

Pediatric Acute Disseminated Encephalomyelitis: Difficulties in Predicting the Outcome

Carolina Albuquerque¹, Ângela Luz², Cristina Martins³, Maria José Fonseca³, José Paulo Monteiro³

Port J Pediatr 2019;50:23-31

DOI: <https://doi.org/10.25754/pjp.2019.13321>

Abstract

Introduction: Acute disseminated encephalomyelitis is a central nervous system demyelinating disease characterised by encephalopathy and multifocal neurological symptoms. This study intends to characterise a series of 15 hospitalised children diagnosed with acute disseminated encephalomyelitis and to identify the outcome prediction factors.

Methods: Retrospective observational study about a series of children hospitalised with the diagnosis of acute disseminated encephalomyelitis, admitted between 1993 and 2015, through data collected from patient medical records. Microsoft Office Excel[®] and R 3.1.2[®] software were used for the data analysis and statistical analysis, respectively. The statistical analysis included logistic regression models, log-ratio test, t-test and odds ratio with a 95% confidence interval.

Results: Most of the patients had a polysymptomatic presentation, mainly with encephalopathy, pyramidal motor signs, cranial neuropathies and ataxia. Serological and microbiological findings were positive in 53% of the children. Fourteen children were treated with glucocorticoids and four with intravenous immunoglobulin as rescue therapy. One patient developed multiphasic disseminated encephalomyelitis. All the patients recovered from the acute event, with a 100% survival rate. In the follow up period, neurologic impairment was present in 53% of the patients, and was considered moderate in more than half of them. Age at the time of diagnosis, gender, preceding symptoms, positive serologic and microbiological findings, fever at admission, length of hospital stay and altered electroencephalogram were analysed, without direct interference in the prognosis. Diagnosis and therapy institution delay did not seem to affect the clinical recovery.

Discussion: It was not possible to find factors that can predict the outcome in this case series. Although future studies with other paediatric patients with acute disseminated encephalomyelitis are necessary in order to

better identify outcome prediction factors, a long-term follow-up should be performed to document recovery and confirm the diagnosis of acute disseminated encephalomyelitis.

Keywords: Child; Encephalomyelitis, Acute Disseminated/diagnosis; Encephalomyelitis, Acute Disseminated/epidemiology; Encephalomyelitis, Acute Disseminated/therapy; Portugal; Prognosis

Introduction

Acute disseminated encephalomyelitis (ADEM), also known as post-infectious encephalitis, is a demyelinating disease of the central nervous system (CNS), which has typically a monophasic course associated with multifocal neurological symptoms and encephalopathy.¹⁻⁴ It is a rare disorder, often preceded by a viral or bacterial infection or, rarely, following vaccine administration. The pathogenesis of ADEM is not yet well known, but several studies hypothesise that it is an autoimmune disease of the CNS triggered by an environmental stimulus in genetically susceptible individuals.²⁻⁴ ADEM may affect people of all ages, although it is more frequent in children.^{3,4} The median age of diagnosis is between 5 and 8 years, and it has male predominance. The diagnosis is the result of a combination of clinical and imaging findings.³⁻⁵ The clinical presentation is nonspecific, which makes the diagnosis difficult. Some patients have acute clinical manifestations, such as a sudden onset of fever, seizures, cranial nerve involvement and encephalopathy, while other patients have an insidious clinical presentation, often only characterised by nonspecific psychiatric symptoms and emotional instability.⁶ Consequently, the diagnosis and subsequent therapy may be delayed.⁷

To improve the diagnosis of ADEM, a head and, if necessary, spine magnetic resonance imaging (MRI) may prove to be extremely useful, as this is currently considered the more sensitive study to identify CNS lesions.^{3,8}

1. Paediatrics Department, Vila Franca de Xira Hospital, Vila Franca de Xira, Portugal

2. Paediatrics Department, Hospital do Espírito Santo, Évora, Portugal

3. Paediatric Neurodevelopment Unit, Paediatrics Department, Garcia de Orta Hospital, Almada, Portugal

Corresponding Author

Carolina Albuquerque

carolinalbuquerque@gmail.com

Avenida José Malhoa, 2 - 13^º andar, Apartamento 1305, 1070-325 Lisboa, Portugal

Received: 18/10/2017 | Accepted: 30/07/2018

Although the differential diagnosis of ADEM is very broad, the presence of infectious meningoencephalitis in the acute phase and multiple sclerosis in the subacute or late phase of the disease are the main disorders to take into account, both requiring different follow-up and therapy comparing to ADEM.^{4,8,9} Neuromyelitis optica should also be considered. Some studies show that a significant percentage of patients with ADEM (18% to 29%) will develop multiple sclerosis.^{2,6,9} Most ADEM cases are characterised by a monophasic episode of the disease, which may last up to three months. When a second event of encephalopathy and multifocal onset neurological symptoms occurs at least three months after the initial event, regardless of prior corticosteroid therapy, multiphasic acute disseminated encephalomyelitis is considered.²

There are no randomised studies on the treatment of ADEM, but the first-line therapy continues to be a high dose intravenous corticosteroid therapy followed by oral taper. When the prognosis is not favourable, intravenous immunoglobulin or plasmapheresis should be considered as rescue therapy.^{3,4,6,9}

Prognosis is favourable in most cases, and the majority of children recover completely or with a slight impairment of CNS function.^{4,10-13} There are rather few studies, however, that associate the onset of symptoms, establishment of a definitive diagnosis and subsequent therapy with the disease progression and prognosis.⁷

This study characterises a series of children admitted with a diagnosis of ADEM in a Portuguese level II hospital over a 20 year period. It aims at understanding whether certain factors, such as gender, age, time from the disease onset to diagnosis and start of therapy, prodrome presence, lesions in the initial head MRI, electroencephalogram (EEG) and hospital length of stay were associated with the prognosis.

Methods

This is a retrospective observational study that reviews 15 cases of children diagnosed with ADEM, in the paediatric neurodevelopment centre of a Portuguese level II hospital. The children were admitted to that hospital between 1993 and 2015, and they were followed at least for one year after the episode of ADEM. The study group included eight boys and seven girls, aged between 5 months and 14 years.

Based on the patients' medical records, clinical presentation, laboratory and imaging investigations, presence of prodrome, time from the onset of symptoms to diagnosis and therapy, and disease progression,

including hospital length of stay and current clinical status of the child, especially regarding cognitive impairment, assessed using the Wechsler Intelligence Scale for Children, third edition (WISC III), was reviewed in all the studied children at least 12 months after the ADEM diagnosis or until the child was 6 years old.

For the diagnosis of ADEM and multiphasic ADEM, the authors relied on the definitions proposed in the international guidelines for the diagnosis of paediatric multiple sclerosis and immune-mediated demyelinating diseases of the CNS, which were reviewed in 2013.⁵

Data analysis was performed in Microsoft Office Excel® 2010 and R® version 3.1.2. The statistical analysis included linear and logistic regression models, independent *t*-test for continuous variables, the likelihood ratio test for binary variables, and the 95% confidence interval (95% CI) for odds ratio (OR). The correlation between the variables age, gender, prodrome, normal EEG at admission, positive serological/microbiological data, time to the establishment of corticosteroid therapy and hospital length of stay, and any degree of intellectual development disorder (IDD) after discharge was assessed.

Results

Prior infection

A prior infection was identified in 73% of patients (*n* = 11), and the most frequent was an upper respiratory infection, present in six cases; two patients had gastrointestinal symptoms, and three patients had nonspecific symptoms, such as fever and headache, prior to the ADEM episode. No immunisation event was associated with the onset of ADEM. The average disease-free interval, between the prior infection and encephalomyelitis, was nine days (a minimum of two days and a maximum of 28 days) (Table 1). No statistically significant relationship between any degree of IDD after discharge and the presence of prodrome was found (Table 2).

Clinical manifestations

The most frequent clinical presentations were altered conscious level and confusion (defined as encephalopathy) that were present in all patients, despite being mild in two patients, followed by pyramidal signs in eight children (53%). Cranial neuropathies were present in six patients, ataxia in five patients and headache in four patients. Two children had nystagmus. Two children had convulsive *status epilepticus* and one infantile focal seizure. Sensory disturbances were also observed in three patients. One patient had clinical myelitis, characterised by acute urinary retention and flaccid paraparesis (Table 1).

Table 1. Epidemiological, clinical and imaging characteristics of patients

Patient	Age and gender	Prodrome (days before presenting ADEM)	Early symptoms	Serological/microbiological findings	Lesions in the head MRI	Lesions in the spine MRI
1	13 Y Male	Respiratory (3 days before)	Paraparesis, encephalopathy	Negative	Cortical grey matter Thalamus Basal ganglia	-
2	22 M Female	-	Tetraparesis, sensorineural disorder, encephalopathy	<i>Herpes simplex IgM + / cytomegalovirus IgM +</i>	Deep subcortical and periventricular white matter	Cervical and lumbar spine
3	5 Y Female	Gastrointestinal (28 days before)	Fever, headache, ataxia, encephalopathy	Negative	Deep subcortical white matter Brainstem Basal ganglia	-
4	22 M Male	-	Ataxia, encephalopathy	<i>Mycoplasma pneumoniae/ cytomegalovirus IgM +</i>	Basal ganglia Cerebellar white matter	No abnormalities
5	2 Y Female	-	Hemiparesis, involvement of cranial nerves, convulsive status epilepticus, encephalopathy	<i>Mycoplasma pneumoniae IgM +</i>	Deep subcortical and periventricular white matter Thalamus Basal ganglia	-
6	3 Y Male	Fever (5 days before)	Ataxia, hemiparesis, encephalopathy	<i>Coxsackievirus IgM +</i>	Basal ganglia	-
7	3 Y Male	Respiratory (4 weeks before)	Nystagmus, encephalopathy	-	Deep subcortical white matter Left optic neuritis	-
8	8 Y Female	Respiratory (7 days before)	Involvement of cranial nerves, nystagmus, ataxia, encephalopathy	-	Brainstem	-
9	2 Y Male	Respiratory (7 days before)	Ataxia, dysarthria, spasticity, encephalopathy	-	Periventricular white matter Cerebellar white matter and peduncles Basal ganglia Thalamus Brainstem	-
10	12 Y Female	Respiratory (11 days before)	Hemiparesis, sensory disorder, headache, encephalopathy	-	Deep subcortical white matter Thalamus Brainstem	-
11	5 M Male	Respiratory (3 days before)	Hemiparesis, spasticity, convulsive status epilepticus, encephalopathy	<i>Cytomegalovirus IgM +</i>	Periventricular white matter Thalamus Cerebellar white matter and peduncles	-
12	2 Y Female	Fever (2 days before)	Paraparesis, spasticity, focal seizures, encephalopathy	<i>Herpes simplex Ig M +</i>	Cortical grey matter Thalamus Basal ganglia	No abnormalities
13	13 Y Male	Gastrointestinal (12 days before)	Sensory disorder, paraparesis, urinary retention, encephalopathy	<i>Mycoplasma pneumoniae Ig M +</i>	Cerebellar white matter and peduncles	Cervical and lumbar spine
14	14 Y Male	Fever and headache (6 days before)	Fever, headache, encephalopathy	PCR for <i>influenza A</i> (nasopharyngeal secretions)	Cortical grey matter Basal ganglia Cerebellar white matter and peduncles Basal ganglia Brainstem	Cervical and lumbar spine
15	14 Y Female	-	Fever, headache, encephalopathy	-	Cortical grey matter Deep subcortical white matter Basal ganglia Cerebellar peduncles	No abnormalities

ADEM - acute disseminated encephalomyelitis; CSF - cerebrospinal fluid; IgM + - positive immunoglobulin M; M - months; MRI - magnetic resonance imaging; PCR - polymerase chain reaction; Y - years.

Table 2. Odds ratio for factors predictive of presence of cognitive deficit after discharge

Variables	OR (95% CI)	p
Age at diagnosis	0.92 (0.74 - 1.13)	0.48
Male	0.75 (0.09 - 5.86)	0.78
Prodrome (presence)	1.20 (0.10 - 13.31)	0.88
Positive serological/microbiological findings	4.00 (0.48 - 44.24)	0.22
Hospital length of stay	1.20 (1.02 - 1.61)	0.03
Abnormal electroencephalogram	0.33 (0.03 - 3.09)	0.34
Time to corticosteroid therapy	0.92 (0.72 - 1.07)	0.35

CI - confidence interval; OR - odds ratio.

Using the significance level of 5%, a statistically significant association was assumed when the confidence interval for the odds ratio did not contain the value 1.00. *p* value was obtained using the independent *t*-test for continuous variables, and the likelihood ratio test for binary variables through linear and logistic regression models. For continuous variables, the 95% confidence interval for the odds ratio indicates the value of higher or lower probability of a bad prognosis when that variable varies in one unit.

Laboratory investigation

Laboratory investigation included a lumbar puncture for the analysis of the cerebrospinal fluid (CSF) in all children. Patients 1 and 13 showed slightly increased protein levels (1-90 mg/dL, 13-57 mg/dL), and patients 5 and 15 had a considerable increase of the protein levels (413 mg/dL and 110 mg/dL, respectively). Eleven patients had pleocytosis (a minimum of 16 cells and a maximum of 1,000 cells), with a predominance of lymphocytes, usually less than 70 cells/ μ L, except for patients 1, 5, 13 and 15, who had 390, 1,000, 253 and 300 cells/ μ L, respectively.

Oligoclonal bands testing was performed in all cases, but was always negative (Table 1). Anti-myelin oligodendrocyte glycoprotein (MOG) and anti-aquaporin 4 (AQP4) antibodies testing was only performed in patient 15 with a negative result. Polymerase chain reaction (PCR) in the nasopharyngeal secretions was positive for influenza A in one case. Serological tests identified an antigenic trigger in eight cases: *Mycoplasma pneumoniae* (3/15), *cytomegalovirus* (3/15), *herpes simplex virus* (2/15), and *coxsackievirus* (1/15). The association between positive serological/microbiological findings and any cognitive impairment after discharge was not statistically significant (Table 2).

Head imaging

A head computed tomography (CT) scan was performed at admission in 11 of 15 patients, and it was abnormal in only four patients. A gadolinium-enhanced head MRI was performed during the first week after admission in all patients and it confirmed the diagnosis of ADEM, showing disseminated hyperintense CNS lesions on T2-weighted and FLAIR images. The lesions found in the head MRI affected predominantly the basal ganglia

(9/15), the deep/subcortical white matter (6/15), the thalamus (6/15), the cerebellar white matter (5/15) and the peduncles (5/15). The periventricular white matter, the brainstem and the cortical grey matter were relatively spared, with four children having lesions in these regions (Figs. 1, 2, 3). In six patients, a spine MRI was performed that showed hyperintense lesions in the cervical and lumbar spine in half of these patients.

Electroencephalogram

An EEG was performed in fourteen patients and it was often abnormal (9/14) showing diffuse slow activity, which was asymmetric in one case. The association between abnormal EEG at admission and any degree of IDD after discharge was not statistically significant (Table 2).

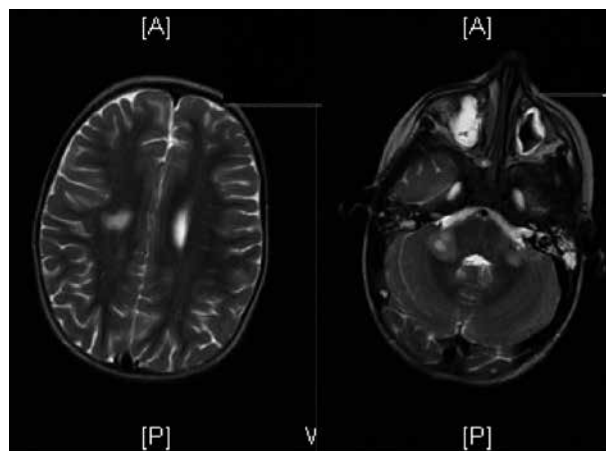


Figure 1. T2-weighted axial head magnetic resonance imaging of patient 9 on day 3 of the disease.

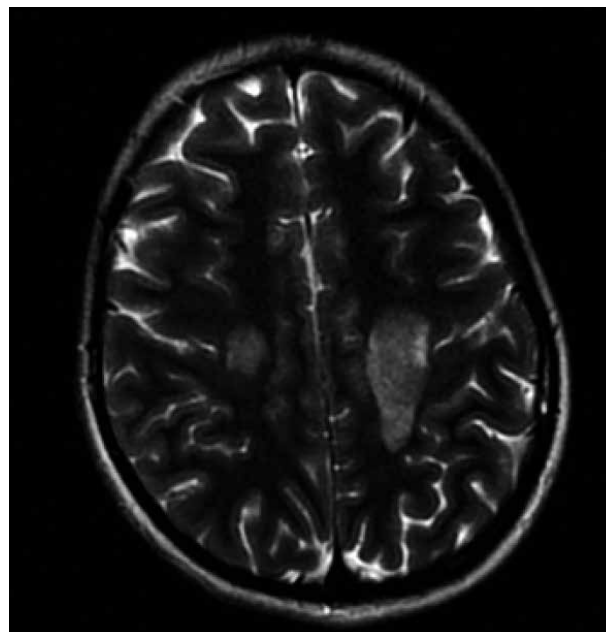


Figure 2. T2-weighted axial head magnetic resonance imaging of patient 10 on day 2 of the disease.

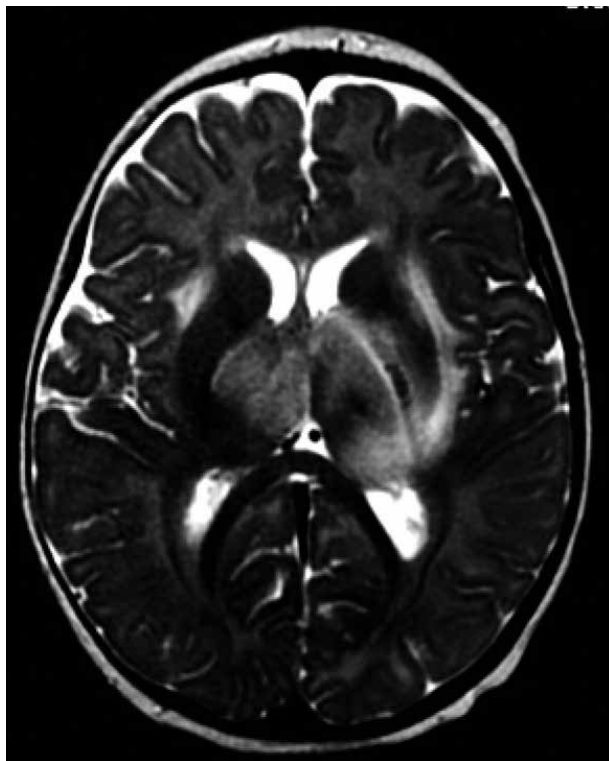


Figure 3. T2-weighted axial head magnetic resonance imaging of patient 11 on day 3 of the disease.

Treatment

The time interval between diagnosis and treatment was very variable, with an average of seven days, ranging from one to 30 days (Table 3).

Fifty-three per cent of patients initially received empirical antiviral treatment (acyclovir), and 47% of patients received antibiotics. As soon as the diagnosis of ADEM was established, 14 patients received corticosteroid treatment. There was no statistically significant relationship between time to starting corticosteroid treatment and any cognitive impairment after discharge (Table 3). Of these, 11 patients initially received intravenous pulses of methylprednisolone 30 mg/kg/day, followed by oral prednisolone for a period ranging from two to 12 weeks. The other patients only received oral prednisolone. One patient had an extremely significant improvement, with symptom resolution in three days despite not receiving corticosteroid treatment. Four patients received intravenous immunoglobulin (total dose of 1.5-2 mg/kg divided in two to three days) after a course of corticosteroids. None of the patients received plasmapheresis.

Follow-up

All of the patients received follow-up medical care in the neuropaediatric clinic in the same hospital after the episode of ADEM until the end of the study if under the age

of 18 years or until the age of 18 years. The median follow-up period of these patients was 10 years (between two and 16 years). Despite the severe clinical presentation in the majority of cases, there was a complete recovery of acute symptoms in the majority of patients. The survival rate was 100%. During follow-up, however, three patients had a motor deficit (mild in one case), three patients were subsequently diagnosed with epilepsy and, after the completion of the WISC (12 months after diagnosis or after completing 6 years of age), three patients were found to have mild IDD and four patients were found to have moderate IDD (Table 3).

A head MRI was performed during follow-up in 80% of patients, about 12 months after the episode of ADEM. One patient had a complete resolution of the lesions, and the other patients showed a partial resolution of the lesions (Table 3).

Fourteen patients had a single episode of ADEM during the follow-up period. However, patient 14 developed new lesions in the head MRI and new clinical symptoms three months later, and was treated with corticosteroids, with a favourable response. The predictive factors for the development of IDD (any degree) after discharge are summarised in Table 2. Of all the reviewed variables, only the increased hospital length of stay predicts an increased likelihood of presence of IDD after discharge (Table 2, 95% CI > 1, and $p < 0.05$ in the likelihood ratio test).

Discussion

In this study, children admitted in a Portuguese level II hospital with a diagnosis of ADEM were characterised regarding the clinical, laboratory and imaging findings, treatment, and clinical follow-up. Few studies on ADEM were conducted in Portugal, and this is the first study with a follow-up of up to 16 years.

According to the literature, the majority of patients with ADEM (73%) probably had a prior viral infection.^{1,4,10} The average interval of nine days between the prior infection and ADEM confirms that this is a post-infectious condition.^{4,10} This association leads to the investigation of a possible infectious trigger, although there was no standard protocol for testing. In our study, 53% of cases had positive serological/microbiological results, mainly positive serologies. The infectious agents detected in the patients in this study were previously described in ADEM case series.^{14,15} There was no relationship with prior vaccination, but recent series show that less than 5% of the patients had ADEM after vaccination.¹⁴

As previously described, the diagnosis of ADEM is based on clinical and imaging findings.^{3,6,8} Most patients in

Table 3. Time to treatment, therapeutic regimen, clinical and head magnetic resonance imaging follow-up

Patient	Time to corticosteroid treatment (days)	Therapy (duration)	Time to discharge (days)	Follow-up (years)	Head MRI follow-up	Clinical follow-up
1	12	Oral prednisolone (1 week)	49	5	Smaller lesions and mild cortical atrophy	Mild IDD Mild motor deficit
2	11	Oral prednisolone (8 weeks)	22	16	Residual lesions	Mild IDD
3	30	Oral prednisolone (4 weeks)	22	13	Residual lesions	Normal
4	2	MP (3 days) Oral prednisolone (4 weeks) IV Ig	47	16	Smaller lesions	Moderate IDD
5	2	MP (3 days) Oral prednisolone (4 weeks) IV Ig	38	14	Smaller lesions	Moderate IDD Motor deficit Epilepsy
6	-	-	10	13	Smaller lesions	Normal
7	1 day	MP (3 days)	5	13	Residual lesions	Normal
8	2	MP (3 days) Oral prednisolone (4 weeks) IV Ig	11	12	Normal	Mild IDD
9	5	MP (3 days) Oral prednisolone (4 weeks)	11	10	Smaller lesions	Normal
10	7	MP (3 days) Oral prednisolone (6 weeks)	8	9	Residual lesions	Normal
11	2	MP (3 days) Oral prednisolone (8 weeks)	18	5	Smaller lesions	Moderate IDD Motor deficit Epilepsy
12	3	MP (3 days) Oral prednisolone (2 weeks)	16	5	Smaller lesions	Moderate IDD Epilepsy
13	11	MP (3 days) Oral prednisolone (4 weeks)	6	4	-	Normal
14	8	MP (3 days) Oral prednisolone (6 weeks)	11	3	Normal	Mild IDD Mild motor deficit
15	3	MP (3 days) Oral prednisolone (12 weeks) IV Ig	15	2	-	Normal

IDD - intellectual development disorder; IV Ig - intravenous immunoglobulin; MP - intravenous pulses of methylprednisolone; MRI - magnetic resonance imaging.

our study had a polysymptomatic presentation, with encephalopathy, pyramidal signs, cranial neuropathies and ataxia as the most frequent neurological symptoms, as reported in the literature.¹⁰ The biochemical analysis of CSF was compatible with ADEM in the majority of cases, with lymphocytic pleocytosis and slightly increased protein levels. The presence of oligoclonal bands in the CSF is a non-specific finding, but it is frequently associated with multiple sclerosis and was negative in all cases.¹⁴ There has been a growing interest in

the measurement of anti-MOG antibodies due to their association with the optic neuritis and of anti-AQP4 antibodies due to their association with neuromyelitis optica. When positive, the diagnosis of multiple sclerosis seems to be excluded.⁴ Nevertheless, antibody measurement was only conducted in the more recently admitted patient and was negative.

In some patients, the head CT scan showed no abnormalities, confirming the limitation of this study in ADEM diagnosis.¹³ As opposed to the tomography, the head

MRI showed multiple bilateral characteristic lesions, sometimes asymmetrical, mainly affecting the basal ganglia and the thalamus, and deep and subcortical white matter lesions, which are a sign of demyelination (Figs. 1, 2, 3).^{6,16-18} In this study, a spine MRI was performed only in six children, according to their clinical presentation, and half showed abnormalities.

Although there are no prospective data from clinical trials to determine the optimal treatment, including dose or duration, the mainstay of therapy continues to be high dose corticosteroid administration, with pulses of methylprednisolone.⁶ In our study, all children, except one, were treated with corticosteroids, although three patients did not receive pulses of methylprednisolone. There was a good response and tolerance to corticosteroids and clinical recovery was achieved in most patients. Oral prednisolone was subsequently used for a variable period according to the clinical progression, followed by a taper.

Treatment with intravenous immunoglobulin was used as rescue therapy only in four children whose response to corticosteroids was not favourable. A patient did not require pharmacological treatment due to spontaneous clinical improvement.

The median follow-up time of these patients was eight years (minimum of two years and maximum of 16 years). During this time period, all patients, but one, showed a monophasic disease history. The development of relapse (new symptoms and new lesions in the head MRI) suggested the diagnosis of multiphasic acute disseminated encephalomyelitis in patient 14.

In our study, the overall survival rate was 100%. During follow-up, 7/15 patients had a complete recovery, and 4/15 patients had mild IDD (two patients had an additional motor deficit), accounting for 73% of children. One patient had moderate IDD, one patient had moderate IDD and motor deficit, and two patients had epilepsy, motor deficit and moderate IDD. As comorbid conditions, it is of note a behavioural disorder in patients 3 and 6. When compared to other studies,^{12,13} this study found a greater number of children with a neurological deficit. This may be explained by a longer patient follow-up, with screening for learning difficulties and minor neurological deficits. A long-term follow-up is essential to confirm the complete recovery and a definitive diagnosis of ADEM, as relapses suggest alternative diagnoses, such as multiphasic acute disseminated encephalomyelitis (patient 14) or multiple sclerosis.^{2-4,6,9,19,20} As neurocognitive sequelae were found in more than half of these children during follow-up, it is recommended to conduct neuropsychological tests in all patients, including in the absence of apparent neurolog-

ical deficits at discharge.²¹⁻²⁵

During follow-up, the head MRI showed complete or partial resolution of the abnormalities in the majority of ADEM cases. It is known that residual gliosis and demyelination may persist in some cases. Although there is no consensus, some authors suggest obtaining at least two additional head MRIs after the first episode of ADEM in order to confirm the absence of new inflammatory demyelinating lesions.¹⁶ In this study, however, only one follow-up head MRI was obtained in most patients. A statistically significant relationship between time from symptom onset to diagnosis/treatment and absence of IDD was not found (Table 2). This suggests that a small delay in the diagnosis and administration of therapy does not affect the patients' clinical recovery. A more prolonged regimen of oral corticosteroids was administered to patients with residual symptoms, such as in patient 15, who reported recurrent headache for a period of eight weeks after discharge. However, there is no convincing evidence that this may influence the prognosis.^{1,26} Nevertheless, the fact that a longer hospital length of stay is associated with an increased likelihood of IDD after discharge (Table 2) may be due to increased clinical severity of the condition not identified using the study variables.

There are some limitations in this study, including the small patient sample (15) and the retrospective nature of the study. The inclusion period of patients in this study is long, which may explain the differences in the approach to diagnosis and therapy. The majority of patients (14/15), however, were treated with corticosteroids, which did not allow the authors to compare the prognosis of these children with a group of untreated patients. The treatment regimen was not exactly the same in all children, as some patients did not receive intravenous pulses of methylprednisolone. Nevertheless, considering the small number of patients, it was not possible to identify the differences between different therapeutic regimens administered regarding the prognosis.

In conclusion, in the presence of acute encephalopathy and multiple focal neurological signs related to an infectious prodrome, the diagnosis of ADEM should be considered, and the indicated treatment should be initiated. However, in this particular study, the delay in diagnosis and therapy does not seem to have affected the prognosis. A study with ADEM patients with long-term clinical follow-up should be conducted in order to confirm the diagnosis of this condition and to document complete clinical recovery.^{2,3}

Cognitive sequelae were found in a significant number of patients emphasising the importance of conducting a

detailed neuropsychological assessment and the long-term follow-up of these patients. Future studies with more ADEM patients are necessary to understand the pathophysiology of this condition and to identify the factors that may predict patient clinical progression.

WHAT THIS STUDY ADDS

- In the presence of acute encephalopathy and multifocal neurological signs related to an infectious prodrome, the diagnostic hypothesis of acute disseminated encephalomyelitis should be considered, and the indicated treatment should be initiated.
- In this study, the delay in diagnosis and therapy does not seem to have affected the prognosis.
- Long-term follow-up of these patients should be performed in order to document the recovery and confirm the diagnosis of acute disseminated encephalomyelitis, including conducting a detailed neuropsychological assessment.
- Further studies with patients diagnosed with acute disseminated encephalomyelitis are needed to better assess the pathophysiology of this condition and to identify the factors that may predict patient clinical progression.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

Acknowledgments

The authors thank Susana Cordeiro, from the Pediatric Cardiology Department of Santa Cruz Hospital, who collaborated in the data statistical analysis.

References

1. Dale R, Sousa C, Chong W, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. *Brain* 2000;123:2407-22.
2. Pena J, Lotze T. Pediatric multiple sclerosis: Current concepts and consensus definitions. *Autoimmune Dis* 2013;2013:673947. doi: 10.1155/2013/673947.
3. Rodriguez Fernandez C, López-Marin L, López-Pino M, Gutiérrez-Solana L, Soto-Insuga V, Conejo-Moreno D. Análisis de una serie de casos con diagnóstico inicial de encefalomyelitis aguda diseminada en el período 2000-2010. *Rev Neurol* 2013;57:297-305.
4. Pohle D, Alper G, Van Haren K, Kornberg AJ, Lucchinetti CF, Tenenbaum S, et al. Acute disseminated encephalomyelitis. Update on an inflammatory CNS syndrome. *Neurology* 2016;87:S38-45. doi: 10.1212/WNL.0000000000002825.
5. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: Revisions to the 2007 definitions. *Mult Scler* 2013;19:1261-7. doi: 10.1177/1352458513484547.
6. Koelman D, Mateen F. Acute disseminated encephalomyelitis: Current controversies in diagnosis and outcome. *J Neurol* 2015;262:2013-24. doi: 10.1007/s00415-015-7694-7.
7. Omata T, Fujii K, Tanabe Y, Arai H, Motojima T. Acute disseminated encephalomyelitis: The time until diagnosis and its subsequent course in children. *J Child Neurol* 2014;29:28-30. doi: 10.1177/0883073812465013.
8. Duman O, Yürekli V, Gencpinar P, Karaali K, Gümüş H, Okuyaz Ç, et al. Unusual clinical cases that mimic acute disseminated encephalomyelitis. *Acta Clin Croat* 2015;54:371-7.
9. Brenton JN, Banwell B. Therapeutic approach to the management of pediatric demyelinating disease: Multiple sclerosis and acute disseminated encephalomyelitis. *Neurotherapeutics* 2016;13:84-95. doi: 10.1007/s13311-015-0396-0.
10. Incek F, Herguner O, Altunbasak S. Acute disseminated encephalomyelitis: An evaluation of 15 cases in childhood. *Turk J Pediatr* 2013;55:253-9.
11. Alper G, Heyman R, Wang L. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow-up: Comparison of presenting features. *Dev Med Child Neurol* 2009;51:480-6. doi: 10.1111/j.1469-8749.2008.03136.x.
12. Hynson JL, Kornberg AJ, Coleman LT, Shield L, Harvey AS, Kean MJ. Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. *Neurology* 2001;56:1308-12.
13. Tenenbaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: A long-term follow-up study of 84 pediatric patients. *Neurology* 2002;59:1224-31.
14. Stonehouse M, Gupte G, Wassmer E, Whitehouse WP. Acute disseminated encephalomyelitis: Recognition in the hands of general paediatricians. *Arch Dis Child* 2003;88:122-4. doi: 10.1136/adc.88.2.122.
15. Tenenbaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. *Neurology* 2007;68:S23-36. doi: 10.1212/01.wnl.0000259404.51352.7f.
16. Callen DJ, Shroff MM, Branson HM, Li DK, Lotze T, Stephens D, et al. Role of MRI in the differentiation of ADEM from MS in children. *Neurology* 2009;72:968-73. doi: 10.1212/01.wnl.0000338630.20412.45.
17. Verhey LH, Branson HM, Shroff MM, Callen DJ, Sled JG, Narayanan S, et al. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination.

nation: A prospective national cohort study. *Lancet Neurol* 2011;10:1065-73. doi: 10.1016/S1474-4422(11)70250-2.

18. Baum PA, Barkovich AJ, Koch TK, Berg BO. Deep gray matter involvement in children with acute disseminated encephalomyelitis. *AJNR Am J Neuroradiol* 1994; 15:1275-83.

19. Gulati S, Chakrabarty B, Kumar A, Jain P, Patel H, Saini L. Acquired demyelinating disorders of central nervous system: A pediatric cohort. *Ann Indian Acad Neurol* 2015;18:48-55. doi: 10.4103/0972-2327.164829.

20. Mikaeloff Y, Caridade G, Husson B, Suissa S, Tardieu M. Acute disseminated encephalomyelitis cohort study: Prognostic factors for relapse. *Eur J Paediatr Neurol* 2007;11:90-5. doi: 10.1016/j.ejpn.2006.11.007.

21. Shilo S, Michaeli O, Shahar E, Ravid S. Long-term motor, cognitive and behavioral outcome of acute disseminated encephalomyelitis. *Eur J Paediatr Neurol* 2016;20:361-7. doi: 10.1016/j.ejpn.2016.01.008.

22. Jacobs RK, Anderson VA, Neale JL, Shield LK, Kornberg AJ. Neuropsychological outcome after acute disseminated

encephalomyelitis: Impact of age at illness onset. *Pediatr Neurol* 2004;31:191-7. doi: 10.1016/j.pediatrneurol.2004.03.008.

23. Jayakrishnan MP, Krishnakumar P. Clinical profile of acute disseminated encephalomyelitis in children. *J Pediatr Neurosci* 2010;5:111-4. doi: 10.4103/1817-1745.76098.

24. Kuni BJ, Banwell BN, Till C. Cognitive and behavioral outcomes in individuals with a history of acute disseminated encephalomyelitis (ADEM). *Dev Neuropsychol*. 2012;37:682-96. doi: 10.1080/87565641.2012.690799.

25. Suppiej A, Cainelli E, Casara G, Cappellari A, Nosadini M, Sartori S. Long-term neurocognitive outcome and quality of life in pediatric acute disseminated encephalomyelitis. *Pediatr Neurol* 2014;50:363-7. doi: 10.1016/j.pediatrneurol.2013.12.006.

26. Anlar B, Basaran C, Kose G, Guven A, Haspolat S, Yakut A, et al. Acute disseminated encephalomyelitis in children: Outcome and prognosis. *Neuropediatrics* 2003;34:194-9. doi: 10.1055/s-2003-42208.

Encefalomielite Aguda Disseminada em Pediatria: Dificuldades na Predição do Prognóstico

Resumo:

Introdução: A encefalomielite aguda disseminada é uma doença desmielinizante do sistema nervoso central, caracterizada por encefalopatia e sintomas neurológicos multifocais. O objetivo deste estudo é caracterizar uma série de 15 crianças hospitalizadas com o diagnóstico de encefalomielite aguda disseminada e procurar fatores que permitam prever o prognóstico.

Métodos: Estudo observacional retrospectivo sobre uma série de casos de crianças hospitalizadas com encefalomielite aguda disseminada entre 1993 e 2015, através da consulta dos processos clínicos. Foram utilizados o *software* Microsoft Office Excel® 2010 e R versão 3.1.2® e a análise estatística incluiu modelos de regressão logística, teste de razão logarítmica, teste de *t*, e *odds ratio* com um intervalo de confiança de 95%.

Resultados: A maioria dos doentes teve uma apresentação polissintomática, maioritariamente com encefalopatia, sinais motores piramidais, neuropatias cranianas e ataxia. Encontraram-se dados serológicos e microbiológicos positivos em 53% dos doentes. Catorze crianças foram tratadas com glucocorticoides e quatro com imunoglobulina endovenosa como terapêutica de resgate. Um doente desenvolveu encefalomielite aguda disseminada multifásica. Todas as

crianças recuperaram do evento agudo, com uma taxa de sobrevivência de 100%. No seguimento, 53% dos doentes apresentavam perturbação do desenvolvimento intelectual, considerada moderada em mais de metade dos mesmos. A idade no momento do diagnóstico, o género, a presença de pródromo de infeção, os achados serológicos, febre à admissão, o tempo de internamento e as alterações do eletroencefalograma na admissão foram dados analisados, sem interferência direta no prognóstico. O atraso no diagnóstico e consequente instituição terapêutica não pareceu interferir com a recuperação clínica dos doentes.

Discussão: Não foi possível encontrar fatores preditivos do prognóstico na série de casos apresentados. Apesar de serem necessários mais estudos com séries de doentes em idade pediátrica com encefalomielite aguda disseminada, um seguimento a longo prazo deve ser realizado para documentar a recuperação e confirmar o diagnóstico de encefalomielite aguda disseminada.

Palavras-Chave: Criança; Encefalomielite Aguda Disseminada /diagnóstico; Encefalomielite Aguda Disseminada/epidemiologia; Encefalomielite Aguda Disseminada/terapia; Portugal; Prognóstico