

## SHORT REPORT

## A unique familial leukodystrophy with adult onset dementia and abnormal glycolipid storage: a new lysosomal disease?

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### Abstract

**Two adult siblings with early onset dementia are described. At presentation, in their early 30s, they showed poor judgment and disinhibition. A progressive dementia ensued over several years. Brain MRI disclosed diffusely increased T2 signal in the cerebral white matter, suggestive of a leukodystrophy. Numerous lysosomal enzyme assays including leucocyte arylsulphatase A and galactocerebrosidase activities, plasma and fibroblast very long chain fatty acid concentrations, and urinary sulphatide concentrations were normal, as were CSF analyses. A brain biopsy disclosed periodic acid Schiff (PAS) and Sudan black positive material in perivascular macrophages which, by electron microscopy, consisted of stacks of straight or curvilinear paired membranes within angulate lysosomes, indicative of abnormal glycolipid accumulation. The combination of clinical, radiological, biochemical, and pathological features of this degenerative disease is not consistent with that of any of the known leukodystrophies or lysosomal storage disorders. These findings suggest a previously undescribed familial glycolipid storage disorder causing an adult onset leukodystrophy and presenting with behavioural symptoms that mimic a psychiatric disorder.**

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Although most inherited leukodystrophies are paediatric disorders, adult onset presentations occur in some, including X linked adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe's disease, orthochromatic leukodystrophy, polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, and Alexander's disease.<sup>1,2</sup> Each is associated with characteristic clinical and pathological features and, in the case of X linked adrenoleukodystrophy, metachromatic leukodystrophy, and Krabbe's disease, with specific biochemical and molecular abnormalities. The onset of demen-

tia, particularly in younger patients, necessitates an aggressive search for potentially treatable aetiologies. Although effective treatments for most leukodystrophies remain a hope for the future, progress towards this goal will require the appropriate classification of patients. In addition, the identification of an aetiology for a patient's clinical condition has important implications for others in the family who may be at risk for developing symptoms and who may benefit from genetic counselling for family planning.

We report here a brother and sister with onset in their 30s of a progressive dementia associated with diffuse changes in cerebral white matter. The biochemical and pathological changes identified in these patients do not conform to the patterns reported for any of the known leukodystrophies.

### Case 1

Patient 1 was a 37 year old man with a six year history of progressive cognitive decline and poor judgment as manifested by inappropriate dressing for the weather and urination in public. He was institutionalised in a psychiatric facility at the age of 33.

He was born after a full term gestation and had normal developmental milestones and no evidence of psychiatric or neurological disease before the age of 31. He worked as a welder until the age of 32 and was divorced at that age.

The family history was notable for a similarly affected older sister (case 2). The parents, two brothers (30 and 36 years old), and a younger sister (24 years old) were reported to be clinically normal, as were the 4 year old son of patient 1 and the 18 year old son of his affected sister. The paternal grandmother was reported to have Parkinson's disease. There was no known consanguinity.

Physical examination at the age of 34 disclosed a non-dysmorphic person whose general medical examination was unremarkable. Mental status examination showed inattention. There was paucity of speech and limited thought content, but language and recent memory were intact. Affect was blunted.

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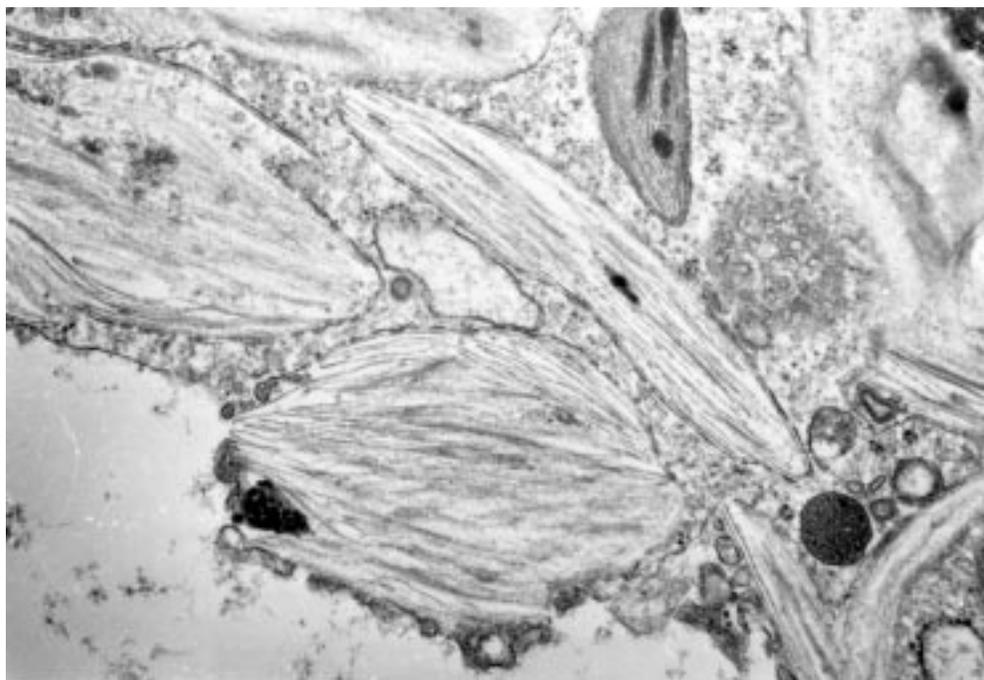
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Electron micrograph of abnormal membrane profiles present within a macrophage from the brain biopsy of patient 1. The material is predominantly contained within membrane bound compartments. Original magnification  $\times 19\,000$ .

Motor restlessness was apparent. Palmar grasp reflexes were absent. A slight postural tremor of the upper limbs was present. Neurological examination was otherwise unremarkable including normal extraocular movements and deep tendon reflexes. At this time, an EEG and EMG with nerve conduction studies were normal. T2 weighted MRI of the brain disclosed diffusely increased signal involving much of the white matter of the cerebral hemispheres and brainstem. At the age of 36, physical examination disclosed inattention and marked frontal release signs including poor word list generation, difficulty with Luria sequences, palmar grasp reflexes, and a visually evoked sucking reflex. Apraxia was notably absent. There was marked motor restlessness. Pendular nystagmus and diffuse hyperreflexia were present. By the age of 37 he was non-verbal and had absent deep tendon reflexes in the lower limbs.

Laboratory evaluation is summarised as follows: a low TSH was due to Graves' disease, which was treated with propylthiouracil. A right frontal brain biopsy showed slight patchy pallor of myelin, mild gliosis, and occasional groups of perivascular macrophages in the subcortical white matter containing periodic acid Schiff (PAS) positive and Sudan black positive but non-metachromatic granules consistent with glycolipid. Axons within the white matter were irregularly swollen and rare axonal spheroids were noted. The cerebral cortex was normal without evidence of abnormal storage material or inflammation. Electron microscopical analysis showed perivascular macrophages containing numerous angulate lysosomes filled with stacks of straight or curvilinear, non-branching paired membrane profiles (figure). Each membrane pair consisted of two roughly 2.5 nm thick membranes separated by a uniform 2.5–3.0 nm electron lucent space. In

larger angulate lysosomes, these membranes were admixed with coarsely clumped, variably osmophilic material resembling lipofuscin, as well as more uniformly granular osmophilic material. Scattered cortical neurons contained coarse, irregular, densely osmophilic material and round lipid droplets (lipofuscin). Within some of the clumps, straight or slightly curved acicular clefts and rare paired membrane profiles were identified.

#### Case 2

Patient 2, the 38 year old sister of patient 1, had a 5 year history of cocaine and alcohol misuse and progressive cognitive decline. She was the product of a full term gestation and had normal developmental milestones and no evidence of psychiatric or neurological disease before the age of 33. She graduated from high school and worked as a cashier and hairdresser until the age of 33. Shortly thereafter, her personality gradually changed. She became disinhibited, manifested by urination in public and two arrests for indecent exposure. Her family noted her to have poor judgment, impaired short term memory, and incontinence of urine and faeces. There were several psychiatric admissions between the ages of 34 and 38, including at least one for alcohol and cocaine misuse. She was placed in a neuropsychiatric facility at the age of 38.

Physical examination at the age of 38 disclosed no dysmorphic features and a normal general physical examination. Mental status examination showed inattention, perseveration, and emotional lability with impaired executive functions but intact language. Palmar grasp reflexes were absent. Neurological examination was otherwise unremarkable including normal articulation and intact extraocular movements without nystagmus. Formal neuropsychiatric

testing at the age of 38, 6 months after institutionalisation, disclosed progression of cognitive deficits. T2 weighted MRI of the brain disclosed diffusely increased signal intensity involving much of the white matter in the cerebral hemispheres and brainstem, similar in distribution and severity to the MRI findings in patient 1.

### Laboratory investigations

Serum studies with normal results in both patients included quantitative serum amino acids, very long chain fatty acid concentrations, beta-N-acetylhexosaminidases A and B,  $\beta$ -mannosidase (tested in patient 1 only),  $\alpha$ -fucosidase,  $\alpha$ -mannosidase, and lactate. Normal leucocyte studies included arylsulphatase A, galactocerebrosidase,  $\alpha$ -N-acetylgalactosaminidase, ceramidase,  $\beta$ -galactosidase,  $\alpha$ -mannosidase, and  $\alpha$ -galactosidase. Studies in fibroblasts in both patients disclosed normal very long chain fatty acid (VLCFA) concentrations, plasmalogen synthesis, phytanic acid oxidation, arylsulphatase A, cerebrosidase sulphatase, sulphatide loading test, and  $\beta$ -glucosidase. Normal urine studies included sulphatides, neutral oligosaccharides, sialic acid-containing oligosaccharides, free sialic acid, and bile acids (in patient 2 only). Analysis of CSF showed no leucocytes in patient 1, 3 lymphocytes in patient 2. Protein and glucose in CSF were normal in both patients; CSF lactate and quantitative amino acids were normal in patient 2. Leucocyte karyotype was normal in patient 1 (46 XY). Leucocyte and fibroblast karyotypes in patient 2 were normal (46, XX). Light and electron microscopical analysis of skin biopsies disclosed no abnormalities in either patient. A cortrosyn stimulation test was normal in patient 1. TSH was low in patient 1 (<0.3 mU/l, normal 0.5–5), with a high T4 (19  $\mu$ g/l, normal 0.8–2.3) and borderline T3 uptake (41%, normal 80–200). TSH was normal in patient 2. Other studies that were normal (tested in one or both patients) included B12, folate, ceruloplasmin, copper, HIV, rapid plasma reagin test, and erythrocyte sedimentation rate.

### Discussion

We report here two siblings with a progressive adult onset dementia associated with a leukodystrophy by MRI and a brain biopsy disclosing membrane enclosed glycolipid inclusions within perivascular macrophages. Extensive laboratory investigations did not disclose biochemical defects associated with any of the known leukodystrophies. To our knowledge, the combination of clinical, pathological, and biochemical findings in these siblings has not previously been reported.

A central issue in these patients is whether the disorder in question is a primary genetic lysosomal storage disease versus a secondary accumulation of substrate within lysosomes of perivascular CNS macrophages. Electron microscopy of those cells disclosed a pathological accumulation of straight and curvilinear membranes within angulate lysosomes. Histological

analysis using PAS and Sudan black stains indicated that the stored substrate(s) was glycolipid.

Pathological storage within angulate lysosomes is noted in many conditions, both genetic and non-genetic.<sup>3</sup> In general, angulate lysosomes develop whenever macrophages accumulate material, usually lipid, that imparts an angulate shape to the lysosomes in which it is stored. This is noted to occur by either of two mechanisms: (1) pathological storage of material derived from endocytosed cells or cell membranes that accumulates because the degradative capacity of the otherwise normal macrophage is exceeded, or (2) pathological storage because of a primary metabolic deficiency, usually in lipid catabolism.<sup>3</sup>

The occurrence of this leukodystrophy in siblings with normal parents constitutes a strong argument that the underlying pathogenetic process is genetic and likely autosomal recessive. However, we are unaware of any described genetic disorder that is consistent with the entirety of findings noted here. The clinical and radiological findings in our patients suggested the possibility of metachromatic leukodystrophy, which can present in adults with dementia.<sup>4</sup> However, neither patient had deficient arylsulphatase A activities. In addition, normal urinary sulphatide concentrations and a normal fibroblast sulphatide loading study ruled out all known forms of metachromatic leukodystrophy. The lack of metachromatic staining and the ultrastructural findings also are inconsistent with a diagnosis of metachromatic leukodystrophy.

X linked adrenoleukodystrophy is a peroxisomal disorder of very long chain fatty acid (VLCFA) catabolism.<sup>5</sup> The adult onset form of X linked adrenoleukodystrophy, adrenomyeloneuropathy, usually presents in young adult men with spastic paraparesis. Rare cases of patients with adult onset X linked adrenoleukodystrophy with progressive dementia or psychosis but without signs of spinal cord involvement have been reported.<sup>5,6</sup> The ultrastructural features of the macrophage inclusions in the brain biopsy of patient 1 are similar to those described in X linked adrenoleukodystrophy.<sup>3,7</sup> Cytoplasmic inclusions are found in many cell types in the disease, but in macrophages, the inclusions are located within angulate lysosomes. However, the normal serum and fibroblast VLCFA analyses rule out a diagnosis of X linked adrenoleukodystrophy.<sup>8–10</sup> In addition, the disease is X linked, and whereas female heterozygotes can be symptomatic,<sup>11</sup> The phenotype and radiological findings of patient 2 would be unusual for that disorder.

Thyroid disease has been incidentally associated with X linked adrenoleukodystrophy,<sup>12</sup> but it is not a common feature. However, our patients were discordant for thyroid disease and the neurological symptoms in patient 1 continued to progress despite successful therapy for hyperthyroidism. Therefore, thyroid abnormalities do not account for the leukodystrophy in our patients.

Other inherited leukodystrophies that can present in adults, such as Krabbe's disease,

orthochromatic leukodystrophy, polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (membranous lipodystrophy), and Alexander's disease do not present with isolated dementia.<sup>2-13</sup> The normal galactocerebrosidase activity in both patients also rules out Krabbe's disease. In addition, the brain biopsy of patient 1 did not show the characteristic features associated with these disorders such as the globoid cells of Krabbe's disease or the Rosenthal fibres of Alexander's disease.

Chronic solvent vapour inhalation can cause a demyelinating disorder in the CNS associated with inclusions within membranous vesicles in macrophages similar to those seen in the brain biopsy of patient 1.<sup>14</sup> However, neither patient had a history of solvent vapour misuse. The continued progression of the disease in both patients while in institutional care, when they likely do not have access to drugs of misuse, also argues against solvent vapour misuse as a factor in these patients.

The current patients are also distinct from previous reports of patients with unique leukodystrophies. For example, Axelsson *et al*<sup>15</sup> reported a familial hereditary leukoencephalopathy presenting with dementia in adults. However, the pattern of inheritance was autosomal dominant and axonal spheroids was a prominent histopathological feature, thus distinguishing their patients from those presented here. Yates *et al*<sup>16</sup> described a patient with a leukodystrophy and adult onset dementia with motor and cranial nerve deficits, but the striking cholesterol ester accumulation seen in that patient was absent in ours.

We have identified a unique familial leukodystrophy presenting as dementia in adults. A brain biopsy disclosed abnormal accumulation of glycolipid within macrophages. To the best of our knowledge, the constellation of clinical, radiographic, biochemical, and pathological data of our patients does not correspond to any described genetic or non-genetic leukodystrophy. Increased turnover of myelin membrane and resultant intralysosomal accumulation of glycolipid within CNS macrophages as a result of demyelination theoretically might explain the histological and ultrastructural findings reported here. However, this is an unlikely explanation as similar pathological findings are

not noted in demyelinating disorders of the CNS. The intralysosomal pathology is likely due to a new genetic lysosomal enzyme deficiency disorder associated with defective glycolipid catabolism. However, an alternative explanation, that the lysosomal storage is a secondarily produced pathology caused by a non-lysosomal genetic abnormality cannot be excluded. Identification of the substrate(s) stored in the CNS macrophages may be helpful in differentiating between these possibilities and in establishing the primary biochemical lesion.

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