



# Idiopathic isolated adrenocorticotrophic hormone deficiency: a systematic review of a heterogeneous and underreported disease

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## Abstract

Isolated adrenocorticotrophic hormone deficiency (IAD) is considered to be a rare disease. Due to the nonspecific clinical presentation, precise data on the prevalence and incidence are lacking. In this systematic review, we aimed to analyse the clinical characteristics, association with autoimmune diseases, and management of acquired idiopathic IAD cases. A structured search was conducted after developing a search strategy combining terms for acquired (idiopathic) IAD. Articles describing an adult case with a diagnosis of ACTH deficiency using dynamic testing, no deficiency of other pituitary axes, and MRI of the brain/pituitary protocolled as normal, were included. Exclusion criteria were cases describing congenital IAD, cases with another aetiology for IAD, and articles where full text was not available. In total 42 articles were included, consisting of 85 cases of acquired idiopathic IAD. Distribution by sex was approximately equal (F:M; 47:38). Lethargy was the most common presenting symptom (38%), followed by weight loss (25%), anorexia (22%), and myalgia/arthralgia (12%). Eight cases (9.5%) presented with an Addison crisis. 31% of cases had an autoimmune disease at diagnosis of which Hashimoto hypothyroidism was the most frequent. Data about follow-up was scarce; dynamic testing was repeated in 4 cases of which 2 showed recovery of the adrenal axis. We report the largest case series of acquired idiopathic IAD to date. Our systematic review highlights the lack of a clear definition and diagnostic work-up. Based on the findings in this review a proposition is made for a flowchart to diagnose acquired idiopathic IAD.

**Keywords** Idiopathic isolated ACTH deficiency · Adrenal insufficiency · Acquired · Anti-pituitary antibody · Hypopituitarism

## Introduction

Except for glucocorticoid-induced adrenal deficiency, insufficiency of the hypothalamic-pituitary-adrenal (HPA) axis is most commonly associated with failure of multiple pituitary axes and is rarely isolated. Isolated adrenocorticotrophic hormone deficiency (IAD) has been first described by Steinberg et al. in 1954 [1]. Since the clinical presentation of IAD is nonspecific, it is estimated that a considerable number of patients are undiagnosed, and thus precise data on the

prevalence and incidence are lacking [2]. An emerging cause of IAD is hypophysitis secondary to immunotherapy for cancer.

In 1989, Nowakowski et al. published a case of an IAD without an obvious aetiology, and the term acquired idiopathic IAD (AIIAD) was coined [3]. Currently, AIIAD is defined by secondary adrenal insufficiency (AI) in the absence of dysfunction of other pituitary axes, absence of structural pituitary defects, no history of prolonged glucocorticoid therapy or radiotherapy and exclusion of the following pathologies: inflammatory pituitary lesions, primary hypophysitis including lymphocytic and immunotherapy-induced hypophysitis, Sheehan's syndrome and traumatic brain injury (TBI). More recently, opioids have gained attention as a possible cause of secondary AI [4]. Previously published cases with idiopathic IAD did not always meet this definition.

Idiopathic IAD is a diagnosis of exclusion, which leads to a heterogeneous patient population. The largest case

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series of AIIAD in the literature comprised 46 cases [5]. That article focused on immunofluorescence analysis of the sera of patients with AIIAD aiming to clarify the significance of the presence of anti-pituitary antibodies. Important to note regarding anti-pituitary antibodies is that their presence is not specific for lymphocytic hypophysitis and they have been described in a variety of auto-immune disorders and pituitary diseases, including IAD [6, 7]. In this descriptive systematic review, we aimed to analyse the clinical characteristics, association with autoimmune disease, and management of previously published AIIAD cases and propose a diagnostic flowchart.

## Methods

### Search strategy

We systematically searched Pubmed and Web of Science after developing a search strategy combining terms for acquired (idiopathic) isolated ACTH deficiency. We limited our results to English and French articles. Search results until June 2023 were included.

### Eligibility criteria

We included studies that met the following inclusion criteria:

- 1) Adult cases ( $18 \geq$  years).
- 2) Diagnosis of ACTH deficiency using dynamic testing (cosyntropin® test (CST), glucagon stimulation test (GST), insulin tolerance test (ITT), and/or corticotropin releasing hormone (CRH) stimulation test).
- 3) No deficiency of other pituitary axes.
- 4) MRI of the brain/pituitary protocolled as normal.
- 5) Studies identified as case reports, case series, letters to the editors, and/or other describing a patient presentation.

The exclusion criteria were:

- 1) Cases in children or cases describing congenital IAD (CIAD).
- 2) Cases with an aetiology for secondary AI (immune therapy, TBI, past and current glucocorticoid use, use of opiates, alcoholism and liver cirrhosis, Sheehan syndrome or radiotherapy, nephrotic syndrome) or abnormality on MRI (e.g. empty or partial empty sella, sellar tumor, pituitary gland and/or stalk enlargement).
- 3) Articles where full text was not available.

As previously mentioned, because of the lack of specificity of anti-pituitary antibodies, their presence was not seen as an exclusion criterion.

### Data extraction

The authors extracted the following information from the articles: (1) study characteristics (year of publication), (2) patient demographics (age and sex), (3) presenting complaints, duration of these complaints if mentioned, and necessity of IV glucocorticoids, (4) type of dynamic testing (CST, ITT, GST and/or CRH stimulation test), (5) findings on the MRI, (6) results of basal cortisol, basal ACTH and dynamic testing, (7) presence of hyponatremia, hypoglycemia or peripheral eosinophilia, (8) presence of autoimmune disease or autoantibodies, (9) thyroid function and presence of thyroid peroxidase antibodies (TPO), (10) presence of pituitary antibodies if tested, (11) if described: follow up of the patients and/or repeat dynamic testing, (12) if initially another diagnosis was made and (13) if there was any malignancy associated.

If the information in the article was not satisfactory, every possible attempt was made to contact the authors for additional clarification.

### Data analysis

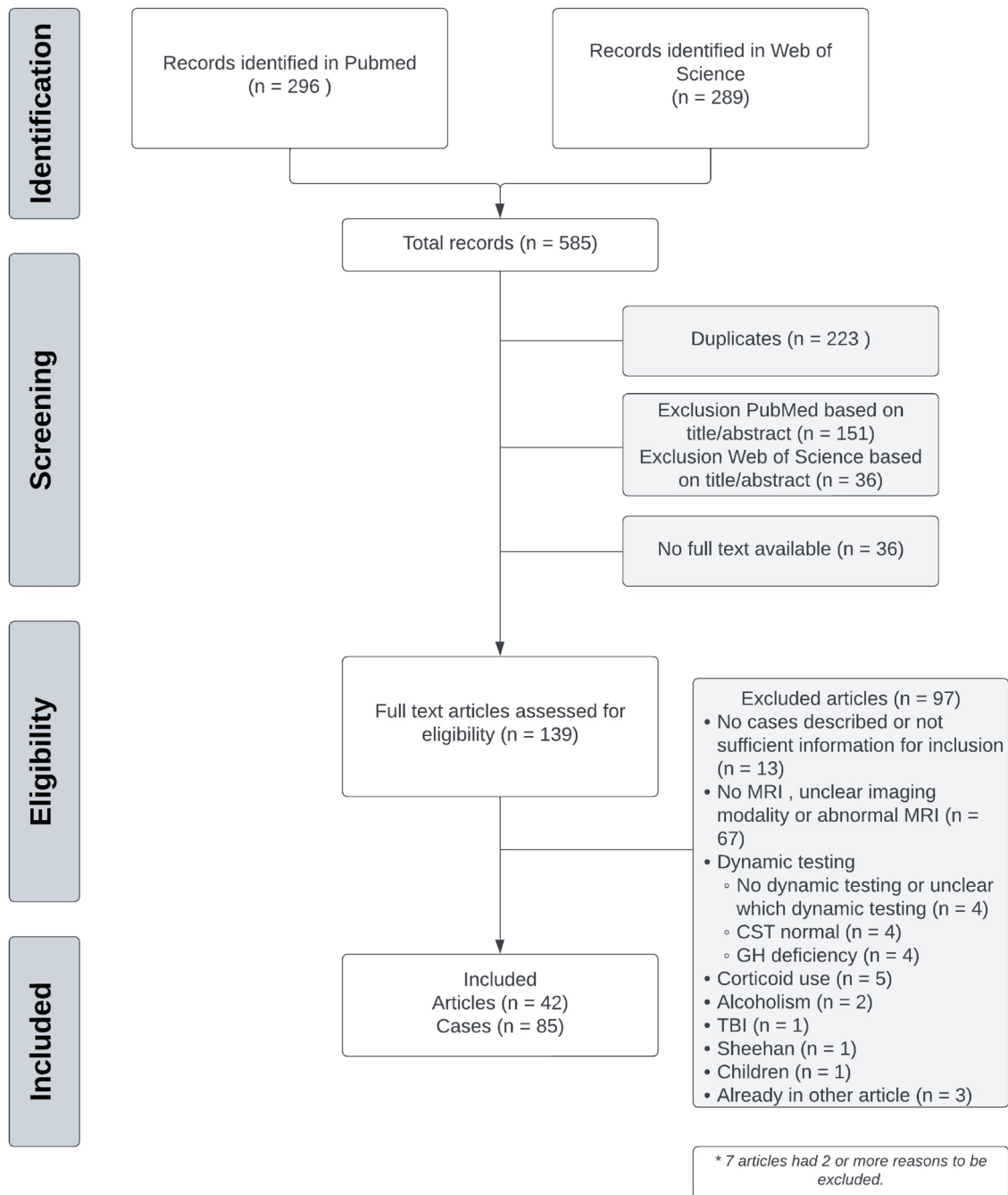
Descriptive statistics were used in this review to report demographics and clinical characteristics using means and standard deviations for continuous variables if normally distributed and median and interquartile range if not normally distributed. Statistical significance was ascertained using independent samples T-test for normally distributed variables, the Mann-Whitney U test for non-normally distributed variables and the Chi-square test for categorical variables. Statistical analysis was performed using IBM SPSS® Statistics v. 28 (IBM Analytics).

## Results

Our search yielded a total of 585 results of which 139 were assessed for eligibility. 97 articles were excluded based on the aforementioned criteria. The result of the search process is summarized in a flowchart (Fig. 1). A final number of 42 articles were included consisting of 37 case reports and 5 case series, resulting in a total population of 85 cases.

### Baseline characteristics at diagnosis

Of the 85 included cases, 47 (55%) were women. The mean age at diagnosis was  $53.7 \pm 18.1$  years. Women were significantly younger at diagnosis ( $49.5 \pm 17.1$  years) compared to men ( $58.8 \pm 18.2$  years) ( $p=0.017$ ). All cases underwent dynamic testing of the hypothalamic-pituitary-adrenal axis,



**Fig. 1** Flowchart of the search strategy and study selection. *MRI* magnetic resonance imaging; *CST* cosyntropin ® stimulation test; *GH* growth hormone; *TBI* traumatic brain injury

of which one third of cases (n=28) had 2 or more tests. The following dynamic tests were performed: CST (n=48), ITT (n=33), GST (n=5), and CRH stimulation test (n=33).

### Symptoms at presentation

The most common presenting symptom was lethargy, present in 32 cases (38%), being more frequently reported in

women than men (51% vs. 21%,  $p=0.028$ ). The other most frequent symptoms at presentation were: weight loss (25%), anorexia (22%), and myalgia/arthritis (12%). Anorexia and weight loss were more common in men than in women (37% vs. 11%,  $p<0.001$  and 32% vs. 19%,  $p=0.032$ ).

Less frequently described symptoms at presentation were: nausea and/or vomiting (8%), cognitive dysfunction (8%), fever or a subfebrile state (6%), gait disturbances (4%),

oedema (5%), flexion contractures (4%), a depressed mood (4%), dizziness (2%), amenorrhea (2%), weight gain (2%) and abdominal pain (2%).

Hypotension, hyponatremia, and hypoglycaemia were described in 13%, 30%, and 15% of the cases, respectively. Hypothyroidism, defined as an elevated TSH and/ or intake of L-thyroxin, was seen in 26 (31%) cases. Normalisation of TSH level was described in 4 cases after starting glucocorticoid substitution.

Duration of symptoms was described in 35 cases ranging from 1 day to 7 years. The median duration of symptoms in women and men was 8 months (0.5–36) and 6 months (2.75–12.5), respectively. Eight cases presented with an Addison crisis, which were equally distributed between men (n=4; 11%) and women (n=4; 9%).

Initially, a different diagnosis was established at diagnosis in twelve cases (14%). Interestingly, in five of these cases, at first, a psychiatric diagnosis was made. Duration of time before diagnosis was not significantly different in the patients initially misdiagnosed as psychiatric disease, than in the other patients (p=0.421).

### Autoimmune disease

Twenty-six of the 85 cases had an autoimmune disease at diagnosis. No gender difference was seen as 30% of women had an autoimmune disease compared to 32% of men. The most frequent autoimmune disease was Hashimoto hypothyroidism, present in 14 of the 85 cases. Pernicious anaemia was seen in 3 of the 85 cases and 2 of the 85 cases had type 1 diabetes mellitus. TPO-antibodies were positive in 20 of the 49 cases in whom they were measured. Other associated autoimmune diseases at diagnosis are shown in Table 1. Pituitary antibodies were measured in 22 cases and were positive in 6 cases.

### Management

In 34 of the 85 cases the type of corticosteroid therapy was specified. In these 34 patients, 74% of the patients were treated with hydrocortisone, 21% with prednisolone and 6% with dexamethasone. In 32 cases, the daily dose of the corticosteroid therapy was specified. The median hydrocortisone equivalent dose was 20 mg (15.0–26.3).

Data about the follow-up were scarcely reported. Dynamic testing was repeated in 4 cases of which 2 cases showed recovery of the HPA axis. The time interval to recovery of the HPA axis was 2 years in the first case and was undefined in the second case. Of the 2 other cases in which the dynamic tests were repeated, but in which the HPA axis did not recover, a new onset growth hormone deficiency (GHD) was found.

**Table 1** Associated auto-immune diseases at diagnosis

	Reported auto-immune diseases (n=26)
Auto-immune hypothyroidism	14 (17%)
Vitamin B12 deficiency (pernicious anaemia)	3 (4%)
Insulin antibodies	3 (4%)
Rheumatoid arthritis	1 (1%)
Guillain-Barré	1 (1%)
Elevated ANA	1 (1%)
ALS	1 (1%)
IgA nephropathy	1 (1%)
Crohn's disease	1 (1%)
Graves' disease	1 (1%)

ANA anti-nuclear antibodies, ALS amyotrophic lateral sclerosis; IgA immunoglobulin A

\*In 1 patient a combination of two auto-immune diseases was reported

### Discussion

This systematic review identified a total of 42 articles consisting of 85 cases of AIIAD and is, to the best of our knowledge, the largest case series to date. AIIAD or adult idiopathic isolated ACTH deficiency is a diagnosis of exclusion. There is lack of a clear definition of AIIAD. Six articles that explicitly described a so-called idiopathic IAD had to be excluded since no MRI was performed (n=2), MRI showed a pituitary abnormality (n=3) and/or association of GHD (n=3) [3, 8–12].

### Aetiology of IAD

Previous use of glucocorticoids is widely accepted as an aetiology for IAD, but in the literature, no clear timeframe is proposed after which temporary use of glucocorticoids is no longer expected to induce IAD. Previously, it was assumed that only chronic and/or supraphysiological doses of glucocorticoid administration could induce IAD, but recent reports suggest similar findings in short-term (<4 weeks) or low-dose (<5 mg prednisone equivalent per day) courses [13]. In this review we excluded all cases with glucocorticoid use, also if used as an antiemetic for chemotherapy.

Concerning opiate-induced IAD (OIIAD), there is also still a lot to be uncovered. Opiate-induced endocrinopathy most often presents as opiate-induced hypogonadism, but opiate-induced suppression of the HPA axis has been increasingly reported in the last few years [14, 15]. Increasing opioid dose and longer duration of action have been identified as risk factors for the development of OIIAD, but it is unclear as of which morphine-equivalent daily dose (MEDD) OIIAD may occur [16]. In this review, cases in

which opiate use was explicitly mentioned were excluded. However, opiate use was often not specifically reported, so it was not possible to rule out every possibility of past or present opiate use in the included cases.

Alcohol abuse has also been hypothesized to be a possible rare cause of IAD. Excessive alcohol consumption is known to activate the HPA axis and is one of the causes of pseudo-Cushing syndrome. However, in chronic alcoholism, suppression of the HPA axis is also seen. The mechanism of this suppression is as of yet not completely elucidated [17]. Several cases of IAD attributed to alcohol consumption have been reported in the last few years [18–20]. Again, there is no clear consensus on the cut-off of alcohol dose at which IAD can occur. We excluded cases with alcohol abuse.

Regarding TBI, there is also no unanimity on which degree of injury is severe enough to cause IAD but the higher the severity of the TBI, the higher risk of post-traumatic pituitary deficiency. The most common pituitary defect is GHD. Long-term ACTH deficiency is considered to be relatively rare (< 10%) and occurs mostly in association with deficiencies of other pituitary axes [21].

In summary, there is still a lot of uncertainty concerning the other aetiologies for IAD, which further complicates the diagnosis of a “real idiopathic” IAD. In addition, one limitation of this review is that a certain amount of included cases may have used glucocorticoids, opioids, alcohol, or had a TBI but it was not reported by the author.

## Pathogenesis and autoimmunity

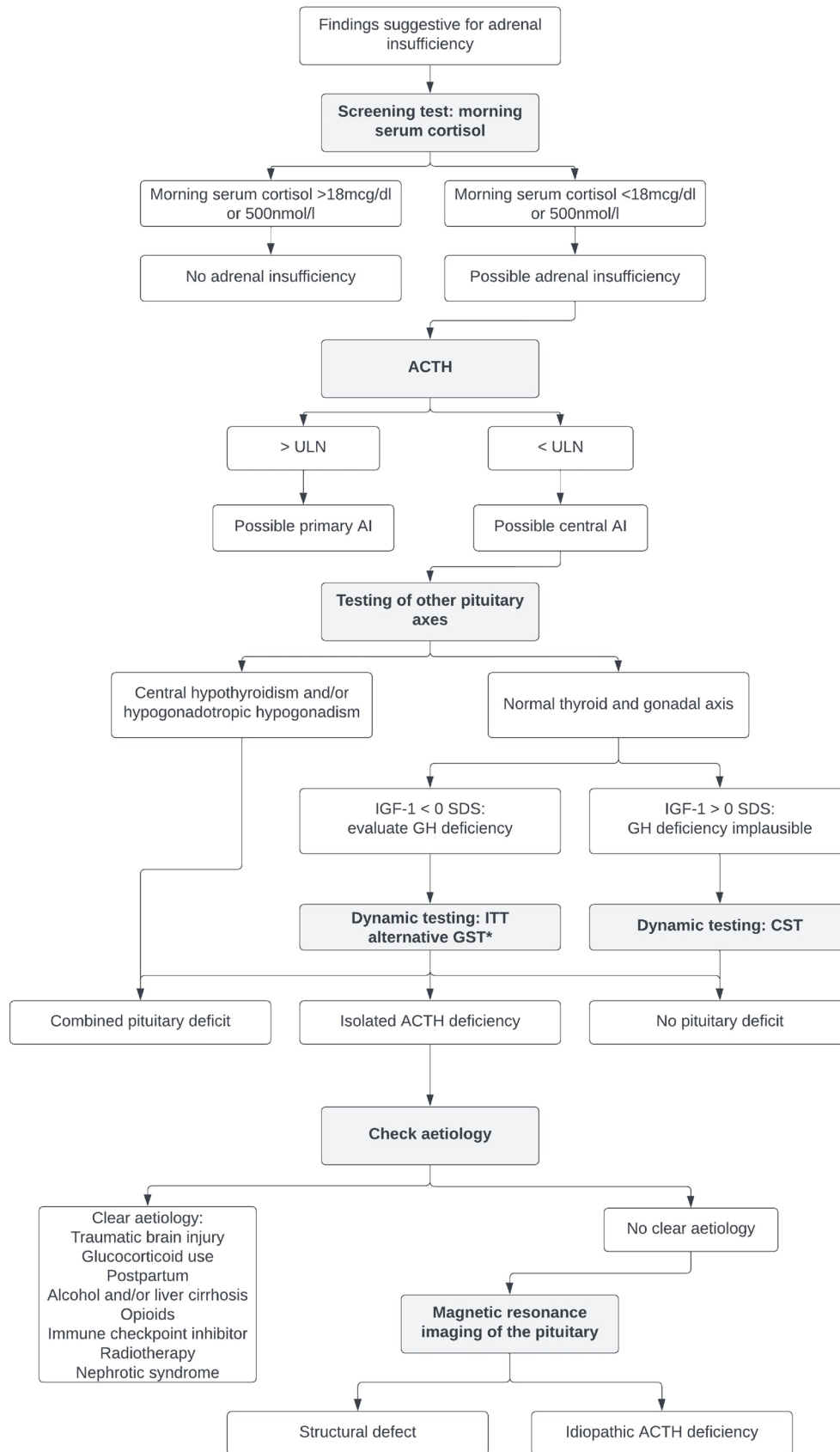
The pathogenesis of AIIAD remains largely unknown but an underlying autoimmune aetiology has been suggested, based on the association of AIIAD with autoimmune thyroid diseases, anti-pituitary antibodies, and lymphocytic infiltration and fibrosis on histopathology [5, 22, 23]. AIIAD frequently emerges concomitantly with autoimmune diseases, especially autoimmune hypothyroidism, as was described in the case series of Hannon et al. [22]. In this review, the prevalence of concomitant autoimmune disease(s) was 31%. The prevalence of autoimmune hypothyroidism in this study population was 17% which is twice the prevalence described in the general European population (8%) [24]. It is important to recognise that hypothyroidism can also be secondary to glucocorticoid deficiency instead of an associated autoimmune disease and that it may recover when glucocorticoids are substituted. 31% of cases showed primary hypothyroidism at diagnosis, but in more than half of the cases, TPO-antibodies were negative (12 cases) or not measured (5 cases).

The second reason to suggest that autoimmunity may cause at least a component of AIIAD is the finding of anti-pituitary antibodies, particularly anti-corticotroph antibodies. Anti-pituitary antibodies are a marker of involvement

of autoimmunity in the pituitary gland and are present in several pituitary diseases [23, 25]. Their presence has been described in lymphocytic hypophysitis, but are certainly not specific to this disease [6]. Anti-pituitary antibodies are not regularly determined and mass spectrometry analysis to measure these antibodies is not readily available. In this review, anti-pituitary antibodies were measured in 22 of 85 cases and were present in only 6 cases. The review of Fujita et al. aimed to clarify the significance of the presence of anti-pituitary antibodies [5]. In 33 cases with AIIAD presence of pituitary-antibodies were analysed of which 19 (58%) presented anti-corticotroph antibodies. The presence of these antibodies suggested severe injury to the corticotrophic cells as plasma ACTH levels were extremely low. First, we would like to note that the study population of Fujita et al. was described in a limited manner and it was not clear if all subjects underwent an MRI of the pituitary or if MRI was reported as normal. Second, it was not defined at what time serum ACTH was measured and if the same immunoassay was used in all subjects. Hannon et al. recommend determining anti-pituitary antibodies in all cases suspected of AIIAD if available [22]. While this recommendation could be interesting, its value as a diagnostic criterion of AIIAD is still unclear.

The third reason to suggest an autoimmune aetiology is the finding of lymphocytic infiltration and fibrosis of the pituitary on autopsy examination in cases with AIIAD. However, when critically looking at these references, this hypothesis is based on only 2 case reports from 1980 to 1997 of which 1 article is not available and the second article does not describe a case report of true AIIAD as imaging showed a pituitary lesion [26, 27]. A third autopsied case with IAD was published in 2003, in whom no lymphocytic infiltration could be detected, but selective loss of the corticotrophs was seen [28]. However, this autopsy was performed after the case had been treated with a physiological dose of hydrocortisone for 9 years. None of the included cases in this review underwent a biopsy or autopsy.

Recent reports have suggested that AIIAD could be a paraneoplastic manifestation, which could manifest itself after the diagnosis of malignancy but also long before [23, 29]. A case that is frequently referenced in this regard, is the case of a 42-year-old woman in which 3 years after diagnosis of IAD a pulmonary large cell neuroendocrine carcinoma was diagnosed [30]. However, it can be argued if this case represents a true IAD as GH levels during the ITT only reached a peak of 3.0 ng/mL, indicating GH deficiency [31]. Searching the literature, 4 other cases with a malignancy [gastric cancer (n = 2), non-Hodgkin lymphoma (n = 1), and breast cancer (n = 1)] were diagnosed with an IAD but were not included in our review because these cases were treated with chemotherapy with glucocorticoid administration and one case was found to have



**Fig. 2** Diagnostic flowchart of AIIAD. *ACTH* adrenocorticotropic hormone; *ULN* upper limit of normal; *AI* adrenal insufficiency; *IGF-1* insulin-like growth factor 1; *SDS* standard deviation score; *ITT* insulin tolerance test; *GST* glucagon stimulation test; *CST* cosyntropin ® stimulation test; *ACTH* adrenocorticotropic hormone. \*If ITT is contra-indicated

a pituitary adenoma [32–35]. In our review 2 cases with malignancy were included: one case describing AIIAD occurring five years after left upper lobectomy and adjuvant chemotherapy (without glucocorticoids) for lung adenocarcinoma and one case describing a treatment-naive new diagnosis of Philadelphia chromosome-positive acute lymphocytic leukaemia [36, 37]. All the authors of the included articles were contacted to try to obtain if malignancy had been diagnosed in the years following diagnosis of AIIAD, however, no reply was received. Kwon et al. have recently retrospectively screened for AI in an adult population (n = 184) with malignancy and suggestive symptoms [38]. In this study, 35% of patients were diagnosed with AI with the majority of cases being secondary to glucocorticoid use (61.5%). In 2015 Han et al. screened for AI in cancer patients receiving chemotherapy with dexamethasone [39]. In that prospective study, 16% of patients with a normal adrenal response before chemotherapy were diagnosed with AI after 3 cycles of chemotherapy with dexamethasone. Based on the currently available literature we do not agree with the speculation that in patients with AIIAD, occult malignancy may be present, as was stated by Bando et al. [40]. We rather suggest that AI in cancer patients secondary to dexamethasone or other glucocorticoids as an antiemetic or morphinomimetics is unrecognized.

## Clinical features

The clinical presentation of AIIAD lacks specificity which can complicate the diagnosis, similar as described in primary adrenal deficiency. In this systematic review, the most common symptoms at presentation were lethargy (38%), followed by weight loss (25%) and anorexia (22%). In contrast to congenital IAD (CIAD), which presents acutely after birth with seizures with hypoglycaemia, fever, shock, and jaundice, the symptomatology of AIIAD can be more subtle [41, 42]. CIAD is associated with a high mortality in the neonatal period if not correctly recognized and timely glucocorticoid treatment is vital to lower the risk of recurrent hypoglycaemia and uncontrolled epilepsy. In AIIAD the median duration of symptoms before diagnosis can sometimes even span multiple years, which illustrates the more gradual onset and protracted course of the symptomatology. Only 8 cases (10%) in our review presented with an Addison crisis.

## Diagnosis

The dynamic tests used in the different cases were very variable which illustrates the lack of a common worldwide diagnostic work-up for secondary ACTH deficiency. In our descriptive review following dynamic tests were performed: CST (n = 48), ITT (n = 34), GST (n = 5), and CRH stimulation test (n = 34).

To be able to make the diagnosis of AIIAD, an MRI of the brain/pituitary should be performed to exclude structural defects. In our review, (partial) empty sella was seen as an exclusion criterion for AIIAD due to endocrine abnormalities being documented in around 19–51% of patients with empty sella [43, 44]. The exact prevalence of endocrinopathies in partial empty sella is not certain, but several case reports have been published showing an association between partial empty sella and pituitary axis deficiencies such as hypogonadotropic hypogonadism or a combination of GHD and transient central AI [45, 46]. Whereas some authors consider partial or complete empty sella not to be an exclusion criterion in the definition of AIIAD, other authors regard empty sella as a clear aetiology for ACTH deficiency [5, 47]. In this review, cases with complete and partial empty sella were excluded.

Figure 2 illustrates a suggested algorithm in the form of a flowchart for the diagnosis of AIIAD. In patients with signs and symptoms suggestive of adrenal insufficiency, we suggest following the Endocrine Society guidelines for diagnosis of central adrenal insufficiency, consisting of a morning serum cortisol concentration as a first step [48–50]. If central AI is suspected, other pituitary axes should be tested including anterior pituitary hormones (prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and TSH) and target hormones (fT4, IGF-1, estradiol for females and testosterone for males) [51, 52]. Concerning the choice of dynamic testing, we suggest to perform the ITT if the IGF-1 standard deviation score (SDS) is below 0. If IGF-1 SDS is above 0, we propose performing the CST as a dynamic test. The Growth Hormone Research Society's claim that an IGF-1 level above 0 SDS at any age makes the diagnosis of GHD unlikely led us to choose the cut-off of 0 for IGF-1 SDS [53]. In patients with a suspicion of GHD but with a contraindication for the ITT, a GST can be carried out as alternative testing [54]. A thorough systemic anamnesis and examination should be conducted to exclude other causes of IAD such as TBI, glucocorticoid use, postpartum state, alcohol and/or liver cirrhosis, use of opiates, immune checkpoint inhibitor therapy, radiotherapy, and nephrotic syndrome. If no clear aetiology can be found, an MRI of the pituitary should be performed to rule out structural pituitary abnormalities. In this review, empty sella and partial empty sella are considered to be a pituitary abnormalities. Autoimmune comorbidities should be checked and if possible testing for

pituitary-antibodies should be performed. Screening for autoimmune comorbidities should be carried out according to the clinical picture. We would suggest to screen for vitamin B12 deficiency due to pernicious anaemia if macrocytic anaemia is present. However, we would suggest to analyse TPO-Ab regardless of the presence of primary hypothyroidism, because of the potential application of TPO-Ab as a general marker of autoimmunity rather than a disease-specific antibody [55].

## Management

In our review, in the 32 of the total 85 cases where the daily dose of the corticosteroid therapy was specified, the median daily hydrocortisone equivalent dose was 20 mg. This is in line with the recommendations of the Endocrine Society in which a total daily dose of 15–20 mg is endorsed [48]. In almost three-quarters of the patients hydrocortisone was used, following recommendations, but still one-quarter of the patients received longer-acting glucocorticoids. The reason for this was not specified in the articles.

Data about the follow-up of AIIAD is scarce as only one article has presented the follow-up data of 4 cases of which 2 cases showed recovery of the HPA axis and the other 2 cases developed GHD, not present at diagnosis [22].

Repeat testing should encompass dynamic testing of the HPA axis and testing of the other pituitary axes. The choice between CST and ITT again depends on the IGF-1 levels. Due to the paucity of data, we would suggest pragmatically following the same frequency of repeat dynamic testing as in glucocorticoid-induced IAD, of which more follow-up data is available. In central adrenal insufficiency due to glucocorticoid use, Pofi et al. suggest repeating CST in function of the 30-minute cortisol level during the CST. If the 30-minute cortisol level is above 12.7 mcg/dl or 350 nmol/l repeat testing should be performed after six months and if the 30-minute cortisol is below 12.7 mcg/dl or 350 nmol/l repeat testing should be delayed for one year after diagnosis [56]. Possibly, these results can be extrapolated to the ITT.

## Strengths and weaknesses

This review has several limitations. Firstly, case reports have a long tradition in medicine but are inherently anecdotal evidence, and should therefore be judged carefully. The cases included in this review were not systematically assessed for study quality with a standardized tool. Due to the large number of different articles by different authors, the clinical information was reported in a non-systematic manner, and in some articles, certain data was missing. However, we did analyse the diagnostic work-up of the articles and only included articles where it was explicitly stated which dynamic testing was performed. We also only included

articles that clearly mentioned MRI as imaging modality. In some articles, the diagnostic work-up of ‘isolated’ ACTH deficiency and therefore the exclusion of deficiency of the other pituitary axes were not specified or were not according to guidelines (e.g. using normal growth hormone and IGF-1 levels as an exclusion for GHD and not using dynamic testing such as the ITT). Due to the paucity of high-quality case reports, we chose to abstain from excluding these articles from the review. In some studies, it also was not explicitly stated if all other aetiologies for IAD were excluded (e.g. Sheehan, glucocorticoids, opiate use). However, if an underlying cause for IAD was cited, the article was excluded. Finally, patients from the case series were included meaning that aggregated data were used, which resulted in missing individual case details. Despite these limitations, the strength of this study is that this is the first systematic review that aims to summarize the clinical information of all the published case reports concerning AIIAD. A flowchart is suggested, to help diagnose AIIAD.

## Conclusion

AIIAD is defined by a secondary AI with an otherwise normal pituitary axis, absence of structural pituitary defects, no history of prolonged glucocorticoid therapy, and exclusion of other causes of failure of the HPA axis. In this systematic review we report clinical characteristics, association with autoimmune diseases, and management of 85 previously published AIIAD cases, making this the largest case series to date. Based on the data an association between AIIAD and underlying autoimmune aetiology is hypothesized due to the high prevalence of autoimmune diseases in this population. The value of the presence of anti-pituitary antibodies has yet to be investigated. In this review, we could not withhold AIIAD as a form of paraneoplastic syndrome as authors have recently suggested. Our systematic review highlights the lack of a clear definition and diagnostic work-up for AIIAD and we believe this may be due to the heterogeneity seen in cases with this disease. To help diagnose AIIAD we propose a diagnostic flowchart. Follow-up data in literature are scarce, but we encourage considering to rechallenge the HPA and other pituitary axes.

**Author contributions** CDH conceptualised the article. CDH and EVM designed a search strategy. EVM performed the literature search. EVM carried out the data analysis, supervised by CDH. EVM prepared the original draft. CDH and CDB critically revised the work. All authors reviewed and approved the final version of the manuscript.

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## Declarations

**Competing interests** The authors have no competing interests to declare that are relevant to the content of this article.

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