Endocrine Dysfunction in X-Linked Adrenoleukodystrophy

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KEYWORDS

• X-linked adrenoleukodystrophy • Adrenomyeloneuropathy • Adrenal insufficiency
• Addison disease • Testicular dysfunction • Androgen deficiency • ABCD1
• Very-long-chain fatty acids

KEY POINTS

- Primary adrenal insufficiency is a common finding in males with *ABCD1* gene mutations associated with X-linked adrenoleukodystrophy (X-ALD).
- When left untreated, primary adrenal insufficiency is associated with high morbidity and mortality.
- Newborn screening technology has advanced to detect males with and female carriers of X-ALD before the onset of symptoms.
- The purpose of this review is to summarize the concerns for endocrine dysfunction associated with X-ALD and provide guidance for monitoring, diagnosing, and managing adrenal insufficiency.

INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder and has variable phenotypic presentations, affecting the nervous system, adrenal cortex and testicular function. Descriptions of patients with the condition were first reported as early as the late 19th century. In the last quarter of the 20th century, the underlying mechanisms, including the causative *ABCD1* gene mutations, of the disease were described.[1–4] Recently, newborn screening (NBS) for X-ALD has been implemented in New York State and asymptomatic patients, at risk for developing neurologic and endocrine dysfunction, are being identified.[5] Much of the attention for X-ALD has focused on the devastating neurodegenerative manifestations associated with the condition, including cerebral ALD and adrenomyeloneuropathy (AMN).

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The purpose of this review is to summarize the endocrine considerations with a particular focus on screening for and treatment of adrenal insufficiency.

PATHOPHYSIOLOGY

X-ALD is caused by mutations in the *ABCD1* gene located at Xq28. There are more than 1000 mutations described in the *ABCD1* gene database (http://www.x-ald.nl) with no obvious genotype-phenotype correlation, even within families and monozygotic twins.[6,7] The inheritance pattern has been classically described as X-linked recessive, although female carriers can become symptomatic, typically in the fifth and sixth decades of life. The product of *ABCD1*, ALD protein (ALDP), is an ATP-binding cassette protein transporter, which is thought to be responsible for the transport of very-long-chain fatty acids (VLCFA) across the peroxisome membrane.[8–10] The result of the inability of VLCFA to cross the peroxisome membrane is an excess of hexacosanoic (C26:0) and lignoceric (C24:0) acids, the VLCFA, on biochemical profile. The mechanisms by which the VLCFA lead to cerebral ALD and AMN are debated and are likely due to a combination of disruption of cell membranes as well as an induction of oxidative stress and apoptosis.[11,12] However, the accumulation of VLCFA in the adrenocortical cells and Leydig cells seem to directly affect adrenal and testicular function, respectively. In the adrenal cortex, there tends to be a preferential accumulation of VLCFA in the zona reticularis and zona fasciculata, with a relative sparing of the zona glomerulosa.[13,14] As a result, the adrenal manifestations of X-ALD tend to be more primary cortisol insufficiency as well as androgen deficiency (cortisol is primarily produced in the zona fasciculate and androgens are primarily produced in the zona reticularis). The VLCFAs may also be incorporated into the lipid cell membranes and interfere with adrenocorticotropic hormone (ACTH) and gonadotropins binding to their receptors.[15] It has also been suggested that the high levels of VLCFA lead to a relative shortage of precursor cholesterol for steroidogenesis of cortisol and androgens.[16]

EPIDEMIOLOGY OF X-LINKED ADRENOLEUKODYSTROPHY AND ADRENAL INSUFFICIENCY

X-ALD has been reported in all ethnic backgrounds. There is considerable phenotypic variability with males more significantly affected than female carriers (**Table 1**). The incidence of X-ALD has been reported to be 1:21,000 in males and 1:14,000 in females.[21] Published epidemiology reports suggest a relative disproportion of female carriers to males diagnosed with X-ALD. This disproportion may be a reflection of morbidity related to adrenal insufficiency in males before diagnosis of X-ALD. It is notable that before the advent of NBS for congenital adrenal hyperplasia (CAH), there seemed to be a relatively higher incidence of severe CAH in females, which reflected mortality before CAH diagnosis in affected males. With initiation of NBS, the incidence of CAH was reported to be equal between sexes, consistent with the autosomal recessive pattern of inheritance.[22] The de novo mutation rates for X-ALD are reported to be between 4.1% and 19.0% (Of note, 15% to 20% of female carriers will have normal plasma VLCFA testing, which may account for some of the higher reported de novo mutation rates in studies that did not sequence for *ABCD1* mutations).[23]

Primary adrenal insufficiency is reported to develop in up to 86% of males with X-ALD.[24] Adrenal insufficiency is much rarer in females, occurring in fewer than 1% of carriers.[18,20] A study of 71 female heterozygotes found only one patient to have overt adrenal insufficiency, which had been diagnosed at 9 years of age; the other 70 patients had normal cortisol response to cosyntropin.[25] Testicular dysfunction has not been extensively reported in X-ALD; but in case series more