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Review

A DESCRIPTION OF ADDISON'S DISEASE, AND ITS NEUROPSYCHIATRIC MANIFESTATIONS COMPARING THE DISEASE AS IT IS NOW TO THE DISEASE AS EXPERIENCED BY SAINT ELIZABETH OF THE TRINITY IN 1906

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SUMMARY

We describe Addison's disease, which is the disease caused by Adrenal Gland Insufficiency. Addison's disease is an uncommon endocrine disorder characterised by inadequate production of hormones, predominantly aldosterone and cortisol, by the adrenal glands. This condition occurs due to damage to the adrenal cortex, the region responsible for hormone synthesis. Clinical manifestations of Addison's disease are often insidious and nonspecific, including symptoms such as myasthenia, persistent fatigue, unintentional weight loss, hypotension, and hyperpigmentation of the skin, especially in areas subjected to friction. A number of Neuropsychiatric manifestation, including Depression, and Psychosis can also occur. The aetiology is primarily autoimmune adrenalitis, where the immune system erroneously attacks and destroys adrenal cortical cells. Other aetiologies include infectious agents like Mycobacterium tuberculosis, which can infiltrate and impair the adrenal glands. Hemorrhagic damage to the adrenal cortex can occur secondary to severe stress, trauma, or coagulopathies. Additionally, metastatic neoplasms may involve the adrenal glands, leading to their destruction. Less frequently, genetic disorders such as adrenoleukodystrophy can compromise adrenal function by affecting both the cerebral white matter and adrenal cortex. Adrenal cortex damage can also result from adrenalectomy or the administration of medications that inhibit steroidogenesis. The pathophysiology of Addison's disease involves the disruption of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in cortisol deficiency, which is critical for regulating metabolism, immune function, and stress responses. Aldosterone deficiency leads to dysregulation of sodium and potassium homeostasis, causing hypotension and dehydration. Management of Addison's disease requires lifelong glucocorticoid and mineralocorticoid replacement therapy, typically with hydrocortisone or fludrocortisone, along with ongoing monitoring and dosage adjustments during periods of stress, illness, or surgical interventions. While describing Addison's Disease we describe the illness as experienced by Elizabeth of the Trinity, a Catholic Nun who suffered the illness in the early part of the Twentieth Century, whose illness is described from her letters and eyewitness accounts, taken for her beatification and canonisation findings. We describe how the illness it was viewed then, when it was seen as incurable, with great deficiencies in both diagnosis and treatment, and how the aetiology has changed over the years. Hence we show how the suffering endured by this person had both mental and physical aspects.

Key words: *Addison's disease - adrenal insufficiency - physical symptoms - mental symptoms – diagnosis – treatment - Elizabeth of the Trinity*

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INTRODUCTION

Addison's disease is an uncommon endocrine disorder characterised by inadequate production of hormones, predominantly aldosterone and cortisol, by the adrenal glands. This condition occurs due to damage to the adrenal cortex, the region responsible for hormone synthesis. In this article we describe the manifestations of this illness in order to describe how it presents and is treated today, but we also describe how it was seen in France, in the first decade of the twentieth Century, when a well known Catholic Carmelite Nun, Saint Elizabeth of the Trinity suffered and died from it. We wish to pay particular attention to the neuropsychiatric aspects of this condition.

EPIDEMIOLOGY OF ADDISON'S DISEASE

Addison's Disease is a rare disease. Addison's disease may affect persons of any age, sex, or ethnicity, however it typically presents in adults between 30 and 50 years of age (nhs.uk. 2018, Volpé 1990, Griffing 2024). There are no significant predispositions based on ethnicity (Griffing 2024). Elizabeth of the Trinity (Élisabeth Catez) was born in 1880 and died of Addison's Disease in 1906, so she was slightly younger than the average patient who suffered the disease.

The frequency rate of Addison's disease in the human population has been estimated at one in 100,000 of the population (Brennan 2007). Other estimates put the number closer to 40–144 cases per million population (1/25,000–1/7,000) (National Institute of Diabetes and Digestive and Kidney Diseases 2014, Griffing 2024, nhs.uk. 2018).

Today, about 70% of Addison's disease diagnoses occur due to autoimmune reactions, which cause damage to the adrenal cortex (National Organization for Rare Disorders 2018), whereas in Elizabeth's time, tuberculosis was the main cause of the disease (Addison 1855, Patnaik 2008).

HISTORY OF ADDISON'S DISEASE

In 1855, Thomas Addison described the autopsy findings of six patients who suffered from adrenal tuberculosis (Addison 1855, Patnaik 2008, Bancos 2014). Thus, all of the cases originally treated by Addison had Tuberculosis. Adrenal tuberculosis remains one of the most common causes of adrenal insufficiency in the developing world, to the extent that Guo et al. (Guo 2006) have recently published the contrast enhanced CT scan features of the adrenal glands in 42 patients with adrenal tuberculosis (Guo 2006). Elizabeth of the Trinity is said to have suffered from Addison's disease secondary to Tuberculosis (Macca 1972). In Elizabeth of the Trinity's Time, 1905, the Illness was not widely known in France so Elizabeth's doctors did not Recognise Addison's Disease and missed the Diagnosis. Today, about 70% of Addison's disease diagnoses occur due to autoimmune reactions, which cause damage to the adrenal cortex (National Organization for Rare Disorders 2018).

AETIOLOGY OF ADDISON'S DISEASE

At the Present time, most people with Addison's disease develop or have a pre-existing autoimmune disease (Hahner 2021). Therefore most common aetiology is autoimmune adrenalitis, where the immune system erroneously attacks and destroys adrenal cortical cells. Thus, common comorbid conditions which often occur with Addison's disease are; autoimmune thyroid disease (40% of people with Addison's), premature ovarian failure (up to 16% of people with Addison's), type 1 diabetes (11% of people with Addison's), pernicious anemia (10% of people with Addison's), vitiligo (6% of people with Addison's) celiac disease (2% of people with Addison's) (Hahner 2021).

Two rare syndromes are associated with Addison's disease. The combination of Addison's disease with mucocutaneous candidiasis, hypoparathyroidism, or both, is referred to as autoimmune polyendocrine syndrome type 1 (GARD 1917). The combination of Addison's disease in addition to autoimmune thyroid disease, type 1 diabetes, or both, is called autoimmune polyendocrine syndrome type 2. (GARD 1917).

As has been said, In the past, tuberculosis was the major cause of Addison’s disease, and it remains a prominent cause of the condition in developing countries (Guo 2006). Here the infectious agents Mycobacterium tuberculosis, infiltrates and impairs the adrenal glands. Other infectious causes of Addison’s disease include the diseases histoplasmosis and blastocmycosis as well as and opportunistic infections related to HIV/AIDS (Oelkers 1996, Guo 2006). Oncological conditions which can cause Addison’s disease are adrenal metastases. Such metastatic neoplasms may lead to the destruction of the adrenal glands. and primary adrenal tumours may also occur (Oelkers 1996, Guo 2006).

Bleeding into the adrenal glands can cause hemorrhagic damage to the adrenal cortex (Mehmood 2023) secondary to severe stress, trauma, or coagulopathies, thus causing Addison’s disease.

Less frequently, genetic disorders such as adrenoleukodystrophy (Raymond 2023) can compromise adrenal function by affecting both the cerebral white matter and adrenal cortex. Adrenal cortex damage can also result from adrenalectomy (Li 2023) or the administration of medications that inhibit steroidogenesis. (These include ketoconazole, levoketoconazole, metyrapone, osilodrostat) (Fleseriu 2016, Castinetti 2021). All these conditions can be rare causes of Addison’s disease.

SYMPTOMS OF ADDISON'S DISEASE

Addison's disease has a very Insidious Onset, often over several months. Sometimes another stressful event, for example an illness or injury may make the symptoms worse, or make them apparent for the first time.

The symptoms of Addison's disease usually include Extreme fatigue, which steadily gets worse over time, loss of appetite and unintentional weight loss, areas of darkened skin, causing patches of dark skin (or hyperpigmentation), especially around scars and skin creases and on the gums, but eventually this may cover whole body. The hyperpigmentation is described as being a copper colour. In Addison's disease, patients have a markedly low blood pressure, - which can cause light-headedness or dizziness upon standing and even fainting. Patients experiencing a craving for salt, and for salty food. Patients have a low blood sugar, that is, hypoglycemia. Patients often experience nausea, diarrhoea or vomiting. They can experience abdominal pain, muscle pain, muscle spasms and joint pain. Patients can experience dehydration. Female patients with Addison's disease may have abnormal menstruation, they may lose their body hair, and they may have a decreased sexual drive. Patients with Addison's disease can experience Irritability, they may experience changes in mood and behaviour, depression and poor concentration (Bancos 2014, Joersjö 2019, Anglin 2006, Abdel-Motleb 2012, Mayo Clinic 2024, Cleveland Clinic 2022). All of the above symptoms were present in the case of Elizabeth of the Trinity and, in particular the Tiredness, weakness and from time to time the abdominal pain and vomiting seem to have caused her great distress, particularly because they prevented her from continuing her work in her monastery (De Bono 2018).

ACUTE ADRENAL FAILURE, KNOWN AS ADDISONIAN CRISIS

An "adrenal crisis" or "Addisonian crisis" is a constellation of symptoms that indicates severe adrenal insufficiency. Sometimes the symptoms of Addison's disease appear suddenly and severely. Acute adrenal failure can lead to life-threatening shock. This is known as an Addisonian crisis. An addisonian crisis is life threatening, therefore emergency treatment is necessary.

The Causes of an Addisonian Crisis are as follows; It may be the result of either previously undiagnosed Addison's disease, or it may be caused by a disease process suddenly affecting adrenal function, such as adrenal hemorrhage, or it may be caused by an intercurrent problem, such as a Severe infection or illness, trauma or injury or a time of intense stress in someone known to have Addison's disease (Bancos 2014, Joersjö 2019, Anglin 2006, Abdel-Motleb 2012, Mayo Clinic 2024, Cleveland Clinic 2022).

The Symptoms of Addisonian crisis include: Severe, extreme weakness, Severe lethargy 'Confusion, fear, restlessness, and "other mental changes", including psychosis, slurred speech, Sudden Pain in the lower back or legs, severe abdominal pain, severe vomiting and diarrhoea, leading to dehydration, reduced consciousness or delirium, Syncope (loss of consciousness and ability to stand), Loss of Consciousness, Convulsions, Fever, Markedly Low blood pressure, Hypoglycemia (reduced level of blood glucose), Hyponatremia (low sodium level in the blood), Hyperkalemia (elevated potassium level in the blood) and Hypercalcemia (elevated calcium level in the blood) (Bancos 2014, Joersjö 2019, Anglin 2006, Abdel-Motleb 2012, Mayo Clinic 2024, Cleveland Clinic 2022).

It is known that Elizabeth of the Trinity suffered several Addisonian crisis in her illness (De Bono 2018).

PSYCHIATRIC AND NEUROPSYCHIATRIC SYMPTOMS OF ADDISON'S DISEASE

Addison’s disease may present with psychiatric symptoms (Abdel-Motleb 2012, Anglin 2006). Indeed, Addison is quoted as saying in 1855 that AD patients might present with “attacks of giddiness, anxiety in the face, and delirium.” (Addison 1855). A review of the literature indicates that disturbances in mood, motivation, and behaviour are associated with Addison’s disease (Abdel-Motleb 2012, Anglin 2006). Mild disturbances in mood, motivation and behaviour are core clinical features of Addison’s disease. When reference is made to mood disorders, the reference is to Depression; Depression can be presenting symptom of Addison's disease. It has been said that the Neuropsychiatric symptoms of Addison's disease include, but are not limited to, depression, lack of energy, and sleep disturbances (Abdel-Motleb 2012, Anglin 2006).

Psychosis occurs less frequently, but can be the presenting symptom of a life-threatening adrenal crisis. Thus, Psychosis and extensive cognitive changes, including delirium, appear to occur more rarely, but are associated with severe disease and may be the presenting feature of Addisonian crisis. The Psychotic symptoms can be very severe (Anglin 2006, Abdel-Motleb 2012). One case of psychosis described in the literature described the symptoms of agitation, aggression, disinhibition, severe delusions, and at times appearing to respond to auditory and visual hallucinations (Anglin 2006).

Many physicians, including psychiatrists, are not aware that Addison’s disease may present with psychiatric symptoms (Iwata 2004). Physicians need to be aware that Addison’s disease may present solely with psychiatric symptoms and maintain a high index of suspicion for this potentially fatal condition (Anglin 2006, Abdel-Motleb 2012, Iwata 2004). Four case series published in the 1940s and 1950s found the prevalence of psychiatric symptoms in Addison’s disease to be between 64% and 84% (Anglin 2006, Abdel-Motleb 2012). Many physicians, including psychiatrists, are not aware that Addison’s disease may present with psychiatric symptoms (Iwata 2004, Anglin 2006, Abdel-Motleb 2012) and this may lead to mysdiagnosis.

Potential mechanisms for the neuropsychiatric symptoms of Addison’s disease include electrophysiological, electrolyte and metabolic abnormalities, glucocorticoid deficiency, increased endorphins, and an associated Hashimoto encephalopathy (Anglin 2006, Abdel-Motleb 2012).

From the data presented in the book that we have studied, it does appear that Elizabeth did suffer from depression as part of her suffering from Addisons Disease, to the extent of having suicidal thoughts, (having thoughts of throwing herself from a window), but she was able to deal with these thoughts, stating that this was not how a Carmelite should think (De Bono 2018). It is also clear that there were no symptoms of Psychosis, there is no evidence of any of the psychotic symptoms described in the medical literature on Addisons disease. This validates her experiences as she describes them, since they are consonant with her religious beliefs.

Regarding Psychosis, it should be commented that the Delusions and Hallucinations in described cases of Addisons Disease are very bizarre, while by contrast, Elizabeth's thoughts, and her relationship with the Trinity were perfectly rational, and totally consonant with her beliefs as a Roman Catholic and a Carmelite Nun, this is so even when she would tell her Mother that she would consult "Her Three" as she referred to the

Trinity, hence they were Normal Thoughts and certainly not delusions (De Bono 2018). It is to be remembered that the definition of delusion is " a belief that is clearly false and that indicates an abnormality in the affected person's content of thought. The false belief is not accounted for by the person's cultural or religious background or his or her level of intelligence, (Kiran 2009)" and as has been pointed out, Elizabeth's thoughts were are consonant with her religious beliefs. Thus Elizabeth of the Trinity did not suffer psychotic symptoms during her illness from Addisons Disease.

LABORATORY INVESTIGATIONS IN ADDISON'S DISEASE

Routine laboratory investigations in cases of Addison's disease will show the following abnormalities: a Low blood sugar, a low blood sodium, a high blood potassium, a level of high thyroid-stimulating hormone (TSH), and haematology shows eosinophilia and lymphocytosis (Ten 2001)-

The low blood sodium is due to loss of production of the hormone aldosterone, as well as to the kidney's inability to excrete free water in the absence of sufficient cortisol, and also to the effect of corticotropin-releasing hormone to stimulate secretion of ADH(Ten 2001). The high blood potassium is caused by the loss of production of the hormone aldosterone (Ten 2001).

In Addison's disease, there is also Metabolic acidosis (increased blood acidity), caused by the lack of the hormone aldosterone because sodium reabsorption in the distal tubule is linked with acid/hydrogen ion (H+) secretion(Ten 2001). Absent or insufficient levels of aldosterone stimulation of the renal distal tubule leads to sodium wasting in the urine and H+ retention in the serum (Ten 2001).

In suspected cases of Addison's disease, low adrenal hormone levels even after appropriate stimulation (referred to as the ACTH stimulation test or synacthen test) using synthetic pituitary ACTH hormone tetracosactide is required in order to diagnose the condition (Dorin 2003, Holt 2008).

PATHOPHYSIOLOGY OF ADDISON'S DISEASE

Addison's disease, also known as primary adrenal insufficiency, is a rare long-term endocrine disorder characterized by inadequate production of the steroid hormones cortisol and aldosterone by the two outer layers of the cells of the adrenal glands (adrenal cortex), causing adrenal insufficiency.Addison's disease arises when the adrenal gland does not produce sufficient amounts of the steroid hormones cortisol and aldosterone. Our body has two adrenal glands, which are located above the kidneys. One of their functions is to produce cortisol and aldosterone, which once produced are directed in the blood stream from the adrenal glands towards the hypothalamus, a small organ located in the brain, which releases Corticotropin-releasing hormone (CRH) (Goh 2010, Papadimitriou 2009, Tsigosa 2002). CRH is a key regulator of the hypothalamic-pituitary-adrenal (HPA) axis, which controls the body's stress response (Goh 2010, Papadimitriou 2009, Tsigosa 2002). CRH stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), which then acts on the adrenal cortex of the adrenal glands, which again stimulates the production of cortisol and aldosterone according to the needs of the body at that particular time (Goh 2010, Papadimitriou 2009, Tsigosa 2002). The pathophysiology of Addison's disease involves the disruption of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in cortisol deficiency, which is critical for regulating metabolism, immune function, and stress responses (Goh 2010, Papadimitriou 2009, Tsigosa 2002). Aldosterone deficiency leads to dysregulation of sodium and potassium homeostasis, causing hypotension and dehydration (Goh 2010, Papadimitriou 2009, Tsigosa 2002).

TREATMENT OF ADDISON'S DISEASE

Treatment of Addison's disease requires lifelong glucocorticoid and mineralocorticoid replacement therapy, typically with hydrocortisone or fludrocortisone, along with ongoing monitoring and dosage adjustments during periods of stress, illness, or surgical interventions.

Glucocorticoid replacement therapy to replace the missing cortisol, is usually in the form of hydrocortisone tablets, or prednisone tablets in a dosing regimen that replicates the physiological concentrations of cortisol. When prednisolone is used, the dose is one-quarter of the hydrocortisone dose to give an equivalent glucocorticoid effect. Treatment is usually lifelong (The Lecturio Medical Concept Library 2024, wikipedia 2024, Joersjö 2019, Anglin 2006).

Many persons also require fludrocortisone as a replacement for the missing aldosterone (The Lecturio Medical Concept Library 2024, wikipedia 2024, Joersjö 2019, Anglin 2006).

Patients with low aldosterone levels may also benefit from a high-sodium diet (wikipedia 2024).

Patients with Addison's disease may also benefit from an increase in their dietary intake of calcium and vitamin D (wikipedia 2024).

In the time of Elizabeth of the Trinity, there was no known treatment for Addison's disease. Furthermore, Elizabeth's doctors did not recognise Addison's Disease and missed the diagnosis (de Bono 2018).

TREATMENT OF ADDISONIAN CRISIS

Treatment for Addisonian Crisis includes intravenous injections of glucocorticoids and large volumes of intravenous saline solution together with glucose. This treatment usually is successful in bringing about rapid improvement. Intramuscular injection of glucocorticoids can be used If intravenous treatment is not immediately possible (Abdel-Motleb 2012, Wikipaedia 2024). Once the patient is able to swallow fluids and medications by mouth, the amount of glucocorticoids is decreased until a maintenance dose is achieved (Abdel-Motleb 2012, Wikipaedia 2024). If aldosterone is deficient, then oral doses of fludrocortisone acetate are part of the maintenance therapy (Abdel-Motleb 2012, Wikipaedia 2024). In Elizabeth of the Trinity's time, 1906, the above treatment was entirely unavailable (de Bono 2018).

PROGNOSIS OF ADDISON'S DISEASE

Today, patients who have Addison's Disease are usually good with adequate treatment, and most patients can expect to live relatively normal lives (NHS Choices 2016).

When symptoms of an "Addison's crisis" occurs, as a result of the patient experiencing stress due to possible excessive exercise or illness, emergency treatment for the crisis needs to be given, possibly by intravenous injection(NHS Choices 2016).

Individuals with Addison's disease have more than a doubled mortality rate (Bergthorsdottir 2006) compared to the average population. Furthermore, individuals with Addison's disease together with diabetes mellitus have an almost four-fold increase in mortality compared to individuals with only diabetes (Chantzichristos 2016). The risk ratio for cause mortality from Addison's Disease in males is 2.19 andin females is 2.86 (Bergthorsdottir 2006). Death occurs to individuals with Addison's disease usually occurs due to cardiovascular disease, infectious disease, and malignant tumours (Bergthorsdottir 2006), though, naturally, other possibilities may occur. By contrast in Elizabeth of the Trinity's time, 1906, the illness was invariably fatal because there was no known treatment available, and furthermore, the illness was not recognised and so not diagnosed in her case (de Bono 2018).

CONCLUSION

Since no treatment was available in her time, the Account of Elizabeth of the Trinity's illness gives us an interesting picture of the "natural Progression of the disease." The history of Addisons ' disease shows how the treatment and thence the of prognosis of this illness has been completely changed by the advent of steroid treatment.

This description of Addison's disease illustrates that this is a rare illness and that there is the necessity of keeping a high index of suspicion in order not to miss this condition. It needs to be necessary to remember that this condition may appear to present with Psychiatric symptoms alone.

Furthermore, it is clear from the account of Elizabeth of the Trinity's last illness that the severe tiredness and weakness are symptoms which caused Elizabeth to suffer greatly, but Elizabeth also gets suicidal thoughts, such as thoughts of jumping from a window (de Bono 2018).

These thoughts suggest but do not prove depression, which is said to be a core symptom of Addisons ' disease. Thus Addisons ' disease does demonstrate an impressive intermingling of both physical and psychiatric symptoms.

In reality, Elizabeth's doctors remarked on her resilience and courage, and Elizabeth was able to deal with her suicidal ideation by taking the view that "a Carmelite did not think that way." (de Bono 2018).

Finally, the assessment of Elizabeth of the Trinity shows the need of distinguishing between a normal mental state in a patient who is experiencing a mystical state and abnormal delusions, the distinguishing point being the normality of the person's beliefs including those in her previous history and development. Even in Crisis, Elizabeth of the Trinity's mental state remained normal, and consonant with the beliefs she held as a young Catholic lady of her time and a Carmelite nun (de Bono 2018). By contrast, the published accounts of the psychotic symptoms experienced in crisis by patients with Addisons ' disease demonstrate chaotic paranoid delusions (Anglin 2006).

Elizabeth of the Trinity may well have survived many years if modern treatment with steroids had been available in her lifetime.

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Both authors contributed to the literature search and the drafting of the text.

Both authors approved the final manuscript.

References

1. *Abel-Motleb M: The Neuropsychiatric Aspect of Addison's Disease: A Case Report. Innov Clin Neurosci 2012; 9:34–36*
2. *Addison T: On The Constitutional And Local Effects Of Disease Of The Supra-Renal Capsules. London: Samuel Highley, 1855*
3. *Anglin RE, Rosebush PI, Mazurek MF: The Neuropsychiatric Profile of Addison's Disease: Revisiting a Forgotten Phenomenon. J Neuropsychiatry Clin Neurosci 2006; 18:4*

4. Bancos I, Hahner S, Tomlinson J, Arlt W. "Diagnosis and management of adrenal insufficiency". The Lancet Diabetes & Endocrinology 2014; 3 (3): 216–226.
5. Bergthorsdottir R, Leonsson-Zachrisson M, Odén A, Johannsson G (December 2006). "Premature mortality in patients with Addison's disease: a population-based study". The Journal of Clinical Endocrinology and Metabolism. 91 (12): 4849–4853
6. Brennan D., How Does Addison's Disease Affect the Skin? MedicineNet. 2007
7. Castinetti F, Nieman LK, Reincke M, Newell-Price J: Approach to the Patient Treated with Steroidogenesis Inhibitors J Clin Endocrinol Metab 2021; 106:2114–2123
8. Chantzichristos D. Persson A. Eliasson B., Johannsson G., et al.: Incidence, prevalence and seasonal onset variation of Addison's disease among persons with type 1 diabetes mellitus: Nationwide, matched cohort studies. European Journal of Endocrinology 2017; 178:EJE-17-0751
9. Clevelandclinic 2022. https://my.clevelandclinic.org/health/diseases/15095-addisons-disease
10. De Bono J. Il Perche Della Sofferenza Elisabetta Della Trinita Edizioni OCD Rome 2018
11. Dorin RI, Qualls CR, Crapo LM. "Diagnosis of adrenal insufficiency". Annals of Internal Medicine. 2003; 139:194–204
12. Fleseriu M., Castinetti F. Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies Pituitary. 2016; 19(6): 643–653.
13. GARD Autoimmune polyglandular syndrome type 1 | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program". rarediseases.info.nih.gov. 2017
14. GARD Autoimmune polyglandular syndrome type 2 | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program". rarediseases.info.nih.gov 2017
15. Goh C Agius M The Stress-Vulnerability model. How does stress impact on Mental Illness at the level of the Brain and what are the consequences? Psychiatr Danub, 2010; 22(2): 198–202
16. Griffing G.T. Addison Disease Treatment & Management Medscape Updated: Mar 27, 2024
17. Guo YK, Yang ZG, Li Y, Ma ES, Deng YP, Min PQ, Yin LL, Hu J, Zhang XC, Chen TW. Addison's disease due to adrenal tuberculosis: Contrast-enhanced CT features and clinical duration correlation. Eur J Radiol 2006; 62:126–131
18. Hahner S, Ross RJ, Arlt W, Bancos I, Burger-Stritt S, Torpy DJ, et al. "Adrenal insufficiency". Nat Rev Dis Primers 2021; 7:19
19. Holt E.H. "ACTH (cosyntropin) stimulation test". MedLine Plus 2008 U.S. National Library of Medicine. 2016-07-05
20. Iwata M, Hazama GI, Shirayama Y,et al. A case of Addison's disease presented with depression as a first symptom. Seishin Shinkeigaku Zasshi 2004; 106:1110–1116
21. Kiran C, Chaudhury S: Understanding delusions Ind Psychiatry J 2009; 18:3-18
22. Li A.Y., Dream S. Adrenalectomy StatPearls [Internet]. National Library of Medicine [Internet].2023
23. Macca V. OCD Elizabeth of the Trinity in Saints of Carmel Editor Saggi L. 1972 Carmelite Institute Rome.
24. Mehmood K.T., Sharman T. Adrenal Hemorrhage StatPearls [Internet].National Library of Medicine [Internet].2023
25. Mayo Clinic Staff https://www.mayoclinic.org/diseases-conditions/addisons-disease/symptoms-causes/syc-20350293
26. National Endocrine and Metabolic Diseases Information Service. "Adrenal Insufficiency and Addison's Disease". National Endocrine and Metabolic Diseases Information Service. 2011
27. National Institute of Diabetes and Digestive and Kidney Diseases. "Adrenal Insufficiency and Addison's Disease". May 2014.
28. NHS "Addison's disease". nhs.uk. 2018-06-22
29. NORD (National Organization for Rare Disorders) "Addison's disease" 2018
30. Oelkers W. Adrenal insufficiency. N Engl J Med 1996; 335:1206–1212
31. Papadimitriou A, Priftis KN: Regulation of the Hypothalamic Pituitary-Adrenal Axis Neuroimmunomodulation 2009; 16:265–271
32. Patnaik MM, Deshpande AK: Diagnosis–Addison's Disease Secondary to Tuberculosis of the Adrenal Glands. Clin Med Res 2008; 6:29
33. Raymond G.V., Moser A.B., BA, Fatemi A., X-Linked Adrenoleukodystrophy Gene Reviews® National Library of Medicine [Internet].2023
34. The Lecturio Medical Concept Library Adrenal Insufficiency and Addison Disease Last updated: May 17, 2024
35. Ten S., Maria New M., Noel Maclaren N. Addison's Disease The Journal of Clinical Endocrinology & Metabolism 2001; 86:2909–2922
36. Tsigosa C., George P. Chrousos G.P. Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress Journal of Psychosomatic Research 2002; 53: 865 – 871
37. Volpé R. Autoimmune Diseases of the Endocrine System. 1990 CRC Press. p. 299.
38. Wikipedia Addison's disease https://en.wikipedia.org/wiki/Addison%27s_disease

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