International Journal of Medical and Pharmaceutical Case Reports
5(5): 1-10, 2015; Article no.IJMPCR.19364
ISSN: 2394-109X, NLM ID: 101648033

SCIENCEDOMAIN *international*
www.sciencedomain.org

Intravenous Immunoglobulin in the Treatment of Patient with Acute Disseminated Encephalomyelitis: Case Report

Iryna Lobanova[1*]

[1]Department of Neurology, National Medical University, T. Shevchenko Av., 13, Kiev City, 01601, Ukraine.

Author's contribution

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

Article Information

DOI: 10.9734/IJMPCR/2015/19364
Editor(s):
(1) Rakesh Kumar Tiwari, Chapman University School of Pharmacy, Chapman University, Harry and Diane Rinker Health Sciences Campus, Irvine, CA, USA.
Reviewers:
(1) A. Martin Lerner, Oakland University, USA.
(2) Moses Rodriguez, Mayo Clinic, USA.
(3) Or Cohen-Inbar, University of Virginia Health Care Center, USA.
Complete Peer review History: http://sciencedomain.org/review-history/11717

Case Report

Received 5th June 2015
Accepted 17th September 2015
Published 7th October 2015

ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is a monophasic process nevertheless sometimes aggravated by relapses (so-called multiphase course of the disease). The treatment of ADEM must be targeted at reducing clinical manifestations of the disease and prevention of its relapses.
Case Presentation: We report a 42-year old woman with a diagnosis of acute disseminated encephalomyelitis. The patient received intravenous immunoglobulin in the dose of 0.4 g per 1 kg of body mass 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 as a method of ADEM monotherapy.
The positive dynamics of clinical symptoms was recorded 5 days after the beginning of the treatment (tendon anisoreflexia and swaying reduced). The treatment was followed by monthly administration of human normal immunoglobulin in the dose of 0.4 mg/kg. Three, nine and eighteen months after the beginning of the treatment the patient had two more MRI investigations of the brain that showed positive dynamics of the disease: reduction of demyelination foci and no

**Corresponding author: E-mail: lobanovanmu@gmail.com;*

accumulation of contrast agents. Her neurological deficits disappeared completely in 3 months. No relapses were observed over 24 months of observation.
Conclusion: This case report confirms a positive therapeutic efficacy of intravenous immunoglobulin in the treatment of patient with ADEM – reduction of clinical manifestations of the disease, in particular a decrease in neurological deficit level. Monthly intravenous immunoglobulin administration also helps to prevent the disease relapses (multiphase ADEM course).

Keywords: Acute disseminated encephalomyelitis; treatment; intravenous immunoglobulin; case report.

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, being caused by infectious disease or vaccination, in the central nervous system [1-6]. The following infections may be the triggering factors for ADEM: viral factors (measles, rubella, mumps, parainfluenza viruses [7-11], hepatitis A and B [7,12,13], whooping cough, tetanus [7,14,15], Epstein-Barr virus, cytomegalovirus and bacterial factors (Mycoplasma pneumonie [7,16-20], Campylobacter [7,21-23], Borrelia Burgdogferi [7, 24,25], Leptospira, Chlamydia, Legionella, B - hemolytic streptococcus group A [7,26-28]. However, in most cases there is an evidence of a nonspecific upper respiratory tract infection and there is no serologic evidence of pathogen [7,24, 29,30]. Vaccines that may lead to ADEM development include vaccines against influenza, measles, hepatitis B, rabies, tetanus, chicken pox [7,26,31-34]. There are also cases of spontaneous development of the disease [7,35-37].

The criteria necessary for the diagnosis of acute disseminated encephalomyelitis are given in the book of Harris C, et al. [4]. In 2007, the International Pediatric Multiple Sclerosis Study Group defined ADEM as “the first clinical event with a poly-symptomatic encephalopathy, with an acute or subacute onset, showing focal or multifocal hyperintense lesions predominantly affecting the CNS white matter” [7,4]. This definition shows how difficult it may be to differentiate ADEM from a multiple sclerosis at an early stage [38]. Magnetic resonance imaging can help in differentiating ADEM from multiple sclerosis. In ADEM, lesions are typically extensive but poorly defined. They are mainly found in the white matter but can also extend to the deep gray matter. Multiple sclerosis lesions are commonly found in the periventricular white matter and corpus callosum and are less likely to involve the gray matter [38].

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 [39]. Some authors consider ADEM as polysymptomatic demyelinating inflammatory disease which is characterized by an acute or subacute onset, no data about preceding lesion of CNS, significant improvement of patient’s condition after the treatment [39,40]. Also ADEM is 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) [41,42].

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 possible relapses of ADEM that have already been known since 1932, as described by van Bogaert, who published the paper “ADEM with relapses” [36,43]. ADEM relapses can be considered as a multiphasic course of this disease or its transformation into multiple sclerosis (MS) (according to the McDonald Criteria) [43,44-50]. The relapse rate of ADEM has been described, ranging from 5.5% to 24% [43,51-58].

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) [43].

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 [12,43,58]. In the researchers' opinion 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 [43,59]. The multiphasic course of disseminated encephalomyelitis can be diagnosed in the case of disease relapse appearance at least 3 months after its initial presentation [12,36,43,57,59]. 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) [43,50,60]. Relapses of acute disseminated encephalomyelitis are called multiphase course of the disease [24,43]. 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 [43,61,62].

There is also a lack of evidence-based, prospective clinical trial data for the management of ADEM [63]. 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 [43,64-68]. 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 [43,63,69-74]. However, in some cases where the efficacy of pulse-therapy with corticosteroids is insufficient, intravenous administration of immunoglobulin is used [43,75-84]. Plasmapheresis method is also used for the treatment of patients with the diagnosis of ADEM [43,63,84-89]. However, the effectiveness of these treatments (glucocorticoids, intravenous immune globulin, and plasma exchange) for ADEM has not been definitively confirmed, as there are no prospective clinical trial data to determine optimal treatment, including dose or duration.

2. CASE REPORT

A 42-year old female was being treated at the neurological department of the Kyiv City Clinical Hospital № 4 (Kyiv, Ukraine) after a 5-day history of numbness in the lower extremities. The patient denied visual changes, seizure, headache, mental status changes, bowel or bladder dysfunction, or speech or language difficulties. There was no history of toxin ingestion. There was a history of an upper respiratory tract illness ~1 week before her first symptom.

The patient's general physical examination was unremarkable. Her vital signs were stable, and she was afebrile. She was alert, oriented, and cooperative. MMSE (Mini - Mental State Examination) [90] was used to measure key constructs in cognitive psychology such as verbal learning and delayed recall, sustained attention and concentration as well as memory, attention and orientation in time and space assessment and showed 27 points (normal ranges are 28-30 points). Her speech was fluent. According to the neurological examination, the patient had weak convergence of eyeballs, asymmetry of face, tongue deviation to the right, positive subcortical reflexes, increase of deep reflexes with anisoreflexia (S>D), reduction of abdominal reflexes, patchy loss of vibration and temperature sensation in distal parts of lower extremities, swaying when performing the Romberg test.

MRI investigation showed the signs of disseminated demyelination process in the brain (multiple foci of hyperintensive signal on T2-weighted image without clear contours with the perifocal edema (up to 10-12 mm in diameter) were seen in the white and grey matter of the cerebral hemispheres in the frontal and parietal lobes subcortically).

Various laboratory tests were ordered (Table 1). These included routine blood tests, urinalysis, cerebrospinal fluid analysis, screening for autoimmune diseases. An ophthalmic exam also was performed. Cerebrospinal fluid examination

demonstrated 8 white blood cells with 100% lymphocytes. CSF culture for bacteria was negative. Polymerase chain reaction (PCR) analysis of CSF for herpes simplex virus (HSV) 1 and 2, and Epstein-Barr virus (EBV) were negative. Veneral Disease Research Laboratories tests (VDRL) of CSF as well as serum fluorescent treponemal antibodies were negative. Serologic studies for HIV, cytomegalovirus (CMV), toxoplasma, HSV, hepatitis A, B, C viruses, rubella, measles, EBV and leptospira were unremarkable. Anaerobic bacteria were not isolated. Oligoclonal IgG bands in cerebrospinal fluid were not detected. Screening for autoimmune diseases remained negative.

According to the indications the treatment of the patient was preceded by premedication with hormonal pulse-therapy, using methyl-prednisolone in the dose of 500 mg daily in 200 ml of isotonic sodium chloride solution (within 5 days). The patient was also 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 as a method of ADEM monotherapy.

The positive dynamics of clinical symptoms was recorded 5 days after beginning of the treatment (tendon anisoreflexia and swaying reduced). At this time-point CSF cell count normalized (4 white blood cells with 100% lymphocyte). The treatment was followed by monthly administration of human normal immunoglobulin in the dose of 0.4 mg/kg. Three, nine and eighteen months after beginning of the treatment the patient had two more MRI investigations of the brain that showed positive dynamics of the disease: reduction of demyelination foci and no accumulation of contrast agents (Figs. 1 and 2). Her neurological deficits disappeared completely in 3 months. No relapses were observed over 24 months of observation.

3. DISCUSSION

Immunobiological action of immunoglobulin is believed to contribute to the treatment efficacy due to the presence of antibodies against various infectious agents (virus of measles, influenza, varicella, parotitis, poliomyelitis, rubella, herpes-associated roup, hepatitis A and B, pneumococcus) [43,91-101]. Its efficacy has been demonstrated in several controlled studies [98]. A broad spectrum of immunological mechanisms is thought to be relevant in

Table 1. Laboratory tests and results

Test	Result
CBC, UA	all within normal limits
ESR	all within normal limits
ALT/AST/bilirubin	all within normal limits
Electrolytes, BUN/Cr	all within normal limits
ECG	normal
Ophthalmic exam	normal
CSF	8 white blood cells with 100% lymphocytes
PCR analysis of CSF for HSV 1 and 2	negative
PCR analysis of CSF for EBV, CMV	negative
VDRL of CSF	negative
Oligoclonal IgG bands	not detected
Serum fluorescent treponemal antibodies	negative
Serologic tests for HIV	negative
Serologic tests for CMV	negative
Serologic tests for toxoplasma	negative
Serologic tests for HSV	negative
Serologic tests for rubella	negative
Serologic tests for measles	negative
Serologic tests for EBV	negative
Serologic tests for leptospira	negative
Viral hepatitis serology	negative
Anaerobic bacteria	negative
Screening for autoimmune diseases	negative

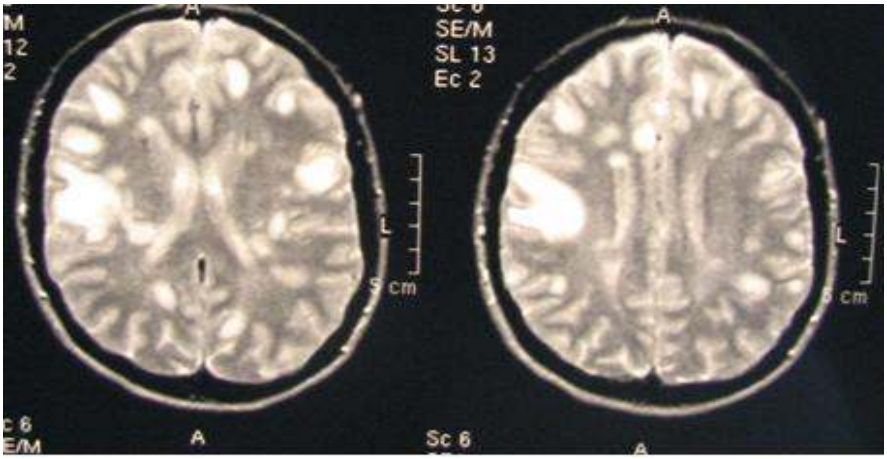

Fig. 1. Contrast-enhanced T2-weighted MRI data of the patient G., 42 years old. Multiple, large foci of high intensity of signal (of different sizes) in the T2 mode, located in the frontal, temporal and parietal lobes of both hemispheres

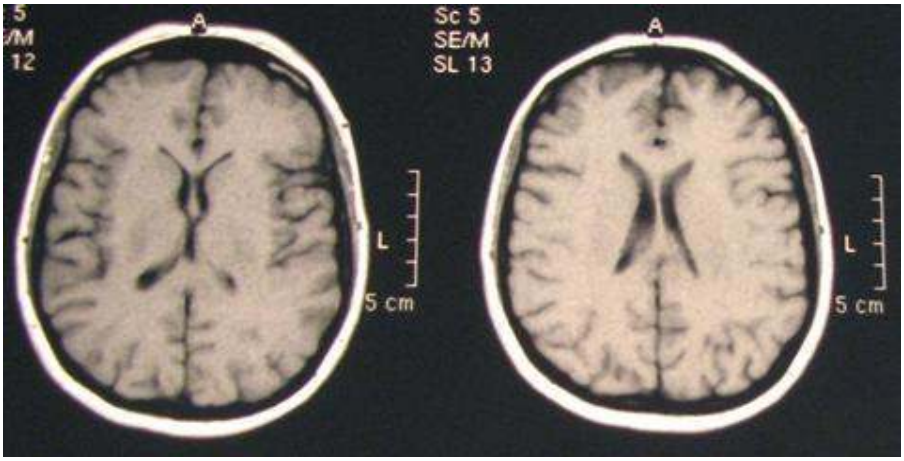

Fig. 2. MRI data of the same patient after 9 months from the beginning of the treatment

explaining the properties of IV Ig therapy, such as supply of idiotypic antibodies, neutralization of complement-mediated effects [1,101,102], 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 [43,100]. Experimental data show that in case of inflammatory diseases immunoglobulin may influence the local immune response in the central nervous system, regulating nitric oxide release and microglia function [43,103]. Remyelination stimulation can be a possible consequence of immunoglobulin use [43,103,104].

The use of intravenous immunoglobulin (IVIG) has been reported in several case studies as well, either alone [43,105] or in combination with corticosteroids [43,106]. There is a lack of specific recommendations for the long-term management of recurrent and multiphasic ADEM [107]. But several studies have reported a reduction of relapses after the long-term administration (every 4 weeks for 48 weeks) of intravenous immunoglobulin to patients with relapsing-remitting multiple sclerosis [107]. The results of the studies [43] have shown more significant reduction of the level of neurological disorders of the patients who received 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, using methylprednisolone in the dose of 500-1000 mg

daily in 200 ml of isotonic sodium chloride solution (within 5 days), comparing to the patients with placebo treatment (200 ml of isotonic sodium chloride solution) after the hormonal pulse-therapy. Over a 24-month observation period, the patients of the main group (who received 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) had fewer relapses of disseminated encephalomyelitis comparing to the patients with placebo treatment. The results of the other studies and this case report proved that immunoglobulin administration contributes not only to the reduction of clinical manifestations of the disease by decreasing the level of neurologic deficit but also helps to prevent the disease relapses.

4. CONCLUSION

This case report confirms a positive therapeutic efficacy of intravenous immunoglobulin in the treatment of patient with ADEM – reduction of clinical manifestations of the disease, in particular a decrease in neurological deficit level. Monthly intravenous immunoglobulin administration helps to prevent the disease relapses (multiphase ADEM course).

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

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.)

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Alexander M, Murphy JM. Acute disseminated encephalomyelitis; An update. Arch Neural. 2011;62(11):1673-1680.
2. 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.
3. Fridinger SE, Alper G. Severe Acute disseminated encephalomyelitis with clinical findings of transverse myelitis after herpes simplex virus infection. J Child Neurol. 2014;29:1519-1523.
4. Harris CC, Harris K, Lee J. Acute disseminated encephalomyelitis. Neurosci. Nurs. 2007;39(4):208–212.
5. Hasim HZ, Ibrahim NM, Wanyahua N, Tan HJ, et al. A case of biopsy proven of acute disseminated encephalomyelitis with haemorrhagic lecoencephalitis. Ann Acad Med Singarope. 2011;40(4):197-200.
6. Hoche F, Pfeifenbring S, Vlaho S, et al. Rare brain biopsy findings in a first acute disseminated encephalomyelitis- like event of pediatric MS: histopathologic, neuroradiologic and clinical features. J. Neural Transm. 2011;118(9):1311-1317.
7. Lobanova I. The characteristics of cognitive functions in patients with acute disseminated encephalomyelitis. International Neuropsychiatric Disease Journal. 2015;3(4):141-149.
8. Chowdhary J. Measles with Acute Disseminated Encephalomyelitis (ADEM). Indian Pediatrics. 2009;46.
9. Ogava Y. A case of acute disseminated encephalomyelitis presenting with vertigo. Auris Nasus Larynx. 2008;35:127–130.
10. Sawanyawisuth K. MRI findings in acute disseminated encephalomyelitis following varicella infection in an adult case reports. J. Clinical Neuroscience. 2007;14:1230–1233.
11. Voudris KA. Acute disseminated encephalomyelitis associated with parainfluenza virus infection of childhood. Brain Dev. 2002;24(2):112–124.
12. 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.
13. Kinomoto K. Acute encephalomyelitis associated with acute viral hepatitis type B. Inter. Med. 2009;48:241–243.

14. Cahnzos-Romero T. Demyelinating disorders: Not only multiple sclerosis. Abstracts from 8th congress of the European Federation of Intern. Medicine. 2009;20:282–283.
15. Gard RK. Acute disseminated encephalomyelitis. Postgraduate Medical Journal. 2003;79:11–17.
16. 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.
17. Njeukui TJ. Acute disseminated encephalomyelitis associated with mycoplasma pneumonia infection. Rev. Med. Brux. 2008;29(2):103–106.
18. Stam B. Neuroinvasion by mycoplasma pneumoniae in ADEM. International Journal of STG and AIDS. 2006;17(7): 493–495.
19. Stam B. Neuroinvasion by mycoplasma pneumoniae in acute disseminated encephalomyelitis. Emerg Infect Dis. 2008;14(4):641–643.
20. Termote B. Encephalitis following mycoplasma pneumonia (2007: 6b). Acute disseminated encephalomyelitis. Eur. Radiol. 2007;17(9):2436–2438.
21. Gaing C. Acute disseminated encephalomyelitis associated with *Campylobacter jejuni* infection and antiganglioside GM1 Ig G antibodies. J. Neurol. 2005;252:613–614.
22. Omata T. Child with Acute Disseminated Encephalomyelitis (ADEM) initially presenting with psychiatric symptoms. No To Hattatsu. 2008;40(6):465–468.
23. Orr D. Acute disseminated encephalomyelitis temporally associated with Campylobacter gastroenteritis. J. Neurol. Neurosurg. Psychiatry. 2004;75(5): 792–793.
24. Murthy JM. Acute disseminated encephalomyelitis. Neurol. 2002;50:238–243.
25. Dale RC. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain. 2000; 123:2407–2224.
26. Gard RK. 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 poststreptococcal 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. Sejvar JJ. Neurologic adverse events associated with smallpox vaccination in the United States 2002-2004. JAMA. 2005; 294:2744–2750.
32. Hamidon BB. Acute disseminated encephalomyelitis (ADEM) presenting with seizures secondary to anti-tetanus toxin vaccination. Med. J. Malaysia. 2003;58(5): 780–782.
33. Jorge D. Machicado, Bhavana Bhagya-Rao, Giovanni Davogustto, Brandy J. McKelvy. Acute Disseminated encephalomyelitis following seasonal influenza vaccination in an elderly patient. Clinical and Vaccine Immunology. 2013; 20(9):1485-1486.
34. Pellegrino P, Carnovale C, Perrone V, Pozzi M, Antoniazzi S, et al. Correction: Acute disseminated encephalomyelitis onset: Evaluation based on vaccine adverse events reporting systems. PLoS ONE. 2013;8(12):10.1371.
35. Ann Yeh E. Detection of coronavirus in the central nervous system of a child with acute disseminated encephalomyelitis. Pediatrics. 2004;113:73–76.
36. Tenembaum S. Acute disseminated encephalomyelitis: A long-term follow-up study of 84 pediatric patients. Neurology. 2002;22(59(8)):1224–1231.
37. Tenembaum S. Disseminated encephalomyelitis in children. Clinical Neurology and Neurosurgery. 2008;110: 928–938.
38. Alper G. Acute disseminated encephalomyelitis. J Child Neurol. 2012; 27(11):1408-1425.
39. Krupp LB. 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.
40. Sonneville RT, Klein de Broucker J. Post-infectious encephalitis in adults: Diagnosis

and management. Infection. 2009;58:321–328.
41. Ogava Y. A case of acute disseminated encephalomyelitis presenting with vertigo. Auris Nasus Larynx. 2008;35:127–130.
42. Suppiej A, Vittorini R, Fontanin M. Acute disseminated encephalomyelitis in children: Focus on relapsing patients. Pediatr Neurol. 2008;39(1):12–17.
43. Lobanova I, Myalovitska O. The efficacy of intravenous immunoglobulin in the treatment of patients with acute disseminated encephalomyelitis. Journal of Advances in Medical and Pharmaceutical Sciences. 2015;2(4):154-163.
44. Brass SD. Multiple sclerosis and acute disseminated encephalomyelitis in childhood. Pediatr. Neurol. 2003;29(3): 227–231.
45. McGovern RA, DiMario FJ. Acute disseminated encephalomyelitis: A retrospective pediatric serie. Ann. Neurol. 2003;54(7):127–129.
46. Neuteboom RF, Catsman-Berrevoets CE, Hintzen RQ. Multiple sclerosis in children. Ned Tijdschr Geneeskd. 2007;151(26): 1464–1468.
47. Pohl D, Hennemuth I, Kries R. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: Results of a nationwide survey. Eur. J. Pediatr. 2007; 166:405–412.
48. Toshiyuki O, Shunsaku H. Reccurence of acute disseminated encephalomyelitis after a 12-year symptom-free interval. Interval Medicine. 2004;43(8):746–749.
49. Tur C, Téllez N, Rovira A. Acute disseminated encephalomyelitis: Study of factors involved in a possible development towards multiple sclerosis. Neurologia. 2008;23(9):546–554.
50. Polman CH, Reingold SC, Banwell B, Clanet M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the "McDonald Criteria". Ann Neurol. 2011; 69(2):292–302.
51. Hung KL. The spectrum of postinfectious encephalomyelitis. Brain Dev. 2001;23:42–45.
52. Anlar B. Acute disseminated encephalomyelitis in children: Outcome and prognosis. Neuropediatrics. 2003; 34(4):194–199.
53. Huynh W, Cordato DJ, Kehdi E. Post-vaccination encephalomyelitis: Literature review and illustrative case. J. Clinical Neuroscience. 2008;1315–1322.
54. Mikaeloff Y, Caridade G, Husson B, et al. Acute disseminated encephalomyelitis cohort study: Prognostic factors for relapse. Eur. J. Paediatr. Neurol. 2007; 11(2):90–95.
55. Dale RC, Sousa C, Chong WK. Acute disseminated encephalomyelitis, multiphasic disseminated encephalo-myelitis and multiple sclerosis in children. Brain. 2000;123:2407–2224.
56. Leake JA. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr. Infect. Dis. J. 2004;23: 756–764.
57. Cohen O. Recurrence of acute disseminated encephalomyelitis at the previously affected brain site. Arch. Neurol. 2001;58:797–801.
58. Dale RC, Branson JA. Acute disseminated encephalomyelitis or multiple sclerosis: can the initial presentation help in establishing a correct diagnosis. Arch. Dis. Child. 2005;90:636–639.
59. Divya SK, Mrlvin JJ, Sanjeev VK. Acute disseminated encephalomyelitis in children: Discordand neurologic and neuroimaging abnormalities and response to plasmapheresis. Pediatrics. 2005; 166(2):431–436.
60. Kanter DS, Horensky D, Sperling RA. Plasmapheresis in fulminant acute disseminated encephalomyelitis. Neurology. 1995;45:824–827.
61. Aboagye-Kumi M, et al. ADEM in a renal thansplantation recipient; A case report. Transplantation proceedings. 2008;40: 1751-1753.
62. Khurana DS, Melvin JJ, Kothare SV. Acute disseminated encephalomyelitis in children: Discordant neurologic and neuroimaging abnormalities and response to plasmapheresis. Pediatrics. 2005; 116(2):431–436.
63. Pohl D, Tenembaum S. Treatment of acute disseminated encephalomyelitis. Curr Treat Options Neurol. 2012;14(3):264-75.
64. Ravaglia S. Severe steroid-resisnant post-infectious encephalomyelitis: General features and effects of IVIg. J. Neurol. 2007;254(11):1518–1523.
65. Shahar E. Outcome of severe encephalomyelitis in children: effect of high-dose methylprednisolone and immunoglobulin. J. Child Neurol. 2002;17: 810–814.

66. Sonneville R. Acute disseminated encephalomyelitisin the intensive careunit: Clinical features and outcome of 20 adults. Intensive Care Med. 2008;24(3):528–532.
67. Tenembaum S. Acute disseminated encephalomyelitis. Neurology. 2007;68: 23–26.
68. Van Dam NC, Eron Syed S, Ostrander M. Severe postvaccinal encephalitis with ADEM: Recovery with early intravenous Ig, high-dose steroids and Vaccina Ig. clinical Infectious Disease. 2009;48:47–49.
69. Fu DC, Montgomery JR. High-dose, rapid-infusion IVIG in postvaccination acute disseminated encephalomyelitis. Neurology. 2008;71:294–295.
70. Joshua Rothenberg, Angie Lastra, Gemayaret Alvarez, Robert Irwin. Acute disseminated encephalomyelitis responsive to cyclophosphamide therapy: A case report. Journal of Medical Cases. 2015;6(7):290-294.
71. Kazushi Ichikawa, Hirotaka Motoi, Yoshitaka Oyama, Yoshihiro Watanabe, Saoko Takeshita. Fulminant form of acute disseminated encephalomyelitis in a child treated with mild hypothermia. Pediatrics International. 2013;e149–e151.
72. Kotlus BS, Slavin ML, Guthrie D. Ophthalmologic manifestations in pediatric patients with acute disseminated encephalomyelitis. J AAPOS. 2005;9(2): 179–183.
73. Meca-Lallana JE. Plasmaferesis: Its use in multiple sclerosis and other demyelinating processes of the central nervous system. An oaservational study. Rev. Neurol. 2003; 37:917–926.
74. Ohya T, Nagamitsu S, Yamashita Y. Serial magnetic resonance imaging and single photon emission computed tomography study of acute disseminated encephalomyelitis patient after Japanese encephalitis vaccination. Kurume Med. J. 2007;54(3-4):95–99.
75. Berrak S, Seda Sirin Kose, Serdar Saritas, Engin Kose, Ali Kanik, Mehmet Helvaci. Severe Acute Disseminated Encephalomyelitis with clinical findings of transverse myelitis after herpes simplex virus infection. J Child Neurol, 2014; 29:1519-1523.
76. Konstantin Huhn, De-Hyung Lee, Ralf A Linker, Stephan Kloska, Hagen B Huttner, Corresponding author: Konstantin Huhn. Pneumococcal-meningitis associated acute disseminated encephalomyelitis (ADEM) – case report of effective early immunotherapy. SpringerPlus. 2014;3: 415.
77. Lu Z, Zhang B, Qiu W, Kang Z, Shen L, Long Y, et al. Comparative brain stem lesions on MRI of acute disseminated encephalomyelitis, neuromyelitis optica, and multiple sclerosis. PLoS ONE. 2011; 6(8):e22766
78. Nishicava M, Ichiama T. Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis. Pediatr. Neurol. 1999;21(2):583–586.
79. Pittock SJ. Rapid clinical and CSF response to intravenous gamma globulin in acute disseminated encephalomyelitis. Eur. J. Neurology. 2001;8:723–725.
80. Shiraiwa N, Yoshizawa T, Ohkoshi N. A case of acute disseminated encephalomyelitis (ADEM) associated with peripheral neuropathy. Rinsho Shinkeigaku. 2007;47(4):169–172.
81. Straussberg R. Improvement of atypical acute disseminated encephalomyelitis with steroids and intravenous immunoglobulins. Pediatric Neurology. 2001;24:139–143.
82. Sunnerhagen KS, Johansson K, Ekholm S. Rehabilitation problems after acute disseminated encephalomyelitis. J. Rehabilitation Medicine. 2003;35:20–25.
83. Unay B. Intravenous immunoglobulin therapy in acute disseminated encephalomyelitis associated with hepatitis A infection. Pediatr. Int. 2004;46(2):171–173.
84. Varilek BZ, Eron Syed S, Ostrander M. Acute disseminated encephalomyelitis following pleural empyema owing to Boerhaave's syndrome. J. Child Neurol. 2004;19(3):224–227.
85. Laderman M, Gabelin P, Lafrenz M. Acute disseminated encephalomyeltis malaria caused by Varicella Zoster Virus reactivation. Amer. J. Trop. Med. Hyg. 2005;72(4):478–480.
86. Lin CH, Jeng JS, Yip PK. Plasmapheresis in acute disseminated encephalomyelitis. J. Clin. Apher. 2004;19(3):154–159.
87. Ramachandran NR, Parameswaran MG. Acute disseminated encephalomyelitis treated with plasmapheresis. Singapore Med J. 2005;46(10):561–563.
88. Ramachandran NR. Plasmapheresis in childhood acute disseminated encephalomyelitis. Indian Pediatr. 2005; 42(5):479–482.

89. Refai D. Decompressive hemicraniectomy for acute disseminated encephalomyelitis. Neurosurgery. 2005;56(4):870–872.
90. 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.
91. Azulay JP, Verschueren A, Attarian S. Guillain-Barre syndrome and its frontiers. Rev. Neurol. 2002;158(123):21–26.
92. Barohn RJ, Saperstein DS. Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy. Semin. Neurol. 1998;18(1):49–61.
93. De Grandis E, De Negri E, Montaldi L. Intravenous immunoglobulins as therapeutic option in the treatment of multiple sclerosis. J. Neurol. 2006;253:50–58.
94. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: Clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology. 1997;48(2):321–328.
95. Smith-Jensen T, Burgoon, M, Anthony G, et al. Comparison of IgG heavy chain sequences in MS and SSPE brain reveal an antigen-driven response. Neurology. 2000;54:1227–1232.
96. Takigawa T, Yasuda H, Terada M. The sera from GM1 ganglioside antibody positive patients with Guillain-Barre syndrome or chronic inflammatory demyelinating polyneuropathy blocks Na+ currents in rat single myelinated nerve fibers. Intern. Med. 2000;39(2):123–127.
97. Villa AM, Molina H, Sanz OP. Chronic inflammatory demyelinating poly-neuropathy. Findings in 30 patients. Medicina. 1999;59(6):721–726.
98. Vital C, Vital A, Gbikpi-Benissan G. Postvaccinal inflammatory neuropathy: Peripheral nerve biopsy in 3 cases. J. Peripher. Nerv. Syst. 2002;7(3):163–167.
99. Wittstock M, Zettl UK. Adverse effects of treatment with intravenous immunoglobulins for neurological diseases. J Neurol. 2006;5:75-79.
100. Basta M, Kirshbom P, Frank MM, Fries LS. Mechanism of therapeutic effect of high-dose intravenous immunoglobulin. Attenuation of acute, complement-dependent immune damage in a guinea pig model. J Clin Invest. 1989;84:1974-1981.
101. Frank MM, Basta M, Fries LF. The effects of intravenous immune globulin on complement dependent immune damage of cells and tissues. Clin Immunol Immunopathol. 1992;62:S82-S86.
102. Frank MM, Basta M, Fries LF. The effects of intravenous immune globulin on complement dependent immune damage of cells and tissues. Clin Immunol Immunopathol. 1992;62:S82-S86.
103. Marchioni E, Marinou-Aktipi K, Uggetti C. Efficacy of intravenous immunoglobulin treatment in adult patients with steroid-resistant monophasic or recurrent acute disseminated encephalomyelitis. J. Neurol. 2002;249(1):100–104.
104. Giovanni SR, Ceroni PM. Severe steroid-resistant post-infectious encephalomyelitis. General features and effects of IVIg. Neurol. 2007;254:1518–1523.
105. Kleiman M, Brunquell P. Acute disseminated encephalomyelitis: Response to intravenous immunoglobulin. J Child Neurol. 1995;10:481-483.
106. Shahar E. Outcome of severe encephalomyelitis in children: effect of high-dose methylprednisolone and immunoglobulins. J. Child Neurol. 2002; 17:810–814.
107. Fazekas F, Lublin FD, Li D, Freedman MS, et al. Intravenous immunoglobulin in relapsing-remitting multiple sclerosis. A dose-finding trial. Neurology. 2008;71(4): 265-271.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/11717