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Acute disseminated encephalomyelitis in children and adolescents – 20-year single-center experience in Serbia

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SUMMARY
Introduction/Objective Acute disseminated encephalomyelitis (ADEM) is the most common demyelinating disease of the central nervous system in pediatric patients. We aimed to evaluate the clinical profile of children with ADEM and to discern prognostic factors for disease outcome.
Methods A 20-year retrospective–prospective study was conducted in a cohort with the diagnosis of ADEM.
Results The study included 36 patients, with range of follow-up period of 6–120 months (median of 26 months). Prior infection was reported in 72.2% of the patients. In the clinical presentation of the disease, motor deficit was most common (81.1%), followed by ataxia (77.8%). More than a third of patients had back and limb pain or abdominal visceral pain, which highly correlated with MRI findings of myelitis. Abnormal brain CT findings were evident in 22.2% of the patients, and this was associated with higher Expanded Disability Status Scale (EDSS) and quicker progression of the disease. Median EDSS was 0 at the most recent follow-up visit, in all the patients. EDSS 0–2.5 was verified in 29 (80.6%) of the patients, while three (8.3%) patients scored 7–9.5 at the last visit. Two patients had a lethal outcome.
Conclusions ADEM is a serious disease in pediatric patients, but with a good prognosis, which is illustrated by the fact that 80.6% of our patients had a complete or almost complete recovery.
Keywords: encephalomyelitis; demyelination; children; adolescents; prognosis

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the central nervous system (CNS), characterized by disseminated demyelinating lesions, predominantly in the brain's white matter and the spinal cord. In absence of specific biomarkers, a diagnosis of ADEM is based on the clinical presentation and neuroradiological findings. In 2007, the International Pediatric Multiple Sclerosis Society Group (IPMSSG) published consensus criteria for demyelinating disorders of childhood, including ADEM, which was updated in 2013 [1, 2]. These criteria have significantly contributed to the accuracy of diagnosis and better management of demyelinating disorders in childhood. According to these criteria, ADEM is an acute or subacute disease characterized by signs of encephalopathy and multifocal neurological deficit. Magnetic resonance imaging (MRI) of the brain shows typically large, poorly demarcated white matter lesions, although involvement of the cortical gray matter is not uncommon [3, 4, 5]. The disease is usually monophasic; however, relapses are possible [5, 6, 7].

In 50–75% of ADEM patients, there is evidence of recent infection or immunization [8, 9, 10]. Most commonly, these are non-specific upper respiratory tract infections, which explains a higher incidence of the disease in winter and spring months. Inflammation is believed to be the result of a transient immune response to myelin or other autoantigens through a molecular mimicry mechanism or non-specific activation of autoreactive T cell clones. There is numerous evidence that ADEM is a T cell-mediated autoimmune disease. The yearly incidence of ADEM in children is estimated at 0.4–0.54 per 100,000 persons and is somewhat higher than in adults [3, 9].

The aims of our study were to evaluate 20-year experience from a single institution in Serbia in treating children and adolescents diagnosed with ADEM, and to examine relationships between clinical features, microbiology, neuroimaging, treatment, and outcomes of the disease.

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METHODS

This is a retrospective and prospective study of all patients diagnosed with ADEM at the Dr Vukan Čupić Mother and Child Health Care Institute of Serbia in Belgrade over a period of 20 years, from January 1999 to March 2020. This is a retrospective study in the period from 1999 to 2007 and a prospective one from 2008 to 2020, after the publication of Krupp's criteria in 2007 [1]. Clinical information was obtained from the inpatient medical records. Diagnosis of ADEM was based on the definition proposed by the IPMSSG [1, 2]. This definition was used to define the inclusion and exclusion criteria of our study.

The inclusion criteria were the following: 1) acute or subacute disease onset, 2) multifocal neurological disorder, 3) signs of encephalopathy, defined on the basis of at least one of the following two criteria: a) behavioral disorder, i.e. confusion, extreme irritability and/or b) disorder of consciousness (lethargy, somnolence, coma), 4) neuroimaging-verified areas of demyelination of the CNS. The exclusion criteria were the following: 1) previously registered lesions in the brain's white matter, 2) other neurological disorders, 3) congenital metabolic diseases, 4) infective or immunological diseases of the CNS, 5) absence of signs of encephalopathy, 6) presence of clinically isolated syndromes like optic neuritis, transverse myelitis, and brainstem encephalitis.

We retrospectively applied IPMSSG criteria to subjects treated for encephalitis and myelitis in our hospital from 1999 to 2007 in order to recruit ADEM cases. After the publishing of the IPMSSG criteria in 2007, we regularly use these criteria in our clinical practice for diagnosing ADEM.

The following demographics as well as clinical data were collected for each patient: sex, age, previous illnesses in personal history (including fevers with rashes and neurological diseases like febrile/afebrile epileptic seizures), preceding infection or vaccination within 2–30 days before clinical presentation of ADEM, interval between the previous infection/vaccination and the onset of ADEM, season, systemic and neurological symptoms and signs, clinical course and length of hospitalization. We evaluated consciousness disorder level according to the modified Glasgow Coma Scale (GCS) score [10]. We collected inflammation-related laboratory parameters (sedimentation, C-reactive protein, leukocyte count), cerebrospinal fluid (CSF) samples (cytological, biochemical, and bacteriological). An extensive work-up for bacterial and viral infections was performed. Bacteriological cultures and serological testing for numerous infectious agents in the serum and the spinal fluid, as well as by direct detection of DNA through the polymerase chain reaction for the herpes simplex virus (HSV) and the Epstein–Barr virus (EBV). Antibody titers were determined in the serum and the spinal fluid for the following agents: HSV1, HSV2, EBV, cytomegalovirus, varicella zoster virus, morbilli virus, rubella virus, *Mycoplasma pneumoniae*, *Borrelia burgdorferi* and seldom human immunodeficiency virus. The complement attachment reaction was used to test the possibility of an infection by the following viruses: influenza A and B, parainfluenza 3, adenoviruses, and lymphocytic choriomeningitis virus. A few patients were tested for serum anti-N-methyl D-aspartate (NMDA) receptor antibodies (anti-NMDAR) and anti-aquaporin-4 antibodies.

Computed tomography (CT) and MRI of the brain and the spinal cord were performed initially and during the follow-up of patients. Large, confluent or tumefactive MRI lesions > 2 cm were considered severe. Electroencephalogram (EEG), nerve conduction studies, visual evoked potentials and brainstem evoked response audiometry were analyzed. The Kurtzke Expanded Disability Status Scale (EDSS) was applied for assessment of the level of neurological damage during follow-up [11]. The main outcomes in the focus of our study were EDSS and patient survival.

Statistical analysis

Mann–Whitney test was used to compare the differences between two groups with non-parametric data. We used Pearson's χ^2 test in the form of contingency tables to analyze two attributive properties. Correlation of non-parametric variables was established by Spearman correlation method. To identify predictors of EDSS score at the last follow-up visit, we used the linear regression analysis, while logistic regression was used to assess risk factors for a fatal outcome. Independent variables were selected for regression analysis on the basis of previous knowledge of risk factors, assessment of potential other risk factors related to pediatric age, and also those variables that could affect the conclusions as confounding factors. In all analytical methods applied, the significance level was 0.05.

The study protocol was in accordance with the tenets of the Declaration of Helsinki and its later amendments. The study was approved by the Ethics Committee of our institution.

RESULTS

Thirty-six patients who met the inclusion criteria for ADEM were included in this study. Mean age of patients was 6.7 years (SD 3.58, median 5.7 years), ranging from six months to 14.2 years. The sex distribution was equal (1:1) among the patients older than 10 years, while in younger patients, male sex was more prevalent (1.5:1) ($p > 0.05$). Prior infection was reported for 26 patients (72.2%): respiratory illness in 14 (38.9%), non-specific febrile episode in five (13.9%), gastrointestinal infection in four patients, while rubella, varicella, and dental infection were reported in single patients. Previous acute infections of the upper respiratory tract and gastrointestinal tract were viral non-specific infections. There were no patients with recent vaccination. No trigger was identified in 10 patients (27.8%). The median period between the occurrence of the triggering event and the onset of ADEM was seven days (range 2–30 days). The shortest latency was found after non-specific respiratory illness (median seven days) and the longest after non-specific fever (15 days), ($p > 0.05$). The presence of the trigger was associated with significantly lower EDSS in

comparison with patients without an identifiable triggering factor for ADEM ($p < 0.05$). The presence of a trigger did not significantly affect survival (p 0.524). The majority of patients are diagnosed in winter (38.9%) and summer (25%) months, but the seasonal variation did not reach the point of statistical significance ($p > 0.05$). The overview and frequency of clinical manifestations of ADEM in the studied group are shown in Table 1.

Table 1. Initial signs and symptoms of acute disseminated encephalomyelitis

Signs and symptoms	Frequency n (%)
General signs and symptoms	
Fever	25 (69.4)
Headache	22 (61.1)
Vomiting	19 (52.8)
Pain (back, legs, abdomen)	14 (38.9)
Respiratory manifestations	9 (25)
Neurologic signs and symptoms	
Altered consciousness	36 (100)
Ataxia	28 (77.8)
Speech disturbance	27 (75)
Cranial neuropathy	19 (52.8)
Tetraparesis/tetraplegia	16 (44.4)
Hemiparesis/hemiplegia	8 (22.8)
Nystagmus	7 (19.4)
Paraparesis/paraplegia	5 (13.9)
Senzory neuropathy	5 (13.9)
Seizures	5 (13.9)
Extrapyramidal signs	4 (11.1)

Median time period from signs and symptoms' onset to the maximum of the clinical manifestations was 3.5 days (range 0–13). The rate of the disease progression did not significantly affect survival ($p > 0.05$). Moreover, there was no significant correlation between the period of disease progression and final EDSS ($p > 0.05$). The modified pediatric GCS ranged 3–14, with a median value of 11. Deep comma (GCS ≤ 8) developed in 30.6% of patients, moderate affection of consciousness (GCS 9–12) in 41.7%, and mild affection of consciousness (GCS ≥ 13) in 27.8%. There was no significant correlation between GCS and EDSS ($p > 0.05$). The length of hospital stay ranged 8–100 days, with a median of 28 days. Survival was not significantly affected by the length of hospitalization ($p = 0.284$). Additionally, the length of hospitalization showed no significant correlation with EDSS ($p = 0.493$).

CSF analysis was done in 34 patients. CSF cell count ranged 1–63 cells/ml with the median value of 6.5. Pleocytosis was found in 23 (67.6%) patients, with predominance of mononuclear cells. Glycorrhachia ranged 2.1–5.4 mmol/L with a mean of 3.81 mmol/L (SD 1.1). There were no patients with hypoglycorrhachia. CSF protein concentration ranged 137–780 g/L, with a median of 283.5 g/L. Elevated CSF proteins were found in 27.2% of patients. Spinal fluid cultures were sterile in all patients (100%). EDSS correlated significantly with CSF protein concentration (Spearman correlation coefficient = +0.39, $p = 0.02$) and negatively with CSF glucose concentration (Spearman correlation coefficient = -0.43, $p = 0.01$). OCB (oligoclonal bands) analysis in CSF and serum was done in 20 patients and was positive in four patients. One child had OCB only in CSF, while three patients had OCB in both CSF and serum.

Almost two-thirds (64.9%) of patients had diffusely slow EEG activity, while focal slow activity was found in 13.5%. There was no statistically significant difference of EDSS or GCS in regard to EEG findings ($p > 0.05$). Initial EEG features showed no significant association with later occurrence of epilepsy ($p > 0.05$).

Median time from disease onset to first CT scan was three days. Abnormal brain CT findings (oedema or hypodense lesions) were evident in 22.2% of patients. Abnormal brain CT scan was associated with higher EDSS (3.19 *vs*. 1.48).

Initial brain MRI scan was performed at median time of 10 days (range 2–98) after the symptoms' onset in 34 patients. Gadolinium enhancement was found in 36.1% of initial MRI scans with severe pathologic changes present in 61.1%. Patients with large and confluent brain lesions with mass effect did not have significantly different final EDSS when compared to patients with small brain lesions on MRI ($p > 0.05$). Furthermore, the presence of gadolinium enhancement was not found to affect EDSS ($p > 0.05$). Children with MRI lesions of spinal cord more commonly experienced pain (71.4%) when compared to children with normal spinal cord MRI (18.2%) (Pearson $\chi^2 = 10.21$, $p = 0.001$). Control MRI scans (median of 92 days after disease onset) showed regression of all changes in 83.3% of patients, stable findings in 8.3%, and worsening in further 8.3%. Overview of the localization of brain MRI lesions observed in studied patients is presented in Table 2.

Table 2. Localization of brain magnetic resonance imaging (MRI) lesions in patients with acute disseminated encephalomyelitis

Brain MRI changes	Frequency n (%)
Subcortical and deep white matter	24 (66.7)
Brainstem	20 (55.6)
Periventricular white matter	15 (41.7)
Basal ganglia	14 (38.9)
Spinal cord	14 (38.9)
Thalamus	12 (33.3)
Cerebellum	12 (33.3)
Cortical grey matter	8 (22.2)
Capsula externa	8 (22.2)

Antibacterial and antiviral treatments were administered until an infectious disease process was ruled out. Therapy for brain edema was universally administered. Most commonly used drug for the treatment of our patients was methylprednisolone in 80.6% of the cases, followed by dexamethasone in 13.9% and intravenous immunoglobulins in 25% of the patients. Therapeutic plasma exchange (TPE) was administered in two patients (5.6%). Corticosteroids were the first line of therapy in all the patients and initiated 1–45 days after the onset of the disease (median of eight days). There was no significant correlation between the length of treatment delay and final EDSS ($p > 0.05$).

The analysis of the complications of the disease shows that three children had urinary tract infection, two children had pneumonia, while sepsis, cardiopulmonary arrest, and thrombophlebitis of deep leg veins were found in single patients. Mechanical ventilation due to coma was used in six children over a period ranging 8–40 days (median of 21.8 days).

Outcomes

Only eight patients (22%) had normal neurological status at discharge, while 56% of the patients had completely normal findings at the most recent neurological exam. Median EDSS was found to be 0 at the most recent follow-up visit for surviving patients, after the range of follow-up period of 6–120 months (median of 26 months). EDSS in a range of 0–2.5 was verified in 29 (80.6%) patients, while three (8.3%) patients scored 7–9.5. Most recent neurological examination showed normal findings in 20 patients (55.6%) without any consequences and was abnormal in 14 patients. The frequency of different neurological sequelae is represented in Table 3. In our sample of subjects, ADEM caused two lethal outcomes. One patient died during the acute stage of the disease. In the second patient with lethal outcome, criteria for ADEM were initially present, but during the follow-up period the diagnosis of multiple sclerosis was established. We do not have more detailed data about the death of the patient with MS, because he died in another hospital.

Table 3. Frequency of neurological sequelae in acute disseminated encephalomyelitis patients at the most recent follow-up visit (median of follow-up period 26)

Neurologic signs and symptoms	Frequency n (%)
Cognitive impairment	8 (22.2)
Epilepsy	5 (13.9)
Hemiparesis/hemiplegia	5 (13.9)
Paraparesis/paraplegia	3 (8.3)
Tetraparesis/tetraplegia	3 (8.3)
Visual impairment	2 (5.6)
Hearing impairment	2 (5.6)

Patients treated before the publication of Krupp's criteria had significantly higher EDSS score in comparison to the group of patients treated after 2007 ($p = 0.003$). This finding was further supported by linear regression analysis showing that EDSS was significantly affected by the time period when the treatment was initiated. When binary regression was used to assess the impact or multitude of potential risk factors (demographic and clinical) to the lethal outcome of ADEM, not any factor was significantly affecting survival.

DISCUSSION

Our study is the first study aimed at evaluating pediatric patients with ADEM in the Serbian population. Our main goal was to assess the long-term outcomes of pediatric patients suffering from ADEM and prognostic factors for disease outcome.

The mean age at disease onset in our cohort was 6.7 years, which corresponds well to previously reported range (3.6–7 years) [12, 13, 14]. The sex ratio was equal in the cohort as a whole, while there was a predominance of males under the age of 10. A number of studies also showed an equal sex ratio among patients [13], but several authors reported male prevalence, especially at younger age [14, 15, 16], as in our study. Precipitating event over a four-week period before the onset of the clinical picture of ADEM was registered in 72.2% of the cases, similar to previous researches [14, 17]. There was no case with previous vaccination, unlike in some previous studies [3, 4]. Children with ADEM occurring after infection had a better long-term outcome compared to cryptogenic cases; in fact, analysis showed significantly lower final EDSS in the postinfectious group of patients (mean of 2.6) when compared to cryptogenic cases (mean of 1.4).

Tenembaum et al. [18] reported that neurological symptoms worsened after a mean period of 4.5 days in their group of 84 patients, while in our study that period averaged 3.5 days. Nishiyama et al. [19] presented the detailed clinical course of 24 pediatric ADEM patients in Japan and established that neurological progression typically took 4.1 ± 3.7 days with improvement onset on day 7 ± 4.5.

Each subject in our study had two or more general disease symptoms or signs, the most common being fever, headache, and vomiting, similar to other studies [13]. Motor deficit was most common (81.1%), which was also suggested by the majority of other published studies [10, 18, 20]. The initial presentation of the disease revealed that ataxia was found in a high percentage (77.8%) of the patients, but its presence did not affect EDSS significantly in the studied group. More than a third of our patients had back and limb pain or abdominal visceral pain, which was highly correlated with MRI findings of myelitis. The pain existed in 72% of our patients with MRI lesion in the spinal cord, while Barakat et al. [21] detected pain in 88% of 24 children with acute transverse myelitis. The pain in demyelinating disorders is the result of damage of the spinothalamic pathway or the dorsal column of the spinal cord. There is little research regarding pain in pediatric spinal cord demyelinating disease, in contrast to adult population. Barakat et al. [21] conducted research on pain and new quantitative MRI techniques (diffusion tensor imaging, magnetization transfer imaging) for spinal cord examination in children with demyelinating disease, which may be useful for monitoring the efficacy of management for myelitis in the future.

Interesting fact is that EDSS correlated significantly positively with CSF protein concentration and negatively with CSF glucose concentration, which could mean that higher degree of inflammation has adverse influence on disease outcome. OCB were positive in serum and CSF in three patients (15%), of 20 patients who were tested. One of them had OCB in CSF only and not in the serum. This patient developed MS later on. According to Dale et al. [20], out of their 35 patients, six (17%) had positive OCB

in CSF. Intrathecal oligoclonal bands were only present in 0–20% of the cases in other studies [3, 13]. It would be important to determine the biochemical markers in the CSF on the basis of which we could predict the outcome of the disease, in future research. We have not been able to determine the presence of anti-MOG antibodies in the cerebrospinal fluid before; however, it has been shown that MOG-Abs were identified in 33–66% of pediatric patients with ADEM [12, 22]. Rossor et al. [23] demonstrated that a higher relapse rate in children with MOG-Ab-associated ADEM, and a trend towards a greater risk of post-ADEM epilepsy. However, MOG-Ab alone are not sufficient to induce the disease. Proinflammatory cytokines are of great importance in the process of pathogenesis [24].

Hypodense CT lesions in the first days of the disease in our patients were associated with faster progression of the disease and poorer outcome. Brain edema was present on CT scan in one patient who died in the acute phase of the disease. Although we know that MRI is a much more sensitive method for detecting demyelinating lesions in ADEM [15], CT images can also be very important in the early diagnosis of brain edema. Distribution of demyelinating MRI lesions in our study was similar to other studies [13, 20, 25]. We failed to prove that there was a significant association between the extensiveness of lesions on brain MRI and the final outcome of the disease. Most recently repeated MR scans (median of 92 days after disease onset) in our study showed regression of all changes in 83.3% of patients, in accordance with data from other studies [10, 15].

Our first-choice treatment was i.v. administration of methylprednisolone in high doses for five days, followed by oral administration of prednisone in tapering doses. In case of failure to achieve significant clinical improvement early after starting corticosteroid therapy, intravenous immunoglobulins (IVIG) were used as the second treatment line. TPE was applied in two patients, with poor recovery from corticosteroids and IVIG and proved to be a very successful therapy. If there was no improvement within two weeks after IVIG administration, we decided to apply TPE. We applied five sessions of TPE on alternate days. There are no studies comparing the efficacy of corticosteroids, IVIG, and plasmapheresis.

In accordance with previous studies, our study asserts that children with ADEM have mostly favorable outcome [3, 15, 26]. Patients who developed epilepsy during the follow-up period did not have seizures in the acute phase of the disease. Five patients had acute attacks, but only one of them had subsequent attacks during the follow-up period. All patients with epilepsy after ADEM had large MRI lesions in acute stage of the disease, as depicted in Figure 1, showing brain MRI in a four-year-old boy.

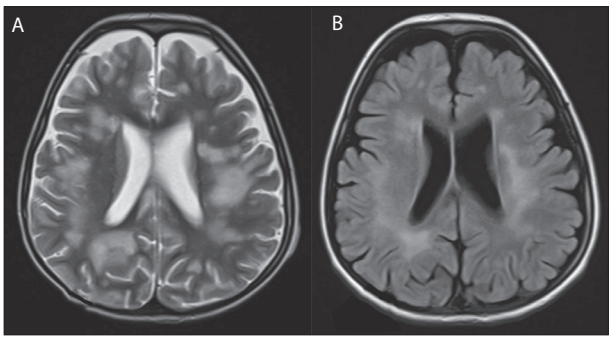

Figure 1. Acute disseminated encephalomyelitis in a four-year-old boy; A) T2W sequence of brain magnetic resonance imaging (MRI) scan shows large dissemianted hyperintense lesions; B) follow-up brain MRI obtained 15 months later shows a decrease and no appearance of new lesions

The main advantages of our study stem from long experience of treating children with ADEM. Our sample of children and adolescents was homogenous in terms of inclusion criteria. We also provide a realistic overview of clinical approach to pediatric patient with ADEM in a tertiary-level health care hospital in Serbia. This is the first decade-long study regarding pediatric ADEM in the region of the Balkans. The main disadvantage of our study is the variable length of patients' follow-up periods.

CONCLUSION

Our 20 years of experience have shown that ADEM is a serious disease in children, but with a good prognosis in the majority of patients, illustrated by 80.6% rate of complete or near-complete recovery, after a follow-up period ranging 6–120 months. Poor prognostic factors for disease outcome in terms of disability were the following: absence of previous infection as ADEM trigger, findings of brain edema or hypodense CT lesion in the first days of the disease, as well as higher values of protein in the CSF. Finding that EDSS was significantly better in ADEM patients treated after Krupp's criteria publication poses an important proof of their value in the clinical practice.

Conflict of interest: None declared.

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Акутни дисеминовани енцефаломијелитис код деце и адолесцената – двадесетогодишње искуство у једном центру у Србији

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САЖЕТАК

Увод/Циљ Акутни дисеминовани енцефаломијелитис (АДЕМ) најчешћа је демијелинизациона болест централног нервног система код педијатријских болесника. Циљ нашег рада је био да проценимо клиничке карактеристике деце са АДЕМ и да установимо прогностичке факторе за исход болести.

Методе Спроведена је двадесетогодишња ретроспективно-проспективна студија у кохорти болесника са дијагнозом АДЕМ.

Резултати Студија је обухватила 36 болесника, са периодом праћења 6–120 месеци (медијана 26 месеци). Претходна инфекција је пријављена код 72,2% болесника. У клиничкој презентацији болести моторни дефицит је био најчешћи (81,1%), а затим атаксија (77,8%). Више од трећине болесника је имало бол у леђима и екстремитетима или абдоминални висцерални бол, што је било у високој корелацији са МР налазима мијелитиса. Абнормални налази КТ мозга су описани код 22,2% болесника, што је било удружено са вишим скором на Проширеној скали степена онеспособљености (*Expanded Disability Status Scale, EDSS*) и бржим напредовањем болести. Медијана *EDSS* за целу кохорту на последњем контролном прегледу је износила 0. Код 29 (80,6%) болесника *EDSS* се кретао у опсегу 0–2,5, док су три (8,3%) болесника имала скор 7–9,5. Два болесника су имала летални исход.

Закључак Акутни дисеминовани енцефаломијелитис је озбиљна болест код педијатријских болесника, али са добром прогнозом, што илуструје податак да је 80,6% наших болесника имало потпуни или скоро потпуни опоравак.

Кључне речи: енцефаломијелитис; демијелинизација; деца; адолесценти; прогноза