Newer Aspects of Primary Adrenal Insufficiency

Keith L. Parker
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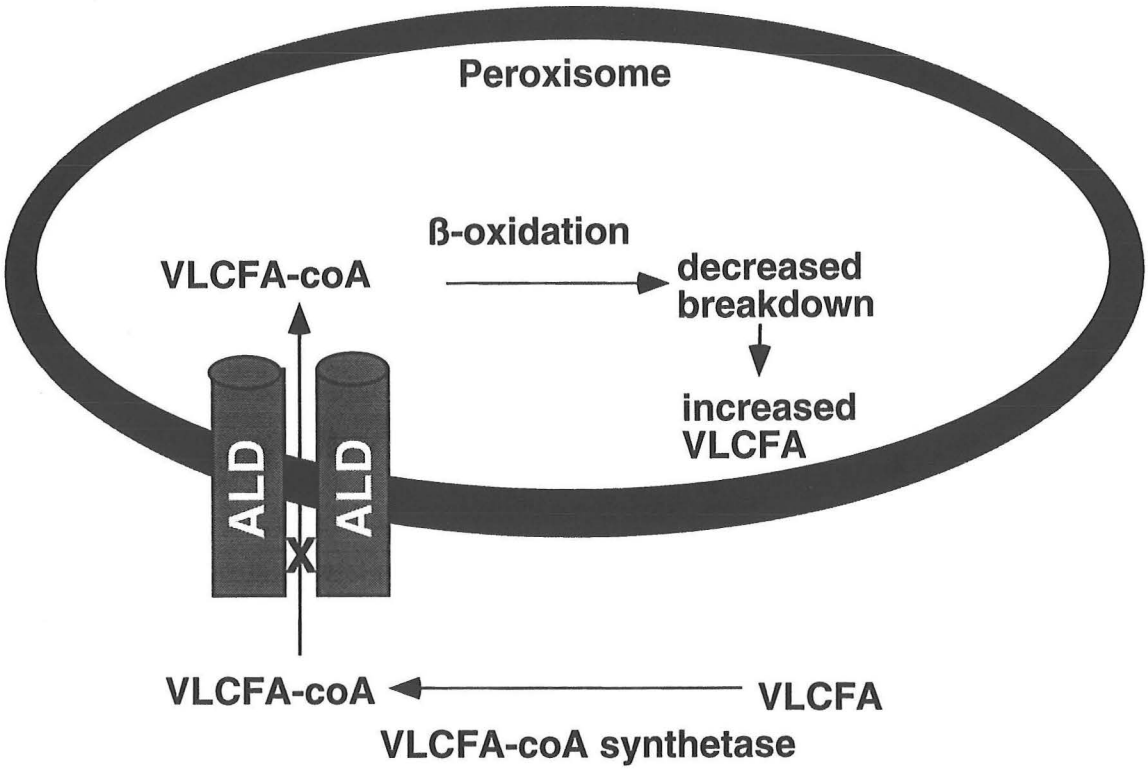
Pathogenesis of Adrenoleukodystrophy



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Dr. Parker is interested in the genetic mechanisms that control the development and function of the adrenal cortex and gonads. His studies have focused on steroidogenic factor 1, an orphan nuclear receptor that is essential for adrenal and gonadal development, function of pituitary gonadotropes, and development of the ventromedial hypothalamic nucleus.

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I. INTRODUCTION

Thomas Addison first described the manifestations of primary adrenal insufficiency in 1855 (Addison 1855). One year later, Charles Brown-Sequard provided definitive evidence in experimental animals that the adrenal glands were essential for survival (Brown-Sequard 1856). Subsequently, steroid hormones were shown to be the essential products of the adrenal glands, as patients with adrenal insufficiency could be restored to health with steroid replacement therapy.

Primary adrenal insufficiency is an uncommon condition, with an annual incidence of approximately 6 cases/million adults/year and a prevalence in the general population of 40-110 cases/million adults. Nonetheless, its pleiotropic clinical manifestations and potential for life-threatening crises make it mandatory to consider this diagnosis in patients presenting with relatively common symptoms such as weakness, fatigue, weight loss, orthostatic dizziness, or abdominal pain (Oelkers 1996).

Although most of the patients that Addison described had evidence of active tuberculosis, at least one patient had vitiligo, suggesting an autoimmune etiology for his adrenal insufficiency. While these two disorders still cause most cases of primary adrenal insufficiency, recent years have witnessed spectacular advances in our understanding of the molecular pathogenesis of several different specific disorders that cause primary adrenal insufficiency (Carey 1999).

II. CLINICAL MANIFESTATIONS

As noted above, the clinical manifestations of primary adrenal insufficiency are non-specific, and the vast majority of patients who present with these complaints ultimately are not found to have adrenal insufficiency. In the setting of the appropriate symptom complex, more specific manifestations (e.g., hyperpigmentation, vitiligo, salt craving) may be particularly helpful in identifying patients with adrenal insufficiency.

Clinical Manifestations of Primary Adrenal Insufficiency

Common Manifestations (>80% of cases)

- Weakness and lassitude
- Anorexia
- Nausea
- Vomiting
- Weight Loss
- *Hyperpigmentation*
- Low Blood Pressure

Less Common (<50% of cases)

- Abdominal pain
- Diarrhea
- Dizziness
- *Salt Craving*
- *Vitiligo*

III. ETIOLOGY OF PRIMARY ADRENAL INSUFFICIENCY

A. Infectious Adrenalitis
   Tuberculosis
   Fungal Infections
   HIV-1
B. Autoimmune Adrenal Insufficiency
   Isolated
   Polyglandular Autoimmunity Type I
   Polyglandular Autoimmunity Type II
C. Bilateral Adrenal Hemorrhage
   Meningoccemia
   Sepsis
   Burns, Trauma
   Thromboembolic disease or coagulopathy (lupus anticoagulant)
D. Neoplasia
   Lung, breast cancer metastases
   Melanoma
   Lymphoma
E. X-linked Adrenoleukodystrophy
F. Inherited Defects of Steroidogenic Enzymes
   21-hydroxylase deficiency
   11ß-hydroxylase deficiency
   Congenital lipoid adrenal hyperplasia (StAR mutations)
   3ß-hydroxysteroid dehydrogenase deficiency
G. Adrenal Hypoplasia Congenita (DAX-1)
H. Steroidogenic Factor 1 (SF-1) Mutation
I. Familial Glucocorticoid Deficiency due to ACTH receptor mutations
J. Triple A syndrome (Addison's Disease, Alacrima, Achalasia)
K. Other Causes
   Sarcoidosis
   Amyloidosis
   Hemochromatosis

A. Infectious Adrenalitis

AIDS

Infection with human immunodeficiency virus 1 (HIV-1) has received considerable attention as a cause of primary adrenal insufficiency (Piedrola et al. 1996). It should be noted that all published studies on adrenal insufficiency and AIDS antedated the advent of HAART, and thus the scope of the problem may be further diminished in developed countries where regimens employing multiple anti-retroviral agents are routinely employed. Although symptoms suggestive of primary adrenal insufficiency are common in AIDS and affected patients frequently exhibit abnormal responses to the standard 250 µg ACTH stimulation test, frank adrenal insufficiency is uncommon. Nonetheless, patients with HIV infection, particularly those with advanced stages of AIDS, are at increased risk for adrenal insufficiency. A number of factors can compromise

adrenocortical function in HIV-1-infected patients. Most AIDS patients with clinically significant adrenal impairment have concomitant infection with cytomegalovirus, the most common pathogen identified in autopsy examinations of the adrenal glands. Other opportunistic pathogens causing adrenal dysfunction include *M. avium-intracellulare*, *toxoplasma*, and *pneumocystis* species. The adrenals also may be infiltrated with Kaposi's sarcoma. Impaired adrenal function may be unmasked in AIDS patients treated with drugs such as ketoconazole, which inhibits cytochrome P450 steroidogenic enzymes, or rifampin, which accelerates the metabolic clearance of cortisol. Finally, the high circulating levels of cytokines in patients with AIDS may suppress the hypothalamic-pituitary adrenal axis without overt adrenal destruction.

B. Autoimmune Adrenal Insufficiency

In developed countries, tuberculosis generally is effectively diagnosed and treated, and autoimmune destruction of the adrenal cortex accounts for between 70% and 90% of cases of primary adrenal insufficiency. Although the relative pathogenetic importance of cell-mediated versus humoral mechanisms in the autoimmune destruction is debated, autoantibodies against the adrenal cortex are detectable by immunofluorescence or immunoprecipitation assays in up to 90% of patients with a recent clinical diagnosis of autoimmune Addison's disease (Betterle et al. 1999). The 21-hydroxylase enzyme is the major autoantigen recognized by anti-adrenal autoantibodies, and these antibodies mark the destructive phase of the autoimmune process in the adrenals. Thus, the levels of anti-21-hydroxylase antibodies correlate with the degree of adrenal dysfunction, while the presence of antibodies against 21-hydroxylase in subjects with other organ-specific autoimmune processes (e.g. Type I diabetes mellitus) indicates an increased risk of developing overt adrenal insufficiency (Laureti et al. 1999; Yu et al. 1999). Autoantibodies against other steroidogenic enzymes, such as the cholesterol side-chain cleavage enzyme and 17α-hydroxylase, also are found in some patients with Addison's disease (particularly those with primary gonadal failure) but do not necessarily correlate with the degree of adrenal dysfunction or risk of progression to frank adrenal insufficiency.

Approximately 50% of patients with autoimmune Addison's disease have one or more associated autoimmune endocrine disorders. The converse is not true, as Addison's disease is seen only rarely in patients with more common autoimmune endocrine diseases such as type 1 diabetes mellitus or Graves' disease. Based on clinical features and genetics, two discrete subsets of patients with polyglandular autoimmune syndromes (PGAs) have been defined.

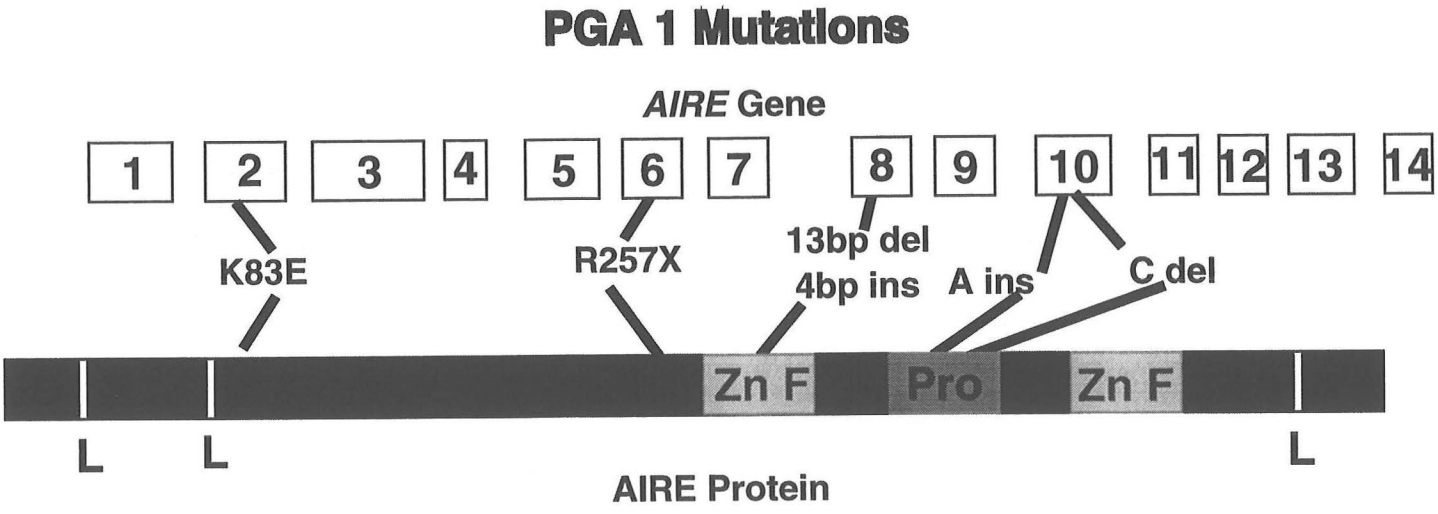
PGA 1

PGA Type I (also designated autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, or APECED), an autosomal recessive disorder consisting of a clinical triad of Addison's disease, hypoparathyroidism, and chronic mucocutaneous candidiasis (Betterle et al. 1998). Less frequent manifestations include autoimmune gonadal and thyroid disease, pernicious

anemia, chronic active hepatitis, vitiligo, and hypoplasia of the dental enamel. In most populations, PGA I is a very rare disorder, but its prevalence is 1 in 25,000 in Finland and 1 in 900 in Iranian Jews.

The major manifestations of PGA I appear within the first two decades of life. Chronic mucocutaneous candidiasis typically presents before five years of age and involves the skin, nails, and oral and perianal mucosa. Hypoparathyroidism usually appears before age 10, whereas adrenal insufficiency often is not apparent until several years after the other features first appear. The candidiasis apparently results from a selective defect in T cell-mediated responses to *Candida* antigens. The specific antigenic target(s) that cause hypoparathyroidism are not known, but sera of some PGA I patients contain antibodies that recognize the extracellular domain of the calcium-sensing receptor on parathyroid cells. While 21-hydroxylase is the principal autoantigen in isolated autoimmune adrenal insufficiency, it may play a lesser role in PGA I, as antibodies directed against 17α-hydroxylase and the cholesterol side-chain cleavage enzyme also have been identified in sera from affected patients.

The gene responsible for PGA I, designated *AIRE* for "autoimmune regulator", has been mapped to chromosome 21q22; it is expressed in the thymus, fetal liver, and other lymphoid tissues such as spleen, and encodes a protein that contains 2 two zinc finger domains, a proline-rich region, and 3 LXXLL motifs characteristic of co-activators and co-repressors that interact with nuclear receptor family members. Presumably, AIRE modulates the expression of genes involved in the pathogenesis of the polyendocrine autoimmunopathy (Aaltonen et al. 1996; Peterson et al. 1998). The autoimmune pathogenesis of PGA I has led to the proposal that severely affected PGA I patients may benefit from treatment with immunosuppressive agents. In one report, certain clinical and biochemical parameters improved following treatment with cyclosporine, although normal adrenal function was not restored (Ward et al. 1999).



PGA II

Patients with PGA II, the more common form of polyglandular autoimmune syndrome, have adrenal insufficiency associated with autoimmune thyroid disease or, less frequently, type 1 diabetes mellitus or hypogonadism (Betterle et al. 1996). Primary adrenal insufficiency often is their first manifestation. Associated conditions include thyroid disease (primary hypothyroidism or Graves disease), diabetes mellitus, Sjogren's syndrome, and celiac disease. Although PGA II is linked to the HLA major histocompatibility complex--particularly to the HLA-DR3 and HLA-DR4 alleles--there is no clear evidence of monogenic transmission. Thus, PGA II, unlike PGA I, probably involves interactions among several different susceptibility genes.

C. Bilateral Adrenal Hemorrhage

Bilateral adrenal hemorrhage can occur in children or infants with severe infection, particularly with meningococcemia or *Pseudomonas* sepsis. Largely due to improved imaging techniques, bilateral adrenal hemorrhage also increasingly is recognized as a cause of primary adrenal insufficiency in adults (Xarli et al. 1978, Rao et al. 1989). Most frequently, this occurs in patients who are gravely ill due to sepsis, trauma, or extensive burns, especially if there is an associated risk factor such as thromboembolic disease, coagulopathy, or postoperative state. Clinical manifestations of bilateral adrenal hemorrhage include the acute onset of flank or back pain, hypotension, a decrease in hematocrit, and electrolyte abnormalities consistent with corticosteroid deficiency, although--perhaps due to the rapidity of the process and the severity of the underlying illness--the classical biochemical manifestations may be absent or may be attributed to other causes. The pathogenesis of this disorder is not known; apparently, elevated ACTH levels increase adrenal perfusion until it exceeds the capacity for venous drainage. Adrenal function may recover to some degree if corticosteroid replacement therapy is implemented promptly after the diagnosis is made.

D. Neoplastic Disease

The adrenal glands are frequent sites of metastasis from a number of different primary tumors. Because clinical manifestations generally do not occur until more than 90% of the cortex is destroyed, clinically significant adrenal insufficiency is relatively uncommon, although some studies suggest that a subset of patients with bilateral adrenal metastases have partial adrenal insufficiency and benefit from glucocorticoid therapy. Tumors most frequently causing overt adrenal insufficiency include cancers of the lung and breast, melanoma, and lymphomas.

E. X-linked Adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is characterized by defective ß-oxidation of fatty acids within peroxisomes, with resultant demyelination in the central nervous system and development of adrenal insufficiency (Moser 1997; Dubois-Dalcq et al. 1999; van Geel et al. 1997). Increased accumulation of very long chain fatty acids (VLCFA) is demonstrable in tissues and body fluids. Three principal phenotypes are recognized. Childhood cerebral ALD typically presents in early childhood; affected boys exhibit neurologic manifestations of demyelination of cerebral white matter, usually initially in the corpus callosum but also involving the internal capsules and brainstem. The neurologic disease is generally progressive, with development of spastic quadriparesis, blindness, dementia, and death. Adrenomyeloneuropathy refers to a more attenuated form, presenting in young adulthood with weakness, spasticity, and peripheral neuropathy and progressing more slowly than does childhood cerebral ALD. Both of these conditions are associated with primary adrenal insufficiency, the development of which may precede by many years the appearance of neurologic signs and symptoms. Hence, the third phenotype is termed "Addison's only". It increasingly is appreciated that some heterozygous female "carriers" exhibit mild CNS manifestations resembling those of adrenomyeloneuropathy. Their neurological disorder--which presumably reflects X-chromosome inactivation of the normal allele--rarely progresses and only occasionally causes overt adrenal insufficiency.

In young men, who are affected less frequently with autoimmune adrenal insufficiency, ALD is a frequent cause of Addison's disease and adrenal insufficiency can be its first manifestation. The demonstration of elevated plasma levels of VLCFAs in patients with idiopathic adrenal insufficiency is of value both for prognosis and genetic counseling (a flowchart for determining the etiology of idiopathic adrenal insufficiency based on new advances is given below). ALD results from mutations in a gene at Xq28 that encodes a peroxisomal membrane transporter that apparently is required for ß-oxidation of very long chain fatty acids (see cover for a schematic model of the presumed pathway by which VLCFA are metabolized in peroxisomes). It is not clear if the disease results from accumulation of excessive levels of VLCFAs within the cell, or from a failure to convert VLCFAs to essential derivatives. It further is not known why the adrenal cortex is affected more severely than other organs, although VLCFAs do accumulate, particularly in the zona fasciculata. Analyses of the mutations associated with this disorder have revealed a high degree of clinical heterogeneity, even within a given kindred carrying the same mutation. Further analyses of the *ALD* gene hopefully will provide new insights into the molecular basis for this clinical heterogeneity and may lead to new approaches to treatment.

The movie "Lorenzo's Oil" depicted the efforts of the Oddine family to develop dietary treatment for their son Lorenzo, who suffered from childhood cerebral ALD. Their apparent success in combining a low-fat diet and glyceryl-oleate/-erucate supplementation sparked worldwide efforts at dietary treatment for ALD patients. Unfortunately, careful longitudinal studies have not documented any sustained clinical response to this treatment (Restuccia et al. 1999), and most experts no longer initiate dietary therapy in ALD patients.

The only proven therapy for ALD is allogeneic bone marrow transplantation. Presumably, bone marrow stem cells give rise to glial cells that

can correct the biochemical defect within the CNS. In some patients, this approach has produced impressive clinical responses, and transplantation from an HLA-compatible sibling currently is viewed as the treatment of choice. Efforts are underway to use retroviral gene therapy to correct the gene defect in autologous bone marrow cells. Other proposed therapies include plasmaphoresis (which corrects the elevated levels of VLCFAs but does not cause clinical improvement) and statins (which also correct the biochemical defect but have not been shown to cause clinical improvement).

F. Inherited Defects of Steroidogenic Enzymes

In pediatric patients, genetic deficiencies of the enzymes that convert cholesterol to biologically active steroid hormones comprise the most frequent cause of primary adrenal insufficiency. Hypoglycemia is a frequent presenting manifestation in infants with primary adrenal insufficiency.

1. 21-hydroxylase deficiency

The most frequent enzyme defect is 21-hydroxylase (occurring in approximately 1 in 10,000 newborns), which is required for the production of both glucocorticoids and mineralocorticoids. Females with this disorder generally are diagnosed at birth because of urogenital abnormalities due to excessive production of adrenal androgen precursors in utero. Males appear normal at birth and are not diagnosed until they present with acute adrenal crisis, generally 1-2 weeks after birth. Some states (including Texas) mandate routine screening of neonates for elevated levels of 17-hydroxyprogesterone, the steroid intermediate that accumulates in the absence of 21-hydroxylase activity.

2. 11ß-hydroxylase deficiency

Deficiency of steroid 11ß-hydroxylase is the second most frequent cause of congenital adrenal hyperplasia. The clinical presentation parallels that of 21-hydroxylase deficiency, with impaired production of cortisol and increased production of adrenal androgens. 11ß-hydroxylase is not required for the production of aldosterone, so patients do not develop salt-wasing; they may even have hypokalemia and develop hypertension due to mineralocorticoid effects of deoxycorticosterone.

3. Lipoid CAH

This rarest and most severe genetic form of adrenal steroidogenic defect is inherited in an autosomal recessive pattern. All classes of steroid hormones are deficient, including glucocorticoids, mineralocorticoids, and sex steroids. Patients generally present as neonates with manifestations of acute adrenal insufficiency--such as failure to thrive, vomiting, lethargy, and hyperpigmentation--and laboratory abnormalities that include hyponatremia, hyperkalemia, and hypoglycemia. On histologic examination, the steroidogenic

cells of the adrenal cortex and gonads exhibit a characteristic vacuolated appearance due to lipid deposits.

Originally attributed to mutations in the cholesterol side-chain cleavage enzyme, lipoid CAH results from mutations in the gene encoding the steroidogenic acute regulatory protein (StAR), a mitochondrial protein that mediates the delivery of cholesterol substrate to the inner mitochondrial matrix where steroidogenesis commences (Bose et al. 1996). Because of these mutations, steroid biosynthesis is extremely inefficient and patients are deficient in glucocorticoids, mineralocorticoids, and sex steroids.

G. Adrenal Hypoplasia Congenita

Adrenal hypoplasia congenita (AHC) is an X-linked disorder that results in adrenal insufficiency in childhood. AHC patients subsequently exhibit hypogonadotropic hypogonadism secondary to compound defects at both the hypothalamic and pituitary levels. Adrenal hypoplasia congenita is caused by mutations in the orphan nuclear receptor DAX-1, which is expressed in the adrenal cortex, gonads, gonadotropes, and ventromedial hypothalamic nucleus (Peter et al. 1998; Reutens et al. 1998). As a result of these mutations, development of the definitive adrenal cortex is impaired and the adrenal gland appears hypoplastic on imaging studies. Like ALD, there is considerable phenotypic variability, even in patients with the identical genetic mutation.

H. Steroidogenic Factor 1 (SF-1)

Studies in knockout mice revealed that the orphan nuclear receptor steroidogenic factor is essential for development of the adrenal glands and gonads. SF-1 in humans is expressed in many of the same sites, suggesting that it also plays essential roles in humans. Direct support for such a role has now been reported (Acherman et al. 1999). The index case presented initially with adrenal insufficiency, with low levels of all steroid classes, associated with 46, XY sex reversal of the external genitalia. These findings prompted a clinical diagnosis of lipoid CAH. In preparation for sex steroid therapy at the time of normal puberty, additional studies caused a revision of this diagnosis. The patient was found at laparoscopy to have normal female Mullerian structures and streak gonads--which are inconsistent with lipoid CAH. Genomic sequencing showed that one allele of the gene encoding SF-1 contained a mutation in the DNA binding domain that precludes its ability to transactivate target genes. Intriguingly, the other SF-1 allele in this patient contained no detected mutation, suggesting that haploinsufficiency for SF-1 in humans is sufficient to impair endocrine development. Thus, further studies are needed to resolve these apparent discrepancies between humans and knockout mice.

I. Familial glucocorticoid deficiency

Familial glucocorticoid deficiency is a rare, autosomal recessive disorder (Clark and Weber 1998). Patients present in childhood with manifestations of impaired production of glucocorticoids (weakness, hypoglycemia) and elevated ACTH levels (hyperpigmenation); these patients generally have normal

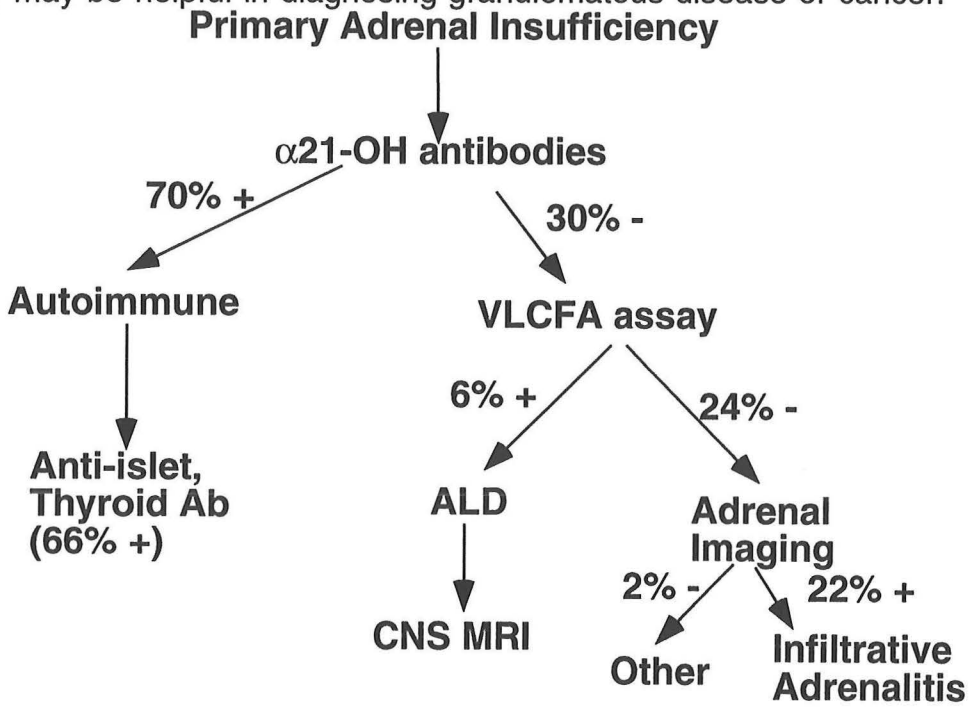
mineralocorticoid biosynthesis, and do not exhibit marked electrolyte abnormalities or elevated plasma renin. In most kindreds, FGD is caused by mutations in the G protein-coupled receptor that mediates adrenal stimulation by ACTH, designated the melanocortin-2 receptor (MCR-2). Other patients with identical clinical manifestations lack detectable mutations in the *MCR-2* gene, suggesting that other genes can cause the same endocrine defect.

J. Triple A Syndrome

A subset of pediatric patients with primary adrenal insufficiency have the "Triple A syndrome", a complex, autosomal recessive disorder that includes adrenal insufficiency, achalasia, and alacrima. Other associated features include mental retardation, optic atrophy, sensorineural deafness, and autonomic dysfunction. Presentation is generally delayed relative to patients with inborn errors of the steroidogenic enzymes, suggesting that the disease is associated with degeneration of the zonae fasciculata/reticularis after birth. The cloning of the gene whose mutation causes the Triple A syndrome, which has been mapped to chromosome 12q13, undoubtedly will provide new insights into mechanisms of adrenocortical development.

IV. Diagnosis of Specific Etiology of Adrenal Insufficiency

After the diagnosis of adrenal insufficiency is confirmed (see below), it is important to delineate the specific etiology. A proposed flowchart for the diagnostic work-up of patients with idiopathic adrenal insufficiency relies on the improved utility of antibodies against 21-hydroxylase and the appreciation of the relative importance of ALD is young male patients (Laureti et al. 1998). In the absence of anti-21-hydroxylase antibodies or elevated plasma levels of VLCFAs, imaging of the adrenals should be performed to detect enlarged adrenals or adrenal calcification indicative of infectious or neoplastic infiltration of the adrenal glands. If the adrenals are enlarged, CT-guided fine needle biopsy may be helpful in diagnosing granulomatous disease or cancer.



V. LABORATORY DIAGNOSIS

Standard laboratory screening tests may provide clues to the diagnosis of adrenal insufficiency. In primary adrenal insufficiency, hyponatremia and hyperkalemia are common. These abnormalities are unusual in patients with secondary adrenal insufficiency. Rarer laboratory abnormalities include eosinophilia and hypercalcemia. Because neither the patient's symptoms nor these laboratory abnormalities are specific for adrenal insufficiency, additional laboratory tests invariably are required to confirm the clinical suspicion of acute adrenal insufficiency. It cannot be overemphasized, however, that therapy of patients with suspected acute adrenal insufficiency must not be delayed until a definitive diagnosis has been reached.

The definitive diagnosis of adrenal insufficiency involves the demonstration of inadequate cortisol secretion, as well as a determination of whether the insufficiency reflects primary adrenal disease or ACTH deficiency. In addition, potentially reversible causes of adrenal insufficiency, if present, must be identified.

Basal morning plasma cortisol levels may be useful in establishing the diagnosis of adrenal insufficiency (Haqq et al. 1987). A very low early morning plasma cortisol (<138 nmoles/liter, 5 µg/dl) is highly suggestive of adrenocortical insufficiency, but lacks sensitivity because most patients with adrenal insufficiency have cortisol levels exceeding this value. Sensitivity is increased by raising the cut-off for a presumptive diagnosis to 275 nmol/liter (10 µg/dl), but this considerably decreases the specificity. On the other hand, an 8 AM cortisol exceeding 415 nmol/liter (15 µg/dl) makes the diagnosis of adrenal insufficiency unlikely, as values above this level predict a normal response in the dynamic tests described below. Cortisol levels drawn later in the day are useful only in the setting of severe stress, when a very low cortisol level (i.e., less than 138 nmoles/liter, 5 µg/dl) strongly suggests adrenal insufficiency and a level above 500 nmoles/liter (18 µg/dl) makes adrenal insufficiency unlikely.

A. Testing for suspected primary adrenal insufficiency

Simultaneous measurement of cortisol and ACTH, particularly under conditions of stress from intercurrent illness, can identify most patients with primary adrenal insufficiency: ACTH levels are high while cortisol levels are low. Because results from the ACTH immunoassay take longer to obtain than cortisol levels, the standard approach is to assess the ability of the adrenal gland to respond to exogenous ACTH.

The standard diagnostic test when adrenal insufficiency is suspected has been the rapid ACTH stimulation test, which can be performed at any time of day. After blood is obtained for a baseline cortisol level, synthetic ACTH (α 1-24 ACTH, cortrosyn, 0.25 mg) is injected intravenously or intramuscularly. After 30 minutes to 60 minutes, a second plasma cortisol level is obtained. A normal result (i.e., a post-ACTH cortisol level of >20 µg/dl) essentially excludes the diagnosis of primary adrenal insufficiency.

In circumstances where treatment must not be delayed, the short ACTH stimulation test will be valid even after the initiation of therapy with

dexamethasone (which is not measured in the cortisol assay), as long as the test is performed before suppression of the HPA axis can occur.

B. Testing for suspected secondary or tertiary adrenal insufficiency

In conditions that impair ACTH response to stress (e.g., intrinsic diseases of the hypothalamus and pituitary or chronic treatment with pharmacologic doses of glucocorticoids), it may be more important to test the integrity of the entire hypothalamic-pituitary-adrenal axis.

1. Insulin-induced hypoglycemia

Insulin-induced hypoglycemia traditionally has been the standard test for this purpose (Erturk et al. 1998), although this test is contraindicated in elderly patients and in subjects with known seizure disorders or psychiatric or cardiovascular disease. A physician must be present throughout the test and informed consent should be obtained. After a blood sample is obtained for basal cortisol and ACTH levels, regular insulin (0.1-0.15 U/kg body weight) is administered intravenously or intramuscularly and post-insulin blood samples are obtained at 30, 60, and 90 minutes after the insulin. Hypoglycemia (i.e., a blood glucose of <45 mg/dl) usually occurs between 30 and 45 minutes after insulin administration. Diaphoresis is a useful clinical indicator that an adequate hypoglycemic response has been achieved. The test is terminated, and 10% or 50% dextrose is infused, if adverse symptoms occur or if the blood glucose falls to less than 35 mg/dl. In settings where hypoglycemia is achieved, plasma cortisol levels should exceed 500-550 nmoles/liter (18-20 µg/dl). Criteria based on the increase in cortisol level over baseline are less useful diagnostically.

2. Metyrapone stimulation test

Pharmacological inhibition of cortisol production also can be used as an alternative to insulin-induced hypoglycemia to evaluate the integrity of the entire axis. Metyrapone is a relatively selective inhibitor of 11ß-hydroxylase, which catalyzes the terminal reaction in the biosynthesis of glucocorticoids—the conversion of 11-deoxycortisol to cortisol. Metyrapone (30 mg/kg, maximum dose of 3 gm) is administered orally with a snack at midnight, and plasma cortisol and 11-deoxycortisol are measured at 8 AM the next morning. A plasma cortisol of less than 7 µg/dl validates adequate inhibition of 11ß-hydroxylase. In patients with an intact hypothalamic-pituitary-adrenal axis, CRH and ACTH levels rise in response to the falling cortisol levels, increasing the flow of steroid precursors down the biosynthetic pathway. Thus, an 11-deoxycortisol level of <7 µg/dl is highly suggestive of impaired hypothalamic-pituitary-adrenal function. An abnormal response does not identify the site of the defect—either hypothalamic CRH release, ACTH production, or adrenal biosynthetic capacity could be impaired. The test should not be performed on an outpatient basis if adrenal insufficiency is considered to be reasonably likely, as further impairment of glucocorticoid production can precipitate adrenal crisis. To lessen the risk of precipitating adrenal insufficiency, some clinicians

prescribe hydrocortisone (10-15 mg po for one or two doses) after blood has been obtained for steroid measurements.

3. Low dose ACTH stimulation test

The standard 250 µg ACTH stimulation test uses a supraphysiologic dose of ACTH that sometimes can elicit a normal increase in cortisol level despite relative ACTH deficiency, particularly if the impairment of ACTH release is of recent onset. To increase the sensitivity of this test, a "low-dose" ACTH stimulation test has been proposed (Dickstein et al. 1991). This low-dose test involves the administration of 1 µg of ACTH intravenously, with cortisol measurement taken immediately before and 30 minutes after the ACTH administration. As a 1 µg dose is not widely available, the standard ampoule of Cortrosyn (250 µg) must be diluted to permit delivery of the low dose. Care must be taken to ensure proper dilution, to avoid adsorption of the ACTH to plastic tubing, and to measure the plasma cortisol precisely at 30 minutes after the administration of cosyntropin.

Published recommendations regarding the "low-dose" test have been mixed. In some analyses, the low-dose Cortrosyn stimulation test was more sensitive than the standard test (Abdu et al. 1999; Broide et al. 1995; Tordjman et al. 1995), whereas the two tests performed comparably in other reports (Mayenknect et al. 1998). In addition, efforts to establish uniform criteria for using ACTH stimulation are complicated by the use of different commercially available radioimmunoassays for measuring serum cortisol and sex- and body weight-dependent variations in responses to the lower dose of ACTH (Clark et al. 1998).

C. Current Recommendations

Both the low-dose and standard ACTH stimulation tests are effective in detecting patients with primary adrenal insufficiency. Thus, the major debate involves patients in whom the diagnosis of secondary adrenal insufficiency is entertained. In the public hospital setting, the need to dilute the cosyntropin in a non-standard manner, to administer the ACTH test dose intravenously, and to draw the post-ACTH blood sample at a precise time after challenge (i.e. 30 minutes) pose significant obstacles to the routine use of the low-dose test. In the absence of definitive clinical data supporting the supremacy of the low dose test, the standard ACTH stimulation test should continue to be the preferred approach at Parkland Memorial Hospital. It is important to remember that neither test excludes the possibility of adrenal insufficiency. Thus, any patient in whom there is a significant clinical suspicion of adrenal insufficiency—especially if the response to ACTH stimulation is near the cut-off value for a positive response—should be assumed to have hormone deficiency and treated accordingly.

VI. SELECTED ASPECTS OF THERAPY

A. Chronic Adrenal Insufficiency

Therapy for both primary and secondary adrenal insufficiency involves chronic replacement with oral glucocorticoids. Patients with intrinsic adrenal disease lack both glucocorticoids and mineralocorticoids, and replacement with both classes of steroid hormones usually is required. Since both primary and secondary adrenal insufficiency impair the normal response to stress, patients and their families must be educated to adjust steroid doses in response to stresses (e.g., fever, upper respiratory infection) and to promptly seek medical attention in more stressful situations.

The predominant glucocorticoid synthesized by the adrenal cortex is hydrocortisone (cortisol) and traditional replacement therapies have given this compound in doses of 20-30 mg/day. Cortisone acetate, which is inactive until converted to cortisol by 11ß-hydroxysteroid dehydrogenase type 1, also has been used at doses ranging from 25-37.5 mg/day. Because some patients cannot convert cortisone to cortisol (Nordenstrom et al. 1999), it seems logical to use hydrocortisone as the standard regimen. Cortisone and hydrocortisone traditionally have been given in divided doses, with two-thirds of the dose in the morning and one third in the afternoon. Isotope dilution studies have established a lower daily cortisol production rate of 9-11 mg/m^2 body surface area (Esteban et al. 1991; Kraan et al. 1998). Furthermore, clinical studies indicate that subtle degrees of glucocorticoid excess occur in many subjects on conventional replacement doses, leading in some cases to decreased bone density (Zelissen et al. 1994; Peacey et al. 1997). Because of this, a maintenance hydrocortisone dose of 20 mg/day is currently recommended. On this lower dose, some patients develop symptoms suggestive of adrenal insufficiency in the early afternoon, and some experts recommend t.i.d hydrocortisone (10 mg on awakening, 5 mg at lunch, and 5 mg in late afternoon) to facilitate patient well-being without the adverse consequences of overtreatment (Howlett 1997). Other authorities prefer long-acting glucocorticoids, since compliance may be better with a once-daily schedule and regimens with shorter-acting steroids cannot reproduce the peak serum cortisol levels that normally occur prior to awakening in the morning. Long-acting glucocorticoids (e.g., dexamethasone, 0.25-0.75 mg or prednisone, 2.5-7.5 mg) usually are administered as a single daily dose (some advocate at bedtime--if this results in insomnia, the dose can be administered immediately upon awakening). The superiority of any of these regimens has not been rigorously demonstrated. The standard dose of glucocorticoid often requires adjustment in patients who are concomitantly receiving drugs that accelerate the metabolic clearance of glucocorticoids, such as phenytoin, barbiturates, and rifampin.

The adequacy of glucocorticoid replacement therapy is judged by clinical criteria and biochemical measurements. The subjective well-being of the patient is an important clinical parameter in both primary and secondary disease, while the disappearance of hyperpigmentation and the resolution of electrolyte abnormalities are valuable indicators of adequate replacement in patients with primary insufficiency. Overtreatment may cause manifestations of Cushing's syndrome in adults and decreased linear growth in children. Plasma

ACTH levels may be used to monitor therapy in patients with primary adrenal insufficiency; the early morning ACTH level should not be suppressed, but should be less than 100 pg/ml (20 pmoles/liter). Although advocated by some endocrinologists, the assessments of daily profiles of cortisol based on multiple blood sampling or measurements of urinary free cortisol have been used more frequently as research tools than in clinical practice and are probably not cost-effective in routine practice.

All patients with adrenal insufficiency should wear a medical alert bracelet or tag that lists their diagnosis, and carries information about their steroid regimen. Moreover, the patient and family must be instructed in the proper adjustment of glucocorticoid dose to compensate for the stress of intercurrent illness. During acute illness, the glucocorticoid dose should be doubled. For more severe illness--or if nausea and vomiting preclude the retention of oral medications--the patient and family members should be taught to administer parenteral dexamethasone (4 mg subcutaneously or intramuscularly). They then should seek medical attention immediately.

Based largely on empirical data, glucocorticoid doses also are increased when patients with adrenal insufficiency undergo either elective or emergent surgery. In this setting, the doses are designed to approximate or exceed the maximal cortisol secretory rate of 200 mg/day; a standard regimen is hydrocortisone, 100 mg parenterally every 6-8 hours. Following surgery, the dose is halved each day until reduced to routine maintenance levels. Although data from experimental animals and clinical studies suggest that increases in dose to this degree are not essential for survival in major surgery and that patients can merely be treated with their maintenance dose (Glowniak et al. 1997), this approach at present remains standard clinical practice.

Patients with primary adrenal insufficiency also usually require mineralocorticoid replacement, although this may not be required in those consuming large amounts of salt. The synthetic mineralocorticoid 9α-fluorohydrocortisone (fludrocortisone) is used, since the naturally-occurring mineralocorticoids aldosterone and deoxycorticosterone are rapidly degraded after oral administration. Deoxycorticosterone can be given parenterally, but it is not available in the U.S. and is rarely used in the treatment of adults. The usual dose of fludrocortisone is 100 µg/day, but patients treated with hydrocortisone may require lower doses (e.g., 50 µg/day) because of its intrinsic mineralocorticoid activity.

Mineralocorticoid therapy is monitored routinely by assessment of blood pressure, volume status, and serum electrolyte concentrations. In particular, the standard mineralocorticoid dose may need to be increased in patients who must work or exercise in hot conditions. The presence of orthostatic hypotension or hyperkalemia may suggest inadequate therapy, while hypertension, edema, and hypokalemia will result from excess levels of mineralocorticoid. Plasma renin activity sometimes can be helpful in assessing the adequacy of mineralocorticoid replacement (Flad et al. 1996). In some patients, however, a dose of fludrocortisone that completely normalizes plasma renin activity may result in hypertension, and it is not always wise to increase the fludrocortisone dose in asymptomatic, normokalemic patients with mildly elevated plasma renin activity.

B. Glucocorticoid Tapering

Abundant evidence indicates that pharmacologic therapy with glucocorticoids can suppress the HPA axis and cause adrenal insufficiency upon steroid discontinuation. While individuals vary greatly in their susceptibility to HPA suppression, a useful rule-of-thumb is that any patient taking a daily dose of ≥10 mg prednisone (or equivalent) for longer than 3 weeks is at risk for suppression of the HPA axis (Furst et al. 1999). Patients who have received lower doses or for a shorter duration generally do not need endocrine evaluation, as their risk of adrenal insufficiency is very low. Endocrine evaluation also is not necessary in patients who have received ≥20 mg/day of prednisone for more than three weeks or who have clinically apparent Cushing's syndrome. In the event that these patients become acutely ill or require operation, they should be assumed to have HPA axis suppression and treated accordingly.

Although much discussion has been directed at the optimal approach to diminish the likelihood of precipitating adrenal insufficiency, very few studies are available to guide the clinician in this regard and definitive support for any one approach is lacking. Moreover, the most frequent impediment to discontinuing steroids is worsening of the underlying disease rather than precipitating adrenal insufficiency. Nonetheless, several different regimens for steroid tapering have been proposed. One widely-used approach is to gradually decrease the glucocorticoid dose (e.g. decreases of 5 mg prednisone every 1-2 weeks at doses ≥20-30 mg, decreases of 2.5 mg every 1-2 weeks to a dose of 10 mg, decreases of 1 mg every 1-2 weeks) until a dose equivalent to normal physiological replacement (e.g. 20 mg hydrocortisone, 5 mg prednisone, 0.75 mg dexamethasone) is reached The patient then is switched to hydrocortisone (20 mg/day), which has a relatively short half-life (Byyny 1976). The hydrocortisone dose is then decreased by 2.5 mg/week until the patient is taking 10 mg hydrocortisone each morning. At 4 week intervals, an 8 AM plasma cortisol is obtained before the patient takes the hydrocortisone. A cortisol of greater than 10 µg/dl provides some confidence that the HPA axis has recovered, and that further therapy with glucocorticoids is not required to avoid adrenal insufficiency. Other authorities believe that the cost of routinely measuring is not justified and prefer simply to discontinue steroids following a gradual taper.

An alternate tapering protocol is to switch to alternate day steroid dosing, as this will theoretically allow the HPA axis to recover during the off days. After the patient has been tapered to a dose of 20-30 mg of prednisone/day, the dose on the alternate day is decreased by 5 mg every 1-2 weeks until the prednosone dose is 20-30 mg alternating with 10 mg. The alternate day dose is then decreased by 2.5 mg every 1-2 weeks until the alternate day dose is 0. Thereafter, the qod dose is tapered by 2.5 mg every 1-2 weeks until a dose of 10 mg is achieved, followed by decreases in daily dose of 1 mg every 1-2 weeks until steroids are discontinued.

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