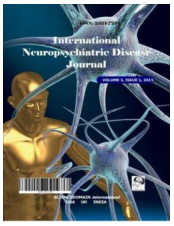

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The Characteristics of Cognitive Functions in Patients with Acute Disseminated Encephalomyelitis

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Introduction: The clinical picture of acute disseminated encephalomyelitis is characterized not only by a variety of neurological signs, but also by disorders of higher cortical functions. Disorders of higher cognitive functions often remain undetected during routine examination of patients and the use of specialized neuropsychological tests enables timely diagnosis of cognitive disorders.
Methods: The assessment of cognitive impairment was carried out in 67 patients with ADEM (28 male and 39 female, aged 16 – 50, mean age - 31.6±2.3). All the patients were being treated at the Kiev city centre of multiple sclerosis (Ukraine). The diagnosis of ADEM was based on neurological examination, MRI of the brain and CSF analysis. The cognitive impairment in patients with ADEM was assessed during the first three days after the onset of the disease. The neurological status was assessed by Kurtzke an Expanded Disability Status Scale (EDSS) and Functional Systems Scores (FSS). Patients performed neuropsychological tests that enabled evaluation of short-term and long-term visual and auditory memory, various parameters of attention as well as ability to concentrate, orientation in time and space.
Results: The assessment of cognitive functions in patients with ADEM demonstrated impaired short-term and long-term memory indices according to "memorizing 10 words" test (34.6±1.5 words compared with control 42.7±1 words, P <0.001), verbal learning and delayed recall according to "California Verbal Learning Test "(12.3±1.9 words compared to control 14.6±1.1 words, P <0,01) and sustained attention and concentration according to "Symbol Digit Modalities Test "(54.5±10.2

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compared to control 57.8±9.6, P> 0.05). In addition, assessment of memory, attention, orientation in time and space according to MMSE test (Mini - Mental State Examination) showed reduction of these functions in patients of the main group (27.2±0.24 points, compared with control 29.9±0.04 points, P <0.001). Demyelination foci in patients with cognitive disorders are most often localized to the periventricular regions in the frontal and parietal lobes, and in the cerebellum, where multiple demyelinating lesions are often observed.

Conclusion: We have detected cognitive disorders that require therapeutic correction in case of carrying out treatment-rehabilitation measures in patients with acute disseminated encephalomyelitis that will improve their quality of life.

Keywords: Acute disseminated encephalomyelitis; cognitive functions.

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 [1,2]. ADEM occurs in 1 of 500 cases of rubella, 1,000 cases of measles, 10,000 cases of smallpox, 4,000 cases of vaccination against chicken pox [3,4]. In 74% of cases, there was an infectious disease in the medical history of a patient a month before the onset of neurological signs [5-8]. The following infections may be the triggering factors for ADEM: viral factors (measles, rubella, mumps, parainfluenza viruses [9-12], hepatitis A and B, [13,14], whooping cough, tetanus [15,3], Epstein-Barr virus, cytomegalovirus [16]) and bacterial factors (Mycoplasma pneumonie [17-21], Campylobacter [22-24], Borrelia Burgdogferi [4,25], Leptospira, Chlamydia, Legionella, B -hemolytic streptococcus group A [26-28]. However, in most cases there is evidence of a nonspecific upper respiratory tract infection and there is no serologic evidence of pathogen [4,29,30]. Vaccines that may lead to ADEM development include vaccines against influenza, measles, hepatitis B, rabies, tetanus, chicken pox [26,31,32]. The cases of spontaneous development of the disease have also been noted [5,7,33].

Infectious factor is closely associated with the pathogenesis of ADEM, but it is not localized in the central nervous system or spinal fluid, virus replication in brain cells does not arise. It is not clear how it leads to the development of demyelinating disease that is why there is a hypothesis of molecular mimicry [4]. According to this theory, some infectious agents have peptides similar to immune-dominant epitope of myelin basic protein (MBP). It means that these infectious pathogens can activate T-cells autoreactive to MBP in case if phenotype of certain antigens is present in HLA (Human Leukocyte Antigen). It is known that HLA-system has two classes of molecules: I (A, B, C) is expressed on all nuclear cells and II (DR, DQ, DP) is expressed on cells involved in antigen presentation. Currently, ADEM is associated with genotype DRB1*01 and DRB1*03(017). However it is not clear why so many infectious agents can cause one disease. Another hypothesis assumes that direct penetration of neurotropic virus in the central nervous system (CNS) opens brain antigens, previously closed to the immune system, and myelin proteins, causing an inflammatory response that leads to immune-mediated demyelination [3,4].

The development of experimental models, including experimental allergic encephalomyelitis (EAE), has made an important contribution to the understanding of immunopathogenesis of acute disseminated encephalomyelitis [4]. EAE in Theiler's virus model is an autoimmune condition that can be reproduced in animals by administering myelin antigens such as MBP, proteolipid protein and glycoprotein of oligodendrocytes [3], causing primary systemic impulse in autoimmune reaction appearance. Penetrating into peripheral blood, antigen is phagocyted by macrophages that present it on their surface as a part of receptors of main complex of histocompatibility (HLA). The antigen is subsequently recognized by CD4 + T-cells-helpers that stimulate the formation of proinflammatory cytokines, resulting in lesion of the blood-brain barrier (BBB), after that autoreactive T-cells with CD4-phenotype to the antigens - myelin basic protein (MBP), proteolipid protein or myelin-oligodendrocyte glycoprotein get into the central nervous system from peripheral blood. In brain tissue they are reactivated by cytotoxic T-cells, B-cells, macrophages and glial cells, and enhance cascade of immunopathological reactions: expression of adhesion molecules and antigen-presenting molecules (HLA-molecules) to the

endothelium of the brain vessels and gliocytes; increased production of proinflammatory cytokines – gamma-interferon, tumor-necrosis factor-alpha (TNFα), interleukins (IL-1, SHL-2, IL-12, IL-15), autoantibodies of proteases, chemokines, free radicals, nitric oxide; decreased synthesis of proinflammatory cytokines - IL-4, IL-10, beta-interferon. It leads to violation of BBB permeability, activation of B cells and all components of humoral immunity, complement system and monocytes/macrophages [3]. These autoimmune and pathobiochemical reactions cause formation of disseminated perivascular foci of inflammation, especially around capillary, venous structures (small and medium), causing an inflammatory reaction cascade, destruction of myelin (demyelination), lesion of axons. Thus, the pathogenesis of acute disseminated encephalomyelitis has autoimmune nature and is accompanied by typical pathological changes.

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 [34].

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 [34,35]. 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) [10,36].

The clinical picture of acute disseminated encephalomyelitis is characterized not only by a variety of neurological signs, but also by disorders of higher cortical functions [1,37]. Disorders of higher cognitive functions often remain undetected during routine examination of patients and the use of specialized neuropsychological tests enables timely diagnosis of cognitive disorders. According to some authors, the vast majority of patients with ADEM have disorders of higher cortical functions of various severity [1,2,37]. The sequelae of cognitive disorder include negative impact on daily life activities, employment, social functioning and relations. Neuropsychological examinations can be conducted for detecting cognitive changes, monitoring treatment effects, characterizing deficit of rehabilitation planning or documenting the range of patient's impairment for guiding decisions regarding disability.

The aim of the study was assessment of cognitive functions in 67 patients with acute disseminated encephalomyelitis.

2. METHODS

The assessment of cognitive impairment was carried out in 67 patients with ADEM (28 male and 39 female, aged 16 – 50, mean age - 31.6 $\pm$2.3). All the patients were being treated at the Kiev city centre of multiple sclerosis (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 [34]. The onset of disease in all patients was acute with evident disseminated lesion of central nervous system, increase of neurological deficit was observed during the short period of time (hours – days) and sudden development of encephalopathy. All patients underwent magnetic resonance imaging (MRI) studies of the brain and / or of the spinal cord to detect the location of the lesions of demyelination, lesion-load and size. The patients did not have other medical conditions that could affect their cognition, had normal results of fundosopic and transcranial doppler ultrasound exam, all were under 50 years old. The cognitive impairment in patients with ADEM was assessed during the first three days after the beginning of the disease. The neurological status was assessed by Kurtzke an Expanded Disability Status Scale (EDSS) and Functional Systems Scores (FSS) [38]. Based on a standard neurological examination, the 7 functional systems (plus "other") were rated.

These ratings are then used in conjunction with observations and information concerning gait and use of assistive devices to rate the EDSS. Each of the FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. The EDSS is an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. The FSS include pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental), and other. The average point according to EDSS scale in patients with acute disseminated encephalomyelitis was 2.5±0.8 points. All patients were treated 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).

At the beginning of the study cognitive functions were also assessed in 15 (8 male and 7 female) healthy, age matched control subjects (average age 32.5±0.7years) with no systemic or neurological diseases. Patients of both clinical groups performed the same neuropsychological tests that enabled evaluation of short-term and long-term visual and auditory memory, various parameters of attention as well as ability to concentrate, orientation in time and space.

The "memory for numbers" and "memory for words" methods enabled evaluation of short-term and long-term visual memory. The patients were shown 20 numbers (or words) for over 30 seconds and then attempted to recall them (immediately and after 1 hour). Method of 10 words memorizing included evaluation of short-term and long-term auditory memory. The patients were read 10 words, which were not related semantically, 7 times within 30 seconds. Each time the patients were asked to repeat the words immediately (assessment of short-term memory) and one hour later (assessment of long-term memory). California Verbal Learning Test [39] and Symbol Digit Modalities Test [40] were used to to measure key constructs in cognitive psychology such as repetition learning, serial position effects, semantic organization, intrusions, and proactive interference. MMSE (Mini - Mental State Examination) [41] enabled assessment of verbal learning and delayed recall, sustained attention and concentration as well as memory, attention and orientation in time and space.

In the statistical analysis the t-test was used for two-group comparisons of the cognitive functions of persons with acute disseminated encephalomyelitis and healthy individuals. Five percent for two tailed tests was chosen as the level of significance. Association between the severity of cognitive impairment according to the results of neuropsychological tests and EDSS scale score as well as the size of demyelination lesions on MRI were evaluated with Spearman rank correlation analysis.

3. RESULTS

Demographic and clinical data are shown in Table 1 and Table 2.

Table 1. Demographic and clinical profile of participants

Variables	Number of patients (%)
Overall numbers (%)	67 (100%)
Baseline age, (mean±SD) years	31.6 ±2.3
Gender	
• Men	28 (42)
• Women	39 (58%)
Race	
• White	67 (100%)
Educational attainment (years)	16.1±0.24
>=12 years	61 (91%)
<12 years	6 (9%)
Medical comorbidities	
• Depression	-
• Other psychiatric disorders	-
• Hypertension	3
• Diabetes mellitus	-
• Hyperlipidemia	-
• Atrial fibrillation	-
• Cigarette smoking	5
Disability level according to the EDSS scale, points	2.5±0.8 points.

Taking into consideration the case history, significant negative impact of the disease on cognitive functions was subjectively noted by 23 (34%) patients of the main group. Patients with ADEM showed significantly worse results in performing the tests aimed to study cognitive functions compared to those of healthy individuals (control) (Table 3).

Table 2. Clinical presentation of patients with ADEM

Variables	Number of patients (%)
Prior infection	4 (5,97%)
Prior immunization	4 (5,97%)
Polysymptomatic presentation	60 (89,6%)
Monosymptomatic presentation	7 (10,1 %)
Motor disturbances	57 (85,1 %)
Numbness/abnormal sensation	29 (43,3%)
Brain stem symptoms	11 (16,4%)
Unilateral optic neuritis	6 (8,95%)
Bilateral optic neuritis	1 (1,5%)
Cerebellar symptoms	48 (71,6%)
Encefalitis	5 (7,5%)
Myelitis	5 (7,5%)
Encephalopathy	63 (94,0%)
Seizures	17 (25,4%)

Magnetic resonance tomography changes in all the patients constituted presence of demyelination foci – hyperintensive in T2-weighted image and hypointensive in T1-weighted image with the size 7±0,6 mm. Size of single foci of demyelinization (28.8%) was 9.8±1.75 mm, of multiple ones (84.8%) – 4.4±0.4 mm.

Localization and frequency of brain lobes lesions in patients with ADEM accompanied by cognitive disorders is shown in Table 4 and 5.

We analyzed the correlation between the severity of cognitive impairment according to the results of neuropsychological tests and EDSS scale score (Table 6) as well as the size of demyelination lesions on MRI.

There was statistically significant inverse relationship between short-term memory and attention, as assessed by the results of “10 words memorizing” (correlation coefficient r = -0.48; P <0.05), long-term auditory memory, as assessed by the results of "memory for words" (correlation coefficient r = -0.57; P <0.01), verbal learning and delayed recall, as assessed by the results of "California Verbal Learning Test", and the degree of disability according to EDSS scale score (correlation coefficient r = -0.4; P <0.05). Correlation analysis revealed no relation between the severity of cognitive impairment according to the results of neuropsychological tests and the size of demyelination foci on MRI. There was statistically significant inverse relationship between verbal learning and delayed recall, as assessed by the results of "California Verbal Learning Test" and lesion load of demyelinating process in frontal lobes of hemispheres (correlation coefficient r = - 0.5; p <0.05).

Table 3. Results of short-term and long-term memory study in patients with ADEM

Tests			Main group	Control group
“Memory for numbers” method	short-term	quantity of numbers	7.32±0.63*	13.6±0.49
		points	3.44±0.3*	6.45±0.22
	long-term	quantity of numbers	2.64±0.44*	9.3±0.54
		points	1.24±0.19*	4.4±0.28
“Memory for words” method	short-term	quantity of words	9.6±0.55*	13.04±0.28
		points	4.44±0.29*	8.2±0.7
	long-term	quantity of words	2.4±0.52*	8.4±0.25
		points	1.16±0.23*	3.45±0.11
“10 words memorizing” method		quantity of words	34.6±1.5*	42.7±1
		points	6.24±0.25^	7.4±0.2
California Verbal Learning Test		long term verbal recall	12. 3±1.9^	14.6±1.1
		Long term recognition	14.3±1.2	15.5±1.1
Symbol Digit Modalities Test			54.5±10.2	57.8±9.6
MMSE, points			27.02±0.24*	29.9±0.04

*Note. * - Reliability of indices difference between groups of patients is P<0.001, ^ - reliability of indices difference between groups of patients is P<0.01*

Table 4. The frequency of demyelinating process lesion of different lobes of the brain in patients with ADEM

Lobe of the brain	Frequency of lesion, in %
Periventricular	72
Frontal lobes of hemispheres	33.6
Parietal lobes of hemispheres	28.8
Cerebellum	28.8
Subcortical	25.6
Pons	25.6
Thalamus	20
Semioval centres	19.2
Internal capsule	18
Temporal lobes of hemispheres	14.4
Corona radiate	14.4
Basal ganglia	12.8
Brainstem	6.4
Cerebral peduncle	6.4
Medulla oblongata	6.4
Occipital lobe	3.2

Table 5. The frequency of combined demyelinating process lesions of different lobes of the brain in patients with ADEM

Lobe of the brain	Frequency of lesion, in%
Periventricular and pons	20.8
Parietal and frontal lobes of hemispheres	19.2
Periventricular and parietal lobes of the brain	16
The frontal lobes of hemispheres and cerebellum	12.8
Subcortical and frontal lobes of hemispheres	11.2
Cerebellum and pons	11.2
Periventricular, frontal and parietal lobes of the brain	9.6
Periventricular, cerebellum and pons	8
Periventricular, frontal and temporal lobes of hemispheres	6.4
Periventricular, subcortical and cerebellum	6.4

Table 6. Correlation analysis between the results of neuropsychological tests in patients with ADEM, age of patients and number of points according to EDSS scale

Tests			Number of points according to EDSS scale	Degree of reliability
"Memory for numbers" method	short-term	Quantity of numbers	-0.2	P>0.05
		points	-0.13	P>0.05
	long-term	Quantity of numbers	-0.22	P>0.05
		points	-0.29	P>0.05
"Memory for words" method	short-term	Quantity of numbers	-0.13	P>0.05
		points	-0.34	P>0.05
	long-term	Quantity of numbers	-0.54	P<0.05
		points	-0.57	P<0.05
"10 words memorizing" method		Quantity of numbers	-0.52	P<0.05
		points	-0.48	P<0.05
California Verbal Learning Test		Long term verbal recall	-0.4	P<0.05
		Long term recognition	-0.4	P<0.05
Symbol Digit Modalities Test			0.02	P>0.05
MMSE			-0.32	P>0.05

4. CONCLUSION

Analysis of the obtained results showed that patients with ADEM had significantly lower cognitive scores of cognitive functions such as short and long term visual and auditory memory, verbal learning and delayed recall, sustained attention and concentration as well as memory, attention and orientation in time and space. There was statistically significant inverse relationship between short-term memory and attention, long-term auditory memory, verbal learning and delayed recall and the degree of disability according to EDSS scale score.

It has been found that the severity of neuropsychological impairment correlated with the severity of neurological dysfunction in patients with ADEM. Demyelination foci in patients with cognitive disorders are most often localized to the periventricular regions in the frontal and parietal lobes, and in the cerebellum; where multiple demyelinating lesions are often observed.

The sequelae of cognitive disorders include negative impact on daily life activities, employment, social functioning and relations. Therapeutic correction of cognitive disorders in case of carrying out treatment-rehabilitation measures in patients with acute disseminated encephalomyelitis will improve the quality of life of patients.

The further research should focus on the study of cognitive impairments in patients some time after the development of demyelinating disease, providing an opportunity to assess the results of treatment and make a comparative analysis of cognitive impairments according to the different types of ADEM course (monophasic, multiphasic and transformation into multiple sclerosis). The further research should also be dedicated to the comparison of cognitive impairments and loss of brain parenchymal volume in whole brain as well as in selected regions of the brain (hippocampus, ventricles, middle temporal lobe, fusiform and entorhinal volume loss).

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Bergner M, Bobbit R, Carter W, Gilson B. The Sickness Impact Profile: Development and Final Revision of a Health Condition Measure. Med Care. 1981;8:787-805.
2. Harris C. C. Harris, K. Lee J. Acute disseminated encephalomyelitis. Neurosci. Nurs. 2007;39 (4):208–212.
3. Gard R.K. Acute disseminated encephalomyelitis. Postgraduate Medical Journal. 2003;79:11–17.
4. Murthy JM. Acute disseminated encephalomyelitis. Neurol. 2002,50:238–243.
5. Ann Yeh E. Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. Pediatrics. 2004;113:73–76.
6. Sonneville R. Post-infectious encephalitis in adults: Diagnosis and management. J. Infection. 2009;58:321–328.
7. Tenembaum S. Acute disseminated encephalomyelitis: a long-term follow-up study of 84pediatric patients. Neurology. 2002;22(59,8):1224–1231.
8. Yamamoto Y. Acute disseminated encephalomyelitis following dengue fever. J. Infect. Chemother. 2002;8(2):175–177.
9. Chowdhary J. Measles with Acute Disseminated Encephalomyelitis (ADEM). Indian Pediatrics. 2009;46.
10. Ogava Y. A case of acute disseminated encephalomyelitis presenting with vertigo. Auris Nasus Larynx. 2008;35:127–130.
11. Sawanyawisuth K. MRI findings in acute disseminated encephalomyelitis following varicella infection in an adult Case Reports. J. Clinical Neuroscience. 2007;14:1230–1233.
12. Voudris KA. Acute disseminated encephalomyelitis associated with parainfluenza virus infection of childhood. Brain Dev. 2002;24(2):112–124.
13. Dale RC. Early relapse risk after a first CNS inflammatory demyelination episode: examining international consensus definitions. Dev. Med. Child Neurol. 2007;49(12):887–893.
14. Kinomoto K. Acute Encephalomyelitis Associated with Acute Viral Hepatitis Type B. Inter. Med. 2009;48:241–243.

15. Cahnzos-Romero T. Demyelinating disorders: not only multiple sclerosis. Abstracts from 8th congress of the European Federation of Intern. Medicine. 2009;20:282–283.
16. Fujimoto T. Epstein-Barr virus infections of the central nervous system. Intern. Med. 2003;42:33–40.
17. John W Young. Acute inflammatory encephalomyelitis following Campylobacter enteritis associated with high titre antiganglioside GM1 IgG antibodies Case Reports J. Clinical Neuroscience. 2009;16:597–598.
18. Njeukui TJ. Acute disseminated encephalomyelitis associated with mycoplasma pneumonia infection. Rev. Med. Brux. 2008;29(2):103–106.
19. Stam B. Neuroinvasion by Mycoplasma Pneumoniae in ADEM. International Journal of STG and AIDS. 2006; 17(7):493– 495.
20. Stam B. Neuroinvasion by Mycoplasma pneumoniae in acute disseminated encephalomyelitis. Emerg Infect Dis. 2008;14(4):641–643.
21. Termote B. Encephalitis following Mycoplasma pneumonia (2007: 6b). Acute disseminated encephalomyelitis. Eur. Radiol. 2007;17(9):2436–2438.
22. Gaing C. Acute disseminated encephalomyelitis associated with Campylobacter jejuni infection and antiganglioside GM1 Ig G antibodies. J. Neurol. 2005;252:613–614.
23. Omata T. Child with acute disseminated encephalomyelitis (ADEM) initially presenting with psychiatric symptoms. No To Hattatsu. 2008;40(6):465–468.
24. Orr D. Acute disseminated encephalomyelitis temporally associated with Campylobacter gastroenteritis. J. Neurol. Neurosurg. Psychiatry. 2004; 75(5):792–793.
25. Dale R.C. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain. 2000;123: 2407–2224.
26. Gard R.K. Acute disseminated encephalomyelitis. Postgraduate Medical Journal. 2003;79:11–17.
27. Ito S. Acute disseminated encephalomyelitis and poststreptococcal acute glomerulonephritis. Brain Dev. 2002;24(2):88–90.
28. Noel S. Adult acute disseminated encephalomyelitis associated with post streptococcal infection. J. Clin. Neurosci. 2005;12(3):298–300.
29. Fujikiet F. Aseptic meningitis as initial presentation of ADEM. J. Neurol. Sci. 2008;272:129–131.
30. Samile N. Acute disseminated encephalomyelitis in children. A descriptive study in Tehran, Iran. Saudi Med J. 2007;28(3):396–399.
31. Hamidon B.B. Acute disseminated encephalomyelitis (ADEM) presenting with seizures secondary to anti-tetanus toxin vaccination. Med. J. Malaysia. 2003;58(5): 780–782.
32. Sejvar J.J. Neurologic adverse events associated with smallpox vaccination in the United States 2002-2004. JAMA. 2005;294:2744–2750.
33. Tenembaum S. Disseminated encephalomyelitis in children. Clinical neurology and neurosurgery. 2008;110: 928–938.
34. Krupp L.B. International Pediatric Multiple Sclerosis Study Group 2007 Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology. 2007;68(16 suppl 2):7–12.
35. Sonneville R, T. Klein de Broucker J. Post-infectious encephalitis in adults: Diagnosis and management. Infection. 2009;58:321–328.
36. Suppiej A, Vittorini R, Fontanin M. Acute disseminated encephalomyelitis in children: focus on relapsing patients. Pediatr Neurol. 2008;39(1):12–17.
37. Hahn CD. Miles BS, MacGregor DL. Neurocognitive outcome after acute disseminated encephalomyelitis. Pediatr. Neurol. 2003;29(2):117–123.
38. Kurztke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33: 1444-1452.
39. Delis DC, Kramer JH, Kaplan E, Ober BA. The California Verbal Learning Test. San Antonio, TX: Psychological Corporation; 1987.
40. Benedet MJ. Alejandre MA. Test de aprendizaje verbal Espana-Complutense (TAVEC). TEA Idiciones. Madrid; 2001.

41. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975;12(3):189–98.

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