Idiopathic Isolated Adrenocorticotropic Hormone Deficiency: A Single-Center Retrospective Study

Authors
Chengyan Yang[1], Xinpei Li[2], Xiaoqing Ma[3]

Affiliations
1 Shandong First Medical University, Jinan, China
2 Jining Medical University, Jining, China
3 Jining No 1 People's Hospital, Jining, China

Key words
idiopathic isolated adrenocorticotrophic hormone deficiency, pathogenesis, clinical features, diagnosis, treatment and prognosis

received 08.04.2023
revised 08.07.2023
accepted 14.07.2023
published online 08.09.2023

Bibliography
Exp Clin Endocrinol Diabetes 2023; 131: 523–531
DOI 10.1055/a-2135-7708
ISSN 0947-7349

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Xiaoqing Ma
Jining NO.1 People's Hospital
272100 Jining
Jining City
Shandong Province
China
984654637@qq.com. East Campus

ABSTRACT

Idiopathic isolated adrenocorticotrophic hormone deficiency (IIAD) is rare, with high clinical omission and misdiagnosis rates. This study retrospectively collected information on clinical presentation, laboratory findings, and treatment response of 17 patients with IIAD at Jining No. 1 People's Hospital from January 2014 to December 2022. The clinical characteristics were summarized, and the pertinent data were analyzed. As a result, most of the patients with IIAD were male (94.12 %), with age at onset ranging from 13 to 80 years. The primary manifestations were anorexia (88.24 %), nausea (70.59 %), vomiting (47.06 %), fatigue (64.71 %), and neurological or psychiatric symptoms (88.24 %). The median time to diagnosis was 2 months and the longest was 10 years. Laboratory tests mostly showed hyponatremia (88.24 %) and hypoglycemia (70.59 %). The symptoms and laboratory indicators returned to normal after supplementing patients with glucocorticoids. IIAD has an insidious onset and atypical symptoms; it was often misdiagnosed as gastrointestinal, neurological, or psychiatric disease. The aim of this study was to improve clinicians' understanding of IIAD, patients with unexplained gastrointestinal symptoms, neurological and psychiatric symptoms, hyponatremia, or hypoglycemia should be evaluated for IIAD and ensure early diagnosis and treatment.

Introduction

Idiopathic isolated adrenocorticotrophic hormone (ACTH) deficiency (IIAD) is characterized by the sole involvement of the pituitary-adrenal axis (HPA axis), low serum cortisol levels, and low or normal ACTH levels, with no impairment or transient reversible changes in the thyroid axis, gonad axis, prolactin axis, and growth hormone axis function. Pituitary magnetic resonance imaging (MRI) is mostly normal or displays empty sella syndrome. IIAD is divided into congenital IIAD (CIIAD), which is thought to be genetic and heredity, whereas, in adult IIAD (AIIAD), the etiology is unclear and often considered to be related to autoimmunity. The clinical manifestations of IIAD are widespread and lack specificity, and many patients remain undiagnosed for a long time. The aim of the study was to improve clinicians' understanding of IIAD to improve the diagnosis rate.

Materials and Methods

Study subjects

The inclusion criteria for IIAD were as following: functional decrease in the HPA axis only, serum cortisol levels below the normal range (AM: 185–624 nmol/L, PM: < 276 nmol/L), ACTH levels within the normal range (AM: 1.6–13.9 pmol/L, PM: < 1.6 pmol/L) or low (cortisol and ACTH levels were measured by chemiluminescent immunoassay), normal levels of other anterior pituitary hormones, and

pituitary MRI is normal or shows empty sella. The exclusion criteria for IIAD were as follows: abnormalities in other axes of the anterior pituitary, history of glucocorticoid therapy, history of pituitary surgery, and patients with tumors.

Clinical indicators

We collected the following patient information: gender, age at onset, length of time from symptom onset to diagnosis, drinking history, first department visit, clinical manifestations, routine blood tests (leukocytes, lymphocytes, eosinophils, hemoglobin), blood glucose, electrolytes, the function of the HPA axis, thyroid axis, gonad axis, and growth hormone axis; pituitary MRI, adrenal gland computed tomography (CT), and type and dose of medication.

Statistical methods

Data were processed by SPSS 26.0. Normality testing of quantitative data was performed by the Shapiro-Wilk test. Data that conformed to the normal distribution were expressed as mean ± standard deviation ($X \pm SD$), non-normally distributed data were expressed as median (interquartile range) (*M [IQR]*), and qualitative data were expressed as percentages.

Ethics approval

This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Medical Ethics Committee of Jining No.1 People's Hospital approved this study.

The study was not registered to a clinical trials registry (CTR)

The study was not registered to a CTR because it is a retrospective study.

Informed consent

In this retrospective study, ethics approval was obtained, and written informed consent was not needed.

Results

General clinical characteristics

Sixteen patients were male and one was female. The minimum age at symptom onset was 13 years and the maximum age was 80 years (median: 62 years). The length of time from symptom onset to diagnosis ranged from 0 to 10 years (median: 2 months)(▶ **Table 1**), and were mostly misdiagnosed as gastrointestinal diseases (6 cases), neurological or psychiatric diseases (3 cases), and thyroid disease (1 case).

Fourteen patients had both gastrointestinal and neurological or psychiatric symptoms (82.35 %). Among the 17 patients, the clinical manifestations included anorexia (n = 15, 88.24 %), nausea (n = 12, 70.59 %), fatigue (n = 11, 64.71 %), vomiting (n = 8, 47.06 %), unconsciousness (n = 7, 41.18 %), and weight loss (n = 4, 23.53 %) (▶ **Fig. 1**). Furthermore, one patient had transient hypotension and there was no decrease in blood pressure in three hypertensive patients. There were also some rare manifestations, including loss of axillary and pubic hair (case 6).

Regarding the department that visited first, only four patients (23.53 %) were triaged to the endocrinology department for hypoglycemia or hyponatremia, and among them, case 5 was first triaged to the endocrinology department because of a history of hypothyroidism; 11 patients were triaged to the gastroenterology department (64.71 %); and two patients were triaged to the neurology or psychiatry department (11.76 %). Case 8, who had already been diagnosed with IIAD 1 year prior, was triaged to the gastroenterology department again when he showed gastrointestinal symptoms.

Five patients (cases 4, 7, 14, 15, 17) had a history of cerebral infarction and case 1 had a history of cerebral hemorrhage. Three patients (cases 5, 10, 11) were diagnosed with depression; their symptoms improved after changing to cortisol therapy, so whether their depressive state was due to hyponatremia cannot be excluded.

Laboratory tests

Fifteen patients had hyponatremia (88.24 %), 11 patients had hypochloremia (64.71 %), one patient had hypokalemia, and none had hyperkalemia. The median of blood glucose was 3.5 mmol/L, and 12 patients (70.59 %) had varying degrees of hypoglycemia (range: 1.1–3.7 mmol/L), with three cases of hypoglycemic coma (case 2, 16, 17) and one of type 2 diabetes (case 1) who took metformin glibenclamide previously, his fasting blood glucose was 3.17 mmol/L, which increased (6.6–9.4 mmol/L) after supplementing with glucocorticoids.

Three patients had leukopenia, nine had anemia, two had eosinophilia, and none had lymphocytosis.

Anterior pituitary function and imaging findings

HPA axis function was decreased in all 17 cases (▶ **Table 2**). The median serum cortisol and ACTH were 10.91 nmol/L and 1.04 pmol/L, respectively. Thyroid antibodies were collected in 13 of the 17 patients. Seven patients (41.18 %) had thyroid disease, including elevated thyroid stimulating hormone (TSH) in six patients (35.29 %) and positive thyroid autoantibodies in one patient (7.69 %). Case 8 was previously diagnosed with hypothyroidism due to Hashimoto's thyroiditis. Three patients (17.65 %) had hyperprolactinemia, but no occupancy was found on pituitary MRI and no prolactinoma. Growth hormone levels were examined in two patients and were found to be normal. Pituitary MRI was performed in 16 patients, and no pituitary abnormality was seen in the remaining one patient by cranial CT; the final results of imaging were empty sella in seven patients (▶ **Fig. 2**) and normal in the remaining 10 patients. Adrenal CT examination found no abnormalities in seven patients.

Treatment and follow-up

No oral preparation of hydrocortisone was available in our center; therefore, all patients were given prednisone tablets (mean dose: 7.21 mg/day) after a clear diagnosis of IIAD. Although case 11 was a minor, his gonad axis was initiating and his predicted outcome was satisfactory; thus, he was administered prednisone tablets. At follow-up, the HPA axis function had not recovered in all patients at the time of writing this article. Fig. 3 shows the ACTH and cortisol levels of case 9 at multiple follow-ups.

Following prednisone supplementation, clinical symptoms and laboratory indicators mostly returned to normal. Ten of 11 reviewed

▶ **Table 1** Summary of the characteristics of 17 patients with IIAD (n = 17)

	Indicators	IIAD (Frequency [Frequency], *X* ± *SD* or *M [IQR])*
	Male, n (%)	16 (94.12%)
	Female, n (%)	1 (5.88%)
	Age at onset (years)	62 (20)
	Length of time from symptom onset to diagnosis (months)	2 (29.8)
	Drinking history, n (%)	2/16 (12.5%)
First department visited	▪ Endocrinology department, n (%)	4 (23.53%)
	▪ Gastroenterology department, n (%)	11 (64.71%)
	▪ Neurology or psychiatry department, n (%)	2 (11.76%)
Gastrointestinal symptoms	▪ Anorexia, n (%)	15 (88.24%)
	▪ Nausea, n (%)	12 (70.59%)
	▪ Vomiting, n (%)	8 (47.06%)
Neurological and psychiatric symptoms	▪ Unconscious, n (%)	7 (41.18%)
	▪ All symptoms, n (%)	15 (88.24%)
	Fatigue, n (%)	11 (64.71%)
	Weight loss, n (%)	4 (23.53%)
	Hypotension, n (%)	1 (5.88%)
Blood glucose	▪ Hypoglycemia, n (%)	12 (70.59%)
	▪ Blood glucose level (mmol/L)	3.5 (1.11)
Blood routine tests	▪ Leukocytopenia, n (%)	3 (17.65%)
	▪ Anemia, n (%)	9 (52.94%)
	▪ Lymphocytosis, n (%)	0 (0%)
	▪ Eosinophilia, n (%)	2 (11.76%)
Electrolytes	▪ Hyponatremia, n (%)	15 (88.24%)
	▪ Hypochloremia, n (%)	11 (64.71%)
	▪ Hypokalemia, n (%)	1 (5.88%)
	▪ Hyperkalemia, n (%)	0 (0%)
Function of the anterior pituitary	▪ Cortisol level (nmol/L)	10.91 (33.33)
	▪ ACTH level (pmol/L)	1.04 (2.95)
	▪ TSH elevated, n (%)	6 (35.29%)
	▪ Positive thyroid antibodies, n (%)	1/13 (7.69%)
	▪ Hyperprolactinemia, n (%)	3 (17.65%)
	▪ Growth hormone deficiency, n (%)	0/2 (0%)
Pituitary MRI	▪ Normal, n (%)	10 (58.82%)
	▪ Empty sella, n (%)	7 (41.18%)
Medication	▪ Using prednisone tablet, n (%)	17 (100%)
	▪ Prednisone tablet dose (mg/day)	7.21 ± 2.63
	▪ Using levothyroxine tablet, n (%)	4 (23.53%)

IIAD idiopathic isolated adrenocorticotropic hormone deficiency, X ± SD mean ± standard deviation, M (IQR) median (interquartile range), ACTH adrenocorticotropic hormone, TSH thyroid stimulating hormone, MRI magnetic resonance imaging.

patients with hyponatremia had returned to normal, although this was not so in case 8, which was considered to be related to discontinuing prednisone tablets > 10 days before follow-up. All eight reviewed patients with hypoglycemia recovered, and two reviewed patients with leukopenia were normal. Of the four reviewed patients with anemia, two returned to normal and one reviewed case of eosinophilia returned to normal. Of the three reviewed patients with elevated TSH, one (case 10) returned to normal, and one (case 11) showed a downward trend (8.76 to 6.59 µIU/mL).

Discussion

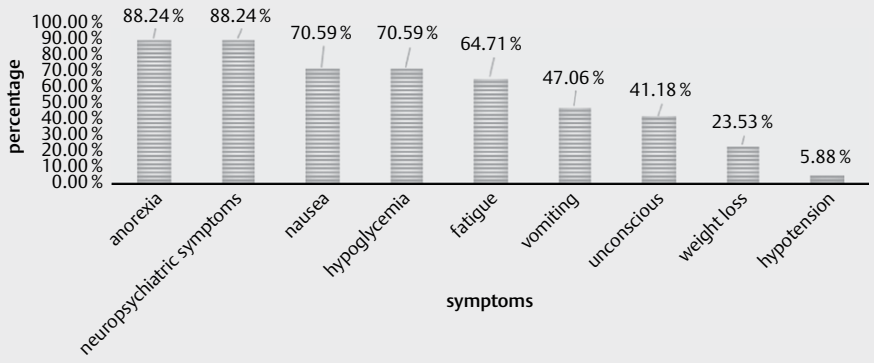
IIAD is a rare disease first proposed by Steinberg [1]. It is usually documented in case reports or small case series in China [2]. The exact prevalence of IIAD is difficult to establish as there is no consensus on the disease definition. In the past 9 years, 17 cases of IIAD were reported at our center; the low incidence of this disease may be due to insidious symptoms and lack of sufficient understanding of IIAD. This article provides a comprehensive account of the whole process of diagnosis and treatment of IIAD cases to improve physicians' understanding of IIAD and increase the diagnosis rate.

Potential pathogenesis of idiopathic isolated adrenocorticotrophic hormone deficiency

The specific pathogenesis of IIAD is unknown; it may be related to genetic defects, autoimmunity, pituitary ischemia, long-term alcohol consumption, drugs, etc. (▶ **Table 3**). Proopiomelanocortin (POMC) is a precursor of ACTH, POMC deficiency syndrome is a genetic defect disease, of which IIAD is one of the manifestations [3]. TBX19 encodes a transcription factor specifically expressed in pituitary ACTH cells. Mutations in TBX19 eventually lead to ACTH deficiency [4], accounting for 65% of neonatal IIAD cases [5]. In our study, we observed an adolescent patient (13 years old); unfortunately, neither he nor his parents had undergone genetic screening. NFKB2 encodes a transcription factor that regulates the expression of several immune-related genes, and mutations in NFKB2 may lead to IIAD [6]. Prohormone convertase 1 (PC1) catalyzes the conversion of POMC proteins into ACTH; a structural mutation in PC1 can ultimately lead to ACTH deficiency [7].

Autoimmunity is currently considered to be the most likely pathogenesis of IIAD due to the following reasons. (1) IIAD is often observed in combination with autoimmune diseases [8], such as Hashimoto's thyroiditis, primary hypothyroidism, type 1 diabetes, Crohn's disease, etc. [2]. Thyroid disease may be due to the similarity between certain antigens in ACTH cells and thyroid follicular epithelial cells [9]. (2) Pituitary tissue from IIAD patients exhibits infiltration of lymphocytes [10]. Fujita's study confirmed the presence of anti-ACTH antibodies in 58% of IIAD patients [11]. (3) Patients with traumatic brain injury were also diagnosed with IIAD due to immune system attacks on exposed ACTH cells [12]. (4) Immune checkpoint inhibitors (ICIs) cause IIAD in 0.8% of patients [13], because over-activated immune cells lead to autoimmune damage. (5) The formation of the empty sella may be related to autoimmunity [14]. Seven patients in our center showed an empty sella, providing much evidence to suggest that autoimmunity is involved in the pathogenesis of IIAD.

Some vascular high-risk factors or pituitary ischemic diseases, such as type 2 diabetes, hypertension [15], cerebral hemorrhage [9], cerebral infarction, etc., may lead to inadequate pituitary perfusion and cause IIAD. Our center has one patient with type 2 diabetes, three hypertensive patients, one cerebral hemorrhage pa-



▶ **Fig. 1** Percentage of clinical presentations.

tient five cerebral infarction patients. Furthermore, studies have reported that a history of chronic alcoholism may be associated with the development of IIAD [16, 17]. Chronic alcohol intoxication can cause ultra-microscopic pathological changes in the endocrine cells of the rat adenohypophysis, resulting in pituitary damage [18]. In our study, two patients had a long-term history of alcohol consumption; however, the the relationship between alcoholism and IIAD remains unknown. Long-term history of the use of opioid drugs can inhibit endogenous endorphin production and the generation of ACTH [19, 20].

The pathogenesis of IIAD has not yet been fully defined. It is a complex condition involving multiple factors, and further clinical studies are needed to summarize and confirm these factors. Of course, IIAD may be a heterogeneous group of conditions; future developments will allow us to better subclassify different types of IIAD, and at that point, we will develop a more fitting name for this condition.

Clinical characteristics of idiopathic isolated adrenocorticotrophic hormone deficiency

The clinical manifestations of IIAD are diverse and lack specificity. As a result, patients with IIAD may often first visit the department of gastroenterology and not the endocrinology department. Many patients remain undiagnosed for a long time. The population with IIAD is predominantly middle-aged and elderly, and predominantly male. One study involving 72 patients, reported the male-to-female ratio as 1.2:1, and although the disease was distributed in all age groups, it was predominant in the 50–60 years age group [16]. Our study included 16 male and only one female, and the median age was 62 years; the clinical manifestations usually started with gastrointestinal symptoms or neurological symptoms, manifesting as anorexia, nausea, fatigue, vomiting, unconsciousness, and weight loss. Likewise, the major clinical manifestations of Iglesias's study were fatigue, anorexia, nausea or vomiting [21]. Patients with CIIAD usually have severe hypoglycemia, seizures, and prolonged cholestatic jaundice [22]. The clinical manifestations of the patients in our study were generally consistent with those reported in previous studies in China and foreign countries [8, 23]. Laboratory tests in our study mostly showed hyponatremia (88.24 %) and hypoglycemia (70.59 %), with hyponatremia also being the most common laboratory finding in the studies by Iglesias (68.2 %) [21] and Hannon (39.13 %) [8]. In one study, eosinophilia (31.8 %) was common in IIAD caused by ICIs [21], while our study only had two patients with eosinophilia (11.76 %); this discrepancy is considered to be related to ICI because eosinophils are involved in immunity.

In Japan, approximately 10 % of the more than 300 IIAD cases were found to be complicated with thyroid disease, with Hashimoto's thyroiditis being the most common [24]. Murakami's study speculated that elevated TSH is mostly related to cortisol deficiency rather than autoimmunity [25]. However, data derived from the National Pituitary Database of Ireland showed that 12 (56.52 %) of 23 patients had autoimmune disease, including nine patients (39.13 %) with documented autoimmune hypothyroidism, highlighting an autoimmune basis for patients with autoimmune hypothyroidism and IIAD [8]. Two patients with high prolactin levels were reported in the study by Sun Chan, which returned to normal after supplementing with glucocorticoids. The high prolactin levels may be related to cortisol deficiency because prolactin was found to overreact in patients with IIAD in response to thyrotropin-releasing hormone, which resumed to normal level after glucocorticoid replacement [26]. There were three hyperprolactinemia cases in our study, and pituitary MRI excluded prolactinoma. Unfortunately, the lack of follow-up information restricts our ability to know whether the prolactin levels of these patients decreased after glucocorticoid supplementation.

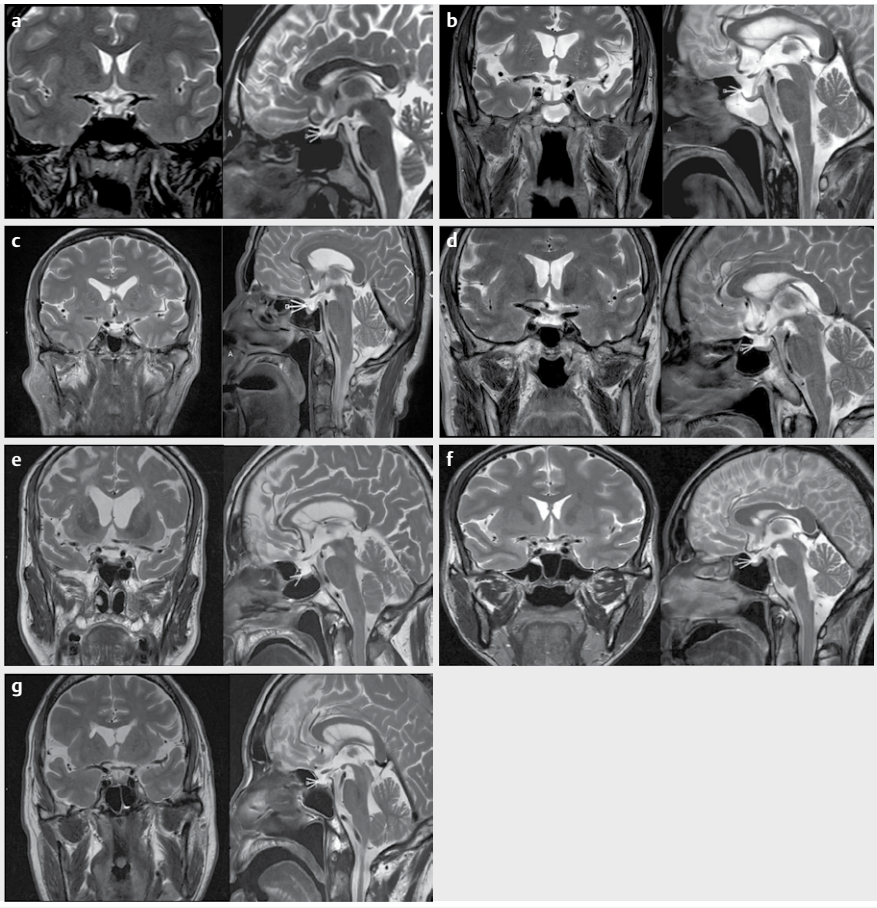
Diagnosis of idiopathic isolated adrenocorticotrophic hormone deficiency

The key to diagnosing IIAD is evaluating anterior pituitary function (▶ **Fig. 4**). The diagnosis of IIAD includes the following elements: the fasting serum cortisol at 8 am without stress of < 80 nmol/L (3 µg/dL) (> 500 nmol/L [18 µg/dL] can be excluded) [27], the ACTH levels should be either low or normal, and other anterior pituitary hormones levels are normal. If available, ACTH excitation tests can be performed to confirm that the hypoadrenocorticism in the patient is secondary (in patients with longer disease duration, ACTH stimulation tests may give false negative results). In addition, pituitary MRI shows it to be mostly normal or empty sella, and the

▶ **Table 2** Anterior pituitary functions and imaging findings in 17 patients with IIAD (n = 17)

Case number	gender	Age at onset (years)	COR nmol / L	ACTH pmol/L	TT3 nmol/L	TT4 nmol/L	FT3 pmol/L	FT4 pmol/L	TSH uIU/mL	Tg Ab IU/mL	TPOAb IU/mL	PRL ng/mL	FSH mIU/mL	LH mIU/mL	E2 pmol/L	P nmol/L	T nmol/L	GH ng/mL	Pituitary MRI	Adrenal gland CT
1	M	60	10.06	0.41	1.55	136.17	5.15	12.23	2.76	–	–	30.64	1.98	4.6	180	0.353	7.01	–	normal	normal
2	M	21	0.49	0.32	1.7	116.59	3.91	11.32	10.27	0	0.4	23.7	4.29	9.26	114.2	< 0.159	24.73	0.07	empty sella	normal
3	M	53	10.91	< 0.22	1.56	102.63	4.13	8.38	20.74	8.1	1.8	18	1.72	8.48	123.1	–	24.32	–	normal	–
4	M	63	75.91	5.65	0.64	126.26	2.79	15.83	2.223	0	15.7	11.46	3.34	2.6	115.9	–	17.23	–	normal	–
5	F	43	7.52	0.45	2.15	128.91	5.26	8.85	2.697	0.8	4.7	86.91	32.56	22.21	325.3	< 0.159	< 0.09	–	normal	–
6	M	62	7.31	< 0.22	1.37	123.7	3.77	12.97	2.67	–	–	28.49	4.23	2.51	99.33	0.513	23.42	–	normal	–
7	M	76	9.61	0.28	1.46	130.54	4.42	8.77	5.12	1.9	13.8	53.09	8.74	12.36	200.8	0.266	33.14	–	empty sella	normal
8	M	61	26.56	2.6	–	–	2.53	0	52.18	> 2464	213.3	22.65	9.93	8.82	97.36	–	21.13	–	empty sella	normal
9	M	62	18.7	4.69	1.85	144.43	5.5	19.22	2.67	0.2	0.2	17.68	4.02	4.95	165	< 0.159	34.41	–	empty sella	normal
10	M	60	7.09	< 0.22	1.52	97.83	4.23	12.83	6.37	0.6	0.9	18.76	7.75	5.94	211.2	–	27.08	–	normal	normal
11	M	13	98.24	3.68	0.95	105.92	3.9	15.88	8.76	0	0.3	34.84	8.53	9.02	31.04	0.344	12.13	–	normal	–
12	M	80	17.35	3.42	1.96	117.71	5.44	10.61	3.99	1.5	1.1	24.03	8.6	12.35	237.2	0.827	40.75	–	normal	–
13	M	64	54.49	3.08	–	–	3.98	10.72	3.61	42.9	1.4	61.5	10.23	17.47	–	–	18.12	2.06	normal	–
14	M	67	88.04	2.26	0.63	119.24	2.84	9.71	2.84	–	–	25.19	5.88	6.26	148.9	< 0.159	19.44	–	empty sella	normal
15	M	72	1.61	0.65	1.57	150.52	5.19	18.78	2.88	0	0.2	28.05	5.04	11.59	225.4	–	39.24	–	normal	–
16	M	32	17.7	1.04	0.99	113	2.89	18	3.01	10.9	< 9	10.6	2.22	3.77	144	< 0.16	15.3	–	empty sella	–
17	M	68	3.25	< 1.11	2.19	96.43	4.45	8.28	7.31	–	–	13.88	8.43	11.95	185.01	0.47	18.26	–	empty sella	–

M male, **F** female, **COR** cortisol (am:185–624, pm: < 276 nmol/ L), **ACTH** adrenocorticotropic hormone (8:00–10:00 am, 1.6–13.9, pm: < 1.6 pmol/L), **TT3** triiodothyronine (1.25–2.73 nmol/L), **TT4** tetraiodothyronine (69.97–152.52 nmol/L), **FT3** serum free triiodothyronine (3.8–7 pmol/L), **FT4** free thyroid hormone (7.64–16.03 pmol/L), **TSH**, thyrotropin (0.34–5.6 uIU/mL), **TgAb** thyroglobulin antibody (0–4 IU/mL), **TPOAb** thyroid peroxidase antibody (0–9 IU/mL), **PRL** prolactin (male: 4.0–15.2, female: 4.8–23.3 ng/mL); **FSH** follicle stimulating hormone (male: 1.5–12.4, female: post-menopausal 25.8–134.8 mIU/mL), **LH** luteinizing hormone (male:1.7–8.6, female: post-menopausal 7.7–58.5 mIU/mL), **E2** estradiol (male: 94.8–223, female: post-menopausal < 18.4–505 pmol/L), **P** progesterone (male: 0.7–4.3, female: post-menopausal 0.3–2.5 nmol/L), **T** androgen (male: 9.9–27.8, female: 0.2–2.9 nmol/L), **GH** growth hormone (male: 0.003–0.97, female: 0.01–3.61 ng/mL), - none.



▶ **Fig. 2** Pituitary magnetic resonance imaging in seven patients with empty sella (T2 image).

▶ **Table 3** Potential pathogenesis of IIAD

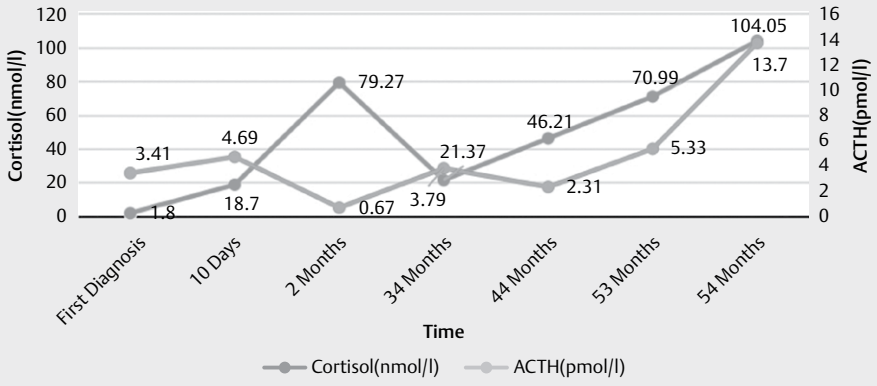
Potential pathogenesis of IIAD	Details
Genetic defects	▪ POMC genetic defects [3], TBX19 mutations [4], NFKB2 mutations [6], structural mutation in PC1 [7].
Autoimmunity(highest probability)	▪ IIAD is often associated with many autoimmune diseases: Hashimoto's thyroiditis, primary hypothyroidism, Graves' disease, type 1 diabetes, ulcerative colitis, Crohn's disease, etc., especially autoimmune thyroid disease [2, 8];
	▪ Infiltration of lymphocytes was found in pituitary tissue [10];
	▪ Patients with traumatic brain injury develop IAD due to immune system attack on exposed ACTH cells [12];
	▪ 0.8 % of patients developed IIAD after ICI therapy [13];
	▪ The formation of the empty sella may also be related to autoimmunity [14].
Pituitary ischemia	▪ Various vascular risk factors, such as hyperglycemia and hypertension, can cause inadequate perfusion of the pituitary, resulting in ischemic damage to the pituitary [9, 15].
Alcohol	▪ Chronic alcohol intoxication can cause ultra-microscopic pathological changes in the endocrine cells [16–18].
Drugs	▪ Long-term using of narcotic psychotropic drugs may cause IIAD [19, 20].

IIAD idiopathic isolated adrenocorticotropic hormone deficiency, **PC1** Prohormone convertase 1, **ACTH** adrenocorticotropic hormone, **ICI** immune checkpoint inhibitor.

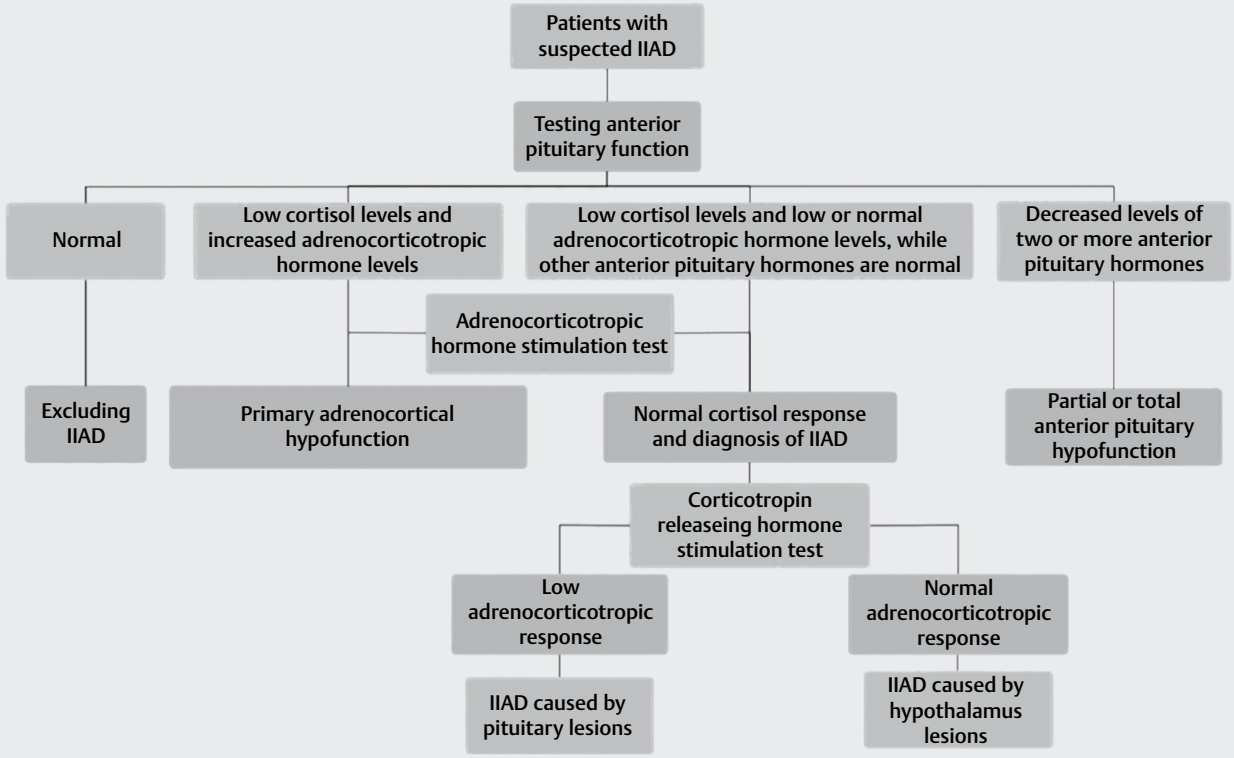
adrenal gland can be shriveled due to a prolonged lack of ACTH [28]. Hematological examination mostly shows hyponatremia and hypoglycemia, and if available, anti-pituitary antibody testing should be implemented to assess the involvement of immune factors. Furthermore, genetic screening should be performed when a newborn is suspected to have IIAD.

Differential diagnosis of idiopathic isolated adrenocorticotrophic hormone deficiency

Being familiar with the differential diagnosis of IIAD helps to improve the diagnosis rate. For example, compared with primary adrenocortical hypofunction, patients with IIAD do not have skin pigmentation and a reduction in cortisol and ACTH. In addition,



▶ **Fig. 3** Folding graph of cortisol and ACTH levels in case 9.



▶ **Fig. 4** Diagnostic process of IIAD.

the non-specific symptoms of patients with IIAD are often similar to those of gastrointestinal disease, cardiovascular disease, and neurological or psychiatric disease; however, the symptoms of gastrointestinal disease are regular, whereas IIAD patients lack regular symptoms and symptomatic treatment is invalid. Hypotensive shock and coma associated with cardiovascular disease mostly occur with underlying vascular diseases, while coma and seizures in patients with IIAD are mostly due to hypoglycemia and hyponatremia. These symptoms are recovered quickly after supplementing IIAD patients with glucocorticoids.

Treatment and prognosis of idiopathic isolated adrenocorticotrophic hormone deficiency

The treatment of IIAD broadly follows the treatment principles of secondary adrenocortical hypofunction [29]. Glucocorticoid supplementation is the first choice, and the main oral drugs are hydrocortisone and prednisone, and hydrocortisone is generally pre-

ferred [13]. The doses of hydrocortisone are as follows: 10–25 mg/day for adults and 8–10 [mg/m2]/day for children. The mode of administration is mostly half to two-thirds of the total dose at 8 am, followed by the remaining dose given divided and given once or twice at noon and/or in the evening. Adult patients can be administered prednisone [30]. The dose is 3–7.5 mg at 8 am alone. The selection of drug dose should be individualized; mild patients do not require interventions during non-stressful conditions, but glucocorticoid supplementation is required during stressful conditions. In other patients, the dose should be adjusted upward during stressful conditions, such as fever, surgery, and adrenal crisis. Whether the supplement dose is appropriate is mainly based on clinical manifestations and laboratory tests rather than cortisol and ACTH levels. Prenatal diagnosis is recommended for pregnant women with a family history of IIAD, and tumor patients treated with ICIs require monitoring of the HPA axis function both during treatment and following treatment completion because the effects of ICIs persist even after discontinuation [31, 32].

The symptoms and laboratory indicators of IIAD mostly return to normal after glucocorticoid supplementation; however, the HPA axis function had not recovered in all patients at the time of writing this article. In another study, some patients progressed to hypofunctioning of multiple pituitary axes [8]; strictly speaking, these patients cannot be diagnosed with IIAD and be more appropriately diagnosed with partial or total hypopituitarism.

Conclusions

In conclusion, IIAD has an insidious onset and atypical symptoms and can seriously affect the quality of life. The possibility of IIAD should be considered in any patient with acute, unexplained recurrent anorexia, fatigue, hyponatremia, or hypoglycemia. In addition, for patients with hypertension or diabetes, we should be alert to the possibility of IIAD when a sudden drop or significant improvement in blood pressure or blood glucose occurs or even with the appearance of non-drug-related hypotension or hypoglycemia [15]. Finally, more cases are required to understand the clinical characteristics of IIAD, thus further improving the diagnosis rate.

The limitations of this study are as follows: (1) the study focused on a rare disease; thus, the sample size was small, (2) due to limited laboratory conditions and the physical condition of the patients, the study failed to complete ACTH provocation test and insulin stress test, and (3) no pathological evidence was available.

Ethics Approval and Informed Consent

This retrospective study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Medical Ethics Committee of Jinjing No.1 People's Hospital approved this study. In this retrospective study, ethics approval was obtained, and the written informed consent was not needed.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Steinberg A, Shechter FR, Segal HI. True pituitary Addison's disease, a pituitary unitropic deficiency; fifteen-year follow-up 1954; 14: 1519–1529

[2] Guo QH, Chen K, Lu JM et al. Analysis of three patients with adult idiopathic isolated ACTH deficiency and literature review. Chin J Endocrinol Metab 2014; 30: 38–42

[3] Candler T, Kühnen P, Prentice AM et al. Epigenetic regulation of POMC; implications for nutritional programming, obesity and metabolic disease. Front Neuroendocrinol 2019; 54: 100773

[4] Weijing K, Liping Z, Tiantian Z et al. A case of congenital isolated adrenocorticotropic hormone deficiency caused by two novel mutations in the TBX19 gene. Front Endocrinol (Lausanne) 2019; 10: 251

[5] Kardelen AlAD, Poyrazoğlu Ş, Aslanger A et al. A rare cause of adrenal insufficiency – isolated ACTH deficiency due to TBX19 mutation: Long-term follow-up of two cases and review of the literature. Horm Res Paediatr 2019; 92: 395–403

[6] Shi C, Wang F, Tong A et al. NFKB2 mutation in common variable immunodeficiency and isolated adrenocorticotropic hormone deficiency: A case report and review of literature. Medicine (Baltimore) 2016; 95: e5081

[7] Nussey SS, Soo SC, Gibson S et al. Isolated congenital ACTH deficiency: A cleavage enzyme defect? Clin Endocrinol (Oxf) 1993; 39: 381–385

[8] Hannon AM, Hunter S, Smith D et al. Clinical features and autoimmune associations in patients presenting with Idiopathic Isolated ACTH deficiency. Clin Endocrinol (Oxf) 2018; 88: 491–497

[9] Xing J, Guo ZX. Two cases of isolated ACTH deficiency in adults. J Shanxi Medical University 2016; 47: 1134–1136

[10] Yamamoto M, Iguchi G, Bando H et al. Autoimmune pituitary disease: New concepts with clinical implications. Endocr Rev 2020; 41: bnz003

[11] Fujita Y, Bando H, Iguchi G et al. Clinical heterogeneity of acquired idiopathic isolated adrenocorticotropic hormone deficiency. Front Endocrinol (Lausanne) 2021; 12: 578802

[12] Ishizuka T, Asano M, Fujioka K et al. Two cases of traumatic isolated ACTH deficiency. Int J Clin Endocrinol Metab 2018; 4: 004–007

[13] Iglesias P, Peiró I, Biagetti B et al. Immunotherapy-induced isolated ACTH deficiency in cancer therapy. Endocr Relat Cancer 2021; 28: 783–792

[14] Chiloiro S, Giampietro A, Bianchi A et al. Empty sella syndrome: Multiple endocrine disorders. Handb Clin Neurol 2021; 181: 29–40

[15] Yin HJ, Zhao YM. A case of type 2 diabetes combined with isolated ACTH deficiency and primary hypothyroidism missed diagnosis. J Pract. Diabetes 2018; 14: 15–16

[16] Zhang LY, Chen GF, Liu C et al. Report of three cases of isolated ACTH deficiency in adults and review of the literature. Int J Endocrinol Metab 2017; 37: 284–286

[17] Skowrońska-Jóźwiak E, Orzechowski S, Piętak W et al. Rare clinical problem - isolated ACTH deficiency associated with chronic alcohol abuse. Endokrynol Pol 2022; 73: 778–783

[18] Xing LQ, BO AH, Tian CS. Effects of chronic alcoholism on the ultrastructure of endocrine cells in rat pituitary gland. J Zhangjiakou Medical College 2002; 35–37

[19] Raj R, Jacob A, Elshimy G et al. Isolated adrenocorticotropic hormone deficiency secondary to chronic opiate use. Cureus 2020; 12: e9270

[20] Müssig K, Friess E, Wudy SA et al. Secondary adrenal failure due to long-term treatment with flunitrazepam. Clin Endocrinol (Oxf) 2006; 65: 549–550

[21] Iglesias P, Sánchez JC, Díez JJ. Isolated ACTH deficiency induced by cancer immunotherapy: A systematic review. Pituitary 2021; 24: 630–643

[22] Yan ZL, Li CP. Three cases of isolated ACTH deficiency and review of the literature. J Doubtful. Diseases 2010; 9: 752–754

[23] Wu HY, Wang X, Xu YH et al. Report and clinical analysis of three cases of isolated ACTH deficiency in adults with hyponatremia as the primary performance. Sichuan. Medicine 2021; 42: 1064–1068

[24] Yamazaki K, Takahashi H, Taga M et al. Polyarthralgia as the initial manifestation of isolated ACTH deficiency. Ryumachi 2000; 40: 904–909

[25] Murakami T, Wada S, Katayama Y et al. Thyroid dysfunction in isolated adrenocorticotropic hormone (ACTH) deficiency: Case report and literature review. Endocr J 1993; 40: 473–478

[26] Shibutani Y. Prolactin dynamics in a patient with isolated ACTH deficiency accompanied by hyperprolactinemia. Am J Med Sci 1988; 295: 140–143

[27] Yanase T, Tajima T, Katabami T et al. Diagnosis and treatment of adrenal insufficiency including adrenal crisis: A Japan Endocrine Society clinical practice guideline [Opinion]. Endocr J 2016; 63: 765–784

[28] Yu JW, Zhang X, Quan HB. Two cases of isolated adrenocorticotropic hormone deficiency combined with Hashimoto's thyroiditis in adults. J Clin Intern Med 2020; 37: 665–666

[29] Obesity Group, Endocrinology Branch, Chinese Medical Association. Expert consensus on perioperative glucocorticoid management in patients with hypoadrenocorticism. Chin J Endocrinol Metab 2022; 38: 1–6

[30] Smith DJF, Prabhudev H, Choudhury S et al. Prednisolone has the same cardiovascular risk profile as hydrocortisone in glucocorticoid replacement. Endocr Connect 2017; 6: 766–772

[31] Takeno A, Yamamoto M, Morita M et al. Late-onset isolated adrenocorticotropic hormone deficiency caused by nivolumab: A case report. BMC Endocr Disord 2019; 19: 25

[32] Boudjemaa A, Rousseau-Bussac G, Monnet I. Late-onset adrenal insufficiency more than 1 year after stopping pembrolizumab. J Thorac Oncol 2018; 13: e39–e40