International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Acute Encephalitides: Spectrum of Etiologies in 12 Pediatric Patients

Aida Bushati[1,2], Kristi Aleksi[3], Aferdita Tako Kumaraku[1,2], Armand Shehu[1,2]

[1]Service of Pediatrics, Mother Teresa University Hospital Center, Tirana, Albania

[2]Department of Pediatrics, Faculty of Medicine, University of Medicine, Tirana, Albania

[3]Faculty of Medicine, University of Medicine, Tirana, Albania

Corresponding author: Kristi Aleksi, MD

Abstract: ***Background: Encephalitis is the inflammation of the brain parenchyma caused by various infectious and non-infectious etiologies. Aims: To describe etiologies, clinical presentations, and outcomes of patients with acute encephalitis of various etiologies. Methods: We retrospectively reviewed the medical records of pediatric patients diagnosed with acute encephalitis at Mother Teresa University Hospital Center, Tirana, Albania between May 2018 and July 2019. Results: In this study, we included 12 patients (9 males and 3 females) with a median age of 4 years (range 1-12 years). Etiologies included (i) infectious encephalitis (n=5): herpes simplex virus type 1 (n=3), varicella-zoster virus (n=1), human herpes virus 6 (n=1); (ii) immune-mediated encephalitis (n=3): acute disseminated encephalomyelitis (n=1), anti-N-methyl-D-aspartate receptor antibody encephalitis (n=1), anti-glutamic acid decarboxylase antibody encephalitis (n=1); and encephalitis of non-identified origin (n=4). Out of 12 patients, 9 were responsive to the first-line therapy, while in 3 others second-line therapy was necessary. Good outcome at discharge was achieved by all patients. The mortality rate was 0. Conclusions: Diagnosis and differential diagnosis between viral and immune-mediated encephalitides in pediatric patients is often challenging; although viral etiologies are the most prevalent, autoimmunity should always be considered as a cause, therefore evaluated.***

Keywords: acute encephalitis, infectious encephalitis, viral encephalitis, immune-mediated encephalitis, autoimmune encephalitis, encephalitides

1. Introduction

Acute encephalitis is the inflammation of the brain parenchyma triggered by various infectious and non-infectious etiologies, which precipitate neurological dysfunction. It is characterized by the acute onset of fever, altered mental status and behavior, seizures, and the onset of focal neurologic deficits [1]. The annual incidence of acute encephalitis worldwide is estimated to be 1.9 to 14.3 people per 100,000. Although its diagnosis and treatment have improved, mortality rates range between 5.6–39.3% in affected patients according to reports from different countries [2].

Of all the pathogens reported to cause infectious encephalitis, most are viruses including herpes simplex virus type 1 and 2, varicella-zoster virus, Epstein-Barr virus, human herpes virus type 6 and 7, cytomegalovirus, arboviruses, but also bacteria like Neisseria meningitides, Streptococcus pneumonia, Listeria monocytogenes, Staphylococcus aureus, Haemophilus influenza, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Toxoplasma gondii, Rickettsia rickettsii, Bartonella henselae, and fungi such as Cryptococcus neoformans and Candida lusitaniae [3,4]. Conversely, non-infectious, immune-mediated encephalitides such as autoimmune encephalitis or acute disseminated encephalomyelitis (ADEM), are presumed to be mediated by an immune response to an antecedent antigenic stimulation provided by a previous infectious microorganism, immunization, neoplastic disease, systemic disease or medications [3]. Different types of autoimmune encephalitis are known to date, including anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, leucine-rich glioma-inactivated 1 (LGI1) antibody encephalitis, anti-contactin-associated protein-like 2 (CASPR2) antibody encephalitis, anti-gamma aminobutyric acid (GABA) receptor encephalitis, anti-glutamic-acid-decarboxylase 65 (GAD65) encephalitis, Hashimoto encephalitis and even seronegative autoimmune encephalitis [5].

A combination of major and minor criteria is essential for the correct diagnosis of encephalitis. Encephalitis is defined by presentation with altered mental status lasting more than 24 hours, with at least 3 of the following associated manifestations: (i) fever ≥38°C within 72 hours before or after the presentation, (ii) seizures not attributable to a preexisting seizure disorder, (iii) new onset of focal neurologic findings, (iv) white blood cell count ≥5/mm3 in cerebrospinal fluid, (v) new or acute onset neuroimaging abnormalities consistent with encephalitis, and (vi) EEG abnormality [1].

2. Materials and Methods

Study Design

This is a retrospective, descriptive study.

Data collection

We reviewed the charts and recorded the demographics, clinical presentation, physical examination, laboratory, and imaging test results of patients diagnosed with encephalitis, hospitalized and treated in the Service of Pediatrics at Mother Teresa University Hospital Center, Tirana, Albania.

Inclusion/exclusion criteria
Patients were included in our study if they: (i) satisfied the diagnostic criteria of acute encephalitis and were admitted to the service of pediatrics between May 2018 and July 2019, (ii) were from 1 month to 14 years old, (iii) did not have encephalopathy secondary to sepsis, toxins, or metabolic disorders.

3. Results

We identified 12 patients (9 boys and 3 girls) with a median age of 4 years (range 1 to 12 years) who fulfilled the criteria during the study period. Based on the final diagnosis, the patients were categorized into 3 groups: infectious encephalitis, immune-mediated encephalitis, and encephalitis of non-identified origin. Etiologies included: (i) infectious encephalitis (n=5): herpes simplex virus type 1 (n=3), varicella-zoster virus (n=1), human herpes virus 6 (n=1); (ii) immune-mediated encephalitis (n=3): acute disseminated encephalomyelitis (n=1), anti-N-methyl-D-aspartate receptor antibody encephalitis (n=1), anti-glutamic acid decarboxylase antibody encephalitis (n=1); and (iii) encephalitis of non-identified origin (n=4) (Table 1).

Clinical, laboratory, and imaging findings. All of our patients showed altered mental status, seizures were present in 8 patients, cognitive impairment was present in 4 patients, behavioral changes were present in 11 patients, psychiatric symptoms were present in 2 patients, cutan signs were present in 1 patient, gastro-intestinal sign was present in 4 patients, motor deficits were present in 3 patients, and other non-specific symptoms were present in 10 patients. Detailed information on the clinical findings of these 3 groups is presented in Table 2. Blood and cerebrospinal fluid (CSF) examinations as well as electroencephalography (EEG) were performed on all the children at presentation and during the hospitalization period. Blood, CSF and EEG findings at presentation are detailed in Table 2. All of our patients underwent radiologic examination by either computed tomography (CT) or magnetic resonance imaging (MRI) scan. Radiologic findings are presented in Table 2.

Diagnosis and treatment. In patients with viral encephalitis, the presence of the virus was detected by polymerase chain reaction (PCR) of CSF. ADEM diagnosis was confirmed by MRI, anti-NMDAR, and anti-GAD encephalitides diagnoses were confirmed by enzyme-linked immunosorbent assay (ELISA) which detected the presence of autoantibodies in the serum. All patients underwent the first-line treatment, to which only 9 were responsive. The 3 others underwent then the second-line treatment.

Outcome. Throughout the hospitalization period, laboratory and imaging examinations were applied to all patients. In all cases, clinical improvement was evidenced. The mortality was zero, whereas the morbidity should be estimated in longer terms.

Table 1: Demographics and etiologies

Sex	
female	3/12 patients
male	9/12 patients
Age intervals	
<1 year	0/12 patients
1-5 years	7/12 patients
6-10 years	4/12 patients
11-14 years	1/12 patient
Age mode	2 years
Median	4 years
Age range	1-12 years
Etiology of encephalitis	
(i) Infectious	5/12 patients
HSV-1	3/5 patients
VZV	1/5 patient
HHV-6	1/5 patients
(ii) Immune-mediated encephalitis	3/12 patients
ADEM	1/3 patient
anti-NMDAR	1/3 patient
anti-GAD	1/3 patient
(iii) Non-identified origin	4/12 patients

ADEM, acute disseminated encephalomyelitis;**HHV-6**, human herpesvirus 6; **GAD**, glutamic acid decarboxylase; **HSV-1**, herpes simplex virus type 1; **NMDAR**, N-methyl-D-aspartate receptor; **VZV**, varicella-zoster virus

4. Discussion

In Western countries, herpes simplex virus type 1 (HSV-1), an α-herpesvirus of the Herpesviridae family [6], is the most prevalent cause of acute viral encephalitis [7]. The second most frequent etiology of viral encephalitis is varicella-zoster virus (VZV) [8], an α-herpesvirus of the same family as HSV-1, known as the virus of varicella or "chickenpox" and herpes zoster [9]. In children, VZV encephalitis commonly occurs concurrently with varicella or its immunization, or as a subacute complication. It might, however, occur as a reactivation of a previous infection [10]. Another viral pathogen known for affecting the nervous system is human herpesvirus 6 (HHV-6), a β-herpesvirus of the Herpesviridae family, widely known as one of the causative pathogens of roseola infantum and exanthema subitum in children [11]. The majority of primary infections are asymptomatic, and by the age of two, more than 90% of the general population is seropositive for HHV-6. The virus then becomes latent in the body [12].

Concurrently, one of the most common types of autoimmune encephalitis is that associated to anti-N-methyl-D-aspartate receptor (NMDAR) antibodies. NMDA receptor channel is the most distinct subtype of glutamate receptors, which plays a critical role in the regulation of neuronal communication and synaptic function in the central nervous system [13]. Acute disseminated encephalomyelitis (ADEM) is another immune-mediated inflammatory demyelinating disease of the central nervous system which happens to occur after a viral, mainly exanthematous disease (such as varicella, measles, rubella) or vaccination [14].

Table 2: Summary of clinical, laboratory and imaging data

No./ age/ sex	Group	Etiology	Clinical findings	Blood tests	CSL test	EEG	MRI
1/1/M	1	HHV-6	disorientation, fever, seizures, skin rash, colic, vomiting	mild thrombocytopenia, mild elevation of glucose, elevated ESR.	mild pleocytosis, normal glucose, normal proteins	slow beta waves	T2-hyperintensities in frontal and temporal lobes.
2/2/M	3	unknown	fever, weakness, seizures, nuchal rigidity, disorientation, altered behavior	non-significant	non-significant	unremarkable	unremarkable
3/2/M	1	HSV-1	fever, weakness, seizures, altered mental status and behavior, fatigue, headache	non-significant	normal glucose, mild elevation of proteins and cell count	slow beta waves	hyperintense areas on the T2-weighted image located at fronto-temporal lobes
4/2/F	1	HSV-1	fever, weakness, seizures, altered mental status and behavior, vomiting	non-significant	normal glucose, elevation of proteins and cell count	slow beta waves	hyperintense areas on the T2-weighted image located at fronto-temporal lobes
5/2/M	3	unknown	fever, weakness, nuchal rigidity, disorientation, altered behavior, lack of concentration	mild thrombocytopenia, mild elevation of glucose, ESR elevated.	mild pleocytosis, normal glucose, normal proteins	slow beta waves	unremarkable
6/4/M	3	unknown	fever, headache, general weakness, disorientation, agitation, lack of concentration, hallucinations, ataxia, vomiting	non-significant	non-significant	unremarkable	T2-hyperintensities in both parietal lobes
7/4/M	1	HSV-1	fever, headache, general weakness, seizures, altered mental status and behavior, aphasia, vomiting.	non-significant	normal glucose, elevated proteins and cell count	epileptiform discharges	hyperintense areas on the T2-weighted image located at fronto-temporal lobes
8/6/M	1	VZV	high temperature, headache, general weakness, seizures, altered mental status and behavior, no vesicular rash or seizures.	mild leukocytosis, mild elevation of glucose	mild elevation of glucose, proteins and cell count	unremarkable	unremarkable
9/6/M	3	unknown	disorientation, agitation, hallucinations, lack of concentration, ataxia, memory impairment	non-significant	mild elevation of glucose, proteins and cell count	slow beta waves	unremarkable
10/7/F	2	ADEM	fever, weakness, headache, seizures, nuchal rigidity, altered mental status, and behavior	mild leukocytosis, CRP elevated	elevated cell count, elevated proteins normal glucose	epileptiform discharges	subcortical regions of high signal, with surrounding mild edema
11/8/F	3	anti-GAD	headache, disorientation, agitation, emotional liability, lack of concentration, memory impairment, aphasia, vomiting	mild leukocytosis, mild elevation of glucose	minimal pleocytosis, normal glucose, normal proteins	slow right frontotemporal alpha waves	unremarkable
12/12/M	2	anti-NMDAR	fever, weakness, headache, seizures, nuchal rigidity, alteration of mental status, and behavior.	leukocytosis, CRP elevated	elevated cell count, elevated proteins, normal glucose	epileptiform discharges	unremarkable

ADEM, acute disseminated encephalomyelitis; **CRP**, C-reactive protein; **CSL**, cerebrospinal liquid; **EEG**, electroencephalogram; **ESR**, erythosedimentation rate; **F**, female; **HHV-6**, human herpesvirus 6; **HSV-1**, herpes simplex virus type 1; **M**, male; **NMDAR**, N-methyl-D-aspartate receptor; **VZV**, varicella-zoster virus

5. Conclusion

Encephalitides present a variety of issues for pediatric neurologists. To begin with, there is clinical presentation variability not only across various forms of encephalitides but also among the same type in different pediatric patients. Furthermore, children often display atypical clinical forms of encephalitis such as presenting only psychiatric symptoms in absence of signs and symptoms of neuroinflammation. Viral etiologies are among the primary considerations in establishing a diagnosis, with HSV-1 being the most prevalent pathogen. Autoimmune etiologies should not be underestimated. Early diagnosis is an important key in reducing the risk of sequelae.

Acknowledgements
All-included patients' parents had signed a general informed consent form allowing their medical records to be used for research purposes.

Declarations
Funding: No funding declared.
Conflict of interest: No conflict of interest declared.

References

[1] Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, Stahl JP, Mailles A, Drebot M, Rupprecht CE, Yoder J. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clinical Infectious Diseases. 2013;57(8):1114-28.
[2] Wang H, Zhao S, Wang S, Zheng Y, Wang S, Chen H, Pang J, Ma J, Yang X, Chen Y. Global magnitude of encephalitis burden and its evolving pattern over the past 30 years. Journal of Infection. 2022;84(6):777-87.
[3] Hasbun R, editor. Meningitis and encephalitis: Management and prevention challenges. Cham: Springer International Publishing; 2018.
[4] Erickson TA, Muscal E, Munoz FM, et al. Infectious and Autoimmune Causes of Encephalitis in Children. Pediatrics. 2020;145(6):e20192543
[5] Types of Autoimmune Encephalitis [Internet]. Aealliance.org. Available from: https://aealliance.org/types-of-autoimmune-encephalitis/
[6] Arduino PG, Porter SR. Herpes Simplex Virus Type 1 infection: overview on relevant clinico-pathological features. Journal of oral pathology & medicine. 2008;37(2):107-21.
[7] De Tiège X, Rozenberg F, Héron B. The spectrum of herpes simplex encephalitis in children. European journal of paediatric neurology. 2008;12(2):72-81.
[8] Grahn A, Studahl M. Varicella-zoster virus infections of the central nervous system–Prognosis, diagnostics and treatment. Journal of Infection. 2015;71(3):281-93.
[9] Pergam SA, Limaye AP, AST Infectious Diseases Community of Practice. Varicella zoster virus (VZV). American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2009;9(Suppl 4):S108.
[10] Costa BK, Sato DK. Viral encephalitis: a practical review on diagnostic approach and treatment. Jornal de Pediatria. 2020;96:12-9.
[11] Yamanishi K, Shiraki K, Kondo T, Okuno T, Takahashi M, Asano Y, Kurata T. Identification of human herpesvirus-6 as a causal agent for exanthem subitum. The Lancet. 1988;331(8594):1065-7.
[12] Kimberlin DW, Whitley RJ. Human herpesvirus-6: neurologic implications of a newly-described viral pathogen. Journal of neurovirology. 1998 Jan 1;4(5):474-85.
[13] Köhr G. NMDA receptor function: subunit composition versus spatial distribution. Cell and tissue research. 2006;326(2):439-46.
[14] Wender M. Acute disseminated encephalomyelitis (ADEM). Journal of neuroimmunology. 2011;231(1-2):92-9.