Adrenoleukodystrophy: a trap for the physician

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INTRODUCTION

Adrenoleukodystrophy (X-ALD) is an X-linked recessive disorder, primarily affecting the adrenal glands and CNS white matter. It usually manifests between the ages of 4 and 8 years – adult presentation is uncommon (3%) (Moser et al, 1991). This article describes a case of X-ALD that presenting during an outbreak of echovirus meningoencephalitis (Carrol et al, 2002), illustrating the trap when uncommon conditions can mimic the common.

DISCUSSION AND REVIEW

X-ALD is a disorder of peroxisomes transmitted as an X-linked recessive trait. It is characterized by the accumulation of saturated very long chain fatty acids (VLCFA) resulting in the progressive dysfunction of CNS white matter and the adrenal cortex (Moser, 1995, 1997; van Geel et al, 1997). It is considered to be a disorder of lipid metabolism, particularly involving the peroxisomes. These are intracellular organelles present in all cells except mature erythrocytes, especially those cells that specialize in lipid metabolism. Deficiency of lignoceroyl-CoA ligase which catalyses the formation of CoA derivatives of VLCFA results in accumulation of saturated unbranched VLCFA in the rough endoplasmic reticulum of tissues, particularly the adrenal cortex and the CNS white matter.

CASE REPORT

A 40-year-old man presented to the accident and emergency department having suffering a generalized tonic-clonic seizure. Despite intravenous diazepam and phenytoin he continued to have focal seizures. His Glasgow Coma Scale fluctuated between 6 and 11 out of 15, he was haemodynamically stable and, apart from focal seizures, systemic examination was unremarkable.

Investigations revealed a mild leucocytosis. Biochemical parameters (urea and electrolytes, liver function tests including gamma glutamyl transferase) were within normal range. A computed tomography scan of the brain showed generalized white matter changes (low attenuation) particularly in the frontal lobes. The patient was sedated, ventilated and transferred to the intensive therapy unit.

Initial history from relatives suggested that he suffered with Addison's disease and was on replacement hydrocortisone and fludrocortisone for this. His former partner claimed alcohol abuse and behavioural problems, which had worsened recently. He had suffered a head injury a few months earlier but had been discharged within 24 hours as observations had remained stable. There was no other significant past medical history.

It transpired that his alcohol intake was moderate. At the time of his admission there was an outbreak of echo 30 virus meningoencephalitis in Merseyside. His presentation with confusion, fluctuating levels of conscious and seizures led to a working diagnosis of encephalitis and aciclovir was commenced. Differential diagnoses included alcohol excess or withdrawal fits and stimulant drug overdose. A toxicology screen was negative and no alcohol was detected in the blood.

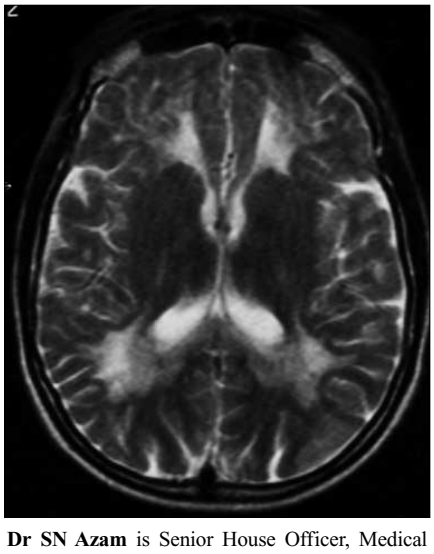
A diagnostic lumbar puncture showed clear and colourless CSF with glucose 2.8 mmol/litre (blood glucose 4.6 mmol/litre), protein 0.91 g/litre (normal 0.15–0.4 g/litre), red blood cell count $2x10^6$/litre, white blood cell count $<1x10^6$/litre, with no organisms seen on microscopy and no growth on cultures. CSF polymerase chain reaction tests for meningococcus, herpes simplex virus and enterovirus (including echovirus) were negative. Blood, urine, throat swab and sputum cultures showed no growth. Human immunodeficiency virus 1 and 2 antibodies were not detected.

Following successful extubation he was transferred to the infectious diseases unit but behavioural problems persisted. A more extensive history revealed multiple family episodes of Addison's disease, all four of his male siblings having been diagnosed, two of whom had died as young children. His sister's son also suffered from Addison's disease, suggesting a pattern of recessive X-linked inheritance. A magnetic resonance scan of the brain was performed. This revealed high intensity signal changes in the periventricular white matter, sparing the basal ganglia and most marked in the frontal and occipital areas (*Figure 1*). This appearance could be seen in inflammatory, ischaemic, neoplastic or degenerative processes, but the distribution was more suggestive of a white matter degenerative disease.

Adrenoleukodystrophy was suggested to account for hypoadrenalism, white matter changes and the suggested inheritance pattern. Further information from his family revealed that he had undergone tests for an inherited disorder 10 years earlier but there was no ongoing follow up.

An assay of very long chain fatty acids and genetic studies were requested. However, recovery of old notes confirmed that these tests had indeed been previously undertaken and that the patient was already diagnosed with X-linked adrenoleukodystrophy. Seizure free, but with some behavioural and cognitive dysfunction, he was discharged with neurological follow up arranged.

Figure 1. Magnetic resonance scan showing X-linked adrenoleukodystrophy.



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Classification

The usual age of onset is 4–8 years. The prevalence is 1:20 000 to 1:100 000 (Moser et al, 1984, 1995).

Classification has been described as arbitrary; the authors include the six main variants (van Geel et al, 1997) of which the childhood cerebral form and adrenomyeloneuropathy (AMN) account for approximately 80% of cases (Moser et al, 1991, 1995).

1. The childhood cerebral form manifests most commonly between 4 and 8 years of age. It initially resembles an attention deficit disorder, but is followed by progressive impairment of cognition and behaviour, vision, hearing, and motor function. These often lead to total disability within 2 years. The vegetative state may continue for more than 10 years. Pathologically it is characterized by rapidly progressive demyelination (Schaumberg et al, 1975).
2. AMN manifests most often in the late 20s as slowly progressive paraparesis, sphincter disturbances, and varying degrees of distal sensory loss.
3. The Addison's-only form (10%) presents with primary adrenocortical insufficiency between 2 years of age and adulthood (most commonly by 7.5 years of age) without evidence of neurological abnormality; however, some degree of neurological disability (most commonly AMN) usually develops later.
4. Adolescent cerebral ALD accounts for about 5% of cases. Usual age of onset is 10–21 years and it has similar manifestations to childhood ALD but slower progression.
5. Asymptomatic ALD is present in approximately 8% of cases and is diagnosed on family screening.
6. Adult cerebral ALD (ACALD) accounts for 3% of cases (Moser et al, 1991). A number of cases of ACALD have been reported, presenting primarily with neuropsychiatric symptoms (Angus et al, 1994; Munchau et al, 1997) but none with status epilepticus. There is a case reported of a patient who developed status epilepticus 1 year after presenting with a personality change and seizures (Angus et al, 1994).

Approximately 20% of carriers develop neurological manifestations resembling AMN, but have a later (35 years or later) and milder onset than affected males.

In this case the onset of Addison's disease with neurological symptoms was seen towards the end of the 4th decade. The behavioural problems were initially assigned to excess alcohol intake. They appeared to worsen significantly after a head injury a few months before this admission. He was admitted to another institution for observation at that time but no imaging was carried out and he was discharged home.

Head injury causing contusion may precipitate or accelerate demyelination (Wilkinson et al, 1987; Weller et al, 1992). The authors surmise that he suffered from a rare atypical form of ALD and the head injury may have provoked or precipitated his decline. The other unusual presentation is the generalized seizure on admission. As no other cause for this was found it may have been a rare symptom of his ALD.

Diagnosis

The diagnosis is suspected in patients with Addison's disease who develop signs consistent with demyelination or where there is an X-linked pattern of either Addison's disease or features consistent with demyelination.

Diagnostic tests include very high VLCFA levels in the plasma, red blood cell or cultured skin fibroblasts, being found in 100% of affected males and 85% of carrier females; high levels of C26 and an abnormal ratio of C26:C22 and C24:C22 fatty acids are also found. Hyponatraemia, hyperkalaemia, mild metabolic acidosis and low serum cortisol levels with elevated adrenocorticotrophic hormone levels are seen with adrenal insufficiency.

Computed tomography or magnetic resonance scans show white matter lesions even in the early stages. Two types may be seen: low attenuation lesions representing areas of degeneration/demyelination, and high attenuation lesions representing zones of intense perivascular lymphocytic infiltration, with concomitant breakdown of the blood–brain barrier. Genetic studies are available.

Management

Management is generally supportive and can include steroid replacement, behavioural therapy and special education, baclofen for acute muscle spasms and anticonvulsant for seizure activity, dietary modifications to decrease exogenous VLCFA, and decrease endogenous VLCFA production with the use of monounsaturated VLCFA (Lorenzo's oil) or bone marrow transplant.

CONCLUSIONS

Given the context of an outbreak of echovirus meningoencephalitis, the initial diagnosis is reasonable. However, one should remain open to other possibilities, particularly when recovery is not uneventful. Common conditions present commonly, but uncommon conditions can also mimic the commonplace. This case emphasizes the importance of a good history, clinical acumen and appropriate investigations. If an initial first diagnosis is unconfirmed or grounds for questioning it remain, it is never inappropriate to re-visit the history. HM

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