Metelski Jakub, Metelska Aleksandra, Sereda Dominika, Nieścior Hubert, Szwed Monika. Primary adrenal insufficiency - Addison's disease. Journal of Education, Health and Sport. 2022;12(8):540-547. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2022.12.08.057
https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.08.057
https://zenodo.org/record/6997370

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Received: 29.07.2022. Revised: 07.08.2022. Accepted: 16.08.2022.

Primary adrenal insufficiency - Addison's disease

Metelski Jakub
https://orcid.org/0000-0002-7110-9332
jakub.metelski@o2.pl
Provincial Specialist Hospital of the name Stefan Cardinal Wyszyński, Aleja Kraśnicka 100, 20-718 Lublin
Metelska Aleksandra
https://orcid.org/0000-0002-3166-1296
metelskaaleksandra@gmail.com
Provincial Specialist Hospital of the name Stefan Cardinal Wyszyński, Aleja Kraśnicka 100, 20-718 Lublin
Sereda Dominika
https://orcid.org/0000-0003-4189-1674
dominika.sereda1902@gmail.com
Independent Public Clinical Hospital No. 4 in Lublin, Jaczewskiego 8, 20-954 Lublin
Nieścior Hubert
https://orcid.org/0000-0002-4709-4396
hniescior@gmail.com
Medical University of Lublin, Aleje Racławickie 1, 20-059 Lublin
Szwed Monika
https://orcid.org/0000-0002-5711-2172
monika.pi3karska@gmail.com
Provincial Specialist Hospital of the name Stefan Cardinal Wyszyński, Aleja Kraśnicka 100, 20-718 Lublin

Abstact

Introduction and aim

Addison's disease is defined as primary adrenal insufficiency, the symptoms of which result from hormonal deficiencies: glucocorticosteroids, mineralocorticosteroids and androgens. Currently, autoimmunity is considered the most common cause of Addison's disease. Antibodies are most often directed against the enzymes 21-hydroxylase and 17-hydroxylase involved in steroidogenesis.
The aim of the study is to present a typical clinical course, diagnostic path and current therapeutic options for Addison's disease.

Description of the state of knowledge

Currently, in developed countries, the number of cases is 100-140 people per million people. Initially, Addison's disease runs secretly. The clinical picture is closely correlated with the degree of adrenal cortex destruction. The most common symptoms include hypotonia, weight loss, weakness, salt craving, gastrointestinal disorders, and hyperpigmentation of the skin and mucous membranes. In extreme cases, adrenal crisis may develop, characterized by rapid clinical deterioration with hypotension, fever, vomiting, dehydration, and loss of consciousness.
Diagnostics uses the measurement of the concentration of morning cortisol and corticotropin (ACTH) in the blood, and in doubtful situations, additionally a stimulation test using synthetic ACTH.

Summary

A diagnosis of Addison's disease requires lifelong hormonal replacement therapy. For this purpose, hydrocortisone or prednisone and fludrocortisone are used. In stressful situations, the doses of glucocorticoids should be adequately increased. Patients with adrenal crisis require intensive fluid resuscitation to restore intravascular volume, correct hypoglycemia and electrolyte disturbances, and administer rapidly high doses of hydrocortisone.

Key words: Addison’s disease, fludrocortisone, hydrocortisone, adrenal crisis, ACTH

Introduction

Addison's disease is defined as primary adrenal insufficiency, the symptoms of which result from a hormonal deficiency. The adrenal cortex is responsible for the secretion of three groups of hormones, which include: glucocorticosteroids, mineralocorticosteroids and androgens. The long-term deficiency of cortisol, belonging to the group of glucocorticosteroids (GKS), is particularly dangerous, which may lead to adrenal crisis. It is a state of immediate threat to life. The main cause of Addison's disease is autoimmunity in an isolated form or as one of the elements of autoimmune polyglandular hypothyroidism APS I and II with a genetic basis. Antibodies are most often directed against the enzymes 21-hydroxylase and 17-hydroxylase involved in steroidogenesis. It is estimated that up to 80% of all Addison's disease cases are autoimmune. Other causes of primary adrenal insufficiency include: infections (bacterial, viral, fungal, parasitic), neoplasms (bilateral primary adrenal cortex cancer, lymphomas, bilateral adrenal metastases mainly from lung, breast, colon cancers), drugs (ketoconazole, metyrapone, fluconazole, tyrosine kinase inhibitors, rifampicin), sarcoidosis or amyloidosis [1,2].

Epidemiology

Addison's disease is a rare disease. According to Andreas Barthel in his study, it is estimated that currently in developed countries the number of cases may be 100-140 people per million people. A significant increase in the prevalence of this disease has been noticed in relation to the previous age, especially in women with more autoimmune disorders. It can be assumed that this is related to the improvement of diagnostic methods, but also to the actual increase in morbidity [1]. Changes in the background of the disease were also noticed. In the previous century, tuberculosis was identified as the main cause, and now autoimmunity [3]. The incidence of Addison's Disease increases with the prolonged survival of the society. With age, the probability of chronic diseases increases, in the course of which, as a result of their progression and treatment, primary adrenal insufficiency may develop [1].

Diagnostics

In patients suspected of Addison's disease, the measurement of morning cortisol and corticotropin (ACTH) in the blood is performed first. In clinical practice, it is believed that the

concentration of cortisol <138 mmol/L (5 μg/dL) and the concentration of ACTH more than twice the upper limit of normal allow the diagnosis of primary adrenal insufficiency. If the cortisol measurements are borderline, and the patient has symptoms characteristic of Addison's disease, a stimulation test using synthetic ACTH is additionally performed, which is considered the gold standard in the diagnosis of primary adrenal insufficiency. The ACTH concentration reported in this study varies with age. In infants the dose is 15 μg/kg body weight, in children under two years of age 125 μg, and in children over two years of age and adults 250 μg. Cortisol concentration is tested 30 and 60 minutes after ACTH administration. With a peak cortisol level below 500 mmol/L (18 μg/dL), it is possible to diagnose Addison's disease.

Aldosterone deficiency, which belongs to the mineralocorticosteroids, manifests itself in laboratory tests in the form of hyperkalemia and hyponatremia.

The diagnosis of Addison's disease requires further diagnostic tests to detect the etiology of the disease, e.g. search for antibodies against hydroxylase-21 and hydroxylase-17, computed tomography of the adrenal glands or control of pharmacotherapy by the patient [4].

Clinical picture

The clinical picture of Addison's disease is closely correlated with the degree of adrenal cortex destruction. In the rapidly progressive insufficiency of the cortex and the lack of its protection with appropriate pharmacological treatment, adrenal crisis may develop, which is a direct threat to life. In other cases, the disease is chronic.

The first symptoms in the chronic form of this disease are usually weight loss, weakness, fatigue, anorexia, and gastrointestinal disturbances. Hypotension, present in up to 90% of cases, may evolve into shock in severe cases. Usually it is accompanied by symptoms of orthostatic hypotension.

A characteristic feature of Addison's disease is hyperpigmentation of the skin and mucous membranes resulting from increased concentrations of ACTH, which stimulates the secretion of melanin in the skin. Hyperpigmentation is a factor that distinguishes primary adrenal insufficiency from secondary. Symptoms suggesting mineralocorticoid deficiency are mainly dizziness and salt craving [5,6].

Another clinically significant aspect is the absence of menstruation, which can be caused by both primary ovarian failure in the spread of multi-glandular autoimmune syndrome, as well as weight loss or protracted disease. The symptoms of the underlying disease complete the entire disease picture [5].

Adrenal crisis is characterized by a rapid deterioration of the clinical condition in hypotensive patients with adrenal insufficiency (systolic blood pressure <100 mmHg), often refractory to norepinephrine infusion. Risk factors include chronic adrenal insufficiency, infection, trauma, and surgery. It may also appear as the first symptom in approximately 8 out of 100 patients with adrenal insufficiency each year. Additionally, the clinical picture shows increased body temperature, nausea and vomiting, dehydration, hypoglycaemia and significant weakness, including loss of consciousness. As hypovolemic shock is a common symptom of adrenal crisis, Addison's disease should be considered in patients with unexplained vascular collapse [5].

Chronic treatment

A diagnosis of Addison's disease requires lifelong hormonal replacement therapy. It aims to maintain the physiological level of glucocorticoids and mineralocorticoids.
Usually, 5-25 mg/day of hydrocortisone in divided doses 2 or 3 times a day or prednisone 3-5 mg/day are used in glucocorticoid replacement. In children, the initial dose of hydrocortisone is 8 mg/m2/day orally in a divided dose 3-4 times a day.
Doses should be adjusted individually depending on the clinical response and the normalization of electrolyte disturbances. Due to the potential side effects, the lowest possible dose should be aimed at controlling disease symptoms.
Due to its large fluctuations in serum, ACTH cannot serve as a dose titration tool. Certain drugs such as rifampicin, which increase the metabolism of glucocorticoids in the liver and inactivate cortisol, also affect the dosage of glucocorticoids. Due to the difficult dose adjustment and the risk of developing Cushing's syndrome, Dexamethasone is not a suitable choice for maintenance treatment. In stressful situations, such as infection, surgery, physical exertion, the doses of GCS should be adequately increased, because the destruction of the adrenal glands prevents an adequate physiological response [7,8].

Fludrocortisone at a dose of 0.05 to 0.2 mg daily is used in mineralocorticoid substitution. Fludrocortisone should be administered at a dose sufficient to maintain plasma renin levels within the reference range. Increased renin levels suggest the need to increase the dose of fludrocortisone. The dose of mineralocorticoids should also be adjusted to the level of stress.
Apart from hormone substitution, therapy should also take into account the treatment of the underlying disease [8].

Treatment of adrenal crisis

Patients with adrenal crisis require intensive fluid resuscitation with intravenous saline to restore intravascular volume. Initial fluid therapy may involve a bolus of saline followed by 5% glucose in isotonic saline, which will further allow for gradual correction of hypoglycemia. In addition, immediate correction of the deficiency of hormones, both glucocorticoids and mineralocorticosteroids, is required. The basis is the administration of hydrocortisone as an initial dose of 100 mg intravenously as a bolus, followed by 50 to 100 mg intravenously every 6 hours for 24 hours. In children, the dose is 50 mg/m2 (maximum 100 mg) intravenously as a bolus, followed by 50 to 100 mg/m2. As such high doses of hydrocortisone show mineralocorticoid activity, substitution with fludrocortisone in the acute phase is not necessary. In an emergency department setting, intravenous bolus administration of 4 mg of dexamethasone may be considered due to its long action and lack of influence on the biochemical determinations of endogenous glucocorticosteroids, which may facilitate diagnosis in patients without confirmation of Addison's disease. It is worth bearing in mind that dexamethasone and prednisone do not exhibit mineralocorticoid activity [8].

Summary

Addison's disease is defined as primary adrenal insufficiency, the symptoms of which result from hormonal deficiencies: glucocorticosteroids, mineralocorticosteroids and androgens. The long-term deficiency of cortisol, belonging to the group of glucocorticosteroids (GKS), is particularly dangerous, which may lead to an adrenal crisis. It is a state of immediate threat to life.

Currently, autoimmunity is considered the most common cause of Addison's disease. It can take place in an isolated form or as one of the elements of the autoimmune polyglandular hypothyroidism APS I and II. Antibodies are most often directed against the enzymes 21-hydroxylase and 17-hydroxylase involved in steroidogenesis.

Initially, Addison's disease runs secretly. The clinical picture is closely correlated with the degree of adrenal cortex destruction. The most common symptoms include hypotonia, weight loss, weakness, salt craving, gastrointestinal disorders, and hyperpigmentation of the skin and mucous membranes. In extreme cases, adrenal crisis may develop, characterized by rapid

clinical deterioration with hypotension, fever, vomiting, dehydration, and loss of consciousness.

Diagnostics uses the measurement of the concentration of morning cortisol and corticotropin (ACTH) in the blood, and in doubtful situations, additionally a stimulation test using synthetic ACTH.

A diagnosis of Addison's disease requires lifelong hormonal replacement therapy. For this purpose, hydrocortisone or prednisone and fludrocortisone are used.

Contribution of authors:

J.Metelski - study concept and design; critical revision of the manuscript for important intellectual content; study supervision;

A.Metelska- acquisition of data; analysis and interpretation of data; technical support;

D.Sereda- acquisition of data; analysis and interpretation of data; technical support;

H.Nieścior- acquisition of data; analysis and interpretation of data; technical support

M. Szwed- acquisition of data; analysis and interpretation of data; technical support

Disclosures:

Financial support: No financial support was received.

Conflict of interest: The authors declare no conflict of interest.

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