A 33-year-old gentleman presented in December 2002 with complaints of giddiness, vomiting, abdominal pain, loose motions and pigmentation around the umbilicus. He had confirmed hyponatremia (Na-122 mEq/l) and a subnormal synacthen test (cortisol at 30 min was 287 nmol/l) and was diagnosed with Addison’s disease and was commenced on hydrocortisone and fludrocortisone replacement. He had a stable disease throughout except for two episodes of Addisonian crisis secondary to gastroenteritis requiring intravenous steroids.

Six years later, he presented with complaints of bladder disturbance (polyuria, urgency and dysuria). He was hospitalized thrice in a very short span of time with confirmed urinary tract infections. One such episode led a complete retention of urine for which he had to be catheterized for 2 days. Digital examinations of the prostate, ultrasound of the urinary tract and flow metric studies were all normal. Investigations revealed normal glucose, potassium, calcium, plasma and urinary osmolality. The only abnormality noted then was presence of patchy alopecia and absence of hair on lower limbs and axillae. A year later, he started to develop leg symptoms in the form of weakness and progressively worsening mobility. He had difficulty in protracted standing and walking but still managed to do things for himself independently. This was not accompanied by any sensory, bowel or bladder symptoms and clinical examination of his lower limbs was quite unremarkable.

We tried to explore his recent neurological presentation by revisiting his family history, which was very interesting (Figure 1). His half brother presented at the age of 7 years initially (1978) with an inability to write followed by an unsteadiness of gait. Subsequently, he developed weakness of arms and legs, incoordination of limbs, incontinence and myoclonic jerks. His developmental milestones were normal but had clinical evidence of mental retardation, spasticity of arms and legs, facial and tongue muscle weakness with equinus deformity of his feet. He was noted to have bilateral optic atrophy on ophthalmoscopy and his brain scan showed a large fourth ventricle and low attenuation changes in the white matter. An electroencephalogram revealed gross abnormal activity of the posterior half of brain and an electromyogram revealed generalized reduction in action potential and amplitude. He was tested for enzymes of metabolic pathways, all of which were within normal limits. His autoantibodies for thyroid, parietal cell, smooth muscle, mitochondria, adrenal and pituitary were also within normal limits. Urine was negative for
metachromatic material and levels of adrenocorticotropin hormone (ACTH) were 28 ng/l at 10.00 a.m. and 14 ng/l at 12 noon (normal 10–60 ng/l). The inferences derived from these investigations was that he was suffering from a leukodystrophy and demyelinating disorder and a suspicion on Addison–Schilder disease was raised but at that time the only accessible test would have been a adrenal biopsy which was thought to be too invasive for the young boy and was not done. He died shortly at the age of 10 years with complications.

Taking a leaf out of the significant family history that this patient’s brother had, we suspected about the possibility of adrenoleukodystrophy as a potential reason for this gentleman’s Addison’s disease and his neurological presentation. This was confirmed with negative 21 hydroxylase antibodies (21OHAb) and positive VLCFAs (Table 1). The patient had significantly increased C26 with an increased C26/C22 and C24/C22 ratios strongly indicative of X-linked adrenoleukodystrophy (X-ALD). Surprisingly, his magnetic resonance imaging of brain and spine showed normal appearance with no evidence of demyelination.

**Table 1** Levels of VLCFAs

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Levels</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docosanoate (C22)</td>
<td>51 µmol/l</td>
<td>15–112 µmol/l</td>
</tr>
<tr>
<td>Tetracosanoate (C24)</td>
<td>82 µmol/l</td>
<td>14–80 µmol/l</td>
</tr>
<tr>
<td>Hexacosanoate (C26)</td>
<td>4.02 µmol/l</td>
<td>0.33–1.50 µmol/l</td>
</tr>
<tr>
<td>C24/C22</td>
<td>1.61</td>
<td>0.44–0.97</td>
</tr>
<tr>
<td>C26/C22</td>
<td>0.079</td>
<td>0.005–0.30</td>
</tr>
<tr>
<td>Phytanate</td>
<td>1.3 µmol/l</td>
<td>0.2–19.3 µmol/l</td>
</tr>
<tr>
<td>Pristanate</td>
<td>0.11 µmol/l</td>
<td>0.00–1.88 µmol/l</td>
</tr>
</tbody>
</table>

**Discussion**

ALD is progressive disorder that affects both the adrenal glands and myelin. This is an inherited disorder of peroxisomal metabolism with lack of fatty acyl coenzyme A (acyl CoA) synthetase leading to accumulation of VLCFAs, leading to progressive dysfunction of adrenals, nervous system and testes. Six different phenotypes are possible of which childhood cerebral ALD and adrenomyeloneuropathy are the commonest ones.

Addison’s disease may precede the development of neurological features of ALD by many years or decades and many have scanty scalp hair like our
patient. Many patients may tend to have significant leucoencephalopathy with spastic paraparesis or psychiatric presentations in later adult life. Other presentations include impaired vision and auditory discrimination, seizures and progressive dementia and subclinical testicular insufficiency and difficulty in urination. Very rarely patients with X-ALD may have symptoms resembling features of spinocerebellar degeneration. In 15–20% of females, the symptoms may develop in late middle age and may have milder form of weakness and stiffness of legs and urinary incontinence. The risk of developing neurological features in asymptomatic patients is high, and often chronic progressive multiple sclerosis is suspected in symptomatic carriers.

The estimation of VLCFAs forms the mainstay of diagnosis. Measurement of absolute levels of C26:0 as well as calculation of C24:0/C22:0 and C26:0/C22:0 ratios are usually done which reveal elevated values as in our patient. There is no association between absolute levels of VLCFAs and adrenal or neurological involvement. Our patient was also negative for 21 hydroxylase (21OHAb), which was also noted by Laureti et al. suggesting that 21OHAb and VLCFAs are specific markers of two distinct causes of primary adrenal insufficiency namely autoimmune adrenal insufficiency and X-ALD respectively, and hence presence of 21OHAb rules out the need for VLCFAs and adrenal imaging. Other test includes measurement of cortisol and ACTH levels, synacthen test and estimation of testosterone and gonadotropins. MRI is useful to demonstrate areas of demyelination in the different parts of the central nervous system. Brainstem evoked response potentials and conduction velocities in peripheral nerves are often abnormal. Utility of family history if very important like in our case and attempts should be made to identify heterozygous women in ALD families to whom prenatal diagnosis could be advised. Genetic counselling and DNA linkage studies also form an essential part of the investigation work up.

In summary, Adrenoleukodystrophy is an important cause of primary adrenal insufficiency. Our case highlights the importance of screening male patients for VLCFAs with adrenal insufficiency having significant family history, neurological and bladder dysfunctions and negative 21OHAb. Proper early diagnosis is essential in predisposed individuals so that appropriate genetic counselling can be provided and measures taken to delay the progression of the disease.

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