

# AN INDEX CASE OF ADRENO MYELONEUROPATHY IN A CHINESE MAN

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## ABSTRACT

*X-linked adrenomyeloneuropathy (AMN) is a phenotypic variant of adrenoleukodystrophy (ALD) presenting in early adult life with progressive ataxia and spasticity, and on occasion with adrenal insufficiency. We describe a 26-year-old Chinese man with a 2-year history of gait difficulty due to spasticity, absent pattern shift visual evoked (VER) responses and posterior white matter lesions on T2 weighted brain magnetic resonance images. His parents are clinically normal and his 24-year-old brother has hyperreflexia in the legs but normal VER latencies.*

*The patient's ACTH levels were elevated and the serum cortisol did not rise with either Synacthen or corticotropin releasing hormone. Assay of his plasma confirmed elevation of very long chain fatty acids (VLCFA) consistent with a defect in peroxisomal VLCFA metabolism. This is the first local report of a patient with AMN.*

**Keywords:** adrenomyeloneuropathy, Chinese man, very long chain fatty acids, adrenal insufficiency

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## INTRODUCTION

Adrenomyeloneuropathy (AMN)<sup>(1,2)</sup> is a phenotypic variant of adrenoleukodystrophy (ALD), often presenting in the third decade, the clinical features of which were first described by Budka et al in 1976<sup>(3)</sup>. This X-linked neurometabolic disorder's principal abnormality is in the impaired metabolism of very long chain fatty acids (VLCFA)<sup>(4,5)</sup>. We describe a patient with adrenomyeloneuropathy and review the available literature on this often unrecognised condition.

## CASE REPORT

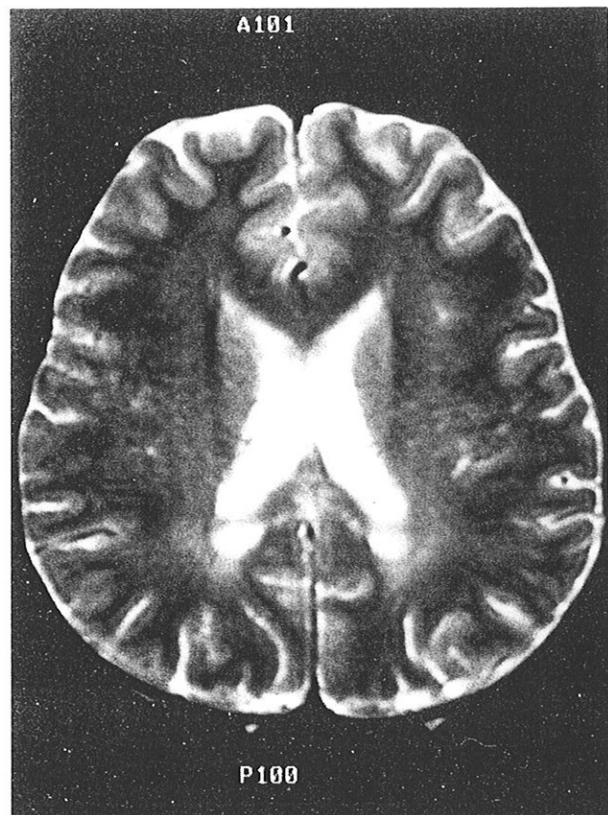
AGS, a 26-year-old Chinese man, was first seen for the complaint of progressive gait difficulty over 2 years. There was associated urinary overflow incontinence on occasion but no initial sensory complaints. His memory was normal although he had difficulty with visual tasks as he developed vertigo with protracted upgaze and downgaze.

Examination revealed a well nourished adult male with no skin hyperpigmentation and normal supine and erect blood pressure. The mini mental state examination was normal. His cranial nerves were intact, with no afferent pupillary light defect and normal fundi. The ocular pursuit and saccadic movements were normal. The patient's gait was spastic and broad-based: tandem was impossible. There was no muscle wasting and motor power was grade 5 (MRC) in both upper and lower limbs. The tone in the legs was spastic, with +++/+++ tendon reflexes in

both the arms and legs. Sustained ankle clonus was present with bilateral extensor plantar responses. Pin-prick, light touch and vibration sensation were intact as was joint position and thermal sensitivity.

MRI of the brain revealed high signal changes in the corpus callosum and periventricular white matter on T2 weighted images, which involved the occipital areas and extended to the upper brainstem (Fig 1 and 2). The pattern shift visual evoked (VER) P100 latencies were prolonged (Rt 210ms; Lt 216ms), as were the somatosensory evoked responses (Rt median N/P19 48 ms; Rt posterior tibial N/P37 70 ms). Peripheral nerve conduction velocities were slightly reduced.

Fig 1 – 1.5 Tesla T2 weighted axial MRI image of the brain showing periventricular white matter signal changes.



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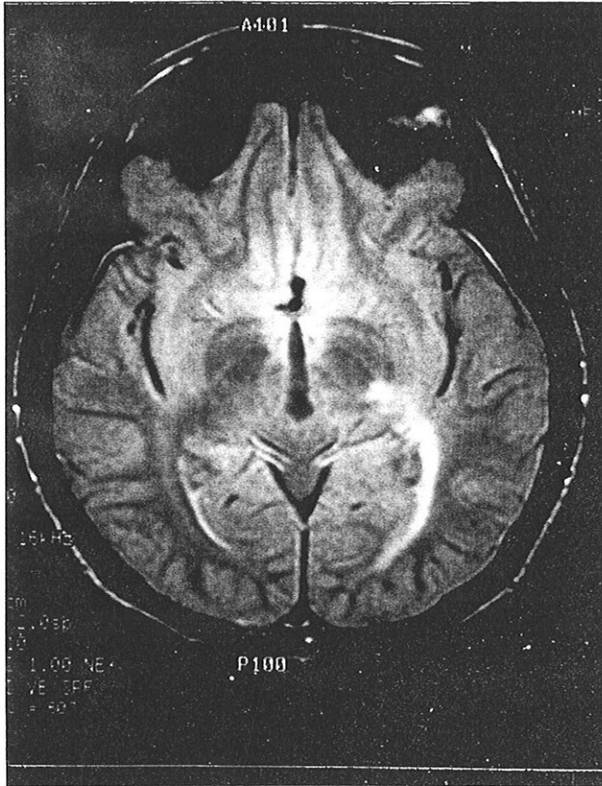
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**Fig 2 – T2 weighted axial MRI of the brain with signal abnormalities over the occipital areas**



The cerebrospinal fluid (CSF) examination was negative for oligoclonal bands. His 24 hour urinary cortisol was 218 mmol (27-221), the urinary 17-ketosteroids 14.6 umol/day (34.7-86.7) and the 17-OH corticosterone 5.9 umol/day (17.3-79.7). The random serum ACTH was 75.5 mU/L (10-50). The short synacthen test resulted in cortisol levels of 292, 309, 359 and 376 nmol/l at baseline, 30 minutes, 60 minutes and 90 minutes respectively, with corresponding 17-OH-progesterone values of 6.4, 5.1, 4.9 and 5.4 nmol/l. A corticotropin releasing hormone (CRH) stimulation test produced ACTH levels of 101, 170, 159, 132, 59.1 and 44.6 mU/l (at 0, 20, 40, 60, 80 and 100 minutes) with no elevation of cortisol. These results are consistent with primary adrenal failure.

Plasma VLCFA assay by capillary gas chromatography revealed c24:0% 1.740 (0.78 ± 0.32), c25:0% 0.080 (0.03 ± 0.03), c26:0% 0.083 (0.01 ± 0.01), c24/c22 1.999 (0.84 ± 0.08), c26/c22 0.095 (0.01 ± 0.01) and c26:0 1.201 ug/ml (0.33 ± 0.18) (The Kennedy Institute for Handicapped Children, courtesy of HW Moser). These values are consistent with a defect in peroxisomal fatty acid metabolism. Phytanic acid levels were not elevated.

The patient has a younger brother with early gait difficulty, hyperreflexia in the legs and inability to walk tandem, but both parents are asymptomatic, unrelated and clinically normal. Their plasma VLCFA estimations confirmed an asymptomatic carrier state in the mother and similar VLCFA elevations as our index case in the brother.

## DISCUSSION

Adrenoleukodystrophy is an X-linked disorder, secondary to defective  $\beta$  oxidation of VLCFA<sup>(5)</sup> principally by lignoceryl-CoA ligase with resultant accumulation of these fatty acids in the brain and adrenal cortex. This defect resides in the peroxisome and has been mapped to Xq28<sup>(6)</sup>. The commonest clinical

phenotype is ALD, presenting in boys in early childhood and progressing to a vegetative state and death over 1 to 5 years<sup>(2,5)</sup>.

AMN is the other common presentation, with a later onset often in the third decade<sup>(2)</sup>, and a slow variable progression. The neurological features are dominated by progressive spastic paraparesis, distal symmetric polyneuropathy, chronic primary Addison's disease and occasional hypogonadism. The endocrine abnormalities and elevation in VLCFA are similar to ALD. The initial presentation may, however, be with adrenal failure. Carrier females have elevated VLCFA levels and such heterozygous females may have neurological signs with demonstrable endocrine abnormalities<sup>(2,5)</sup>.

Both AMN and ALD result in typical changes on computed tomography (CT) of the brain producing hypodensities in white matter with a characteristic contrast enhancement<sup>(7)</sup>. Early in the disease, these lesions may be asymmetric. MRI is even more sensitive and symmetric periventricular white matter lesions are typically seen in the posterior parietal and occipital lobes<sup>(8,9)</sup>. Characteristic neurophysiological findings include abnormal BAER waveforms beyond wave I, absent VERs and, in AMN, slowing of peripheral nerve conduction<sup>(9)</sup>.

This condition probably occurs in all races. ALD has recently been reported in a Chinese boy<sup>(10)</sup> and AMN in 3 Chinese patients<sup>(11)</sup>. Our patient is the first confirmed local patient with AMN with a clinically affected younger brother, hence an X-linked inheritance pattern is likely.

Treatment is currently being evaluated in ALD/AMN patients and one strategy is dietary manipulation with the addition of glyceryl trioleate oil and erucic acid<sup>(12,13)</sup>. This approach can lower and normalise VLCFA levels but has not been shown to reverse the neurological features although peripheral nerve function improvement in AMN has been reported<sup>(12)</sup>. Other modalities of therapy which have been tried include bone marrow transplantation<sup>(14)</sup>, immunosuppression and plasma exchange<sup>(15)</sup>. We have prescribed a diet low in VLCFA for our patient and plan to add glyceryl trioleate and erucic acid to his intake.

## CONCLUSION

AMN is an important neurometabolic condition that can present in adult life, and should be considered in the differential diagnosis of patients with spastic paraparesis<sup>(16)</sup> and/or primary adrenal failure. Genetic counselling is necessary and plausible as techniques of carrier detection and prenatal diagnosis are available. Specific treatment of proven benefit is currently unavailable but dietary manipulation and bone marrow transplantation are under evaluation.

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