

**The efficacy of intravenous immunoglobulin in the treatment of patients
with acute disseminated encephalomyelitis**

Abstract.

Background: Acute disseminated encephalomyelitis (ADEM) is a monophasic process nevertheless sometimes aggravated by relapses (so-called multiphase course of the disease). In such case the treatment must be targeted at reducing clinical manifestations of the disease and prevention of its relapses. The **aim** of our work was to analyze efficacy of intravenous immunoglobulin as therapeutic option in the treatment of patients with ADEM.

Methods: Therapeutic efficacy of intravenous **immunoglobulin** was analyzed in the treatment of 27 patients with ADEM: 12 men and 15 women aged 17 – 53 (average index 31.7 ± 1.6). All patients were being treated at the Kiev city centre of multiple sclerosis (Kiev city hospital number 4, Alexandrovskaya City Clinical Hospital, Kiev city, Ukraine) and were under observation for 2 years. The patients were daily administered intravenous immunoglobulin – 0.4 g per 1 kg of body mass within 5 days. The treatment was followed by monthly administration of immunoglobulin – 0.4 g per 1 kg of body mass within 24 months.

Results: 1 month after beginning of the treatment patients of both groups demonstrated the decrease of neurological deficit, measured according to the EDSS scale, compared to the indices before treatment ($p < 0.01$). 24 months after beginning of the treatment even more significant reduction of the level of neurological disorders of the patients of the main group ($p < 0.05$) and its increase in the patients of the control group ($p < 0.05$) was observed, which is explained by development of demyelination disease relapses over a 24-month observation period. Over a 24-month observation period, the patients of the main group had 2 relapses of disseminated encephalomyelitis, the patients of the control group – 7 relapses, two of them demonstrated transformation of ADEM in two MS.

Conclusions: The investigation proved positive therapeutic efficacy of intravenous immunoglobulin in the treatment of patients with ADEM – reduction of clinical manifestations of the disease, in particular a decrease in neurological deficit level. Monthly intravenous immunoglobulin administration also has great prognostic significance in prevention relapses of the disease (multiphase ADEM course).

Keywords: acute disseminated encephalomyelitis, treatment, intravenous immunoglobulin

Abbreviations: ADEM - acute disseminated encephalomyelitis

MDEM - multiphasic disseminated encephalomyelitis

MRI - Magnetic resonance imaging

1. Introduction:

Increasing the efficacy of the treatment of patients with acute disseminated encephalomyelitis (ADEM) remains an actual problem for clinical neurology. ADEM is an autoimmune disease characterized by presence of inflammation and demyelination foci, having been caused by infectious disease or vaccination, in the central nervous system [1]. In most cases, ADEM is characterized by the monophasic course accompanied by considerable variations concerning the duration of the disease and period of convalescence of the patient. However, there are also possible relapses of ADEM that have already been known since 1932, as described by van Bogaert, who published the paper “ADEM with relapses” [2]. ADEM relapses can be considered as a multiphasic course of this disease or its transformation into multiple sclerosis (MS) (according to the McDonald Criteria) (see, e.g., the works [3, 4, 5, 6, 7, 8, 9]).

ADEM relapses have been described with the following frequencies: in 1/18 patients (5.5%) [10], in 4/31 (13%) [11, 12], in 24/132 (18%) [13], in 7/35 (20%) [14], in 9/42 (21%) [15], in 5/21 (24%) [16].

Appearance of new clinic symptoms three months after initial signs of this disease is considered as a relapse of ADEM. In the case of this disease relapse, the pathological process comprises new parts of brain and/or spinal cord (which is usually confirmed by clinical investigations and neurovisual methods).

If the relapse appears in a short time interval after initial signs and is combined with further infection or cancelled hormonal therapy, the term multiphasic disseminated encephalomyelitis (MDEM) should be used [17, 18]. In the opinion of researchers, MDEM is characterized by poly-symptomatic manifestations of this disease, availability of demyelination nidi in Magnetic resonance imaging (MRI) data mainly in subcortical parts of brain, in less degree located periventricularly, with total or partial disappearance of foci during the convalescent period [19]. The multiphasic course of disseminated encephalomyelitis can be diagnosed in the case of disease relapse appearance at least 3 months after its initial presentation [16, 18, 19, 20]. Appearance of new clinic symptoms and new foci in MRI data 12 to 18 months after the primary episode of the disease is indicative of its possible transformation into multiple sclerosis (MS) (according to the McDonald Criteria) [9, 21]. Relapses of acute disseminated encephalomyelitis are called multiphase course of the disease [14, 22]. Therefore treatment of acute disseminated encephalomyelitis must be aimed at reducing intensity of neurological impairment and prevention of the disease relapses.

There is a lack of controlled clinical trials and no proven standard treatment for ADEM. Most treatment options are based on empirical and observational evidence. Once ADEM is diagnosed and an acute infectious etiology exclude, treatment should be instituted as soon as possible [23, 24].

In case of ADEM demyelination foci occur due to sensitization of lymphocytes to the brain tissues leading to the inflammatory response against antigens of the brain

[25-29]. As far as development of the disease is caused by autoimmune response, patients are recommended pathogenetic immunosuppressive therapy aimed at suppression of the immune response to infectious agent or vaccination with the high doses of corticosteroids [30-34]. Hormone therapy is also recommended due to its ability to block or modify the course of experimental allergic encephalomyelitis. In addition to its anti-inflammatory and immunosuppressive action, hormone therapy restores the function of blood-brain barrier, activates phagocytosis and immunoglobulin synthesis. Intravenous administration of corticosteroids over a period of several days followed by their peroral administration is considered to be the most common treatment scheme [35-38]. However, in cases where the efficacy of pulse-therapy with corticosteroids is insufficient, intravenous administration of immunoglobulin is used [39-45]. Plasmapheresis method is also used for the treatment of patients with the diagnosis of ADEM that is proved by the results of multiple investigations [46-50].

The **aim** of our work was to analyze the efficacy of intravenous immunoglobulin as therapeutic option in the treatment of patients with ADEM.

Methods: Therapeutic efficacy of intravenous immunoglobulin was **prospectively** analyzed in the treatment of 27 patients with ADEM: 12 men and 15 women aged 17 – 53 (average index 31.7 ± 1.6). Influence of the treatment on changes in neurological status of patients as well as variations in the disease course **were** studied.

All patients were being treated at the Kiev city centre of multiple sclerosis (Kiev city hospital number 4, Alexandrovskaya City Clinical Hospital, Kiev city, Ukraine). The diagnosis of ADEM was based on neurological examination, MRI of the brain and CSF analysis. All ADEM patients met the recently published diagnostic criteria [51]. The patients were separated into two groups depending on the treatment method. The first (main) group included 27 patients who were daily administrated intravenous immunoglobulin in the dose of 0.4 g per 1 kg of mass of body within 5 days. The treatment was followed by monthly administration of human normal immunoglobulin – 0.4 g per 1 kg of body mass within 12 months as a method of ADEM monotherapy. The control group included 20 patients aged 19 – 51 (average index 36 ± 3) with the same demographic characteristics. Intravenous administration of human normal immunoglobulin was not used in the treatment of control group patients. The participants of this group were given placebo treatment. Neither main nor control group received any medication prior to this study.

According to indications, in some cases the treatment in both main and control group and was preceded by premedication with hormonal pulse-therapy, using methylprednisolone in the dose of 500-1000 mg daily in 200 ml of isotonic sodium chloride solution (within 5 days). In case of the disease relapses, the patients of both main and control group received the same hormonal pulse-therapy, using methylprednisolone in the dose of 500-1000 mg daily in 200 ml of isotonic sodium chloride solution (within 5 days).

Therapeutic efficacy of the performed treatment of patients with ADEM has been assessed by the amount of restored neurological functions (in points), using the Kurtzke – Expanded Disability Status Score (EDSS) scale [52] and by the number of demyelination disease relapses over a 12-month period of observation. The decrease of neurological disorders index by 1.5-2 points according to EDSS scale was considered a significant improvement, the decrease by 1 point – a moderate improvement, the decreased by 0.5 point – an insignificant one. The absence of restored neurological functions according to the EDSS scale was assessed as an absence of therapeutic effect.

All the patients were under observation for 2 years. If during this period (2 years) no relapse of demyelination disease was detected, we interpreted it as the monophasic type of the ADEM course. In the case when disease relapses appeared, having the signs of disseminated encephalomyelitis from the clinical viewpoint and after neuro-visual patient examination, it was considered as the multiphasic option of the disease course. In the case of clinically confirmed multiple sclerosis (in accord with the McDonald criteria [9]), we interpreted it as transition of ADEM into multiple sclerosis.

In the statistical analysis the t-test was used for two-group comparisons of the clinical and demographic variables of persons with acute disseminated encephalomyelitis. Five percent for two tailed tests was chosen as the level of significance.

According to the decision of the Ethics Committee of the O.O. Bogomolets National Medical University (Kyiv city, Ukraine), the investigations described in these articles have been carried out according to modern scientific standards. All patients signed informed consent form. There have been provided the measures ensuring safety of the patients, respect of their rights and dignity as well as moral and ethical standards in accordance with the human rights principles of the Declaration of Helsinki. Ethics Committee does not have any objections against publishing these articles (protocol number 48 dated 29.09.2010.)

Results:

Demographic data are shown in Table 1.

Table 1. Demographic characteristics of participants

Variable	Main group	Control group	P value
Overall numbers (%)	27	20	
Baseline age, years	31.7±1.6	31.9±1.5	0.2
Gender			
Male	12 (40%)	7 (35%)	0.6
Female	15 (60%)	13 (65%)	0.6
Race			
White	27 (100%)	20 (100%)	-
Other	-	-	-

Education (years)

15.49±0.4

15.3±0.24

0.5

The analysis of pre-treatment clinical and neurological examination data shows that disability level at baseline (in points) was the same in both clinical groups (Table 2). The disability of patients according to the EDSS scale mostly had mild and moderate level, much less frequently – severe one.

The use of immunomodulating method – human normal immunoglobulin for intravenous administration – in the treatment of the patients with ADEM had the positive influence on restoring the neurological functions and reducing the disability level in the EDSS points. It has been confirmed by the results of therapy of patients of the main and control groups (their average disability indices are given in Table 2 and 3 and Figs 1).

Table 2. The disability baseline level in patients with ADEM of different clinical groups.

Clinical group of patients with ADEM	Disability level according to the EDSS scale, points		
	mild (1.0-3.5)	moderate (4.0-6.0)	severe (6.5-9.0)
main (n = 27)	n = 16 (3 ± 0.1)	n = 10 (4.8±0.2)	n = 1 (6.5)
control (n = 20)	n = 12 (3.1 ± 0.1)	n = 8 (4.3±0.2)	–

Note. In brackets – average index of the total number of patients.

Table 3. Changes of average index of EDSS functional system in patients with ADEM of different clinical groups (M±m).

Functional systems	Clinical group of patients with ADEM	Disability level according to the EDSS functional system, points	
		Before treatment	1 month after beginning of the treatment
Impairment of pyramidal tract	main	4.5±0.3	3,1±0.3*
	control	4.1±0.3	3.5±0.3
Impairment in coordination sphere	main	3.5±0.3	2,7±0.3*
	control	3.6±0.3	3,1±0.3
Urine bladder disorders	main	2,1±0.3	1.8±0.1
	control	2,3±0.3	2.1±0.1

Note. *– reliability of difference between the indices before and after the treatment, $p<0.05$.

Table 4. Dynamics of average index of disability in patients with ADEM of different clinical groups according to the EDSS scale after the treatment (M±m).

Clinical group of patients with ADEM

Disability level according to

Results of therapy		the EDSS scale, points	
		Before treatment	1 month after beginning of the treatment
Main (n=27)	average score	3.8±0.2	3.0±0.2
	significant improvement (n=2)	3.5	2
	moderate improvement (n=13)	4.0±0.3	3.0±0.3*
	insignificant improvement (n=9)	4.2±0.5	3.7±0.5
	no improvement (n=3)	3.3±0.5	3.3±0.5
Control (n=20)	average score	3.9±0.2	3.4±0.2
	moderate improvement (n=6)	4.7±0.2	3.7±0.2*
	insignificant improvement (n=8)	3.6±0.3	3.1±0.3
	no improvement (n=6)	3.3±0.4	3.3±0.4

Note. *– reliability of difference between the indices before and 1 month after beginning of the treatment, $p<0.05$.

The data in Table 4 show that among the patients of the main group who were administered intravenous immunoglobulin, significant and moderate improvement was observed in 55.6% of patients, significant improvement was observed in two patients (7.4%) and 13 patients (48.2%) showed persistent moderate improvement of neurological functions: increase of strength in paretic extremities, reduction of the increased muscle tone, decrease of expressed static and dynamic ataxia, improvement (or normalization) of urination function. The decrease of the average indices of disability according to the EDSS scale from 4 ± 0.3 to 3 ± 0.3 points ($p<0.05$) was observed. 9 patients (33.3%) showed a mild clinical improvement: reduction of neurological deficit according to the EDSS scale from 4.2 ± 0.5 to 3.7 ± 0.5 points ($p>0.05$). 3 patients of the main group (11.1%) did not demonstrate any significant changes in the neurological status. The efficacy of treatment of the patients in the control group was significantly lower: moderate improvement was observed in 6 patients (30%), mild improvement – in 8 patients (40%), the effect was absent in 6 patients (30%).

The results of neurological examination of patients over a 24-month period are shown in Table 5 and Fig. 2. One month after beginning of the treatment patients of both groups demonstrated the decrease of neurological deficit, measured according to the EDSS scale, compared to the indices before treatment ($p<0.01$). The patients of the main group showed some decrease of neurological deficit 12 months after leaving the hospital ($p>0.05$); the patients of the control group on the contrary showed the increase of neurologic deficit, yet not confirmed statistically ($p>0.05$). During the

second examination after 12 months (24 months after beginning of the treatment) even more significant reduction of the level of neurological disorders of the patients of the main group ($p<0.05$) and its increase in the patients of the control group ($p<0.05$) was observed, which is explained by development of demyelination disease relapses over a 24-month observation period.

Table 5. Dynamics of changes in neurological status of patients with ADEM over a 24-month observation period.

Group of patients	Disability level according to the EDSS scale, points			
	Before treatment	1 month after beginning of the treatment	After 12 months	After 24 months
main (n=27)	3.8±0.2	3.0±0.2	2.8±0.3	2.3±0.4
control (n=20)	3.9±0.2	3.4±0.2	3.8±0.3*	4.1±0.3^

Note. * – reliability of difference between the indices of the main and control groups,

$p<0.05$; ^ – $p<0.001$.

As can be seen from the Table 5, six and twelve months after beginning of the treatment, the patients of the control group demonstrated the increase of neurological deficit compared to the patients of the main group. Over a 24-month observation period, the patients of the main group had 2 relapses of disseminated encephalomyelitis, the patients of the control group – 7 relapses, two of them demonstrated transformation of ADEM in two MS (according to the McDonald Criteria). One woman had two relapses over the year) (Table 6).

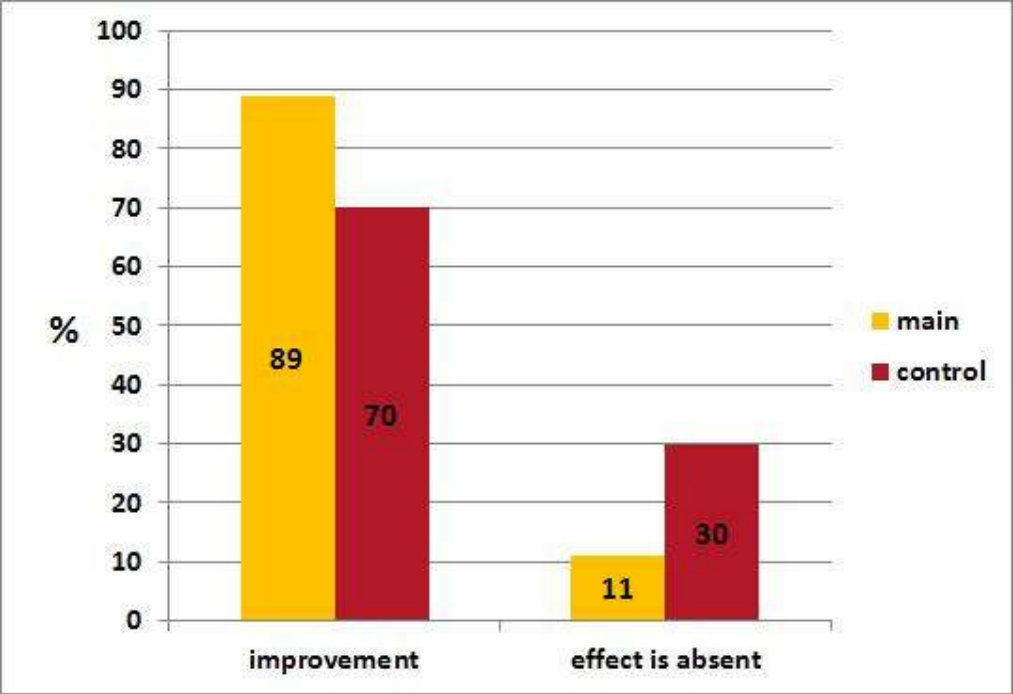
Table 6. Frequency of relapses in the patients with ADEM over a 24-month observation period.

Clinical group of patients with ADEM	Observation period					
	1 month	6 months	12 months	18 months	24 months	Total number of relapses
main (n=27)	–	1	1	–	–	2
control (n=20)	–	1	2	2	2	7

To illustrate the clinical efficacy of human normal immunoglobulin a clinical observation is given below.

247 Observation No. 1. Patient K. (woman) was being treated at the neurological department of
248 the Alexandrovskaya City Clinical Hospital with a diagnosis of acute disseminated
249 encephalomyelitis. According to the neurological examination, the patient had problems
250 with movement of right eyeball outwards, animation of deep reflexes with anisoreflexia
251 (S>D), swaying when performing the Romberg test as well as reduction of vibration
252 sensitivity of hands and feet to 9-10 seconds. MRI investigation showed the signs of
253 disseminated demyelination process in the brain (multiple foci of hyperintensive signal on
254 T2-weighted image without clear contours (up to 12 mm in diameter) were seen in the white
255 matter of the cerebral hemispheres supratentorially and periventricularly, in the brainstem,
256 cerebellum, right ophthalmic nerve). After the pulse-therapy with glucocorticoids, the
257 patient was daily administered human normal immunoglobulin intravenously in the dose of
258 0.4 g per kg (within 5 days). The positive dynamics of clinical symptoms was recorded 7
259 days after beginning of the treatment (movements of right eyeball outwards became more
260 frequent, tendon anisoreflexia reduced). The treatment was followed by monthly
261 administration of human normal immunoglobulin in the dose of 0.4 g/kg. No relapses were
262 observed over 12 months of observation.

265 Fig. 1. Dynamics of restoring neurological functions of patients with ADEM in
266 different clinical groups as a result of treatment.



269 Fig. 2. Dynamics of changes in neurological status of patients with ADEM according
270 to the EDSS scale over a 24-month observation period.

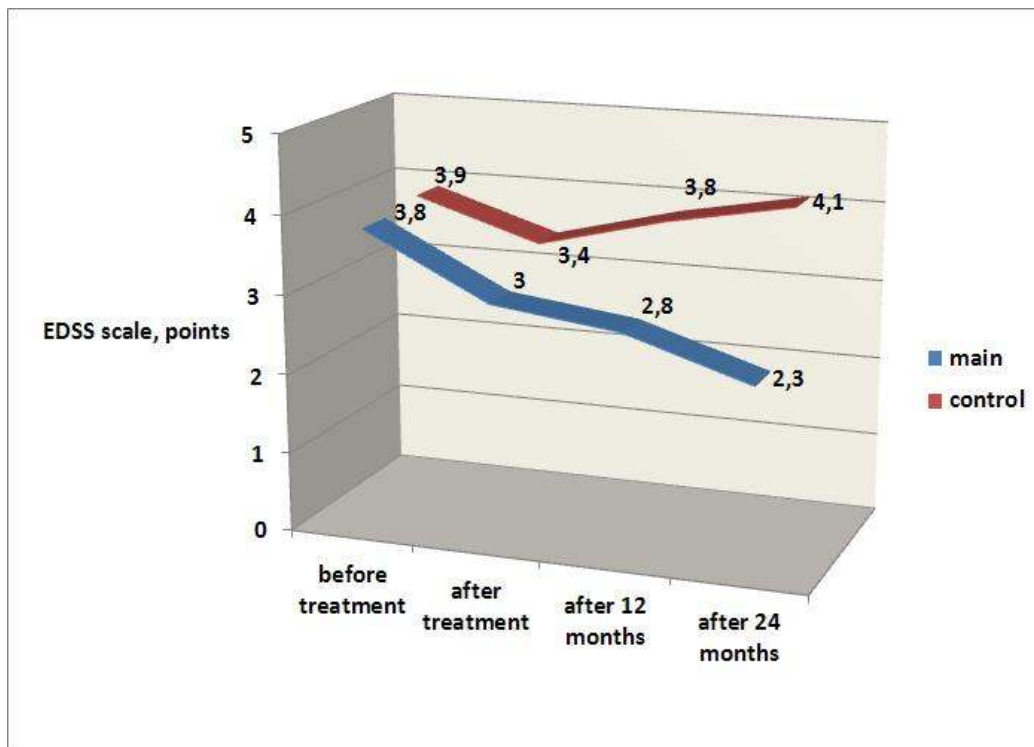


Fig. 3. MRI data of the patient G., 37 years old. Multiple, large foci of high intensity of signal (of different sizes) in the T2 mode, located in the frontal, temporal and parietal lobes of both hemispheres (dated 21.01.2011).

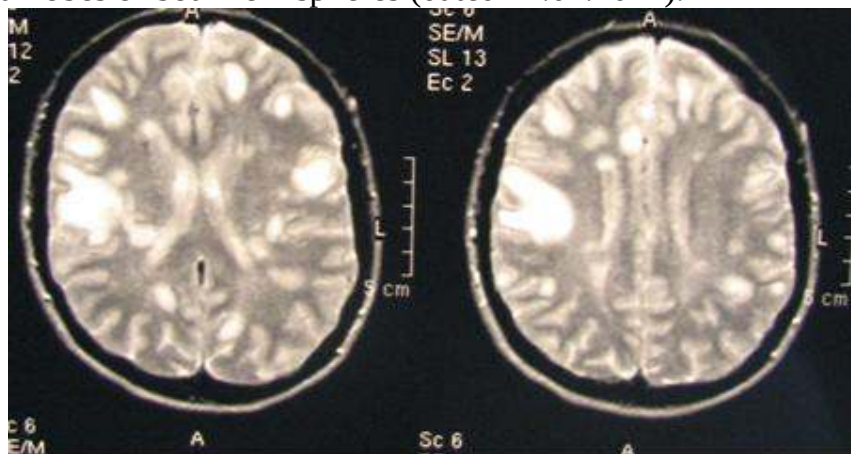


Fig. 4. MRI data of the patient D., 37 years old. Multiple, large foci of high intensity of signal (of different sizes) in the T1 mode, located in the frontal, temporal and parietal lobes of both hemispheres (dated 21/03/2011).



Discussion:

The performed investigations prove the positive therapeutic efficacy of intravenous administration of human normal immunoglobulin in the treatment of patients with acute disseminated encephalomyelitis.

Immunobiological action of immunoglobulin is believed to contribute to treatment efficacy due to the presence of antibodies against various infectious agents (virus of measles, influenza, varicella, parotitis, poliomyelitis, rubella, herpes-associated group, hepatitis A and B, pneumococcus) [53-62]. Its efficacy has been demonstrated in several controlled studies [61]. A broad spectrum of immunological mechanisms is thought to be relevant in explaining the properties of IV Ig therapy, such as supply of idiotypic antibodies, neutralization of complement-mediated effects [62, 63], inhibition of complement binding and prevention of membranolytic attack complex (MAC), modulation of Fc receptors or T-cell function. In the treatment of neurological autoimmune disorders, only a few of these mechanisms seem to be relevant like the modulation of complement activation and activation and activity of macrophages [61, 64]. Experimental data show that in case of inflammatory diseases immunoglobulin may influence on the local immune response in the central nervous system, regulating nitric oxide release and microglia function [65]. Remyelination stimulation can be a possible consequence of immunoglobulin use [65, 66].

The use of intravenous immunoglobulin (IVIG) has been reported in several case studies as well, either alone [67] or in combination with corticosteroids [68]. Positive therapeutic efficacy of its use consists of reduction of neurologic deficit in patients with ADEM. The results of our investigation proved that immunoglobulin administration contributes not only to the reduction of clinical manifestations of the disease by decreasing the level of neurologic deficit. According to the results of our study, monthly administration of human normal immunoglobulin is of great prognostic importance, preventing the multi-phase course of the acute disseminated encephalomyelitis.

The major limitation of our work was that the period of observation was too short (24 months). Further research should be aimed at investigation of therapeutic efficacy of immunoglobulin in the treatment of patients with ADEM during a longer period.

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