de Hashimoto; Hiperprolactinemia e Síndrome de Gilbert.

Resumen
Los síndromes poliglandulares autoinmunes (APSS) son asociaciones de dos o más enfermedades endocrinas de origen autoinmune que afectan entre un 5-10% de la población. La agrupación de estas enfermedades depende de factores genéticos y ambientales, sus diferentes presentaciones permiten la distinción de los subtipos de SAF. El objetivo es reportar el caso de un paciente con síndrome autoinmune poliglandular tipo III A, caracterizado por tiroiditis de Hashimoto y diabetes mellitus tipo 1 asociada a hiperprolactinemia y síndrome de Gilbert. El paciente comenzó a presentar los síntomas del síndrome a los 10 años de forma progresiva. Se está realizando el tratamiento de cada enfermedad, sin que en la literatura haya un tratamiento específico para el síndrome.
Palabras clave: Síndrome poliglandular autoinmune tipo III; Diabetes mellitus tipo 1; Tiroiditis de Hashimoto; Hiperprolactinemia y Síndrome de Gilbert.

1. Introduction

It will be reported a case of a 10-years-old Brazilian patient with autoimmune polyglandular syndrome type III A with Hashimoto's thyroiditis associated with type 1 Diabetes Mellitus (DM1). She also has Gilbert's syndrome and hyperprolactinemia. Diagnosis, treatment and clinical evolution are described.

Autoimmune polyglandular syndromes (APSS) are associations of two or more endocrine diseases of autoimmune origin and their different presentations allow the distinction between APS subtypes. The juvenile APS type I of monogenetic inheritance and the adult APS in which several genes contribute to its etiopathogenesis and is subdivided into types II to IV (Borba et al., 2018). Type III is characterized by the presence of autoimmune thyroid disease (ATD) associated with other autoimmune diseases excluding the involvement of the adrenal gland. Also, APS type III is divided into 4 groups, from A to D (Brenta et al., 2013; Czyzyk & Kurzawa, 2019). The patient belongs to group A represented by the association between ATD and DM.

APSS are more prevalent in women and usually appear in middle age. It is believed that this prevalence is due to a hereditary component associated with human leukocyte antigen (HLA) class II (Brenta et al., 2013; Dittmar & Kahaly, 2010).

The main cause of hypothyroidism is Hashimoto's thyroiditis (HT), characterized by the presence of autoantibodies that attack and destroy thyroid cells leading to decreased thyroid hormone production and an increase in TSH levels. The symptoms are nonspecific. The treatment is carried out with levothyroxine (Eira et al., 2017). In this case, the patient is asymptomatic and with normal TSH levels, not using the medication as recommended by the doctor.

Diabetes manifests itself with hyperglycemia and symptoms such as polyuria, polydipsia, weight loss, polyphagia and blurred vision (Fernandes et al., 2003). Insulin therapy is the main treatment for DM1. There are other treatments like gene therapy and induced β cell regeneration that have not been widely introduced to manage diabetes (Gross et al., 2002). In this patient, after diagnosis, treatment is being carried out with insulin therapy.

Another existing endocrine comorbidity is Gilbert's Syndrome, an error in the bilirubin glucuronidation and defect in the genotype, resulting in hyperbilirubinemia. The diagnosis is made through clinical presentation, biochemistry and genotyping. In addition, hyperprolactinemia may have a psychological, pharmacological or pathogenic origin in which blood prolactin elevation occurs. Symptoms depend on the degree of elevation, the most common being galactorrhea (Hansen et al., 2015; Kahaly & Frommer, 2018).

The aim of this work is to report the case of a patient with type III A polyglandular autoimmune syndrome, characterized by Hashimoto's thyroiditis and type 1 diabetes mellitus plus hyperprolactinemia and Gilbert's syndrome.

2. Methodology

It is a case report in which the information was acquired through interview with the patient, review of the medical record, understanding of the clinical history, analysis of exames and laboratories images, recording of the diagnostic methods to

which the patient was submitted and review of literature. After data collection we employed content analysis techniques for qualitative studies. (Pereira et al, 2018).

The search for references was carried out based on SciELO and PubMed research.

3. Case Report

A 10-year-old female patient went to an endocrinologist for screening tests due to a family history of hypothyroidism in 2010. Blood tests and images were requested for thyroid analysis, the anti-TPO antibody (thyroxoxidase) and Anti-Thyroglobulin were altered in the blood 124 IU / mL and 27 IU / mL, both increased in relation to the reference values, whereas the TSH value was increased. The image report presented normal dimensions with minimal diffuse ecotextural alterations, the diagnosis of Hashimoto's thyroiditis was suggested due to the aspects; there are small bilateral images of nonspecific appearance, which may be secondary to thyroiditis. No treatment institution.

In the following two years, the imaging exams remained with the same reports, but with minor changes in larger bilateral, non-specific images that became nodes, it remained as secondary to HT.

In 2014, she sought another endocrinologist, who asked for further tests to be followed up. The blood sample brought the Anti-TPO antibody still altered, 215.00 IU / mL, however TSH and free T4 were altered. The imaging study found the same data as before, and treatment with the Puran T4 drug was instituted.

In 2014, she went through another specialist, because her sclera showed jaundice on the days she was menstruating. Bilirubin, which was altered in all forms, direct 0.9 mg / dL, indirect 1.5 mg / dL and total 2.4 mg / dL respectively. With these tests and symptoms, Gilbert's Syndrome was diagnosed.

In the following year, 2015, new tests were performed to monitor thyroiditis, the Anti-TPO antibody continued to be significantly increased and the TSH was normal, however the Anti-thyroglobulin antibody changed the value to 1 IU / mL, staying within the reference value, less than 4 IU / mL. Therefore, Puran T4 was withdrawn.

In 2017, exams for thyroiditis screaning were performed with having changes with small bilateral nodules, highlighting a small hypoechogenic nodule in the right lobe and a solid / cystic nodule in the left lobe. In the same year, prolactin was measured, due to a gynecologist noticing galactorrhea in one of the patient's breasts. A change in prolactin levels, 60.33 ng / mL, was found, elevated to the standards of 3.30 to 26.70 ng / mL. The tests were repeated three times for confirmation, diagnosing hyperprolactinemia. Resonance examination was performed and the tumor of the saddle was discarded.

At the end of February 2018, the patient reports polyuria, polyphagia and polydpsy that were persistent. In an exam done with a glucometer to measure fasting blood glucose, the value of 280 mg / dL was found, in the second measurement it was already higher than 300 mg / dL.

A new blood glucose test was performed on the same day, which resulted in 338mg / dL. She was referred to the hospital, performing urine tests, where ketones ++ / ++++, blood gas analysis did not show basic acid imbalance. Serum and insulin were instituted, with referral to an endocrinologist. Treatment with rapid insulin (Humalog) was recommended, as well as regular insulin (lantus) at a dose of 20u in the morning.

The next day, after treatment was instituted, new tests were performed. The results were glucose of 165 mg / dL, Anti GAD antibodies 162 IU / mL and Anti IA2 antibodies 2816 IU / mL, showing reagent in both and low peptide C 0.55 ng / mL. In the urine, glucose and ketones ++ / ++++ are present. Soon, the diagnosis of DM1 was confirmed. In addition, tests were performed to monitor thyroiditis, which remained the same, unchanged.

On 10/31/2018, other tests were performed to monitor with glycemia of 113 mg / dL, HbA1C 7.2%, still above the ideal 7%. Prolactin continued increased, 73.26 ng / mL, and TSH and T4 within expected levels. Glycemia targets were established

as preprandial: 120mg / dL and postprandial: 160mg / dL. The application of ultra fast insulin is done by counting carbohydrates, in which 1 IU for every 15 g of carbohydrate and 1 IU drops 50 mg / dL of glucose, in addition to the regular one that is applied in the morning with 20 IU.

4. Discussion

Polyglandular autoimmune syndromes (PAS) are defined by the coexistence of at least two autoimmune endocrinopathies (Borba et al., 2018). Autoimmune thyroid diseases and DM1 are the most common autoimmune endocrine disorders. They often occur together, as in the patient in question. This combination of diseases is called type III autoimmune polyglandular syndrome, a disorder characterized by autoimmunity in relation to the thyroid and pancreatic islet cells, two diseases that are components of autoimmune genesis, but with a distinct pathogenesis (King & Armstrong, 2019). The treatment of these autoimmune diseases consists mainly of hormone replacement, modification of endocrine function, symptomatic therapy and prevention of possible complications (Borba et al., 2018).

DM1 is an endocrine disorder with approximately 50 susceptibility genes. These genes carry a potential risk of several autoimmune diseases occurring simultaneously or within a limited time frame. They can explain to some extent why additional endocrine autoimmune diseases are comorbid in one third of patients with DM1. Associated autoimmune disorders are glandular diseases, such as Addison's disease or autoimmune thyroid disease, which lead to polyglandular autoimmune syndrome (PASS) or non-glandular autoimmune diseases, for example, rheumatoid arthritis or celiac disease. The variation of these comorbidities may be the key to understanding the pathogenesis of autoimmune diseases, but it also makes the diagnosis and treatment of DM1 difficult (Orbach & Shoenfeld, 2007).

TH is the most prevalent autoimmune disease associated with DM1 and Anti-TPO antibodies (thyroperoxidase) are present in 15 to 30% of adults and in 5 to 22% of children with DM1. Up to 50% of positive patients for Anti-TPO antibodies progress to manifestations of autoimmune thyroid disease (Orbach & Shoenfeld, 2007).

Autoimmune thyroid disease is predominantly the clinical expression of cell-mediated immunity, leading to the destruction of thyroid cells (Paknys et al., 2009). This is defined by the presence of Anti-TPO antibodies (thyroperoxidase) or Anti-thyroglobulin antibodies and high TSH concentrations in the absence of drugs. Although many individuals with HT are hypothyroid, there is a positive subgroup for thyroid autoantibodies that are euthyroid, as described in this case, in which the patient continues without changes in TSH and T4 values (Orbach & Shoenfeld, 2007).

The development of HT depends on an immunological defect in an individual with genetic susceptibility, together with environmental factors; however, the pathogenesis of the disease is not yet fully understood. Morphologically, it consists of a gradual atrophy of the thyroid tissue after the glandular invasion with lymphocytic cells. This leads to the development of hypothyroidism, although the disease can occur with normal thyroid activity (Pyzik et al., 2015).

Both autoimmune thyroid diseases as for DM1 are mediated by organ-specific T cells, in which the endocrine glands are affected by autoantibodies. In both disorders, T cell infiltration occurs with subsequent dysfunction and destruction. Autoimmune thyroid disease is oftenly combined with DM1, they occur more often together than would be expected by the prevalence of the population of each disease (Pyzik et al., 2015).

The patient in question has hyperprolactinemia, and about 90% of patients with HT have significantly higher prolactin levels associated with reduced cortisol titers (Strassburg, 2010). Data on the correlation between prolactin level and disease activity is controversial (Tan et al., 2019).

Prolactin is secreted by the pituitary gland, other organs and cells, especially lymphocytes, which have an immunostimulatory effect, promote autoimmunity and impair the negative selection of self-reactive B lymphocytes during the

maturation of B cells. Prolactin has an anti-effect -opoptotic, improves the proliferative response to antigens and mitogens and improves the production of immunoglobulins and autoantibodies (Tan et al., 2019).

Gilbert's syndrome diagnosed in the patient is a hereditary condition characterized by intermittent episodes of jaundice and mild and intermittent elevation of unconjugated (indirect) bilirubin levels, in the absence of hemolysis or abnormal liver function tests. Although elevated levels of inditerate bilirubin are generally mild, the severity can increase in the midst of physiological stress, increasing up to four times above the upper limit of normal. Fasting, sleep deprivation, alcohol consumption, dehydration, surgery and concomitant illnesses can precipitate episodes of jaundice. In general, a patient with Gilbert's Syndrome should be asymptomatic and may have a slightly jaundiced sclera, signs of precipitating factors, but it should not have hepatosplenomegaly or signs of chronic liver disease (Tavares & Kahwage, 2019).

5. Conclusion

The patient was diagnosed with Type III Polyglandular Autoimmune Syndrome because she had DM1 and HT, being treated with insulin without treatment for thyroiditis because she was asymptomatic. She was also diagnosed with hyperprolactinemia and Gilbert's syndrome, both without clinical treatment because they did not impair the functioning of the organism in the short and long term.

New research on autoimmune endocrine diseases and their correlations should be conducted, considering the high incidence of cases. It needs specific treatment for the syndrome as a whole and not only for specific pathologies. Therefore, this article is relevant to improve and continue studies that aim to increase this knowledge.

References

Borba, V. V., Zandman-Goddard, G., & Shoenfeld, Y. (2018). Prolactin and autoimmunity. *Frontiers in Immunology*, *9*(FEB), 1–8. https://doi.org/10.3389/fimmu.2018.00073

Brenta, G., Vaisman, M., Sgarbi, J. A., Bergoglio, L. M., de Andrada, N. C., Bravo, P. P., Orlandi, A. M., & Graf, H. (2013). Diretrizes clínicas práticas para o manejo do hipotiroidismo. *Arquivos Brasileiros de Endocrinologia e Metabologia*, *57*(4), 265–298. https://doi.org/10.1590/S0004-27302013000400003

Czyzyk, A., & Kurzawa, R. (2019). Hyperprolactinemia associated with macroprolactinoma in a 17-year-old: A case report. *Case Reports in Women's Health*, *22*, e00111. https://doi.org/10.1016/j.crwh.2019.e00111

Dittmar, M., & Kahaly, G. J. (2010). Genetics of the autoimmune polyglandular syndrome type 3 variant. *Thyroid : Official Journal of the American Thyroid Association*, *20*(7), 737–743. https://doi.org/10.1089/thy.2010.1639

Eira, C., Mota, Â., Silvério, R., Monteiro, R., Bastos, M., & Monteiro, A. (2017). Caso Clínico Síndrome Poliglandular Autoimune Tipo III. *Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo*, *12*(2), 200–205.

Fernandes, A. P. M., Maciel, L. M. Z., Foss, M. C., & Donadi, E. A. (2003). Como entender a associação entre o sistema HLA e as doenças auto-imunes endócrinas. *Arquivos Brasileiros de Endocrinologia & Metabologia*, *47*(5), 601–611. https://doi.org/10.1590/s0004-27302003000500015

Gross, J. L., Silveiro, S. P., Camargo, J. L., Reichelt, A. J., & Azevedo, M. J. de. (2002). Diabetes Melito: Diagnóstico, Classificação e Avaliação do Controle Glicêmico. *Arquivos Brasileiros de Endocrinologia & Metabologia*, *46*(1), 16–26. https://doi.org/10.1590/s0004-27302002000100004

Hansen, M. P., Matheis, N., & Kahaly, G. J. (2015). Type 1 diabetes and polyglandular autoimmune syndrome: A review. *World Journal of Diabetes*, *6*(1), 67–79. https://doi.org/10.4239/wjd.v6.i1.67

Kahaly, G. J., & Frommer, L. (2018). Polyglandular autoimmune syndromes. *Journal of Endocrinological Investigation*, *41*(1), 91–98. https://doi.org/10.1007/s40618-017-0740-9

King, D., & Armstrong, M. J. (2019). Overview of Gilbert's syndrome. *Drug and Therapeutics Bulletin*, *57*(2), 27–31. https://doi.org/10.1136/dtb.2018.000028

Orbach, H., & Shoenfeld, Y. (2007). Hyperprolactinemia and autoimmune diseases. *Autoimmunity Reviews*, *6*(8), 537–542. https://doi.org/10.1016/j.autrev.2006.10.005

Paknys, G., Kondrotas, A. J., & Kėvelaitis, E. (2009). Hašimoto tiroidito rizikos veiksniai ir patogenezė. *Medicina (Kaunas)*, *45*(7), 574–583. https://doi.org/10.3390/medicina45070076

Pereira, A. S., Shitsuka, D. M., Shitsuka, R., & Parreira, F. J. (2018). Metodologia da pesquisa científica. Universidade Federal de Santa Maria, 1, 70 – 72.

Pyzik, A., Grywalska, E., Matyjaszek-Matuszek, B., & Roliński, J. (2015). Immune disorders in Hashimoto's thyroiditis: What do we know so far? *Journal of*

Immunology Research, *2015*. https://doi.org/10.1155/2015/979167

Strassburg, C. P. (2010). Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). *Best Practice and Research: Clinical Gastroenterology*, *24*(5), 555–571. https://doi.org/10.1016/j.bpg.2010.07.007

Tan, S. Y., Mei Wong, J. L., Sim, Y. J., Wong, S. S., Mohamed Elhassan, S. A., Tan, S. H., Ling Lim, G. P., Rong Tay, N. W., Annan, N. C., Bhattamisra, S. Candasamy, M. (2019). Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, *13*(1), 364–372. https://doi.org/10.1016/j.dsx.2018.10.008

Tavares, J. V., & Kahwage, A. M. (2019). Síndrome poliglandular autoimune tipo III: uma rara associação entre doença de graves, vitiligo e miastenia gravis. *Revista Eletrônica Acervo Saúde*, *11*(5), e245. https://doi.org/10.25248/reas.e245.2019