SHORT REPORT

The clinicopathological spectrum of Rosenthal fibre encephalopathy and Alexander's disease: a case report and review of the literature

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Alexander's disease is a leucodystrophy that usually presents in early childhood, but can infrequently arise in adults. It is characterised pathologically by megalencephaly, demyelination, and the presence of numerous Rosenthal fibres. Most cases have been shown to be due to mutations in the gene encoding glial fibrillary acidic protein. In rare instances, numerous Rosenthal fibres have been found at autopsy in patients who have suffered protracted debilitating systemic illnesses, some with associated brain stem signs, and in very rare instances in patients with no apparent neurological abnormality. The term "Rosenthal fibre encephalopathy" is used to distinguish these cases from those of Alexander's disease. We report the first case of Rosenthal fibre encephalopathy in a young man with AIDS, and review the literature.

Alexander's disease is a sporadic disorder affecting central nervous system (CNS) white matter. It usually presents in infancy with megalencephaly, dementia, spasticity, and seizures,¹ but may also present in later childhood and rarely in adulthood,^{2,3} where the disease progression may be slow and can cause clinical confusion with multiple sclerosis.⁴ Pathologically, Alexander's disease is characterised by eosinophilic cytoplasmic inclusions, termed Rosenthal fibres, within astrocyte processes, adjacent to areas of demyelination.⁵ Rosenthal fibres contain glial fibrillary acidic protein (GFAP), ubiquitin, and the heat shock proteins hsp-27 and $\alpha\beta$ -crystallin.^{6–9} It has been postulated that they form as a consequence of a metabolic disturbance of astrocytes that in turn leads to the degradation of excessive amounts of glial filaments.¹⁰

There have been rare case reports of adults dying with a variety of systemic and neurological disorders who have been found at autopsy to have prominent Rosenthal fibre deposition, but without the clinical features or demyelinating lesions that are typical of Alexander's disease.^{11–13} In these cases the distribution of Rosenthal fibres is predominantly perivascular, subependymal, and subpial in location, resembling that seen in Alexander's disease, but largely confined to the brain stem. To distinguish these cases from those of Alexander's disease, the term "Rosenthal fibre encephalopathy" has been suggested, despite the lack of consistent clinical findings.¹² We report a case of Rosenthal fibre encephalopathy in a young man with AIDS, an association that has hitherto not been reported.

CASE REPORT

A 33 year old man was diagnosed with AIDS after presenting with a six month history of weight loss and malaise associated with superficial lymphadenopathy, oral hairy leucoplakia, and

molluscum contagiosum. Neurological examination was normal, but a magnetic resonance imaging (MRI) scan of the head disclosed several discrete enhancing intracerebral lesions. Haematological investigations revealed a neutropenia with a CD4 count of $0.03 \times 10^9/l$ and a haemoglobin of 80 g/l. Lamivudine, zidovudine, zalcitabine, dapsone, and pyrimethamine were commenced. Six weeks later the patient re-presented with a severe occipital headache. Repeat MRI brain imaging showed the lesions had progressed. The patient was treated symptomatically with dexamethasone; he died five days later.

At postmortem examination, internal examination was restricted to the cranial cavity. The brain weighed 1688 g and appeared diffusely swollen. The leptomeninges were translucent. Coronal slices through the cerebral hemispheres revealed a macroscopically normal cortical ribbon. There was, however, some yellow discolouration of the white matter, particularly in the left frontal region, and softening and brown discolouration were seen in the left corpus striatum and caudate nucleus. Areas of yellow discolouration and softening were also noted in the midbrain and cerebellum.

Histological examination of the cerebellum revealed extensive infiltration with high grade malignant non-Hodgkin's lymphoma, which was confirmed to be of B cell type by strong immunocytochemical expression of the B cell marker CD79a. Lymphoma was also present within the left caudate nucleus, midbrain, and pons (fig 1A). Scattered lymphoma cells showed nuclear signal following in situ hybridisation using probes directed against Epstein-Barr virus.¹⁴ In addition, multiple microglial nodules were seen throughout the cerebral cortex, cerebellum, and brain stem, and within some of them occasional cytomegalovirus (CMV) inclusions were seen, indicating a low grade CMV encephalitis (fig 1B).

An unexpected finding was the presence of numerous Rosenthal fibres in the brain stem. These were particularly numerous in subpial regions, where they were arranged perpendicularly to the pial surface, producing a pallsadated arrangement around blood vessels (fig 1C). In addition Rosenthal fibres were present at nerve root entry zones in the brain stem, in subependymal regions of the floor of the fourth ventricle and, to a lesser extent, beneath the ependyma of the lateral ventricles. Rosenthal fibres were not found in other parts of the cerebrum or cerebellum. The Rosenthal fibres were strongly immunoreactive with antibodies to GFAP, ubiquitin, and $\alpha\beta$ -crystallin (fig 1D). Demyelination was not present, and the distribution of Rosenthal fibres was not related to other pathological changes in the brain.

Abbreviations: CNS, central nervous system; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging

Figure 1 (A) High grade diffuse B cell lymphoma showing large pleomorphic lymphocytes. (B) Microglial nodule from cerebral cortex showing intranuclear inclusion typical of cytomegalovirus. (C) Midbrain showing pallidated arrangement of Rosenthal fibres around blood vessels (arrowheads). (D) High power view of Rosenthal fibres showing α -crystallin immunoreactivity.

DISCUSSION

It is generally accepted that both Alexander's disease and Rosenthal fibre encephalopathy are attributable to disorders of astrocytes, but the overlap between these two disorders has hindered attempts to define consensus clinicopathological criteria for each disease. This has led to misclassification of reported cases. To rectify this problem we sought to reclassify published cases in order to comply with stricter definitions of each disease. Typical adult onset Alexander's disease is characterised pathologically by the presence of diffuse Rosenthal fibres, and demyelinating and cavitating cerebral lesions, and clinically by progressive dementia, ataxia, spasticity, and seizures.¹² Cases which display all the pathological characteristics of Alexander's disease, but apparently lack neurological involvement, have been classified in the latter category in view of the difficulty in ascertaining the rigour of the neurological evaluation. In contrast, Rosenthal fibre encephalopathy is typified by a preponderance of Rosenthal fibres in the brain stem without demyelination or accompanying clinical evidence of neurological involvement, often in the context of debilitating systemic illness.¹² The presence of neurological signs in some of the latter cases can lead to confusion and misdiagnosis as Alexander's disease, but their presence can be readily explained in most of these cases by additional CNS pathology (see table 1).

The wide spectrum of clinical presentations in adult onset Alexander's disease and Rosenthal fibre encephalopathy is clear from a review of published cases. A Medline search from 1968 to the present, generated 15 publications and 25 patients

(table 1). Of these, 15 patients had Alexander's disease and 10 patients (11 patients including the present case) could be classed as having Rosenthal fibre encephalopathy, using the above definitions. The age range of adult onset Alexander's disease was 23–61 years and 19–85 years for Rosenthal fibre encephalopathy. The male to female ratio for Alexander's disease was 0.5:1 and for Rosenthal fibre encephalopathy 0.8:1 (including this case). The clinical spectrum of adult onset Alexander's disease remains controversial, but atypical neurological presentations are also recognised; for example, palatal myoclonus has been described in one of the cases reported by Howard and colleagues,¹⁵ and in three of the cases of Schwankhaus and colleagues.¹⁶ In all other respects the clinical features of these cases conform well to other reported cases of adult onset Alexander's disease. Both groups identified familial versions of adult onset Alexander's disease, although Howard and colleagues¹⁵ avoided explicit use of this term, presumably because of the familial rather than sporadic incidence and the unusual presentation. Of the 15 cases classified as Alexander's disease, typical pathological changes were confirmed at postmortem examination in seven cases. In two other cases myelin pallor rather than frank demyelination was associated with Rosenthal fibre deposition. Pathological confirmation of Alexander's disease was not obtained in four cases, all with familial presentations, as the diagnosis had been confirmed in the other siblings.^{15, 16} In only two cases were Rosenthal fibres the sole pathological finding, but the diagnosis in one of these cases was based on brain biopsy, which may not be representative because of sampling bias. In both instances a compelling case can be made for a diagnosis

Table 1 Summary of published cases of adult onset Alexander's disease and Rosenthal fibre encephalopathy

		Neurological involvement		
Age and sex	Systemic disease [toxins/drugs]	Yes	No	Postmortem CNS findings
Diagnosis of Alexander's disease				
27 Male ¹⁵		Bulbar palsy, tongue fasciculations, ataxia, spasticity	–	
32 Male ²	TB, intestinal obstruction, renal tract infection [anti-TB drugs]	Bulbar palsy, ataxia, spasticity		Diffuse RF, cavitating brain lesions
37 Male ²³		Epilepsy, dementia, ataxia, spasticity		Diffuse RF
39 Male ⁵		Ataxia, aphasia, cranial polyneuropathy, spasticity		Diffuse RF, demyelination
61 Male ⁴		Spasticity, ataxia, nystagmus		Diffuse RF and demyelination
23 Female ⁴	Hepatic and renal failure, alcoholic, depression [alcohol/psychotropic drugs]		+	Diffuse RF and demyelination in dentate nucleus
25 Female ¹⁵		Palatal myoclonus, tongue fasciculation, spasticity		*Brain stem and periventricular RF, myelin pallor
26 Female ²⁴		Ataxia, spasticity, visual deficit, dysphagia		*Cerebellar RF
29 Female ¹⁵		Ataxia, dysphonia, spastic monoparesis		–
37 Female ⁴	Asthma	Spasticity, ataxia, nystagmus		RF and demyelination
39 Female ³	Perinatal hypoxia	Childhood seizures, ataxia, dementia, spasticity, pseudobulbar palsy		Diffuse RF, demyelination, calcified basal ganglia
43 Female ¹⁶		Bulbar palsy, palatal myoclonus, ataxia, urinary incontinence		–
43 Female ²⁵	[alcohol/psychotropic drugs]		+	Diffuse RF, demyelination
48 Female ¹⁶		Diplopia, palatal myoclonus, spastic quadriparesis, ataxia, urinary and faecal incontinence		Diffuse RF, myelin pallor, astrogliosis
49 Female ¹⁶		Bulbar palsy, palatal myoclonus		–
Diagnosis of Rosenthal fibre encephalopathy				
19 Male ²⁶	Metastatic testicular carcinoma, intestinal obstruction, septicaemia, low Mg ²⁺ /PO ₄ [–] [i.v. feeding]	Seizures		Predominantly brain stem RF and central pontine myelinolysis
22 Male ¹²	Schizophrenic, septicaemia, ARDS [solvent abuse, antipsychotics analgesics, procyclidine]	Cognitive impairment, seizures, peripheral neuropathy		Brain stem RF, demyelination, basal ganglia calcification
32 Male (current case)	AIDS, lymphoma, CMV [anti-retroviral/toxo.]		+	Brain stem RF, CMV infection, lymphoma
66 Male ²⁷	Stokes-Adams attacks, DM	Dementia, seizures, pseudobulbar palsy, spasticity		Brain stem and cerebellar RF, multiple infarcts
70 Male ¹¹	COAD, cor pulmonale, AF, DM, PUD, myelofibrosis		+	Predominantly brain stem RF
19 Female ²⁷	Reticulum cell sarcoma [chemotherapy, steroids]		+	Brain stem and upper cervical cord RF, metastatic reticulum cell sarcoma
54 Female ²⁷	Metastatic melanoma [chemotherapy]	Dementia, ataxia		Brain stem RF, melanoma
65 Female ¹¹	Ovarian carcinoma, DVT, ARF [chemotherapy]		+	Predominantly brain stem RF
§78 Female ¹⁷	Rheumatic fever, hypertension, OA, cataracts	TIA, parkinsonism, dementia		Cerebral infarction, brain stem RF
82 Female ²⁷	Hypertension, CAD, gallstones, renal failure, GI bleed		+	Diffuse(?) RF, pontine infarction
85 Female ²⁸	DM, CAD, hypertension, hypoglycaemia		+	Brain stem RF, early Alzheimer's disease, Lewy bodies in locus coeruleus and raphe nuclei

RFE, Rosenthal fibre encephalopathy; RF, Rosenthal fibres; CAD, coronary artery disease; AF, atrial fibrillation; GI, gastrointestinal; DM, diabetes mellitus; ARF, acute renal failure; PUD, peptic ulcer disease; ARDS, adult respiratory distress syndrome; COAD, chronic obstructive airways disease; DVT, deep vein thrombosis; OA, osteoarthritis; TB, tuberculosis; i.v., intravenous; anti-retroviral/toxo., anti-retroviral, and anti-toxoplasmosis therapy.

*Possible RFE (see text for details).

*These pathological changes were found on brain biopsy.

The numeric reference to each case is indicated in superscript.

RFE, Rosenthal fibre encephalopathy; RF, Rosenthal fibres; CAD, coronary artery disease; AF, atrial fibrillation; GI, gastrointestinal; DM, diabetes mellitus; ARF, acute renal failure; PUD, peptic ulcer disease; ARDS, adult respiratory distress syndrome; COAD, chronic obstructive airways disease; DVT, deep vein thrombosis; OA, osteoarthritis; TB, tuberculosis; i.v., intravenous; anti-retroviral/toxo., anti-retroviral, and anti-toxoplasmosis therapy.

§Possible RFE (see text for details).

*These pathological changes were found on brain biopsy.

The numeric reference to each case is indicated in superscript.

of Alexander's disease, on the basis of the compatible clinical findings for which there was no other pathological explanation.

In rare instances the pathological appearance of Alexander's disease may be mimicked by antemortem exposure to neurotoxins, as in the case of the 22 year old man who was deemed to have Rosenthal fibre encephalopathy at postmortem examination rather than Alexander's disease, because the co-occurrence of demyelination could be explained by a history of solvent abuse.¹² It could be argued that the case of progressive parkinsonism with Rosenthal fibres, tentatively labelled as senile onset Alexander's disease by the authors,¹⁷ merits a distinct category of its own, but it would be more appropriate to avoid classifying this case as a separate nosological entity unless additional cases with identical clinico-pathological findings are identified. We have reclassified this

case as possible Rosenthal fibre encephalopathy in view of the absence of demyelination, the preponderance of Rosenthal fibres in the brain stem, and the lack of any of the typical clinical features of Alexander's disease (see table 1).

The recent discovery of spontaneous, non-conservative, dominant point mutations in the open reading frame of the *GFAP* gene in infantile onset Alexander's disease may be an important step towards elucidating the molecular genetic basis of this disease.¹⁸ Of 13 patients with pathologically confirmed, infantile or childhood onset Alexander's disease, *GFAP* mutations involving arginine residues were found in 12.¹⁸ In the latter series, the ratio of male to female cases was 0.6:1, similar to the gender ratio of adult onset Alexander's disease, suggesting that across the age spectrum the disease may be more frequent in females than in males. In childhood and juvenile onset cases, the pathological changes correlate well

with abnormalities on MRI, which include frontal predominance of white matter abnormalities and atrophy of subcortical structures.¹⁹ The presence of *GFAP* mutations in 14 of 15 patients with probable Alexander's disease who were diagnosed on the basis of compatible clinical presentations and suggestive radiological abnormalities, confirmed that the mutations are a reliable molecular marker for infantile forms of the disease.²⁰ The potential of screening for *GFAP* mutations in suspected childhood onset cases broadens the antemortem diagnostic modalities available beyond MRI in this subgroup.¹⁹

Two cases in the latter molecular genetic studies, one with onset in childhood and the other with infantile onset, were still alive at follow up aged 48 years and 20 years, respectively.^{18, 20} These cases have not been included in the table because of the onset of disease prior to adulthood. Consistent with a distinct pathophysiological mechanism for adult onset Alexander's disease, mutations in *GFAP* have yet to be shown in any cases of adult onset, including the cases cited in table 1. In only a single case of adult onset Alexander's disease, aged 45 years at onset, has a limited analysis of the *GFAP* gene excluded the presence of any of the known mutations.²¹ In this, as in other cases of adult onset disease, it will be important to sequence the whole gene to exclude the possibility of novel mutations. Other mechanisms in adult onset Alexander's disease and Rosenthal fibre encephalopathy that have yet to be explored include *GFAP* gene polymorphisms and mutations in genes encoding proteins that are known to interact with *GFAP*, such as the $\alpha\beta$ -crystallin gene.

This is the first description of Rosenthal fibre encephalopathy in a patient with AIDS and who showed no neurological impairment despite having CNS lymphoma and cytomegalovirus infection. Rosenthal fibre formation in this setting has a number of possible explanations. First, overexpression of *GFAP* in transgenic mice is sufficient to induce the formation within astrocytes of protein aggregates that are biochemically and morphologically indistinguishable from Rosenthal fibres.²² The underlying viral infection or neoplastic disorder may have provoked an over-expression of the *GFAP* gene resulting in the formation of Rosenthal fibres. Second, polymorphisms in the *GFAP* gene favouring alterations in the tertiary structure of the protein that promote *GFAP* aggregation or enhanced stability are possibilities that need to be explored. Third, it is interesting to note that five of the 11 cases of Rosenthal fibre encephalopathy, including this one, were associated with immunosuppression. At present it is unclear whether there is a causal link.

NOTE ADDED IN PROOF

Since the submission of this article, it has been reported for the first time that novel missense mutations in the *GFAP* gene have been detected in two Japanese brothers with hereditary adult onset Alexander's disease, with postmortem confirmation in one case. This finding extends the role of pathogenic mutations in *GFAP* to the aetiology of familial subtypes of adult onset Alexander's disease (Namekawa M, Takiyama Y, Aoki Y, *et al.* Identification of *GFAP* gene mutation in hereditary adult-onset Alexander's disease. *Ann Neurol* 2002;**52**:779–85).

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