Addison Disease: The First Presentation of the Condition May Be at Autopsy

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ABSTRACT

Addison disease is chronic primary adrenal insufficiency, which, in developed countries, is most commonly due to autoimmune destruction of the cortex (termed autoimmune or idiopathic Addison disease). Although the disease process has some classic features, such as increased pigmentation, salt craving, and signs and symptoms related to decreased blood pressure, the initial clinical presentation may be vague and/or insidious. Following an acute stressor such as a gastrointestinal (GI) infection, the patient may experience an adrenal crisis, which can cause sudden death. As such, knowledge of this disease process and the diagnostic criteria in the postmortem period is essential for the practicing forensic pathologist. The diagnosis of autoimmune Addison disease at autopsy is aided by several factors including 1) history, including salt craving, features consistent with orthostatic hypotension, and GI complaints including nausea, vomiting and pain, 2) physical examination findings of increased pigmentation and small or unidentifiable adrenal glands, 3) serologic testing for 21-hydroxylase antibodies, 4) serum cortisol concentrations, and 5) vitreous electrolyte testing. While the listed historical information, the increased pigmentation, decreased serum cortisol concentrations, and evidence of hyponatremia may be found in all forms of Addison disease, small or unidentifiable adrenal glands and 21-hydroxylase antibodies are found exclusively in the autoimmune form of Addison disease. While other causes of Addison disease, such as tuberculosis, metastatic tumor, or other infiltrative processes would have enlarged adrenal glands, these diseases would lack 21-hydroxylase antibodies. The purpose of this paper is to focus on the diagnosis of autoimmune Addison disease. *Acad Forensic Pathol.* 2016 6(2): 249-257

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INTRODUCTION

Adrenal insufficiency can be a primary disease process, occurring due to abnormalities of the adrenal cortex or can be a secondary or tertiary process occurring due to abnormalities of the pituitary gland or hypothalamus (1, 2). Adrenal insufficiency can have an acute onset or be due to a chronic process. Chronic primary adrenal insufficiency is also known as Addison disease (2-4). Historically, chronic primary adrenal insufficiency was most often due to an infection with *Mycobacterium tuberculosis*. Currently, in the United States and other developed countries, most cases of Addison disease are an autoimmune process affecting the adrenal glands (1, 5). Due to the nonspecific and subtle signs and symptoms of the chronic phase of Addison disease, the clinical diagnosis may be missed until the acute decompensation phase, known as an adrenal crisis, which may manifest in response to a physiologic stressor, most often a gastrointestinal (GI) infection (6, 7). As an adrenal crisis may be the first presentation of Addison disease and may cause sudden death, awareness of Addison disease and specifically how to make the diagnosis at autopsy is important information for the practicing forensic pathologist.

DISCUSSION

Causes of Adrenal Insufficiency

Adrenal insufficiency is a descriptive diagnostic term for the pathophysiologic changes induced by a variety of medical conditions that, as their endpoint, can impair the normal production of adrenocortical hormones, including mineralcorticoids (i.e., aldosterone) and glucocorticoids (i.e., cortisol). Adrenal insufficiency can be either a primary, secondary, or tertiary disorder and the onset can be either acute or chronic (1, 2). Secondary and tertiary causes of adrenal insufficiency, originating in the pituitary gland and hypothalamus, respectively, can be combined under the label of central adrenal insufficiency (3); however, some authors choose to group disorders causing tertiary adrenal insufficiency within the category of secondary adrenal insufficiency (1, 8).

Secondary and tertiary adrenal insufficiency are due to disruption of the normal hormonal axis that stimulates the adrenal gland (1). Abnormalities of the hypothalamus, leading to decreased production of corticotrophin-releasing hormone (CRH), or pathology of the pituitary gland leading to decreased production of adrenocorticotrophic hormone (ACTH) both can lead to adrenal insufficiency (1). Damage to the pituitary gland can occur due to a variety of conditions, including hemorrhage and necrosis (e.g., pituitary apoplexy), neoplasms (e.g., pituitary adenoma, craniopharyngioma), autoimmune disease (e.g., lymphocytic hypophysitis), infiltrative processes (e.g., sarcoidosis), exogenous use of glucocorticoids, and empty sella syndrome (1, 2). Empty sella syndrome is caused by pituitary gland atrophy secondary to herniation of arachnoid through an incompetent diaphragm sella. The most common cause of tertiary adrenal insufficiency is the use of exogenous glucocorticoids; however, damage to the hypothalamus from tumors (e.g., craniopharyngioma), surgery, infections or an infiltrative processes (e.g., tuberculosis, hemochromatosis), and trauma (e.g., fracture of the base of the skull) can also lead to tertiary adrenal insufficiency (9).

Primary adrenal insufficiency is due to destruction of the adrenal cortex, leading to decreased production of adrenal cortical hormones, namely aldosterone, cortisol, and androgens. This destruction can be either acute in onset or part of a chronic disease process. Acute causes of primary adrenal insufficiency include hemorrhage, infarction and thrombosis, such as occur in meningococcal infection associated Waterhouse-Friderichsen syndrome, sepsis, warfarin therapy, or a coagulopathy, including anti-phospholipid antibody syndrome (2). The list of diseases that cause chronic primary adrenal insufficiency is long, including autoimmune adrenalitis (**Image 1**), infectious organisms (e.g., *Mycobacterium tuberculosis*, various fungi, cytomegalovirus), primary or metastatic neoplasms, and infiltrative processes (e.g., sarcoidosis, amyloidosis, hemochromatosis) (1, 2). In children, congenital adrenal hyperplasia can also cause chronic primary adrenal insufficiency (1). The label of Addison disease can be applied to any form of chronic primary adrenal

insufficiency, with the autoimmune form referred to as autoimmune or idiopathic Addison disease (2-4).

In the United States, the most common cause of chronic primary adrenal insufficiency, or Addison disease, is autoimmune adrenalitis (1). Michels et al. state that in developed countries about 70-90% of cases of Addison disease are autoimmune in origin and 10-20% of cases are the result of tuberculosis (5). In about 40% of cases, autoimmune Addison disease is isolated; however, the other 60% of cases occur as part of a polyglandular syndrome (4). There are four types of autoimmune polyglandular (or, polyendo-

crine) syndromes (APS), alternatively listed as polyglandular autoimmune syndrome (PGAS) (10, 11). In APS type I, II and possibly in type IV, adrenal insufficiency is a component of the disease process (11). In APS type III, patients have no adrenal insufficiency (11). Although the list of conditions associated with APS type I or II is fairly long, in APS type I, adrenal insufficiency, hypoparathyroidism, and mucocutaneous candidiasis are most typical (10). In APS type II (i.e., Schmidt syndrome), adrenal insufficiency, thyroid disease (either hyperthyroidism or hypothyroidism) and insulin-dependent diabetes mellitus are most typical (11). In APS type IV, a patient will have

Image 1: Chronic adrenalitis. The cortex of the adrenal gland is infiltrated by chronic inflammatory cells, including lymphocytes (H&E, x200).

two or more organ systems with specific autoimmune diseases (12). The mean age at diagnosis of Addison disease is 40 years; however, one published study gave an age range of 17 to 72 years (2). In patients younger than the age of 20 years, Addison disease is more common in males; however, in older patients, the disease is more common in women (4). In their series, Hahner et al. reported a 4-6:1 ratio of females to males (6).

Clinical Diagnosis of Adrenal Insufficiency

The symptoms of Addison disease are numerous, and, unfortunately, not necessarily specific, which can result in a delayed diagnosis of the disease (4). In their study of 426 patients, Erichsen et al. reported that 30% of patients were diagnosed within one month of the start of symptoms, but that 40% were diagnosed more than six months after the start of symptoms (13). Between one and 20 physicians were consulted by each patient to make the diagnosis (with a median of two consults per patient). Erichsen et al. indicated that the timing between onset of symptoms and diagnosis of Addison disease was more rapid in their group of patients than reported in other literature reviews, which they attributed to a function of the health care system, specifically, increased awareness of the disease process (13). Because of the nonspecific nature of the presenting symptoms, Addison disease can be misdiagnosed as a GI disorder or even a psychiatric condition (14, 15).

The most specific symptoms of Addison disease are increased skin or oral mucosa pigmentation, hypotension, and salt craving (13). Increased pigmentation is most frequently found in the palmar creases, the buccal mucosa, and the extensor surfaces of the body, but can occur anywhere (1, 4, 14, 17). Papierska and Rabijewski describe pigmentation on palmar creases, elbow flexures, and the areola in 57 of 60 patients, with the other three patients having vitiligo (16). In primary Addison disease, excess ACTH from the pituitary gland is produced in an attempt to stimulate the hypofunctional adrenal cortex. As ACTH is derived from the proto-hormone, pro-opiomelanocortin (POMC), which includes melanocyte stimulating

hormone (MSH) in its structure, the increased skin pigmentation seen in primary Addison disease is related to MSH stimulation of skin melanocytes. In contrast, secondary adrenal insufficiency results from a lack of ACTH; therefore, there is no excess melanocyte stimulation and no skin hyperpigmentation. Salt craving and postural hypotension are also characteristic of Addison disease and are due to the decreased production of aldosterone (1, 4, 14, 17). Other than increased pigmentation and signs and symptoms associated with aldosterone deficiency, patients with Addison disease can have numerous other, albeit less specific symptoms, including fever, weight loss, fatigue, nausea, vomiting, diarrhea, and abdominal pain (1-2, 4, 13-14, 17), most of which are related to the lack of glucocorticoids. Laboratory testing performed on patients with Addison disease can reveal hyponatremia, hyperkalemia, hypercalcemia, hypoglycemia, lymphocytosis, and anemia (1-2, 4, 17). Because of the nonspecific nature of the signs and symptoms caused by Addison disease, combined with the potential morbidity and mortality related to an acute adrenal crisis, a high index of suspicion is required to make the diagnosis (5).

The clinical diagnosis of Addison disease is made by checking a morning basal cortisol concentration, often around 0800 hrs (1, 2). A result of <3 µg/dL indicates adrenal insufficiency (2, 4, 14); however, some advocate a cut-off of <5 µg/dL (1). A concentration of 18 µg/dL or higher excludes adrenal insufficiency. If the result of a morning cortisol concentration testing is equivocal (i.e., 3.1 to 17.9 µg/L), a stimulation test can be performed. Several types of stimulation tests are used: insulin-induced hypoglycemia, metyrapone, CRH, conventional-dose ACTH, and low dose ACTH (8). In the ACTH stimulation test, if the cortisol concentration does not rise above 18 µg/dL at 0, 30 or 60 minutes following the stimulation dose, the results indicate adrenal insufficiency (1, 4, 18). In interpreting the concentration of cortisol in the blood, it must be remembered that the concentration of cortisol fluctuates both according to time of day and the clinical scenario. For example, in the setting of shock, a patient's cortisol is expected to rise. Therefore, in such a setting, a measured cortisol concentration of <20 µg/

dL is indicative of adrenal insufficiency (1). If there is stress, Taub et al. indicate that a random cortisol of <4 µg/dL indicates adrenal insufficiency (17).

Other clinical indicators of autoimmune Addison disease can include the identification of small adrenal glands via imaging or the identification of antibodies against the adrenal cortex. Papierska and Rabijewski, in their study of 60 patients, reported that all patients had small adrenal glands, which were identified via abdominal computed tomography (CT) scans (16). Adrenal cortex antibodies are identified in a large number of cases. Anti-adrenal antibodies were first identified in 1957 (19). In 1992, Wingyist and Karlson identified that the major antigen promoting antibody formation in people with autoimmune Addison disease was 21-hydroxylase (20). Erichsen et al., in their study of 426 patients with autoimmune Addison disease, reported that 86% of patients have 21-hydroxylase antibodies (13) and Papierska and Rabijewski found a significant titer for 21-hydroxylase antibodies in 49 of their 60 patients (82%), 28 of whom were not in crisis (16). The antibodies are IgG1 or IgG2a (4). Brandão Neto et al. proposed that the antibodies may be produced secondary to damage to the adrenal cortex, and are not the primary destructive agent for the adrenal gland (4); however, Bizzaro, in his review, indicated that the autoantibodies are found in healthy patients who later develop Addison disease (21). Also, in their studies of adrenal insufficiency, Kasperlik-Zaluska et al. identified six patients with tuberculosis as the underlying cause (22) and Colls et al. identified nine patients with tuberculosis as the underlying cause and none of the 15 patients had adrenal gland directed autoantibodies (23). Therefore, as the antibodies precede the clinical development of the disease in many cases, and as destructive processes of the adrenal gland (e.g., tuberculosis) do not apparently elicit an autoimmune response, it seems more likely that the antibodies are primary in nature, and not secondary to adrenal cortex damage. While anti-21-hydroxylase antibodies are the most common type found in autoimmune Addison disease, antibodies against 17 α -hydroxylase and the cholesterol side-chain cleavage enzyme have also been identified (3).

Adrenal Crisis

While Addison disease is a chronic disease process, it can be punctuated by acute episodes termed adrenal crises, which may be the first presentation of Addison disease and carry significant morbidity and mortality. In an adrenal crisis, a patient will have hypotension, hypovolemia, and can have abdominal pain, nausea, and vomiting, among other symptoms (4, 14). The major and potentially lethal physiologic changes of an adrenal crisis are most often due to the mineralcorticoid deficiency (14). In most cases, an adrenal crisis is precipitated by some factor such as an infection, surgery, or trauma, as these conditions increase the need for cortisol, thus precipitating the crisis (4, 7). Hahner et al. reviewed 444 patients over 6092 patient-years and found 384 episodes of adrenal crisis (6). The most common underlying cause was a GI infection, followed by a general category of other infectious disease or fever. Gastrointestinal infections and this second more general category accounted for 56% of the episodes of adrenal crisis. Other causes of an adrenal crisis can include major pain, surgery, psychic distress, and pregnancy. Paur et al. opined that GI infections are the most common precipitating cause of an adrenal crisis because glucocorticoids are absorbed in the GI tract, and thus, a GI infection would impair the absorption of oral steroids (7). An adrenal crisis can be the presenting form of Addison disease. In their study, Papierska and Rabijewski reviewed 60 patients. In 13 patients, the first diagnosis of adrenal insufficiency was made during an adrenal crisis, and in 13 other patients, the symptoms prompting the diagnosis were consistent with an impending adrenal crisis (16).

Autopsy Diagnosis of Adrenal Insufficiency

To make the clinical diagnosis of Addison disease, Brandão Neto et al. proposed four criteria: 1) basal cortisol of <3 µg/dL, 2) normal or small adrenal glands, 3) anti-adrenal cortex antibodies or anti-21-hydroxylase antibodies, and 4) exclusion of other causes (4). For the purposes of autopsy diagnosis, these same criteria are applicable. Although the difference in size between the normal adrenal gland and the adrenal gland from a patient with Addison disease illustrated

in **Image 2** is easy to appreciate, more subtle changes may not be. Weighing of the adrenal glands may help, as reference ranges for normal adrenal gland weights are available (24), and, in combination with histologic examination of the adrenal gland assessing for the presence of chronic inflammation, may assist in the diagnosis of Addison disease. In addition, the external autopsy examination may reveal hyperpigmentation, the history may offer symptoms consistent with the disease process, and vitreous electrolyte testing may reveal hyponatremia, all of which can help direct the forensic pathologist to the diagnosis of Addison disease. Of note, while vitreous sodium concentrations

are considered to be stable and reflective of serum sodium concentrations for a period of time after death, low vitreous sodium concentrations are associated with decomposition, and therefore, that the concentration of vitreous sodium decreases at some point after death must be considered in the interpretation of its postmortem value (25).

Several case reports and a small series regarding the autopsy diagnosis of adrenal insufficiency have been published. Burke and Opeskin reviewed five cases (26). At autopsy, no macroscopic adrenal tissue was identified in three individuals and the other two had

Image 2: Autoimmune Addison disease. Cross-sections of adrenal glands from two individuals are illustrated. The adrenal gland at the top is normal in size and structure, while the adrenal gland remnants at the bottom is from a patient with Addison disease and illustrate the effects of the disease on the gland.

small adrenal glands. Microscopic examination of the adrenal glands revealed infiltrates of lymphocytes and plasma cells. In some of the five cases, postmortem analyses included testing for antibodies and evaluation of the cortisol concentration. In the three cases where antibody analysis was performed, two patients had antibodies detected at autopsy and one patient had no detectable antibodies. Serum cortisol concentrations were measured in three cases, with results ranging from 14 nmol/L to 43 nmol/L (normal range: 120-650 nmol/L). In these autopsy cases, both antibody testing and cortisol measurements were performed on a blood sample obtained at the postmortem examination.

Sperry and Lantz reported a case of autoimmune adrenocortical necrosis combined with Hashimoto thyroiditis (Schmidt syndrome) (27). Small adrenal glands were identified grossly, with subtotal cortical necrosis and a lymphocyte infiltrate identified microscopically. A postmortem cortisol concentration was 2 µg/dL and anti-adrenal antibody testing was positive. Clapper et al. reported a case of acute adrenal insufficiency due to hemorrhage (28). A postmortem cortisol concentration was 0.2 µg/dL, and antemortem blood showed decreasing cortisol after surgery. Davis described an adrenal insufficiency due to hypophysitis (29). A postmortem cortisol concentration was 0.4 µg/dL. While not Addison disease, the case reports by Clapper et al. (28) and Davis (29) illustrate the utility of postmortem cortisol testing.

Testing for antibodies is readily available (30). To evaluate for 21-hydroxylase antibodies (i.e., 21-OH Ab, adrenal antibody, hydroxylase antibody, anti-adrenal antibody), serum in a red top tube is preferred; however, a specimen in a serum gel tube is acceptable. One milliliter is required for testing and mild lipemia, mild hemolysis, and mild or gross icterus of the specimen are acceptable.

Although the authors listed above (26-29) pursued postmortem cortisol testing, two caveats regarding this step should be addressed. First, in a frequently cited but not currently replicated study by Finlayson, the author noted a small but statistically insignificant decrease in blood cortisol levels measured within

the first 18 hours of death (31). Therefore, this study suggested that serum cortisol concentrations may decrease with increasing postmortem interval, potentially confounding a diagnosis of Addison disease. In addition, this study utilized a precise sampling protocol that may not be practical in the forensic setting, with samples recovered from patients with known times of death who were refrigerated within four hours of death and serum samples prepared within eight hours of death. Second, regarding the interpretation of cortisol concentrations obtained in the postmortem period, the peak concentration of plasma cortisol occurs around 0800, and the plasma cortisol concentration can vary from 7 to 25 µg/dL in the morning, and 2 to 14 µg/dL in the evening (32); thus, a normal evening cortisol concentration of 2 µg/L would meet the criteria for adrenal insufficiency. As is most often the circumstances in forensic cases, the time of death of an individual is unknown, and therefore, if a postmortem cortisol concentration is obtained, care must be taken in interpretation of the obtained value. While a high postmortem serum cortisol concentration may exclude the diagnosis of Addison disease, a low concentration does not necessarily confirm it. Future studies assessing the normal range of postmortem serum cortisol concentrations encountered at autopsy could help strengthen the use of this testing to confirm the diagnosis of Addison disease by autopsy.

CONCLUSION

An acute crisis due to adrenal insufficiency can be, as described above, the initial presentation of a patient with Addison disease, and, as Salvatori indicated, should always be considered as a possible explanation for unexplained cardiovascular collapse and sudden death (8). As forensic autopsies are conducted commonly on individuals who, for one reason or another, do not seek timely treatment for their conditions, forensic pathologists are likely to encounter this potentially lethal disease. To make the diagnosis of adrenal insufficiency, a forensic pathologist should utilize historical information, autopsy findings, and laboratory testing. Being aware of the nonspecific nature of the symptomatology of adrenal insufficiency (fatigue, nausea, vomiting, abdominal pain, weight loss) pre-

ceding a collapse is important, and can guide further historical interviews, such as searching for any history of salt craving or signs of postural hypotension, such as spells of dizziness or lightheadedness. Autopsy examination can include a search for skin or oral hyperpigmentation, including of the palmar creases, extensor surfaces of the body, or buccal mucosa; and, internal examination can reveal small or essentially non-identifiable adrenal glands. Microscopic examination of these adrenal glands can reveal a lymphocytic infiltrate. Postmortem testing can include vitreous electrolytes to assess the sodium concentration, serum cortisol concentrations, and 21-hydroxylase antibodies. With the caveats that cortisol concentration fluctuates during the day, peaking in the morning and that no study of the postmortem concentrations of cortisol as collected under conditions normally seen by forensic pathologists is apparently available for reference, a cortisol of $<3 \mu\text{g/dL}$ could support the diagnosis of Addison disease, particularly when combined with the appropriate clinical history, autopsy findings, and ancillary testing, such as postmortem testing for 21-hydroxylase antibodies.

REFERENCES

- Friedman TC. Cecil essentials of medicine. 6th ed. Philadelphia: WB Saunders; c2004. Chapter 66, The adrenal gland; p. 603-14.
- Oelkers W. Adrenal insufficiency. *N Engl J Med*. 1996 Oct 17; 335(16):1206-12. PMID: 8815944. <http://dx.doi.org/10.1056/nejm199610173351607>.
- Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. *Lancet*. 2014 Jun 21; 383(9935):2152-67. PMID: 24503135. [http://dx.doi.org/10.1016/s0140-6736\(13\)61684-0](http://dx.doi.org/10.1016/s0140-6736(13)61684-0).
- Brandão Neto RA, de Carvalho JF. Diagnosis and classification of Addison's disease (autoimmune adrenalitis). *Autoimmun Rev*. 2014 Apr-May; 13(4-5):408-11. PMID: 24424183. <http://dx.doi.org/10.1016/j.autrev.2014.01.025>.
- Michels AW, Eisenbarth GS. Immunologic endocrine disorders. *J Allergy Clin Immunol*. 2010 Feb; 125(2 Suppl 2):S226-37. PMID: 20176260. PMID: PMC2835296. <http://dx.doi.org/10.1016/j.jaci.2009.09.053>.
- Hahner S, Loeffler M, Bleicken B, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *Eur J Endocrinol*. 2010 Mar; 162(3):597-602. PMID: 19955259. <http://dx.doi.org/10.1530/eje-09-0884>.
- Puar TH, Stikkelbroeck NM, Smans LC, et al. Adrenal crisis: still a deadly event in the 21st century. *Am J Med*. 2016 Mar; 129(3):339.e1-9. PMID: 26363354. <http://dx.doi.org/10.1016/j.amjmed.2015.08.021>.
- Salvatori R. Adrenal insufficiency. *JAMA*. 2005 Nov 16; 294(19):2481-8. PMID: 16287959. <http://dx.doi.org/10.1001/jama.294.19.2481>.
- Nicolaides NC, Chrousos G, Charmandari E. Adrenal insufficiency. In: De Groot LJ, Beck-Peccoz P, Chrousos G, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000- [cited 2016 Mar 22]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK279083/>.
- Cutolo M. Autoimmune polyendocrine syndromes. *Autoimmun Rev*. 2014 Feb; 13(2):85-9. <http://dx.doi.org/10.1016/j.autrev.2013.07.006>.
- Meyerson J, Lechuga-Gomez EE, Bigazzi PE, Walfish PG. Polyglandular autoimmune syndrome: current concepts. *CMAJ*. 1988 Apr 1; 138(7):605-12. PMID: 3281737. PMID: PMC1267738.
- Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev*. 2002 Jun; 23(3):327-64. PMID: 12050123. <http://dx.doi.org/10.1210/edrv.23.3.0466>.
- Erichsen MM, Løvås K, Skiningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. *J Clin Endocrinol Metab*. 2009 Dec; 94(12):4882-90. PMID: 19858318. <http://dx.doi.org/10.1210/jc.2009-1368>.
- Tucci V, Sokari T. The clinical manifestations, diagnosis, and treatment of adrenal emergencies. *Emerg Med Clin North Am*. 2014 May; 32(2):465-84. PMID: 24766944. <http://dx.doi.org/10.1016/j.emc.2014.01.006>.
- Isaac ML, Larson EB. Medical conditions with neuropsychiatric manifestations. *Med Clin North Am*. 2014 Sep; 98(5):1193-208. PMID: 25134879. <http://dx.doi.org/10.1016/j.mena.2014.06.012>.
- Papierska L, Rąbiejewski M. Delay in diagnosis of adrenal insufficiency is a frequent cause of adrenal crisis. *Int J Endocrinol*. 2013; 2013:482370. PMID: 23864857. PMID: PMC3707239. <http://dx.doi.org/10.1155/2013/482370>.
- Taub YR, Wolford RW. Adrenal insufficiency and other adrenal oncologic emergencies. *Emerg Med Clin North Am*. 2009 May; 27(2):271-82. PMID: 19447311. <http://dx.doi.org/10.1016/j.emc.2009.01.008>.
- Neary N, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. *Curr Opin Endocrinol Diabetes Obes*. 2010 Jun; 17(3): 217-23. PMID: 20375886. PMID: PMC2928659. <http://dx.doi.org/10.1097/med.0b013e328338f608>.
- Anderson JR, Goudie RB, Gray KG, Timburt GC. Auto-antibodies in Addison's disease. *Lancet*. 1957 Jun 1; 272(6979):1123-4. PMID: 13439984. [http://dx.doi.org/10.1016/s0140-6736\(57\)91687-2](http://dx.doi.org/10.1016/s0140-6736(57)91687-2).
- Winqvist O, Karlsson FA, Kämpe O. 21-hydroxylase, a major autoantigen in idiopathic Addison's disease. *Lancet*. 1992 Jun 27; 339(8809):1559-62. PMID: 1351548. [http://dx.doi.org/10.1016/0140-6736\(92\)91829-w](http://dx.doi.org/10.1016/0140-6736(92)91829-w).
- Bizzaro N. The predictive significance of autoantibodies in organ-specific autoimmune disease. *Clin Rev Allergy Immunol*. 2008 Jun; 34(3):326-31. PMID: 18085442. <http://dx.doi.org/10.1007/s12016-007-8059-5>.
- Kasperlik-Zaluska AA, Migdalska B, Czarnocka B, et al. Association of Addison's disease with autoimmune disorders—a long-term observation of 180 patients. *Postgrad Med J*. 1991 Nov; 67(793): 984-7. PMID: 1775423. PMID: PMC2399126. <http://dx.doi.org/10.1136/pgmj.67.793.984>.
- Colls J, Betterle C, Volpato M, et al. Immunoprecipitation assay for autoantibodies to steroid 21-hydroxylase in autoimmune adrenal disease. *Clin Chem*. 1995 Mar; 41(3):375-80. PMID: 7882511.
- Ludwig J. Handbook of autopsy practice. 3rd ed. Totowa (NJ): Humana Press; 2002.

- 25) Coe JI. Postmortem chemistry update: Emphasis on forensic application. *Am J Forensic Med Pathol*. 1993 Jun; 14(2):91-117. PMID: 8328447. <http://dx.doi.org/10.1097/00000433-199306000-00001>.
- 26) Burke MP, Opeskin K. Adrenocortical insufficiency. *Am J Forensic Med Pathol*. 1999 Mar; 20(1):60-5. PMID: 10208340. <http://dx.doi.org/10.1097/00000433-199903000-00015>.
- 27) Sperry K, Lantz P. Autoimmune adrenocortical necrosis with Hashimoto's thyroiditis (Schmidt's syndrome). *ASCP Case Reports: Forensic Pathology*. 1990: FP 90-4 (FP-171).
- 28) Clapper A, Nashelsky M, Dailey M. Evaluation of serum cortisol in the postmortem diagnosis of acute adrenal insufficiency. *Am J Forensic Med Pathol*. 2008 Jun; 29(2):181-4. PMID: 18520491. <http://dx.doi.org/10.1097/paf.0b013e318174e7c8>.
- 29) Davis, GG. Lymphocytic hypophysitis, adrenal insufficiency, and sudden death. *ASCP Case Reports; Forensic Pathology*. 1996; FP 96-8 (FP-219).
- 30) Mayo Medical Laboratories Test Catalog [Internet]. Rochester (MN): Mayo Clinic Mayo Medical Laboratories; c1996 - [cited 2016 Mar 10]. Available from: <http://www.mayomedicallaboratories.com/test-catalog/Overview/81970>.
- 31) Finlayson NB. Blood cortisol in infants and adults: A postmortem study. *J Pediatr*. 1965 Feb; 67(2):248-252. [http://dx.doi.org/10.1016/s0022-3476\(65\)80247-5](http://dx.doi.org/10.1016/s0022-3476(65)80247-5).
- 32) Bakerman S, Bakerman P, Strausbauch P. Bakerman's ABC's of interpretive laboratory data. 5th ed. Scottsdale (AZ): Interpretive Laboratory Data, Inc; 2014. 682 p.