



Case Report

# An Unusual Case of Polyautoimmunity with Concomitant Presentation of Postural Tachycardia Syndrome, Antiphospholipid Syndrome and Hashimoto's Thyroiditis

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**Abstract:** Introduction: Postural tachycardia syndrome (POTS) is a chronic form of autonomic dysfunction characterized by symptoms of orthostatic intolerance, often accompanied by sudomotor dysfunction and gastrointestinal dysmotility. In a subgroup of patients with POTS, autoantibodies against adrenergic or cholinergic receptors suggest an immune-mediated etiology. Antiphospholipid syndrome (APS) is a hypercoagulative autoimmune disorder associated with anti-phospholipid-antibodies that causes arterial and venous thromboses. Concurrent occurrence of APS and immune-mediated POTS is rare. Methods and Results: Here, we report a 28-year-old female that experiences symptoms of orthostatic intolerance, vasovagal syncope, gastrointestinal dysmotility and sudomotor dysfunction. She fulfills the formal diagnostic criteria of POTS showing a heart rate increment of  $\geq 30$  beats per minute (bpm) within 10 m of head-up tilt in the absence of orthostatic hypotension, accompanied by symptoms of orthostatic intolerance. The thermoregulatory sweat test reveals severe patchy anhidrotic areas. Gastric emptying scintigraphy shows an impaired gastrointestinal motility. Plasma norepinephrine levels and a skin biopsy appear normal. Finally, serological persistence of anti-alpha-1-adrenergic autoantibodies suggest an immune-mediated pathogenesis. Several years after initial presentation of POTS symptoms, the patient develops APS with recurrent venous emboli and persistent anti-phospholipid-antibodies. Recently the patient is diagnosed with Hashimoto's thyroiditis (HT) expressing high levels of thyroid-stimulating hormone and high titers of anti-thyroid antibodies. Conclusion: To our knowledge, this is the first report of consecutive immune-mediated POTS, APS and HT in a young woman, possibly displaying a unique combination of three disorders of autoimmune etiology.

**Keywords:** polyautoimmunity; postural tachycardia syndrome; antiphospholipid syndrome; Hashimoto's thyroiditis; autoimmune thyroid disease; autoimmune cluster; case report



**Citation:** Edwards, E.; Z'Graggen, W.; Bassetti, C. An Unusual Case of Polyautoimmunity with Concomitant Presentation of Postural Tachycardia Syndrome, Antiphospholipid Syndrome and Hashimoto's Thyroiditis. *Clin. Transl. Neurosci.* **2021**, *5*, 20. <https://doi.org/10.3390/ctn5030020>

Academic Editor:  
Dominik Straumann

Received: 21 September 2021

Accepted: 26 October 2021

Published: 29 October 2021

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## 1. Introduction

The term polyautoimmunity was first used in the literature by Sheehan and Staton-King [1]. It is defined as the presence of two or more autoimmune diseases within an individual [2]. In a cohort of different autoimmune diseases, polyautoimmunity was observed in 34% of cases and seemed to follow a cluster-like pattern [3]. The recognition of polyautoimmunity seems relevant in both prognosis and treatment decision [4]. Here, we describe a young woman with a possibly new and unique combination of three disorders of suspected autoimmune etiology.

## 2. Case

A 28-year-old woman originating from the Balkan area was referred to our outpatient unit for further evaluation of a tachycardia, severe orthostatic intolerance as well as heat

intolerance. The symptoms had started gradually 3 years ago. There was no documentation of an infection preceding symptom manifestation. The family history revealed that her brother suffered from an unknown kidney disease that necessitated a kidney transplant. Her grandfather had a cardioverter-defibrillator implanted; however, the underlying disease could not be further determined. The family history regarding autoimmune diseases was inconclusive. Her past medical history had been otherwise unremarkable. She works as manager of her own beauty salon.

### 2.1. Postural Tachycardia Syndrome

The young woman complained of experiencing symptoms of orthostatic intolerance such as lightheadedness, palpitations, tremulousness, blurred vision, headaches and brain fog upon standing. Recurring vaso-vagal syncope and presyncope were also reported. Furthermore, non-orthostatic symptoms such as nausea after food consumption and heat intolerance interfered with daily life activities, causing persistent suffering. The patient rated her limitations as 8–10/10 on the visual analogue scale.

Diagnosis of neuropathic POTS was established according to published criteria. Both repeated Schellong tests as well as tilt table test revealed a pathologic excessive tachycardia while standing with a heart rate increase of >30 beats/min (53 m to 121 m) within 10 m accompanied by clinical complaints of orthostatic intolerance that were typical for the patient. Blood pressure regulation was normal while standing without signs of orthostatic hypotension. The thermoregulatory sweat test revealed severe patchy anhidrotic areas upon visual analysis with an indicator substance. Gastric emptying scintigraphy showed markedly impaired gastrointestinal motility. Duodenal biopsies did not show histopathological alterations. Supine plasma epinephrine and norepinephrine levels appeared normal. A skin biopsy did not show signs of a small fiber neuropathy or other alterations. Finally, serologic screening for anti-alpha-1 and 2 adrenergic auto-antibodies (AAbs) and anti-muscarinic-cholinergic AAbs subtype M1-5 revealed elevated anti-alpha-1-adrenergic AAbs suggesting an immune-mediated pathogenesis. A further extensive serologic screening including hormonal, infectious, rheumatologic and vitamin-deficiency causes of neuropathy appeared normal in the initial diagnostics.

Treatment with fludrocortisone 0.1 mg 3-0-0 and midodrine 2.5 mg 5/day led to sufficient and persistent symptom control in particular regarding the orthostatic symptoms. Supportive therapy consisted in recommendation of compression stockings, increase of salt intake up to 9 g/d as well as fluid intake of 2–3 L/d. The patient furthermore practiced regular aerobic training with sufficient breaks and cold showers and followed a regular sleep schedule. Her subjective rating improved to 2/10 on the visual analogue scale, allowing an almost unimpaired daily life.

### 2.2. Antiphospholipid Syndrome

Three years into the first symptoms of the POTS two consecutive syncope on one day, accompanied by chest pain and difficulty of breathing led to the diagnosis of a right paracentral pulmonary embolism confirmed in a chest MRI. There were no provoking factors such as hormonal contraception, smoking, prolonged resting or dehydration. Furthermore, the patient had never suffered from venous or arterial thromboses or miscarriage. The family history was unremarkable for thromboembolic events and two sisters had had uncomplicated pregnancies. Further examination did not provoke suspicion of a rheumatologic disease on clinical or serologic bases. A tumor screening was negative, both regarding serology and imaging with abdominal and chest CT as well as a gynecological examination. However, the patient showed persistently elevated levels of anti-cardiolipin AAbs as well as anti-beta2-glycoprotein AAbs (both >20 CU) leading to the diagnosis of APS. FVIII-activity was elevated to 265%. Genetic analysis for prothrombin and Factor V Leiden were normal.

Following the EULAR-criteria for long-term prophylaxis of APS a recommended treatment with phenprocoumon 15 mg/d was initiated. However, we could not succeed

to establish therapeutic levels for the international normalized ratio, even after increasing dosage and switching to acenocoumarol. VKORC1 gene was not mutated. Presuming disturbed gastrointestinal drug absorption due to the severe gastroparesis, a subsequent change to subcutaneous treatment with fondaparinux 7.5 mg/d was needed to achieve therapeutic anti-Xa levels.

### 2.3. Autoimmune Thyroid Disease

Recently, five years into the first symptoms of the POTS, the patient gave reason to suspicion of an autoimmune thyroid disease (AITD) expressing high levels of thyroid-stimulating hormone (5.7 mU/L) on a routine examination, while free triiodothyronin and free thyroxin levels were in the normal range. This led to the discovery of very high titers of anti-thyroid antibodies, namely anti-thyroglobulin- (89 U/mL) and anti-thyroperoxidase-AAbs (2739 U/mL). Notably, thyroid hormones had been measured repeatedly both at first manifestation of POTS symptoms as well as routinely throughout the disease course and only recently appeared as pathologic. Finally, sonography revealed a slightly inhomogeneous and hypoechoic thyroidal parenchyma, which led to the diagnosis of Hashimoto's thyroiditis (HT). Interestingly, three months after the first measurement of elevated thyroid-stimulating hormone, levels dropped to normal (2.4 mU/L) without specific intervention. Clinically the patient does not expose any new symptoms since the diagnosis of AITD 6 months ago. Seeing the stable clinically state, annual controls of thyroid autoantibodies and hormone levels are recommended.

## 3. Discussion

Over a 5-year period this young woman developed successively three diseases of autoimmune origin, revealing a unique combination of polyautoimmunity. According to a metaanalysis of polyautoimmunity in 1083 patients with autoimmune diseases, APS and AITD seemed to represent a possible distinct cluster of autoimmunity [3]. That cluster could also include Systemic Lupus Erythematosus and Sjögren's syndrome. Immune-mediated POTS as manifested initially in our patient has not yet been reported amongst this polyautoimmunity combination pattern.

The recognition of polyautoimmunity seems relevant for both prognosis and treatment decision. 4. For example, patients with both Systemic Lupus Erythematosus and APS follow a more severe disease course [5]. In contrast in other autoimmune diseases polyautoimmunity seems to have no influence or even a better prognosis [6,7]. For example, myasthenia gravis associated with autoimmune thyroid diseases displayed a milder clinical manifestation and disease course [6]. HLA polymorphisms and common triggering environmental factors such as viral infections and molecular mimicry in predisposed subjects are thought to constitute a multifactorial etiopathogenesis, called the autoimmune tautology [2]. An association between polymorphisms in HLA-DRB1 and -DQA1 alleles (DRB1 \* 04, DRB1 \* 07, DRB1 \* 1302, DQA1 \* 0102, DQA1 \* 0201, DQA1 \* 0301, DQB1 \* 0302 and DQB1 \* 0604) with anti-cardiolipin -AAbs has been demonstrated in APS [8]. HLA DQA1 and DQB1 polymorphisms (HLA-DQA1 \* 0201, DQA1 \* 0301, DQB1 \* 0201) are involved in the susceptibility for AITD [9]. Finally, a prominent DQB1 \* 06:09 association was present in patients with autoimmune origin of POTS [10]. In our patient the HLA phenotype could not be established due to cost restrictions imposed by the health insurance, however the literature suggests that some overlapping HLA polymorphisms may exist between these diseases.

In our case, symptoms of POTS preceded the first manifestation of APS with a pulmonary embolism by about three years and the manifestation of HT by five years. The autonomic symptoms improved markedly with symptomatic treatment with midodrine and fludrocortisone as well as supportive lifestyle modifications, allowing the patient to follow a normal life again. The oral treatment of the APS was switched to a subcutaneous application due to subtherapeutic plasma anti-Xa levels probably as a result of reduced drug absorption due to gastroparesis. The diagnosis of HT followed a routine thyroid-

stimulating hormone test and sonography and was not triggered by any new clinical symptoms suggesting a thyroid disease. Interestingly, currently the patient regained an euthyroid state without specific therapeutic intervention and remains clinically stable. Annual autoantibody as well as hormonal laboratory is recommended.

Larger studies are needed to understand a possible common etiopathogenesis, HLA-associations, prognosis and the best tailored treatment options.

#### 4. Conclusions

In summary, the coexistence of autoimmune POTS, APS and AITD could be a novel cluster pattern of polyautoimmunity. Considering to screen for the respective autoimmune conditions early on and regularly, could help uncover subclinical disease, trigger preemptive therapy and prevent potentially life-threatening complications.

**Author Contributions:** Conceptualization, E.E.; writing—original draft preparation, E.E.; writing—review and editing, W.Z.; supervision, C.B.; All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Written informed consent was obtained from the patient. According to the guidelines of the Ethics Committee of the Canton Bern, no separate ethical approval for case reports is necessary if the patient has given informed consent. No animals and no further human data or tissues were studied.

**Informed Consent Statement:** Written informed consent has been obtained from the patient to publish this paper.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of the research participant.

**Conflicts of Interest:** The authors declare no conflict of interest.

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