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Consensus

Group 3: Strategies for identifying the cause of adrenal insufficiency: diagnostic algorithms☆

Groupe 3 : stratégies d'identification des causes d'insuffisances surrénales : algorithmes diagnostiques

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1. Adult patients

1.1. Primary adrenal insufficiency in adults

1.1.1. Causes and pathophysiological mechanisms

1.1.1.1. Primary adrenal insufficiency of autoimmune origin. In Europe, primary adrenal insufficiency (PAI) has been reported to have an autoimmune origin in 78–96% of cases, depending on the target population and the age of the published study [1,2]. Autoimmune PAI can appear alone (in 14, 39 or 41% of cases, depending on the study) [2–4], or associated with other autoimmune manifestations in the setting of autoimmune polyendocrinopathy syndromes (APS), most frequently in type 2 (45% of cases reported by Betterle [4]), and more rarely in type 1 (13% of cases reported by Betterle [4]), The classification introduced by Neufeld has been used over a long period to distinguish between different types of APS [5], however, the similarity in pathophysiology of APS types 2,3 and 4 has led some authors to group these together using the terminology autoimmune polyendocrinopathy syndrome type 2 (APS2) [6]. APS2 is more frequently found, with a mean prevalence of 1/20,000, and a gender ratio of 1:3 (male:female). The frequency of adrenal insufficiency (AI) varies from 18–40% of cases, depending on the study and the classification that was used [7,8]. PAI in APS2 appears at a mean age of 35 yrs, although there are reported cases in pediatric patients and some geriatric patients [3,4,8]. Clinically isolated adrenal insufficiency is equally seen in adults, slightly earlier than in APS2 (mean age of 28 yrs) [4]. Transmission is non-Mendelian, autoimmune isolated PAI occurs in a familial context in 10% of cases [2]. Though the role of HLA class II is well-established in the development of this polygenic-derived pathology, other genes involved in adaptive and innate immunity have also been implicated in its development, both in isolated and non-isolated adrenal insufficiency (see Table 1) [9].

Conversely, APS1 or autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is a rare monogenic autosomal recessive pathology, linked to mutations in the *AIRE* gene. In France, its prevalence is estimated at 1/500,000 [10]. It frequently arises in childhood or adolescence. AI is present in 60–70% of cases [11], and generally appears around age 15 yrs

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☆ SFE/SFEDP adrenal insufficiency consensus.

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Table 1
Principal etiologies in adult primary adrenal insufficiency and their clinical characteristics [3,4,7,9,12,13,15,16,76].

Etiology	Origin	Clinical manifestations associated with adrenal insufficiency (in order of frequency)	Diagnostic criteria
Autoimmune			
APS1 (APECED)	Monogenic Mutations of *AIRE* gene	Candidiasis (83–100%) Hypoparathyroidism (79–93%) AI (60–70%) Ovaritis (60%) Dental enamel hypoplasia (77%) Alopecia (29–37%) Keratitis (12–35%) Malabsorption (15–18%) Hepatitis (12–20%) Gastritis (13–15%) Vitiligo (12–13%) Thyroiditis (3–10%) Diabetes (type 1) (2–12%) Hypophysitis (7%) Interstitial nephritis, obliterative bronchiolitis, febrile cutaneous rash (more rare)...	At least 2 components of Whitaker triad (1 alone if siblings affected): candidiasis, AI with positive Ab anti-21-hydroxylase, hypoparathyroidism Sequencing of *AIRE* gene Anti-interferon-ω or anti-IL22 AB if available
APS 2	Polygenic: -*HLA: class II*: DR3-DQ2, DR4-DQ8, DRB1*0404 and *0301, *class I*: DR3-B8 Other molecules: linked to CMH: MICA, CIITA, co-stimulators of CMH: CTLA-4, PTPN22, linked to Ly B: FcRL3 promoter, innate immunity: CLEC16A, NALP1, vitamin D receptor...	Thyroiditis (65–75%) Diabetes type 1 (50–60%) AI (19–40%) Ovaritis (5–10%) Gastritis (5–29%) Celiac disease (3–10%) Vitiligo (10–20%) Alopecia (2–6%) Hypoparathyroidism (3%) Hypophysitis (2%)	AI associated with other autoimmune pathologies, principally thyroiditis and/or type 1 diabetes Anti-21-hydroxylase Ab
Isolated autoimmune AI	Polygenic (cf. APS2)		Anti-21-hydroxylase Ab Context of familial autoimmune pathologies
Infectious			
Bacterial	Tuberculosis (Mycobacterial), *Haemophilus influenzae*, Syphilis (*Treponema pallidum*)	Other systemic manifestations of the pathology	Adrenal CT, IDR, IGRA, culture, PCR
Viral	HIV, CMV, HSV...		
Parasitic	African Trypanosoma (*Trypanosoma brucei*)		
Fungal	*Pneumocystis carinii*, histoplasmosis, cryptococcosis, cocciodiomycosis, blastomycosis	Opportunistic infections	
Hemorrhagic	Anticoagulants, inhibitor of tyrosine kinase (sunitibib) Anti-phospholipid antibody syndrome Meningococcal sepsis (Waterhouse-Friderichsen) Disseminated intravascular coagulation	Acute adrenal insufficiency	Adrenal CT (hemorrhage)
Post-surgical Bilateral adrenalectomy	Uncontrolled cushing syndrome, bilateral adrenal masses, bilateral phaeochromocytoma		Context dependent
Tumoral: secondary, rarely primary	Bilateral metastases pulmonary, renal, gastric, breast, colon, pancreatic, melanoma, lymphoma		CT
Infiltrative	Amylosis, hemochromatosis, sarcoidosis, xanthogranulomatosis		
Drug-related	Ketoconazole, fluconazole, etomidate, metyrapone	Inhibition of cytochrome P450-dependent enzymes (CYP11A1, CYP11B1)	Context dependent
	Phenobarbital, phenytoin, rifampicine	Induction of cytochrome P450-dependent enzymes (CYP2B1, CYP2B2, CYP3A4) increasing cortisol metabolism	
	Mitotane	Cytotoxic mechanism	
	Anti-CTLA4 (Ipilimumab) associated or not with anti-PD1/PDL1 (Nivolumab, Pembrolizumab)	Autoimmune mechanism	
Genetic (cf. Table 2, pediatric)	Adrenoleukodystrophy (mutation of *ABCD1*)	cf. Table 2, pediatric	

IGRA: interferon-γ release assay: QuantiFERON-Tb Gold in Tube® (Cellestis Ld. Carnegie, Victoria, Australia) or T-SPOT.TB @ (Oxford Immunotec Ld., Abingdon, UK).