PAS the Salt: *A Case of Autoimmune Polyglandular Syndrome Type II*

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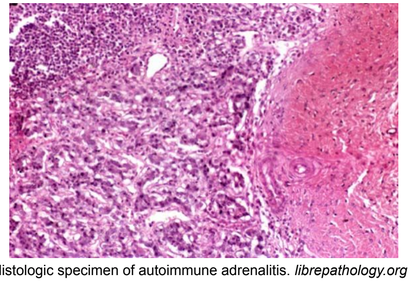
CASE SUMMARY

Here we present the case of a 71-year-old female with a decades-long history of Hashimoto thyroiditis and vitiligo who developed Addison Disease. Routine labs showed serum sodium (Na) of 124, and the patient reported fatigue and lightheadedness on follow-up with her primary care doctor. Despite discontinuation of HCTZ taken for hypertension, subsequent labs showed Na of 112, so she was sent to the ED and found to have hypoosmolar hyponatremia consistent with SIADH. Fluid restriction, saline infusion, and later NaCl tablets failed to improve Na two days after admission. Further investigation revealed low morning cortisol that did not respond to ACTH stimulation, demonstrating adrenal insufficiency. Later workup revealed elevated serum ACTH and positive anti-21-hydroxylase antibodies consistent with autoimmune adrenalitis; this, coupled with Hashimoto thyroiditis, also brings a diagnosis of Autoimmune Polyglandular Syndrome type 2.



Histologic specimen of autoimmune adrenalitis. *librepathology.org*

PAS: DEFINITION

- Autoimmune Polyglandular Syndromes (PAS) are a diverse group of disorders defined by the presence of two or more autoimmune endocrinopathies.
- PAS-II is defined as Addison Disease (AD) plus either type 1 diabetes mellitus (T1DM) or autoimmune thyroid disease (AITD).
- Patients may also exhibit other autoimmune conditions such as:
  - Pernicious anemia
  - Premature ovarian failure
  - Alopecia
  - Vitiligo
  - Celiac disease
  - Inflammatory bowel disease
  - Autoimmune hepatitis
  - Hemolytic anemia
  - Myasthenia gravis, or
  - Multiple sclerosis
- Some controversy of definition exists in the literature, but the above shares the most consensus.

PAS: EPIDEMIOLOGY, PATHOLOGY, MANAGEMENT

How common is PAS-II?

- The estimated prevalence of PAS-II is 1.4-2.0 per 100,000.
- PAS-II is more likely to occur in women, with a female-male ratio of 2-3.7. (Betterle)
- Due to time elapsed between diagnoses of endocrinopathies, the prevalence of incomplete, subclinical forms of adult PAS types (II-IV) is estimated to be 150 per 100,000. (Kahaly).

Why does PAS occur?

- The etiology of PAS is multifactorial; there is a hereditary component, but genes are not the sole determinants of disease state (Kahaly).
- Often PAS-II follows a pattern of autosomal dominant inheritance with incomplete penetrance. (Betterle)
- PAS-II is strongly associated with HLA polymorphisms, specifically in haplotypes with DR3/DQ2, DR4/DQ8, or DRB1*0404. (Pham-Dobor)
- There is limited evidence linking PAS-II to specific environmental risk factors, but proposed factors include infections (e.g., rubella), nicotine use, and hormonal influence. (Kahaly)

How is PAS-II diagnosed and treated?

- PAS-II is usually recognized upon diagnosis of the endocrinopathy by which a patient fulfills the definition of the syndrome, e.g., a patient with T1DM who later develops autoimmune adrenalitis by definition has PAS-II.
- Screening for concomitant endocrine insufficiencies in patients with preexisting endocrine disease, via clinical symptoms or serological testing, can identify early stages of disease. For example, a patient with T1DM or AITD who has 21-hydroxylase antibodies but not adrenal insufficiency is considered to have potential or subclinical PAS-II. (Betterle)
- However, in the absence of clinical symptoms or suggestive family history, serological screening for AD in patients with T1DM or AITD is controversial due to the low prevalence of AD in patients with T1DM or AITD. (Graves)
- Treatment of PAS-II is accomplished via management of the endocrinopathies it comprises, e.g., glucocorticoid replacement for AD, insulin replacement for T1DM, thyroid hormone replacement for AITD, gluten-free diet for celiac, AChE inhibitors for MG, &c.

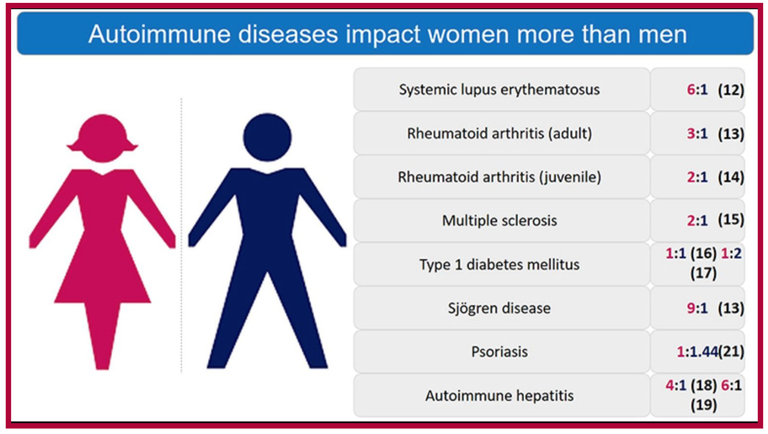


Figure 1: Sex differences in prevalence ratio of autoimmune diseases
Desai, M. K., & Brinton, R. D. (2019). Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan. *Frontiers in Endocrinology, 10.* https://doi.org/10.3389/fendo.2019.00265

CLINICAL SIGNIFICANCE

Autoimmune diseases disproportionately affect women

- Women account for 78% of patients with autoimmune disease.
- Among patients with autoimmune disease, women are at increased risk of developing multiple autoimmune diseases, accounting for 85% or more of such patients. (Desai)

Autoimmune diseases cause substantial harms.

- They encompass debilitating diseases that pose harms ranging from the inconvenience of taking daily medications to acute, life-threatening states such as the adrenal crisis seen in this patient.
- Patients with multiple autoimmune diseases incur the cumulative harms from their discrete conditions plus the synergistic effect of suffering multiple chronic illnesses.
- Having one or more chronic diseases may worsen quality of life via psychological stress, impaired ability to pursue employment or recreation, and the financial burden of costly lifelong treatments. (Desai)

Early identification of autoimmune disease can reduce morbidity and mortality.

- In autoimmune adrenalitis, the production of anti-21-hydroxylase antibodies may precede symptom onset by years to decades, so disease may be recognized long before symptoms appear.
- The early symptoms of adrenal insufficiency may be subtle, nonspecific, and insidious, e.g., fatigue, weakness, GI upset, and weight loss, gradually worsening over several years.
- Compared to patients with known and treated disease, those with undiagnosed adrenal insufficiency are at increased risk of life-threatening adrenal crisis and death. (Michels)

Patients with monoglandular AI endocrinopathies should be screened for concomitant AI disorders soon after the initial diagnosis and throughout their lives.

- Particularly those with a family history of polyendocrinopathy, due to the genetic component of PAS.
- Particularly women, due to the increased prevalence of PAS among women and the increased prevalence of polyendocrinopathy in general among women.
- Despite the associated costs, screening guidelines ought to account for family histories and sex differences in the prevalence of polyendocrinopathies.

CONCLUSION

This case is intended to exemplify how the disproportionate representation of women among patients with autoimmune disease should shape recommendations for serological screening for concomitant disease in women with preexisting autoimmune conditions, which can result in earlier detection and thereby reduce overall disease burden and curb acute severe disease manifestations.

REFERENCES

- Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocrine reviews. 2002 Jun 1;23(3):327-64.
- Desai MK, Brinton RD. Autoimmune disease in women: endocrine transition and risk across the lifespan. Frontiers in endocrinology. 2019 Apr 29;10:265.
- Graves III L, Klein RM, Walling AD. Addisonian crisis precipitated by thyroxine therapy: a complication of type 2 autoimmune polyglandular syndrome. Southern medical journal. 2003 Aug 1;96(8):824-8.
- Kahaly GJ, Frommer L. Polyglandular autoimmune syndromes. Journal of endocrinological investigation. 2018 Jan;41(1):91-8.
- Michels A, Michels N. Addison disease: early detection and treatment principles. American family physician. 2014 Apr 1;89(7):563-8.
- Pham-Dobor G, Hanák L, Hegyi P, Márta K, Párniczky A, Gergics M, Sarlós P, Erőss B, Mezősi E. Prevalence of other autoimmune diseases in polyglandular autoimmune syndromes type II and III. Journal of endocrinological investigation. 2020 Sep;43(9):1-9.