

## ORIGINAL ARTICLE

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

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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.

The term X linked adrenoleucodystrophy (X-ALD) denotes a group of diseases caused by defects in the ALD gene at Xq28, which encodes a peroxisomal ATP binding cassette transporter protein.<sup>1</sup> Gene defects result in an extremely variable phenotype (see table 1), including a presymptomatic form, isolated adrenal insufficiency, devastating childhood cerebral ALD (C-ALD), adult C-ALD, and adrenomyeloneuropathy (AMN)—a disease causing spastic paraparesis and peripheral neuropathy in the second decade or beyond and leading to progressive impairment and early death. Despite this array of subtypes and identification of at least 200 different mutations, there appears to be no phenotype/genotype correlation.<sup>1</sup>

The tissues and body fluids of patients with X-ALD contain abnormally high concentrations of unbranched saturated very long chain fatty acids (VLCFA), particularly hexacosanoic acid (C26:0) and tetracosanoic acid (C24:0). This excess is most striking in the cholesterol ester and ganglioside fractions of affected brain white matter and adrenal cortex, but is present to varying degrees in virtually all tissues and body fluids.<sup>1</sup> Diagnosis is made on the basis of raised concentrations of VLCFA in plasma and/or cultured skin fibroblasts.<sup>1–3</sup>

Adrenocortical insufficiency is present in at least 50% of patients with C-ALD/AMN, but may be the only clinical manifestation of X-ALD in up to 10% of cases. As a consequence of the rarity of X-ALD (minimum incidence of approximately 1 in 20 000 white males<sup>1</sup>), this disease only accounts for a small proportion of all cases of adrenal insufficiency. However, it has recently been recognised in high frequency in young males with idiopathic Addison's disease; representative series report 5/8 boys,<sup>4</sup> and 2/2,<sup>5</sup> 4/12,<sup>6</sup> 5/14,<sup>7</sup> and 5/24<sup>8</sup> adolescent or adult males to be affected.

In order to both emphasise and extend these observations we report our findings in the only 12 boys in whom Addison's disease has been diagnosed in the south west of England since 1987. Ten of these boys were affected by X-ALD.

## 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 dystrophy) 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 a standard Synacthen test. A standard dose of 250 µg of synthetic ACTH was administered and a peak cortisol value of less than 500 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

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

Adapted from Moser *et al.*<sup>1</sup>

presented to paediatric care with Addison's disease at the age of 5 years. Of these 12 patients, none had idiopathic disease; two had autoimmune disease proven by positive adrenal autoantibodies, and the remaining 10 all had elevation of VLCFA, diagnostic of underlying X-ALD.

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 Arneil's textbook of paediatrics*.<sup>9–11</sup> This is largely a consequence of the majority of cases being females with 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.<sup>1</sup> However, two false negative plasma VLCFA assays have been reported.<sup>2,3</sup> In 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 ascertainment 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.<sup>4</sup>

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 leucoencephalopathy (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 5 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.<sup>12</sup> 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.<sup>12–15</sup> 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 2** Summary of clinical and laboratory data in patients with X-ALD presenting with Addison's disease

Patient (age)*	Significant past history	Clinical and biochemical features	Peak cortisol (nmol/l)	ACTH (ng/l)	Renin (pmol/ml/h)	Age at diagnosis of ALD	What prompted diagnosis of ALD	Diagnostic delay	VLCFA (C26, $\mu\text{mol/l}$ )	Subsequent clinical course
A (5 y)	Unremarkable	Pneumonia, Na 122, K 4.0, glucose 2	310	2068	6.3	7 y	Neurological deterioration, behavioural problems, school failure, decreased vision	2 y	2.88	Rapid neurological deterioration, severely handicapped, requires gastrostomy feeds
B (3.7 y)	Unremarkable	Abdominal pain, vomiting, convulsion, hyperpigmentation, Na 124, K 4.6, glucose 4.5	84	384	5.8	3.8 y	Physician awareness of ALD	1 mth	4.30	MRI and neuropsychology normal at 14 y of age
C (9 y)	Unremarkable	Severe vomiting and diarrhoea with dehydration, Na 120, K 4.4, glucose 3.6	201	246	4.6	9 y	Maternal request (due to disease in maternal uncle who developed Addison's disease at 11 y, AMN at 39 y, died at 42 y)	1 mth	3.64	MRI and neuropsychology normal at 12 y of age
D (5 y)	Prolonged afebrile seizure at 2.5 y, FTT, developmental delay since 3.5 y	Severe vomiting and listlessness, Na 120, K 4.9, glucose 1.5	294	299	8.6	5.5 y	Author's survey	6 mth	2.97	Rapid neurological deterioration, died aged 6 y
E (3 y)	Numerous minor infections, FTT since 8 months old	Vomiting and decreased consciousness, hyperpigmentation, Na 120, K 4.9, glucose 2	113	150	3.2	4 y	Author's survey	1 y	3.87	MRI changes at 8.5 y, neuropsychological performance stable
F (5 y)	Unremarkable	Severe vomiting, abdominal pain, collapse with decreased BP, hyperpigmentation	Low baseline cortisol	No results available (diagnosis 34 y before)	Not done	34 y	Urinary voiding problems at 34 y, bladder neck excision for presumed outflow obstruction, parasthaesia and gait problems	29 y	3.05	Continues to have gait problems, poor coordination, parasthaesia and neurogenic bladder

\*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  $\mu\text{mol/l}$ .

**Table 3** Summary of clinical and laboratory data in patients who developed Addison's disease after initial diagnosis of X-ALD

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

\* Age at diagnosis of ALD.

**Figure 1** MRI scan of brain, showing diffuse high signal abnormalities in the periventricular white matter of both parietal and occipital lobes (marked by arrows) in an advanced case of childhood onset C-ALD.

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.<sup>16</sup>

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.<sup>1</sup> 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 counselling, carrier detection, and antenatal diagnosis, and so the potential for radically reducing the incidence of this devastating disease. For this reason above all, assessment of plasma VLCFA concentrations should be regarded as mandatory in the investigation of males with unexplained Addison's disease.

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## ECHO

### Obesity and asthma are linked . . . really



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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.

▲ *Thorax* 2001;**56**:835–838.