CHAPTER 1

ACUTE DISSEMINATED ENCEPHALOMYELITIS

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Abstract: Acute disseminated encephalomyelitis (ADEM) is a disorder of the central nervous system (CNS) characterized by an acute event, typically with encephalopathy, in which diffuse CNS involvement occurs. It may follow an infectious event and occurs more commonly in young children. Pulse steroid treatment is frequently used to treat ADEM. Although ADEM is typically described as a benign condition, with children generally recovering motor function and resolution of lesions on magnetic resonance imaging (MRI), residual cognitive deficits may occur. This chapter aims to review the clinical features, typical presentation, differential diagnosis, treatment and prognosis of ADEM.

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder affecting the central nervous system (CNS). It typically presents in early childhood, but has been documented throughout the lifespan.[1,2] According to the consensus definition of the International Pediatric MS Study Group (IPMSSG), ADEM is a "first clinical event with a presumed inflammatory or demyelinating cause, with acute or subacute onset that affects multifocal areas of the CNS".[3] This definition also states that encephalopathy (behavioral change and/or alteration in consciousness) is required to make the diagnosis of ADEM. However, other literature has demonstrated that encephalopathy may be associated with a first episode of what is later diagnosed as multiple sclerosis (MS).[4] Further, not all patients with ADEM present with encephalopathy.[5]

Neurodegenerative Diseases, edited by Shamim I. Ahmad.

Other features of ADEM included in the IPMSSG definition are: (1) neuroimaging of the brain showing focal or multifocal lesions, particularly involving white matter; (2) no history of prior demyelinating episode; (3) absence of other underlying pathology to explain the event (e.g., infection, tumor); and (4) improvement either clinically and/or on magnetic resonance imaging (MRI). The definition goes on to specify that the brain MRI may reveal large (≥1-2 cm), multifocal, hyperintense lesions in the supratentorial or infratentorial white matter regions. Gray matter may also be involved, especially the thalamus and basal ganglia and, in rare cases, there is one large lesion (≥1-2 cm) predominately involving white matter. In addition to abnormalities on brain MRI, MRI of the spinal cord may show confluent intramedullary lesions with variable enhancement.[3]

Although viral infection may precede symptoms of ADEM, the presence of prior infection is not required for diagnosis. Common laboratory findings include elevated white blood cell count and CSF protein. Oligoclonal bands in the CSF may be present but are less frequently found in ADEM compared to MS (see below under laboratory testing).[6]

Relapses have been described in children with an initial diagnosis of acute disseminated encephalomyelitis, with reported rates ranging from 5-21%.[2,7-10] According to consensus definitions proposed by the IPMSSG, symptoms and/or MRI findings associated with an episode of ADEM occurring within 3 months of the initial ADEM event are considered part of the initial event.[3]

Recurrent ADEM (R-ADEM) is defined as the recurrence of initial symptoms and signs of the first ADEM event that occur three or more months after the initial event, without involvement of new clinical areas. The symptoms must occur at least one month after completion of steroid treatment and with no new lesions on MRI.[3]

Multiphasic ADEM (MDEM) is an event that meets criteria for diagnosis of ADEM but involves new areas of the CNS. Again, this event must occur three or more months after the initial event and one month following completion of steroid treatment.[3] It is noted that more than two such events should raise suspicion of MS.[3]

These diagnostic categories were formulated in order to highlight a distinct group of patients that may experience relapses, but whose relapses will be limited to a small number and who will not progress to chronic relapses and neurodegeneration, as in MS. Although controversy regarding recurrent ADEM and MDEM exists, long term follow-up of a small group of children (n = 13) with relapsing forms of ADEM suggests low rates of conversion to MS (mean follow-up 9 years). In this study, only two patients who were classified as MDEM following international definitions experienced further recurrences and received alternate diagnoses (MS and CNS vasculitis).[11] Further systematic evaluation of these definitions using large cohorts of patients is necessary to determine their validity.

See Table 1 for IPMSSG definitions.

INCIDENCE AND PREVALENCE

The annual incidence of ADEM is estimated to be between 0.2 and 0.8 per 100,000.[9,12-15] Incidence varies with geographical location, with estimates of 0.4 per 100,000 (under the age of 20 years) in California,[9] 0.64 per 100,000 (under the age of 15 years) in Japan,[14] 0.07 per 100,000 in Germany,[13] and 0.2 per 100,000 in Canada.[12] Several studies have suggested a slight predominance in males, with M to F ratios ranging from 1:0.8 to 2.3:1.[2,12,14-17] Onset usually occurs early in childhood.[2,5,7-9,16,18-21] Eighty percent of patients with ADEM have onset before the age of 10 years.[15] Adult onset ADEM occurs but is rare.[22-26]

Table 1. International Pediatric MS Study Group (IPMSSG) Definitions[3]

ADEM (monophasic)	• First inflammatory or demyelinating clinical event • Acute onset • Multiple areas of the CNS affected • Polysymptomatic presentation • Presence of encephalopathy (e.g., behavioral change, alteration in consciousness) • Neuroimaging shows focal or multifocal lesions primarily involving white matter • No radiological evidence of previous destructive white matter changes • Improvement either clinically, on MRI, or both, with possible residual deficits • New or fluctuating symptoms within 3 months of initial event considered part of the initial event • No other explanation for presenting symptoms
Recurrent ADEM (R-ADEM)	• New event of ADEM with recurrence of initial symptoms occurring 3 or more months after the initial event • No involvement of new areas • Event occurs at least 1 month after completing steroid therapy • No new lesions on MRI (there can be enlargement of original lesions)
Multiphasic ADEM (MDEM)	• New clinical event of ADEM involving new anatomical areas • Occurring at least 3 months after the initial ADEM event and at least 1 month after completing steroid treatment • Event must have polysymptomatic presentation including encephalopathy • Neurologic symptoms (other than mental status changes) must differ from initial event • Brain MRI must show new areas of involvement with complete or partial resolution of lesions associated with the initial event • **More than 2 events should raise suspicion of MS**

ADEM has been described in children who have recently experienced infections or who have received vaccinations. It is estimated that 70-77% of patients with ADEM are reported to have had clinically evident infection or vaccination during the few weeks prior to onset.[15] It is important to note that ADEM rarely occurs postvaccination (0.1 to 0.2 cases per 100,000).[27] It may occur more frequently after primary vaccination rather than revaccination.[28] Case reports of ADEM after the following vaccines have been published: smallpox,[28,29] measles,[2,30,31] mumps,[32] rubella,[31] Japanese B encephalitis,[33] diphtheria/pertussis/tetanus,[31] pertussis,[15,31] influenza,[34,35] hepatitis B[19] and the Hog vaccine.[36]

Post-infectious ADEM has been described in association with viral infections including measles,[31] mumps,[2,37] rubella virus,[2,31] varicella-zoster,[38] Epstein-Barr virus,[18,39] cytomegalovirus,[40] herpes simplex virus,[2,41] hepatitis A or C,[42,43] Coxsackie B virus,[44] influenza A[45] or B,[7,18] H1N1 influenza,[46] HIV,[47] human T-cell lymphotropic virus-1,[48] human herpes virus 6,[49] Rocky Mountain spotted fever virus,[50] and human coronavirus.[51] Other pathogens include *Mycoplasma pneumonia*,[52] *Borrelia burgdorferi*,[53] *Campylobacter*,[54] *Leptospira*,[55,56] *Chlamydia*,[57] *Legionella*,[58] *Rickettsia*

rickettsii,[50] *Mycoplasma pneumonia*,[52] *Streptococcus*,[59] and group A beta-haemolytic streptococci.[60] ADEM has also been reported after organ transplantation, leukemia and non-Hodgkin's lymphoma.[61-65]

Systematic studies evaluating the relationship between specific infectious agents and ADEM have not been published. One study evaluating the relationship between vaccine and inflammatory demyelination has been published. Mikaeloff and colleagues reported no association between the Hepatitis B vaccination and inflammatory demyelination, although when subgroup analysis was performed on specific brands of vaccine, the Engerix B vaccine was found to increase risk, especially in children with multiple sclerosis (OR 2.77, 1.23-6.24).[66] Further studies of the relationship between vaccination and inflammatory demyelination are needed to confirm the presence or absence of an association.

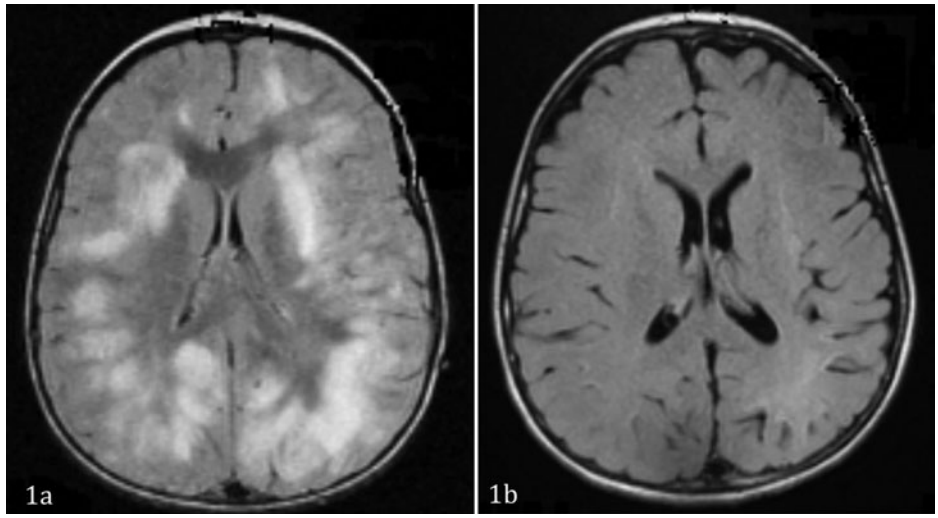
DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS AND ACQUIRED CENTRAL NERVOUS SYSTEM DEMYELINATING DISORDERS IN CHILDREN AND ADOLESCENTS

The differential diagnosis of white matter abnormalities on MRI in childhood is broad. Inflammatory, infectious, metabolic and neurodegenerative disorders may present with white matter abnormalities on MRI.[67,68] Careful history and physical examination are necessary, but not sufficient to distinguish between children with demyelinating disorders, acute infectious or vascular processes, or chronic degenerative/metabolic processes.[69-71] In many cases, MRI evaluation together with a detailed clinical history may help to distinguish metabolic white matter disorders such as Alexander's disease, Canavan's disease, Vanishing White Matter disease, Adrenoleukodystrophy and Metochromatic leukodystrophy from ADEM, particularly if attention is paid to the distribution of white matter lesions.[72] Specifically, ADEM is typically acute to sub- acute in onset and causes diffuse involvement of the deep gray matter and white matter, with prominent involvement of the cerebellum in many cases. Lesions are usually large with bilateral involvement (see Fig. 1).

Importantly, the diagnosis of neuromyelitis optica (NMO) should be considered in all cases of acute demyelination in childhood, particularly in children who present with longitudinally extensive transverse myelitis and/or severe optic neuritis. Cerebral involvement with ADEM-like lesions is frequently seen in these cases; one case describes brain lesions in children who were later diagnosed with NMO.[73]

Even after the diagnosis of an acute demyelinating process has been established, in many cases, it is difficult to distinguish monophasic demyelinating conditions from a first attack of pediatric MS, especially in younger patients. As noted above, proposed definitions suggest that encephalopathy is required for one to diagnose ADEM, but recent reports suggest that encephalopathy may also occur at onset of neuromyelitis optica and MS, especially in younger children.[4] Patients with an ADEM-like presentation whose MRI is suggestive of MS (e.g., periventricular lesions) at onset have an increased risk of developing a second episode.[74]

The sections below review diagnostic testing that may be of utility in distinguishing ADEM from other diseases and predicting whether children with a first presentation of ADEM will later receive the diagnosis of multiple sclerosis.



Figures 1. MRI scan of a 5 year-old child with acute disseminated encephalomyelitis at onset (1a) and 1 year later (1b). Note the diffuse involvement of both cerebral hemispheres (1a) and almost complete resolution of the previously apparent lesions (1b).

DIAGNOSTIC TESTING

Diagnostic testing for acute disseminated encephalomyelitis includes serum and CSF evaluation, visual testing and magnetic resonance imaging (MRI).

Magnetic Resonance Imaging

MRI is of central importance in making the diagnosis of ADEM. In general, as noted above, MRI lesions, associated with ADEM, include those in the deep grey nuclei, with widespread, bilateral involvement of subcortical white matter together with marked cerebellar and brainstem involvement.[7,75] The spinal cord is also frequently involved. These lesions often disappear on repeated imaging.

Much work has been devoted to distinguishing ADEM, from MS. One study has suggested that the presence of well-defined periventricular and corpus callosum lesions may be specific but very insensitive predictors of MS after a first attack of CNS demyelination in childhood (KIDMUS criteria).[74] More recent studies have confirmed these general findings and have found that the presence of any of the adult Barkhof criteria for MS, as well as small, well-defined lesions that are perpendicular to the corpus callosum may be effective in differentiating children with MS from those with a monophasic disease at the time of disease presentation.[76] Another study reported that a combination of two of the following criteria may distinguish a first attack of pediatric MS from ADEM[77]: (1) presence of T1-black holes; (2) presence of two or more periventricular lesions; and (3) absence of diffuse bilateral lesions. Importantly, this study failed to analyze the presence of gadolinium-enhancing foci that may also appear dark on T1-weighted imaging. Recently, these diagnostic criteria have been independently tested and found to be highly specific (95% specificity) and moderately sensitive (75%) in distinguishing ADEM from MS.[78]

CSF Analysis

CSF analysis is central to the diagnosis and treatment of childhood demyelinating disorders. As children with ADEM often present with fever and encephalopathy, standard CSF testing is necessary, including evaluation of cell counts, protein, glucose and testing for infectious agents. Importantly, 64% of children with ADEM are reported to have lymphocytosis on CSF analysis and 60% have CSF protein elevation.[7]

IgG index and oligoclonal bands (OCB) are also useful in distinguishing ADEM from MS in many cases. Up to 29% children with ADEM are reported to have oligoclonal bands in the CSF,[2,6,7,19] while the majority of children with MS are positive for oligoclonal bands in the CSF.[6] Within the French KIDMUS cohort, 94% of children with positive OCB (69/72) went on to develop MS. However, only 40% of established MS patients in this study had OCB, suggesting that this test has a low sensitivity but high specificity for the development of MS when present at disease onset. Similarly, another study reported OCB to be present in the CSF of 92% of children with MS.[6]

It is important to note that the CSF profile in childhood-onset demyelinating disorders may vary by age. OCB may be less frequent in younger children with MS (43% versus 63% in adolescents).[79] These results must be interpreted with caution as information regarding timing of lumbar puncture and of OCB detection was not provided in this paper, nor is it clear how many children included in this study had actually confirmed testing of OCB and/or CSF.[21] The IgG index had been found to be elevated in 68% of adolescents with MS (>11 years), but in 35% of younger children (<11 years),[79] numbers similar to the rate of OCB positivity in younger children with MS and ADEM. The absence of neutrophils in the CSF at onset is predictive of an earlier second neurological episode.[79]

Serum Testing

No serum biomarkers have been found to be sensitive or specific for the diagnosis of ADEM. However, in a small study, children with ADEM and clinically isolated syndrome (CIS) were found to have high serum titres to nMOG (native myelin oligodendrocyte glycoprotein) in comparison to children with other neurological diseases and healthy controls.[80]

Serum testing may reveal leukocytosis in pediatric ADEM: almost 2/3 of patients with ADEM will present with elevated WBC as compared to 22% of children with MS.[7]

For children with severe optic neuritis and/or longitudinally extensive transverse myelitis, in whom the diagnosis of neuromyelitis optica is suspected, NMO IgG antibody testing should be performed. NMO-IgG testing has been found to be positive in 78%[73,81] of children who were diagnosed clinically with relapsing NMO and only 12.5% of those with monophasic NMO.[81]

Visual Testing

Optic neuritis may be seen in up to 60% of children presenting with ADEM,[82] and almost a quarter (23%) of children with a first time demyelinating event.[12] Importantly, optic neuritis in younger children with ADEM is frequently bilateral. One study reported that 23% of children with ADEM present with bilateral optic neuritis.[7] Approximately one-third of children who are later diagnosed with MS experience optic neuritis as an initial presenting symptom.[74,83] Even a higher proportion of children with demyelinating

disorders may experience subclinical abnormalities of the visual pathway.[84] The limited ability of standard Snellen charts to distinguish subtle visual dysfunction is well documented in the adult MS population.[85] Low contrast letter acuity charts (LCLA, Sloan charts) have been shown to provide a sensitive and reliable assessment of visual acuity in cases of pediatric demyelination.[86]

Other tests, such as visual evoked potential (VEP), or pattern reversal visual evoked potentials (PRVEP), have been shown to be of diagnostic utility in childhood demyelinating disorders, with almost half of such patients showing prolonged visual latency.[84]

More recently, optical coherence tomography (OCT), previously used for patients with glaucoma, has been applied to pediatric patients with demyelinating disorders. This procedure uses near infrared light to quantify the thickness of the retinal nerve fiber layer (RNFL) (which contains only nonmyelinated axons). It has been shown to provide a sensitive evaluation of the RNFL thickness in this population, a correlation of optic atrophy.[86] Taken together, VEP, OCT and LCLA testing can provide objective evidence of previous inflammatory insult to the optic nerve in the pediatric population with demyelinating disorders. They may help to establish a diagnosis of MS and may also be used for disease monitoring on follow-up.

CLINICAL AND DEMOGRAPHIC PREDICTORS OF THE RISK TO DEVELOP MS AFTER AN INITIAL DEMYELINATING EVENT

At present, outside of MRI features, no clinical features at the time of presentation can accurately predict whether a child with an acute demyelinating event will develop MS. Clinical studies have been hampered in part by the lack of consistent definitions used across publications and the small numbers of subjects at any one site. In available studies, the risk of developing MS after ADEM has been reported to be 0% in a study from Argentina,[2] 9.5% in a study from San Diego,[9] and 18% to 29% in studies from France.[21,74] Variability in the criteria used to define ADEM and pediatric MS may have contributed to the wide range of published incidence figures.

The KIDMUS study group from France examined pediatric patients with an initial demyelinating event, including CIS-like and ADEM-like events and showed that overall, 57% developed a second attack during a mean follow-up period of 5.4 years.[21] Of patients presenting initially with optic neuritis, 86% developed MS, while 50% of those initially with a brainstem syndrome developed MS. Overall, positive predictive factors for the development of MS were: age at onset 10 years or older and optic nerve involvement. A lower risk of developing MS was found in patients with mental status change at presentation, suggesting that the presence of encephalopathy may be a negative predictive factor. Of patients with an initial diagnosis of ADEM, 29% developed MS. In a subsequent publication by this group, when the diagnosis of ADEM was redefined by the KIDSEP study to include "change in mental status" as a qualifying criterion, 18% of children were found to develop MS, as defined by the development of a second event during follow-up.[10]

Another recent study described presenting characteristics of 89 patients who experienced an acute clinical demyelinating event, and compared those who had a monophasic course and those who ultimately experienced relapses.[5] Age of onset was higher in patients with MS. Family history of MS was present in approximately 23% of MS patients and none of the ADEM cohort. Encephalopathy was present in

approximately 41% of ADEM patients and seizure in 25% of these patients, while neither (seizure or encephalopathy) were present in any of the MS patients. Children without encephalopathy had a significantly higher likelihood of converting to MS. There was no difference between race, sex, history of preceding infection or immunization, or other features of clinical presentation. The most frequent symptom reported in MS patients was paresthesia, while weakness was most frequent in ADEM patients. CSF's white cell count and protein contents did not differ between the groups. Oligoclonal bands were positive in 8/18 MS patients and none of the ADEM (n = 13) patients. IgG index was more frequently elevated in MS patients. MRI abnormalities commonly seen in MS patients included periventricular white matter lesions (generally characterized by periventricular perpendicular ovoid lesions (PVPOLs)). No ADEM patients had PVPOLs.[5] Predominance of periventricular lesions in pediatric MS and relative sparing of this region in ADEM have been previously reported.[7]

Similar findings were reported in another study comparing pediatric MS and ADEM patients after a mean follow-up period of 5.6 years. ADEM patients more frequently experienced the following symptoms: infection prior to disease onset, polysymptomatic presentation, pyramidal signs, encephalopathy and bilateral optic neuritis (ON).[7] In this study, seizures only occurred in ADEM patients and unilateral ON occurred only in MS patients. ADEM patients were also more likely to have blood leucocytosis and nearly half had onset between the ages of 3-5 years, whereas only 23% of MS patients presented under the age of 5 years. ADEM was also more prevalent during the winter months.[7]

Adult onset ADEM may be characterized by a higher likelihood of relapse. One small study found that 35% of adults initially diagnosed with ADEM went on to develop MS,[1] with all relapses occurring within one year of initial presentation.[1] Patients eventually diagnosed with MS were more likely to have periventricular lesions (n = 14, 54%).[1] Another studies identified several factors associated with increased risk of relapse including age over 55 years, elevated CSF albumin (>100 mg/dl), female sex, spinal cord and/or PNS involvement.[23]

Distinguishing characteristics of monophasic ADEM in adults include preceding infection, acute onset, brainstem symptoms (e.g., ocular motor deficits, dysarthria), alteration of consciousness, aphasia, hemiplegia, paraplegia, tetraplegia, seizure, vomiting, bilateral ON, confusion, no oligoclonal bands in the CSF and gray matter involvement.[1,25,87] Overall, adult patients with monophasic ADEM appear to be younger, their onset of symptoms more acute, they experience more severe initial symptoms and have more widespread CNS disturbance, but they respond more favorably to treatment.[1] Information regarding ADEM in adults is limited and is based on small cohorts; therefore, definitive conclusions regarding presentation, prognosis and likelihood for relapse are limited.

See Table 2 for a description of initial presentation in ADEM versus MS in children and adolescents.

TREATMENT

Steroids

There have been no randomized, double blind studies of the treatment of ADEM. However, several retrospective analyses have suggested that high dose steroids may be used with reasonable success,[88] either in the form of oral dexamethasone[2] or high

Table 2. Features of ADEM and MS in children and adolescents

	ADEM	MS
Age of onset	Predominantly younger (<10 yrs)	Adolescent to early adulthood
Sex	Likely greater prevalence in males	Greater prevalence in females
MRI	Larger lesions; resolution of lesions over time; involvement of grey and white matter	Periventricular lesions/ periventricular perpendicular ovoid lesions; new lesions on follow-up
CSF	Increased WBC (neutrophils, lymphocytes)	Oligoclonal bands, elevated IgG index
Visual Testing	Bilateral ON	Unilateral ON
Serum Testing	Leukocytosis, elevated WBC	Normal WBC
Presentation	Polysymptomatic, encephalopathy, acute, at times severe presentation, associated with infection	Monosymptomatic, acute to sub-acute onset

dose IV solumedrol (10-30 mg/kd/d).[88,89] In many cases, the decision to intervene with steroid therapy is a clinical one. Treatment is sometimes reserved for patients with severe neurologic deficits, including visual loss, severe weakness with bowel/bladder involvement, severe encephalopathy/coma or other focal neurologic deficits, including cerebellar and brainstem deficits. One series of cases evaluating 16 patients with ADEM described response to high dose solumedrol within 10 days in 10/16 patients (63%).[88]

IVIg

IVIg therapy has been described in the treatment of ADEM, usually in the setting of steroid resistant cases.[88,90,91] One retrospective study examined the use of IVIg in severe steroid-resistant cases of acute disseminated encephalomyelitis. Cases received steroids as first-line therapy. A small group (n = 6) received IVIg as first line therapy because of contraindications for steroid use. Cases which were steroid resistant were more likely to involve peripheral nervous system damage (89%) and myelitis (95%); 53% of patients (10/19) experienced clinical improvement over the course of the treatment period.[90] Dosing of IVIg for acute treatment of demyelination follows other pediatric IVIg treatment protocols of 2 g/kg total; this is frequently divided over 5 days.[90]

Plasmapheresis

The use of plasmapheresis for ADEM has been described in small retrospective case series of patients who are resistant to steroid therapy and/or IVIg; its benefit in ADEM has not been clearly established. One study has suggested limited recovery, which only occurred months after treatment.[89] In a group of adult patients diagnosed with ADEM (n = 3), neurologic improvement was not seen after the administration of plasmapheresis.[92] Importantly, plasmapheresis is usually reserved for the most treatment-resistant patients and is usually performed days after the onset of symptoms. It is unclear if the effect of this therapy is beneficial if given earlier in the course of the disease.

PROGNOSIS

As mentioned earlier, the prognosis for ADEM is thought to be favorable, with more than half of patients showing complete resolution of clinical symptoms and lesions on MRI.[2,18,60,93] Average time to recovery is generally over several weeks to months.[7,18,94] Prognosis in adults with ADEM has been shown to be somewhat poorer than pediatric patients.[94] Mortality rates are higher,[1,24,25,87] up to 25%, compared to less than 5% in pediatric patients. Persistent deficits (e.g., functional state, sensory or motor disability, cranial nerve abnormality or cognitive impairment)[1,25,87] may also be more common in adult onset ADEM patients (in 35-90%). However, differences noted between adult and pediatric ADEM populations may be due to differences in specific areas tested.[1,24,87] One study describes nearly 90% of adult patients having persistent deficits, mainly mild cognitive impairment;[87] studies of pediatric patients have rarely included neuropsychological data.

Over half of children diagnosed with ADEM are reported to have complete recovery.[2,7-9,18-21] However, most of these studies are limited by a lack of detailed follow-up data. One study described that fewer than 17% (3/18) of ADEM patients had continuing deficits on follow-up (2-60 months post episode).[18] In this study, deficits included urinary symptoms and gait problems. A larger prospective study of 84 patients with ADEM suggested that the use of high-dose corticosteroid treatment was associated with good recovery and resolution of lesions on MRI. The majority of these patients (89%) had either complete recovery with normal neurologic examinations or abnormal signs without disability at follow-up (mean follow-up of 6.6 years). Deficits in the remaining children included hemiparesis, partial epilepsy, decreased visual acuity, paraparesis and mental handicap.[2] Within this cohort, no association could be made between initial MRI findings and outcomes.[2]

Another longitudinal study of 24 patients with ADEM (mean follow-up of 52.8 months) showed that only 3 had mild persistent neurologic signs. Normalization on MRI was seen in 59% of the patients and 36% showed improvement on MRI. Only one patient showed no improvement on MRI.[93] A similar study including 28 pediatric ADEM patients found that 57% made a complete recovery after a mean follow-up duration of 5.8 years. Ninety percent had partial or complete resolution on MRI and no new lesions. Residual symptoms included motor impairment (17%), parasthesia (6%), visual impairment (11%), cognitive impairment (11%) and behavior problems (11%).[7]

Neurocognitive Functioning

Many outcome studies in patients with ADEM fail to include assessment of cognitive and psychosocial functioning, or include only broad outcomes (e.g., IQ) and qualitative descriptions. Studies that have examined neurocognitive functioning in patients with ADEM are limited by their small sample size.

A variety of residual mild cognitive deficits in areas of visuospatial and visuomotor functioning, attention, executive function, mood, behavior and social skills have been found in children with prior diagnosis of ADEM.[75,95-97] Specifically, one case-control study (ADEM n = 19, controls n = 19) showed that MRI lesion load did not correlate with cognitive performance; however, disease severity and earlier onset were associated with poorer cognitive performance.[95] This study showed that early onset ADEM patients (<5 years) had lower IQ and lower academic skills compared to controls, whereas older

onset ADEM patients (>5 years) had poorer verbal processing compared to controls.[95] In a somewhat larger follow-up study of a group of MS, ADEM and MDEM patients (ADEM, n = 28, MDEM n = 7, MS n = 13, with a mean follow-up 5.8 years) Dale et al (2000) found that within the ADEM/MDEM group, 11% had cognitive deficits and 11% had residual behavioral problems. Cognitive and behavioral outcomes were described as diminished IQ (IQ of 70), aggression and obsessive compulsive disorder.[7]

A recent study examining neurocognitive features in children with ADEM suggests mild impairment in divided attention and cognitive flexibility.[96] Another small study showed ongoing cognitive deficits in all patients (n = 6) 2-5 years post ADEM episode, particularly in attention and executive function. This was despite complete (n = 4) or partial resolution on MRI.[97] Cognitive and behavioral sequelae including low IQ, impaired speech and language, low academic achievement and aggressive behavior have also been described in a case series of pediatric ADEM patients with cerebellar involvement.[75]

CONCLUSION

ADEM is a rare condition with a generally favorable outcome which occurs in children, adolescents and adults. However, there is some evidence for poorer outcome in adults, with a higher risk for relapse and mortality. Approximately one-fifth of children go on to have relapses. Some of these children are eventually diagnosed with multiple sclerosis.

No single diagnostic test can reliably predict which patients with ADEM will go on to have relapses, although recently proposed MRI criteria may be helpful in this regard. Earlier detection of patients who will likely go on to have recurrent demyelination may lead to earlier treatment intervention, which may, in turn, have the potential to improve outcomes.

Finally, until recently, ADEM was assumed to be a condition with relatively few lingering deficits. However, there is growing evidence to suggest that neurocognitive impairment may persist even in the face of resolution of lesions on MRI and minimal to no lasting physical deficits. Ongoing research with larger patient samples and greater breadth in evaluation of functioning, including more sensitive measures of neurocognitive functioning, are needed.

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