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Childhood acute disseminated encephalomyelitis: the role of brain and spinal cord MRI

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Abstract *Background*. It is recognised that the clinical and radiological spectrum of childhood acute disseminated encephalomyelitis (ADEM) is wide. *Objective*. To determine whether initial MRI features are predictive of clinical outcome and to determine the role of MRI in the management of ADEM. *Materials and methods*. The MRI scans of ten consecutive children (eight boys, two girls), clinically and radiologically diagnosed to have ADEM, were retrospectively reviewed. Follow-up MRI was available for eight patients. *Results*. Lesions ranged from small and punctate (< 1 cm) to moderate sized and confluent (4–5 cm) to diffuse and extensive. Spinal cord lesions, seen in five of seven children, were contiguous or segmental. Seven children (70%) made good clinical recovery while three children (30%) remained severely handicapped. There was no correlation between the site, extent and pattern of involvement and clinical outcome. However, the evolution of MRI findings on follow-up correlated well with the subsequent clinical course and outcome. *Conclusions*. Although the extent and site of lesions on initial MRI scans are not predictive of clinical outcome, early MRI of the brain and spine is useful in aiding clinical diagnosis, and subsequent follow-up MRI is helpful in monitoring disease progression.

Keywords Childhood · Acute disseminated encephalomyelitis Clinical outcome · MRI

Introduction

Acute disseminated encephalomyelitis (ADEM) is an immunologically mediated inflammatory demyelinating disease of the central nervous system [1, 2]. It is hypothesised to be an autoimmune response to antibody-antigen complexes within the nervous system. In addition to cases that are post-infectious or post-vaccinial, there are some in which no precipitating factor has been traced [1]. The clinical spectrum of ADEM is not completely known and may range from a subclinical episode detected by the appearance of multifocal areas of prolonged T2 relaxation in the brain on MRI scans, to a fulminant rapidly progressive disease with seizures and coma leading to death [3, 4]. MRI is the most sensitive imaging modality for the detection of ADEM lesions [5]. The purpose of our study was to determine whether initial MRI features are predictive of clinical outcome and to determine the role of MRI in the management of childhood ADEM.

Patients and methods

We retrospectively reviewed the MR images of all children clinically and radiologically diagnosed to have ADEM in our institution over a 4-year period (May 1996 to May 2000). The clinical

criteria used for the diagnosis of ADEM were: (1) a previously healthy child with an acute neurological manifestation of a monophasic illness, (2) history of a recent infection or prior vaccination, (3) clinical response to steroid therapy, (4) negative CSF cultures for bacteria, fungi and viruses, and (5) exclusion of demyelination due to other causes.

There were eight boys and two girls with an age range of 18 months to 17 years (mean 9.8 years). MRI of the brain was performed between day 1 and day 30 (mean 8.8 days) of hospital admission for all ten patients. The following sequences were performed: spin-echo T1-weighted (T1-W), fast-spin-echo (FSE) proton-density and T2-weighted (T2-W) in all patients, and fluid-attenuated inversion recovery (FLAIR) in seven patients. Gadolinium-DPTA (0.1 mmol/kg) was administered intravenously to nine patients. In addition, MRI of the whole spine was performed on seven patients using spin-echo T1-W and FSE T2-W sequences. Fourteen follow-up MRI examinations were performed on eight patients between 2 months and 3 years 6 months. The location, extent and description of the abnormal signal in the cerebral white matter (subcortical and deep), cerebellum, cortex, basal ganglia, thalami, brain stem and spinal cord were recorded, as was the presence of contrast enhancement and enhancement pattern. Clinical presentation, laboratory investigations, treatment and clinical outcome were reviewed. The duration of clinical follow-up ranged between 1 year and 4 years 6 months (mean 2 years 5 months).

Results

The results are summarised in Table 1. The presenting symptoms were progressive lower limb weakness ($n=6$), dysarthria ($n=3$), change in sensorium ($n=3$), urinary retention ($n=2$), ataxia ($n=2$), status epilepticus, hemiplegia, monoparesis, constipation and blurred vision due to optic neuritis (each $n=1$). The duration of symptoms before hospitalisation ranged from 1 day to 3 weeks (mean 6.7 days). Prodromal upper respiratory tract infection was present in five patients and one patient received vaccination (measles, mumps and rubella) 1 day prior to the onset of symptoms. The range of prodrome duration was 3 days to 2 months (median 5 days). Oligoclonal bands were absent in the CSF of eight of ten patients tested. The results of CSF glucose and protein tests were normal in eight patients; two patients had slightly raised CSF protein levels; one patient had a mildly elevated CSF lymphocyte count. One patient had a fourfold raised serum mycoplasma titre. All except one had normal CSF opening pressures. EEGs were abnormal in three patients while nerve conduction velocity was abnormal in one patient. Five patients required admission to the intensive care unit for ventilator support. The indication for mechanical ventilation was either decreased sensorium with poor airway protection ($n=2$) or respiratory failure ($n=3$). Four patients were successfully weaned off ventilator support (mean ventilation period 5 days) whereas one patient became ventilator dependent.

The MRI appearances were varied. All ten patients had foci of prolonged T2 relaxation in the brain. Brain lesions were present in the cerebral deep white matter ($n=9$), cerebellar deep white matter ($n=4$), subcortical white matter ($n=8$), thalami ($n=6$), brain stem ($n=6$), basal ganglia ($n=1$), cerebral cortex ($n=1$) and spinal cord ($n=5$). In three patients, brain lesions were extensive. One patient had diffuse T2 prolongation of the deep and subcortical white matter with sparing of only the perirolandic white matter and capsular fibres (Fig. 1). One patient had extensive asymmetrical involvement of the bilateral deep grey matter, cortex and subcortical white matter (Fig. 2). One patient had bilaterally symmetrical lesions diffusely involving the deep and subcortical white matter of the parietal and occipital lobes, corticospinal tracts, dorsal brain stem and cerebellar white matter (Fig. 3). The other patients had multifocal brain lesions, which ranged from small and punctate (<1 cm) to moderate sized and confluent (4–5 cm) (Figs. 4, 5). In three patients, the multifocal lesions were moderately extensive. Contrast enhancement was present in three patients. The enhancement pattern was ring-like, focal and diffuse/patchy (Figs. 4b,c).

Spinal cord MRI was performed on seven patients, of whom five had lesions. All patients with spinal cord lesions had signs of myelopathy and concurrent lesions in the brain, of whom three patients had predominant lesions in the spinal cord. One patient also had abnormal nerve conduction velocity. Spinal cord involvement was contiguous in four patients (Fig. 6) and focal segmental in one patient (Fig. 7). In two patients, the spinal cord lesions were extensive, involving the entire extent of the spinal cord. None of the spinal cord lesions demonstrated contrast enhancement.

No new lesions were detected on follow-up MRI examination. Partial resolution of the lesions was present in three patients (37.5%) and complete resolution was present in a further three patients (37.5%). Marked progressive atrophy of the cerebrum and spinal cord was detected in the remaining two patients (25%). Eight patients received high-dose steroid therapy intravenously (methylprednisolone 15–20 mg/kg/day for a minimum of 3–4 days). Additional immunoglobulin (400 mg/kg for 5 days) therapy was administered intravenously to five patients, beta-interferon treatment to two patients and plasmapheresis to one patient. Two patients received only symptomatic treatment. Steroid therapy commenced 2–30 days after admission (mean 10 days).

Clinical outcome was variable on follow-up. Four patients (40%) had complete recovery of symptoms, three patients (30%) had almost complete resolution of symptoms with mild residual bladder symptoms and ataxia, while three patients (30%) remained severely handicapped. None of the patients had clinical relapses after an average follow-up period of 2 years 5 months.

Further evaluation of the radiological findings and clinical outcome did not reveal a consistent correlation

Table 1 Summary of clinical presentation, MRI findings, treatment and clinical outcome (*LL* lower limb, *V* ventilator, *SCWM* subcortical white matter, *DWM* deep white matter, *BG* basal ganglia, *T* thalamus, *BS* brain stem, *SC* spinal cord, *IVI* intravenous immunoglobulin, *PP* plasmapheresis, *BI* beta-interferon, *NA* not available, *NCV* nerve conduction velocity)

No.	Age (years)	Presentation	V (duration)	Cerebral SCWM	Cerebral DWM	Cerebellar WM	Cortex	BG	T	BS	SC	Steroid commencement	Other treatment	Follow-up MRI	Duration of clinical follow-up	Clinical outcome
1	1.5	Status epilepticus	+ (8 days)	+	+	–	–	–	–	–	NA	–	–	NA	2 years 9 months	Moderate mental retardation, cortical blindness, epilepsy, spastic quadriplegia
2	12	LL weakness abnormal NCV	+ (Dependent)	–	+	–	–	–	–	+	+	+ (day 10)	IVIG, PP, BI	Severe spinal cord atrophy	4 years 3 months	Flaccid quadriplegia, ventilator dependence
3	16	Behavioural change, change in sensorium	+ (3 days)	+			+	+	+	–	NA	+ (day 30)	IVIG	Severe cerebral atrophy	3 years 3 months	Spastic quadriplegia, dyskinesia, dysphasia
4	13	Urinary retention, paraplegia, constipation, lethargy	+ (3 days)	+	–	–	+	+	+	–	NA	+ (day 3)	IVIG	Complete resolution	2 year 6 months	Intermittent catheterisation, otherwise good recovery
5	10	LL weakness, neck pain, headache	+(7 days)	–	+	+	–	–	+	+	+	+ (day 2)	IVIG, BI	Complete resolution	3 years 9 months	Neurogenic bladder, incontinence, otherwise good recovery
6	5	Dysarthria, ataxia, right monoparesis	–	+	+	+	–	–	+	+	–	+ (day 3)	–	Partial resolution	2 years	Complete recovery
7	7	Left hemiplegia, dysarthria	–	+	+	–	–	–	+	–	NA	+ (day 2)	–	Partial resolution	1 year 9 months	Complete recovery
8	6	LL weakness, calf pain, slurring of speech	–	+	+	+	–	–	+	+	+	–	–	Complete resolution	2 years 9 months	Complete recovery
9	10	Confusion hallucination, LL weakness, urinary retention	–	+	+	–	–	–	+	+	+	+ (day 5)	–	NA	1 year 1 month	Complete recovery
10	17	Left LL weakness, slurring of speech, ataxia. Subsequently developed optic neuritis	–	+	+	+	–	–	–	+	–	+ (day 24)	–	Partial resolution	1 year	Mild residual ataxia, otherwise good recovery

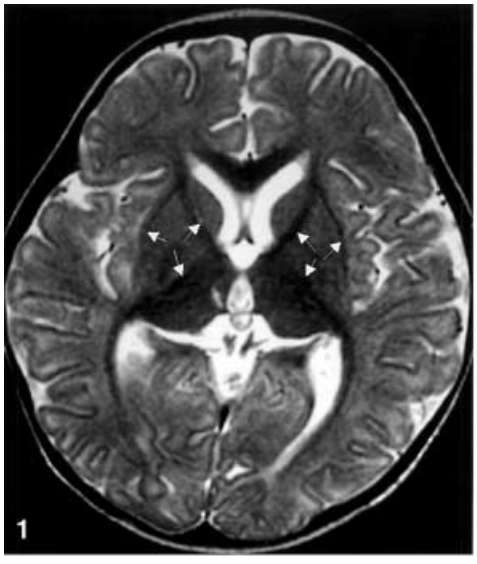

Fig. 1 Patient 1. An 18-month-old girl who presented with status epilepticus 1 day after vaccination (measles, mumps and rubella). FSE T2-W axial MRI performed 18 days after presentation shows diffuse hyperintensity in the deep and subcortical white matter with sparing of the capsular fibres (*arrows*)

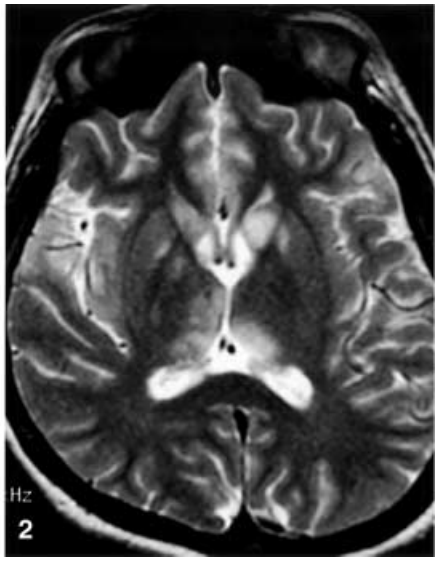

Fig. 2 Patient 3. A 16-year-old girl who presented with a prolonged prodromal behavioural change and change in sensorium for 2 months. FSE T2-W axial MRI shows hyperintense lesions asymmetrically located in the thalami and basal ganglia bilaterally. Other hyperintense lesions were present in the cortex and subcortical white matter, especially in the temporal lobes. Follow-up MRI showed progressive cerebral atrophy

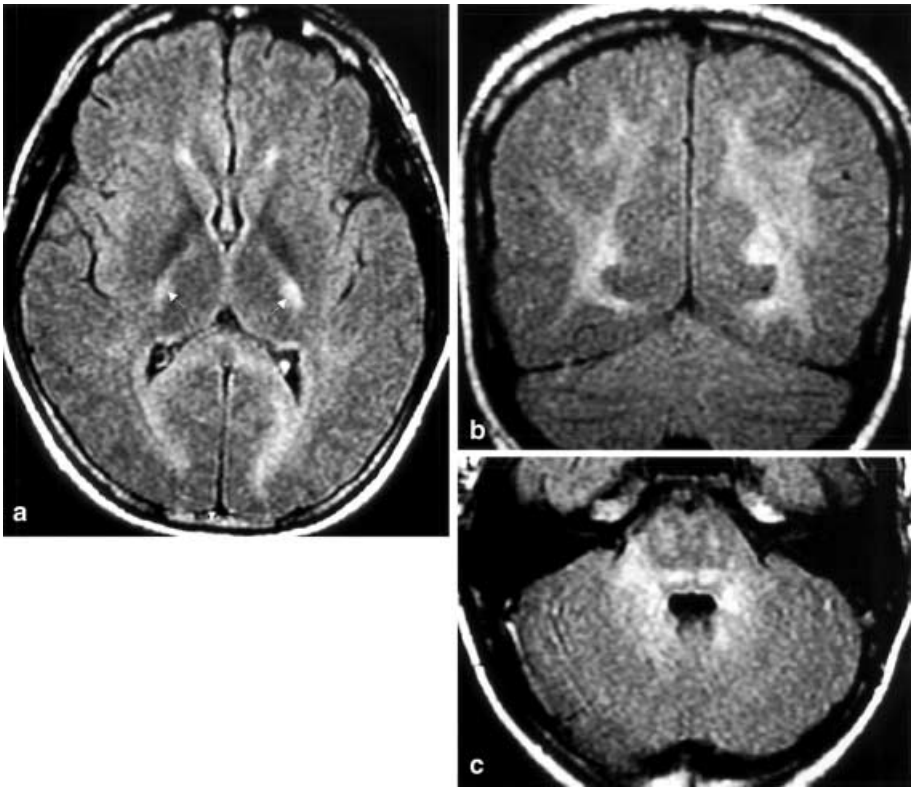

Fig. 3a–c Patient 10. A 17-year-old boy presented with change in sensorium, muscle weakness, slurring of speech and ataxia. **a** Axial and **b** coronal FLAIR images show bilaterally symmetrical white matter hyperintensity diffusely involving the occipito-parietal lobes and the posterior limbs of the internal capsules (*arrows*). **c** FLAIR sequence in the axial plane shows bilaterally symmetrical hyperintense foci in the dorsal pons, middle cerebellar peduncles and cerebellar deep white matter

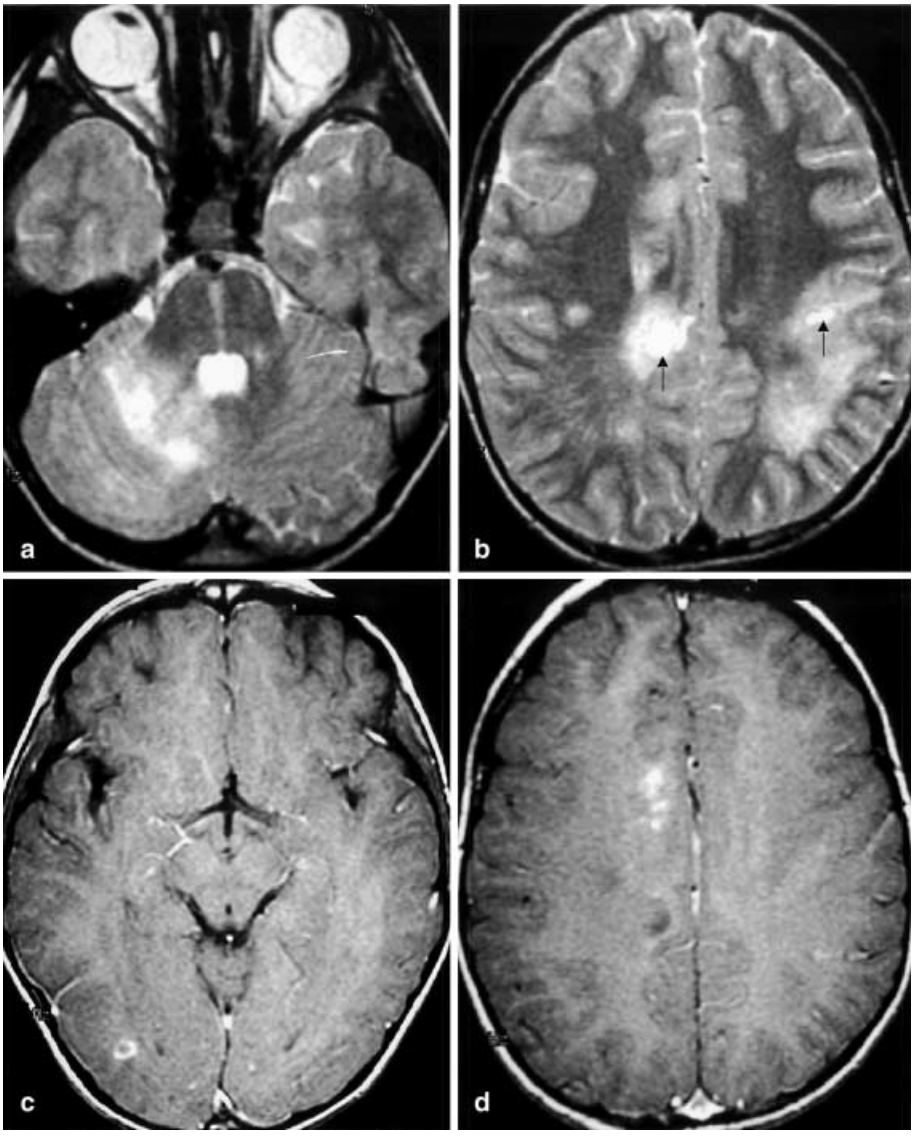

Fig. 4a–d Patient 6. A 5-year-old boy who presented with dysarthria, ataxia and right-sided monoparesis after an upper respiratory tract infection. **a** FSE T2-W axial MRI shows a moderate-sized confluent lesion in the deep white matter of the right cerebellar hemisphere and a linear lesion in the midline of the pons. **b** FSE T2-W axial MRI shows bilaterally asymmetrical lesions in the centrum semiovale. On the left side, there is a moderate-sized area of prolonged T2 relaxation in the deep and subcortical white matter of the parietal lobe and on the right side, several smaller foci are noted in the deep and subcortical white matter of the frontal and parietal lobes. Within these areas, there are focal lesions of higher signal intensity (*arrows*). **c** Post-contrast spin-echo T1-W axial MRI of the same section as **b** shows nodular enhancing lesions in the right frontal lobe. **d** Post-contrast spin-echo T1-W axial MRI shows a ring-enhancing lesion in the right occipital lobe

between lesion site, extent, pattern of involvement and clinical outcome. Of the three patients with extensive cerebral lesions, two remained severely handicapped with moderate mental retardation, cortical blindness, epilepsy, spastic quadriplegia and dysphasia, while one patient had good recovery with mild residual ataxia. Of the two patients with extensive spinal cord lesions, one remained severely handicapped with flaccid quadriplegia and ventilator dependence and the other made good clinical recovery with residual mild neurogenic bladder. Three patients with moderately extensive lesions enjoyed complete recovery of clinical symptoms.

All patients whose follow-up MRI scans showed partial/complete resolution of lesions made good clinical recovery, whereas the patients whose follow-up MRI scans showed progressive atrophy (cerebral/spinal cord) remained severely handicapped.

All three patients who suffered poor clinical outcome had in common a severe illness at presentation requiring ventilator support, delay in diagnosis and subsequent steroid administration.

Discussion

ADEM is mainly a monophasic disease, which may present with widespread central nervous system dysfunction. Most cases involve children or young adults [6] who recover in 2–4 weeks with no residual neurological sequelae [7]. Although previously reported to cause permanent neurological deficit in 10–20% and death in 15–20% of patients [1], recent series report better clinical outcome and no deaths [5, 6, 7, 8]. Pathologically, the prolonged T2 values have been shown in experimental

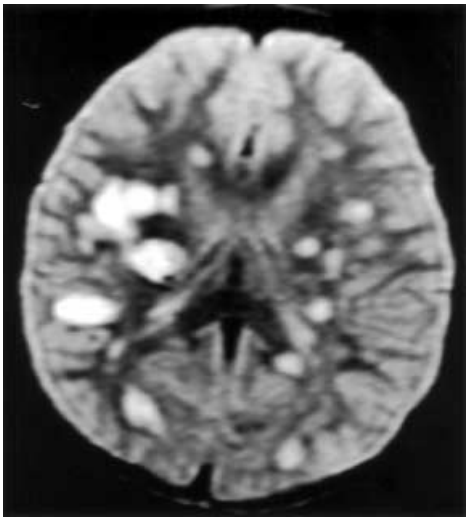

Fig. 5 Patient 7. A 7-1/2-year-old boy who presented with dysarthria and left hemiplegia after an upper respiratory tract infection. FSE proton density axial MRI shows multiple oval-shaped hyperintense lesions in the deep and subcortical white matter of the frontal and parietal lobes. Other similar lesions were noted in the thalamus and in the posterior limb of the right internal capsule

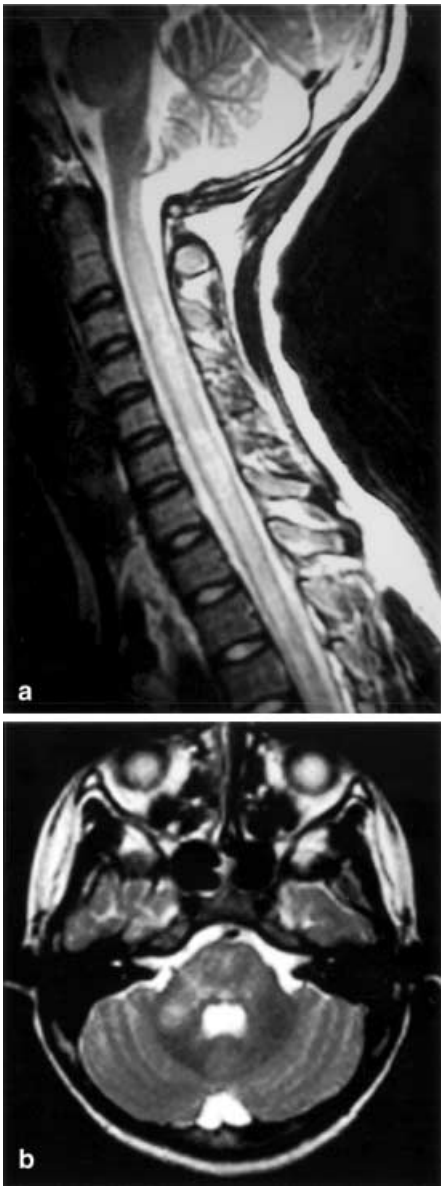

Fig. 6a,b Patient 5. A 10-year-old boy who presented with lower limb weakness. **a** FSE T2-W sagittal MRI of the cervical and upper thoracic spine shows a contiguous hyperintense lesion in the central spinal cord associated with cord expansion. **b** FSE axial T2-W MRI shows foci of prolonged T2 relaxation in the middle cerebellar peduncle and pons

allergic encephalomyelitis to be associated with the presence of inflammation, demyelination and haemorrhagic necrosis [9].

Although classically known to be a disease involving white matter, more recent series have shown that deep grey matter involvement is not uncommon and is now considered part of the radiological spectrum [7]. Our series also showed a high incidence of deep grey matter involvement, occurring in 60% of patients. Distinct from other series, ours showed marked predominance of thalamic lesions compared to the caudate nuclei, globus pallidus and putamen [7]. It has been suggested that involvement of the thalamus may help to distinguish ADEM from multiple sclerosis since lesions in the thalamus are rare in multiple sclerosis [7]. Other differential diagnoses for deep grey matter involvement include mitochondrial disease, which can present similarly. However, involvement was asymmetrical in all our patients, contrary to the symmetrical lesions typically seen in mitochondrial disease. In addition, concurrent spinal cord involvement, prevalent in our series, is a useful clue for the diagnosis of ADEM. Previously described lesions range from small and round to large, amorphous and irregular. Less commonly, solitary tumour-like lesions with mass effect [10] and multiple cystic lesions [11] have been described. Rarely, there is haemorrhage [10] and calcification [12].

Although bilaterally symmetrical multifocal lesions have been described, bilaterally symmetrical diffuse white matter involvement is not considered typical in ADEM and this pattern is more commonly associated with metabolic and toxic demyelination. We describe such a pattern of bilaterally symmetrical diffuse white matter involvement where diagnosis was made after dramatic clinical response to steroid therapy and no evidence of clinical relapse after 1 year (Fig. 3).

Another atypical pattern in our series was one of diffuse, symmetrical and extensive white matter involvement with sparing of only the capsular fibres and

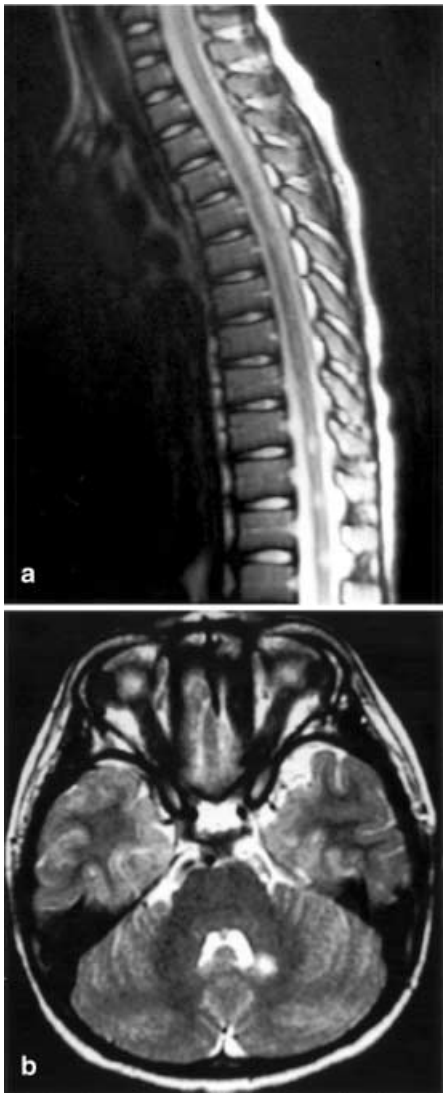

Fig. 7a,b Patient 8. A 6-year-old boy who presented with lower limb weakness and slurring of speech. **a** FSE T2-W sagittal MRI of the thoracic spine shows three focal segmental lesions in the lower thoracic cord. **b** FSE axial T2-W MRI shows a small focal lesion concurrently detected in the left middle cerebellar peduncle

perirolandic white matter (Fig. 1), seen in an 18-month-old girl who presented with status epilepticus 1 day after vaccination.

Contrast enhancement may occur in some lesions when there is a breakdown of the blood–brain barrier. The presence of enhancement in some but not all lesions in the same patient may be due to the different degrees of damage to the blood–brain barrier [7]. The pattern of enhancement is non-specific and may include nodular, diffuse, gyral and ring patterns of enhancement [7, 10].

MRI is sensitive in the detection of lesions in the brain, but it lacks specificity because of the wide radiological spectrum [3, 4, 10, 13, 14] and overlapping appearances with other forms of demyelinating diseases, especially multiple sclerosis and its variants, including diffuse sclerosis (Schilder's disease), Devic's disease etc. Diagnosis is aided by clinical judgment, although it may sometimes be impossible without long follow-up periods to exclude relapses.

The frequency of concurrent spinal cord involvement is unknown. In none of the other reported series of childhood ADEM was the spinal cord routinely imaged in all patients. Instead, imaging of the spinal cord was only performed when there were signs of myelopathy, which occurred in only one out of ten patients in a recent series [7]. In our series, concurrent spinal cord involvement was common, with 71% of patients having lesions. Another notable finding is the common presenting symptom of lower limb weakness in our series, compared to other series where the clinical syndrome is more often characterised by encephalopathy. This difference may represent a regional variation in the spectrum of ADEM. Concurrent demyelination in the brain, spinal cord, optic nerve and peripheral nervous system observed in our series supports the hypothesis that the spectrum of ADEM encompasses isolated demyelinating syndromes of transverse myelitis, optic neuritis and Guillian-Barré syndrome [4, 15, 16].

We did not observe any correlation between the site, extent and pattern of lesions detected on initial MRI scans and clinical outcome. In a recent review of 21 ADEM patients, the authors observed that the initial MRI of patients with resultant disability showed either multifocal lesions or extensive brain stem lesions [8]. Although all patients with poor clinical outcome in our series had extensive involvement on MRI scans, others with similarly extensive involvement did significantly better. In our series, only one out of six patients with brain stem lesions had a poor clinical outcome. We found follow-up MRI useful in monitoring disease progression as there was good correlation between the evolution of follow-up MRI findings and the clinical course of the disease.

It is important to recognise the spectrum of MRI findings in ADEM. Early MRI is useful for lesion detection in a case of suspected ADEM and it is one of the important elements in diagnosis, but it must be considered together with clinical and paraclinical findings.

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