

# X-linked cerebral adrenoleukodystrophy

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## SUMMARY

A man in his 30s presented with a 6-month history of progressive left face, arm and leg weakness. Medical history included epilepsy and vitamin B<sub>12</sub> deficiency. Three maternal second degree relatives died before the age of 7 from various neurological disorders. Examination revealed a mild left facial droop and weakness of the left shoulder, hip and ankle. Reflexes were symmetrical and tone was normal. Differential diagnosis included glioma, subacute infarction, lymphoma and demyelination. MRI brain showed an extensive right sided subcortical white matter lesion, with extension into the brainstem. The patient's weakness progressed over 3 months. Brain biopsy showed evidence of demyelination and gliosis. A pathological diagnosis of tumefactive multiple sclerosis was made, but also rare metabolic disorders such as X-linked adrenoleukodystrophy (X-ALD) were proposed. Serum very long-chain fatty acids were significantly elevated. Genetic testing showed a mutation in the *ABCD1* gene, confirming a diagnosis of X-ALD.

## BACKGROUND

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder caused by defects of the ATP (adenosine triphosphate)-binding cassette subfamily D, member 1 *ABCD1* gene located in Xq28.<sup>1</sup> This gene encodes the peroxisomal membrane adrenoleukodystrophy protein that is located in the membranes of peroxisomes and is involved in the degradation of very long chain fatty acids (VLCFAs).<sup>2</sup> Peroxisomal abnormalities cause VLCFAs to accumulate in the central and peripheral nervous system in addition to the adrenal glands. This results in central nervous system demyelination, axonal neuropathy and adrenal dysfunction.<sup>3</sup>

In this case report, we present an adult male in his 30s with genetically confirmed X-ALD. X-ALD has a wide range of phenotypic variability and may present in many ways, often mimicking other more common neurological or psychiatric disorders. This clinical variability combined with a lack of knowledge of this condition may lead to an underdiagnosis or misdiagnosis of X-ALD. Early recognition is vital to avoid serious complications for patients, such as adrenal dysfunction and advanced cerebral involvement. Identification of patients at an early stage would also give the opportunity to avail of efficacious treatments such as haematopoietic stem cell transplantation (HSCT). This case report aims to increase levels of awareness of X-ALD in the evaluation of young adults with progressive neurological symptoms. We learnt from the present case that family history is essential in facilitating early diagnosis of X-ALD.

## CASE PRESENTATION

An adult male in his 30s presented to neurology outpatient clinic with a 6-month history of progressive weakness of the left face, arm and leg. His mobility was slowly deteriorating.

The patient had a history of epilepsy that began in childhood, and vitamin B<sub>12</sub> deficiency. The aetiology of his vitamin B<sub>12</sub> deficiency was dietary and he had no history of neurological symptoms attributed to this. His epilepsy had been difficult to control at times, and at the time of presentation, he was on three antiepileptic medications, with up to four seizures per year. His last seizure was 4 months prior to presentation. He was a current smoker of 10 cigarettes a day for the last 15 years. He did not drink alcohol or use illicit drugs. In relation to family history, three maternal second degree relatives died at a young age from various neurological disorders. The first maternal second degree relative was 4 years old when he died from a prolonged seizure reportedly due to a brain tumour. Another maternal second degree relative was 7 years old and he was certified at death as having an apparent 'cerebral tumour'. The third maternal second degree relative died aged 7 and was reported to have tuberculous meningitis. X-ALD was never suspected as a diagnosis in these individuals. It was not possible to obtain more precise information regarding the patient's family history, and therefore, the aforementioned diagnoses may be somewhat ambiguous and unrelated to the current case.

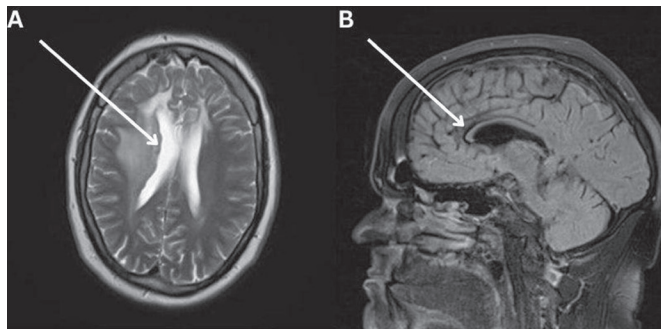
Clinical examination revealed a mild weakness of the left face, left shoulder abduction and left finger extension (Medical Research Council Grade 4). Left hip flexion and left ankle dorsiflexion were also mildly weak (Medical Research Council Grade 4). Deep tendon reflexes and plantar responses were normal. Eye funduscopy examination was normal. There was no evidence of right-sided weakness. Clinical impression at this point was that of a structural or vascular intracranial lesion. A brain MRI scan was urgently requested and showed linear band-like heterotopia along the right lateral ventricle alongside an underlying dysplastic corpus callosum (figure 1). This finding was previously noted on CT scan 9 years earlier when the patient was 28 years old and identified as the cause of the patient's epilepsy. However, there was a new finding of an evolving large right-sided white matter lesion in the cerebral subcortical region, midbrain and brainstem. This lesion demonstrated abnormal linear enhancement postcontrast (figures 2 and 3).

Shortly after the initial presentation, the patient was admitted following a tonic-clonic seizure. On examination, his left-sided weakness had progressed, and he now required a walking frame and supervisory assistance to mobilise. Repeat brain



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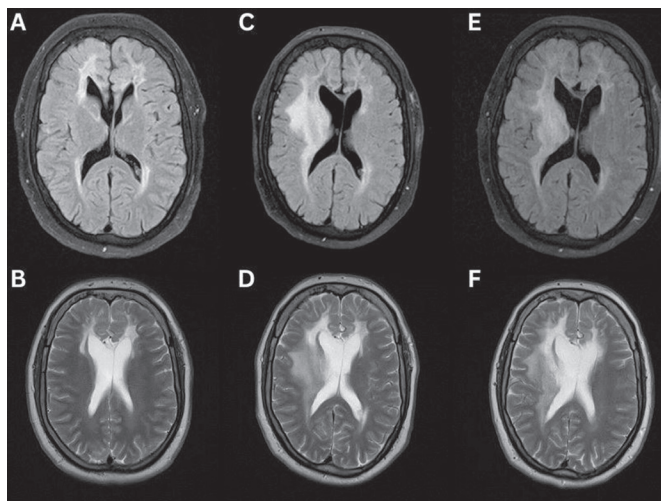
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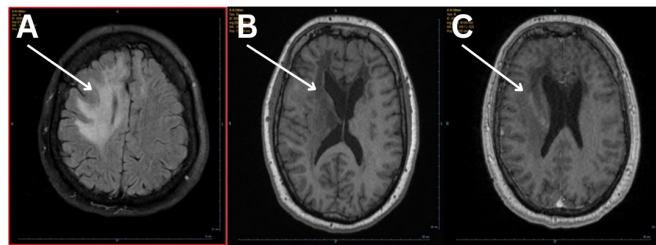
**Figure 1** (A) Axial T2-weighted MRI image showing heterotopia lining the lateral ventricle and bifrontal white matter hyperintensities (Arrow pointing to heterotopia lining the right lateral ventricle). (B) Sagittal FLAIR (Fluid-attenuated inversion recovery) MRI showing a thinned corpus callosum (Arrow pointing to thinned dysplastic Corpus Callosum).

MRI scan showed the previously identified mass was larger (figure 4) and enhanced with intravenous contrast. An opinion was sought from neurosurgery, as there was uncertainty as to the nature of the lesion on MRI scan. Their differential was either a low-grade glioma or subacute infarct. The recommendation was to repeat the scan after 3 months to assess for interval change. A decision on whether to perform a brain biopsy would be made at this point.

After 3 months, the patient's condition continued to deteriorate. He reported complete power loss in his left arm and left leg. He had been unable to mobilise for the last 3 weeks, requiring a hoist and wheelchair for transfers. Clinical examination revealed further progression with a dense left sided hemiplegia. At this point, the clinical findings were more consistent with a tumour vs a vascular event. In addition, MRI showed an increase in white matter oedema supporting this differential. A brain biopsy was subsequently performed.



**Figure 2** Axial T2-weighted serial MRI brain scans showed an evolving, extensive white matter space-occupying lesion that was exerting a mass effect in the right centrum semiovale and thalamus, with extension into the brainstem and pons. Images (A, B) age 31 years and 1 month. Images (C, D) age 37 years and 9 months. Images (E, F) aged 38 years and 1 month.



**Figure 3** (A) Axial FLAIR (Fluid-attenuated inversion recovery) MRI showing increased signal right frontal lobe white matter (Arrow pointing to increased signal right frontal lobe white matter). (B) Axial T1-weighted MRI non-contrast showing white matter hypointensity right frontal lobe (Arrow showing white matter hypodensity right frontal lobe). (C) Contrast-enhanced axial T1-weighted MRI showing abnormal linear marginal enhancement right frontal white matter (Arrow showing abnormal linear marginal enhancement right frontal white matter). Loes score=15.

## INVESTIGATIONS

Full blood count, urea, creatinine, thyroid function and electrolytes were all within normal limits.

ANA, ANCA and cardiolipin antibodies were negative. Vitamin D levels were found to be low (26). ACTH (adrenocorticotropic hormone) was normal (40 ng/L, range 0–47) as were renin and aldosterone concentrations. Vitamin B<sub>12</sub> levels were normal (243 pg/mL). Plasma enzymes for lysosomal storage diseases including a-fucosidase, b-glucuronidase, b-mannosidase and hexosaminidase A were all within normal limits.

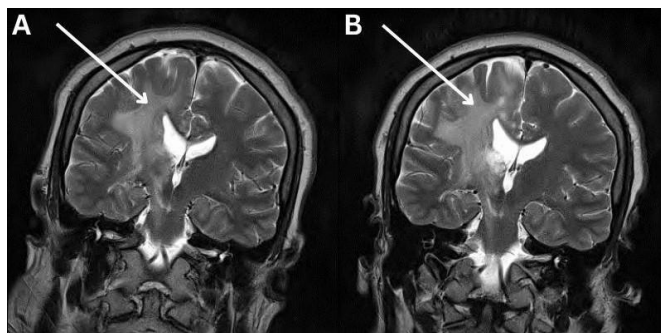
Serial MRI brain scans showed an evolving, extensive white matter lesion that was exerting a mass effect in the right centrum semiovale and thalamus, with extension into the brainstem and pons (figure 2). CT thorax, abdomen and pelvis showed no malignancy.

Navigation guided burr hole biopsy of the mass lesion was undertaken. The site of biopsy was from an area of enhancement in the right basal ganglia. Neuropathology showed perivascular lymphocytic inflammation with predominance of T Cells (figure 5) and demyelination (figure 6). There was no evidence of infection or tumour. Tumefactive multiple sclerosis was suggested as a likely diagnosis; however, the pathologist did comment that these findings could be very occasionally found in rare metabolic diseases such as adrenoleukodystrophy.

Measurement of serum concentrations of VLCFAs showed abnormally elevated levels. C24/C22 ratio was 1.90 and C26/C22 ratio was 0.075 (normal levels 0.44–0.97 and 0.005–0.030, respectively). These results were consistent with a diagnosis of X-ALD. Genetic analysis showed the patient to be hemizygous for the c.1202G>A, p.Arg401Gln pathogenic mutation in exon 3 of the *ABCD1* gene. This result confirmed a diagnosis of X-ALD in this patient.

## DIFFERENTIAL DIAGNOSIS

Based on clinical and radiological findings at initial presentation, the primary causes of the patient's symptoms were attributed to either a tumour or inflammation/demyelination. Subacute infarction was also considered as a possibility. Other differentials considered were lysosomal storage diseases causing adult-onset leukodystrophies such as GM1 gangliosidosis, metachromatic leukodystrophy and krabbe leukodystrophy. In addition, infections such as progressive multifocal leukoencephalopathy were also considered given the asymmetric MRI findings and clinical presentation. The results of the brain biopsy directed further tests looking for metabolic disorders. The demonstration of elevated



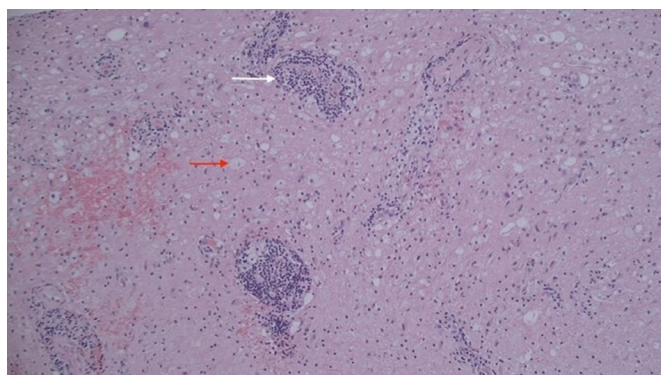
**Figure 4** Serial coronal MRI brain scans showing an evolving, extensive white matter lesion that was exerting a mass effect in the right centrum semiovale and thalamus, with extension into the brainstem and pons. Arrow A pointing to large right sided white matter lesion seen on coronal imaging in the right cerebral cortical region with extension into the brainstem and pons. Arrow B showing increased size of the white matter lesion in the right cerebral cortical region on repeat imaging and enhancement with intravenous contrast.

levels of VLCFAs and subsequent genetic analysis confirmed X-ALD as the underlying diagnosis.

#### TREATMENT

Following the brain biopsy, an initial diagnosis of tumefactive multiple sclerosis was made. The patient was admitted to hospital for 3 days of intravenous methylprednisolone and intensive multidisciplinary rehabilitation including speech therapy, physiotherapy and occupational therapy. On discharge, the patient was commenced on the disease-modifying therapy (dimethyl fumarate) for multiple sclerosis. Following results of serum VLCFAs and subsequent genetic analysis, a diagnosis of X-ALD was confirmed and disease-modifying therapy for multiple sclerosis was discontinued.

The treatment for the majority of patients with X-ALD focuses mainly on symptomatic relief and dietary constraints. Dietary therapy with Lorenzo's oil and a low fat diet has been reported to decrease levels of VLCFAs<sup>4</sup> and has been shown to have a preventative effect in asymptomatic boys.<sup>5</sup> However, Lorenzo's oil does not have a favourable effect on the rate of progression in patients who present at a symptomatic stage with cerebral involvement.<sup>6</sup> Dietary therapy was, therefore, considered to be of no potential benefit for this patient and was not initiated.



**Figure 5** This photomicrograph only shows white matter biopsy samples with vessels showing perivascular inflammation (white arrow) including lymphocyte aggregates and foamy macrophage infiltrate (red arrow). Foamy macrophages are evenly distributed throughout the tissue.

Allogeneic HSCT is considered the only successful treatment option for patients with cerebral X-ALD.<sup>7</sup> When performed at an early stage of the disease, allogeneic HSCT improves functional outcomes and increases survival.<sup>8–10</sup> However, HSCT has been associated with a 20% risk for morbidity and mortality and is not recommended for individuals with severe neurological deficits and significant cerebral involvement.<sup>11–13</sup> Based on clinical and radiological findings, it was concluded that our patient would not be a suitable candidate for HSCT.

Treatment for our patient, therefore, consisted of symptomatic and supportive care including speech therapy, physiotherapy, occupational therapy and psychological support.

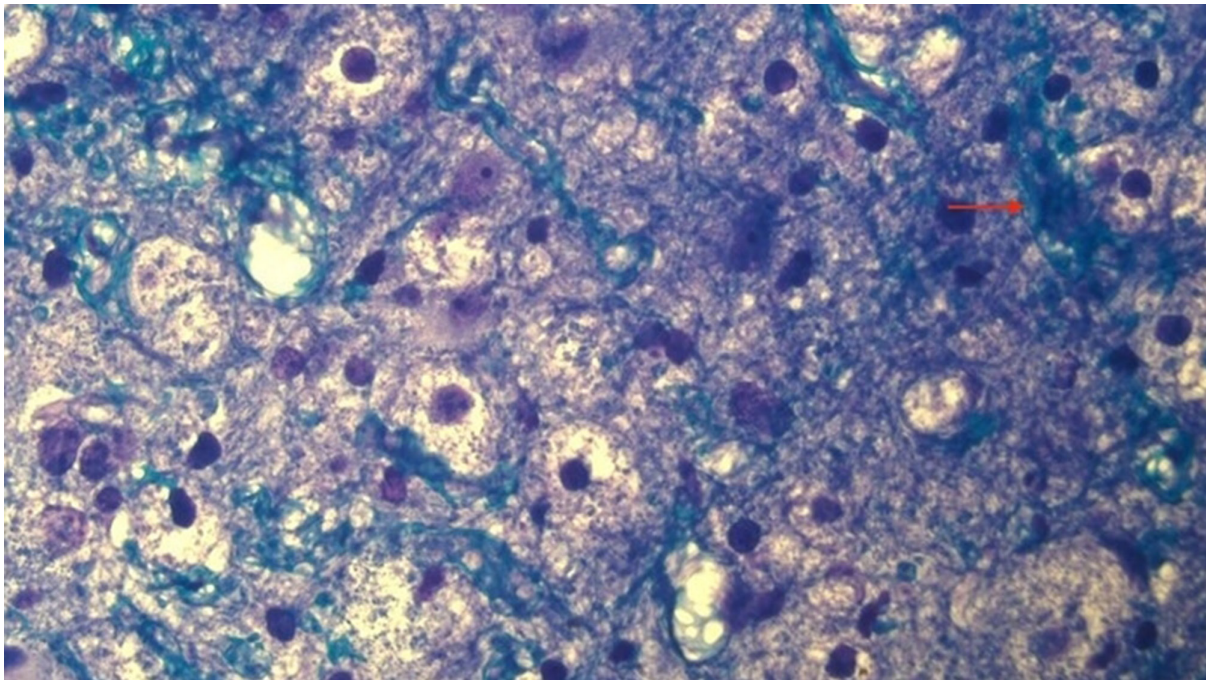
#### OUTCOME AND FOLLOW-UP

For the first year, the patient remained neurologically stable. He subsequently slowly began to deteriorate becoming progressively weaker with increasing right-sided involvement. He began to experience absence type seizures and swallowing difficulties. Unfortunately, he developed an aspiration pneumonia and did not recover from this despite antimicrobial therapy. He received end-of-life care at home and died peacefully in the company of his family. Genetic counselling was offered to his family. A first degree relative of the patient was found to be a heterozygote carrier of the same mutation; however, they were asymptomatic and MRI brain scan was normal for that individual.

#### DISCUSSION

We present a case of an adult male in his 30s with a 6-month history of progressive left face, arm and leg weakness. MRI brain showed an extensive right sided subcortical white matter lesion, with extension into the brainstem. The main differentials considered for this patient were inflammation, malignancy and infection. The insidious onset of weakness and subsequent rapid progression of the patient's hemiplegia were not typical for classical demyelination. In addition, the asymmetrical radiological features were also uncharacteristic for this. Brain biopsy definitively excluded infection and malignancy. The dominant features were that of inflammation and demyelination and it was suggested that the appearances may be consistent with a rare metabolic disease such as X-ALD. In retrospect the confluent MRI changes, contrast enhancement pattern and dilatation of the ipsilateral ventricle were more suggestive of a chronic, long-standing disorder rather than malignancy. On reflection, some signal changes are evident on the left cerebral hemisphere as far back as 2010 which again supports a chronic disorder. In addition to this the T2-weighted images show signal changes that specifically involve white matter with sparing and lack of contiguous involvement of deep grey matter (figure 2A).

X-ALD is a peroxisomal disorder caused by defects of the *ABCD1* gene located in Xq28.<sup>1</sup> Peroxisomal abnormalities cause VLCFAs to accumulate in the central and peripheral nervous system in addition to the adrenal glands. This results in central nervous system demyelination, axonal neuropathy and adrenal dysfunction.<sup>3</sup> The total frequency of X-ALD is estimated at approximately 1:17 000.<sup>14</sup> Childhood cerebral form and adult adrenomyeloneuropathy are the most frequently occurring phenotypes accounting for 80% of patients.<sup>11</sup> The adult cerebral form of X-ALD observed in our patient is the most severe phenotype and occurs less frequently. It is characterised clinically by cognitive decline, visual disturbances, dysarthria, progressive quadriplegia and rarely seizures.<sup>15</sup> Progressive neurological damage with rapid evolution occurs, leading to a vegetative state within 6 months to 2 years after onset of symptoms, followed by death at variable ages.<sup>11</sup> The clinical expression of the disease shows a marked phenotypic variability even in males carrying



**Figure 6** Photomicrograph with higher power of Luxol staining showing residual myelinated axons mainly to right with infiltration by foamy macrophages (red arrow) containing blue ingested material—that is, myelin.

the same mutation in the ALD gene.<sup>16</sup> This is reflected in this current case where the clinical courses of the maternal second degree relatives and the index case were significantly different. The literature reports numerous cases of intrafamilial clinical variability within generations of families affected by X-ALD.<sup>17–28</sup>

The diagnosis of X-ALD is established in a male patient with suggestive clinical and radiological findings and elevated VLCFAs.<sup>29</sup> The most common MRI findings in X-ALD are a characteristic pattern of symmetric enhanced T2 signal in the parieto-occipital region with contrast at the advancing margin occurring in 66% of patients.<sup>30</sup>

Diagnosis of X-ALD is confirmed by genetic analysis demonstrating mutations in the *ABCD1* gene. More than 1300 mutations have been identified to date.<sup>31</sup> The mutation identified in our patient c.1202G>A, p.Arg401Gln has been previously described in other individuals with X-ALD.<sup>32–34</sup> Incecik *et al* described a 6-year-old boy with the cerebral form of X-ALD who presented with behavioural changes, progressive gait difficulties, slurred speech and cognitive impairment.<sup>33</sup> Analysis of the *ABCD1* gene sequencing revealed a c.1202G>A, p.Arg401Gln mutation. A 29-year-old Chinese man experienced progressive lower limb weakness from the age of 8 years.<sup>34</sup> Six years later at the time of presentation, the patient was wheelchair dependant. Neurological examination showed lower limb spasticity, weakness 3/5, hyperactive tendon reflexes, ankle clonus, bilateral positive Babinski sign and pinprick impairment below the fourth thoracic cord symmetrically. The presentation in this case was not as rapidly progressive as our case, signs were also bilateral and had some features of spinal cord involvement. There are no other cases of X-ALD with the c.1202G>A, p.Arg401Gln mutation found in the literature that presented similar to our case with a rapidly progressive, unilateral weakness. The majority of cases of adult cerebral demyelinating forms of X-ALD identified in an extensive literature review presented with either disturbance of gait<sup>35–39</sup> or psychiatric disturbances such as dementia, hallucinations, personality disturbance and delusions.<sup>40–46</sup>

Asymmetric cerebral lesion involvement on MRI as was observed in our case is also rare and occurs in less than 5% of patients.<sup>47</sup> Sakakibara *et al* reported a 25-year-old man with a right caudate lesion that resembled a brain tumour.<sup>48</sup> Waragai *et al* reported a case of a 30-year-old man who presented with progressive cerebellar ataxia and spastic paraparesis. MRI showed asymmetric lesions in the dentate nucleus and pyramidal tracts from the internal capsule to the brain stem.<sup>49</sup> Other cases of asymmetric MRI involvement in X-ALD have been reported although they have mainly been associated with young boys with early onset of the disease.<sup>47 50–52</sup> There were no other adult case reports identified during our literature review with radiological findings of a large tumour-like white matter lesion. Another interesting observation was made regarding the radiological features of this case. A CT scan back in 2007 showed linear band-like heterotopia along the right lateral ventricle alongside an underlying dysplastic corpus callosum. A case report of a 37-year-old man with X-ALD also showed the presence of brain developmental defects including two periventricular nodular heterotopic foci in the parietal areas that had not been previously observed in adult patients.<sup>52</sup> Multiple peroxisomal functions are required for proper brain development and it can only be speculated that the accumulation of VLCFAs in X-ALD could cause specific neurogenesis abnormalities.<sup>52</sup>

This case report highlights the challenges faced by clinicians in diagnosing X-ALD. The underlying cause of the progressive neurological symptoms remained elusive until a brain biopsy suggested the possibility of a metabolic pathology. X-ALD is often underdiagnosed due to lack of knowledge and wide variety of clinical presentations often mimicking other neurological and psychiatric disorders. Early diagnosis is imperative in order to prevent progression, identify complications (such as adrenal dysfunction and cerebral involvement) and to achieve the best possible outcome from interventions such as HSCT. It is currently estimated that approximately 50% of boys with cerebral X-ALD are diagnosed too late for effective treatment with

HSC.T.<sup>9</sup> The importance of early diagnosis in allowing a better prognosis is reflected in the fact that some countries such as the USA and Netherlands have introduced newborn screening for X-ALD. Newborn screening facilitates early detection at birth. A comprehensive family history can also assist in earlier diagnosis and is an important element of the assessment of patients with progressive neurological symptoms. This is supported by a case in the literature where a diagnosis of X-ALD in a 33-year-old man with progressive limb weakness was helped by the presence of a significant family history.<sup>27</sup>

In conclusion young adult males with progressive neurological symptoms should be biochemically tested for X-ALD especially in those with a suggestive family history. It is hoped that this case encourages increased awareness of X-ALD thus facilitating prompt recognition, diagnosis and early intervention.

### Patient's perspective

'The X-ALD diagnosis of our family member was devastating on our family. His cognitive ability decline over the last four years of his life was upsetting to observe. He received excellent care and support when diagnosed and remained at home with family where he was most comfortable. This made a difficult situation somewhat easier as visitor restrictions during Covid would have kept us apart for those final months if he had remained in hospital.

The sad part of this is that if he was born now in certain states in America or in Italy, the heel prick test which is done on newborn babies would pick it up and enable him to have life changing treatment and prevent a life of disability and premature death.

Newborn testing needs to catch up to the likes of Italy, which tests for 49 rare diseases at birth. If diagnosed before symptoms start showing, it's possible to halt the disease and symptoms don't develop.

### Learning points

- ▶ X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder and may occur at a higher prevalence than previously considered.
- ▶ X-ALD causes cerebral demyelination and inflammatory lesions on MRI, thus mimicking more common disorders such as multiple sclerosis.
- ▶ This case highlights the importance of considering X-ALD in adolescent males with progressive neurological symptoms as this has great benefits for early detection and treatment.
- ▶ This case demonstrates the importance of a comprehensive family history in the evaluation of a patient with neurological symptoms.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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