CASE REPORT

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Adrenal Hypofunction and Sudden Death

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ABSTRACT: Adrenal insufficiency is an infrequent and easily overlooked cause of sudden death, often occurring in individuals being treated for other serious disease processes. Three cases are presented to demonstrate some of the clinical presentations encountered, and the symptoms and signs are discussed.

KEYWORDS: pathology and biology, adrenal gland, death

Primary adrenal insufficiency, commonly known as Addison's disease since its description by Thomas Addison in 1849, is a relatively infrequent disease of more than one etiology. Before the advent of antimicrobial therapy, two thirds of all cases were secondary to bilateral involvement of the adrenals by tuberculosis. In modern time the majority of cases have been idiopathic (of unknown origin), and generally considered among the autoimmune disorders because of the frequent occurrence of anti-adrenal antibodies, and the not infrequent simultaneous involvement of other endocrine organs. Other causes of adrenal hypofunction include infections, hemorrhage, amyloid deposition, drug mediated destruction, replacement by metastatic tumor, and suppression by exogenous steroids. The disease is generally classified into a chronic and an acute form, with the acute most often imposed upon a longstanding chronic insufficiency.

The signs and symptoms of chronic adrenal insufficiency are not specific, and may be extremely vague. They are the result of decreased secretion of adrenal cortical steroids—glucocorticoids, mineralocorticoids, and androgens—coupled with resultant increase in adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH) from the pituitary. These hormone abnormalities produce hypoglycemia (with a flat glucose tolerance curve), fluid and electrolyte imbalance (dehydration with a moderate elevation of blood urea nitrogen, hyponatremia, and hyperkalemia), and melanocyte stimulation (pigment production). Normocytic, normochromic anemia is common. The most frequently observed physical findings are weight loss, anorexia and gastrointestinal disturbances (nausea and vomiting, usually more pronounced with impending crisis), fatigue, dizziness and hypotension (especially postural), and pigmentation of the skin in both exposed and unexposed areas with intensification in friction areas. The electrolyte imbalance may occasion lethargy and muscle cramps, and hypoglycemia is accompanied by episodes of weakness, nervousness, and sweating.

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Acute adrenal insufficiency is a life-threatening emergency which, untreated, is often fatal. Symptoms are nonspecific (nausea, vomiting, abdominal pain, fever or hypothermia, and hypotension with shock), and death may be extremely rapid. The following cases illustrate the types of situations likely to come to the attention of a medical examiner or coroner.

Case 1

An apparently normal 13-year-old white girl had had a sore throat for two days (as had her 10-year-old sister). The mother found her dead in bed when she attempted to awaken her for school. Past medical history included intermittent episodes of "croup," and tonsillitis with diarrhea two years before death. At that time mild anemia was noted, and electrolytes were reported as normal. Increased pigmentation of the skin, generalized and especially in scars, was noted in medical records three years prior to her demise. Autopsy revealed severe bilateral adrenal atrophy with fibrosis and minimal chronic inflammation, mild splenomegaly, chronic thyroiditis, and hepatomegaly with cirrhosis and moderate chronic inflammation. Vitreous fluid (drawn within 12 h of the time she was last seen alive) contained sodium, 145 meq/L; potassium, 8.3 meq/L; chloride, 126 meq/L; calcium, 6.3 mg/dL; and glucose, 9 mg/dL.

Case 2

A 26-year-old white male was found semi-comatose on the floor and helped to bed by a friend 17 h before his being discovered dead in bed. He had a history of multiple hospitalizations for severe gastrointestinal disturbances which appeared to date to a motorcycle accident and abdominal surgery three years prior to death. No organic cause for his intestinal problems had been identified, and he had been treated unsuccessfully with chlorpromazine, soft diet, and high protein supplements. Autopsy revealed small adrenals with marked loss of cortical tissue, fibrosis, and chronic inflammatory infiltration; marked chronic thyroiditis; focally severe coronary atherosclerosis; and extensive abdominal adhesions. Vitreous urea nitrogen was 67 mg/dL, sodium was 120 meq/L, potassium was 11.7 meq/L, and chloride was 88 meq/L (drawn within 12 h after discovery of the body).

Case 3

A 65-year-old white woman was hospitalized for hip pain seven years after a radical mastectomy for breast carcinoma. She had received intermittent chemotherapy and prolonged high dose prednisone which had been reduced to maintenance levels when psychological depression and Cushingoid manifestations became unmanageable. After admission to the hospital the steroids were inadvertently discontinued, and the patient experienced nausea, weakness, apprehension, and severe hypotension with fainting when assuming an upright position. She was discovered dead in bed, and a hospital autopsy requested by the family revealed virtual absence of malignancy, and the adrenals were not described. (The death certificate lists the cause of death as metastatic breast carcinoma).

Discussion

Although tuberculosis has been to a large extent eliminated as a cause of Addison's disease, present day noniatrogenic adrenal insufficiency is not uncommon, and usually falls into the category of autoimmune diseases. Frequent association with other autoimmune diseases has been reported (hypoparathyroidism, chronic mucocutaneous candidiasis, diabetes mellitus, pernicious anemia, hypogonadism, chronic active hepatitis, malabsorption syndromes, immunoglobulin abnormalities, alopecia, vitiligo, and autoimmune thyroid diseases) [*1*]. Numerous specific disease combinations have been reported, and Neufeld et al [*1*] have proposed

a classification of polyglandular autoimmune (PGA) syndromes into three groupings. Type I PGA has at least two of a triad of Addison's disease, chronic mucocutaneous candidiasis and hypoparathyroidism. Other immune disorders may be present. Type II PGA is Addison's disease plus either or both autoimmune thyroid disease and insulin dependent diabetes mellitus (Schmidt's syndrome), but without candidiasis or hypoparathyroidism. Other immune disorders may be present. HLA (human leucocyte antigen) testing often reveals A_1 and B_8 antigens. Type III PGA is autoimmune thyroid disease without Addison's disease, but with another autoimmune disorder. An associated encephalopathy has been recognized since Addison's disease was first described [*2*], and later a demyelinating process with lesions grossly and histologically resembling those of multiple sclerosis was identified.

Successful replacement therapy for the endocrine deficiency dates back to at least 1936 when adrenal extracts were administered as replacement therapy [*3*]. Desoxycorticosterone acetate was developed at about the same time, and it was over a decade later that cortisone became available [*3*].

Adrenal suppression and insufficiency after long-term steroid administration is almost invariable, and suppression after short-term corticosteroid therapy for cancer, asthma, cerebral edema, vasculitis, and acute dermatitis has been reported [*4*].

The cases presented are examples of acute adrenal insufficiency superimposed on chronic adrenal insufficiency. Case 1 might be classified as an example of Schmidt's syndrome (Type II PGA), having Addison's disease plus chronic lymphocytic thyroiditis, and a possibly autoimmune hepatic disorder. Case 2 is also a chronic biglandular endocrinopathy with involvement of adrenal and thyroid (Type II PGA), but a possible relationship to the abdominal trauma and surgery cannot be entirely excluded. Case 3 typifies the suppression of adrenal function by exogenous steroids after periods of prolonged administration.

Deaths from adrenal insufficiency are often sudden and unexpected, and will frequently come to the attention of the medical examiner. It is important not only to be aware of these syndromes, but also to examine as a matter of routine the adrenals of all individuals who die suddenly, particularly if death was preceded by vague and nonspecific symptoms.

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