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The Efficacy of Intravenous Immunoglobulin in the Treatment of Patients with Acute Disseminated Encephalomyelitis

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Authors' contributions

This work was carried out in collaboration between both authors. Authors IL and OM conceived the study. Author IL designed the experiments and carried out the research. Both authors prepared the first draft of the manuscript and were involved in the revision of the graft manuscript and have agreed to the final content.

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ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is a monophaseprocess nevertheless sometimes aggravated by relapses (so-called multiphasecourse 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 47 patients with ADEM: 19 men and 28 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 randomly separated into two groups depending on the treatment method. The

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treatment in both main and control group 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). The patients of the main group were daily administrated intravenous immunoglobulin in the dose of 0.4 g per 1 kg of mass of body within 5 days 1 month after the hormonal pulse-therapy. The treatment was followed by monthly administration of human normal immunoglobulin – 0.4 g per 1 kg of body mass within 24 months. The participants of this group were given placebo treatment (200 ml of isotonic sodium chloride solution).

Results: One month after beginning of the treatment in patients of both groups we observed 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 into 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 for prevention of the disease relapses (multiphase ADEM course).

Keywords: Acute disseminated encephalomyelitis; treatment; intravenous immunoglobulin.

ABBREVIATIONS

ADEM- acute disseminated encephalomyelitis; MDEM- multiphasic disseminated encephalomyelitis; MRI- magnetic resonance imaging; EDSS- expanded disability status score; MS- multiple sclerosis.

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 in 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 vanBogaert, 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) [3-9]. The relapse rate of ADEM has been described, ranging from 5.5% to 24% [10-16].

New clinical symptoms appearing three months after initial signs of this disease are considered as a relapse of ADEM. In case of the 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 [16,18-20]. 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 acute infectious etiology is excluded, 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.

2. 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 the 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 ofthebrainandCSFanalysis. All ADEM patients met the recently published diagnostic criteria [51]. 10 patients with ADEM (21%) – 6 patients of the main group (22%) and 4 patients of the control group (20%) have the medical history of preceding signs of infectious process. The onset of disease in all patients was acute with evident disseminated lesion of central nervous system, frequently involving gray matter of the brain, increase of neurological deficit was observed during the short period of time (hours–days) and sudden development of encephalopathy.

The patients were randomly separated into two groups depending on the treatment method. All patients were blinded to their treatment group. According to indications the treatment in both main and control group 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). The first (main) group included 27 patients who were daily administrated intravenous immunoglobulin in the dose of 0.4g per 1kg of mass of body within 5 days 1 month after the hormonal pulse-therapy. The treatment was followed by monthly administration of human normal immunoglobulin – 0.4g per 1kg of body mass within 24 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 (200 ml of isotonic sodium chloride solution).

All the patients were under observation by the same physicians for 24 months. 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 was assessed by the amount of restored neurological functions (in points), using the Kurztke–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 decrease 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, it was 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.

Statistical analysis of the results was made with the use of Stata 12. Generalized characteristic of the investigated indices is represented by the arithmetic mean (X). Variability of parameters was assessed by standard deviation. For comparative analysis there was used t-test(five percent for two tailed tests was chosen as the level of significance) and χ^2 test (α=0.05, two sided). The Fisher criterion was used for two-group comparisonsoffrequency of relapses over a 24-month observation period.

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).

3. RESULTS

Demographic data are shown in Table 1.

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 1). The disability of patients according to the EDSS scale mostly had mild and moderate level, much less frequently – severe one.

CSF was analyzed in all 47 patients (both main and control group). CSF evidence of inflammation (either pleocytosis or elevated protein) was present in 39 patients (82,9%). The CSF White Blood Cells (WBC) count ranged between 0 and 137 with a mean of 40,8 cells/mm 3. WBC count was elevated in 17 patients

Table 1. Demographic and clinical profile 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%)	-
Disability level according to the EDSS scale, points			
Overall score	3.8±0.2	3.9±0.2	0.7
Mild (1.0-3.5)	n = 16 (3±0.1)	n = 12 (3.1±0.1)	0.5
Moderate (4.0-6.0)	n = 10 (4.8±0.2)	n = 8 (4.3±0.2)	0.4
Severe (6.5-9.0)	n = 1 (6.5)	-	-

Note. Averageindexof the points according to the EDSS scale is given in brackets

(25,5%). The CSF protein ranged between 0.33 mmol/L and 0.9 mmol/L with a mean of 0.6mmol/L. The CSF protein elevated in 32 patients (68.1%). CSF glucose concentrations were normal in all patients. Oligoclonal IgG bandsin cerebrospinal fluidwere not detected.

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 Fig. 1).

The results of neurological examination of patients over a 24-month period are shown in Table 3 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 a slight 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.

As can be seen from the Table 3, 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, patients of both groups had on average 9 relapses, thus demonstrating multiphasic course of the disease. The patients of the main group had 2 relapses of disseminated encephalomyelitis and the patients of the control group had 7 relapses (multiphasic course of ADEM). One woman from the control group had two relapses of disseminated encephalomyelitis over the year. Two patients from the control group demonstrated transformation of ADEM into MS, but they werediscarded from the analysis. The frequency of demyelinating disease relapses was much lower in the patients of the main group ($p<0,001$) (Table 4).

4. 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 receptos 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 notonly 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 also of great prognostic importance for prevention of the multiphasic course of acute disseminated encephalomyelitis.

Table 2. Changes of average index of EDSS functional system in patientswith ADEM of different clinical groups

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

*Note. *– t-test estimation, reliability of difference between the indices before and after the treatment, p<0.05*

Table 3. 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. *– t-test estimation, p<0.05; ^ – p<0.001.° - chi-square test for independencegroups*

Table 4. 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 (7,4%)
control (n=20)	–	1	2	2	2	7 (35%) *°

*Note. * - fisher criterion, p<0.001. ° - chi-square test for independent groups*

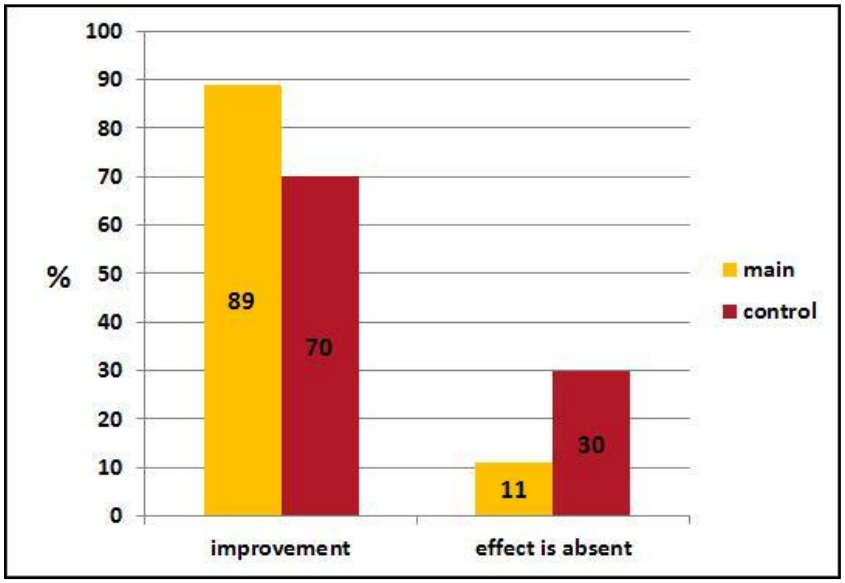

Fig. 1. Dynamics of restoring neurological functions of patients with ADEM in different clinical groups as a result of treatment

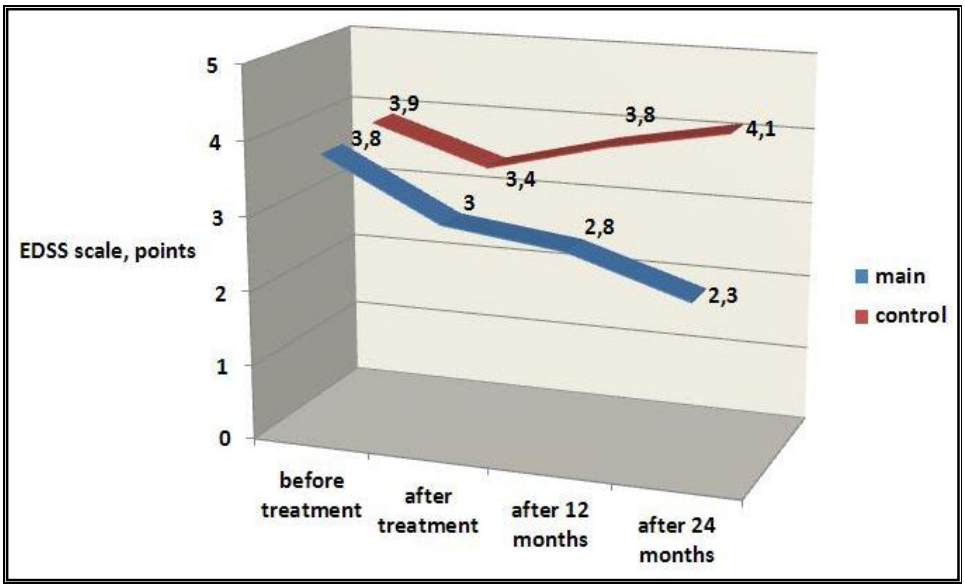

Fig. 2. Dynamics of changes in neurological status of patients with ADEM according to the EDSS scale over a 24-month observation period

5. CONCLUSION

This study has demonstrated a positive therapeutic efficacy of intravenous administration of human normal immunoglobulin in the treatment of patients with acute disseminated encephalomyelitis. Immunoglobulin administration contributes to the reduction of clinical manifestations of the disease by decreasing the level of neurologic deficit and preventing the multi-phasecourse of the acute disseminated encephalomyelitis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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