Brain (2000), **123,** 2407–2422

Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children

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Summary

Forty-eight children with disseminated demyelination of the CNS, 28 with acute disseminated encephalomyelitis (ADEM), seven with multiphasic disseminated encephalomyelitis (MDEM) and 13 with multiple sclerosis were studied for a mean follow-up period of 5.64 years. The presentation findings of the ADEM/MDEM group were compared with those of the multiple sclerosis group. The following findings were more commonly seen in ADEM/MDEM presentation compared with the multiple sclerosis presentations: predemyelinating infectious disease (74 versus 38%, $P < 0.05$); polysymptomatic presentation (91 versus 38%, $P < 0.002$); pyramidal signs (71 versus 23%, $P < 0.01$); encephalopathy (69 versus 15%, $P < 0.002$); and bilateral optic neuritis (23 versus 8%, not significant). Seizures occurred only in the ADEM/MDEM group (17 versus 0%, not significant). Unilateral optic neuritis occurred only in the multiple sclerosis patients (23 versus 0%, $P < 0.01$). There were no differences in the frequencies of transverse myelitis, brainstem involvement, cerebellar signs and sensory disturbance between the two groups. ADEM/MDEM patients were more likely to have blood leucocytosis (64 versus 22%, $P < 0.05$), CSF lymphocytosis (64 versus 42%, not significant) and CSF protein elevation (60 versus 33%, not significant). Patients presenting with multiple sclerosis were more likely to have intrathecal synthesis of oligoclonal bands on presentation (64 versus 29%, not significant). MRI showed that subcortical white matter lesions were almost universal in both groups, though periventricular lesions were more common in multiple sclerosis (92 versus 44%, $P < 0.01$). By contrast, in ADEM/MDEM there was absolute and relative periventricular sparing in 56 and 78% of patients, respectively. Follow-up MRI revealed complete or partial lesion resolution in 90% and no new lesions in the ADEM/MDEM group. All of the multiple sclerosis patients had new lesions on repeat MRI (five during relapse and six during asymptomatic convalescent phases). The outcome in the ADEM patients was mixed; 57% of patients made a complete recovery. The mean follow-up for the 35 ADEM/MDEM patients was 5.78 years (range 1.0–15.4 years). Eight of the 13 multiple sclerosis patients relapsed within the first year; 11 had a relapsing–remitting course, one a primary progressive course and one a secondary progressive course. These differences in the presentation of ADEM/MDEM compared with multiple sclerosis may help in the prognosis given to families regarding the possibility of later development of multiple sclerosis.

Keywords: demyelination; multiple sclerosis; children; neuroimaging

Abbreviations: ADEM = acute disseminated encephalomyelitis; MDEM = multiphasic disseminated encephalomyelitis; VEP = visual evoked potential

Introduction

Post-infectious CNS disease is common in acute paediatric practice. Most commonly, an acute cerebellar syndrome follows varicella in 1 in 1000 cases. Other infection-specific processes include sensorineural deafness following mumps and Sydenham's chorea associated with streptococcal infections.

Other inflammatory diseases of the CNS are more difficult to categorize. Inflammation occurring at an isolated CNS site may occur, such as isolated transverse myelitis or optic neuritis. In these cases, the majority of these children have a single event of inflammation, though both of these presentations may be the first episode of a relapsing inflammatory disease such as multiple sclerosis.

When dissemination of inflammatory disease at multiple

Table 1A *Clinical features of ADEM and MDEM patients*

Age (years), sex	Clinical	Encephal-opathy	Pyramidal	Brainstem	Cerebellar	Visual	Sensory	Myelitis	Follow-up (years)	Diagnosis	Impairment
(**A**) ADEM patients											
3, M	A	+	+	+	+	–	–	–	2.4	ADEM	None
3, M	A	+	+	+	+	+	–	–	3.8	ADEM	None
3, F	A	+	+	+	+	+ (BON)	–	–	13.3	ADEM	↓ VA, ↓ IQ
3, M	A	+	+	+	+	–	–	–	7.4	ADEM	Behaviour, motor
3, M	A	–	+	+	+	–	–	–	12.6	ADEM	None
4, M	A	+	+	+	+	+	–	–	6.6	ADEM	Scoliosis
4, M	A	+	+	+	+	–	–	–	2.3	ADEM	Motor
4, M	A	+	+	+	+	–	–	–	1.4	ADEM	None
4, F	A	+	–	–	–	–	–	–	9.3	ADEM	Epilepsy, motor behaviour, ↓ IQ
4, M	A	+	+	–	–	+ (BON)	–	–	15.4	ADEM	↓ IQ
5, F	A	+	+	+	+	+	–	–	8.7	ADEM	↓ IQ, behaviour
5, M	A	+	+	+	+	–	–	–	3.0	ADEM	Behaviour
5, F	A	+	–	–	+	–	–	+	1.4	ADEM	None
5, M	A	–	+	–	–	–	–	–	1.5	ADEM	None
6, F	A	–	+	–	–	+ (BON)	–	–	1.5	ADEM	None
8, F	A	–	+	–	+	–	+	–	2.3	ADEM	None
9, M	A	+	–	–	+	–	–	+	4.3	ADEM	Motor
9, F	A	+	–	–	–	+ (BON)	–	–	1.0	ADEM	None
10, M	A	+	+	+	–	–	–	+	5.4	ADEM	None
10, F	A	+	–	+	–	+	–	+	15.0	ADEM	Paraplegia, ↓ VA, ↓ IQ
10, M	A	–	+	–	–	–	+	–	2.8	ADEM	None
11, M	A	+	+	+	+	–	–	–	7.3	ADEM	None
11, F	A	–	–	+	–	–	–	+	2.7	ADEM	Paraplegia, neuropathic bladder

Table 1 *Continued*

Age (years), sex	Clinical	Encephal-opathy	Pyramidal	Brainstem	Cerebellar	Visual	Sensory	Myelitis	Follow-up (years)	Diagnosis	Impairment
12, F	A	+	+	–	+	–	+	+	14.3	ADEM	Paraesthesia
13, F	A	+	+	+	+	–	+	–	9.3	ADEM	None
13, M	A	+	–	–	–	+	–	+	1.3	ADEM	None
13, F	A	–	+	–	–	–	+	–	1.5	ADEM	Paraesthesia
15, F	A	+	+	–	–	+ (BON)	+	–	7.3	ADEM	↓↓ VA
(**B**) MDEM patients											
4, F	A	–	+	+	–	–	–	–	1.5	MDEM	None
	R (0.15)	–	+	–	–	+ (UON)	–	–			
4, M	A	+	+	+	+	–	–	–	14.4	MDEM	None
	R (0.1)	–	+	+	+	–	–	–			
6, M	A	–	+	–	–	+ (BON)	–	–	10.0	MDEM	None
	R (0.15)	+	+	–	–	–	–	–			
	R (2.5)	–	–	–	–	+ (BON)	–	–			
7, M	A	+	–	–	–	+ (BON)	–	–	3.0	MDEM	None
	R (0.15)	+	–	+	–	–	–	–			
8, F	A	–	–	–	–	–	–	+	3.5	MDEM	Paraplegia, neuropathic bladder
	R (0.15)	–	–	+	–	–	–	–			
12, F	A	+	–	–	–	+ (BON)	–	–	2.2	MDEM	None
	R (0.3)	+	–	–	–	–	–	–			
	R (1.0)	+	–	–	–	+ (BON)	–	–			
15, M	A	–	+	+	–	–	–	–	2.5	MDEM	None
	R (0.1)	–	+	+	–	–	–	–			

F = female; M = male; A = acute; BON = bilateral optic neuritis; VA = visual acuity; R = relapsing (years to relapse); BON = bilateral optic neuritis; UON = unilateral optic neuritis.

sites within the CNS is monophasic, the disease is termed 'acute disseminated encephalomyelitis' (ADEM). It has been demonstrated that relapses may occur immediately after ADEM. If these relapses are thought to represent part of the same acute monophasic immune process, the term 'multiphasic disseminated encephalomyelitis' (MDEM) is used. If, however, relapses occur that are disseminated with respect to site and time, which support a chronic immune process, multiple sclerosis is diagnosed.

In children, ADEM (and MDEM) is diagnosed more commonly than multiple sclerosis. In adults the opposite is true.

When a child presents with a first episode of disseminated CNS inflammation, the most important issue on recovery is the potential risk of relapse and, therefore, the prognosis. In view of the variable length of time between presentation and relapse in multiple sclerosis, this can be adequately examined only by prolonged follow-up. A follow-up study of disseminated demyelination disease in children was performed. The children who remained monophasic (ADEM/MDEM) were compared with those who had developed clinically definite multiple sclerosis (from now on referred to as multiple sclerosis) to see whether differences exist at disease presentation.

Patients and methods

All children presenting to Great Ormond Street Hospital, London, between 1985 and 1999 with one or more episode of disseminated CNS demyelination were included in the study. Children were excluded if they had a preceding neurological abnormality, isolated optic neuritis or isolated transverse myelitis, infective encephalomyelitis, cerebral vasculitis, systemic lupus erythematosus or other intracranial pathologies. Clinical and investigation findings on disease presentation were accumulated from patient notes. MRIs of the brain and spinal cord were reviewed by two paediatric neuroradiologists (W.K.C. and T.C.S.C.), who were blinded to the clinical findings. The images were assessed for lesion site, size, characteristics and symmetry. Between April and June 2000, a follow-up study was performed. After gaining approval from the research ethics committee of Great Ormond Street Hospital, the GP (general practitioner) of each patient was traced by using regional health authority registers. Written consent was obtained from each GP to re-contact the families of patients. The patient was contacted first by letter (for written consent) and subsequently by telephone. A telephone questionnaire was used to determine residual disability and the incidence of further neurological disease. Only three patients, who had moved abroad, were lost to follow-up. Using this method of tracing patients, the mean follow-up was extended from 2.36 to 5.64 years [5.78 years for the ADEM/MDEM group, 5.3 years for the clinically definite multiple sclerosis (using Poser criteria) group].

The monophasic group (ADEM/MDEM) was compared with the multiple sclerosis group to see if there were differences in clinical and investigation findings at disease presentation. Statistical differentiation was made by calculating the standard error of the difference between the two groups.

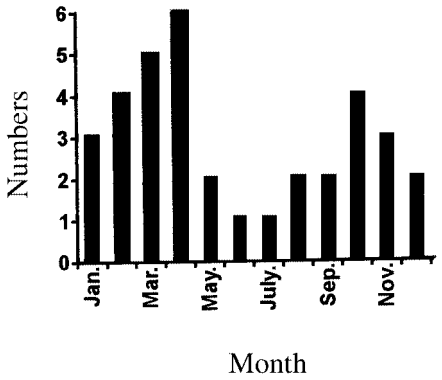

Fig. 1 Seasonal presentation of ADEM/MDEM.

Results

Forty-eight children had evidence of disseminated inflammatory CNS disease. Twenty-eight children fulfilled criteria for the diagnosis of ADEM, seven for the diagnosis of MDEM and 13 for the diagnosis of multiple sclerosis.

Age, sex and family history

ADEM/MDEM

Sixteen female and 19 male patients with ADEM/MDEM were included. Forty-six per cent of the patients were between 3 and 5 years of age (Table 1). No patients presented before 3 years of age. There was no family history of multiple sclerosis in any patient in the ADEM/MDEM group.

Multiple sclerosis

Of the 13 patients with multiple sclerosis, six were female and seven male. Age of presentation was between 4 and 15 years, only three patients (23%) presenting under 5 years of age. One child had a second-degree relative with multiple sclerosis.

Clinical findings

ADEM/MDEM

The presentation of the ADEM/MDEM patients showed a seasonal distribution (Fig. 1), being more prevalent in the winter months. Twenty-six patients (74%) had a preceding illness in the month before presentation. The mean latency between predemyelinating illness and the onset of neurological signs was 13.0 days (range 2–31 days). The preceding illnesses were described as upper respiratory tract infection (9 patients); influenza (3); tonsillitis (4); lower respiratory tract infection (3); vaccination (2); gastroenteritis

(2); varicella (1); and fever of unknown origin (2). Ten children had serological evidence of specific triggers: streptococcus (3); mycoplasma (1); influenza B (1); enterovirus (1); Epstein–Barr virus (1); varicella (1); mumps rubella immunization (1); and BCG vaccine (1).

Neurological presentation varied from an acute explosive onset, with a maximum neurological deficit attained within 1 day, to more indolent progression with maximum deficit at 31 days (mean 7.1 days). Symptoms and signs of systemic disease were common, headache being present in 58%, fever in 43% and meningism in 31%. Seizures occurred in six patients (17%); they were associated with fever in four patients.

The neurological signs are presented in Table 1. A polysymptomatic presentation (having more than one clinical finding) occurred in 32 (91%) of the children. Alteration in mental state and level of consciousness (encephalopathy) occurred in 24 (69%). Four patients needed ventilation due to severely impaired consciousness. Pyramidal motor signs occurred in 25 patients (71%), of whom 16 had symmetrical upper motor neurone weakness and nine asymmetrical weakness.

Cranial neuropathies occurred in 18 patients (51%) (facial weakness, ophthalmoplegia, dysarthria and dysphagia in descending order of frequency). No patient had internuclear ophthalmoplegia. Visual impairment occurred in 13 patients (37%), of whom eight (23%) fulfilled the criteria for clinical bilateral optic neuritis. No patient had unilateral optic neuritis. Impairment in visual acuity was often severe in the optic neuritis group, median visual acuity being 2/60. Seventeen patients (49%) had cerebellar findings and eight (23%) had clinical myelitis causing acute flaccid paraparesis and urinary retention. Sensory disturbance occurred in six children (17%). Infrequent clinical findings included cogwheel rigidity and titubation (1 patient), athetosis (1) and polyuria/polydipsia (1).

Seven children had relapses in the months after presentation (MDEM). Relapses occurred no more than 8 weeks after stopping steroid treatment. One child relapsed within a week of a routine BCG vaccination. The MDEM group was subsequently relapse-free for a mean follow-up period of 5.3 years (range 1.5–14.4 years).

Multiple sclerosis

Two-thirds of the multiple sclerosis patients presented during the six winter months (October to March). On presentation, five (38%) of the children had had an infection in the month preceding neurological onset. The mean latency between predemyelinating illness and the onset of neurological signs was 9 days (range 1–21 days). The preceding illness was upper respiratory tract infection (3), influenza (1) and fever of unknown origin (1). No microbiological agents were incriminated in any patient. Maximum deficit occurred a mean of 9 days after neurological onset (range 1–60 days). Headache occurred in 23%, fever in 15% and meningism in 8% of the patients. Seizures occurred in no patients. The clinical presentation findings and subsequent relapses are presented in Table 2. Eight (62%) of the patients had a monosymptomatic presentation and five (38%) had a polysymptomatic presentation. The involvement of presentation sites, in descending order of frequency, was as follows: optic neuritis 31% (three unilateral, one bilateral); transverse myelitis 31%; brainstem 23%; cerebellar 23%; pyramidal 23% (all hemiplegia); sensory 15%; encephalopathy 15%. Of the brainstem signs, internuclear ophthalmoplegia occurred in two patients.

Investigation findings

ADEM/MDEM

There was frequent investigation evidence of inflammation in the ADEM/MDEM group. Elevation of the white cell count in the blood (33 patients tested) occurred in 64% of patients (mean 14.7×10^9/l, range 6.7–37.3 $\times$ 10^9/l). Neutrophils were abundant, being elevated in 52% of patients. By contrast, the lymphocyte count was elevated in none, and 52% of patients had lymphopenia. The C-reactive protein concentration and erythrocyte sedimentation rate were elevated in 35 and 46% of patients, respectively. Six patients had T-cell subpopulation measurements during the acute phase: one had an activated CD3 population and one had a decreased CD4 count.

CSF evidence of inflammation (either pleocytosis or raised protein) occurred in 75% of 33 patients tested. Lymphocyte CSF pleocytosis occurred in 64% (mean 51 cells/mm^3, range 0–270) and elevated CSF protein concentration occurred in 60% (mean 0.69 g/dl, range 0.1–3.3).

Oligoclonal bands were measured concomitantly in CSF and serum on presentation in 21 patients. Six patients (29%) had evidence of intrathecal synthesis of oligoclonal bands, five (24%) had oligoclonal presence in both CSF and serum and 10 (47%) had no oligoclonal bands in serum or CSF. The six monophasic patients with intrathecal synthesis of oligoclonal bands were followed up for a mean of 6.5 relapse-free years (range 2.2–13.3 years).

Multiple sclerosis

Two children of nine tested (22%) had an elevated peripheral leucocyte (neutrophil) count on presentation. No patient had lymphopenia. Erythrocyte sedimentation rate was elevated in five of seven children (71%) tested in the acute phase, but resolved during convalescence. Twelve children had CSF examination during presentation. CSF evidence of inflammation (elevated cell count or elevated protein) occurred in 58%. Five children (42%) had CSF lymphocytosis (mean 18 cells/mm^3, range 0–130 cells/mm^3). Four children (33%) had CSF protein elevation (mean 0.38 g/dl, range 0.2–0.99 g/dl).

Oligoclonal bands were measured in 11 patients during the acute phase. Intrathecal synthesis of oligoclonal bands

Table 2 *Clinically definite multiple sclerosis: clinical presentation and course*

Age (years), sex	Clinical	Encephal-opathy	Pyramidal	Brainstem	Cerebellar	Visual	Sensory	Myelitis	Follow-up (years)	Diagnosis	Impairment
4, F	A	–	–	–	–	+ (UON)	–	–	11.0	RRMS	Cerebellar ataxia
	R (0.25)	–	–	–	–	+ (UON)	–	–			
	R (9.0)	+	–	–	+	+ (BON)	–	–			
	R (10.0)	–	–	+	–	–	–	–			
5, M	A	+	–	–	–	–	–	+	2.5	RRMS	None
	R (2.0)	–	–	–	–	+ (UON)	–	–			
5, F	A	–	–	–	–	+ (BON)	–	–	8.3	RRMS	None
	R (0.3)	–	–	–	–	+ (UON)	–	–			
	R (0.6)	–	+	–	–	+ (UON)	–	–			
	R (1.0)	–	+	–	–	+ (UON)	–	–			
	R (1.6)	–	+	–	–	+ (UON)	–	–			
	R (4.0)	–	–	–	–	+ (UON)	–	–			
	R (6.0)	–	–	–	–	+ (UON)	–	+			
	R (8.0)	+	–	+	+	+ (UON)	–	–			
6, M	A	–	–	–	–	+ (UON)	–	–	8.0	RRMS	↓ VA 6/24
	R (0.2)	+	–	–	–	–	–	–			
	R (6.0)	–	+	+	+	–	+	–			
	R (8.0)	–	–	–	–	+ (UON)	–	–			
6, F	A	+	–	+	+	–	–	+	9.0	RRMS	Depression, bilateral blindness, neuropathic bladder
	R (0.2)	–	–	+	–	–	–	–			
	R (0.8)	–	–	–	–	–	–	+			
	R (1.7)	–	+	–	–	–	–	–			
	R (5.0)	–	+	–	–	+ (BON)	–	–			
6, M	A	–	–	–	–	–	–	+	7.0	RRMS	↓ VA 6/12
	R (6.0)	–	–	–	–	+ (BON)	–	–			
11, M	A	–	–	+	+	–	–	+	1.3	RRMS	Cerebellar ataxia, euphoria, disinhibition
	R (0.3)	–	+	+	+	–	+	–			
	R (0.9)	–	+	+	–	–	–	–			
	R (1.3)	+	–	–	–	–	–	–			

Table 2 *Continued*

Age (years), sex	Clinical	Encephal-opathy	Pyramidal	Brainstem	Cerebellar	Visual	Sensory	Myelitis	Follow-up (years)	Diagnosis	Impairment
11, M	A	–	+	–	+	–	–	–	4.0	RRMS	Paraplegia, paraesthesia, labile mood
	R (0.3)	–	–	–	–	–	+	–			
	R (0.6)	–	+	–	+	–	–	–			
	R (0.75)	–	–	–	+	–	+	–			
	R (2.0)	–	–	+	–	–	+	–			
	R (3.0)	–	–	–	–	–	–	+			
11, M	A	–	–	+	–	–	–	–	6.0	RPMS	↓ IQ, unilateral blindness, tremor hemiplegia, paraesthesia
	R (0.75)	–	–	–	+	–	+	–			
	R (0.8)	–	–	+	+	–	–	–			
	R (3.0)	–	–	+	–	–	–	–			
	R (4.0)	+	–	–	–	+ (UON)	–	–			
	P (5.0)	–	+	–	–	–	+	–			
14, F	A	–	+	–	–	–	+	–	6.1	RRMS	Unilateral blindness, tremor
	R (1.4)	–	–	–	–	+ (UON)	–	–			
	R (1.9)	–	–	–	–	+ (BON)	–	–			
	R (2.5)	–	–	–	–	–	–	+			
	R (3.0)	–	–	–	–	–	–	+			
14, F	A	–	+	–	–	–	–	–	1.9	RRMS	Tremor
	R (1.2)	–	+	–	+	–	+	–			
14, F	A	–	–	–	–	–	+	–	2.0	PPMS	↓ IQ, paraplegia, internuclear ophthalmia, neuropathic bladder
	P (0.3)	–	+	+	+	+ (BON)	+	–			
15, M	A	–	–	–	–	+ (UON)	–	–	1.4	RRMS	None
	R (1.0)	+	–	–	–	+ (UON)	–	–			

F = female; M = male; A = acute; R = relapsing (years to relapse); P = progressive; UON = unilateral optic neuritis; BON = bilateral optic neuritis; RRMS = relapsing–remitting multiple sclerosis; RPMS = relapsing progressive MS; PPMS = primary progressive multiple sclerosis; VA = visual acuity.

(CSF positive, serum negative) occurred in seven of 11 patients (64%) during the acute phase, though repeat testing during convalescence or on relapse showed that nine of the 11 (82%) had evidence of intrathecal synthesis at some stage of their multiple sclerosis course. The remaining patients had no oligoclonal bands in their serum or CSF.

Neurophysiology

ADEM/MDEM

EEG was performed in 21 patients. Only one patient was normal; all others demonstrated excessive slow-wave activity (asymmetrical in 13, symmetrical in seven). Only one EEG demonstrated epileptiform discharges. Visual evoked potentials (VEPs) were studied in 21 patients. Eleven patients had normal VEPs, whereas 10 showed attenuation, degradation and delay of the waveform (seven bilaterally, three unilaterally). All eight patients with bilateral optic neuritis had abnormal VEPs. Of 13 patients tested without clinical visual impairment, only two had abnormal VEPs.

No patients had abnormal peripheral nerve conduction studies (six tested).

Multiple sclerosis

EEG was performed in seven patients. Five had an abnormal EEG, showing excessive slow-wave activity (three asymmetrical, two symmetrical). No EEG contained epileptiform discharges. The VEP was studied acutely in nine patients; it was abnormal in seven patients, demonstrating attenuation, degradation and delay of the waveform. All four patients with optic neuritis had an abnormal VEP (three unilateral, one bilateral). However, three of five patients without clinical visual impairment had an abnormal VEP.

Neuroimaging

ADEM/MDEM

MRI brain scans were performed in all 35 children, and 32 of the images were available for review. Seventeen of the children had preceding CT scans. Only 59% of the CT scans had been reported as abnormal, whereas all MRI brain scans demonstrated disseminated CNS lesions. MRI FLAIR (fluid-attenuated inversion recovery) sequence and T_2-weighted images demonstrated the abnormalities more readily than T_1-weighted images. The lesion site prevalence is presented in Table 3. In the ADEM group, the lesions were predominantly in the white matter (Fig. 2). Absolute and relative sparing of the periventricular white matter occurred in 56 and 78% of images, respectively. Involvement of the deep and subcortical white matter was nearly universal. Twelve per cent of images had a cortical grey matter lesion. The thalami and basal ganglia were involved in 41 and 28%, respectively. The supratentorial white matter lesions were universally asymmetrical, whereas the thalamic and basal ganglia lesions were symmetrical in 46 and 100%, respectively. The majority of the lesions were large (82% of the scans had at least one lesion measuring >1 cm), had poorly defined margins and were uniform in character (only 22% of the scans had one or more lesions which were non-uniform). One scan had evidence of secondary haemorrhage.

Table 3 *MRI lesion site in ADEM/MDEM patients*

Site	Involvement (percentage of total) (n = 32)
Periventricular white matter	44
Lateral ventricle frontal	16
Lateral ventricle body	16
Lateral ventricle trigone	16
Lateral ventricle temporal	16
Lateral ventricle occipital	16
Third ventricle	16
Fourth ventricle	0
Subcortical/deep white matter	91
Subcortical frontal	66
Subcortical temporal	34
Subcortical parietal	85
Subcortical occipital	53
Cortical grey matter	12
Cortical frontal	12
Cortical temporal	3
Cortical parietal	9
Cortical occipital	6
Brainstem	56
Midbrain	25
Pons	38
Medulla	28
Cerebellar white matter	31
Cerebellar peduncles	9
Thalamus	41
Basal ganglia	28
Internal capsule	28
Spinal cord	28

Imaging was performed during convalescence follow-up in 19 ADEM/MDEM patients (mean 1.5 years after demyelination, range 2 months to 9 years). Seven patients (37%) had complete lesion resolution, 10 (53%) had partial lesion resolution and two (10%) were unchanged. There were no new lesions on convalescent imaging in this group.

Multiple sclerosis

MRI brain scans were performed in all children; 12 of the scans were available for review. T_2-weighted imaging demonstrated the lesions best, though T_1-weighted imaging demonstrated the older lesions adequately on convalescent imaging. The lesion sites at presentation are presented in Table 4. Ninety-two per cent of patients had periventricular lesions predominantly at the trigone or posterior lateral ventricle (Fig. 3). Absolute and relative sparing of the periventricular white matter occurred in 8 and 17% of images, respectively. The lesions were also prevalent throughout the subcortical white matter (92% of images). No patients had any cortical grey matter involvement. The thalami and basal

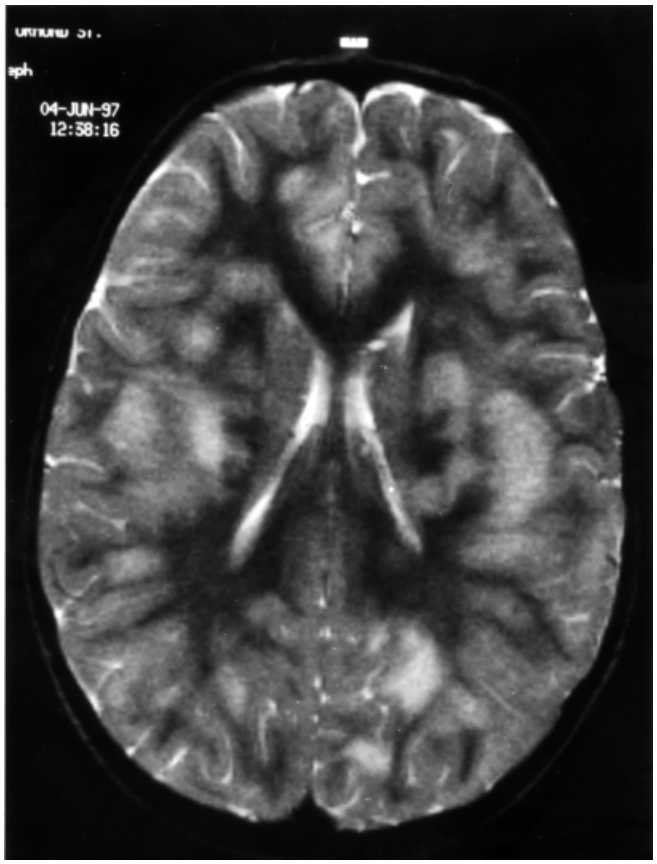

Fig. 2 ADEM. Typical large globular lesions affecting the deep white matter with periventricular sparing.

Table 4 *MRI lesion site on presentation of multiple sclerosis*

Site	Involvement (percentage of total) (n = 12)
Periventricular	92
Lateral ventricle frontal	50
Lateral ventricle temporal	17
Lateral ventricle body	50
Lateral ventricle trigone	75
Lateral ventricle occipital	58
Third or fourth ventricle	0
Subcortical/deep white matter	92
Frontal	66
Parietal	75
Temporal	42
Occipital	67
Cortical grey matter	0
Brainstem	50
Midbrain	17
Pons	33
Medulla	33
Cerebellar white matter	33
Cerebellar peduncles	17
Thalamus	25
Basal ganglia	8
Internal capsule	17
Spinal cord	25

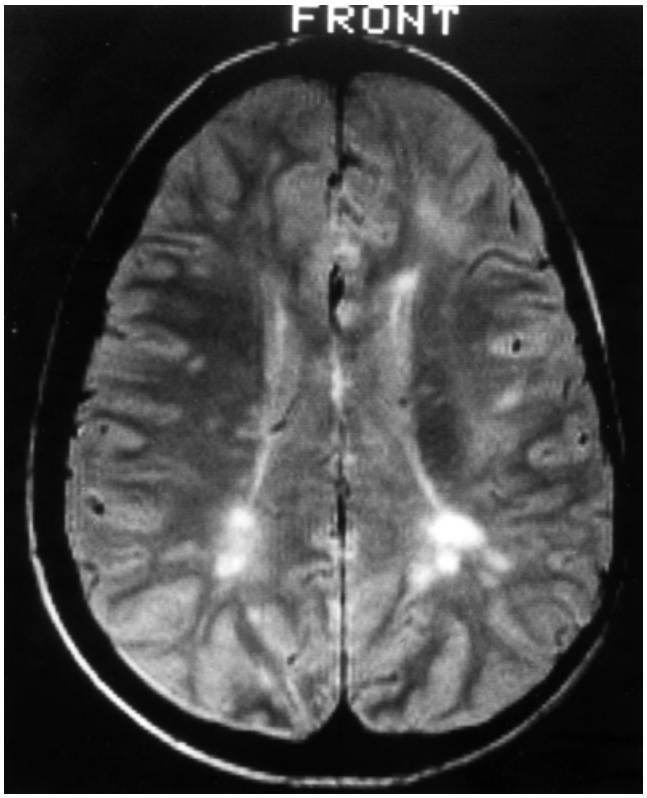

Fig. 3 Multiple sclerosis. Typical periventricular white matter lesions.

ganglia were involved infrequently (25 and 8%, respectively). Fifty-eight per cent of the images had at least one lesion >1 cm in size.

Fifty per cent of the lesions were non-uniform or had a halo appearance. The lesions were reported as well marginated in half of the patients. No patients had evidence of secondary haemorrhage.

Repeat imaging was performed in 11 of the patients during relapses or convalescent phases. No scans showed complete resolution, though all showed partial resolution of previous lesions. New lesions were seen in all 11 patients; five patients were scanned during relapse and six during asymptomatic convalescent phases (mean 8 months, range 3 months to 2 years). Three patients had evidence of cerebral atrophy. Table 5 demonstrates convalescent differences in brain MRI between ADEM/MDEM and multiple sclerosis.

Pathology

ADEM

One patient with ADEM underwent a brain biopsy due to diagnostic uncertainty. No viral particles could be cultured or seen on electron microscopy. On histological examination, one area of white matter showed almost complete loss of myelin but preservation of axons. In other areas there was perivascular myelin loss (Fig. 4), gliosis and a striking inflammatory infiltrate of B and T lymphocytes, plasma cells, eosinophils and foamy macrophages, including thick

inflammatory cell cuffs around small blood vessels, which did not show fibrinoid necrosis or petechial haemorrhages.

Multiple sclerosis

No patient underwent a brain biopsy.

Treatment

ADEM/MDEM

Many children with ADEM presented with neurological deficit, fever and inflammatory changes on blood or CSF investigation. Sixty-six per cent of the children were initially treated for infective meningoencephalitis with antibiotics and antivirals until the correct neuroallergic diagnosis of ADEM had been established. Once the diagnosis had been established, immunomodulatory treatments were considered. Twenty-five patients in this group received steroid treatment (5 days of intravenous methylprednisolone 30 mg/kg/day followed by a weaning regimen of oral prednisolone). Notably, the mean length of steroid treatment in the relapsing MDEM group ($n = 6$) was only 3.17 weeks (range 0.5–8 weeks) versus 6.3 weeks (range 0.5–16 weeks) for the non-relapsing ADEM group ($n = 19$).

Table 5 *Convalescent MRI in ADEM/MDEM and multiple sclerosis groups*

	Diagnosis	
	ADEM/MDEM, $n = 19$ (all convalescent)	Multiple sclerosis, $n = 11$ (5 relapsed, 6 convalescent)
Time after presentation in years (range)	1.5 (0.2–9)	0.75 (0.25–2)
Complete resolution	37%	0%
Partial resolution	53%	100%
Unchanged	10%	0%
New lesions	0%	100%

Multiple sclerosis

Only 23% of the patients were initially suspected as having infective meningoencephalitis and treated with antibiotics or antivirals. Patients were treated with corticosteroids during acute relapses once demyelination had been demonstrated (with the steroid regimen described above). No patient received any other immunomodulation.

Disability

ADEM/MDEM

The mean follow-up period of the ADEM/MDEM patients was 5.78 years (range 1.0–15.4 years). Many of the patients presented with acute aggressive encephalopathy with focal neurological deficits. Despite the often dramatic presentation, the outcome was surprisingly good, with recovery completed between 0.25 and 6 months. The survival in this group was 100%. Twenty (57%) patients had no impairments on follow-up. Six (17%) patients had motor disability. Three of these had severe disability and used a wheelchair (all three had myelitis on presentation and had associated neuropathic bladder and scoliosis). Three had mild motor impairment only. Two (6%) patients have troublesome limb paraesthesia.

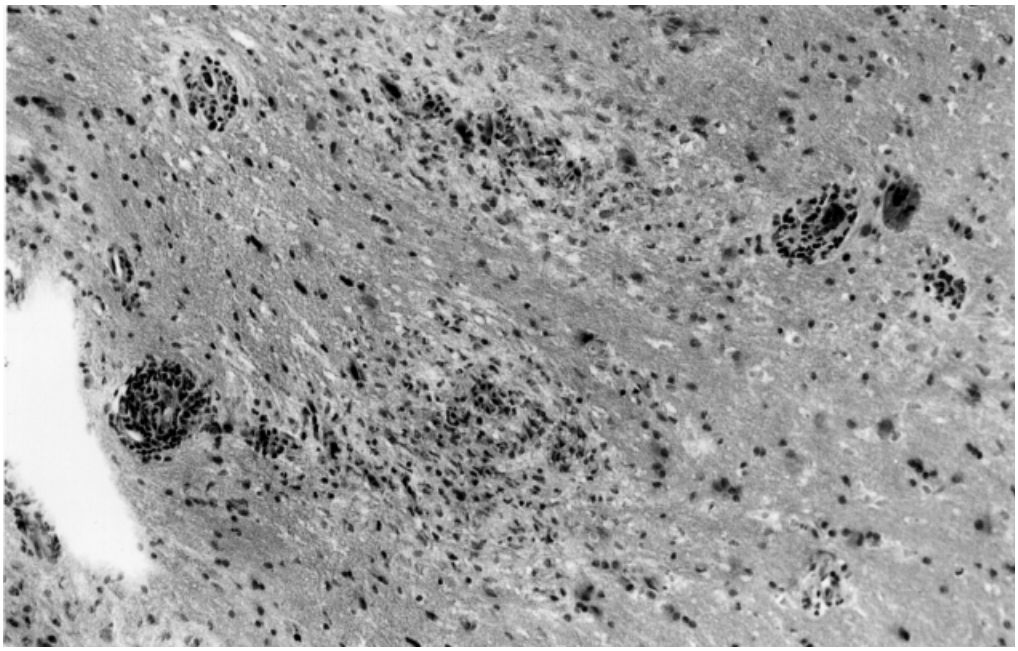

Fig. 4 Brain biopsy from patient with ADEM. This area of white matter shows perivascular sleeves of myelin loss and perivascular inflammatory cuffings. Haematoxylin–eosin stain.

Four (11%) had visual impairment (one bilateral blindness, one unilateral blindness, two minor visual acuity reduction). Four (11%) children had significant cognitive impairment, with an IQ of 70. Four (11%) children had behaviour problems (two obsessive compulsive disorder, two aggression). Three (9%) patients had epilepsy, of whom two had resolution on extended follow-up.

Multiple sclerosis

The initial mean follow-up of the demyelinating cohort of 48 patients was 2.36 years. At this time, 10 (21%) patients within the cohort had clinically definite multiple sclerosis. By extending the follow-up to 5.64 years, a further three patients had a relapse and fulfilled the criteria for the diagnosis of multiple sclerosis (these three multiple sclerosis patients were included within the multiple sclerosis group for all data analysis). Eight of the 13 multiple sclerosis patients relapsed within 1 year. The mean time to relapse was 1.1 years (range 0.2–6 years). The relapse findings are presented in Table 2. Eight (62%) of the first relapses were monosymptomatic. Optic neuritis was again prevalent during the first relapse, occurring in seven patients (five unilateral and two bilateral). There were 39 relapses in 13 multiple sclerosis patients, who were followed up for a mean of 5.3 years (range 1.25–11 years). Eleven of the children had a relapsing–remitting course (three with a benign course). One child had a progressive disease for 1 year from presentation. One child had a relapsing–remitting course for 5 years then a progressive course for 1 year until transfer to adult neurology care. Impairments are recorded in Table 2. No children died during the follow-up period. At follow-up, three children (23%) had no demonstrable disability. Five (38%) children had motor impairment, of whom two (15%) were wheelchair users. Two (15%) patients had troublesome limb paraesthesia. Five (38%) had visual impairment (of whom two were registered blind). Two (15%) had significant cognitive loss and a further three (23%) had alteration of mood. No patients had epilepsy. The significant differences between the two groups are presented in Table 6.

Discussion

In the past, ADEM was observed most frequently following childhood exanthemata, and in one series demyelination was reported as occurring in 1 in 1000 childhood measles infections (Johnson *et al*., 1984). In view of the close relationship between ADEM and infections, the term 'postinfectious encephalomyelitis' has also been used. Infections have also been thought to play an important aetiological role in multiple sclerosis, and various infective agents have been postulated. However, through extensive epidemiological investigation, the aetiology of multiple sclerosis has been shown to be multifactorial, genetic predisposition also having an important role (Poser, 1994).

There are many pathological and clinical similarities between ADEM and multiple sclerosis. However, why some patients (particularly children) suffer an explosive monophasic inflammatory process whereas other patients (particularly adults) suffer a smouldering chronic polyphasic process is unclear.

Our study aimed to review the children seen with disseminated demyelination of the CNS and compare and contrast the clinical and investigation features found in ADEM compared with multiple sclerosis. For the sake of this discussion, the term ADEM will refer to both ADEM and MDEM.

Epidemiology

Children in this series with ADEM and multiple sclerosis showed no sex predominance. Multiple sclerosis series, by contrast, report a female : male ratio of 2 : 1 in adults. Childhood series have similarly reported a ratio between 2.2 : 1 and 3 : 1 (Duquette *et al*., 1987; Ghezzi *et al*., 1997). The predominance of females is most noticeable in adolescence, suggesting that hormonal changes related to puberty in females may have an important role.

The age distribution of children with ADEM in this series showed early childhood predominance. A large amount of accumulated data regarding the age of multiple sclerosis presentation supports a Gaussian curve distribution, with increasing prevalence during adolescence and a peak in young adult life. Childhood presentation of multiple sclerosis is uncommon, accounting for 1.8–4.4% of some multiple sclerosis populations (Duquette *et al*., 1987; Cole and Stuart, 1995; Ghezzi *et al*., 1997).

Antigenic triggers

The seasonal distribution of ADEM presentation in this series supports an aetiological link with infectious disease.

Table 6 *Significant clinical and investigation differences between ADEM/MDEM and multiple sclerosis presentations*

Finding	ADEM/ MDEM (%)	Multiple sclerosis (%)	*P*
Predemyelinating illness	74	38	<0.05
Polysymptomatic presentation	91	38	<0.002
Encephalopathy	69	15	<0.002
Pyramidal	71	23	<0.01
Unilateral optic neuritis	0	23	<0.01
Bilateral optic neuritis	23	8	NS
Seizure	17	0	NS
Blood pleocytosis	64	22	<0.05
CSF lymphocytosis	64	42	NS
Elevated CSF protein	60	33	NS
Intrathecal synthesis OCB	29	64	NS
Periventricular MRI lesions	44	92	<0.01

NS = not significant; OCB = oligoclonal bands.

Infectious disease in childhood is common. However, the 74% incidence in this series of an infectious illness in the month before neurological disease exceeds the expected frequency in childhood (33–50%). Other than the organisms serologically incriminated in this series, HHV-6 (Kamei *et al*., 1997), coxsackievirus B (David *et al.*, 1993), *Campylobacter* (Nasralla *et al*., 1993), *Borrelia burgdorferi*, *Salmonella typhi* (Ramachandran *et al*., 1975), HTLV-1 (Tachi *et al*., 1992) and HIV (Silver *et al*., 1997) have all been incriminated. However, the majority of patients have a preceding infection of the upper respiratory tract, where the actual organism is not serologically identified. Problems in diagnosis and classification may occur with some triggering agents, such as varicella, Epstein–Barr virus, *Borrelia* and mycoplasmas, which can cause ADEM or directly invade the nervous tissue and cause infective encephalitis. Only two children in this series had vaccine-associated ADEM. Vaccines have been reported previously to precipitate ADEM, notably vaccines for influenza (Saito *et al*., 1998), rabies, Japanese B encephalitis (Ohtaki *et al*., 1995) and smallpox. The majority of these vaccines are dead or inactivated, supporting the theory that ADEM is a neuroallergic phenomenon. Considering the number of doses of vaccine that are given, ADEM as a result of vaccination appears to be very rare. This immunological theory is further supported by reports that ADEM has occurred after drug treatments, including gold (Cohen *et al*., 1985) and streptomycin.

The latency between antigenic triggering and neurological signs was ~2 weeks. A similar latency has been described in varicella-associated cerebellar ataxia.

In contrast to the children with ADEM, the children with multiple sclerosis in this series had an incidence of a potential antigenic trigger illness in the month preceding neurological onset of only 38%. There was no serological evidence of specific antigens in these children. Though antigenic triggers (the multiple sclerosis antigen) are felt to have an important role in initiating the immune abnormalities in people predisposed to the development of multiple sclerosis, the gap between antigenic exposure and the onset of neurological disease in multiple sclerosis appears to be months, years or even decades.

Pathogenesis

The interaction between the infectious agent and the immune system in ADEM has not been investigated extensively. Though infective agents are clearly closely implicated in the pathogenesis of ADEM, microorganisms have not been isolated within the CNS or CSF (unlike infective encephalitis) (Johnson, 1982; Johnson *et al*., 1984). How predemyelinating triggers precipitate ADEM is unclear, though a molecular mimicry hypothesis is tempting (Alvord *et al*., 1987). Studies of children with ADEM have demonstrated previously that peripheral and cerebrospinal lymphocytes (particularly Th2 cells) have increased reactivity to myelin basic protein (Lisak and Zweiman, 1977; Pohl-Koppe *et al*., 1998).

By contrast, the immune process in multiple sclerosis has been described extensively (Noseworthy, 1999). Further immunological studies of ADEM are required to determine whether differences exist between the two disease groups.

Despite the obvious pathological similarities between ADEM and multiple sclerosis in multifocal demyelination with lymphocytic and macrophage infiltration, there are important differences (Prineas and McDonald, 1997). Histological studies of patients with ADEM dying at various intervals up to a month after clinical onset have shown that microscopic lesions are very numerous, appear within days of clinical presentation and do not increase in size or number. Over the same period in acute or early multiple sclerosis, the lesions are fewer and larger from the start and increase in both size and number during the course of the illness. By contrast, experimental allergic encephalitis, the animal model of demyelination, is considered by most workers to be closely equivalent to ADEM; ADEM following rabies vaccination is indeed the human form of experimental allergic encephalitis.

Clinical features

Multiple sclerosis has defined criteria for diagnosis (Poser *et al*., 1983). By contrast, ADEM has no such diagnostic criteria. In view of the importance of discrimination between ADEM and multiple sclerosis for prognosis, we have reviewed the clinical and investigation findings in these two groups. Clinical discrimination between ADEM and a first attack of multiple sclerosis can be difficult. However, our study highlights some differences found in the clinical and investigation features of the monophasic group compared with the presentation of multiple sclerosis in children. Symptoms referable to intracranial pathology, including headache, fever, meningism and seizures, were more common in the ADEM/MDEM patients, two-thirds of whom consequently received initial treatment for infective meningoencephalitis.

A florid, polysymptomatic presentation was common in ADEM. Likewise, encephalopathy and symmetrical four-limb pyramidal signs occurred frequently in the monophasic group. The clinical findings in ADEM are often diverse. Some children present with a fulminant encephalopathic illness so shortly after the precipitating trigger that clinical evidence of the trigger infection is still present. By contrast, some patients present more indolently, with a change in behaviour, loss of developmental skills (Perniola *et al*., 1993; Garg and Kleiman, 1994), headache and chronic fatigue (Johnsen *et al*., 1989; Behan and Bakheit, 1991).

In contrast, multiple sclerosis patients were more likely to have a monosymptomatic presentation, such as isolated unilateral optic neuritis, transverse myelitis or a brainstem syndrome. Monosymptomatic predominance in multiple sclerosis patients has been reported in other childhood series (Duquette *et al*., 1987; Boutin *et al*., 1988; Selcen *et al*., 1996; Ghezzi *et al*., 1997).

Optic neuritis was a common sign in both the ADEM and the multiple sclerosis group. Notably, bilateral optic neuritis

was more common in the ADEM/MDEM group, whereas unilateral optic neuritis occurred only in the multiple sclerosis group. The term Devic's disease, or neuromyelitis optica, has been used to describe coexistent optic neuritis and transverse myelitis. There were no patients in this series who fulfilled criteria for this diagnostic entity. There were no other statistical differences between the two groups for brainstem involvement, cerebellar signs, transverse myelitis and sensory disturbance. Although neuroimaging evidence of deep grey matter involvement was common in ADEM, extrapyramidal clinical findings were uncommon. Post-vaccine parkinsonism has been described previously, and was treated successfully with levodopa (Alves *et al*., 1992).

Investigation features

Blood leucocytosis was more common in ADEM than in multiple sclerosis. Lymphopenia was common only in the ADEM group, a finding previously recognized in measles encephalomyelitis (Johnson, 1994). Evidence of CSF inflammation was also more common in ADEM (Boutin *et al*., 1988; Sindern *et al*., 1992), though not significantly so. As shown in this study, intrathecal synthesis of oligoclonal bands may occur in both ADEM and a first presentation of multiple sclerosis (though it is more prevalent in multiple sclerosis). However, convalescent testing in ADEM should show absence of oligoclonal bands in CSF, whereas in multiple sclerosis the oligoclonal bands may remain or become present. Previous researchers have detected oligoclonal IgG intrathecal synthesis in 74–87% of cases of established childhood multiple sclerosis (82% in this series) (Sindern *et al*., 1992; Selcen *et al*., 1996). Research into the predictive value of intrathecal immunoglobulin synthesis in isolated demyelination syndromes has shown a strong correlation between intrathecal IgG synthesis (and an even stronger correlation for IgM) and the subsequent development of multiple sclerosis (Sharief and Thompson, 1991). In the adult group of Sharief and Thompson, 18 of 22 patients (82%) with intrathecal IgG synthesis developed multiple sclerosis after a mean of 18 months. In our childhood group, of 13 children with intrathecal IgG synthesis, seven (54%) developed multiple sclerosis. The six children who remained relapse-free were followed for a mean of 6.5 years. We propose that, while intrathecal synthesis of IgG appears to have a strong predictive value for the development of multiple sclerosis in adults, it may be less predictive in children.

EEG was frequently abnormal in both groups of patients. The slow-wave abnormalities are a non-specific sign of an encephalopathic process. EEG has little part to play in the diagnosis and management of ADEM/multiple sclerosis unless seizures coexist or unless the EEG is used to exclude differentials. VEPs (and brainstem evoked potentials, where appropriate) are, by contrast, very helpful in the diagnosis of demyelinating conditions. Though the abnormalities could not help differentiate between ADEM and multiple sclerosis, it was noticeable that asymptomatic lesions were detected more frequently in the children with multiple sclerosis (three of five patients asymptomatic for visual pathway dysfunction) than in children with ADEM (two of 13 patients).

Neuroimaging

MRI is of central importance in the diagnosis of acute CNS white matter disorders. CT is frequently normal in ADEM (Dunn *et al*., 1986; Caldemeyer *et al*., 1994). Abnormalities of brain MRI have been shown to be positively predictive of the development of multiple sclerosis in adults. In clinically isolated syndromes an abnormal MRI brain on presentation was associated with progression to multiple sclerosis in 83% of patients during 10 years of follow-up (O'Riordan *et al*., 1998). By contrast, a normal MRI was associated with progression to multiple sclerosis in only 11% of patients during the same period. All of the 48 children in this demyelinating cohort had an abnormal MRI brain on presentation, yet only 27% had multiple sclerosis after 5.64 years of follow-up. Comparison of MRI criteria when predicting conversion to multiple sclerosis found that increased number of lesions, infratentorial lesions and periventricular lesions had positive predictive value (Tintore *et al*., 2000). When translated to this childhood demyelinating group, only the presence or absence of periventricular lesions was found to discriminate between the monophasic group and the group with multiple sclerosis. In the ADEM patients, the lesions tended to be in the subcortical white matter, with relative sparing of the periventricular white matter. Conversely, multiple sclerosis lesions tended to be situated both in the subcortical white matter and at the periventricular margin (Boutin *et al*., 1988; Sindern *et al*., 1992). Large reviews of multiple sclerosis in adults have documented the predominance of periventricular lesions (near universal), particularly at the trigone and body of the lateral ventricle (Ormerod *et al*., 1987). Cortical grey lesions, though infrequent, only occurred in the ADEM group. Involvement of the deep grey matter occurred in both groups, though more frequently in the ADEM group, and may be the only imaging finding in ADEM (Baum *et al*., 1994; Kimura *et al*., 1996).

The ADEM lesions tended to be poorly marginated. Some of the MRI changes represented oedema, which is supported by some pathological reports (Kepes, 1993) and explains partly the rapid resolution seen in some convalescent scans. By contrast, the multiple sclerosis lesions had more clearly defined margins.

The asymmetry found in both ADEM and multiple sclerosis white matter lesions are characteristic of acquired demyelinating lesions. Symmetrical white matter abnormalities should prompt consideration of leucodystrophy. In contrast, the deep grey matter abnormalities in the ADEM group were frequently symmetrical.

The majority of patients seen in this series had disseminated lesions throughout the CNS. However, three children with ADEM had only one demyelinating lesion at presentation.

Single demyelinating lesions have been reported previously in adults who had been biopsied because of concern that the lesions represented solid tumours (Kepes, 1993). The increasing recognition of this clinical and radiological presentation has reduced the biopsy rate in this condition.

Convalescent neuroimaging plays a useful role in distinguishing between ADEM and multiple sclerosis. The majority of children with ADEM who were re-imaged showed complete or partial lesion resolution, though residual gliosis and demyelination occurred in some patients (Kesselring *et al*., 1990; O'Riordan *et al*., 1999). Importantly, none of the monophasic group had new lesions when convalescent imaging was performed. By contrast, sequential MRI scanning in adults and children with multiple sclerosis frequently showed new symptomatic lesions (during relapse) or asymptomatic lesions (during convalescence) (Ebner *et al*., 1990).

Treatment

In view of the rarity of ADEM, treatment has not been subjected to controlled trials. Some of the older uncontrolled trials studying the effect of steroids on acute meningoencephalitis demonstrated varying results (Karelitz and Eisenberg, 1961; Ziegra, 1961; Boe *et al*., 1965). However, these studies undoubtedly included children with infective encephalitis and therefore do not represent a pure demyelinating population. Smaller, more recent studies in a definitely demyelinating group have reported improved recovery and reduced disability when the patients were treated with steroids (Pasternak *et al*., 1980). Current opinion supports the use of intravenous methylprednisolone followed by oral prednisolone therapy when infective encephalitis has been excluded and acute postinfectious demyelination is suspected. Notably, however, some children appear to recover fully without any therapeutic intervention (Kimura *et al*., 1996). The children in this series with MDEM had been treated with oral prednisolone for a shorter period than the children with ADEM, suggesting a protective influence of steroid therapy. Relapses on withdrawal of steroids have been documented in other series (Baum *et al*., 1994). A prolonged weaning regimen of 6 weeks or more may therefore be indicated. Other immunomodulatory therapies have been tried previously in ADEM, including successful treatment with immunoglobulin (Kleiman and Brunquell, 1995) and plasmapheresis (Stricker *et al*., 1992). None of these treatment modalities has been subjected to prospective trials.

Relapses and disability

By definition, children with ADEM do not relapse. Children with multiple sclerosis, as defined by the Poser criteria, must have at least two separate attacks separated by at least 1 month with clinical evidence of lesions in both cases (to confirm clinically definite multiple sclerosis). Children with MDEM pose a difficult diagnostic problem. This problem has been recognized by multiple sclerosis investigators (Poser, 1994). They agree that, if relapses occur in the months following a demyelinating presentation characteristic of ADEM, the diagnosis of MDEM should be considered. If the relapse occurs after 6 months, the diagnosis of MDEM becomes less tenable and multiple sclerosis becomes more likely. There were seven children in this group who had clinical and investigation findings consistent with ADEM and who had a relapse shortly after presentation but none thereafter. All of these children with MDEM relapsed within 2 months of stopping steroids. It would seem prudent to avoid stimulating the immune system (such as by vaccination) in the aftermath of ADEM for at least 6 months.

The survival in the ADEM group was 100%, though previous (1950s) series of post-measles ADEM reported 10–30% mortality (Johnson *et al*., 1985; Lisak, 1994).

Two-thirds of patients with multiple sclerosis have a relapsing–remitting course. Progressive disease is less common. A large proportion of children with multiple sclerosis (35–60%) will relapse during the first year (Cole and Stuart, 1995; Ghezzi *et al*., 1997), though some patients may not relapse for many years, as in a case in this series. Disability in early-onset multiple sclerosis has been reviewed in a number of retrospective studies. The outcome did not seem to differ from the long-term disability described in adult patients. The two largest reviews found that disability was mild (defined as an extended disability score of <4) in 40 and 60% of patients after 8 and 10 years of follow-up, respectively (Duquette *et al*., 1987; Ghezzi *et al*., 1997). However, most studies have shown that some children can have an aggressive course, particularly with primary progressive multiple sclerosis (Boutin *et al*., 1988).

Conclusions

After one demyelinating episode, the primary question about recovery is the risk of recurrence. Within this cohort of 48 patients, 10 (21%) had developed multiple sclerosis after a mean follow-up period of 2.36 years and 13 (27%) had multiple sclerosis at 5.64 years. We believe that these data support the existence of a monophasic demyelinating disorder (ADEM/MDEM).

This series has demonstrated some differences in the presentation and investigation of ADEM/MDEM compared with a first presentation of multiple sclerosis, which may help when giving a prognosis to the families (Table 6). Why children are more likely to have an aggressive monophasic disorder as opposed to a smouldering chronic disorder is not clear. Comparative studies are required to see if immunological differences exist.

Acknowledgements

We wish to thank Dr G. Keir and Professor E. J. Thompson of the Department of Neuroimmunology, Institute of Neurology, Queen's Square, London, Dr N. Klein of the Department of

immunology, Great Ormond Street Hospital, London and the parents, patients and GPs involved in the follow-up study.

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Received February 12, 2000. Revised July 16, 2000.
Accepted August 18, 2000