The expanding world of primary adrenal insufficiencies

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The past few years have seen a phenomenal increase in our understanding of three genetic causes of primary adrenal and gonadal hormone deficiency.

Lin and coworkers reported in 1995 (1) that patients with congenital lipoid adrenal hyperplasia have mutations of the steroidogenic acute regulatory protein. This protein has an essential role in the mobilization of cholesterol from lipid stores to the vicinity of cytochrome P450 in the inner mitochondrial membrane and controls steroid synthesis. Congenital lipoid adrenal hyperplasia is a rare autosomal recessive disorder and is characterized by severe adrenal insufficiency in the neonatal period. XY males are born with female external genitalia as a result of the absence of testicular testosterone synthesis.

Adrenal hypoplasia congenita (AHC) is a more common X-linked disorder which appears as primary adrenal insufficiency in most cases before the age of 10, with low serum concentrations of glucocorticoids, mineralocorticoids and androgens. Hypogonadotropic hypogonadism characterized by failure of sexual maturation during adolescence is frequently present in patients. In 1994, Muscatelli et al. identified the AHC gene which encodes a new member of the nuclear hormone receptor family (2). The encoded protein, termed DAX-1, is expressed in a co-ordinate manner with the steroidogenic factor-1 (SF-1) in the first stages of gonadal and adrenal differentiation and in the developing hypothalamus. The similar phenotypes of SF-1 and DAX-1 mutations suggest that the two proteins act in the same pathway of endocrine development, SF-1 probably acting upstream of DAX-1.

Adrenoleukodystrophy (ALD) is another X-linked disorder which is characterized by adrenal insufficiency, testicular dysfunction, demyelination in the central nervous system (CNS) and accumulation of very long chain fatty acids (VLCFA) in blood and tissues. The ALD gene, identified in 1993, encodes a peroxisomal protein (designated ALDP), which is a new member of the ATP-binding cassette transporter family (3). ALDP is thought to homodimerize or heterodimerize with a related partner in the peroxisomal membrane and transport VLCFA into peroxisomes before oxidation.

ALD affects 1 in 15 000–20 000 males and is one of the most frequent causes of Addison’s disease in countries without widespread tuberculosis. In children above 3 years of age, ALD is the cause of 30% of cases of Addison’s disease, regardless of sex. In adults, a recent survey indicated that 13.8% (8/58) of adults with Addison’s disease had ALD (S Laureti, personal communication). The same group reported previously that 35% of males with idiopathic Addison’s disease had ALD (4).

As emphasized by Korenke et al. in this issue (5), the prognosis of ALD is far more serious than other etiologies of primary adrenal insufficiency. During childhood or adolescence, 45% of ALD patients are at risk of developing a severe demyelinating disease of the CNS that leads to death within a few years. During adulthood, another 40% of them are at risk of developing severe paraplegia (this clinical phenotype is termed adrenomyeloneuropathy), and unfortunately one-third of these adults will develop a second stage of cerebral demyelination. Isolated Addison’s disease remains the only manifestation of ALD in no more than 6–8% of patients. It can be estimated that less than 5% of ALD patients will remain free of neurological symptoms after the age of 50 years.

Although the population of ALD patients reported by Korenke et al. includes some bias (adrenomyeloneuropathy represented only 20% of their ALD population) or particularity (in our experience, a mineralocorticoid deficit is present in 30% of ALD patients with Addison’s disease), their data highlight several important findings. Most patients (92% of children and 80% of adults) had endocrinological signs before the onset of neurological deterioration. Yet, these symptoms, which can precede neurological signs for decades, led to the diagnosis of ALD in only 20% of them. Korenke et al. emphasize that the proportion of Addison cases which is attributable to ALD is highest before 15–20 years of age. It must, however, be kept in mind that Addison’s disease due to ALD can be diagnosed in adults who are 40 years old. Importantly, all patients examined by Korenke (as well by other groups) for the presence of adrenocortical antibodies proved negative. These data stress the crucial importance of measuring plasma VLCFA (the specific biochemical test for ALD) in any male with primary adrenal insufficiency between the ages of 3 and 50 years. A subclinical decrease in the glucocorticoid reserve, as measured by ovine corticotropin-releasing hormone testing, is present in 63% of ALD heterozygous women, but overt adrenal insufficiency is exceptional (1.5%) (6).

As reported by several groups, Korenke et al. found no correlation between the ALD gene mutation and the...
endocrinological and/or neurological manifestations of ALD. As for many other genetic disorders, the existence of modifier genes and/or stochastic factors has been suggested to explain this phenotypical variation. The claim that hereditary factors influence the endocrinological more than the neurological phenotype remains questionable. The onset of biological or clinical symptoms of adrenal insufficiency is quite variable among male relatives with the same ALD gene mutation. On the other hand, nearly all patients develop some degree of neurological involvement after the age of 40 years, whereas 15–20% of them will remain with intact adrenal function.

As also shown in this issue by Korenke et al. (5) and Brennemann et al. (7), ALD patients present biological evidence of testicular dysfunction in adulthood. Approximately 50–65% of them show a decrease in serum dehydroepiandrosterone sulfate levels and an increase in serum luteinizing hormone (LH) and/or follicle-stimulating hormone. Inhibin-B concentrations remain normal. Brenneman et al. report that 24 of 49 patients with adrenomyeloneuropathy had a low testosterone/LH ratio but only a minority (3 of 59 in the pooled data from Korenke and Brennemann) had a decreased serum level of testosterone. These data indicate that ALD involves the Leydig cell and, to a lesser degree, the tubuli seminiferi. In our experience, 20% of patients with adrenomyeloneuropathy have moderate signs of hypogonadism at the time of diagnosis (excluding the presence of sparse hairs, which often gives them the appearance of premature aging and for which the mechanism is unclear). Rare observations of ALD patients presenting with hypogonadism as an initial symptom have been reported. It must be remembered that sexual maturation occurs normally in ALD adolescents and that decreased fertility is rare in adult ALD patients. Many of them develop impotence after the age of 35–40 years, but this symptom is mainly due to myelopathy.

The absence of ALDP, or the presence of non-functional ALDP, leads to an impairment of VLCFA transport across the peroxisomal membrane with a secondary deficit in the $\beta$-oxidation of these fatty acids and accumulation within cells. Whereas it remains uncertain whether the VLCFA accumulation is a direct cause of the pathology within the CNS, it seems plausible that accumulation of VLCFA is the main determinant of the adrenal and testicular dysfunction.

The adrenal glands of ALD patients show marked abnormalities of the cortex, which are already present at 17–21 weeks of gestation. They include a progressive atrophy which is more marked in the zona fasciculata and reticularis than in the glomerulosa, and the presence of ballooned cells with lamellar lipid striations and fine clefts which are visible by light microscopy. The medulla is remarkably preserved. The adrenal cortex of ALD patients shows a striking accumulation of cholesterol esterified with VLCFA (up to 30% in ALD versus 1–3% in controls). Cholesterol esters that contain VLCFA are poor substrates for hydrolases and would lead predictably to their accumulation within the cell in the form of lamellar inclusions. The pattern of ALDP expression is strikingly correlated with the site of the pathology in adrenal glands. ALDP is markedly expressed in the three zones of the adrenal cortex, while little expression is found in the medulla. Finally, adrenal glands show (like the liver and cardiac skeletal) muscle high expression of peroxisomal $\beta$-oxidation enzymes. These data suggest strongly that defective $\beta$-oxidation of VLCFA and/or accumulation of these fatty acids could lead to cellular dysfunction and death of adrenocortical cells.

The mechanism of VLCFA toxicity remains unclear however. One study has reported that adrenal glands of ALD patients show depressed activity of several enzymes involved in steroidogenesis (8). Another study has, instead, implicated an impairment of the adrenocorticotropin (ACTH) receptor (9). Adrenocortical cells cultured in a medium enriched in VLCFA show an increased membrane microviscosity and a significant reduction in their cortisol response to ACTH stimulation. These results are indicative of membrane dysfunction and indirectly supported by studies of artificial vesicles using NMR spectroscopy and differential scanning calorimetry. When these vesicles are enriched in VLCFA, they show a higher desorption of these fatty acids than when they are enriched in fatty acids with shorter chains. Accumulation of VLCFA in these artificial vesicles leads also to a strong perturbation of the acyl chains of phospholipids (10). In which subcellular compartment (plasma, reticulum or mitochondrial membranes) these biophysical abnormalities lead to deleterious effects in steroidogenesis and/or signal transduction remains to be clarified.

The testes of children or adults with ALD show less marked abnormalities than adrenal glands. The first changes are observed in Leydig cells where rare trilamellar inclusions identical to those previously described are found to be present by electron microscopy. Other less frequent lesions include hypocellularity and vacuolation of the Sertoli cells, and sometimes maturation arrest and tubular atrophy. Germ cells can also occasionally show vacuolation and necrosis, accompanied by slight tubular atrophy and thickening of the tunica propria. VLCFA accumulate in the testes of ALD patients but at a lower level than in adrenal glands. Studies with Leydig cells cultured in a medium enriched with VLCFA have failed to show any change to LH stimulation. Remarkably, ALDP expression is almost restricted to Leydig cells in adult testis. As for adrenocortical cells, it is therefore tempting to think that accumulation of VLCFA in Leydig cells may have some toxicity. However, the mechanisms that lead to Leydig cell dysfunction remain unknown.

Establishing that idiopathic Addison’s disease is due to ALD has important implications. ALD is a relatively
frequent X-linked genetic disorder (1 in 15 000–20 000 males) with a frequency of only 8% of de novo mutation. The diagnosis of an index case of ALD, therefore, frequently leads to diagnosis of other cases when genetic counseling associated with biochemical screening is performed. This is important in order not only to identify patients with undiagnosed Addison’s disease (this is still frequent, as outlined in Korenke et al., and there are many histories of sudden death in ALD families) but also to detect patients who have no or minimal neurological involvement. Although still in their infancy, some therapeutic approaches are emerging. In the cerebral form, autologous bone marrow transplantation can reverse or stabilize demyelinating lesions. This therapy is, however, effective at only an early stage of the disease. In fact, all ALD patients transplanted with success were patients identified during genetic screening or patients who were initially diagnosed with isolated Addison’s disease and in whom cerebral demyelination appeared secondarily. In neurologically asymptomatic patients, a dietary approach (Lorenzo’s oil) can be proposed to prevent, even if only partially, the onset of the cerebral or spinal cord involvement. This regimen normalizes plasma VLCFA within 2 months, but it must be remembered that its efficacy has not yet been proved. Finally, it is crucial to detect women at risk of being heterozygous and to suggest to them prenatal diagnosis after genetic counseling. The identification of women heterozygous for ALD can be reliably achieved by plasma VLCFA measurement and molecular methods (mutation analysis and/or study of the ALD protein) (11). Prenatal diagnosis relies on the same methods (11).

Animal models of ALD obtained by homologous recombination have recently been obtained in several laboratories and are currently under intensive investigation. These models should help to decipher many unresolved aspects of CNS, adrenal gland and testicular dysfunction. At present, bone marrow transplantation is the only therapeutic intervention with proven efficacy in the lethal cerebral form of ALD. Work is already in progress to target the normal ALD gene into hematopoietic stem cells. The insertion of the normal gene followed by autologous bone marrow transplantation would circumvent the need for a histocompatible donor and decrease the morbidity and mortality risk of the procedure, which could therefore also be proposed for adult ALD patients.

References


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