

Adult Inherited Metabolic Disease: X-ALD presenting as Idiopathic Addison's Disease

Case History

A 35 year old Caucasian male presented to A&E following a 3 week history of constant nausea, vomiting and tiredness. On examination he was noted to be overweight and so severely pigmented that the doctor examining him initially presumed the man to be of Asian descent. The patient had simply assumed his dark skin was a reflection of the amount of time he spent outdoors. There was no significant past medical history. The patient was single and lived at home with his parents.

Preliminary Laboratory Investigations

The biochemistry on admission indicated the patient was dehydrated with hyponatraemia and hyperkalaemia.

Na = 124 mmol/L

K = 5.9 mmol/L

Urea = 26.4 mmol/L

Creatinine = 271 μ mol/L

A short synacthen test was demonstrated a complete failure to respond, leading to a provisional diagnosis of Addison's disease. The patient was started on hydrocortisone and fludrocortisone which produced a rapid clinical improvement and over the next 3 days his renal function improved and his electrolytes normalised.

Cortisol results

T= 0 min 138 nmol/L

T=30 min 137 nmol/L

T=60 min 139 nmol/L

Differential Diagnosis

Adrenal failure can be classified as primary or secondary.

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| Primary adrenal failure | - autoimmune |
| | - malignancy |
| | - infiltration (haemochromatosis, amyloid) |
| | - infection (AIDS, TB, CMV) |
| | - haemorrhage |
| | - X-linked ALD |
| | - X-linked adrenal hypoplasia |
| | - CAH (21 hydroxylase deficiency) |
| | - iatrogenic (drugs, adrenalectomy) |

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| Secondary adrenal failure | - iatrogenic (exogenous glucocorticoids) |
| | - pituitary or hypothalamic disease |

NB. The most common cause of adrenal failure is suppression of the HPA axis by exogenous glucocorticoids.

Recommended Further Investigations

ACTH - probably the next single most important investigation as it helps differentiate between primary and secondary adrenal failure

Other endocrine investigations to investigate the integrity of the HPA axis

Adrenal autoantibodies to investigate autoimmune destruction of the adrenal glands

VLCFA analysis - the possibility of X-Adrenoleukodystrophy should be considered in any case of unexplained primary adrenal failure, particularly if the patient is a young male.

Other investigations – imaging of the adrenals, Brain MRI scan

Results of Further Testing

ACTH = 168 ng/mL

The ACTH is appropriately increased given the low cortisol concentration indicating the presence of primary adrenal disease

TSH = 7.6 mU/L fT4 = 25 pmol/L

LH = 3.8 U/L FSH = 10 U/L

The above results confirm pituitary disease is not present.

Adrenal auto antibodies were negative excluding autoimmune adrenalitis as the cause of adrenal failure.

Testosterone = 6.9 pmol/L

Testosterone was also requested and was found to be below the reference range. Presumably this is a reflection of the fact that adrenal insufficiency results in low concentrations of DHEA, the main precursor of sex steroid synthesis. It is also postulated that accumulation of VLCFA within the outer cell membranes of the adrenocortical cells hinders their capacity to respond to ACTH.

VLCFA analysis.

Plasma VLCFA analysis showed a strongly raised C26:0 with both the C26:0/C22:0 and C24:0/C22:0 ratios raised, consistent with a diagnosis of X-linked adrenomyeloneuropathy.

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| C22 = 65.4 μ mol/L | (31 - 98) |
| C24 = 86.4 μ mol/L | (24 - 66) |
| C26 = 4.52 μ mol/L | (0.15 - 0.91) |
| C24:C22 = 1.32 | (< 0.96) |
| C26:C22 = 0.069 | (< 0.022) |
| Phytanate = 1.1 μ mol/L | (< 15) |
| Pristanate = 1.40 μ mol/L | (< 2) |

Overview of Disease

X linked adrenoleukodystrophy is a peroxisomal disorder with a reported incidence of about 1 in 20,000 males. As the age of onset can vary significantly and because there is such a variety of symptoms, ALD can be divided clinically into 3 separate groups; cerebral ALD, adrenomyeloneuropathy and isolated cases of Addison's disease.

Cerebral ALD

Patients are usually normal at birth and have initially normal development. The early signs of disease tend to present around 7yrs age with behavioural problems (i.e. inattention, hyperactivity, problems at school). As the disease progresses hearing and visual problems can develop and motor coordination is impaired. Once the neurological manifestations appear, progression of the disease is usually rapid, resulting in death or a vegetative state within 1 to 2 years. _

Adrenomyeloneuropathy

The adult onset form of the disease presents in later life with symptoms usually becoming apparent in the twenties. Presenting symptoms include impotence, nausea, adrenal insufficiency and peripheral neuropathy. The pattern of disease is variable – the majority of patients are still able to walk in 10 to 15 years post diagnosis, whereas others deteriorate more rapidly and may develop demyelinating lesions although usually the inflammatory response of white matter is either absent or mild.

Female Carriers

Heterozygote women may also be affected clinically. They tend to present in adulthood with less severe symptoms; adrenal deficiency and demyelination are not usually present although about a fifth of women will develop neurological signs of disease.

Isolated Addison's Disease

Although 50% ALD cases have associated adrenal insufficiency, in 10% cases this is the only clinical sign. A recent study in the south west of England found that between 1987 and 2004, 12 male children had been diagnosed with idiopathic Addison's disease. Ten of the children were subsequently found to have X-ALD and of these, five had initially presented with isolated Addison's disease. ALD must always be considered as the underlying disorder in cases of Idiopathic Addison's disease, especially in young males.

A diagnosis of ALD should **always** be considered in the following situations:

- Any boy with progressive neurological disturbance, vision loss, lack of coordination,
- Young or middle-aged men with progressive gait disorders, leg stiffness or weakness, abnormalities of sphincter control and sexual dysfunction, with or without adrenal insufficiency or cognitive or behavioural deficits
- All males with primary adrenal insufficiency, with or without evidence of neurological abnormality
- Middle-aged or older women with progressive spastic paraparesis, abnormalities of sphincter control, and sensory disturbances mainly affecting the legs.

Further Testing

Mutation analysis of the ABCD1 gene is available for confirmation of diagnosis, carrier identification and pre-natal testing (pregnant female carriers).

Treatment & Monitoring

The adrenal failure can be treated with hydrocortisone and fludrocortisone however, at present there is no available cure for ALD.

Evidence indicates potential benefits may be achieved if patients with pre symptomatic disease are treated with *Lorenzo's oil and essential fatty acid supplements in combination with a restricted fat diet. Such patients should be closely monitored and at the first sign of neurological deterioration a BMT can be offered. However, due to the variable presentation of the disease BMTs cannot be offered to all asymptomatic patients.

Recent reports now indicate that statins and sodium phenylacetate may also be beneficial but these are as yet unvalidated.

* Lorenzo's Oil is a mixture of 4:1 glyceryl trioleate:glyceryl trierucate. Whilst it has been shown to normalise plasma VLCFA concentrations there is a lack of evidence with regard to its clinical benefit as plasma VLCFA concentrations do not correlate with the degree of neurological disability.

Genetics

ALD is a peroxisomal disorder which is inherited in an X-linked fashion.

Carrier identification. Testing of at-risk female relatives for carrier status is a two-step process. Plasma VLCFA concentrations are normal in 15% of female carriers so molecular genetic testing of the disease-causing *ABCD1* mutation is an important tool.

Pre natal diagnosis. Prenatal testing is possible for pregnancies of women who are carriers in whom the risk of having an affected male is 25% (or 50% if the fetus is known to be male). The usual procedure is to determine sex by karyotyping fetal cells obtained by chorionic villus sampling (CVS) at about 10-12 weeks' gestation (gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements) or by amniocentesis at 16-18 weeks' gestation. If the karyotype is 46,XY (male) and if the disease-causing mutation has been identified in a family member, DNA from fetal cells can be analyzed for the known disease-causing mutation. If mutation analysis is not possible, very long chain fatty acids (VLCFA) can be measured in cultured amniocytes or cultured chorionic villus cells. False negative test results with this latter approach have been reported, but may have been related to technical factors.

Summary

ALD should always be considered as a cause of Idiopathic Addison's disease
Diagnosis is important as family screening and genetic counselling are available

References

The peroxisome web site - <http://www.peroxisome.org/>

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Patient Confidentiality

Permission has been obtained from a clinician responsible for the patient's care.