Consensus

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

Consensus

Group 3 : stratégies d’identification des causes d’insuffisances surrénales : algorithmes diagnostiques

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Mots clés : Consensus ; Insuffisance surré nale primaire ; Insuffisance corticotrope ; Adulte ; Enfant ; Auto-immunité ; Anticorps anti-21-hydroxylase ; Corticothérapie ; IRM hypophysaire

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

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Origin</th>
<th>Clinical manifestations associated with adrenal insufficiency (in order of frequency)</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APS 1 (APECED)</td>
<td>Monogenic</td>
<td>Candidiasis (83–100%) Hypoparathyroidism (79–93%) AI (60–70%) Ovariitis (60%)</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Mutations of AIRE gene</td>
<td>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%) Hypoparathyroidism (3%) Hypophysitis (7%)</td>
<td>Anti-interferon-α or anti-IL22 AB if available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial nephritis, obliterator bronchiolitis, febrile cutaneous rash (more rare), . .</td>
<td></td>
</tr>
<tr>
<td>APS 2</td>
<td>Polygenic: -HLA: class II: DR3-DQ2, DR4-DQ8, DRB1*0404 and *0301, class I: DR3-B8</td>
<td>Thyroiditis (65–75%) Diabetes type 1 (50–60%) AI (19–40%) Ovariitis (5–10%) Gastritis (5–29%) Celiac disease (3–10%) Vitiligo (10–20%) Alopecia (2–6%) Hypoparathyroidism (3%) Hypophysitis (2%)</td>
<td>AI associated with other autoimmune pathologies, principally thyroiditis and/or type 1 diabetes Anti-21-hydroxylase Ab</td>
</tr>
<tr>
<td></td>
<td>Other molecules: linked to CMH: MICA, CIITA, co-stimulators of CMH; CTLA-4, PTPN22, linked to Ly B; Fasl3 promoter, innate immunity: CLEC16A, NALP1, vitamin D receptor . .</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>Polygenic (cf. APS 2)</td>
<td></td>
<td>Anti-21-hydroxylase Ab Context of familial autoimmune pathologies</td>
</tr>
<tr>
<td>autoimmune AI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td>Other systemic manifestations of the pathology</td>
<td>Adrenal CT, IDR, IGRA, culture, PCR</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Tuberculosis (Mycobacterial), <em>Haemophilus influenzae</em>, <em>Syphilis (Treponema pallidum)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td>HIV, CMV, HSV . .</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
<td>African Trypanosoma (Trypanosoma brucei)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td><em>Pneumocystis carinii</em>, histoplasmosisis, cryptococciosis, cocciidiomycosis, blastomycosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemorrhagic</strong></td>
<td>Anticoagulants, inhibitor of tyrosine kinase (sunitibib) Anti-phospholipid antibody syndrome Meningoococal sepsis (Waterhouse-Friderichsen) Disseminated intravascular coagulation</td>
<td>Acute adrenal insufficiency</td>
<td>Adrenal CT (hemorrhage)</td>
</tr>
<tr>
<td><strong>Post-surgical</strong></td>
<td>Uncontrolled cushing syndrome, bilateral adrenal masses, bilateral phaeochromocytoma</td>
<td></td>
<td>Context dependent</td>
</tr>
<tr>
<td><strong>Tumoral</strong>: secondary, rarely primary</td>
<td>Bilateral metastases pulmonary, renal, gastric, breast, colon, pancreatic, melanoma, lymphoma</td>
<td></td>
<td>CT</td>
</tr>
<tr>
<td><strong>Infiltrative</strong></td>
<td>Amylosis, hemochromatosisis, sarcoidosis, xanthogranulomatosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug-related</strong></td>
<td>Ketoconazole, fluconazole, etomidate, metyrapone Phenobarbital, phenytoin, rifampicine Miototane Anti-CTLA4 (Iplilimumab) associated or not with anti-PD1/PDL1 (Nivolumab, Pembrolizumab)</td>
<td>Inhibition of cytochrome P450-dependent enzymes (CYP11A1, CYP11B1) Induction of cytochrome P450-dependent enzymes (CYP2B1, CYP2B2, CYP3A4) increasing cortisol metabolism Cytoxic mechanism Autoimmune mechanism</td>
<td>Context dependent</td>
</tr>
<tr>
<td>Genetic (cf. Table 2, pediatric)</td>
<td>Adrenoleukodystrophy (mutation of ABCD1)</td>
<td>cf. Table 2, pediatric</td>
<td></td>
</tr>
</tbody>
</table>

IGRA: interferon-γ release assay; QuantiFERON-Tb Gold in Tube® (Cellestis Ld, Carnegie, Victoria, Australia) or T-SPOT.TB® (Oxford Immunotec Ld., Abingdon, UK).
Table 2
Etiologies of primary adrenal insufficiency in children (adapted from Malikova [64]).

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Gene</th>
<th>OMIM</th>
<th>Associated signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal steroidogenesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital adrenal lipoid hyperplasia</td>
<td>Star</td>
<td>201710</td>
<td>46,XY DSD, gonadal insufficiency</td>
</tr>
<tr>
<td>P450 side chain cleavage deficiency (P450scc)</td>
<td>CYP11A1</td>
<td>118485</td>
<td>46,XY DSD, gonadal insufficiency</td>
</tr>
<tr>
<td>3β-hydroxysteroid dehydrogenase (CAH) deficiency</td>
<td>HSD3B2</td>
<td>201810</td>
<td>46,XY DSD and 46,XX DSD, gonadal insufficiency</td>
</tr>
<tr>
<td>21-hydroxylase deficiency (CAH)</td>
<td>CYP21A2</td>
<td>201910</td>
<td>46,XX DSD, hyperandrogenism</td>
</tr>
<tr>
<td>11β-hydroxylase deficiency (CAH)</td>
<td>CYP11B1</td>
<td>202010</td>
<td>46,XX DSD, hypertension, hyperandrogenism</td>
</tr>
<tr>
<td>17-hydroxylase deficiency (CAH)</td>
<td>CYP17A1</td>
<td>202110</td>
<td>46,XY DSD, hypertension, gonadal insufficiency</td>
</tr>
<tr>
<td>P450 oxidoreductase deficiency (CAH)</td>
<td>POR</td>
<td>613571</td>
<td>46,XY DSD, 46,XX DSD, gonadal insufficiency</td>
</tr>
<tr>
<td>Aldosterone synthase deficiency</td>
<td>CYP11B2</td>
<td>124080</td>
<td>Antley-Bixler syndrome (bone defects)</td>
</tr>
<tr>
<td>Adrenal hypoplasia/dysgenesis</td>
<td></td>
<td></td>
<td>Isolated mineralocorticoid deficiency</td>
</tr>
<tr>
<td>X-linked adrenal hypoplasia</td>
<td>NROB1 (DAX1)</td>
<td>300200</td>
<td>Hypogonadism hypogonadotropic</td>
</tr>
<tr>
<td>SF1 deficiency</td>
<td>NR5A1 (SF1)</td>
<td>184757</td>
<td>46,XY DSD, gonadal insufficiency</td>
</tr>
<tr>
<td>IMAGE syndrome</td>
<td>CDKN1C</td>
<td>614732</td>
<td>Intra-uterine growth retardation, bone defects, genital abnormalities, facial dysmorphism, hypercalcinema</td>
</tr>
<tr>
<td>MIRAGE syndrome</td>
<td>SAMD9</td>
<td>617053</td>
<td>Myelodysplasia, infection, growth retardation, genital abnormalities, enteropathy</td>
</tr>
<tr>
<td>Pallister-Hall syndrome</td>
<td>GLI3</td>
<td>165240</td>
<td>Hypothalamic hamartoma, polydactyly, bifid epiglottis, imperforate anus, genital abnormalities</td>
</tr>
<tr>
<td>Meckel syndrome</td>
<td>MKS1</td>
<td>249000</td>
<td>Polycystic kidney, cerebral malformations, occipital encephalocoele, polydactyly, hepatic fibrosis</td>
</tr>
<tr>
<td>Pena-Shokeir syndrome</td>
<td>DOK7</td>
<td>208150</td>
<td>Arthrogryposis, facial dysmorphism, intra-uterine growth retardation, camptodactyly, pulmonary hypoplasia, cardiac malformation, intestinal malrotation</td>
</tr>
<tr>
<td>ACTH resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial glucocorticoid deficiency</td>
<td>MC2R</td>
<td>202200607398</td>
<td>Absence of mineralocorticoid deficiency, large size</td>
</tr>
<tr>
<td>Triple A syndrome (Allgrove syndrome)</td>
<td>MRAP</td>
<td>AAAS</td>
<td>Alacrimia, achalasia, deafness, neurological defects, hyperkeratosis</td>
</tr>
<tr>
<td>Oxidative stress defect</td>
<td>NNT</td>
<td>614736606448</td>
<td>Affected organs that are rich in mitochondria (myocardiopathy, hypothryoidism, partial GH deficiency)</td>
</tr>
<tr>
<td>DNA repair defect</td>
<td>MCM4</td>
<td>609981</td>
<td>NK cell deficiency, recurrent viral infections, short stature, microcephaly</td>
</tr>
<tr>
<td>Peroxisomol diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>ABCD1</td>
<td>300100</td>
<td>Progressive degenerative neurological damage, deafness, vision problems, convulsions, accumulation of very long chain fatty acids</td>
</tr>
<tr>
<td>Infantile Refsum disease</td>
<td>PHYH, PEX7</td>
<td>266500</td>
<td>Pigmentary retinopathy, deafness, cerebellar ataxia, hypotonia, growth retardation, intellectual disability</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>PEX (PEXI)</td>
<td>214100</td>
<td>Facial dysmorphism, severe hypotonia, epilepsy, severe intellectual disability, blindness, deafness, hepatomegaly, genital abnormalities</td>
</tr>
<tr>
<td>Mitochondrial cytopathies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kearns-Sayre syndrome</td>
<td>Mitochondrial DNA deletion</td>
<td>530000</td>
<td>Progressive ophtalmoplegia, deafness, cardiac abnormalities, ataxia, intellectual disability, myopathy, hormonal deficiencies, renal insufficiency</td>
</tr>
</tbody>
</table>

Autoimmune diseases (cf. Adult table)  
Acquired pathologies (cf. Adult table)  

DSD: disorders of sex development.

[1]. This pathology is classically seen as adrenal insufficiency associated with a mucocutaneous candidiasis and hypoparathyroidism (Whitaker’s triad), and can in reality be a larger group of autoimmune endocrine and non-endocrine pathologies, including infectious and more rarely neoplastic pathologies (see Table 1). Some of these have life-threatening prognoses, such as hepatic, pulmonary, renal and neoplastic manifestations (large granular lymphocytic leukemia, epidermoid oral or esophageal carcinomas) [12–14].

1.1.1.2. Primary adrenal insufficiency of other origins: tuberculosis, adrenoleukodystrophy and other rarer causes. Few recent studies have looked at the relative frequency of other PAI etiologies. Betterle et al. reported on the causes of PAI in 633 adult patients treated in their endocrinology unit over a period of 43 yrs (1967–2010). In this cohort, the non-autoimmune causes of PAI related to 22% of patients, with the most prominent cause amongst these being tuberculosis, found in 9% of cases on average in this period. However, the relative frequency of
tuberculosis has decreased over the last decades, with a parallel increase in autoimmune PAI, and is significantly lower now, being around 3% of cases [1].

Other causes reported in this series of patients represented 8% of cases of PAI including genetic origins (4.6%, the most frequent being adrenoleukodystrophy), tumoral (1.6%), postsurgical (<1%), non-bacillary infection (<1%) and hemorrhage (<1%) [1]. AI linked to infiltrating pathologies or pharmaceuticals were also described (detailed in Table 1) [1,15]. The number of cases deemed to be idiopathic (less than 5% of cases) tends to reduce over time, due to improvements in diagnostic methods to detect immunological and genetic causes [1]. AI occurring in very young patients is less frequently of autoimmune origin, suggesting that other possible etiologies need to be examined [16].

Amongst the genetic origins of PAI, adrenoleukodystrophy (ALD) is one of the rare pathologies where diagnosis is sometimes made in adult patients [1], the other genetic causes being classically recognized in pediatric patients (see Chapter 2, pediatric section). Thus, in ALD, PAI can manifest later, in adolescence or adulthood, in the case of PAI discovered during an episode of adrenal crisis, this may be in adults over 50 yrs of age [17]. It now constitutes the third highest cause of PAI in adult males. The frequency in males is approximately 1/20,000 and may represent 1–5% of adult cases of PAI [1,17]. This peroxisomal metabolic disorder, an X-linked recessive disease, is linked to mutations in the ABCD1 gene. Diagnosis is made by plasma assay for very long chain fatty acids which also accumulate in fibroblasts and tissue. This pathology is characterized by early cerebral demyelination and later medullary axon demyelination, adrenal insufficiency and peripheral hypogonadism [17,18]. Females can also be affected, but generally do not develop signs other than in the CNS. PAI can precede other manifestations of the disorder, remaining isolated over several years or even decades. The reported penetrance is highly variable, depending on the study (from 50–100%) [19].

R3-1: We recommend examination for the etiology of AI to optimize its management and to avoid overlooking causal pathologies that can be treated.

Strong recommendation. Expert opinion.

1.1.2. Biochemical and genetic markers – imaging

1.1.2.1. Anti-21-hydroxylase antibodies. Due to their frequency, autoimmune causes are justified as the first choice for testing. Anti-21-hydroxylase antibodies, measured by radioimmunoassay, are excellent diagnostic markers for autoimmune PAI. They exhibit good sensitivity, particularly in the early stages of the disease, and are better than anti-adrenal antibodies [20]. Anti-21-hydroxylase antibodies are detected in 83–88% of cases [2,3,20–22] while anti-adrenal antibodies, detected by indirect immunofluorescence, are only detected in 48–80% of cases [1,22]. Their specificity is also excellent, since they are not detected in the serum of patients suffering from other causes of PAI (tuberculosis, ALD) [22,23], with the exception of a case of AI linked to Kearns-Sayre syndrome [24]. Generally, the test consists of a commercial kit (FIRS Laboratories, RSR, Cardiff, Great Britain, labeling with 125I), or an assay method used in research laboratories, the assays for anti-21-hydroxylase antibodies appear to give comparable results, though standardization of positive threshold levels and units is necessary [25]. However, though their prevalence is 90% in the two years following diagnosis of the disease, they diminish progressively, to 70% after 12 yrs [26]. Therefore, a negative result does not exclude an autoimmune origin for the pathology, in particular if the disease has been present for several years. In addition, their prognostic value is shown by their presence in asymptomatic patients predicting an approximately 50% risk of developing PAI in the following 10 yrs, with a higher risk in those with higher antibody levels [26].

R3-2: We recommend assay for anti-21-hydroxylase antibodies as first-line testing in adults.

Recommendation: strong, level of evidence ++.

R3-3: We suggest that assay for anti-adrenal antibodies be discontinued.

Recommendation: strong, level of evidence ++.

1.1.2.2. Gene sequencing of AIRE. Amongst those with autoimmune adrenal insufficiencies, it is important to identify those in the setting of APS1. These constitute an important cause of autoimmune PAI in young subjects, and require early diagnosis due to their potential severity, in order to optimize their surveillance and improve their management [12–14]. In case of clinically suspected APS1, diagnosis should be confirmed by sequencing of the AIRE gene [27,28]. However, the time taken to obtain sequencing results can be significant. It therefore can be useful to assay for anti-interferon-γ antibodies [29,30], or anti-interleukin 22 (IL22) antibodies [31,32], which have excellent sensitivity and specificity for APS1, if these assays are available.

R3-4: In young patients with autoimmune adrenal insufficiency, in case of clinical symptoms that are suggestive of autoimmune polyendocrinopathy 1 (APS1) – i.e. candidiasis, hypoparathyroidism, keratitis, alopecia, hypoplasia of dental enamel, malabsorption, ovaritis, hepatitis – we recommend genotyping for the AIRE gene.

Recommendation: strong, level of evidence +.
1.1.2.3. Adrenal imaging. In cases where clinical signs suggest a non-autoimmune PAI, or where anti-21-hydroxylase antibodies are negative, adrenal imaging can show either tumoral mass or infiltrating pathologies. Thin-section CT of the adrenal with density measures before and after injection of contrast (with early and late imaging after washout) is the examination of choice. Magnetic resonance imaging (MRI) has similar performance to CT scanning, but has some drawbacks: the acquisition time is longer (risk of respiratory artefacts), they are generally less available and the cost is greater. MRI can, however, be used in cases where CT is contraindicated. Adrenal CT can detect tumoral invasion, bilateral infiltrate, or hemorrhage depending on the context (anticoagulant treatment, anti phospholipid antibody syndrome, Waterhouse-Friderichsen syndrome,...).

In cases of adrenal tuberculosis, most often the adenals are enlarged, with calcifications visible in around half of these cases [1,33]. However, CT is not specific, some patients with infiltrative or infectious pathologies (particularly tuberculosis) can have normal or even smaller than normal-sized adenals [1,16]. It should be noted that in cases of long-established autoimmune AI, anti-21-hydroxylase antibodies may be negative [20,26]; in this case, CT may then show normal-sized adenals or atrophied/invisible adenals [1].

R3-6: In adult patients, we recommend adrenal CT when tests are negative for anti-21-hydroxylase antibodies or immediately in the case of clinical signs suggesting a general pathology that requires urgent management (tuberculosis, hemorrhage, tumor).
Recommendation: strong, level of evidence ++.

1.1.2.4. Assay for very long chain fatty acids. Adrenoleukodystrophy is a cause of primary adrenal insufficiency in a small but significant number of adolescent male subjects and, more rarely, adult male subjects [22]. Furthermore, PAI may be isolated, preceding other disorders. Early diagnosis allows appropriate management, particularly neurological management, of the index case and further thorough examination of the patient’s family. Thus testing for very long chain fatty acids is warranted in the case of negative tests for anti-21-hydroxylase antibodies and a normal adrenal CT [22]. Its diagnosis is made based on a plasma assay for very long chain fatty acids [19,34].

R3-7: If an autoimmune etiology is not found, and in the case of a normal adrenal CT, assay for very long chain fatty acids should be carried out, particularly in adolescent males but also in adult male subjects.
Recommendation: Expert opinion.

1.1.2.5. Molecular biology. Other causes or PAI are much rarer (see Table 1). The clinical context may suggest other genetic pathologies and molecular biology may allow the suspected diagnosis to be confirmed. The diagnosis of idiopathic PAI should remain a diagnosis to be ruled out by elimination. The course of action to determine the etiology of cases of PAI diagnosed in adulthood is summarized in the form of a decision tree in Fig. 1.

1.2. Corticotropin (ACTH) insufficiency in adults

Aside from iatrogenic ACTH insufficiency, which is induced by corticosteroid therapy, isolated ACTH insufficiency is rare (see Chapter 1, epidemiology of adrenal insufficiency). In fact, ACTH insufficiency is most often associated with other anterior or posterior pituitary deficiencies in the setting of various hypothalamic-pituitary lesions. Two situations are discussed below.

1.2.1. Causes of isolated ACTH insufficiency

A particularly frequent situation to be considered first is ACTH insufficiency secondary to prolonged corticosteroid therapy which can be compared to ACTH insufficiency during treatment for Cushing’s syndrome [35]. Screening should also be done for iatrogenic ACTH insufficiency secondary to non-systemically administered corticosteroids such as inhaled corticosteroids [36], or other unsuspected routes of administration (topical etc.) (see also Chapter 2, diagnosis of adrenal insufficiency).

Isolated ACTH insufficiency can also be found in lymphocytic hypophysitis, in 6% of cases [37–39], both in spontaneous autoimmune hypophysitis [39] or iatrogenic cases [40]. Additionally, anti-CTLA (cytotoxic T-lymphocyte-associated protein 4) or anti-PD1/PDL1 (programmed cell death 1/Programmed cell death ligand 1) therapies which are now frequently used in oncology, can also result in hypophysitis (see below, causes of ACTH insufficiency associated with other pituitary deficiencies). Isolated ACTH insufficiency has been described in patients treated with Ililimumab and Nivolumab [41–44]. Pituitary MRI may thus appear normal, or show a typical appearance of adenohypophysitis or partially empty sella turcica [41–44].

Lastly, isolated ACTH insufficiency has been reported in other situations that are normally known for producing multiple pituitary deficiencies: immediately or delayed post-trauma, Sheehan’s syndrome, after radiotherapy for a cerebral tumor, in the case of empty sella turcica and possibly after an undiagnosed hypophysitis [45,46].
Regarding constitutional isolated ACTH insufficiency, this condition is very rare and will be detailed below in the section “ACTH insufficiency in children”.

1.2.2. ACTH insufficiency associated with other pituitary deficiencies

The majority of acquired hypothalamic-pituitary illnesses with hypothalamicism as a complication, can also give rise to ACTH insufficiency. These include pituitary adenoma, cranioopharyngioma, primary hypophysitis either lymphocytic or secondary to infection, inflammation or infiltrative pathology, cranial trauma, vascular disease, tumors or pituitary metastases [15] (see Table 3). In most of these situations, ACTH insufficiency is associated with other pituitary deficiencies and is, in general, the last to appear [47].

Conversely, in lymphocytic hypophysitis, ACTH insufficiency is particularly frequent (65% of cases), sometimes isolated (see above) and can be the first to appear [39,48]. This diagnosis can be suspected in particular contexts: most often in female patients, in the presence of other autoimmune pathologies in the patient or her family, in the 2nd or 3rd trimester of pregnancy or immediately post-partum and in subjects treated with immunomodulators [39,48]. On MRI imaging, adenohypophysitis is seen as an increased volume in the sella turcica and an intense increase after injection with gadolinium. Enlargement of the pituitary stalk and an absence of stored antidiuretic hormone is found in the case of infundibulo-neurohypophysitis with associated diabetes insipidus [49].

Additionally, as mentioned above, immune checkpoint inhibitors, recently developed drugs that were initially used in treating metastatic melanoma, then more widely in oncology, can result in hypophysitis. In accentuating the immune response directed against the tumor cells, these treatments induce various autoimmune pathologies. Hypophysitis occurs during the first months of treatment, with ACTH insufficiency often associated with a TSH insufficiency. Other additional pituitary insufficiencies may or may not be present [40,44]. Treatment with anti-CTLA4 (Ipilimumab) alone (on average 4% of hypophysitis cases), or associated with anti-PD1/PDL1 (Nivolumab, Pembrolizumab, from 1–4% of cases of hypophysitis); the association of Ipilimumab and Nivolumab appears to be the most potent inducer of hypophysitis (up to 8% of cases) [50]. Lastly, granulomatous hypophysitis, presenting as an ACTH insufficiency after treatment for hepatitis C with Interferon/Ribavirine has also been described in one study [51].

Another cause of iatrogenic ACTH insufficiency should be underlined: this is ACTH insufficiency induced by opiates which seems to be underdiagnosed [52]. Opiates inhibit the ACTH axis at different levels: they induce a reduction in the production of CRH, while also reducing the capacity of the pituitary to respond to CRH stimulation, thus causing a reduction in ACTH production [53]. They can also directly inhibit adrenal production of cortisol and DHEA [54]. This is associated with a dose-dependent gonadotropin deficiency that is better-documented [53].

Lastly, ACTH deficiencies can form part of combined pituitary deficiencies secondary to developmental problems (genetic anomalies that affect the expression of morphogenic factors or pituitary transcription factors). Most often, diagnosis is made in childhood (see paragraph “ACTH insufficiency in children”). It should be noted however, that pituitary deficiencies can appear successively and sometimes decades later, particularly in the
Table 3
Etiologies of ACTH insufficiency in adults (adapted from Charmandari, 2014 [15]).

<table>
<thead>
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<th>Etiology</th>
<th>Pathophysiological mechanisms</th>
<th>Clinical manifestations associated with adrenal insufficiency</th>
<th>Diagnostic criteria</th>
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<tr>
<td><strong>Iatrogenic</strong></td>
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<td>Post-corticosteroid, or post-treatment of Cushing’s syndrome</td>
<td>Inhibition of ACTH axis</td>
<td>Isolated ACTH insufficiency</td>
<td>Context dependent</td>
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<tr>
<td>Opioids</td>
<td>Inhibition of ACTH axis</td>
<td>Gonadotropin insufficiency</td>
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<td>Anti-depressants (imipramine)</td>
<td>ACTH deficiency</td>
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<td>Anti-psychotics (chlorpromazine)</td>
<td>ACTH deficiency</td>
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<tr>
<td>Hypophysitis iatrogenic: Interferon-Ribavirine</td>
<td>ACTH deficiency</td>
<td>ACTH deficiency sometimes indicative</td>
<td>Frequently associated with TSH deficiency</td>
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<tr>
<td>Hypophysitis iatrogenic: Anti-CTLA4 (ipilimumab) ± associated with anti-PD1 (nivolumab, pembrolizumab)</td>
<td>ACTH deficiency</td>
<td>± gonadotropin, GH deficiency, rarely with diabetes insipidus or SIADH</td>
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<td><strong>Tumors</strong></td>
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<td>Hypothalamic: craniopharyngiomas, metastases</td>
<td>CRH deficiency</td>
<td>Other anterior or posterior pituitary deficiencies, ± other clinical manifestations linked to the causal pathology</td>
<td>MRI, context dependent</td>
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<tr>
<td>(lung, breast)</td>
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<tr>
<td>Pituitary: macroadenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, carcinomas (rarely)</td>
<td>ACTH deficiency</td>
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<td><strong>Pituitary surgery or radiotherapy</strong></td>
<td>Deficiency in CRH and/or ACTH</td>
<td>Other anterior or posterior pituitary deficiencies</td>
<td>Context dependent</td>
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<td>(pituitary tumors, cerebral tumors, in the naso-pharyngeal region, leukemias)</td>
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<tr>
<td><strong>Primary hypophysitis</strong></td>
<td>Deficiency in CRH and/or ACTH</td>
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<td>Lymphocytic</td>
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<td>Granulomatous, xanthomatous</td>
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<tr>
<td>IgG4 hypophysitis (IgG4 fibro-sclerosing disease)</td>
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<td><strong>Secondary hypophysitis: due to systemic pathology: infectious</strong></td>
<td>Deficiency in CRH and/or ACTH</td>
<td>Headache, visual problems, other anterior or posterior pituitary deficiencies, ± other clinical manifestations linked to the causal pathology</td>
<td>MRI, context dependent</td>
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<tr>
<td>tuberculosis, syphilis, Actinomycosis, meningitis, abscess; <em>inflammatory</em>: sarcoidosis, ANCA vasculitis, Wegener; <em>infiltrative</em>: hemochromatosis, amyloidosis, histiocytosis</td>
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<td><strong>Vascular</strong></td>
<td>ACTH deficiency</td>
<td>Severe headaches, vision problems, nausea, vomiting, other anterior/posterior pituitary deficiencies</td>
<td>MRI</td>
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<td>Pituitary apoplexy</td>
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<tr>
<td>Sheehan syndrome</td>
<td>Hemorrhage in childbirth/delivery, headaches, vision problems, nausea, vomiting, other anterior/posterior pituitary deficiencies</td>
<td>MRI, context peri-partum</td>
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<tr>
<td><strong>Traumatic</strong></td>
<td>CRH and/or ACTH deficiency (from pituitary hypoperfusion)</td>
<td>Other anterior/posterior pituitary deficiencies (often gonadotropin and GH)</td>
<td>Context dependent</td>
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<tr>
<td>Cranial trauma</td>
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<td><strong>Genetic</strong></td>
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<td>(cf. Fig. 4, pediatric)</td>
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case of ACTH deficiency [55,56]. ACTH deficiency leading to acute adrenal insufficiency has also been reported in Prader-Willi syndrome in situations of increased stress [57].

R3-8: In the case of isolated ACTH insufficiency at presentation, previous or current corticosteroid treatment, either by systemic or local administration, should be suspected.

Strong recommendation. Expert opinion.

R3-9: In the absence of previous corticosteroid treatment or previous management of Cush-

ing’s syndrome, ACTH insufficiency should be explored. This requires a complete examination of pituitary hormones and morphology (pituitary MRI in the absence of contraindication).

Strong recommendation. Expert opinion.

2. Pediatric patients

2.1. Primary adrenal insufficiency in children

2.1.1. Neonatal period, in babies

The principal etiology of PAI is congenital adrenal hyperplasia with a deficiency in enzymes involved in steroidogenesis. This accounts for around 50% of PAI in neonates [58,59]. In 95% of cases, it consists of a deficiency in 21-hydroxylase, diagnosed by specific assay after heel prick for 17OHP progesterone, at day 3 of life in all newborns in France. This enzyme deficiency results in virilization of external genitals in young girls due to the inappropriate secretion of adrenal androgens during the fetal period, glucocorticoid insufficiency and mineralocorticoid insufficiency in more than 75% of cases. Other rarer enzyme deficiencies give, depending on the enzyme function, anomalies in genitals of girls and/or boys and a glucocorticoid deficiency that may or may not be combined with a mineralocorticoid deficiency.

The second principal cause of glucocorticoid and mineralocorticoid adrenal insufficiency is congenital adrenal hypoplasia which represents 1.5–5% of cases of primary adrenal insufficiency [59–61]. It presents as episodes of hypoglycemia in the first month of life, though sometimes can appear later in childhood. It is essentially due to mutations in the DAX1 gene. Adrenal insufficiency can be associated with hypogonadotropic hypogonadism which can appear later, in adulthood. Gene deletion of DAX1 can be part of a syndrome of contiguous gene defects responsible for a triad of disorders: Duchenne’s muscular dystrophy, glycerol kinase deficiency and primary adrenal insufficiency. Mutations in the SF1 gene, responsible for variable phenotype in 46XY gonadal dysgenesis patients, have been reported as the cause of adrenal hypoplasia in rare cases. Adrenal hypoplasia can form part of syndromes including: IMAGE syndrome (intra-uterine growth retardation, skeletal anomalies, facial dysmorphe, genital anomalies, hypercalcemia [mutation in the CDKN1C gene]) [62], MIRAGE syndrome (myelodysplasia, infection, growth retardation, genital abnormalities, enteropathy) [63], Pallister-Hall syndrome (mutation of GLI1 gene), Meckel syndrome (mutation of MKS1 gene) and Pena-Shokeir syndrome (mutation of DOK7 and RAPSN genes) [64].

In case of deficiency restricted to glucocorticoids, resistance to ACTH should be considered as it represents 5% of primary adrenal insufficiencies [59,65]. Familial glucocorticoid deficiency should be explored (MC2R and MRAP mutations) which present as neonatal hypoglycemia, convulsions, abnormal psychomotor development and hyperpigmentation. Recently, abnormalities in oxidative stress have been described linked to the NNT gene, responsible for glucocorticoid insufficiency in general diagnosed in the first two years of life, though sometimes diagnosed later [66]. Mineralocorticoid insufficiency can appear in the development of the latter pathology and thus necessitates regular assay of plasma renin. Other organs can be affected due to the ubiquitous expression of NNT (myocardioopathy, hypothyroidism, partial growth hormone deficiency).

2.1.2. In older children

As in the adult patient, autoimmune adrenal insufficiency is the first cause to consider in older children, by testing for anti-21-hydroxylase antibodies. Autoimmune adrenal insufficiency represents 24–31% of PAI [58,59,67] with a mean age at diagnosis between 11 and 14 yrs. Autoimmune adrenal insufficiency can be part of autoimmune polyendocrinopathy syndrome type 1 or APECED syndrome, these represent 5–13% of cases of PAI. Diagnosis rests on the combination of 2 out of 3 criteria, these being mucocutaneous candidiasis (appearing in childhood), hypoparathyroidism (appearing around age 7 yrs) and adrenal insufficiency occurring between the ages of 5 and 15 yrs, with a progressive increase in prevalence with age [14,68].

Adrenoleukodystrophy (ALD) due to mutation of the ABCD1 gene should be examined in boys when tests for antibodies are negative. This is performed using assay for very long chain fatty acids. ALD represents 5–15% of PAI [59,60,67]. PAI occurs at a mean age of 10–12 yrs (sometimes as young as 3–4 yrs). In the study of Ronghe et al., ALD was diagnosed secondarily in 83% of boys (n = 12) in follow-up after being diagnosed with “idiopathic” PAI [69]. In the study of Polgreen et al., on 90 boys with ALD who were younger than 15 yrs, adrenal insufficiency was the first sign of the disease in 38% of the cohort [70].

Triple A syndrome (Allgrove’s syndrome) consists of a combination of congenital alacrimia, achalasia and Addison’s disease, but also includes progressive neurological problems (4A syndrome). It is responsible for a glucocorticoid deficiency that arises between the ages of 5 and 10 yrs [71]. In a study on 8 children, by Dumic et al., adrenal insufficiency was the first symptom in 50% of cases reported [72]. This syndrome is linked to mutations in the AAAS gene, and represents 1% of cases of PAI [60,61].

Other pathologies can be responsible for destruction of the adrenal parenchyma, such as Zellweger syndrome (PEX
gene), Refsum’s disease (PHYH and PEX7 genes), mitochondrial cytopathies (Kearne Sayre syndrome), and abnormalities in cholesterol synthesis (Wolman syndrome, Smith Lemly Opitz syndrome).

Acquired causes of primary adrenal insufficiency in children are much more rare and include: adrenal hemorrhage, severe infection (septic shock, Waterhouse-Frederichsen syndrome, HIV, tuberculosis, CMV), surgery, infiltrative pathologies (metastases, lymphoma, sarcoidosis, hemochromatosis) and drug-related (ketoconazole, rifampicin, phenytoin). They are included in the etiologies of acquired PAI in adults (see Table 1).

R3-10: In newborns and babies, in the case of glucocorticoid deficiency ± mineralocorticoid deficiency, we recommend examination for congenital adrenal hyperplasia by assays for adrenal steroids using LC-MS/MS. In the absence of evidence of enzyme deficiency, we recommend high-speed sequencing of a panel of genes responsible for other rare causes of adrenal insufficiency.
Recommendation: strong, level of evidence ++.

R3-11: In newborns and babies, in the case of deficiency restricted to glucocorticoids, we recommend high-speed sequencing of the same panel of genes mentioned above (R3-10).
Recommendation: strong, level of evidence ++.

R3-12: In children and adolescents, in the case of glucocorticoid and mineralocorticoid deficiency, we recommend as first-line testing for anti-21-hydroxylase antibodies. In the absence of antibodies, and in males, we recommend assay for very long chain fatty acids to confirm adrenoleukodystrophy. If all tests are negative, examination of DAX-1 (NR0B1) gene can be carried out prior to studying the panel of genes.
Recommendation: strong, level of evidence ++.

The examinations and assays to determine the etiology of a primary adrenal insufficiency in newborns and older children is summarized in the form of a decision tree in Figs. 2 and 3.

2.2. ACTH Insufficiency in children

Only constitutional causes of ACTH deficiency are discussed in this section. Acquired causes, either tumoral or inflammatory, are similar to the adult pathology even though their prevalence may be different.

Constitutional pituitary deficiencies involving an ACTH deficiency consist of three types [73].

Multiple pituitary hormone deficiencies (MPHD) associated with cerebral malformations (septo-optic dysplasia, hydrocephaly, Chiari malformation) or extra-cerebral malformations (ocular, cardiac or renal abnormalities): all known gene defects that affect early pituitary development and that of other organs carry the risk of occurrence of ACTH deficiency in the neonatal period or later (HESX1, SOX3, SOX2, LHX4, OTX2).

Multiple pituitary deficiencies without extra-pituitary anomalies: the known genetic causes of such a phenotype affect the terminal phase of pituitary development. Mutations of POU1F1 do not result in ACTH deficiency. Mutations in PROP1 are the primary cause of pure multiple pituitary deficiency: this gene anomaly carries an elevated risk of developing an ACTH deficiency form birth, but sometimes appears much later with risk of mortality if it is not diagnosed [73]. The case is the same for patients with LHX3 mutation, which is much rarer. Mutations in LHX3 gene have been associated with phenotype features comprising abnormal neck rotation and/or deafness though this is not constant nor specifically characteristic.

Isolated deficiency in ACTH: several clinical entities exist:

• the first is a complete neonatal ACTH deficiency sometimes associated with a transitory deficiency in GH but without extra-pituitary anomalies: genetic analysis in the first instance is by sequencing the TBX19 gene. Demonstration of a mutation in this gene has the advantage of being able to predict the transitory GH deficiency with which it is associated [74], the absence of other deficiencies in the long-term and to provide genetic counseling for possible future pregnancies. The absence of TBX19 mutation in the presence of a complete neonatal ACTH deficiency requires, at a minimum, sequencing of PROP1 and LHX3 genes. In this case, the pituitary deficiency will later become a multiple deficiency necessitating systematic surveillance of other axes;
• the second is the association of ACTH deficiency with common variable immune deficiency (CVID), also known as DAVID syndrome [51]. Genetic analysis in this case should first examine NFKB2 gene. The benefit in this case is to better understand the mechanisms underlying the pathophysiology of the disease, at the same time to start managing the immune
deficiency and to screen for the appearance of other pituitary deficiencies [75]. The hormonal phenotype and its evolution over time must be clarified by clinical observations over time; 
- a defect in production of ACTH from its precursor POMC: mutations in the POMC gene and mutations in type 1 proconvertase (preprotein convertase or PC1) are associated with an ACTH deficiency and early severe obesity [37,76].

R3-14: In the newborn, diagnosis of ACTH deficiency should be followed with a complete examination of the pituitary as well as examinations for cerebral, ocular and cardiac malformations.
Recommendation: strong, level of evidence ++.

R3-15: In the newborn, diagnosis of ACTH deficiency associated with other pituitary deficiencies should be followed by genetic analyses which may be useful for an evolving prognosis. In the presence of mutation of TBX19 gene and neonatal GH deficiency, other axes should be reevaluated around 2 yrs of age, to confirm reversal of the GH deficiency.
Strong recommendation. Expert opinion.

R3-16: In children and adolescents, diagnosis of multiple constitutional non-syndromic pituitary deficiencies should be followed by genetic testing in order to advise the family and a screening of family members if necessary.
Strong recommendation. Expert opinion.

R3-17: In children or adolescents, the presence of isolated ACTH deficiency should be followed by examination for immune deficiency and analysis of the NFKB2 gene. If there is associated childhood obesity, testing for POMC gene anomaly should be performed.
Strong recommendation, level of evidence ++.

The procedures for determining the etiology of ACTH insufficiency in pediatric patients is summarized in the form of a decision tree in Fig. 4.

Disclosure of interest

The authors declare that they have no competing interest.
Fig. 3. Strategy for identifying the cause of primary adrenal insufficiency in the child and adolescent.

Fig. 4. Decision tree for identifying the genetic cause of ACTH insufficiency.
References


