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Analysis of Prognostic Significance of Clinical and Paraclinical Indices in Case of Different Types of Acute Disseminated Encephalomyelitis Course

Iryna Lobanova[1*], Olena Myalovitska[1], Anatolii Saliuk[2] and Serhii Lobanov[3]

[1]Department of Neurology, National Medical University, T. Shevchenko Av.,13, Kiev City 01601, Ukraine.
[2]Department of Biochemistry National University of Food Technologies. str. Vladimirskaya 68, Kiev City 01601, Ukraine.
[3]Second Surgical Department, Kyiv City Clinical Emergency Hospital, Bratislavskaya Street, 3, Kyiv City 02166, Ukraine.

Authors' contributions

Authors IL and OM conceived the study. Author IL designed the experiments and carried out the research. All 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. The authors AS and SL have conducted statistical processing of investigation results.

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ABSTRACT

In most casesacute disseminated encephalomyelitis (ADEM) is characterized by monophasic course, but occurring relapses of the disease can be interpreted as multiphasic course of acute disseminated encephalomyelitis or its transformation into multiple sclerosis (MS).
This work is aimedat assessing the clinical/ paraclinical predictors of relapses and transformation to MS in patients presenting with ADEM/MDEM.
We have examined 101 patients with the diagnosis ADEM, namely: 28 men and 73 women aged 17 - 53 (average age value 31.7±1.01). Comparison groups included patients with monophasic and multiphasic types of acuted is seminated encephalomyelitis evolved to MS.

**Corresponding author: Email: lobanova_iryna@ukr.net;*

The investigated clinical and paraclinical parameters included: the number of points according to EDSS scale,number of demyelination foci and their diameter, the presence of perifocal edema. In case of multiphasic type of course of the disease and its transformation into multiple sclerosis, an increase in the number of points on the EDSS as well as in number of demyelination foci, and decrease of foci diameter and perifocal edema (more pronounced in case of the transformation into multiple sclerosis) were observed. Thus, all the investigated clinical and paraclinical indices andtheir changes during the period of observation have prognostic significance for assessment of the type of ADEM course (monophasic, multiphasic and transformation in multiple sclerosis).

Keywords: Acute disseminated encephalomyelitis; prediction; multiphasic course of acute disseminated encephalomyelitis; multiple sclerosis.

1. INTRODUCTION

ADEM is an autoimmune disease characterized by presence of inflammation (demyelination) foci in the central nervous system, which occur after infectious disease or vaccination [1].

The criteria necessary for the diagnosis of acute disseminated encephalomyelitis are given in the book of Harris C. et al. [2]. The authors state that for diagnostics of acute disseminated encephalomyelitis it is important to consider the medical history of preceding signs of infectious process, acute onset of the disease with evident disseminated lesion of central nervous system, frequently involving gray matter of the brain, increase of neurological deficit during the short period of time (hours – days), sudden development of encephalopathy and even disorders of consciousness, monophasic course of the disease and absence of metabolic and infectious disorders.

According to the recent studies of International Pediatric Multiple Sclerosis Study Group (IPMS), ADEM is regarded as polysymptomatic disease with multifocal lesion of CNS. Encephalopathy and disorders of consciousness are part of the presentation [3].

Some authors consider ADEM as polysymptomatic demyelinating inflammatory disease which is characterized by acute or subacute onset, no data about preceding lesion of CNS, significant improvement of patient's condition after the treatment [3,4]. ADEM is also characterized by the signs of systemic inflammatory response (headache, dizziness, nausea, fever, myalgia), appearing a few days – weeks after the infectious disease (so-called latent period) [5,6].

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, relapses of the disease also occur – that has already been known since 1932, as described by van Bogaert, who published the paper "ADEM with relapses" [7]. ADEM relapses can be considered as a multiphasic course of this disease or its transformation into multiple sclerosis (according to the McDonald Criteria) (see, e.g., the works [8-14].

ADEM relapses have been described with the following frequencies: in 1/18 patients (5.5%) [15], in 4/31(13%) [16,17], in 24/132 (18%) [18], in 7/35 (20%) [19], in 9/42 (21%) [20], in 5/21 (24%) [21].

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).

A new clinical relapse of the disease, that developed not earlier than 3 months after the first relapse and not later than 1 month after the patient stops taking steroids, corresponding to ADEM criteria and involving new anatomic zones (that is proven clinically and by MRI) is considered multiphasic acute disseminated encephalomyelitis (MDEM) [22,23].

MDEM is characterized by poly-symptomatic manifestations of this disease, availability of demyelination foci in Magnetic resonance imaging (MRI) data mainly in subcortical parts of brain, and to a lesser extent located periventricularly, with total or partial disappearance of foci during the convalescent period [24]. The multiphasic course of disseminated encephalomyelitis can be

diagnosed in the case of disease relapse appearance at least 3 months after its initial presentation [21,23,24,25]. 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 (according to the McDonald Criteria) [14,26].

The course of ADEM may vary significantly [21,23,24,25,26]. The results of observations that have been targeted at the course of this disease in 40 patients with the ADEM diagnosis show that 14 (35%) of them developed multiple sclerosis one year after the primary ADEM episode [20]. Another investigation showed that 5 (23.8%) of 21 patients demonstrated relapses of disseminated encephalomyelitis, and 2 (9.5%) of these 21 patients had multiple sclerosis. Recent investigations have shown that 4 (13%) of 31 patients with ADEM had manifestations of ADEM relapses, while 10 (40%) of 25 patients had clinically confirmed multiple sclerosis [27]. As it follows from the data of Schwarz S. et al. [28,29], 14/40 patients (35%) developed MS over a 38 month period of observations (which was confirmed using the Poser criteria). In the study by Alan et al. 13 (33.3%) of 39 patients faced the relapses of demyelination disease [16,28]. For the long period of observations (8 years), only 1/11 patient with ADEM showed new foci of demyelination in MRI data [27].

The investigations performed in France indicate that 57% patients with ADEM can acquire multiple sclerosis in 2.9 years, on average. Investigation of 48 patients with ADEM showed that 10 of them (20.8%) acquire multiple sclerosis in 2.36 years, while 13 (27%) – in 5.64 years [19].

Two follow-up studies in France and Germany reported that children with a first demyelinating episode demonstrated a surprisingly high percentage (57 and 82% retrospectively) of progression to MS [19,25]. A 12-year prospective study was conducted in 68 patients with a first episode of central nervous system demyelinating pathology and 76% showed progression to MS during the follow-up [30].

The objective of this research was to assess the prognostic significance of clinical and paraclinical indices for different types of acute disseminated encephalomyelitis course and its transformation into multiple sclerosis.

2. METHODS

We have examined 101 patients with the diagnosis ADEM, namely: 28 men and 73 women in the age from 17 up to 53 years (average age value 31.7±1.01).

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 [3]. The disability degree of the patients was assessed by authors with the use of Kurztke Expanded Disability Status Score (EDSS) [31].

28 patients (5 men and 23 women aged 18 to 55 years, (average age value 31.8±1.02)) were diagnosed with post Herpes virus infection. Persistence of herpes viruses was defined by the means of serological study of cerebrospinal fluid for detection of antibodies to herpes-associated viruses and DNA viruses by the method of polymerase chain reaction.

As a result of the serological study of cerebrospinal fluid, DNA of associated herpes virus infection was as follows: herpes simplex virus 1 (HSV-1) and 2 (HSV-2) types – respectively 67.8% and 35.7%, cytomegalo virus (CMV) – 32.1%, Epstein-Barr virus (EBV) – 35,7%, human herpes virus 6 (HHV-6), 7 (HHV-7) and 8 (HHV-8) type – respectively 14.3%, 3.6% and 7.1%. These data influenced the treatment policy chosen. All 28 patients with ADEM after infectious disease were assigned antiviral therapy with acyclovir (250 - 500 mg) or cimeven (500 mg) intravenously, followed by hormonal pulse-therapy, using methylprednisolone in the dose of 500-1000 mg daily in 200 ml of isotonic sodium chloride solution during a five day period. The patients who did not have an infectious agent, were assigned only pulse therapy with methylprednisolone. But to determine the prognostic significance of clinical and paraclinical indices in case of different types of acute disseminated encephalomyelitis course only the clinical and neuroimaging characteristics were considered.

All the patients with ADEM were being kept under observation for 3 years. During this period neurological examination, MRI ofthebrain and CSF analysis were done every 6 months. If during this period (3 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 view point and after neuro-visual patient examination, it was considered as the multiphasic option of the disease course (MDEM). In the case of clinically confirmed multiple sclerosis (in accord with the McDonald criteria [14]), we interpreted it as transition of ADEM into multiple sclerosis.

Comparison groups were formed depending on the type of pathology course. The comparison was made between monophasic acute disseminated encephalomyelitis and multiphasic acute disseminated encephalomyelitis transferred to multiple sclerosis.

The change of investigated indices was assessed for the following periods: period 0 - beginning of the observation and period 1 – 1 year after the observation. The patients were observed with intervals not less than once per month. Investigated clinical and paraclinical indices included: the number of points according to EDSS scale, number of demyelination foci and their diameter, the presence of perifocal edema, which was measured on MRI.

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. Change of parameters is presented in % with 95% confidence interval. For comparative analysis there was used t-test, chi-square test and Wilcoxon rank test.

3. RESULTS

Our research, carried out during a 3-year period, showed the following variations of the disease course: 49 patients (48.5%) demonstrated monophasic variant of acute disseminated encephalomyelitis, 25 patients (24.8%) – multiphasic variant of its course, 27 patients (26.7%) noted the transformation of acute disseminated encephalomyelitis into multiple sclerosis (Table. 1).

Monophasic course of acute disseminated encephalomyelitis is more frequent than acute disseminated encephalomyelitis evolved to multiple sclerosis and multiphasic course of the disease.

The patients with MDEM had relapses in average 11,4±1,3 months after the occurrence of the first episode of the disease. The patients with acute disseminated encephalomyelitis transformation into multiple sclerosis demonstrated development of multiple sclerosis on average after 12,04±1,75 months. Demographic characteristic of patients with monophasic, multiphasic course of ADEM and ADEM transformation into multiple sclerosis is shown in Tables 2 and 3.

Table 1. Differentiation of patients with ADEM depending on the type of the course

Type of the course	Number of patients	%
Monophasic	49	48,5
Multiphasic	25	24,8
Transformation into MS	27	26,7

Table 2. Demographic characteristic of patients with monophasic course of ADEM and its transformation into multiple sclerosis

Index	Type of the course		p
	Monophasic	Transformation into multiple sclerosis	
Age (X±σ)	32.1±7.9	31.8±8.5	0.851*
Sex (n, %)			
Male	9 (18%)	11 (41%)	0,165**
Female	40 (82%)	16 (59%)	

** - t-test estimation;*
***-chi-square test for independence groups*

Table 3. Demographic characteristic of patients with multiphasic course of ADEM and its transformation into multiple sclerosis

Index	Type of the course		p
	Multiphasic	Transformation into multiple sclerosis	
Age (X±σ)	30.1±7.5	31.8±8.5	0.829*
Sex (n, %)			
Male	8 (32%)	11 (41%)	0,263**
Female	17 (68%)	16 (59%)	

** - t-test estimation;*
*** - chi-square test for independencegroups*

Thus, the study groups are comparable in sex and age composition. Clinical presentation of monophasic, multiphasic course of ADEM and ADEM transformation into multiple sclerosis is shown in Table 4.

Table 4. Clinical presentation of monophasic, multiphasic course of ADEM and its transformation into multiple sclerosis

Index	Type of the course				
	Transformation into multiple sclerosis	Monophasic	p	Multiphasic	p
Prior infection	3 (11,1%)	9 (18%)	>0.05	5 (20,0%)	>0.05
Prior immunization	2 (7,4%)	5 (10,2%)	>0.05	3 (12,0%)	>0.05
Polysymptomatic presentation	19 (70,4%)	43 (87,8%)	>0.05	17 (68,0%)	>0.05
Monosymptomatic presentation	1(3,7%)	2 (4,1%)	>0.05	3 (12,0%)	>0.05
Motor disturbances	20 (74,1%)	43 (87,7%)	>0.05	17 (68,0%)	>0.05
Numbness/abnormal sensation	11 (40,7%)	17 (34,7%)	>0.05	9 (36,0%)	>0.05
Brain stem symptoms	13 (48,1%)	17(34,7%)	>0.05	13 (52,0%)	>0.05
Unilateral optic neuritis	3 (11,1%)	5 (10,2%)	>0.05	3 (12,0%)	>0.05
Bilateral optic neuritis	1 (3,7%)	-	>0.05	-	>0.05
Cerebellar symptoms	14 (51,8%)	23(46,9%)	>0.05	15 (60%)	>0.05
Encefalitis	1 (3,7%)	5 (10,2%)	>0.05	2 (8,0%)	>0.05
Myelitis	1(3,7%)	3 (6,1%)	>0.05	1 (4,0%)	>0.05
Encephalopathy	25 (92,6%)	47 (95,9%)	>0.05	21 (84,4%)	>0.05
Seizures	2 (7,4%)	5 (10,2%)	>0.05	3 (12,0%)	>0.05

** - t-test estimation between groups of patients with transformation into multiple sclerosis and monophasic course and transformation into multiple sclerosis and multiphasic course of the disease*

There were no significant differences between clinical presentation of monophasic, multiphasic course of ADEM and ADEM that evolved to MS.

Comparative assessment of the changes of clinical and paraclinical indices in groups with different types of ADEM course is shown in Tables 5, 6. Statistically significant difference is found for all indices during 1 year period between comparable periods ($p < 0.0001$). However the direction of change of some parameters is different depending on the type of course. Thus, in the group with monophasic course number of demyelination foci decreased almost to 0 after 3 months of observation - 91.8% of patients with monophasic course of disseminated encephalomyelitis had 0 number of nidi and respectively 0 diameter of nidi size. Intensity of perifocal edema reduced and number of points according to EDSS scale also significantly decreased.

The group of patients with ADEM transformation into multiple sclerosis demonstrate statistically significant ($p < 0.0001$) increase of demyelination foci number, but decrease of their diameter and intensity of perifocal edema. The intensity of neurological symptoms also significantly increases; it is reflected in the increase of number of points on EDSS scale.

The main features that create statistically significant difference for the monophasic type of ADEM course and its transformation into multiple sclerosis are reduction of the number of demyelination foci (-99.03%) and the number of points according to EDSS scale in case of monophasic course (-73.1%), as well as worsening (increase) of these indices in case of ADEM transformation into multiple sclerosis (respectively 32.6% and 71.9%). Thus, the nature of the changes of demyelination foci and the number of points according to EDSS scale are prognostically significant signs for assessment of monophasic course of ADEM and its transformation into multiple sclerosis (Table 6).

Statistically significant difference between the studied indices of patients with ADEM in different periods of observation is detected both in case of multiphasic course of the disease and its transformation into multiple sclerosis.

Increase of the number of demyelination foci in case of multiphasic course (31.8%) and in patients with ADEM transformation into multiple sclerosis (32.6%) does not differ statistically. As for other indices, statistically significant difference in their changes during the period of observation can be detected.

Table 5. Comparative characteristic of groups with monophasic, multiphasic type of ADEM course and its transformation into multiple sclerosis (X±σ)

Index	Type of the course								
	Transformation into multiple sclerosis		p	Monophasic		p	Multiphasic		p
	Period 0	Period 1		Period 0	Period 1		Period 0	Period 1	
Number of points according to EDSS scale	2.6±0.4	4.4±0.59	<0,0001	2.5±0.5	0.7±0.35	<0,0001	2,6±0,41	4,8±0,5	<0,0001
Number of demyelination foci	10.3±2.9	13.2±2.7	<0,0001	8.4±1.7	0.1±0.3	<0,0001	9,8±3,1	12,4±2,7	<0,0001
Diameter of demyelination foci	9.1±0.7	4.9±1.6	<0,0001	9.5±0.9	0.35±1.2	<0,0001	9,2±0,7	6,0±1,5	<0,0001
Perifocal edema	9.7±2	3.5±2.1	<0,0001	10.0±2.1	0.16±0.56	<0,0001	9,7±1,9	5,5±0,61	<0,0001

p - Wilcoxon rank test estimation

Table 6. The changesof clinical and paraclinical indices in groups with monophasic, multiphasic type of ADEM course and its transformation into multiple sclerosis (∆ - % (95% CI))

Index	Type of the course				
	Transformation into multiple sclerosis	Monophasic	p	Multiphasic	p
Number of points according to EDSS scale,∆,% (95%CI)	+71.9 (65.3 – 78.4)	-73.1 (-75.3 – -70.8)	<0,0001	+85.4 (76.2 – 94.7)	<0,0001
Number of demyelination foci, ∆,%(95%CI)	+32.6 (27.5 – 37.7)	-99.03 (-100 – -98.04)	<0,0001	+31.8 (24.5 – 39.1)	0,742
Diameter of demyelination foci,∆,%(95%CI)	-45.5 (-50.8 – -40.1)	-95.93 (-99.9 – -91.9)	<0,0001	-33.6 (-41.9 – -25.3)	<0,0001
Perifocal edema,∆,% (95%CI)	-62.4 (-69.2 – -55.6)	-98.2 (-100.0 – -96.3)	<0,0001	-40.6 (-46.5 – (-34.7))	<0,0001

p – t-test estimation, CI – confidential interval, ∆ - change of the index in %

In case of multiphasic course (compared to the transformation into multiple sclerosis) reduction of the diameter of demyelination foci and perifocal edema is less pronounced, but increase of points according to EDSS scale is more intense ($p < 0.0001$).

4. DISCUSSION

All the investigated clinical indices (number of points according to EDSS scale, number of foci of demyelination and their diameter, the presence of perifocal edema) and their changes during the period of observation are prognostically important for assessing the type of ADEM course (monophasic and transformation into multiple sclerosis). The given parameters (except changes of demyelination foci) significantly differ in case of multiphasic course of ADEM and its transformation into multiple sclerosis, that proves their diagnostic value.

In case of monophasic type of ADEM course during a short period of time (up to 3 months) a decrease of number of points according to EDSS scale, a decrease of number and diameter of demyelination nidi (up to their almost complete reduction in 91.8% of patients) and a decrease of perifocal edema were observed.

In case of multiphasic type of ADEM course and in case of its transformation into multiple sclerosis, an increase in the number of points (according to EDSS scale) as well as an increase in number of demyelination nidi and reduction of their diameter and perifocal edema, more pronounced in the case of transformation of ADEM into MS, were observed. The results of our research coincide with results of other investigations dedicated the course of multiphasic type of ADEM and its transformation into multiple sclerosis [14,21,23-26].

The major limitation of our work was retrospective character of the study, not allowing correct identification of prognostic factors.

Further studies should be aimed at determination of the prognostic significance of different methods of treatment of acute disseminated encephalomyelitis (therapy with corticosteroids, antiviral therapy) for prediction of different types of ADEM course.

5. CONCLUSION

When assessing the possible course of ADEM it is necessary to pay special attention to the clinical-paraclinical indices (number of points according to EDSS scale, number of foci of demyelination and their diameter, the presence of perifocal edema on MRI) in the process of dynamic observation. The changes of these indices have great value for prediction of monophasic, multiphasic types of ADEM course and its transformation into MS.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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