REVIEW ARTICLE

Acute Disseminated Encephalomyelitis

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Summary

Acute disseminated encephalomyelitis (ADEM) is an uncommon inflammatory demyelinating disease of the central nervous system. The true incidence of the disease in India is undetermined and is likely to be more frequent than reported, as the common antecedent events, exanthematous fevers and Semple antirabies vaccination, which predispose to ADEM, are still prevalent. The existing evidence suggests that ADEM results from a transient autoimmune response towards myelin or other self-antigens, possibly via molecular mimicry, or by non-specific activation of auto-reactive T cell clones. ADEM is a monophasic illness with favourable long-term outcome. Involvement of neuroaxis is variable and can be diffuse or multifocal and site restricted. Magnetic resonance imaging (MRI) is highly sensitive in detecting white matter lesions and the lesions described are rather extensive and subcortical in location. Involvement of the deep gray matter, particularly basal ganglia, is more frequent. Oligoclonal bands in CSF are usually absent. No therapy has been established by controlled trials in ADEM. Use of high-dose methylprednisolone, plasma exchange, and IVIG are based on the analogy of the pathogenesis of ADEM with that of multiple sclerosis (MS). Differentiation of ADEM from the first attack of MS is important from prognostic as well as therapeutic point of view. However, in the absence of biological marker, at times differentiation of ADEM from the initial presentation of MS may not be possible even by combination of clinical, CSF analysis, and MRI. This differentiation is more relevant to India where the incidence of MS is low.

Key words : Acute disseminated encephalomyelitis, Semple antirabies vaccine, MRI, Methylprednisolone.

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Acute disseminated encephalomyelitic (ADEM) is an uncommon inflammatory demyelinating disease of the central nervous system (CNS) and can be defined strictly as scattered focal or multifocal (disseminated) inflammation of brain and/or spinal cord.[1] In contrast to multiple sclerosis (MS), ADEM is usually a monophasic disorder with favourable long-term prognosis. There are many differences that distinguish ADEM from the first episode of MS (Table I). However these features are not always seen in ADEM or exclusive of ADEM. This differentiation of ADEM from MS has prognostic and therapeutic implications because early treatment of MS may be advantageous.

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Table I

Clinical and Laboratory Features that Differentiate ADEM from Initial First Episode of MS

Clinical	Monophasic time course Preceding infection/vaccination Abrupt onset More common in children No gender difference More severe syndrome Associated mortality – 10 – 25%
CSF	Moderate pleocytosis Oligoclonal bands, intrathecal IgG production uncommon or transient

Epidemiology

The true incidence of AEDM is unknown and in India, the disease is surely more frequent than reported.[2,3] The exanthematous fevers, which predispose to ADEM, are still endemic in India.[2] Similarly Semple antirabies vaccination is still in use.[3,6] The New Castle experience indicates that about 1 per 1000 children with exanthematous fevers develop AEDM.[4] The reported incidence of neuroparalytic complications with Semple vaccine varied between 1 per 600 to 1 per 1575 vaccinations.[5] However, the rate of complications with duck embryo vaccine was in the order of 1 per 25,000 vaccinations.[6]

Antecedent Events

ADEM typically begins within 6 days to 6 weeks following an antigenic challenge. Approximately 70% of patients report a precipitating event, e.g. viral or bacterial infections or vaccination.[7] Viral infections associated with ADEM include measles, mumps, rubella, varicella-zoster, Epstein Barr virus, cytomegalo virus, herpes simplex virus, Hepatitis A, and coxsackie virus. Disease specific reported incidence rates are 1 per 1000 for measles, 1 per 5000 for rubella, and 1 per 1000 for varicella.[8] The main bacterial trigger appears to be mycoplasma pnuemoniae. Other bacterial infections like Borrelia borgdorgeri, Leptospira, and Group A beta-hemolytic Streptococci have also been implicated. The only epidemiologically and pathologically proven association of the vaccinations is with the antirabies vaccination.[9-11] Other vaccinations associated with ADEM include pertusis, diphtheria, measles, mumps, rubella, and influenza.[12] ADEM has also been described following administration of antisera.[13] The hyperacute form, acute hemorrhagic leukoencephalomyelitis (AHLE), typically follows influenza or upper respiratory infection.

With advances in disease control, ADEM in developed countries is now seen most frequently after nonspecific upper respiratory infections, where the etiological agent is unknown.[7,14] Even in developing countries, there seems to be a changing trend. In a recent study in children from Taiwan, causative agents of postinfectious encephalomyelitis have changed from those of traditional exanthematous diseases to nonspecific respiratory infections.[15] In India, still specific viral infections account for significant proportion of antecedent events. Semple antirabies vaccination is the common vaccination associated with ADEM.[10] In a recent study, specific viral infections and Semple antirabies vaccination together accounted for 56.2% of antecedent events.[2]

Pathogenesis

The existing evidence suggests that ADEM results form a transient autoimmune response towards myelin or other self-antigens, possibly via molecular mimicry, or by non-specific activation of auto-reactive T cell clones. This hypothesis is supported by striking similarities between experimental allergic encephalomyelitis (EAE), post rabies vaccine encephalomyelitis, and encephalomyelitis following infections. There is similar latency, a similar acute, usually monophasic disease, associated with perivenular mononuclear cell inflammation and demyelination.[14,16] EAE is mediated by autoreactive CNS-specific T-cells.[17] T-cells directed to microbial epitopes may recognize amino acid sequences shared with myelin antigens and launch an autoaggressive attack on CNS structures (‘molecular mimicry’), alone or in synergy with antibodies. Viral or bacterial superantigens could like wise trigger autorective T cells. Semple rabies vaccine contains neural antigens that could excite a cross-reactive T-cell response. Studies on patients who developed encephalomyelitis following antirabies vaccination showed lymphocytic proliferation on exposure to myelin basic protein correlating with encephalomyelitis or polyneuritis.[11] This suggests that myelin basic protein is the encephalitogenic protein in encephalomyelitis following Semple anti rabies vaccination.

The pathogenesis of acute cerebellar ataxia following varicella-zoster infection is also thought to be an immune-mediated encephalomyelitis.[14] The benign

nature of this syndrome points to a rapidly reversible pathology. However MRI studies have not shown white matter signal alterations in these patients.[18-20] Recent studies have shown that polymerase chain reaction is often positive for varicella-zoster DNA in the CSF of patients with ataxic syndrome. This is in spite of repeatedly negative brain and CSF cultures.[21]

Pathology

The pathology of ADEM reveals inflammation predominantly in the Virchow Robin spaces and diffuse, often symmetric, perivenular demyelination. The lesions are of similar histological age and most numerous, in white matter but also involve the deeper cortical laminae, thalami, hypothalamus, and other gray matter structures. Reactive astrocytes are relatively inconspicuous, consisting of a few enlarged cells at the edges of the lesions. Axons within demyelinated lesions are preserved relative to myelin. The characteristic features of AHLE consist of multifocal petechial hemorrhages distributed diffusely throughout the brain. The perivascular lesions consist chiefly of ball or ring hemorrhages surrounding necrotic venules, sometimes with fibrinous exudates present within the vessel wall or extending into adjacent tissue. Perivenular demyelinating lesions identical to those seen in ADEM also may be present. Perivascular cuffs of mononuclear cells often with neutrophils are present.

Clinical Features

ADEM is generally a monophasic disorder and can occur at any age. It is more common in children because of higher frequency of immunization and exposure to antigen. Both sexes are affected with equal frequency, as opposed to female preponderance in MS. The onset of symptoms is usually rapid, with peak dysfunction occurring within several days. The onset of symptoms is preceded by a prodromal phase of several days of fever, malaise, and myalgia in some cases. Involvement of neuroaxis is variable and can be diffuse or multifocal and site restricted[2,7,8] (Table II). Some forms of clinical syndromes are more common following certain antecedent events. Myelitis and myeloradiculitis are more commonly reported following Semple antirabies vaccination[8] and acute cerebellar ataxia following varicella infection.[22-24]

Characteristic clinical features include sudden onset multifocal neurologic disturbances such as bilateral optic neuritis, visual field defects, aphasia, motor and sensory deficits, ataxia, movement disorders, and signs of an acute meningoencephalopathy with meningism, a depressed level of consciousness, focal or generalized seizures, and psychosis. Majority of cases of ADEM belong to this form[8] and account for more than 50% of cases.[2] There are some differences in the clinical features between adults and children. Headache, fever, and meningism are relatively infrequent in adults. Sensory deficits are more frequent and optic neuritis is rare in adult ADEM.

Table II

Clinical forms of Acute Disseminated Encephalomyelitis

I	Diffuse or multifocal
II	Site restricted forms
	Brainstem syndromes
	Acute cerebellitis
	Optic neuritis
III	Myeloradiculitis

Cerebellar ataxia in the absence of other sings is more common following varicella-zoster infection.[25] 50% of post varicella encephalitis may present with cerebellar ataxia.[22] The encephalitic symptoms may precede the rash, or occur simultaneously with rash, or follow the rash. This form is more benign and prognosis is very good. Monosymptomatic optic neuritis and monosymptomatic hemiplegia as a manifestation of ADEM are rare. Hemiplegic form has been described following measles, rubella and mumps infection[11] and vaccination,[26] and is associated with poor prognosis.

Acute hemorrhagic leukoencephalopathy is a very rare disorder and has been observed in all age groups. Clinically AHEL manifests by abrupt onset of fever, neck stiffness, hemiplegia or other focal sings, seizures, and impaired consciousness. The CSF usually demonstrates increased pressure, proteins, and both white and red cells.

Laboratory Evaluation

The CSF is usually abnormal (in > 67% of cases), often showing a moderate pleocytosis with increased protein content.[8,28,29] CSF only rarely shows intrathecal oligoclonal immunoglobulin (IgG) production, which almost invariably ceases as patients improve.[28,29]

Magnetic Resonance Imaging

Magnetic resonance imaging is the premier modality of investigation in the diagnosis of ADEM. The MRI

findings in ADEM are a reflection of the histopathology of the disease.[27] The pathological hallmark lesion in ADEM and MS is perivenular inflammation and demyelination.[9,13] Pathological correlation in experimental allergic encephalitis (EAE) has shown long T1 and T2 values to be associated with the presence of inflammation, demyelination, and hemorrhagic necrosis. The distribution of lesions is heterogeneous and multiple foci of demyelination in the cerebrum, cerebellum, and brain stem have been described.[18,30,31] The lesions described are rather extensive and symmetric or asymmetric and more often located in the peripheral subcortical cerebral white matter. Lesions in the thalami are more often described in ADEM than MS[18,30-35] and may be a useful finding that suggests ADEM. Lesions in the internal capsule have low sensitivity (30%) in MS.[31,33] Tumor-like lesions have also been described in MRIs of ADEM patients.[18] The frequency and distribution of white matter lesions seems to be similar in patients with ADEM following specific viral infections, Semple antirabies vaccination, and presumably viral infections.[18,34] Usually all the lesions enhance with contrast, but in some patients there may be enhancement of some lesions without enhancement of others. This is because the lesions in ADEM may evolve over several weeks.[28,30,32] Lesions resolve partially in two thirds and vanish in nearly a third of patients.[28,29] In our study[18] and in the patients reported by others,[19,20] MRI did not show any signal alterations in patients with cerebellar ataxia following varicella. The importance of these findings in the pathogenesis of ataxic syndrome following varicella infection needs to be studied in detail.

'Recurrent ADEM' - Is It Recurrence of ADEM or Relapsing MS?

Although ADEM is typically described as a monophasic illness, episodes of 'recurrent ADEM' have been described, which are usually triggered by infections.[36-39] It is possible that episodes of 'recurrent ADEM' are multiple episodes of MS. In the absence of a biological marker, differentiation of ADEM from the initial presentation of MS, at times, may not be possible. Criteria for the differentiation between recurrent ADEM and multiple episodes of MS have not yet been developed. Certain clinical and MRI features distinguish ADEM from MS (Table I), however, they are not always seen in ADEM and are not exclusive for ADEM. Early relapses in patients with ADEM may represent a protracted single phase rather than a new episode as in some patients the symptoms and signs evolve over several weeks.[29] The problem is with relapses occurring several months later. In the longest follow-up (8 years) of 11 patients with ADEM, none experienced a new clinical attack during follow-up and new white matter lesions were detectable in only one patient. In this study the mean age of the patients at presentation was 21 years (range 4-48 years) and mean period of follow-up was 8 years (range 3.5-11 years).[40] In children late relapses are rare. However in adults late relapses represent multiple episodes of MS. In a recent series reported by Schwarz et al,[28] of the 40 patients initially diagnosed as ADEM, 35% patients developed clinically definite (Poser criteria) MS over a mean observation period of 38 months. The newly revised diagnostic criteria for MS allow the diagnosis to be made after one attack, if stringent MRI criteria[33] are met. It has been emphasized that in monophasic demyelinating disease, such as ADEM, a diagnosis should be withheld unless new symptoms and signs or imaging abnormalities appear, more than 3 months after the onset of clinical symptoms.[41] Differentiation of ADEM from the first attack of MS has relevance for developing countries, where the incidence of MS is low.[18] The issue of whether ADEM can be the presentation of MS is also important from the therapeutic point of view. Recent trials support early initiation of therapy in MS.[42,43]

Differential Diagnosis

In the absence of a biological marker, the distinction between ADEM and MS cannot be made with certainty at the time of first presentation. However certain features are more indicative of ADEM (Table III). A viral prodrome, early-onset ataxia, high lesion load on MRI, involvement of the deep gray matter, and absence of oligoclonal bands are more indicative of ADEM.[18,29] Lesions in the thalami are more often described in ADEM than in MS.[18,30.32,33,35]

In countries endemic to rabies, neuroparalytic complications following Semple antirabies vaccination need to be differentiated from dumb or paralytic rabies. About 20% of cases of rabies result in spinal distribution producing a clinical syndrome of ascending paralysis. Paresthesiae at the site of bite, onset of weakness in the limb of bite, and significant autonomic disturbances suggest paralytic rabies.[44]

Treatment

Spontaneous improvement has been repeatedly noted

Table III

Comparison of Clinical Characteristics in ADEM and MS

Features	ADEM	MS
Antecedent events	Infections or vaccination	No recognized antecedent infections or vaccination
Clinical characteristics	Meningism, stupor, focal signs	Focal signs
Course	Non progressive, monophasic	Relapsing and remitting or progressive
Recovery	Recovery is rapid and often complete	Recovery variable, may be rapid and complete

in patients with ADEM.[36] However, complete recovery is less frequently seen in patents not receiving some form of treatment.[45] No therapy has been established by controlled trials in ADEM. Use of high-dose steroids, plasma exchange, and IV immunoglobulin are based on the analogy of the pathogenesis of ADEM with that of MS.[46] High-dose intravenous methylprednisolone, in a dosage, standard for MS relapses, has been found to be effective.[28,29] Plasmapheresis, beginning with a course of four to six plasma exchanges, has been shown to be associated with moderate to marked improvement and the response is sustained.[47-49] In the study of plasmapheresis for severe attacks of central nervous system demyelination, by Keegan et al,[44] male sex, preserved reflexes, and early initiation of treatment were associated with moderate and marked improvement. Successfully treated patients improved rapidly and improvement was sustained. If high-dose corticosteroids fail, it is reasonable to advise plasma exchange.[28] Intravenous immunoglobulin is a third potential therapeutic modality. Initial administration of intravenous immunoglobulins might be of therapeutic value.[50,51]

Prognosis

A mortality rate of up to 20% has been reported in earlier studies, with a high incidence of neurologic sequelae in those who survived.[8] Recent studies suggest a more favourable prognosis.[2,28,29] Patients may recover rapidly. Prolonged disturbances in level of consciousness have a poor prognosis for both morbidity and mortality. Multiple or isolated extensive lesions on MRI may be associated with significant disablity.[18] AHLE is usually associated with fatal outcome.

Prognosis is also related to the antecedent factors. ADEM following measles is associated with significant mortality (~40%) and morbidity (60%).[8,52] The mortality of post varicella-zoster encephalomyelitis is around 10% and associated morbidity is 25%.[8] Prognosis of acute cerebellar ataxia following varicella-zoster is very good.[8,53]

References

1. Alvord BC Jr : Demyelinating diseases. In : Handbook of clinical neurology, Vinken PJ, Bruyen GW, eds. Elsevier Publisher BV, Amsterdam.1985; **3** : 467-502.
2. Murthy JMK, Yangala R, Meena AK et al : Clinical, electrophysiological and magnetic resonance imaging study of acute disseminated encephalomyelitis. *J Assoc Physicians India* 1999; **47** : 280-283.
3. Singhal BS : Multiple sclerosis and related demyelinating disorders in Indian context. *Neurol India* 1987; **35** : 1-12.
4. Compston A : Non-infective inflammatory demyelinating and paraneoplastic diseases of the nervous system. In : Brains's diseases or the nervous system. Walton J (ed.). Oxford University Press, New Delhi. 1994; 351-392.
5. Appellbaum E, Greenberg M, Nelson J : Neurological complications following antirabies vaccinations. *JAMA* 1953; **151** : 188-191.
6. Label LS, Batts DH : Transverse myelitis caused by duck embryo rabies vaccine. *Arch Neurol* 1982; **39** : 426-430.
7. Sriram S, Steinman L : Post-infectious and post-vaccinial encephalomyelitis. *Neurol Clin* 1984; **2** : 341-353.
8. Miller HG, Stanton JB, Gibbons JL : Parainfectious encephalomyelitis and related syndromes. *QJM* 1956; **25** : 427-505.
9. Swamy HS, Shankar SK, Satishchandra P et al : Neurological complications due to beta-propriolactone (BPL) inactivated antirabies vaccination. *J Neurol Sci* 1984; **63** : 111-128.
10. Hemachudha T, Phanuphak P, Johnson RT et al : Neurological complications of Semple type rabies vaccine: clinical and immunological studies. *Neurology* 1987; **37** : 550-556.
11. Hemachudha T, Griffin DE, Giffles D et al : Myelin basic protein as an encephalitogen in encephalomyelitis and neuritis following rabies vaccination. *N Eng J Med* 1987; **316** : 369-374.
12. Fenichel GM : Neurological complications of immunization. *Ann Neurol* 1982; **12** : 119-128.
13. Miller HG, Stanton JB : Neurological sequelae of prophylactic inoculation. *QJM* 1954; **23** : 1-27.
14. Johnson RT, Griffin DE : Postinfectious encephalomyelitis. In : Infections of the nervous system. Kennedy PGE, Johnson RT, (eds.) Butterworth, London. 1987; 209-226.
15. Hung KL, Liao HT, Tsai ML : Postinfectious encephalomyelitis: etiologic and diagnostic trends. *J Child Neurol* 2000; **15** : 666-670.

16. Morris JH, Schoene WC : The nervous system. In : Pathogenic basis of disease. Robbins SL, Cotran RS, Kumar V, (eds.). 3rd edn. Philadelphia, Sanders. 1984 : 1412-1413.
17. Gold R, Hartung HP, Toyka KV : Animal models for autoimmune demyelinating disorders of nervous system. *Mol Med Today* 2000; **62** : 88-91.
18. Murthy JMK, Yangala R, Meena AK et al : Acute disseminated encephalomyelitis: clinical and MRI study from South India. *J Neurol Sci* 1999; **165** : 133-138.
19. Delerus D, Houdart P, Dester A : Memory defects in chicken pox encephalitis. *Revue Neurologique* 1990; **46** : 301-303.
20. Klockgether T, Doller G, Wullner U et al : Cerebellar encephalitis. *J Neurol* 1992; **24** : 17-20.
21. Snodgrass SR : Syndrome diagnosis in parainfectious neurologic disease: varicella ataxic syndrome. *J Child Neurol* 1998; **13** : 83-85.
22. Appelbaum E, Rachelson MH, Dolgopol VB : Varicella encephalitis. *Am J Med* 1953; **15** : 25-31.
23. Johnson RT, Milbourn PK : Central nervous system manifestations of chicken pox. *Can Med Assoc J* 1977; **102** : 831-834.
24. Murthy JMK, Kishore LT : Neurological complications of varicella infection: a clinical, electrophysiological and MRI study. *Neurol India* 1996; **44** : 195-201
25. Johnson RT : Viral infections of nervous system. Raven Press, New York. 1982.
26. Sackey AH, Brodhead RL : Hemiplegia after measles, mumps, and rubella vaccination. *BMJ* 1993; **306** : 1169.
27. Fog T : The tomography of plaques in multiple sclerosis with special reference to cerebral plaques. *Acta Neurol Scand* 1960; **14** (suppl 15): 157-160.
28. Schwaz S, Mohar A, Knauth M et al : Acute disseminated encephalomyelitis: a follow-up study of 40 patients. *Neurology* 2001; **56** : 1383-1318.
29. Hynson JL, Kornberg AJ, Coleman LT et al : Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. *Neurology* 2001; **56** : 1257-1260.
30. Kesselring J, Miller DH, Robb SA et al : Acute disseminated encephalomyelitis. *Brain* 1990; **113** : 291-302.
31. Andreula CF, Recchia Luciana NMA, Milella D : Magnetic resonance imaging in the diagnosis of acute disseminated encephalomyelitis. *International Journal of Neuroradiology* 1997; **3** : 21-34.
32. Baum PA, James Barkovich A, Koch TK et al : Deep gray matter involvement in children with acute disseminated encephalomyelitis. *AJNR* 1994; **15** : 1275-1283.
33. Barkhof F, Fillipi M, Miller DH et al : Comparison of MRI criteria at presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; **120** : 2059-2069.
34. Murthy JMK : MRI in acute disseminated encephalomyelitis following Semple antirabies vaccine. *Neuroradiolgy* 1998; **40** : 420-423.
35. Okumura A, Hayakawa M, Watanabe K et al : Two cases of acute disseminated encephalomyelitis with lesion in the thalamus or basal ganglia. *No to Hattatsu* (Japanese) 1992; **24** : 278-282.
36. Rust RS, Dodson W, Prensky A et al : Classification and outcome of acute disseminated encephalomyelitis. *Ann Neurol* 1997; **42** : 491.
37. Khan S, Yaqub BA, Poser CM et al : Multiphasic disseminated encephalomyelitis presenting as alternating hemiplegia. *J Neurol Neurosurg Psychiatry* 1995; **58** : 467-470.
38. Mancini J, Chabrol B, Moulene E et al : Relapsing acute encephalopathy: a complication of diphtheria – tetanus – poliomyelitis immunization in a young boy. *Eur J Pediatr* 1996; **155** : 136-138.
39. Shoji H, Kusuhara T, Honda Y et al : Relapsing acute disseminated encephalomyelitis associated with chronic Epstein–Barr virus infection: MRI findings. *Neuroradiology* 1992; **34** : 340–342
40. O'Riordan JI, Gomez-Anson B, Moseley IF et al : Long term MRI follow-up of patients with post infectious encephalomyelitis: evidence for a monophasic disease. *J Neurol Sci* 1999; **167** : 132-136.
41. McDonald WI, Compston DAS, Edan G et al : Recommended diagnostic criteria in multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; **62** : 121-127.
42. Jacobs LD, Beck RW, Simon JH et al : Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Eng J Med* 2000; **343** : 898-904.
43. Comi G, Fillipp M, Barkhof F et al : Early interferon treatment on conversion to to definite multiple sclerosis. *Lancet* 2001; **357** : 1576-1582.
44. Chopra JS, Banerjee AK, Murthy JMK et al : Paralytic rabies: a clinicopathological study. *Brain* 1980; **103** : 789-802.
45. Francis GS, Deguette P, Antel JP : Inflammatory demyelinating disease of the central nervous system. In : Neurology in clinical practice. Bradely WG, Daroff RB, Fenichel GM (eds.). Boston, Butterworth Heinemann, 2ed 1995; **2** : 1307-1343.
46. Tselis A : Acute disseminated encephalomyelitis. *Curr Treat Options Neurol* 2001; **3** : 537-542
47. Pittock SJ, Keir G, Alexander M et al : Rapid clinical and CSF response to intravenous gamma globulin in acute disseminated encephalomyelitis. *Eur J Neurol* 2001; **8** : 725.
48. Keegan M, Pineda AA, McClelland RL et al : Plasma exchange for severe attacks of CNS demyelination: Predictors of response. *Neurology* 2002; **58** : 143-146.
49. Miyazawa R, Hikima A, Takano Y et al : Plasmapheresis in fulminant acute disseminated encephalomyelitis. *Brain Dev* 2001; **23** : 424-426.
50. Nishikawa M, Ichiyama T, Hayashi T et al : Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *Pediatr Neurol* 1999; **21** : 583-586.
51. Pradhan S, Gupta RP, Shashank S et al : Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. *J Neurol Sci* 1999; **165** : 56-61.
52. Aarli JA : Nervous complications of measles: clinical manifestations and prognosis. *Eur Neurol* 1974; **12** : 79-93.
53. Underwood EA : The neurological complications of varicella: a clinical, epidemiological study. *Br J Child Dis* 1942; **32** : 83-107, 177-96, 241-63.

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