

Hashimoto's
thyroiditisCeliac
disease

Polyautoimmunity

The role of general practitioners in identifying and managing polyautoimmunity

A guide to identifying, testing and referring patients with overlapping autoimmune diseases so they reach symptom relief faster

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Summary

Autoimmune diseases are complex enough on their own, but when multiple autoimmune diseases coexist—referred to as polyautoimmunity—the challenges multiply, both for patients and their physicians. For patients, symptoms overlap and intensify, and the road to diagnosis often feels endless. For general practitioners (GPs), the stakes are high: early detection and coordinated management can transform lives by reducing diagnostic delays and preventing the progression of the disease. You are the first line of defense for your patients and an ally in early detection of these diseases.

As the prevalence of autoimmune diseases rises globally,¹⁻³ so does the need for GPs to recognize the unique patterns of polyautoimmunity. This manuscript is designed to support you in identifying, testing, referring and treating (according to specialists' guidance) these cases with confidence and clarity—ensuring patients receive timely, effective care.

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What is polyautoimmunity?

Polyautoimmunity refers to the presence of more than one autoimmune disease in a single patient.⁴ Unlike isolated autoimmune diseases, polyautoimmunity presents unique challenges in diagnosis due to the overlapping symptomatology of co-occurring diseases.⁵

Research indicates that polyautoimmunity is more common among certain populations, with contributing factors that include:



Gender

Higher prevalence in females.⁶



Family history

A history of autoimmunity in immediate family members significantly raises the risk.⁶⁻⁸



Genetic predisposition

Specific genetic markers or predispositions are often associated with a higher likelihood of developing multiple autoimmune conditions.⁸



How prevalent is polyautoimmunity?

Autoimmune diseases are increasingly observed to co-occur, with approximately **25% of patients diagnosed with one autoimmune disease** developing additional autoimmune conditions over time.⁹

Rising worldwide burden: The incidence and prevalence of polyautoimmunity is part of a broader increase in autoimmune diseases globally.¹⁻³ This trend is linked to a range of **environmental and lifestyle factors**:¹⁰

Dietary changes and xenobiotics:

Shifts in food sources and exposure to foreign substances in food.

Air pollution and climate change:

Environmental stressors believed to impact immune system function.

Infections and lifestyle stressors:

Increased stress, combined with infections and other lifestyle factors, appears to increase autoimmune susceptibility.

Isolated vs. combined autoimmunity: While many autoimmune diseases are not very common, they tend to cluster, with patients often developing more than one.⁹ **GPs play a vital role** in this context:

By recognizing early signs and symptoms of potential polyautoimmunity, GPs can initiate timely diagnostic testing and make qualified referrals.¹¹

By providing essential ongoing management and referrals for follow-up care, GPs help ensure that patients receive coordinated treatment across specialties.^{11,12}



Does polyautoimmunity change patient management?

Polyautoimmunity introduces unique challenges to patient care, requiring a tailored approach to managing multiple, overlapping autoimmune diseases.⁵

Differential approach and tailored treatment plans:

For patients with polyautoimmunity, individualized care plans are essential. Because coexisting autoimmune diseases can interact, intensifying symptoms or altering disease progression, a one-size-fits-all approach is typically insufficient. GPs may need to work with specialists to adjust medications and coordinate multidisciplinary care.^{5,11}

The need for additional clinical trials:

Further research is needed to develop standardized protocols for managing polyautoimmunity. Clinical trials can play a crucial role in establishing optimized care pathways, identifying best practices for managing multiple autoimmune conditions and providing evidence-based guidance on effective combination treatments.

Proactive monitoring and adaptability:

Proactive monitoring and adaptable care are essential. Regular assessments of disease progression, symptom changes and treatment efficacy can help physicians make timely adjustments, reducing the risk of serious disease progression and improving long-term outcomes for patients.^{5,11,12}

Patient impact and the role general practitioners play in polyautoimmunity

Polyautoimmunity presents unique challenges for patients and their physicians. For patients, the presence of multiple autoimmune diseases often means an increased physical burden, compounded by emotional and psychological strain. For GPs, understanding these impacts is essential to providing comprehensive and compassionate care.

Mental health effects of autoimmune diseases

Autoimmune diseases can profoundly impact patients' lives, often leading to prolonged periods of uncertainty and psychological distress. Studies show that delays in diagnosis not only worsen physical symptoms but also contribute to significant mental health challenges, such as anxiety, depression and mistrust in the healthcare system.¹³⁻¹⁵

“The [message] that probably did the most detriment to me as a human was ‘but you look fine.’ Because of that sentence... I would push through and completely stopped listening to my body... I would tend to overexert myself to the point of exhaustion or illness... trying to prove to everyone that I can do it.”

— 27-year-old patient with rheumatoid and psoriatic arthritis¹⁴

“I was told that I was addicted to drama... that because I worked a lot, I brought this onto myself through stress... I gave up expressing how bad I felt and replaced it with the lie everyone loves so much: ‘I’m fine.’”

— 29-year-old patient with celiac disease¹⁴

The GP’s role in early intervention, empathy and referrals

As primary care providers, GPs are often the first point of contact for patients experiencing symptoms of autoimmune diseases. Their role is critical in **early identification, intervention and referral**, which can significantly improve patient outcomes.¹¹ An article from 2023 stated that on average, patients see four doctors over four years before receiving an accurate diagnosis of an autoimmune condition.¹⁴

Timely referrals and intervention:

Delayed diagnosis can lead to severe complications, irreversible damage and prolonged patient suffering. GPs can mitigate these risks by identifying early warning signs, offering empathetic care and making timely referrals to specialists.^{11,13-15}

Challenges of misdiagnosis:

Patients are sometimes labeled as “chronic complainers” or have their symptoms dismissed, contributing to diagnostic delays. Proactive and compassionate care by GPs can help counter these biases, ensuring that patients receive a timely, accurate diagnosis and appropriate treatment.¹⁴

Polyautoimmunity awareness: A critical tool for general practitioners

Awareness of polyautoimmunity provides GPs with a unique opportunity to make a meaningful difference in patient care. By recognizing symptom overlaps and utilizing appropriate diagnostic tools, GPs can reduce diagnosis delays, provide patients with answers and enhance outcomes through qualified referrals.

Examples of autoimmune diseases in polyautoimmunity:¹⁶

- Autoimmune thyroid diseases (AITDs): Graves' disease, Hashimoto's thyroiditis
- Celiac disease (CeD)
- Connective tissue diseases (CTDs): Sjögren's syndrome, systemic lupus erythematosus (SLE)
- Inflammatory bowel diseases (IBDs): Crohn's disease (CD), ulcerative colitis (UC)
- Pernicious anemia
- Psoriasis
- Rheumatoid arthritis (RA)
- Type 1 diabetes mellitus (T1DM)

Classification of autoimmune diseases:¹⁷

- **Organ-specific:** Includes conditions that target a specific organ, such as AITDs and T1DM
- **Systemic:** Includes conditions that affect multiple areas and organs, such as SLE and RA

Diagnostic testing: Helping prevent delayed diagnosis

Recognizing symptoms early allows GPs to select appropriate diagnostic algorithms, including specific tools such as autoantibody tests, to investigate for suspected autoimmune diseases and support secondary care specialists in identifying polyautoimmunity.¹¹ There is no single test for polyautoimmunity; instead, patient history, symptoms and diagnostic tests for specific autoimmune diseases are important in forming a comprehensive diagnosis.¹²

With early testing, GPs can help reduce delays in diagnosis and early intervention can prevent serious complications and improve patients' quality of life.



Preventative impact of early diagnosis and intervention in autoimmune diseases

Examples include:

Autoimmune thyroid diseases: Reduced likelihood of severe secondary conditions, improving patient outcomes. ¹⁸	Celiac disease: Reduced risk of malnutrition and osteoporosis. ¹⁹
Inflammatory bowel diseases: Lower rates of hospitalization and surgery by preventing severe bowel damage. ²⁰	Systemic lupus erythematosus: Prevention of accelerated accumulation of damage, fatigue and increased mortality. ¹⁵

For patients with polyautoimmunity, overlapping symptoms often complicate diagnosis and delay appropriate treatment. Recognizing these symptoms and understanding common overlaps enable GPs to select relevant diagnostic tests, guide patients to symptom relief and provide timely referrals.

Examples of common autoimmune diseases, their symptoms and overlapping conditions:

Autoimmune disease	Symptoms	Common comorbidities
Autoimmune thyroid diseases (AITDs)	Fatigue, weight changes, mood disturbances ¹⁶	Celiac disease, pernicious anemia, rheumatoid arthritis, type 1 diabetes mellitus, vitiligo ²¹
Celiac disease (CeD)	Gastrointestinal issues (diarrhea, bloating), anemia, dermatitis herpetiformis, fatigue ¹⁶	Autoimmune thyroid diseases, Sjögren's syndrome, type 1 diabetes mellitus, inflammatory bowel diseases ¹⁹
Connective tissue diseases (CTDs)	Joint pain, skin rashes, organ dysfunction, fatigue ¹⁶	Antiphospholipid syndrome, autoimmune liver diseases, autoimmune thyroid diseases, rheumatoid arthritis ¹²
Inflammatory bowel diseases (IBDs)	Abdominal pain, diarrhea, weight loss, fatigue ²⁰	Autoimmune hepatitis, celiac disease, type 1 diabetes mellitus, psoriasis ²²

The big picture: Symptom overlap analysis

AITD and CeD: Frequently co-occur with T1DM and present similar symptoms, such as fatigue and gastrointestinal issues. ^{16,21}	IBD and CeD: Diarrhea, abdominal pain and extraintestinal manifestations like iron-deficiency anemia, short stature or osteoporosis. ²³	SLE and RA: SLE and RA symptoms often overlap, with joint pain and organ-related symptoms being common across these conditions. ¹⁶
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Case study: Levothyroxine malabsorption and undiagnosed celiac disease in a patient with Hashimoto's thyroiditis²⁴

This case highlights the challenge of diagnosing **celiac disease** in patients with **autoimmune thyroid disease**, specifically **Hashimoto's thyroiditis**. Levothyroxine malabsorption, as seen in this patient, is a commonly unrecognized symptom of underlying celiac disease.

Patient history and background

Patient demographics: 33-year-old female

Anamnesis: Unintentional weight loss, diffuse hair loss and poor appetite persisting over eight months

Medical history: Diagnosed with Hashimoto's thyroiditis

Lab findings and interpretations:

Test	Results	Interpretations
Hemoglobin (Hb)	9.4 mg/dl	Anemia
Mean corpuscular volume (MCV)	71.12 fl	Low, indicating microcytosis
Thyroid-stimulating hormone (TSH)	80 μ IU/l	Elevated (normal range: 0.34–5.6)
Free T4 (FT4)	0.12 ng/dl	Low (normal range: 0.58–1.64)
Free T3 (FT3)	0.23 ng/dl	Low (normal range: 2.5–3.9)
Anti-thyroid peroxidase (anti-TPO) antibody	Elevated	Confirms autoimmune thyroiditis
Iron profile	Iron-deficiency anemia	

Treatment history and challenges

Medication initiation: Started on 25 μ g of thyroxin and oral iron supplements, initially improving anemia.

Increasing levothyroxine requirements: Despite medication compliance, her TSH levels rose consistently, peaking at 400 μ IU/l. The levothyroxine dose was gradually increased from 25 μ g to 250 μ g with no significant improvement.

Medication adherence and symptom assessment

Compliance: Review confirmed high adherence to prescribed medication regimen.

Additional symptoms: The patient denied fever, cough, vomiting, loose stools or abdominal pain. Physical exam showed she was thin, without signs of edema, clubbing or lymphadenopathy. Thyroid examination was unremarkable.

Medical records review: Reported a history of joint pain, an indicator that may suggest underlying autoimmunity.

Further diagnostic testing and results

Testing ordered: Given her autoimmune profile and lack of response to increased thyroxine doses, a **celiac disease panel** was ordered.

Results: Positive for **IgA anti-tissue transglutaminase (tTG) antibodies**, indicative of celiac disease. Upper endoscopy and biopsy showed crypt hyperplasia and villous atrophy, confirming celiac disease.

Patient management plan

Dietary intervention: Patient was advised to adopt a strict gluten-free diet to address celiac disease.

Outcome:

Follow-up results: Marked improvement was observed on a gluten-free diet. Hemoglobin increased to 11.5 mg/dl, and her levothyroxine dose was gradually reduced from 250 µg to 25 µg.

Final TSH levels: Stabilized at 5.4 µIU/l at the last follow-up, indicating improved thyroid function.

Conclusion

This case demonstrates the presence of a coexisting gastrointestinal autoimmune disease, particularly **celiac disease**, in a patient with autoimmune thyroid dysfunction. Studies suggest a strong association between celiac disease and Hashimoto's thyroiditis. **Levothyroxine malabsorption** may be an early, silent indicator of celiac disease in such patients.

Clinical implication: **Celiac disease should be considered** in cases of increased T4 requirements and levothyroxine malabsorption, particularly when symptoms suggest gastrointestinal involvement.

About celiac disease

Celiac disease is a **permanent intolerance to dietary gluten**, causing mucosal damage in the proximal small intestine. Characterized by inflammation, crypt hyperplasia and villous atrophy, these effects can regress when gluten is removed from the diet.²⁵

Considerations in managing polyautoimmunity

Managing polyautoimmunity requires a nuanced approach, as each patient's journey with overlapping autoimmune diseases can vary widely. Among the complexities of polyautoimmunity management is understanding its impact on the severity of coexisting conditions.

Impact on disease severity

Research on polyautoimmunity's impact varies. Some studies suggest it can **exacerbate autoimmune disease severity**, leading to more complex and aggressive symptoms, while others find that it may have no substantial effect on outcomes. This variability highlights the need for individualized patient care and proactive management.⁵



Diagnostic nuances and strategic testing

Effective management of polyautoimmunity requires understanding symptom overlaps and careful selection of diagnostic tests. While autoantibody testing is essential, improper test ordering can increase costs, delay diagnosis and can be misleading.²⁶ To ensure efficient testing, general practitioners should collaborate closely with their laboratory partners and consider these key questions:

What testing options are available?

Identifying appropriate tests for specific symptoms reduces unnecessary testing. Examples of important tests to identify polyautoimmunity include:

- Anti-tTG IgA to help in diagnosis of celiac disease.
- ANA/ENA screen to help in diagnosis of connective tissue diseases.
- Fecal calprotectin to help in diagnosis of inflammatory bowel diseases.
- Anti-TPO, anti-TG and anti-TSH-R to help in diagnosis of autoimmune thyroid diseases.

Who can advise on test selection?

Laboratory and secondary care specialists can guide GPs on optimal test choices and interpretations.

What resources support test interpretation?

Access to lab resources and education improves test result accuracy.

Lab lessons

A strategic approach to testing supports faster, more accurate diagnosis, reducing both patient burden and healthcare costs. By aligning with laboratory partners, both GPs and secondary care specialists can improve diagnostic accuracy and optimize outcomes for polyautoimmunity patients.

Empowering general practitioners with the full picture to transform polyautoimmunity care

As healthcare providers on the frontlines, GPs play an indispensable role in the early detection and management of polyautoimmunity—a role that is more impactful today than ever. With the rising prevalence of autoimmune diseases and the challenges associated with their overlapping symptoms, GPs are uniquely positioned to drive positive change for their patients.^{1-3,5,11,16}

Polyautoimmunity presents a nuanced landscape, one where symptoms are often complex, diagnosis can be delayed and the need for personalized, integrated care is essential. By staying informed, recognizing symptom overlaps and leveraging appropriate diagnostic tools, GPs can help patients navigate the often uncertain path of autoimmune diseases, reducing the time to diagnosis and setting them on the road to effective treatment sooner.

Practical recommendations for GPs:

Think beyond individual diagnoses:

Polyautoimmunity awareness encourages GPs to look for patterns and comorbidities rather than isolated symptoms. By expanding the diagnostic lens, GPs can help identify multiple autoimmune diseases earlier, supporting patients with access to targeted treatments and preventing unnecessary complications.^{5,11}

Empathize with the patient journey:

Patients with polyautoimmunity often face prolonged distress and mental health challenges due to delayed diagnoses and uncertainty. A proactive, empathetic approach can make a profound difference in their quality of life, instilling hope and trust in their healthcare journey.^{13,14}

Take action with strategic testing and referrals:

With the right diagnostic tools and partnerships with laboratory and secondary care specialists, GPs can help reduce healthcare costs and improve outcomes. By strategically selecting tests, interpreting results accurately and ensuring timely referrals, GPs support comprehensive patient care and minimize the risk of misdiagnosis.¹¹

Early identification of polyautoimmunity can mitigate irreversible damage, optimize long-term health outcomes and improve patients' lives by reducing the burden of undiagnosed or untreated autoimmune conditions. GPs have the power to accelerate this process, ultimately transforming the care pathway for those affected by polyautoimmunity.

Informed, compassionate and proactive care can make all the difference. Through awareness and action, GPs can truly empower patients with polyautoimmunity to live healthier, fuller lives.

Ready to take proactive steps in polyautoimmunity care?

Visit thermofisher.com/polyautoimmunity to explore advanced diagnostic tools, in-depth resources and the latest insights to support you in identifying autoimmune diseases.



Graves'
 disease

 Sjögren's
 syndrome

Polyautoimmunity

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