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Approach to the Patient

Approach to the Patient: Diagnosis of Primary Adrenal Insufficiency in Adults

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Key Words: primary adrenal insufficiency, Addison's disease, 21-hydroxylase autoantibodies, interferon omega autoantibodies

Abbreviations: AHC, adrenal hypoplasia congenital; ALD, adrenoleukodystrophy; APS, autoimmune polyendocrine syndrome; APS1, APS type 1; APS2, APS type 2; PAI, primary adrenal insufficiency; VLCFA, very long chain fatty acids.

Primary adrenal insufficiency (PAI) is easy to diagnose. The challenge is to consider it as a differential diagnosis since it is rare, symptoms develop gradually and are unspecific and common. In Western countries autoimmune aetiology is easy to confirm by measuring autoantibodies against 21-hydroxylase, but it can be more challenging to determine the aetiology in patients without such autoantibodies. Finding the underlying cause is important since this may have prognostic and therapeutic consequences. The cases presented here illustrate the diversity of causes and suggests a practical approach to diagnosis.

Case 1

An 18-year-old woman contacted her general practitioner because of nausea and abdominal pain. She was previously well except vitiligo, which developed at 3 years of age. An elevated TSH value was found (20 mIE/L, range 0.35-4.9), and she was started on a replacement dose with L-thyroxine. Initially she felt better, but then her symptoms worsened, and she would often throw up after breakfast before going to school. She was referred to an endocrinologist who on suspicion of adrenal insufficiency tested adrenocortical function. In a morning sample he found a serum cortisol at 288 nmol/L (range 60-600), plasma ACTH 5.3 pmol/L (range <11.6), plasma renin 55.8 mIE/L (range 4.4-46.1), and serum aldosterone at 75.1 pmol/L (range 49-1086), all in the normal range except a slightly elevated plasma renin. However, assay of 21-hydroxylase autoantibodies revealed an extremely elevated value at >5000 U/mL (range < 1.0).

Due to persisting symptoms, a standard 0.25 mg cosyntropin test was performed 6 months later. Cortisol climbed from 411 to 595 and 602 nmol/L after 30 and 60 minutes, respectively. ACTH in the basal test was 10.1 pmol/L, renin 149 mIE/L, and aldosterone 90.4 pmol/L. TSH was still elevated, and the L-thyroxine dose was increased. She was also started on fludrocortisone since renin was now clearly elevated and aldosterone relatively low. She was also informed of the risk of overt adrenal insufficiency and prescribed cortisone acetate to use in case she got worse. Fludrocortisone improved her nausea and alleviated dizziness, but she still vomited at least twice a week.

During the next 6 months she moved to another city to start college studies. Her mother, who saw her occasionally, noted darkening of the skin. She was then referred to our hospital and when seen at the first appointment, ACTH levels were strikingly elevated (>278 pmol/L). The corresponding morning cortisol was 209 nmol/L. A new cosyntropin test revealed serum cortisol at 233 nmol/L before and 234 and 225 nmol/L after 30 and 60 minutes, respectively. Daily cortisone acetate replacement was started. Review of her history revealed considerable salt craving.

Case 2

A 29-year-old male was sent to the emergency room after an episode of what seemed to be a seizure. The last 3 weeks before admission he had constant nausea and had vomited repeatedly after food intake and lost 6 kg of weight. At admission his weight was 65 kg and height 193 cm. Two years earlier his weight was 90 kg. Blood pressure was 94/47 mmHg and pulse 77 per minute. Laboratory tests revealed serum sodium of 110 mmol/L and serum potassium 5.3 mmol/L. He felt very dizzy when standing. Intravenous sodium chloride and hydrocortisone were given on suspicion of adrenal insufficiency, and his general condition improved rapidly. Blood tests taken before treatment started showed a serum cortisol at 77 nmol/L and plasma ACTH at 258 pmol/L, confirming the diagnosis of PAI. Autoantibody screening revealed the presence of 21-hydroxylase autoantibodies, securing the diagnosis of autoimmune PAI. Further workup did not disclose other organ-specific autoimmune diseases, and he did not have thyroid autoantibodies. As part of quality control, further autoantibody screening was performed, and, surprisingly, he had high levels of interferon omega autoantibodies.

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Case 3

A 20-year-old woman started to experience muscle weakness in her 20s. She was remitted to a neurologist for suspected myasthenia gravis. Her symptoms included dysphonia, diplopia, ptosis, and dysphagia. A muscle biopsy indicated Kearns-Sayre syndrome, later confirmed by finding a confirmatory 3 to 4 kb mitochondrial DNA deletion. At 32 years of age her condition deteriorated with weight loss, and she was admitted to the hospital for evaluation. Unfortunately, she developed pneumonia and, after a few days, respiratory failure in need of intubation and mechanical ventilation. At admission a low sodium at 120 nmol/L and an elevated potassium at 6.0 mmol/L was noted. Furthermore, TSH was 20 mIE/L and free thyroxine 7.6 pmol/L, indicating primary hypothyroidism. On suspicion of adrenal insufficiency she was treated with intravenous hydrocortisone and saline with rapid improvement, weight gain, and normalization of electrolytes. Workup showed undetectable serum cortisol (<20 nmol/L), elevated ACTH at 181 pmol/L, and autoantibodies against 21-hydroxylase and thyroperoxidase. She started replacement therapy and was discharged from the hospital to her home.

Case 4

A 67-year-old woman was admitted to the hospital after 1 week with epigastric pain. A myocardial infarction was suspected, and she was anticoagulated with dalteparin, acetylsalicylic acid, and clopidogrel as acute coronary intervention was not available. She was transferred to another hospital for percutaneous coronary intervention including blocking and stenting of the right coronary artery, which was performed 2 days later. From an initial serum sodium value of 137 mmol/L, sodium fell to 119 mmol/L over 3 days while serum potassium remained low. Concurrently, thrombocyte levels fell from 124 to 23×10^9/L. On clinical suspicion of adrenal insufficiency, hydrocortisone was administered intravenously, correcting the electrolytes. The following days she developed thrombi in the aorta, which embolized to the lower extremities. Radiologic examination revealed signs of infarctions and hemorrhage in the liver, kidney, and both adrenals. Haematological workup concluded with disseminated intravascular coagulation. Intravenous hydrocortisone was continued and later switched to oral replacement therapy with cortisone acetate and fludrocortisone as her condition improved. A cosyntropin test revealed a basal cortisol of 195 nmol/L with no increase after 30 and 60 minutes (both values 191 nmol/L).

Case 5

A 70-year-old retired builder sought his general practitioner because of 12 kg weight loss during the past 6 months. Lab tests revealed a low hemoglobin, elevated creatinine (250 µmol/L), and microscopic hematuria leading to hospital referral. Ultrasound of the abdominal region 2 weeks before admission did not reveal any pathology, and a gastroscopy a few months earlier had identified a small hiatus hernia. He was started on a proton pump inhibitor. At admission he complained of fatigue, dizziness, and stiff and painful joints but had no fever or night sweats.

Blood pressure was surprisingly low, 96/76 mmHg, and clinical investigation did not identify specific pathologies. Laboratory results revealed serum sodium 133 mmol/L and serum-potassium 6.2 mmol/L. Creatinine was confirmed as elevated at 228 µmol/L. The combination of hyperkalemia and hyponatremia with a pigmented skin prompted assay of cortisol, found to be 98 nmol/L in a morning sample (range 160-600). ACTH taken at the same time was 164 pmol/L, confirming the suspicion of PAI. A cosyntropin test confirmed the diagnosis, showing no increase from the basal value (193 nmol/L) to 175 and 177 nmol/L after 30 and 60 minutes, respectively. Since antibodies against 21-hydroxylase was negative, an adrenal computed tomography (CT) was performed revealing tumors in both adrenals, 4 and 5 cm in diameter, respectively, with Hounsfield units around 35 without contrast. A diagnostic biopsy revealed non-Hodgkin's B-cell lymphoma.

Case 6

A 39-year-old male was admitted to the hospital with severe depression. Since childhood he had trouble with fatigue upon waking, resulting in late arrival at school and later at the workplace. He had also been diagnosed with delayed sleep phase syndrome. At admittance, he was underweight, and he had a slightly low blood pressure. He answered questions with latency, and facial expressions were minimal. Somatic comorbidity was suspected and extended blood testing performed. ACTH was found elevated at 83 pmol/L, but cortisol was relatively normal at 355 nmol/L, and he was referred to an endocrinologist who confirmed the diagnosis of PAI. 21-hydroxylase autoantibodies were not present, and an adrenal CT was described as normal. No neurological findings were present, he had no history of seizures, and very long chain fatty acids (VLFA) were normal, leading to the diagnosis of idiopathic PAI. Replacement therapy with cortisone acetate and fludrocortisone was started with improvement of symptoms and regaining of weight. Over the following years he used extreme doses of oral cortisone (100 mg/d) or hydrocortisone to improve symptoms, despite lab tests showing normal absorption of the drugs. Yet no signs of overdosage developed, including normal bone density tests. Later he developed cataracts, bradycardia (40 beats per minute), and increasing muscle pain and eventually weakness of hands and feet. At 49 years of age, he was re-evaluated, and a magnetic resonance imaging of the brain revealed findings suspicious of neurological disease that could explain many of his symptoms.

PAI is easy to diagnose and treat when suspicion of the disease is raised. Yet, a previous study showed that less than 30% of women and 50% of men are diagnosed within the first 6 months of symptoms, and 20% were symptomatic for more than 5 years before the correct diagnosis was made (1). More than two-thirds consulted at least 3 physicians, and 2 out of 3 were primarily given a wrong diagnosis, most often a psychiatric or gastrointestinal disorder. These examples illustrate that the main difficulty lies in considering PAI as a differential diagnosis as most physicians rarely meet more than a few patients during their career due to the rarity of the disease.

Prevalence numbers vary across populations, and the highest figures have been reported from Scandinavia, notably 15 to 20 cases per 100 000 inhabitants (2, 3). Incidence has been reported at about 5 per million per year. Numbers from other European countries are around 10 per 100 000 (4, 5). There are very few reports from countries outside of Europe, but a

national survey from Korea reported a much lower number at 0.4 per 100 000 (6). Reports from developing countries are missing.

When Should you Suspect Primary Adrenal Insufficiency?

Adding to the difficulty of diagnosis, many of the symptoms and signs of PAI are unspecific and common to many diseases, such as fatigue, malaise, reduced appetite, weight loss, abdominal, and muscle and joint pain, which typically develops over months, sometimes even years. Especially gastrointestinal symptoms are common, and many PAI patients are initially misdiagnosed accordingly. Still, the probability of PAI will be very low if such symptoms present alone.

Chronic nausea escalating to vomiting and exacerbation of weight loss should, however, lead to testing for PAI when no other plausible cause can be found. If hyperpigmentation of the skin and mucous membranes develops, the probability of PAI will increase substantially. The hyperpigmentation caused by high levels of ACTH is particularly evident on skin areas exposed to sun and frictions (Fig. 1). Thus, knuckles and elbows appear particularly dark. In some patients, hyperpigmentation is more subtle, perhaps most evident as dark naevi or areola. Salt craving is also characteristic, and patients can report a particular liking for peanuts, chips, liquorice, and other salty foods. However, many do not volunteer to inform about salt craving unless asked.

Lack of cortisol and aldosterone lowers blood pressure and may result in symptomatic orthostatism, which the patient often reports as dizziness. In addition, low cortisol may lead to hypoglycaemia, and patients with diabetes become more insulin sensitive. A history of autoimmune disease should also sharpen the suspicion of autoimmune PAI, since the majority have or will develop more than 1 organ-specific autoimmune disease.

Can Untreated PAI Reveal Itself in Common Laboratory Parameters?

Sævik et al asked this question and found that 85% of patients had hyponatremia at diagnosis (7). Hyperkalaemia was not as common and was found in less than half of the patients, perhaps because many patients have nausea and vomiting, thus losing potassium. Unexplained hyponatremia should prompt investigation into the presence of PAI, and a concomitant hyperkalaemia strengthens the suspicion and points to lack of aldosterone. Another suspicious sign at presentation is elevated TSH due to hypocortisolism, as 52% had elevated TSH without known hypothyroidism, and only a few had thyroid peroxidase antibodies (7). If an elevated TSH is misinterpreted as hypothyroidism and L-thyroxine treatment started, untreated adrenal insufficiency can worsen and in the worst case precipitate an adrenal crisis.

How Do I Make the Diagnosis of PAI Once It Is Suspected?

As soon as suspicion of PAI is raised, the patient's clinical condition should determine further action. If the patient is acutely ill and circulatory unstable, treatment with intravenous hydrocortisone and saline infusion should be started without delay. If the patient is stable, diagnostic workup is usually relatively straightforward. Since adrenal function often is severely reduced when patients are symptomatic, cortisol is usually very low and ACTH very high. Likewise, low aldosterone is a potent stimulus of the renin-angiotensin system. Thus, the biochemical fingerprint of PAI is high ACTH and low cortisol and even low dehydroepiandrosterone sulphate, high plasma renin or renin activity, and low aldosterone. There is not an exact biochemical definition of PAI, but a cortisol level below 100 nmol/L and an ACTH value 2 times the upper reference limit is diagnostic according to current guidelines (8). Usually both cortisol and aldosterone levels are low at diagnosis, but sometimes insufficiency of either hormone comes first. In the majority of cases, the diagnosis can be made by analyzing a paired cortisol and ACTH test irrespective of time of the day, but in some cases a slower and more gradual adrenal destruction may occur, with residual cortisol production (9, 10). In such cases, the cortisol levels may not be overtly low at presentation, although ACTH and/or renin levels are elevated and aldosterone and/or dehydroepiandrosterone sulfate levels are low. In such cases a cosyntropin stimulation test is needed to gauge the secretory capacity of the adrenal cortex. Current guidelines recommend the standard test where 0.25 mg cosyntropin is given intravenously and cortisol measured before and after 30 and 60 minutes. Traditionally the cut-off has been defined at 550 or 500 nmol/L after 30 and/or 60 minutes. However, introduction of highly specific liquid chromatography tandem mass spectrometry methods has lowered the threshold to 412 after 30 minutes or 485 nmol/L after 60 minutes (11). Females treated with oestrogens will have higher

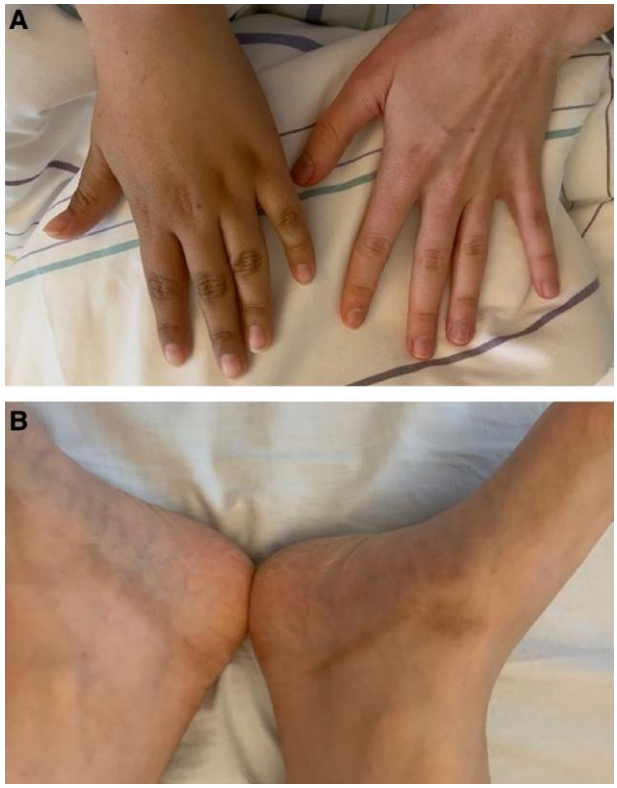

Figure 1. Hyperpigmentation in primary adrenal insufficiency. (A) Hyperpigmentation of the hand of a young female at time of PAI diagnosis compared to a hand with normal pigmentation. (B) Hyperpigmentation around the feet of a young swimmer at time of PAI diagnosis, caused by friction from regular use of swimming fins. Both pictures are published in agreement with the patient. Abbreviations: PAI, primary adrenal insufficiency.

cortisol binding globulin levels and thus higher total serum cortisol, which can mask cortisol deficiency. Defined cut-off values for renin and aldosterone do not exist, but high renin and low aldosterone support the diagnosis.

How to Determine the Cause of PAI

All patients with PAI should have an etiological diagnosis because it profoundly affects treatment and follow-up. The causes of PAI can be divided into several main groups. Most common is destructive PAI, followed by impaired steroidogenesis, adrenal dysgenesis, and ACTH resistance (Table 1). In developed countries, in particular Europe and North America, autoimmune destruction of the adrenal cortex is the main cause, accounting for about 90% of PAI in young and middle-aged adults (12). Thus, in most cases, the diagnosis is easily secured by finding 21-hydroxylase autoantibodies, which is present in more than 90% of newly diagnosed cases (13). Autoimmune PAI is most prevalent in age groups between 20 and 50 years of age but can also occur in childhood and old age. This test is recommended in all patients if the cause is not evident (Fig. 2).

Patients with autoimmune PAI (and particularly women) are at risk of developing autoimmune comorbidities as up to 50% to 65% of patients have 1 or several other autoimmune endocrine diseases (13), called autoimmune polyglandular syndrome (APS). Especially in children and adolescent patients, APS type 1 (APS1) should be considered. APS1 is an autosomal recessive disease caused by mutations in the autoimmune regulator (*AIRE*) gene. *AIRE* is crucial for development of central immunological tolerance, and loss of *AIRE* allows autoreactive T-lymphocytes to enter the circulation (14). Thus, APS1 patients are at high risk of developing additional autoimmune diseases over time, with hypoparathyroidism, chronic mucocutaneous candidiasis, and PAI as main components. Of note, in many patients other features may appear first, such as keratitis, autoimmune bronchiolitis and hepatitis, and intermittent rash with fever (15, 16). Most patients develop some degree of enamel hypoplasia of permanent teeth, a diagnostic clue (17). The prevalence of APS1 is around 1:80 000 in most populations (18), but there is a higher prevalence in more homogeneous populations such as among Persian Jews and Sardinians (19). Almost all patients have autoantibodies against interferon omega and/or alpha, a sensitive biomarker for the presence of mutations in *AIRE* (16). In patients with autoimmune PAI and an unusual phenotype, measurement of interferon autoantibodies can indicate APS1, including presentation of PAI before 30 years of age, hypoparathyroidism, chronic candidiasis, severe vitiligo or alopecia, intermittent fever with rash, keratitis, hepatitis, and pneumonitis (20). APS1 can also present in a nonclassical form with only 1 mutation in *AIRE*. Certain mutations in the PHD1, PHD2, or SAND domains have a dominant negative effect and cause polyendocrinopathy masquerading as APS2, with autoimmune PAI as 1 of the components. This form clusters in families and display dominant inheritance (21).

The term APS2 is sometimes used for PAI in combination with any organ-specific autoimmune disease (22), which most commonly includes autoimmune thyroiditis (48%) (23), but other autoimmune diseases such as primary ovarian insufficiency (10%) (24), type 1 diabetes mellitus (10%), vitiligo, pernicious anaemia, alopecia, and celiac disease are also relatively frequent (2, 25). Nonendocrine autoimmunity such as myasthenia gravis, multiple sclerosis, Sjøgren syndrome, or rheumatoid arthritis can also occur. Diagnosing autoimmune comorbidity requires vigilance both at the time of PAI diagnosis and during long-term follow-up.

Autoimmune destruction of the adrenal can be induced by drugs in rare cases (26). Autoimmune PAI with 21-hydroxylase autoantibodies have been reported in a few cases treated with programmed death 1 inhibitors such as nivolumab (27) and pembrolizumab (28), although pituitary insufficiency and thyroiditis are more common side-effect with these drugs. Finally, deletion of mitochondrial DNA has been linked to autoimmune PAI, eg, in Kearne-Sayer syndrome (29).

What To Do If 21-OH Antibodies Are Negative?

If 21-hydroxylase autoantibodies are absent, other causes must be considered allowing for the age of the patients, history, and clinical findings. The next recommended step is imaging of the adrenals, preferably with an adrenal CT (Fig. 2).

Infectious destruction of the adrenal gland is now rare in Western countries. Tuberculosis was the leading cause of PAI from the 1850s, when Thomas Addison first described the disease, until the 1950s and may still be so in populations where tuberculosis is endemic (30, 31). Usually, an adrenal CT will show visible adrenal enlargement early on and adrenal calcifications or adrenal atrophy in the later stages of infection. Other possible and very rare infectious causes include bacteria [including syphilis (32)], viruses [cytomegalovirus, human immune-deficiency virus (33), herpes virus], and fungal infections [histoplasmosis, cryptococcosis (34), coccidiomycosis, blastomycosis].

On the other hand, adrenal destruction due to bilateral hemorrhage or adrenal infarction is not uncommon, previously often an incidental finding on autopsy but nowadays seen in ill patients examined with abdominal CT without suspicion of PAI (35). The adrenal glands have abundant arterial blood supply with fewer adrenal veins and a rich supply of catecholamines, which increase the risk of thrombocyte aggregations. Risk factors include sepsis, underlying adrenal tumor, COVID-19 infection, major surgery, or adrenal trauma. Also, coagulopathy due to oral anticoagulants and/or underlying conditions such as antiphospholipid syndrome or heparin-induced thrombocytopenia and vaccine-induced immune thrombocytopenia and thrombosis are recognized causes (36). Although anticoagulant therapy is implicated as a possible contributing cause in many cases, it should be pointed out that bilateral adrenal hemorrhage is rare in patients who are anticoagulated (37, 38).

It is important to note that since bilateral adrenal hemorrhage often induce an acute adrenal crisis, the patient will not be hyperpigmented. Hypovolemic shock, hyponatremia, hyperkalaemia, and declining haemoglobin or thrombocyte concentrations should arise suspicion of PAI. Flank and back pain may occur. Again, an adrenal CT can be diagnostic, showing large adrenals, but definitive diagnosis should not delay immediate treatment with intravenous hydrocortisone and fluid/blood resuscitation.

Infiltration can also destroy the adrenals if extensive and affecting both adrenals. Both primary adrenal tumours and adrenal metastases are more common in older individuals (Fig. 2). Adrenal metastases are not uncommon and found

Table 1. Etiologies of primary adrenal insufficiency

Condition/deficiency	Gene	OMIM[a]	Associated clinical signs and symptoms
Autoimmunity			
Autoimmune primary adrenal insufficiency and APS2			Hypothyroidism, hyperthyroidism, premature ovarian insufficiency, vitiligo, type 1 diabetes mellitus, pernicious anaemia, and other organ-specific autoimmune features
APS1	*AIRE*	240300	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders
Immunodeficiency 31C	*STAT1*	614162	Chronic mucocutaneous candidiasis, susceptibility to Staph aureus and other bacterial, viral and fungal infections, polyendocrinopathy including hypothyroidism, type 1 diabetes mellitus, cerebral aneurysms
Peroxisomal defects			
X-linked Adrenoleukodystrophy)	*ABCD1*	300100	Progressive neurodegeneration, behavioural changes, cognitive decline, loss of speech, hearing and vision, dementia, spasticity, seizures
Mitochondrial defects			
Kearns-Sayre syndrome	Mitochondrial DNA deletions	530000	External ophthalmoplegia, retinal degeneration, and cardiac conduction defects; other endocrinopathies
Acquired aetiologies			
Haemorrhage			Bilateral adrenal haemorrhage of the newborn, primary antiphospholipid syndrome, anticoagulation
Trauma/surgery			Bilateral adrenalectomy
Infection			Septic shock, meningococcal sepsis (Waterhouse-Frederichsen syndrome), Tuberculosis, Fungal infections (histoplasmosis, cryptococcosis, coccidiomycosis, blastomycosis), Cytomegalovirus, HIV-1, syphilis
Infiltration			Metastatic cancers, primary adrenal lymphoma, amyloidosis, sarcoidosis, haemochromatosis
Drugs			Ketoconazole, Rifampicin, Phenytoin, Phenobarbital, aminoglutethimide, mitotane, abiraterone, etomidate, suramine, mifepristone, nivolumab, pembrolizumab
Impaired steroidogenesis			
Impaired cholesterol transport			
Steroidogenic acute regulatory protein (congenital lipoid adrenal hyperplasia)	*StAR*	201710	46,XY DSD, gonadal insufficiency
Steroidogenic enzyme/co-factor deficiency causing CAH			
3β-hydroxysteroid dehydrogenase type 2	*HSD3B2*	201810	46,XX and 46,XY DSD, gonadal insufficiency
21-hydroxylase	*CYP21A2*	201910	46,XX DSD, hyperandrogenism
11β-hydroxylase	*CYP11B1*	202010	46,XX DSD, arterial hypertension
CYP17A1 deficiency	*CYP17A1*	202110	46,XY DSD, arterial hypertension, gonadal insufficiency
P450 oxidoreductase	*POR*	201750	46, XX and 46,XY DSD, gonadal insufficiency, bone malformation, affects all endoplasmic CYP450 enzymes
Steroidogenic enzyme deficiency (non-CAH)			
P450 side-chain cleavage enzyme	*CYP11A1*	118485	46,XY DSD, gonadal insufficiency
Aldosterone synthase	*CYP11B2*	124080	Isolated mineralocorticoid deficiency
Defects of cholesterol synthesis or metabolism			
Wolman disease (lysosomal acid lipase deficiency, cholesterol ester storage disease)	*LIPA*	278000	Diffuse punctate adrenal calcification, xanthomatous changes in multiple organs, hypercholesterolaemia, steatorrhea, poor prognosis
Smith-Lemli Opitz disease	*DHCR7*	270400	Mental retardation, craniofacial malformations, limb abnormalities, growth failure
Abeta-lipoproteinaemia	*MTP*	200100	Ataxia, retinopathy, acanthocytosis, fat malabsorption
Adrenal dysgenesis			
X-linked adrenal hypoplasia congenital	*NROB1 (*DAX1)	300200	Combined primary and secondary hypogonadism, DMD in contiguous gene syndrome
Adrenal hypoplasia steroidogenic factor-1 deficiency	*NR5A1 (*SF1)	184757	46,XY DSD, gonadal insufficiency

(*continued*)

Table 1. Continued

Condition/deficiency	Gene	OMIM[a]	Associated clinical signs and symptoms
IMAGe syndrome	*CDKN1C*	300290	Intrauterine growth retardation, metaphyseal dysplasia, adrenal insufficiency, genital anomalies
MIRAGE syndrome	*SMAD9*	617053	Myelodysplasia, infection, adrenal hypoplasia, growth restriction, genital anomalies, enteropathy
ACTH resistance			
Familial glucocorticoid deficiency Type 1	*MC2R*	202200	Tall stature, isolated deficiency of glucocorticoids, generally normal aldosterone production
Familial glucocorticoid deficiency Type 2	*MRAP*	607398	Isolated deficiency of glucocorticoids, generally normal aldosterone production
Impaired redox homeostasis			
Triple A syndrome (Allgrove syndrome)	*AAAS*	231550	Alacrimia, achalasia; neurologic impairment, deafness, mental retardation, hyperkeratosis
Mitochondrial deficiency of free radical detoxification	*NNT*	614736	
	TRXR2	606448	Isolated deficiency of glucocorticoids
	GPX1, PRDX3		Digenic inheritance has been shown in one patient with isolated glucocorticoid deficiency

From Husebye, ES et al, The Lancet, 397, 613-629, 2021.
Abbreviations: APS, autoimmune polyendocrine syndrome; CAH, congenital adrenal hyperplasia; DSD, disorders of sexual differentiation; DMD, Duchenne muscular dystrophy.
[a]Online Mendelian Inheritance in Man (www.omim.org)

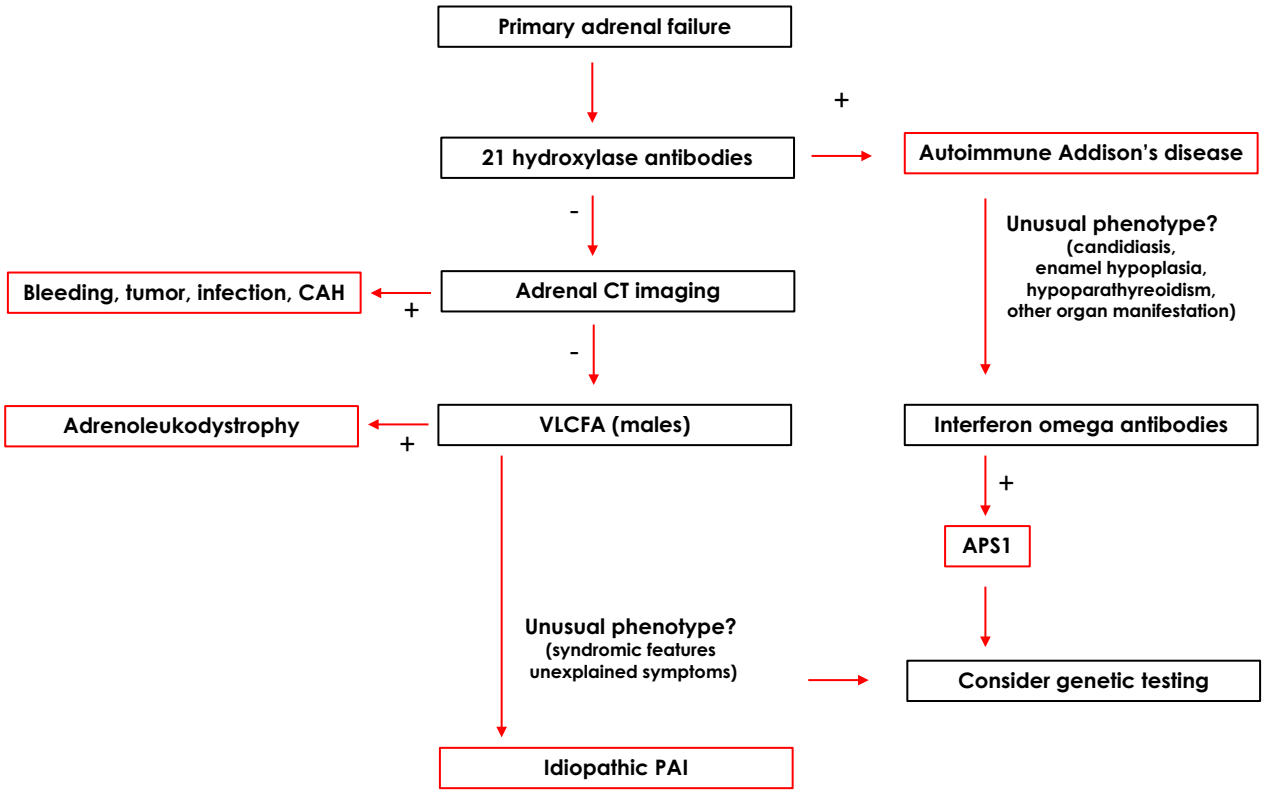

Figure 2. Diagnostic algorithm for etiological diagnosis in primary adrenal insufficiency. From Husebye et al, J. internal Medicine 275, 104-115, 2014.
Abbreviations: APS1, autoimmune polyendocrine syndrome type 1; CAH, congenital adrenal hyperplasia; VLCFA, very long chain fatty acids.

in 40% to 60% of patients with disseminated lung or breast cancer, but clinically evident PAI is less common (39). Primary lymphoma of the adrenals has been reported (40). Infiltration in the course of amyloidosis, hemochromatosis, and sarcoidosis are also rare causes of PAI.

X-linked adrenoleukodystrophy (ALD) is caused by a peroxisomal defect with accumulation of VLFA in the central nervous system, gonads, and adrenals. In the adrenals, VLFA accumulate particularly in zona reticularis and fasciculata, while mineralocorticoid function is spared in most

patients. ALD is caused by mutations in the *ABCD1* gene located on the X-chromosome, affecting males while females are carriers. Affected boys can develop slowly progressive spinal cord disease and/or progressive demyelinating cerebral disease, and around 80% will develop PAI. In its mild form myelopathy and peripheral neuropathy develop in adolescence or adult age with adrenal and gonadal insufficiencies (41). A retrospective study in 159 males with ALD found that PAI was the first manifestation of ALD in more than a third of patients. Fifty percent of ALD patients had PAI at age 14 years, and at 56 years of age 80% had developed PAI. Thus, in 21-hydroxylase negative males, assay for VLFA is recommended (Fig. 2).

Even Rarer Causes of PAI in Adults

Genetic disorders causing PAI are usually diagnosed in childhood but occasionally present in adolescence or early adulthood. Inborn errors of steroidogenesis are a group of disorders where enzymes or cofactors involved in steroidogenesis are mutated, of which congenital adrenal hyperplasia (CAH) caused by mutations in *CYP21A2* (21-hydroxylase) is the most common (42). The more severe forms are diagnosed at birth, and many countries have a neonatal screening programs for CAH. The most severe *CYP21A2* deficiencies cause hyperandrogenism and glucocorticoid deficiency with or without mineralocorticoid deficiency and are traditionally classified as salt-losing or simple virilizing forms. Nonclassical CAH typically does not cause glucocorticoid insufficiency and appears later with manifestations such as early puberty and hirsutism. However, today's view of CAH is a spectrum of 21-hydroxylase deficiencies resulting in a range of phenotypes (43). Sometimes patients are not diagnosed until adult age despite having a relatively severe glucocorticoid deficiency. Large adrenals incidentally discovered sometimes initiate workup leading to the diagnosis. In women, hyperandrogenism is an important diagnostic clue. As 17-hydroxyprogesterone is the main substrate for 21-hydroxylase, an elevated level is a biomarker for CAH (44). Identification of pathogenic variants in *CYP21A2* can confirm the diagnosis. Other genetic disorders causing impaired steroidogenesis are mutations causing lack of specific steroidogenic enzymes other than 21-hydroxylase and defects in cholesterol transport, synthesis, or metabolism (45).

Several monogenic conditions cause adrenal dysgenesis. The most common in this group is congenital adrenal hypoplasia caused by mutations in *DAX1*, also located on the X chromosome. Affected males have both adrenal and gonadal insufficiencies (46). Other clinical components that point to adrenal dysgenesis are metaphyseal dysplasia in iMAGE syndrome and myelodysplasia in MIRAGE syndrome. Thus, in the presence of apparent idiopathic PAI, genetic testing is recommended in case of syndromic features or other unexplained clinical findings. Another example of monogenic cause of PAI is familial glucocorticoid deficiency, due to mutations in melanocortin receptor 2 or the MRAP transport protein results in ACTH resistance and PAI.

Mitochondrial diseases are rare, and mitochondrial disease with PAI even rarer. Both the rate-limiting initial step of steroidogenesis and the final 11-beta hydroxylase step take place in the mitochondria. Thus, it is not surprising that mutations of mitochondrial DNA can affect steroidogenesis. CYP450 enzymes generate free radicals, and impaired redox homeostasis can cause failure of steroidogenesis. Thus, monogenic disorders affecting key enzymes in the redox process such as *AAAS*, *NNT*, and *TRXR2* can cause adrenal insufficiency, reviewed elsewhere (47). These conditions often have syndromic presentations.

Drugs and Adrenal Insufficiency

Several drugs can reduce steroidogenesis and precipitate PAI, and physicians should be aware of these rare but potentially deadly side-effects. Probably best known is the inhibitory effect of ketoconazole and metyrapone on steroidogenesis and the adrenolytic effect of mitotane. All 3 are used in the treatment of Cushing's syndrome. Etomidate, an anaesthetic drug also used to control otherwise uncontrollable Cushing's syndrome, inhibits steroidogenesis, and several deaths have been reported. Abiraterone, a CYP17 inhibitor anti-androgen used in the treatment of prostate cancer, can also cause PAI.

Follow-up and Discussion of Cases

Case 1 illustrates a typical case of autoimmune PAI as part of APS2, which is more common in women than in men and manifests in early adulthood. The majority develop other organ-specific manifestations, in this case vitiligo in childhood and autoimmune hypothyroidism around the time of PAI presentation. Typically, she had a positive family history of autoimmunity. Starting her on L-thyroxine before PAI diagnosis put her at risk of an adrenal crisis, which probably was avoided because adrenal destruction was not complete (cortisol 288 nmol/L) when L-thyroxine was started and illustrates that autoimmune adrenalitis is a gradual and stepwise process (48, 49) (Fig. 3). Initially, 21 hydroxylase antibodies were clearly positive while glucocorticoid and mineralocorticoid production was preserved. Six months later she developed mineralocorticoid deficiency and after another 6 months glucocorticoid insufficiency. Thus, one would expect symptoms to develop later than was reported in this case. However, when asked directly, she admitted use of estrogen-containing contraceptive pills a few months after the first evaluation for PAI, suggesting that her serum cortisol levels at the time of both cosyntropin tests underestimated the degree of glucocorticoid deficiency.

The patient is now followed with annual visits at the endocrine outpatient clinic, with focus on replacement therapy, adrenal crisis prevention, and screening for endocrinopathies such as celiac disease, primary ovarian insufficiency, autoimmune gastritis, and type 1 diabetes mellitus. In autoimmune PAI, we recommend annual assay of HbA1c, TSH, free thyroxine, cobalamin and ferritin, and transglutaminase-2 antibodies every third year (50).

Both case 1 and case 2 presented with typical gastrointestinal symptoms of nausea and vomiting, but case 2 had a more acute presentation with indicators of adrenal crisis at debut. He reported symptoms for 3 weeks only, illustrating the interindividual difference in presentation of autoimmune PAI. The reported seizure leading to hospital admittance was likely a vasovagal syncope due to hypotension. This case looks like a typical case of autoimmune PAI without any associated comorbidity, autoimmune or otherwise. However, since he was enrolled in our national registry, he was screened for interferon omega autoantibodies. Since the test was positive, *AIRE* was sequenced, revealing homozygosity for the common 13 base pair deletion in exon 8 (c.967_979del), the most common

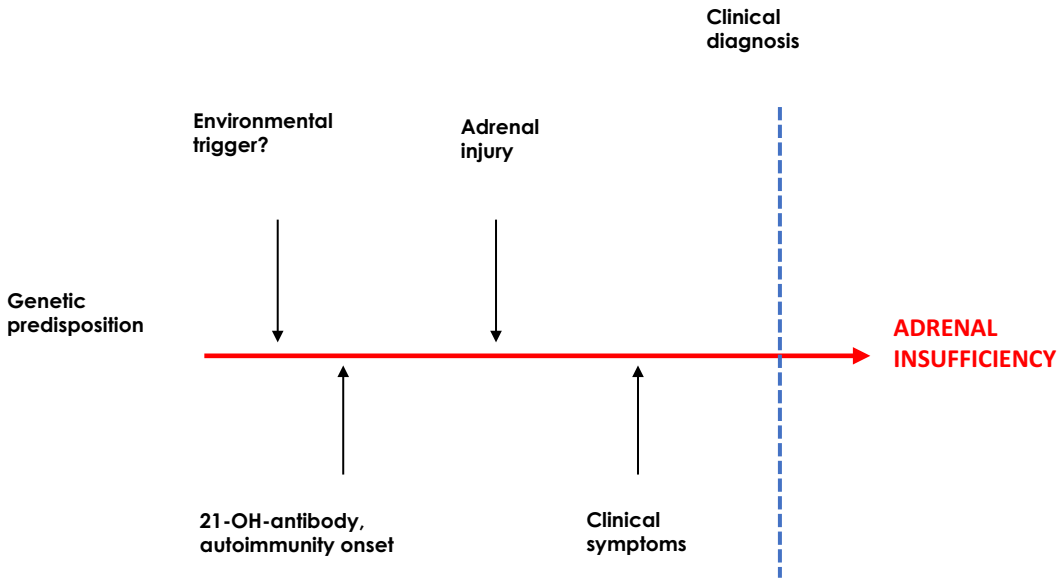

Figure 3. Schematic illustration of pathogenesis timeline in autoimmune primary adrenal failure.

mutation in the Norwegian population. Screening for other typical APS1 manifestation revealed no history of chronic candidiasis or hypoparathyroidism, but a dental examination showed enamel hypoplasia. The case illustrates that the phenotypic spectrum of APS1 can be very diverse, and even patients with 2 clearly pathogenic mutation can have mild disease. When APS1 is diagnosed, siblings should be screened for the disease since 1 in 4 will be affected. APS1 patients also need to be followed more closely than the regular autoimmune PAI patients since several severe complications can occur such as squamous cell carcinoma in the mouth and oesophagus, nephritis, hepatitis, pneumonitis, and autoimmune enteritis with malabsorption.

Case 3 is also an autoimmune PAI case, but here it was already evident that she had Kearns-Sayre syndrome at time of PAI diagnosis. Kearns-Sayre is a mitochondrial disease, a disease group known to interfere with steroidogenesis (47), although overt PAI is rare. Diabetes mellitus is the most frequent endocrinopathy in mitochondrial diseases in general, but adrenal insufficiency does occur. Patients should receive conventional replacement therapy and follow-up to detect other endocrinopathies, especially diabetes. The patient recovered from her critical illness and was stable for many years.

Cases 4 and 5 exemplifies that, in older individuals, nonautoimmune causes of adrenal insufficiencies are common and adrenal imaging should be performed as the next diagnostic step. Case 4, the woman with bilateral adrenal hemorrhage, recovered from the initial adrenal crisis. The case highlights important clues for PAI in the critically ill patient, ie, hyponatremia, hypovolemic shock, thrombocytopenia, and multiple anticoagulant drugs predisposing for adrenal hemorrhage. In her case the cause was probably multifactorial, as she had both disseminated intravascular coagulation and was treated with several anticoagulants. Case 5 turned out to have a primary non-Hodgkin's lymphoma in both adrenals, initially responding well to treatment although without ever regaining normal adrenal function. He died 5 years later from metastatic lymphoma. In cancer patients with PAI, educating the patient about sick-day rules and the need to increase glucocorticoid doses during intercurrent disease is especially important, as vomiting is a common side-effect during chemotherapy and the risk of infections is high.

Case 6 did not have autoantibodies, but an autoimmune cause was suspected as it is the most frequent form and some autoantibody positive cases turn negative over time (51). He was transferred to another hospital after a few years, and the fact that autoantibodies were absent at diagnosis was forgotten. Despite replacement therapy he experienced severe fatigue, sleepiness, and reduced energy, and his general health seemed to deteriorate over the years despite much effort to improve replacement therapy. He was adamant in withholding the high glucocorticoid replacement doses although they did not seem to increase his energy level. However, when he 10 years later developed grip changes and bradycardia, cerebral magnetic resonance imaging revealed a picture typical of Steinert's disease, a form of dystrophia myotonica. He also had frontal balding, which is a typical feature. Sanger sequencing revealed a mutation in the *DMPK* gene, confirming the diagnosis. Dystrophia myotonica is caused by the expansion of repeated units of nucleotides in *DMPK*. Over 50 repeats are diagnostic, and our patient had 109. Typically, the symptom burden increases with the number of repeats. Type 2 dystrophia myotonica, which typically presents in adulthood, has less severe and more easily overlooked symptoms. However, type 2 can progress with increased disability, and there is a risk of serious complications including cardiac conduction disease. Case 6 illustrates several important clinical aspects. First, although the patient is diagnosed with a rare disease with subtle and common symptoms (PAI), all symptoms do not necessarily relate to adrenal insufficiency. Second, increasing the glucocorticoid replacement dose is not always the solution, even if the patient feels somewhat better. Luckily, despite using cortisone doses of 100 mg per day, he never developed Cushingoid side-effects. Third, confirming an etiological diagnosis both will increase understanding of the patient's symptoms and could provide alternative treatment options.

During the past decade, considerable progress has been made in the understanding of genetic causes of PAI, which may prove useful not only in children and teenagers but also in young adults with idiopathic PAI (52). Many cases of

idiopathic PAI can now be attributed to a single genetic defect, and some conditions are not only presenting in childhood as previously thought (53). Thus, in idiopathic PAI, genetic testing may be warranted, as demonstrated for late-onset X-linked adrenal hypoplasia (NR0B1, DAX-1) (54-56).

In conclusion, we here show that PAI can present in many ways, highlighting the importance of a careful history and clinical examination to make the correct diagnosis. The causes of PAI are diverse even among those with 21-hydroxylase autoantibodies (isolated autoimmune PAI, APS2, APS1, immune checkpoint inhibitors, and even mitochondrial disease). In nonautoimmune cases, adrenal destruction by hemorrhage, infection, or tumor should be excluded first. In young males, PAI can be the first manifestation of adrenoleukodystrophy or congenital adrenal hypoplasia. Patients with unexpected symptoms or syndromic features should be evaluated for rare causes.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

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