The importance of testing for adrenoleucodystrophy in males with idiopathic Addison’s disease

M D Ronghe, J Barton, P E Jardine, E C Crowne, M H Webster, M Armitage, J T Allen, C G Steward

ORIGINAL ARTICLE

See end of article for authors’ affiliations

Correspondence to:
Dr C G Steward, BMT Unit, Bristol Royal Hospital for Children, Upper Maudlin Street, Bristol BS2 8BJ, UK; colin.steward@bristol.ac.uk

Accepted
30 November 2001

X linked adrenoleucodystrophy (X-ALD) is considered to be a rare cause of Addison’s disease, although several small series suggest a high incidence in young Addisonian males. A survey in the south west of England identified 12 male patients diagnosed with Addison’s disease in the period 1987–99. In 10 of these (83%) X-ALD was the underlying cause; the other two were of autoimmune aetiology. Five boys had developed Addison’s disease subsequent to the diagnosis of X-ALD. Of the remaining five, in three boys the diagnosis of X-ALD was considerably delayed (by six months to two years from that of Addison’s disease) and in two it was only made as a result of this survey. We also identified a patient who presented with Addison’s disease at the age of 5 years but was only diagnosed as having X-ALD at the age of 34 years; in the interim his diagnosis of adrenomyeloneuropathy had been missed. Our experience highlights the absolute necessity of measuring very long chain fatty acids in all males with idiopathic Addison’s disease.

METHODS

This study was prompted by a child who had presented with Addisonian crisis in response to pneumonia but whose underlying diagnosis of cerebral ALD was only made two years later when he developed behavioural problems and school failure (patient A in table 2). We subsequently performed a search of the diagnostic index at the Royal Hospital for Sick Children, Bristol and sent a questionnaire to paediatricians and endocrinologists throughout the south west of England asking for notification of previous cases of Addison’s disease in boys aged less than 16 years. Children with established aetiology (such as multiple endocrine deficiencies caused by autoimmune disease or autoimmune polyendocrinopathy candidiasis ectodermal dysplasia) were excluded.

The diagnosis of primary adrenal failure was made on the basis of raised basal adrenocorticotrophic hormone (ACTH) concentrations, together with a subnormal cortisol response to an standard Synacthen test. A standard dose of 250 µg of synthetic ACTH was administered and a peak cortisol value of less than 300 nmol/l indicated adrenal insufficiency.

Laboratory investigations

Serum cortisol concentrations were estimated using quantitative sequential immunometric assay on the Immulite 2000 analyser. Serum ACTH concentrations were measured on the Nichols Advantage by a two site chemiluminescence immunoassay, utilising one mouse monoclonal antibody and a goat polyclonal antibody. Plasma renin activity was measured using radioimmunoassay following generation of angiotensin I formed after incubation of plasma at 37°C for three hours in the presence of angiotensin converting enzyme inhibitor.

Plasma concentrations of VLCFA were measured by capillary gas chromatography–mass spectrometry in the regional laboratory. The reference range for C26 was 0.33–1.39 µmol/l; ranges for coefficients C26/C22 and C24/C22 were 0–0.03 and 0.32–0.90 respectively.

RESULTS

In addition to the index patient, our enquiry revealed 11 other boys with Addison’s disease and a 34 year old man who had

Abbreviations: ACTH, adrenocorticotrophic hormone; ALD, adrenoleucodystrophy; AMN, adrenomyeloneuropathy; C-ALD, cerebral ALD; VLCFA, very long chain fatty acid; X-ALD, X linked ALD.
Table 1  Phenotypes seen in male X-ALD patients

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Age of onset</th>
<th>Estimated relative frequency</th>
</tr>
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<tbody>
<tr>
<td>Childhood cerebral</td>
<td>3–10 years</td>
<td>31–35%</td>
</tr>
<tr>
<td>Adolescent</td>
<td>11–21 years</td>
<td>4–7%</td>
</tr>
<tr>
<td>Adrenomyeloneuropathy</td>
<td>19–37 years</td>
<td>40–46%</td>
</tr>
<tr>
<td>Adult cerebral</td>
<td>Adulthood</td>
<td>2–5%</td>
</tr>
<tr>
<td>Olivopontocerebellar</td>
<td>Adolescence or adulthood</td>
<td>1–2%</td>
</tr>
<tr>
<td>Addison’s only</td>
<td>Common before 7.5 years</td>
<td>Varies with age; up to 50% in childhood</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Biochemical abnormality only</td>
<td>Diminishes with age; Common &lt;4 years; Very rare &gt;40 years</td>
</tr>
</tbody>
</table>

Adapted from Moser et al.1

Table 2 gives clinical and biochemical data on the six patients with X-ALD (including the index case) presenting with Addison’s disease; table 3 presents the remaining five patients with X-ALD who went on to develop Addison’s disease later in their disease course.

In addition to a subnormal response to a standard Synacthen test, ACTH concentrations were raised in each boy studied (see tables 2 and 3), indicating primary adrenocortical insufficiency. The reference range of ACTH used was 5–36 ng/l. In addition, renin activity was measured; the reference range used was 0.5–3.1 pmol/ml/h.

Of the 10 patients identified by the survey, five had Addison’s disease as their initial presentation, but in only one case was a prompt diagnosis of biochemical ALD made because of physician awareness (patient B). Of the remaining four boys, two were diagnosed only as a consequence of this study, another because his mother requested a test on the basis of a previous family history (when her son became Addisonian at 9 years of age), and the fourth 29 years after his initial presentation with Addison’s disease. This last patient had undergone bladder neck excision for presumed outflow tract obstruction, but his underlying diagnosis of AMN was only appreciated when he developed paresthesiae and gait problems during convalescence from surgery.

The remaining five had developed Addison’s disease after a primary diagnosis of X-ALD. Two of these five developed Addison’s disease subsequent to an initial diagnosis of severe C-ALD (one had a previous family history of C-ALD in a cousin and could have been screened three years previously, although this had not been offered). The remaining three had a diagnosis of biochemical ALD (raised VLCFA but no other indicator of disease); these patients had all been diagnosed because of a preceding family history of ALD/AMN. In these five patients, the interval between the diagnosis of biochemical ALD or C-ALD and the onset of adrenocortical insufficiency ranged from six months to five years (see table 3).

DISCUSSION

X-ALD is described as a “rare” cause of Addison’s disease in the current editions of the Oxford textbook of medicine and Harrison’s principles of internal medicine, and an “uncommon association” in Forfar and Arnell’s textbook of paediatrics.1,2 This is largely a consequence of the majority of cases being females in autoimmune disease or patients with tuberculosis. However, in the small subset of patients who are young and male, we believe these statements to be dangerously misleading and likely to result in recurrent late diagnosis of X-ALD. This compromises the management of both patients and their extended families. In this series, delay from the diagnosis of Addison’s disease to that of X-ALD ranged from 6 months to 29 years in four of the 11 affected males.

Assay of VLCFA in plasma is the most frequently used test for diagnosis of X-ALD and is accurate in almost all cases. No false negative results were documented in the largest series which included samples from more than 30 000 individuals analysed at the Kennedy Krieger Institute.3 However, two false negative plasma VLCFA assays have been reported.4 It is unlikely that both these cases the diagnosis of X-ALD was subsequently confirmed by assays of VLCFA concentrations in cultured skin fibroblasts. Hence in patients with a high index of suspicion but normal or borderline plasma VLCFA concentrations should also be measured in the cultured skin fibroblasts before excluding the diagnosis of X-ALD, and a close interaction between clinicians and the laboratory is of utmost importance.

The current study does not purport to be free of ascertaining bias, perhaps the best example being inclusion of an adult patient originally diagnosed with Addison’s disease in 1968. However, as a result of the comprehensive tertiary referral service maintained in South West England it is most unlikely that any boys presenting with Addison’s disease in the past decade would have been missed. The finding that 11 of 13 paediatric presentations of Addison’s disease were caused by underlying X-ALD is also consistent with the only previous paediatric series, where 5/8 boys with Addison’s disease had X-ALD.4

Although accurate diagnosis of X-ALD does not affect the management of endocrine problems in the index case, it opens the possibility of therapy before the onset of overt neurological disease. Neurological manifestations of X-ALD range from devastating leukoencephalopathy (fig 1 shows a magnetic resonance imaging (MRI) scan in the index case) within the first decade to spastic paraparesis or psychiatric presentations in later adult life; all may occur within the same family. It is thought that neurological disease will develop in up to 90% of patients with the biochemical defect of X-ALD. In the current series, although the median follow up is only 9 years, only four of the 11 males remain completely free of radiological or clinical signs of this disease. It must be remembered that the delay from onset of adrenal insufficiency to the development of neurological disability is highly variable and may be as long as 32 years.5 This is exemplified by patient F in whom Addison’s disease was diagnosed almost 30 years before developing neurological symptoms.

Current therapeutic choices lie between dietary therapy (including Lorenzo’s Oil) for those with presymptomatic disease and bone marrow transplantation for those with early neuropsychological deterioration caused by incipient C-ALD.6,7 Benefit from the latter appears to rely on slow replacement of CNS microglial cells with cells of donor origin, since these arise from the bone marrow. As the childhood cerebral form of this disease usually progresses rapidly over 6–18 months, it is imperative to identify patients at a presymptomatic stage. Careful monitoring can then be conducted,
<table>
<thead>
<tr>
<th>Patient (age)*</th>
<th>Significant past history</th>
<th>Clinical and biochemical features</th>
<th>Peak cortisol (nmol/l)</th>
<th>ACTH (ng/l)</th>
<th>Renin (pmol/ml/h)</th>
<th>Age at diagnosis of ALD</th>
<th>What prompted diagnosis of ALD</th>
<th>Diagnostic delay</th>
<th>VLCFA (C26, µmol/l)</th>
<th>Subsequent clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (5 y)</td>
<td>Unremarkable</td>
<td>Pneumonia, Na 122, K 4.0, glucose 2</td>
<td>310</td>
<td>2068</td>
<td>6.3</td>
<td>7 y</td>
<td>Neurological deterioration, behavioural problems, school failure, decreased vision</td>
<td>2 y</td>
<td>2.88</td>
<td>Rapid neurological deterioration, severely handicapped, requires gastrostomy feeds</td>
</tr>
<tr>
<td>B (3.7 y)</td>
<td>Unremarkable</td>
<td>Abdominal pain, vomiting, convulsion, hyperpigmentation, Na 124, K 4.4, glucose 4.5</td>
<td>84</td>
<td>384</td>
<td>5.8</td>
<td>3.8 y</td>
<td>Physician awareness of ALD</td>
<td>1 mth</td>
<td>4.30</td>
<td>MRI and neuropsychology normal at 14 y of age</td>
</tr>
<tr>
<td>C (9 y)</td>
<td>Unremarkable</td>
<td>Severe vomiting and diarrhoea with dehydration, Na 120, K 4.4, glucose 3.6</td>
<td>201</td>
<td>246</td>
<td>4.6</td>
<td>9 y</td>
<td>Maternal request (due to disease in maternal uncle who developed Addison’s disease at 11 y, AMN at 39 y, died at 42 y)</td>
<td>1 mth</td>
<td>3.64</td>
<td>MRI and neuropsychology normal at 12 y of age</td>
</tr>
<tr>
<td>D (5 y)</td>
<td>Prolonged afebrile seizure at 2.5 y, FTT, developmental delay since 3.5 y</td>
<td>Severe vomiting and listlessness, Na 120, K 4.9, glucose 1.5</td>
<td>294</td>
<td>299</td>
<td>8.6</td>
<td>5.5 y</td>
<td>Author’s survey</td>
<td>6 mth</td>
<td>2.97</td>
<td>Rapid neurological deterioration, died aged 6 y</td>
</tr>
<tr>
<td>E (3 y)</td>
<td>Numerous minor infections, FTT since 8 months old</td>
<td>Vomiting and decreased consciousness, hyperpigmentation, Na 120, K 4.9, glucose 2</td>
<td>113</td>
<td>150</td>
<td>3.2</td>
<td>4 y</td>
<td>Author’s survey</td>
<td>1 y</td>
<td>3.87</td>
<td>MRI changes at 8.5 y, neuropsychological performance stable</td>
</tr>
<tr>
<td>F (5 y)</td>
<td>Unremarkable</td>
<td>Severe vomiting, abdominal pain, collapse with decreased BP, hyperpigmentation</td>
<td>Low baseline cortisol</td>
<td>No results available (diagnosis 34 y before)</td>
<td>Not done</td>
<td>34 y</td>
<td>Urinary voiding problems at 34 y, bladder neck excision for presumed outflow obstruction, paraesthesia and gait problems</td>
<td>29 y</td>
<td>3.05</td>
<td>Continues to have gait problems, poor coordination, paraesthesia and neurogenic bladder</td>
</tr>
</tbody>
</table>

*Age at diagnosis of Addison’s disease.

FTT, failure to thrive.

Reference ranges: ACTH, 5–36 ng/l; renin, 0.5–3.1 pmol/ml/h; C26, 0.33–1.39 µmol/l.
allowing patients who are developing cerebral ALD to be referred for bone marrow transplantation before overt neurological involvement. More recently lovastatin and sodium phenylacetate have been shown to lower VLCFA in cultured skin fibroblasts, although their therapeutic potential remains unclear.

Of equal importance to these therapeutic considerations are the implications for the patient’s extended family. The identification of X-ALD in a family allows screening of other male relatives who may be at risk for developing Addison’s disease or neurological complications. In addition to providing the option of early treatment, this may avoid deaths in affected males—at least 10 patients are known to have died of Addisonian crisis secondary to X-ALD, some of whom were free of neurological disease.

Similarly, carrier females may develop milder neurological problems such as spastic paraparesis (although curiously Addison’s disease is extremely rare in carriers).

Most importantly, early diagnosis brings the possibility of genetic counseling, carrier detection, and antenatal diagnosis, for example, by means of amniocentesis. It is of paramount importance to ensure that families of affected children have appropriate counseling. We gratefully acknowledge the support of the COGENT Trust; Drs Julian Pleydell-Pearce and Sunil Pullaperuma, who kindly provided patient details; and Drs Charles Pennock and Janet Stone for many helpful biochemical discussions.

### Table 3

<table>
<thead>
<tr>
<th>Patient (age)**</th>
<th>Significant past history</th>
<th>Clinical features at diagnosis of ALD</th>
<th>VLCFA (C26, µmol/l)</th>
<th>Subsequent clinical course</th>
<th>Age at diagnosis of Addison’s disease</th>
<th>Peak cortisol (nmol/l)</th>
<th>ACTH (ng/l)</th>
<th>Renin (pmol/ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G (14 y)</td>
<td>Unremarkable</td>
<td>School failure with poor handwriting and drawing, hyperactive, neurological deterioration, coordination problems, and memory loss</td>
<td>2.86</td>
<td>Developed Addison’s disease 6 mth later, rapid neurological deterioration, died aged 17 y</td>
<td>14.6</td>
<td>269</td>
<td>184</td>
<td>12</td>
</tr>
<tr>
<td>H (1.6 y)</td>
<td>Unremarkable</td>
<td>Family history of ALD in sibling</td>
<td>1.71</td>
<td>Developed Addison’s disease 6 mth later, MRI and neuropsychology normal at 10 y of age</td>
<td>2 y</td>
<td>230</td>
<td>108</td>
<td>3.8</td>
</tr>
<tr>
<td>I (15 y)</td>
<td>Unremarkable</td>
<td>School failure, impaired vision, behavioural problems</td>
<td>3.50</td>
<td>Slowly progressive form of CAID, manages self care, on carbamazepine for generalised epilepsy; developed Addison’s disease 3 y later</td>
<td>18 y</td>
<td>490</td>
<td>227</td>
<td>1.8</td>
</tr>
<tr>
<td>J (5.5 y)</td>
<td>Unremarkable</td>
<td>Family history of X-AMN in maternal uncles</td>
<td>3.41</td>
<td>Developed Addison’s disease 5 y later; progressive neurological deterioration with ataxia, visual problems, memory loss, severely handicapped aged 16 y</td>
<td>10.5 y</td>
<td>447</td>
<td>147</td>
<td>2.1</td>
</tr>
<tr>
<td>K (3 y)</td>
<td>Unremarkable</td>
<td>Accidental skull fracture at 6 mth, has residual left sided hemiplegia</td>
<td>2.86</td>
<td>Diffuse MRI changes consistent with previous head injury, neuropsychological performance stable at 12 y; developed Addison’s disease 3 y later</td>
<td>6 y</td>
<td>386</td>
<td>163</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Age at diagnosis of ALD.
ECHO.................................................................................................................

Obesity and asthma are linked . . . really

To avoid developing asthma fat children should lose weight. A large cross sectional study of children in the United States confirms that obesity increases the likelihood of asthma, but not atopy, as an independent risk factor. Previous studies linking body mass index (BMI) and respiratory symptoms including asthma have been called into question by the recent finding that breastfeeding, which protects against asthma and atopy, is strongly inversely related to BMI in children starting school and is therefore a potential confounder.

Von Mutius et al sought to determine whether the apparent association between BMI and asthma is a true one by analysing data on more than 7000 children from the National Health and Nutrition Examination Study (NHANES) III and data collected for a comprehensive range of variables. Among these were prevalence of asthma and atopy and a whole array of known or potential confounders including birth weight (children aged <12 years) and breastfeeding (children aged <6 years).

Prevalence of asthma and atopy increased significantly across the quartiles of BMI. The relation held true for asthma after adjustment for potential confounders—age, sex, ethnicity, household size, and passive exposure to smoke—and after further controlling for breastfeeding and birth weight. No independent relation was seen between BMI and atopy. As cause and effect cannot be determined by a cross sectional study, the authors point to evidence from studies over time in nurses and children in support of their conclusion—that obesity predisposes to asthma.

References