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Autoimmune Primary Adrenal Insufficiency in Children

Nádia Mourinho Bala[1], Raquel S. Gonçalves[2], Joana Serra Caetano[3], Rita Cardoso[3], Isabel Dinis[3], Alice Mirante[3]

[1]Hospital Beatriz Ângelo, Department of Endocrinology, Loures, Portugal
[2]Pediatric Hospital of Coimbra, Department of Pediatrics, Coimbra, Portugal
[3]Pediatric Hospital of Coimbra, Department of Pediatric Endocrinology, Diabetes and Growth, Coimbra, Portugal

What is already known on this topic?

Autoimmune adrenal insufficiency is a rare condition in pediatric age groups. The symptoms at presentation are frequently non-specific and this disease is often misdiagnosed. In order to avoid adverse outcomes, a prompt diagnosis should be established and the treatment initiated immediately.

What this study adds?

This study describes the demographic characteristics, clinical presentation and laboratorial findings of autoimmune adrenal insufficiency in the pediatric age group in one portuguese reference center. Additionally, by increasing pediatricians' awareness of this potential life-threatening disease, we hope to contribute to an earlier diagnosis.

Abstract

Objective: Primary adrenal insufficiency (PAI) is a rare condition in children, and is potentially life-threatening. The most common cause is congenital adrenal hyperplasia, and autoimmune etiology is the most frequent acquired cause in this age group. Symptoms are usually non-specific and, when suspected, investigation should include adrenocorticotropin hormone (ACTH) and morning serum cortisol measurement and, in some cases, a cosyntropin test to confirm the diagnosis. Prompt treatment is essential to prevent an adverse outcome.

Methods: We retrospectively collected clinical and laboratory data from adrenal insufficiency due to autoimmune adrenalitis, observed from 2015 to 2020 in a pediatric endocrinology department of a tertiary care hospital.

Results: Eight patients were identified, seven males and one female, with age at diagnosis between 14 and 17 years. The symptoms at presentation ranged from non-specific symptoms, such as chronic fatigue and weight loss, to a severe presentation, with altered mental status and seizures. The median duration of symptoms was 4.5 months. The diagnosis was confirmed by serum cortisol and plasma ACTH measurement and all were confirmed to have autoimmune etiology (positive anti-adrenal antibodies). At diagnosis, the most common laboratory abnormality was hyponatremia. All patients were treated with hydrocortisone and fludrocortisone. One patient presented with evidence of type 2 autoimmune polyglandular syndrome.

Conclusion: PAI is a rare condition in the pediatric age group. Due to non-specific symptoms, a high index of suspicion is necessary to establish a prompt diagnosis. Once an autoimmune etiology is confirmed, it is important to initiate the appropriate treatment and search for signs and symptoms of other autoimmune diseases during follow-up.

Keywords: Primary adrenal insufficiency, pediatric adrenal insufficiency, Addison's disease

Introduction

Adrenal insufficiency is a rare condition caused by the dysfunction of the adrenal cortex, resulting in impaired secretion of glucocorticoids and/or mineralocorticoids (1,2). These hormones play an important role in energy, salt and fluid homeostasis. Thus, adrenal insufficiency is a potentially life-threatening condition (2). It comprises a heterogenous group of both congenital and acquired disorders with autoimmune adrenalitis being the most common cause of acquired adrenal insufficiency (1).

Address for Correspondence: Nádia Mourinho Bala MD, Hospital Beatriz Ângelo, Department of Endocrinology, Loures, Portugal
Phone: +00351219847200 **E-mail:** nadia.mourinho@gmail.com **ORCID:** orcid.org/0000-0002-5834-4848

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In children, the diagnosis of adrenal insufficiency can be very challenging. Patients with adrenal crisis generally present with characteristic features of acute dehydration, hypotension, abdominal pain, vomiting and/or altered mental status. However, the features of chronic adrenal insufficiency are vague and non-specific, such as chronic fatigue, anorexia, nausea, vomiting, loss of appetite, weight loss and recurring abdominal pain. These symptoms may mimic gastrointestinal or psychiatric disorders. Hyperpigmentation of skin and mucosal tissue should raise the index of suspicion for primary adrenal insufficiency (PAI) (3,4,5,6). Classic laboratory findings include hyponatremia, hyperkalemia, hypoglycemia, and metabolic acidosis (1,6).

In PAI, cortisol deficiency leads to an activation of the hypothalamic-pituitary axis with a subsequent increase of plasma adrenocorticotropic hormone (ACTH), which enhances stimulation of the adrenal cortex. Due to the disruption of adrenal mineralocorticoid synthesis, there is an increase in renin release by the juxtaglomerular cells of the kidneys (2). Thus, screening tests should include morning cortisol and ACTH levels and plasma renin activity (1,6). Once diagnosis is made, treatment intends to mimic normal cortisol secretion, with replacement of glucocorticoid and mineralocorticoid according to body surface area (7).

The aim of the present study was to describe clinical presentation, biochemical abnormalities, and treatment in patients with autoimmune adrenal insufficiency followed in a department of pediatric endocrinology of a tertiary care hospital.

Methods

This is a retrospective and descriptive study of pediatric patients with the diagnosis of autoimmune PAI (APAI), from January 2015 to December 2020, followed at a single pediatric endocrinology unit of a tertiary hospital in Portugal. The diagnosis of APAI was based on ACTH elevation (> 2 times upper limit), low serum cortisol (< 5 ug/dL) and positive anti-adrenal antibodies. The anti-adrenal antibodies were measured by indirect immunofluorescence assay, using as a substract the primate adrenal cortex. The initial dilution was 1:4. Data was collected from medical records and included demographic characterization, personal and familial history, age of onset of symptoms, clinical and laboratory findings, treatment and evolution. Both the data collection and the analysis were performed were anonymized, respecting patient privacy and ethical considerations. All laboratory testing was performed in our institutional laboratory and the reference ranges are: ACTH 7.6-63 pg/mL; active renin concentration 7-76 uU/mL; aldosterone 40-310 pg/mL; serum Na+ 136-146 mmol/L; and serum K+ 3.5-5.1 mmol/L.

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous data are described as median and interquartile range and categorical data are described as the number of cases (%).

Results

Eight cases were identified (seven males and one female) with median age at diagnosis of 15.1 years (Q1;Q3 13.4;16.1). Five patients had at least one first degree relative with autoimmune disease (AID), namely systemic lupus erythematosus, type 1 diabetes mellitus, Graves disease and APAI. One patient had a second-degree family history of type 1 diabetes mellitus and Graves disease. The most frequent symptoms at presentation were anorexia (n = 5), weight loss (n = 5), chronic fatigue (n = 5), nausea and vomiting (n = 4), hyperpigmentation (n = 3), abdominal pain (n = 2) and myalgia (n = 2). Less frequent symptoms included altered mental status and seizures due to severe hyponatremia (Na+ 113 mmol/L), reported in one case, and salt craving reported in another patient (Table 1). The median duration of symptoms before diagnosis was 4.5 months. On observation, three patients had hypotension and two were febrile. In laboratory evaluation, seven patients presented with hyponatremia (median Na+ 122.5 mmol/L, Q1;Q3 118;126.5), five patients with hyperkalemia (median K+ 5.3 mmol/L, Q1;Q3 5.2;5.5), three patients metabolic acidosis (median pH 7.22) and two patients presented with hypoglycemia (52 mg/dL and 63 mg/dL). At presentation, median serum cortisol was 1.35 µg/dL (Q1;Q3 1;2.2) and ACTH was 1250 pg/mL (Q1;Q3 1040;1250). Seven patients presented with low aldosterone level (median 34.7 pg/mL) and six patients presented with high active renin concentration (median 8180 uU/mL) (Table 2). All patients had strong positive anti-adrenal antibodies, by immunofluorescence assay. Six of these patients had presented to a health service at least once before, with the same symptoms, and were misdiagnosed. The most common diagnosis in these cases was acute gastroenteritis. One patient was admitted one month before the diagnosis due to weight loss, loss of appetite and fatigue and an eating disorder diagnosis was assumed. In this case, having a pre-existing personal history of anorexia nervosa contributed for the misdiagnosis. Patients were treated with hydrocortisone and fludrocortisone, with a median dosage of 16.7 mg/m^2/day and 87.5 mcg/day, respectively. The median time

of follow up was 29 months. During this period, one patient presented with hyperthyroidism in the context of Graves disease, contributing to a diagnosis of polyglandular autoimmune syndrome type 2, and he also had selective IgA deficiency. Another patient presented with increased anti-thyroid peroxidase antibodies, even though he was asymptomatic at the time of writing.

Discussion

APAI is a rare diagnosis in children. In a study published by Perry et al. (8), including 103 patients, the most common cause of PAI in the pediatric population was attributed to congenital adrenal hyperplasia followed by autoimmune etiology (12.7% of all cases). The cases of APAI associated with autoimmune polyendocrinopathy syndrome type 1 (APS1) were diagnosed at a younger age when compared with non-APS1 patients (10.7 vs 14.6 years-old) (8). In our study the median age at diagnosis was 15.1 years and there were no cases in association with APS1. The diagnosis of APAI was more common in males, as reported in other series (9). So, despite APAI being more frequent in females in the general population, in the pediatric age group it seems to be more frequently diagnosed in males.

The usual presentation in adolescent years and with non-specific symptoms (anorexia, weight loss and chronic fatigue) may lead to misdiagnosis, more severe presentation and delayed treatment. Although less frequent than other diagnoses that may present (depression, anorexia nervosa, etc), organic disease should always be excluded, even in this age group. More specific symptoms, such as hyperpigmentation of the skin and mucous membranes and salt craving, were less common. Hypoglycemia was detected in only two cases, traditionally more frequent in cases of central adrenal insufficiency than in cases of PAI. There was a considerable time gap from first symptoms until the diagnosis, frequently over 4-6 months. Most patients had already consulted a medical doctor prior to the diagnosis due to the same symptoms. However, owing to a lack of specificity of symptoms such as chronic fatigue, loss of appetite, weight loss and nausea and vomiting, frequently gastrointestinal illness was diagnosed. In one

Table 1. Patient demographic and clinical characteristics in terms of gender, age at diagnosis, presence of familial history of autoimmune diseases, symptoms at presentation and duration before diagnosis

ID	Gender	Age at diagnosis (years)	Familial history of AID	Presenting symptoms	Symptoms duration (months)
1	M	16	P	Anorexia, astenia, weight loss, back pain, myalgia, hyperpigmentation	3
2	M	15	NP	Astenia, weight loss, abdominal pain, vomiting, myalgias, hyperpigmentation	6
3	M	17	NP	Astenia, anorexia, weight loss	< 1
4	F	15	P	Astenia, anorexia, weight loss, vomiting and postural dizziness	1
5	M	14	NP	Anorexia, weight loss, vomiting, fever	6
6	M	12	P	Hyperpigmentation	6
7	M	16	P	Astenia, anorexia, postural dizziness, salt craving	< 1
8	M	15	P	Seizures, altered mental status, abdominal pain, vomiting	12

M: male, F: female, AID: autoimmune disease, P: present, NP: non present

Table 2. Clinical and laboratory findings at presentation

ID	At presentation										
	Hypotension	Fever	pH	Na + (mmol/L)	K + (mmol/L)	HCO^{3}- (mmol/L)	Serum glucose (mg/dL)	Serum creatinine (mg/dL)	ACTH (pg/mL)	Serum cortisol (µg/dL)	Serum active renin concentration (uU/mL)
1	P	NP	7.37	125	5.13	23.7	88	0.95	> 1250	< 1.0	8785
2	NP	NP	NA	116	4.0	NA	NA	NA	NA	NA	NA
3	P	NP	7.38	128	4.48	26.6	101	0.82	> 1250	2.6	9730
4	NP	P	7.35	120	5.6	23.7	70	0.5	1040	3.6	3505
5	P	P	7.21	120	5.3	24	92	0.46	> 2000	1.7	84
6	NP	NP	7.38	141	4.04	23.7	86	0.43	> 1250	1.8	233
7	NP	NP	7.31	125	5.4	23.7	63	0.86	1241	1	7575
8	NP	NP	7.22	113	5.2	20	52	0.66	802	0.9	20840

P: present, NP: not present, NA: not available, ACTH: adrenocorticotropin hormone

case, an exacerbation of an eating disorder was assumed to be the diagnosis. Similarly to our findings, Hsieh and White (10) described the case of one patient diagnosed with anorexia nervosa and admitted to the inpatient psychiatry unit before a diagnosis of adrenal insufficiency was reached. It is important to include endocrine entities, namely adrenal insufficiency and hyperthyroidism, in the differential diagnosis of an eating disorder. The presence of symptoms, such as fatigue, weight loss, and upper gastrointestinal distress, which are associated with hyponatremia, should always trigger suspicion of adrenal insufficiency, particularly in patients with positive personal or familial history of AID. Nonetheless, the diagnosis is frequently delayed, resulting in a clinical presentation with acute life-threatening adrenal crisis with hypotension, marked acute abdominal symptoms and marked laboratory abnormalities, requiring immediate treatment. In our series, seven of the eight patients presented with adrenal crisis. The only patient that presented in an early stage of the disease had a familial history of autoimmune adrenal insufficiency, and the hyperpigmentation immediately raised suspicion of this diagnosis. When the diagnosis of PAI is suspected, morning serum cortisol and plasma ACTH should be measured. In most cases, the diagnosis is highly probable when cortisol is <5 µg/dL in combination with a plasma ACTH elevated more than 2-fold above the upper limit of the reference interval for the specific assay, in a blood sample collected at 8:00 am (2). In the presence of equivocal values, a cosyntropin test, currently regarded as the diagnostic "gold standard" for the diagnosis of PAI, should be performed (2,6). In our series this test was not necessary, since all patients presented with unequivocally low serum cortisol and high levels of ACTH. The treatment of PAI consists of glucocorticoid and mineralocorticoid replacement (11). The majority of patients presented with mineralocorticoid deficiency at the time of diagnosis. However, even in cases when there is no mineralocorticoid deficiency at presentation, it might eventually occur in the course of the disease. The treatment for children mainly involves the administration of short acting glucocorticoids, particularly hydrocortisone (1). It is important to optimize the doses in order to mimic the physiological circadian rhythm, and to prevent side effects, such as growth suppression, obesity, metabolic syndrome, diabetes and osteoporosis (11). In our series, the patient taking the highest daily hydrocortisone dosage (31.6 mg/m^2/day) had a simultaneous diagnosis of Graves disease, a condition that is well-known to accelerate cortisol metabolism. The thyrotoxic state shortens the half-life of cortisol, due to an increased turnover rate, mediated by 11β-hydroxysteroid dehydrogenase and 5-α reductase enzymes (12). Thus, cortisol requirements are increased, and a higher daily dosage of hydrocortisone is often needed in these cases.

It is recommended to monitor glucocorticoid replacement by clinical assessment in children, using metrics such as growth velocity, weight, blood pressure and energy levels (2). As in other chronic diseases, compliance is a very important factor associated with disease control, and is particularly challenging during adolescence. In the management of adrenal insufficiency, it is extremely important to educate the patients and their families in order to actively increase glucocorticoid dosage when exposed to stress, such as during severe systemic infection or trauma, to minimize the risk of adrenal crisis. When oral hydrocortisone formulations cannot be used, parenteral hydrocortisone should be administered (6). In our patients, not one case of adrenal crisis was registered after diagnosis. Autoimmune adrenalitis is strongly associated with specific HLA haplotypes and with polymorphisms in the gene for cytotoxic T lymphocyte-associated antigen-4, which may be broadly involved in susceptibility to AID (13). About half of adult patients with lymphocytic adrenalitis will also have AID of a different endocrine organ or tissue (14). During the follow-up it is important to be aware of signs and symptoms of other AID, namely thyroid disease, autoimmune gastritis, type 1 diabetes mellitus, celiac disease and premature ovarian failure (2). In our series, one patient presented with type 2 APS that included hyperthyroidism due to Graves disease. The same patient also had IgA deficiency, which has a well-established relationship with AID, more often to type 1 diabetes, autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, celiac disease and myasthenia gravis (15). The association between IgA deficiency and autoimmune adrenal insufficiency is very rare (16). Another patient presented with positive anti-peroxidase antibodies but had no clinical disease at the time of writing.

Study Limitations

Our study has some limitations. Firstly, our study included a small sample size of a single reference center. Secondly, the nature of the study required us to rely on data from medical records.

Conclusion

In conclusion, APAI is a rare, potentially life-threatening diagnosis in children. A high index of suspicion is required for an accurate diagnosis due to non-specific and insidious symptoms. Once diagnosis is made, an adequate treatment should be promptly provided, and clinical and subclinical manifestations of other autoimmune disorders should be

carefully investigated during follow-up. It is also crucial to educate patients and their families regarding treatment adjustments to stress to avoid adrenal crises over time.

Ethics

Ethics Committee Approval and Informed Consent: The study design was approved by the Ethics Committee of the Hospital and University Center of Coimbra (OBS.SF.60-2021 date: 22.09.2021), and the requirement for written informed consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Joana Serra Caetano, Rita Cardoso, Isabel Dinis, Alice Mirante, Concept: Alice Mirante, Design: Alice Mirante, Data Collection or Processing: Nádia Mourinho Bala, Raquel S. Gonçalves, Analysis or Interpretation: Nádia Mourinho Bala, Literature Search: Nádia Mourinho Bala, Raquel S. Gonçalves, Writing: Nádia Mourinho Bala, Raquel S. Gonçalves, Joana Serra Caetano, Rita Cardoso, Isabel Dinis.

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