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ENCEPHALITIS: COMPLETE BRIEF REVIEW

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ABSTRACT

ENCEPHALITIES represents the inflammation of brain parenchyma typically, symptoms of encephalitis occurs including personality change, fever, seizures, consciousness, neurological shortage, and coma. All patients with suspected encephalitis should undergoes blood cultures and HIV testing. Acute viral encephalitis is direct infection of neural cells with perivascular inflammation, neural destruction, and neuronophagia and tissue necrosis. This consider non-viral diseases, which may necessitate urgent treatment and well detect cases due to HSV. Limbic include HSV cause inflammation in the CNS including limbic area of the brain. The etiology remain unknown, despite extensive diagnostic evaluation. The epidemiology of various causes of encephalitis has changed in recent years in the United States and commonly identified HSV, WNV, and Enterovirus. Symptoms include confusion, agitation, seizures, muscle weakness and double vision, and in infants and young children may also include nausea and vomiting, body stiffness, inconsolable crying, poor feeding, irritability. It diagnosed with different ways such as ELISA, CT, MRI, EEG, CSF, and serological testing. Treatment is carried mostly by cases series and experts consensus, which suggest first line therapy with i.v. IgB, high dose corticosteroid, plasmapheresis, or a combination. Used drugs are (acyclovir, ganciclovir, foscarnet). Therapy may be given if required depend on patients conditions.

KEYWORDS: Inflammation, herpes simplex virus (HSV), brain parenchyma.

INTRODUCTION

The inflammatory process of brain, which associated, with clinical indication of the neurological dysfunction termed as “ENCEPHALITIS”. It represents the inflammation of brain parenchyma typically, symptoms of encephalitis occur including personality change, fever, seizures, consciousness, neurological shortage, and coma.[1,2] It may be caused by

infections or autoimmune conditions. Diagnosis is typically made by a combination of clinical, laboratory, neuroimaging, and electro physiologic findings. A number of case definitions have been developed which generally require encephalopathy, as characterized by alteration in consciousness or personality change lasting for a sustained period of time (typically greater than 24 hours).[3,4] All patients with suspected encephalitis should undergo blood cultures and HIV testing. Additional serum should be strained during the acute phase of disease and held for later serologic studies, and if the diagnosis is still indeterminate, a convalescent serum should be collected after 10–21 days. Lumbar puncture (LP) is recommended in all individuals unless contraindicated (i.e., significant mass effect/edema or effacement of basal cisterns on neuroimaging, or suspected skin or soft tissue abscess in the path of the puncture needle).[5] Encephalitis might be an acute condition or a chronic condition. Acute encephalitis is mostly infectious encephalitis, which may be caused by viral, bacterial or parasitic (fungi, Protozoa, rickettsia) agents. Infectious encephalitis may be primary (direct infection to brain tissue) or secondary (spreading from some other systemic infection). Autoimmune encephalitis may result in acute or chronic onset.

A) Acute Encephalities

The form referred simply as acute viral encephalitis is direct infection of neural cells with perivascular inflammation, neural destruction, neuronophagia and tissue necrosis. The pathology is primarily centered in the gray matter. The various matter of different diagnosis of encephalitis is consider non-viral disease which may necessitate urgent treatment and well detect cases due to Herpes simplex virus (HSV) where morbidity and mortality can be greatly reduced with specific antiviral therapy within certain time.[6] Acyclovir started in all patients with distrusted encephalitis; incomplete result of diagnostic studies. Some other empirical antimicrobial agents are initiated on the base of specific epidemiologic or clinical factors with suitable therapy for accepted bacterial meningitis, if clinically shown. In patients with clinical clues suggestive of rickettsia or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens.[7]

B) Limbic Encephalities

Limbic encephalitis (LE), first described in 1960 is characterized by a subacute onset of episodic memory loss and confusion frequently accompanied by seizures, psychiatric symptoms, and lesion involving the medial temporal lobe and hippocampus. Infectious agents such as herpes simplex virus cause inflammation in the central nervous system (CNS)

including the limbic area of the brain, but a substantial number of patients with LE are without clear evidence of CNS infection.[8] Autoimmune etiology is increasingly recognized as a major cause of LE along with the finding of the high prevalence of anti-N-methyl-d-aspartate receptor (NMDAR) antibody associated encephalitis after the discovery of the antibody[9] and the continued identification of additional novel antibodies in LE. AE is classified according to the location of the antigen, either intracellular or on the cell surface, because each classification is associated with different clinical features, especially pertaining to cancer association and immune therapy responsiveness. Some antibodies such as (Hu,Ma,Ri) targeting nuclear and cytoplasmic proteins (onconeuronal antibodies) typically attend malignancy equivalent with recognition of these antibodies called as "paraneoplastic LE." Patients producing these antibodies respond poorly to immunotherapy, but treatment of the cancer often results in neurological improvements.[10-12]

ETIOLOGY

The epidemiology of various causes of encephalitis has changed in recent years in the United States, primarily as a result of the decrease in vaccine-preventable conditions, such as measles, mumps, rubella, and varicella. In the United States most commonly identified etiologies are herpes simplex virus (HSV), West Nile virus (WNV), and the enteroviruses, tailed by other herpesviruses. Although M. pneumonia is the most common agent identified in some studies in patients with encephalitis, the significance is unclear; in many cases of encephalitis (32%–75%), however, the etiology remains unknown, despite extensive diagnostic evaluation. In the California Encephalitis Project, an underlying cause of encephalitis was not identified in 208 (62%) of 334 patients during 1998– 2000, despite extensive testing and evaluation of note, 10% of patients initially thought to have an infectious cause of their encephalitis ultimately received a diagnosis of a noninfectious condition. In a follow-up report of 1570 cases over a 7-year period.[13-14], a confirmed or probable etiologic agent was identified for only 16% of cases of encephalitis, and an additional 13% of cases had a possible etiology identified. Of the confirmed or probable cases, 69% were viral, 20% were bacterial, 7% were prion related, 3% were parasitic, and 1% were fungal. Cardinal clinical features of anti-NMDAR encephalitis include changes in behavior or cognition, seizures, orofacial dyskinesia, and autonomic instability. In a large series of patients in whom both CSF and serum were tested for NMDAR antibodies, approximately 15% of individuals had positive CSF antibodies in the absence of serum antibodies. While more recently, some pediatric cases with neurologic relapse (movement

disorders or new cognitive dysfunction, or both) following herpes encephalitis have been found to have NMDAR antibodies and responded to immunotherapy. These reports suggest that patients who experience a neurologic decline following treatment for HSE should be tested for NMDAR antibodies.[15]

SYMPTOMS

The viral primary symptoms typically consists of fever, headache, nausea and vomiting, lethargy, and myalgia. Encephalitis caused by varicella-zoster virus (VZV), Epstein Barr virus (EBV), cytomegalovirus (CMV), measles virus, or mumps virus may cause rash, lymphadenopathy, hepatosplenomegaly, and parotid enlargements. St Louis encephalitis also causes dysuria and pyuria, while West Nile encephalitis (WNE) manifests as extreme lethargy.

Additional signs and symptoms of more serious encephalitis may include the following:

1. Confusion, agitation or hallucinations
2. Seizures
3. Loss of sensation or paralysis in certain areas of the face or body
4. Muscle weakness
5. Double vision
6. Perception of foul smells, such as burned meat or rotten eggs
7. Problems with speech or hearing
8. Loss of consciousness

Sign and symptoms in infants and young children may also include:

1. Bulging in soft spot of skull in infants
2. Nausea and vomiting
3. Body stiffness
4. Inconsolable crying
5. Poor feeding or not waking for feeding
6. irritability

DIAGNOSIS

Certain diagnostic studies should be performed or considered in patients who present with encephalitis in hopes of identifying treatable infectious etiologies; additional studies are based on specific epidemiologic and clinical findings. The diagnostic evaluation in patients

with encephalitis should include complete blood and urine tests, CT, MRI and EEG may help in diagnosis. CSF analysis & brain biopsy provide 96% sensitivity and 100% specificity. ARBO viruses can be detected by presence of virus specific IgM in CSF by means of simple antibody capture.

ELISA

Different Ways to Diagnose Encephalitis

Cultures- Cultures of specimens of body fluids other than CSF may be useful in establishing the etiologic diagnosis in selected patients with encephalitis. All patients with encephalitis should undergo blood culturing to identify potential bacterial and fungal etiologies, although positive culture results may be indicative of encephalopathy secondary to systemic infection rather than encephalitis.[16] However, a positive result for a vesicular fluid sample does not necessarily indicate that this is the etiology of encephalitis, because varicella zoster virus may be reactivated in the context of CNS disease caused by other agents.[17-18]

1. Serologic testing- Some causes of encephalitis may be diagnosed by detection of IgM antibodies in serum (e.g., primary varicella virus and many arboviruses). In recent years, IgM and IgG capture ELISAs have become the most useful and widely used tests for the diagnosis of arboviral encephalitis, although there may be cross-reactivity, particularly among the flaviviruses (e.g., Japanese encephalitis, St. Louis encephalitis, and West Nile viruses). Plaque reduction neutralization testing is recommended in areas where multiple flaviviridae co circulate or in patients who have received previous vaccination against a related arbovirus (e.g. prior Japanese encephalitis or yellow fever immunization in the setting of suspected flavivirus encephalitis).[19-23] At the time of initial presentation, recommend that serum specimens be stored and tested at later time with convalescent phase serum samples. In other diseases in which encephalitis may be a result of reactivation of previously acquired infection (e.g., toxoplasmic encephalitis in patients with AIDS), detection of serum IgG antibodies may identify persons at risk for encephalitis with a specific agent.[24]
2. EEG- EEG is a sensitive indicator of cerebral dysfunction and may demonstrate cerebral involvement during the early stage of encephalitis. The results of EEG are generally nonspecific but can be helpful in suggesting a specific etiologic diagnosis of encephalitis. In 18% of patients with herpes simplex encephalitis, there is a temporal focus demonstrating periodic lateralizing epileptic form discharges.[25-26]

Antibody. Detection of CSF antibody is a helpful diagnostic tool in some patients with encephalitis. New diagnostic assays have simplified the diagnosis of certain viral CNS infections. The presence of virus-specific IgM in CSF is usually indicative of CNS disease, because IgM antibodies do not readily diffuse across the blood-brain barrier.[27-29]

TREATMENT

Drugs and Therapy

Treatment at present is guided mostly by case series and expert consensus, which suggest first line therapy with I.V. immunoglobulin, high-dose corticosteroids, plasmapheresis, or a combination. Different syndromes and antibody-related disorders respond differently to therapy. Syndromes associated with antibodies against intracellular antigens tend to be more resistant to immune therapy than cell surface antigen related syndromes.[30]

a) Antiviral Drugs

Cases of encephalitis due to certain viruses usually require i.v. antiviral treatments. Antiviral drugs commonly used to treat encephalitis include:

1. Acyclovir (Zovirax)
2. Ganciclovir (Cytovene)
3. Foscarnet (Foscavir)

Acyclovir is ineffective in cytomegalovirus encephalitis. Combination therapy with ganciclovir (5 mg/kg intravenously twice daily) with or without foscarnet (60 mg/kg every eight hours or 90 mg/kg every 12 hours) is currently recommended.[31-32]

Side effect of antiviral drugs may include nausea, vomiting, diarrhea and muscle or joint soreness or pain. Rare serious problems may include abnormalities in kidney or liver function or suppression of bone marrow activity. Appropriate tests are used to monitor for serious adverse effects.

Some viruses, such as insect-borne viruses, do not respond to these treatments. However, because the specific virus may not be identified immediately or at all, treatment with acyclovir is often begun immediately. This drug can be effective against the herpes simplex virus, which can result in significant complications, such as encephalitis, or death when not treated promptly.

THERAPY

Table: Agents which are used in of therapy encephalitis.

TREATMENT	REGIMEN
first line immunotherapy	
1.Methylprednisolone 2. i.v. immunoglobulin 3.plasma exchange	1 g daily, for 3-5 days 2g/kg, over 5 days(400mg/kg/day) 1 session every otherday for 5-7 cycles
second line immunotherapy	
1.Rituximab 2. Cyclophoshphamide	375mg/m2 weekly i.v. infusion for 4 weaks 750mg/m2 monthly for 3-6 months
alternative therapy	
1. Tocilizumab low-dose interleukin-2	intially 4mg/kg followed by an increase to 8mg/kg monthly based on clinical response 1.5million IU/day 4 subcutaneous injection with 3 week interval
sterid sparing agent	
1.Azathioprine	initially 1-1.5mg/kg once daily or devided twice daily, target 2-3 mg/kg/day

CONCLUSIONS

In all cases of acute encephalitis, appropriate investigations and supportive care form the integral part of the management strategy. The availability of acyclovir, an excellent anti-HSV therapy, has led to early initiation of the treatment with substantial improvement in the clinical outcome of HSE.

1. The autoimmune encephalitis comprise a growing group of antibody-mediated disorders with favorable response to immunotherapy.
2. Neuroimaging and CSF studies are necessary but their specificity and sensitivity are limited.
3. Detection of neuronal antibodies is important for the diagnosis, treatment planning and prognostic evaluation.
4. Immunotherapy and if applicable, tumor removal are crucial to expedite neurological improvement and to attain substantial clinical recovery.

REFERENCES

1. Granerod, J.; Ambrose, H.E.; Davies, N.W.; Clewley, J.P.; Walsh, A.L.; Morgan, D.; Cunningham, R.; Zuckerman, M.; Mutton, K.J.; Solomon, T.; et al. Causes of encephalitis

and differences in their clinical presentations in England: A multicenter, populationbased prospective study. Lancet Infect. Dis., 2010; 10: 835–844.

2. Kennedy, P.G. Viral encephalitis: Causes, differential diagnosis, and management. J. Neurol. Neurosurg. Psychiatry, 2004; 75(1): i10–i15.
3. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis., 2010; 10: 835–844.
4. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis., 2013; 57:1114–1128.
5. Roos KL. Lumbar puncture. Semin Neurol, 2003; 23: 105–114.
6. Johnson RT. Acute encephalitis.clin infect Dis., 1996; 23(2): 219-226.
7. Almas KA, Zakareya G, Mohammed MH. "The Clinical Management of the Patient with Encephalitis." In Encephalitis, by Dr. Sergey Tkachev(Ed.), ISBN: 978- 953-51-0925-9, InTech, DOI: 10.5772/55171.
8. Brierley JB, Corsellis JAN, Hierons R, et al. Subacute encephalitis of later adult life – mainly affecting the limbic areas. Brain, 1960; 83: 357–370.
9. Gable MS, Sheriff H, Dalmau J, et al. The frequency of autoimmune N-methyl-Daspartate receptor encephalitis surpasses that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Clin Infect Dis., 2012; 54: 899–904.
10. Corsellis JA, Goldberg GJ and Norton AR. "Limbic encephalitis" and its association with carcinoma. Brain, 1968; 91: 481–496.
11. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain, 2000; 123: 1481–1494.
12. Melzer N, Meuth SG and Wiendl H. Paraneoplastic and non-paraneoplastic autoimmunity to neurons in the central nervous system. J Neurol, 2013; 260: 1215–1233.
13. Glaser CS, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998–2000. Clin Infect Dis., 2003; 36: 731–42.
14. Glaser CS, Honarmand S, Anderson LJ, et al. Beyond viruses: clinical profiles and etiologies associated with encephalitis. Clin Infect Dis., 2006; 43: 1565–77.

15. Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain, 2010; 133: 1655–1667.
16. Scheld WM, Whitley RJ, Marra CM, eds. Infections of the central nervous system. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2004.
17. Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. Lancet, 2002; 359: 507–14.
18. McCarthy M. Newer viral encephalitides. Neurologist, 2003; 9: 189–99.
19. Day JN, Lalloo DG. Neurological syndromes and the traveler: an approach to differential diagnosis. J Neurol Neurosurg Psychiatry, 2004; 75(1): i2–9.
20. Leiby DA, Gill JE. Transfusion-transmitted tick-borne infections: a cornucopia of threats. Transfus Med Rev., 2004; 18: 293–306.
21. Arribas JR, Storch GA, Clifford DB, Tselis AC. Cytomegalovirus encephalitis. Ann Intern Med., 1996; 125: 577–87.
22. Miller GG, Boivin G, Dummer JS, et al. Cytomegalovirus ventriculoencephalitis in a peripheral blood stem cell transplant recipient. Clin Infect Dis., 2006; 42: e26–9.
23. Zerr DM, Corey L, Kim HW, et al. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. Clin Infect Dis., 2005; 40: 932–40.
24. Hankins DG, Rosekrans JA. Overview, prevention, and treatment of rabies. Mayo Clin Proc, 2004; 79: 671–6.
25. Markand ON. EEG in the diagnosis of CNS infections. In: Roos KL, ed. Central nervous system infectious diseases and therapy. New York: Marcel Dekker, 1997; 667–90.
26. Whitley RJ, Tilles J, Linneman C, et al. Herpes simplex encephalitis: clinical assessment. JAMA, 1982; 247: 317–20.
27. Leite C, Barbosa A, Lucato LT. Viral diseases of the central nervous system. Top Magn Reson Imaging, 2005; 16: 189–212.
28. Steiner I, Budka H, Chaudhuri A, et al. Viral encephalitis: a review of diagnostic methods and guidelines for management. Eur J Neurol, 2005; 12: 33–43.
29. Romero JR, Newland JG. Diagnosis of viral encephalities: nonzoonotic-associated viruses. Pediatr Infect Dis J., 2006; 25: 739–40.
30. Jammoul A, Li Y, Rae-Grant A. Autoantibody-mediated encephalitis: not just paraneoplastic, not just limbic, and not untreatable. Cleveland Clinic Journal of Medicine, Jan, 2016; 83(1): 4353.

31. Enting R, de Gans J, Reiss P, et al. Ganciclovir/foscarnet for cytomegalovirus meningoencephalitis in AIDS. Lancet, 1992; 340: 559–60.
32. Hoke CH Jr, Vaughn DW, Nisalak A, et al. Effects of high dose dexamethasone on the outcome of acute Japanese encephalitis. J Infect Dis., 1992; 165: 131–6.