

CLINICOPATHOLOGICAL CONFERENCE

Cognitive decline, behavioural disturbance and motor dysfunction in a young adult

A. F. A. Merrison^{*}, T. H. Moss[†], R. Feller[‡] and N. J. Scolding^{*}

Institute of Clinical Neurosciences, Departments of Neurology^{*} and Neuropathology[†], Frenchay Hospital, Bristol, and [‡]Learning Disability Service, Beaver House, 147–150 Victoria Road, Swindon, UK
Practical Neurology, 3, 36–39

CLINICAL HISTORY

A 29-year-old lady presented with a history of cognitive decline, behavioural disturbance and poor co-ordination. She was assessed, investigated and cared for by the community psychiatric services.

She was born at term, following an uncomplicated delivery, reached early developmental milestones appropriately and attended a mainstream primary school. The first suggestion of cognitive problems was at the age of 8 years when a paediatric psychologist documented a verbal IQ of 65, performance IQ of 75 and general IQ of 66. At 10 years a school report noted visuospatial and motor difficulties but she was able to keep up with her contemporaries.

She went to a secondary school for pupils with mild-to-moderate special needs. She gained no formal qualifications and subsequently participated in sheltered work. She lived with her parents and attended a day centre for disabled young adults.

At the age of 29 years, her parents reported a two-year history of gradual cognitive decline, behavioural change and poor co-ordination. She needed assistance with most activities of daily living. She was unsteady on her feet and had difficulty with basic motor tasks. Her writing, reading, concentration and memory were poor. Her speech was restricted and repetitive. She was withdrawn, low in spirits and irritable. At times she exhibited unusual and compulsive behaviour.

There was no other medical history and no family history of neurological or cognitive problems.

Assessment by a community psychiatrist demonstrated that her understanding and performance were poor. Limited examination suggested ataxia but no localizing signs. Fluoxetine was started and although her mood improved a little, severe cognitive difficulties remained 3 months later (age-equivalent scores on the Leiter International Performance Scale and Test for Auditory Comprehension of Language were 2.5–3 years and 3–3.5 years, respectively). Changing to prothiadine did not improve performance and subsequent withdrawal of antidepressants made little difference.

Physiotherapy assessment suggested possible motor apraxia. Audiometry demonstrated normal hearing in the right ear but hearing impairment at mid-to-low frequencies in the left ear. Consultant ophthalmological assessment revealed mild myopia, with a normal retina.

Two years later she needed constant supervision, had difficulty following simple verbal instructions, was incontinent of urine and intermittently confused and disorientated. Her IQ was less than 30, indicating a marked deterioration in verbal and non-verbal ability. Three years later she required care in a nursing home.

A number of investigations were performed: full blood count, renal function, thyroid function, glucose, vitamin B12, folate, erythrocyte sedimentation rate, protein electrophoresis and arylsulphatase A were all normal. A chest X-ray was normal. An electroencephalogram at the age of 31 years showed normal background activity and no evidence of epileptiform activity. Computer tomography scans of the head at the ages of 30, 31 and 34 years showed generalised cerebral atrophy and a thickened skull vault but no change with consecutive scans. Magnetic resonance imaging of the head at the age of 32 years confirmed the presence of cerebral atrophy but was otherwise normal.

Her cognitive function deteriorated further, she was occasionally verbally and physically aggressive and risperidone did not help. At the age of 38 years she was bed-bound, tone generally increased and she made very little spontaneous movement. She sadly died later that year.

PATHOLOGY

At postmortem, the brain was markedly small with convolutional atrophy. Histological examination demonstrated accumulation of abnormally stored material within the cytoplasm of cortical neurones of the frontal, parietal and temporal areas, most marked in the medial temporal regions. This material was autofluorescent, sudanophilic and PAS-positive (Fig. 1).

Affected neurones appeared distended and there was associated gliosis and neuronal loss, particularly in the outer cortical lamina. Ultrastructural examination showed neuronal perikarya containing a mixture of granular-osmiophilic, fingerprint and lamellar bodies (Fig. 2).

Neurologists are frequently asked to assist in managing patients known to have long-standing and previously static cerebral disease, often labelled 'cerebral palsy', in whom continuing neurological or cognitive deterioration is queried.

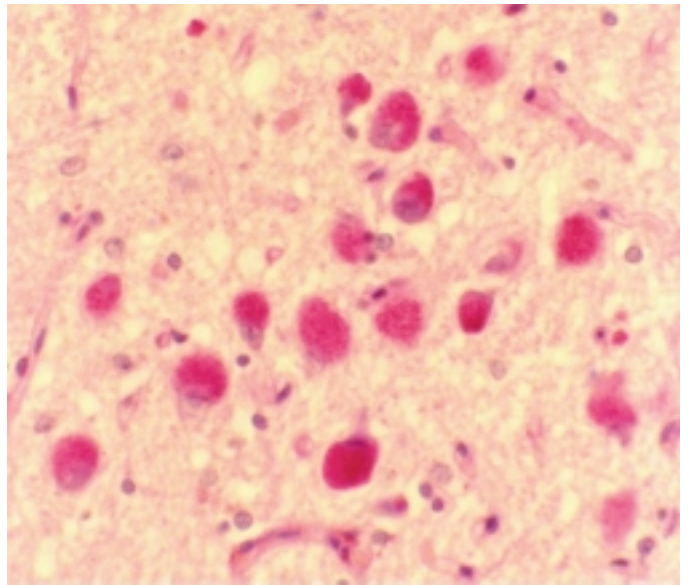


Figure 1 Section of cerebral cortex showing PAS staining of abnormally stored material within the cytoplasm of neurones.

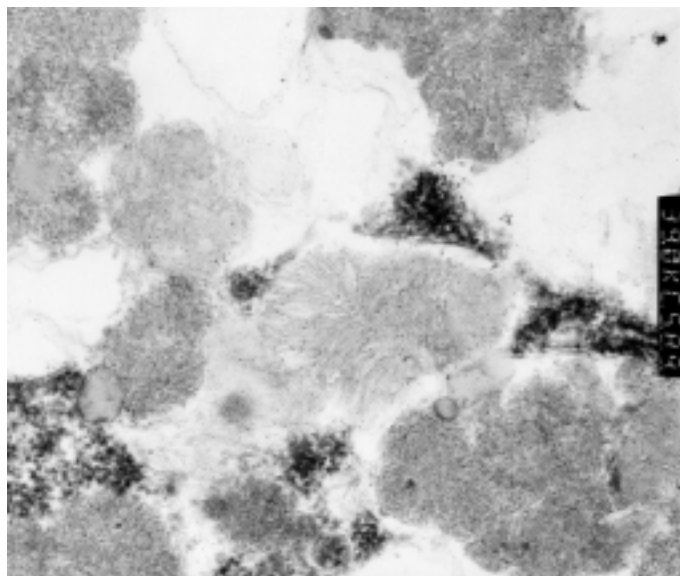


Figure 2 Electron microscopy demonstrating granular-osmiophilic and lamellar bodies causing distension of neurones.

In the cerebral deep grey matter, abnormal storage was limited to some thalamic nuclei and the lateral geniculate body. The inferior olivary nuclei showed some diffuse gliosis. The cerebral white matter, brainstem, cerebellum and upper cervical cord appeared normal.

The microscopic features of this lady's brain are those of neuronal ceroid lipofuscinosis. The presence of mixed inclusion bodies (granular osmiophilic deposits, fingerprint profiles and lamellar bodies) supports a diagnosis of Kuf's disease. The clinical picture is also consistent

with Kuf's disease – adult-onset neuronal ceroid lipofuscinosis (CLN4) type B.

DISCUSSION

The neuronal ceroid lipofuscinoses are a group of inherited (mainly autosomal recessive) neurodegenerative disorders, characterized by loss of neurones and accumulation of autofluorescent lipopigment within the cytoplasm of neurones and other tissues. Lipofuscin and ceroid are pigments produced from the breakdown of a variety of molecules, including lipids, carbohydrates and proteins (Mitchison & Mole 2001).

Light microscopy and histochemistry alone may not distinguish the lipofuscinoses from other storage diseases. Electron microscopy is required to identify the nature of the inclusions formed by this abnormally stored material (Berkovic *et al.* 1988).

Some lipofuscinoses are associated with palmitoyl protein thioesterase 1 (PPT1) deficiency (Van Diggelen *et al.* 2001). PPT1 breaks down palmitoylated proteins, which may play a role in prenatal central nervous system development and subsequent neuronal maintenance. These cases are characterised by granular osmiophilic deposits.

Four major subtypes of neuronal ceroid lipofuscinoses (infantile, late-infantile, juvenile and adult) were initially identified, based on age at onset and differences in the nature and distribution of the abnormally stored material (Berkovic *et al.* 1988). The infantile form has granular, osmiophilic deposits, the late infantile form has curvilinear profiles, the juvenile form has fingerprint bodies and the adult form has mixed inclusion bodies on electron microscopy (Wisniewski *et al.* 2001). The associated genes are attributed the symbols CLN1, 2, 3 and 4, respectively. However, further phenotypes, genes and disease *loci* are emerging.

Most patients present with cognitive decline, behavioural change, motor dysfunction (including ataxia, pyramidal and extrapyramidal problems) and seizures. The childhood forms are also characterised by progressive visual failure secondary to retinal degeneration. Magnetic resonance imaging findings are non-specific, showing cerebral and cerebellar atrophy (D'Incerti 2000). Where the genetic basis is not known (such as the adult-type), the diagnosis relies entirely on clinicopathological findings. Other tissues amenable to biopsy which may provide helpful information include skin, muscle and rectum.

Kuf's disease (adult-onset lipofuscinosis) usually presents at around 30 years of age but has been reported in patients from 11 to 50 years. Unlike the childhood forms, there are no retinal abnormalities. The time from onset to death varies from 7 to 25 years. Two major clinical phenotypes have been described. Type A is characterised by progressive myoclonic epilepsy with dementia, ataxia and later pyramidal and extrapyramidal signs. Type B (less frequently reported) is characterised by behavioural abnormalities and dementia, which may be associated with motor dysfunction, ataxia, extrapyramidal and bulbar signs (Berkovic *et al.* 1988).

The absence of ophthalmological findings and the presence of mixed inclusion bodies suggests that our patient suffered Kuf's disease. Without obvious seizures one would describe this as type B. The age of onset of cognitive difficulties is earlier than that expected in typical Kuf's disease but this condition has been described in early adolescence. It is difficult to dismiss the possibility that she may have had an unusual juvenile form of the disease. It is becoming increasingly recognised that patients may present in a way that overlaps the original clinical subdivisions and that there is phenotypic heterogeneity amongst the lipofuscinoses (Wisniewski *et al.* 2001).

Neurologists are frequently asked to assist in managing patients known to have long-standing and previously static cerebral disease, often labelled 'cerebral palsy', in whom continuing neurological or cognitive deterioration is queried. An understanding of the storage diseases and their manifestations is vital if an antemortem diagnosis is to be made (Coker 1991). Few treatments are yet available but prognostication and genetic counselling can be offered.

REFERENCES

- Berkovic SF, Carpenter S, Andermann F, Andermann E & Wolfe LS (1988) Kuf's disease: a critical reappraisal. *Brain*, **111**, 27–62.
- Coker SB (1991) The diagnosis of childhood neurodegenerative disorders presenting as dementia in young adults. *Neurology*, **41**, 794–8.
- D'Incerti L (2000) MRI in neuronal ceroid lipofuscinosis. *Neurological Science*, **21**, S71–3.
- Mitchison HM & Mole SE (2001) Neurodegenerative disease: the neuronal ceroid lipofuscinoses (Batten disease) *Current Opinion in Neurology*, **14**, 795–803.
- Van Diggelen OP, Thobois S, Tilikete C *et al.* (2001) Adult neuronal ceroid lipofuscinosis with palmitoyl-protein thioesterase deficiency: first adult-onset patients of a childhood disease. *Annals of Neurology*, **50**, 269–70.
- Wisniewski KE, Zhong N & Philippart M (2001) Phenotypic correlations of neuronal ceroid lipofuscinoses. *Neurology*, **57**, 576–81.