Invited review

Approach to recurrent Herpes Simplex Encephalitis in children

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A B S T R A C T
Herpes Simplex Encephalitis (HSE) is one of the commonest viral encephalitis and its recurrence is being increasingly reported were HSE relapse rate came up to 5%. Both herpes simplex virus (HSV) types can lead to encephalitis and it was established that HSV-1 is capable of nervous system invasion, latency, and recurrence. The recurrence of HSE used to be attributed to immunological compromise, but reports show many cases have no obvious immune system impairment. Further investigations revealed genetic predispositions to HSV infection that would explain the host vulnerability to its recurrence. In this review, we discuss the gene mutations that may predispose to recurrent HSE and the importance of early diagnosis and treatment.

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1. Introduction

Herpes simplex virus 1 (HSV-1) encephalitis (HSE) in children is a serious but manageable condition, where its outcome is mainly dependent on early diagnosis and immediate initiation of treatment. Despite advances in diagnostic methods and antiviral medications, it remains a high-risk condition with significant morbidity and mortality [1]. Recurrent herpes encephalitis in children is an uncommon illness and reports were found in the literature for both adult and pediatric age groups [2]. Although it is rare, the management of such condition is challenging in the sense of treatment dose and duration where the recent Infectious Diseases Society of America guideline has demonstrated that relapses were not documented in increased dose and prolonged period of treatment with acyclovir up to 20 mg/kg every 8 h for 21 days (IDSA guideline). Even though this treatment modality has been used, still there are reported cases of relapses long time up to 5 years after initial treatment had stopped provided negative PCR on follow-up in one of the reported cases [3]. Other treatment modalities were also used and are discussed in the treatment section. For the recurrence of HSE Table 1 [4–9] demonstrate some reports of HSE recurrence among pediatric population with proven presence of HSV using PCR in both episodes of encephalitis to role out other causes, e.g., post-herpetic autoimmune encephalitis provided the fact that most reports in the literature labeled as recurrence of herpetic encephalitis positive PCR in both or at least one of the episodes. Giving these facts, many researches were conducted to provide explanations on the pathogenesis behind the recurrence of HSV encephalitis in immunocompetent hosts. In this study, many aspects of recurrent HSE are explained, and approach is provided so that an optimal management plan can be recommended for children with recurrent HSE.

2. Epidemiology

Herpes simplex encephalitis (HSE) annual incidence is 1 in every 250–500 thousand in the developed countries which makes it the
most common virus to cause encephalitis. Encephalitis caused by HSV-1 accounts for most of the cases, and it typically affects older children [10]. There is a peak of incidence in early childhood, which does not reflect the age at primary infection [11]. In the United States, the incidence of viral encephalitis, in general, is 20,000 per year and roughly up to 20% of them are caused by HSV-1, and one in every three patients is a child. It used to be known that HSV-2 is an etiological agent in genital herpes and neonatal cases of herpes encephalitis, but recent studies indicate that both HSV-1 and HSV-2 are capable of causing oral and genital herpes where in regard to herpetic encephalitis HSV-1 is the major cause, but still there are some reports link HSV-2 to cause encephalitis in up to 10% of cases mainly in immunocompromised hosts and neonates [10,12,13]. A large study included 4871 hospital admissions of all age groups in the United States admitted under the diagnosis of herpetic encephalitis revealed that mortality rate among neonates and adults were higher than older children [14]. Recurrence of HSE is uncommon, but relapse rate up to 5% was reported. (IDSA).

3. Virology and pathogenesis

Herpes simplex virus (HSV) also known as human herpesvirus (HHV) is a double-stranded DNA enveloped virus member of the Herpesviridae family generally categorized into two types HSV-1 and HSV-2. Other members of the family include varicella zoster virus (HHV-3), Epstein–Barr virus (HHV-4), cytomegalovirus (HHV-5), HHV-6, HHV-7, and HHV-8. Both HSV type 1 and 2 viruses are capable of invading human central nervous system and can replicate in the neuronal cells a phenomenon known as neurovirulence [15]. For infection to occur an exposed site of damaged skin (e.g. abrasion) or mucosal surface must come in contact with the virus, then replication of the virus is initiated at the site of primary infection followed by retrograde transport of viral parts toward neural ganglion (dorsal root ganglia) [16]. The pathogenesis of HSV is mainly dependent upon host immune response toward the infection and the mechanism in which HSV invade the brain is still not very well explained, but the established latency of HSV in the trigeminal ganglia where colonized ganglia after a stimulus leads to viral reactivation and appearing as mucocutaneous vesicles and ulcers might give a good explanation to HSE predilection to the frontotemporal lobes by retrograde transport into the CNS through trigeminal or olfactory cranial nerves [17], HSE of the forebrain is caused by viral migration through the olfactory bulb, whereas HSE of the brainstem is caused by migration via the trigeminal nerve [18].

4. Genetic predisposition

Most primary immunodeficiencies compromise host immunity to be susceptible for most infections, and some may predispose to certain pathogens due to defect in specific immune pathway involved in particular pathogens (e.g. IL-12/IFN gamma deficiency vulnerability to mycobacterial and salmonella infections) [19]. These immunodeficiencies can come in familial and sporadic forms which makes their screening and diagnosis challenging. Herpetic encephalitis in children is involved in some of these primary immunodeficiencies, and mainly due to defects antiviral respond by cellular interferon, but these defects usually predispose to broad infectious susceptibility and other clinical (or immunological) manifestations [20,21]. Lately many reports found in the literature indicating recurrent HSE in the absence of an underlying immunodeficiency and it usually attributed to latent viral reactivation. Recent studies were published indicating single or multiple gene mutations that linked to increased host susceptibility to HSE and its recurrence in some of the cases without compromising immunity to other pathogens (examples found in Table 2 [21–33]). Toll-like receptor 3 (TLR3) pathway defect account for almost 5% of all HSE cases [22]. Most gene mutations found in HSE cases are leading to a defect in interferon-mediated immunity mainly IFN-α/β and λ [23,34]. These genetic etiologies disrupt cell-autonomous immunity in neurons and oligodendrocytes [35]. An observational study was published in 2010 by Abel et al. involved total of 85 children with HSE concluded a high rate of consanguinity (14%) and some were compatible with Mendelian genetic origin of HSV-1 to cause HSE [11]. HSE of the brainstem was recently shown in a multiplex kindred to be caused by mutations in DBR1, which is the RNA lariat debranching enzyme [18]. Interestingly, other viral infections of the brainstem can also be caused by DBR1 mutations. The genetic etiologies of HSE of the forebrain are mainly due to TLR3-IFN-α/β and their receptor in STAT1 pathways which their mutation would lead to HSE susceptibility of the frontal and temporal lobes of the forebrain.

5. Clinical presentation

In the review of reports found to meet our criteria, the common clinical presentations were abnormal movements/seizure, fever, and altered level of consciousness. Duration of recurrence in majority of the cases varies from 2 weeks up to 1 year and longer durations have been reported. The recurrence has been reported in 50% of pediatric cases with HSE proven by positive PCR for HSV in both episodes while the patients were on Acyclovir. Neurological surgery and treatment with corticotropin for infantile spasms have been reported in patients with recurrent HSE. HSE is strictly limited to the central nervous system. The virus does not disseminate to other tissues or even the bloodstream. Patients with HSE almost never suffer from herpes labialis, not only during HSE but also prior to and after HSE. This reflects the occurrence of HSE during primary infection and its mechanism involving an impairment of CNS-intrinsic immunity. Moreover, the lack of herpes labialis might

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**Table 1**

Relapsing HSE case reports and their management with proven recurrence in all episodes of HSE by positive PCR for HSV [4–9].

| Age      | Gender | Type of HSV | antiviral/s used | Treatment duration | Outcome                  | Author and reported time |
|----------|--------|-------------|------------------|-------------------|--------------------------|--------------------------|
| 17 months| Not reported | HSV-1 | Acyclovir | 38 days | Death | Carpenter et al., 1995 [4] |
| 8 months | Not reported | HSV-1 | Acyclovir | 15 days | Severe impairment | Kimura et al., 1992 [5] |
| 4 months | Male | HSV-1 | Acyclovir | Not specifically reported | Severe sequelae | Ito et al., 2000 [6] |
| 5 years | Female | HSV-1 | Acyclovir | Not specifically reported | Moderate sequelae | Mandyla et al., 2001 [7] |
| 3 months | Male | HSV-1 | Acyclovir | Not specifically reported | Moderate sequelae | Bonkowsky et al., 2006 [8] |
| 5 years | Female | HSV-1 | Acyclovir | 3 weeks | Language and mental function delay | Mario Arturo Alonso-Vanegas et al., 2016 [9] |
| 11 months | Male | HSV-1 | Acyclovir | 3 weeks | Mild developmental delay |                           |
| 7 months | Girl | HSV-1 | Acyclovir | 6 weeks | Clinical improvement |                           |
| 10 years | Girl | HSV-1 | Acyclovir | 8 weeks | Clinical improvement |                           |
result from the high proportion of T cells specific for HSV1 in these patients (quote Shen-Ying Zhang’s recent paper in Journal of Pediatric Infectious Diseases with the Seattle group) [18].

6. Diagnosis

Lumbar puncture (LP) is crucial for the diagnosis of HSE and should be done for all patients with suspicion for HSE provide no contraindication such as an elevated intracranial pressure. Elevated protein and pleocytosis with predominance of lymphocyte are the commonest finding in HSE. CSF glucose is usually normal although CSF with low glucose In HSE has been reported. CSF RBCs are usually normal if not traumatic LP unless the patient has advance HSE (necrosis) or hemorrhagic encephalitis which will increase RBCs in CSF. Normal CSF values has been reported in HSE 5−10%. If HSE highly suspected and the initial CSF result is negative, it is advisable to repeat LP [13,36,37]. The gold standard test for diagnosis of HSE is HSV DNA PCR which is highly sensitive and specific (reach up to 96% in both). HSV DNA PCR can yield negative result if the patient is on suppressive oral antiviral. HSV antibody in CSF is not helpful for early diagnosis, but it helps in retrospective HSE identification. HSV viral culture in CSF is rarely positive [38–40]. The neuroimaging of choice for HSE diagnosis is MRI brain which is more sensitive and specific than CT scan. Edema, hemorrhage, and necrosis in the inferomedial temporal lobe is the common finding in HSE. The brain involvement could be unilateral or bilateral. EEG finding is abnormal in the majority of patient. Periodic lateralization epileptiform discharge is characteristic for HSE. Worsening bilateral abnormality with slow wave activity and recurrent periodic complexes are seen in recurrent HSE [3,41,42].

7. Treatment

High index of suspicion, early diagnosis and prompt start of antiviral pending diagnosis confirmation is crucial. Intravenous Acyclovir is the mainstay of treatment in addition to supportive management and good hydration. The current recommended dose is 45 mg/kg per day in 3 divided doses in children and 60 mg/kg per day in 3 divided doses for neonate. Acyclovir resistant to HSV which mostly due to mutation of the viral thymidine-kinase gene is rare in immunocompetent patient. Foscarnet is an alternative antiviral for the treatment of acyclovir-resistant HSV. There is controversy about adjunct corticosteroids therapy for HSE, and it is not routinely recommended, it may be indicated in HSE complicated by vasoergic brain edema. The role of suppressive oral antiviral is not clear and need further study in patients with recurrent HSE. However, there is reported relapsed cases while they are receiving oral acyclovir prophylaxis. [2,7,43,44]. In the future, it is tempting to speculate that additional recombinant IFN-alpha might help some children, especially those whose genetic lesion disrupts the production of endogenous IFNs in the CNS. Clinical trials are warranted to test this hypothesis.

8. Conclusion

HSV Encephalitis is a life-threatening condition and associated with high rates of morbidity and mortality. HSV is a well-known virus to establish human latency, and some case reports has linked its reactivation to encephalitis recurrence. Recurrent HSE has been associated with certain gene mutations such as IKBKG (NEMO) and STAT1. As early diagnosis is challenging, rapid empirical initiation of Acyclovir as soon as possible will play a major role in preventing devastating complications. To date, there is no strong recommendation to use oral suppressive antivirals to prevent HSV recurrence. Screening for known mutations that might predispose to HSV recurrence could help in early diagnosis and initiation of treatment of recurrent herpetic encephalitis and for future family counseling.

References

[1] Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret’s. Clin Infect Dis 2004;11:57–64. Suppl 2(2).
[2] Valencia I, Miles DK, Melvin J, Khurana D, Kothare S, Hardison H, et al. Relapse of herpes encephalitis after acyclovir therapy: report of two new cases and review of the literature. Neuropediatrics 2004 Nov;35(6):371–6.
[3] M.Salih MA, El Khashab HY, Hassan HH, Kentab AJ, Al Subaei SS, Zeidan RM, et al. A study on herpes simplex encephalitis in 18 children, including 3 relapses. Open Pediatr Med J 2009 Jul 13;3(1):48–57.
[4] Barthez-Carpentier M-A, Rozenberg F, Dussaix E, Lebon P, Goudeau A, Billard C, et al. Relapse of herpes simplex encephalitis. J Child Neurol 1995 Sep 2;10(5):363–7.
[5] Kimura H, Aso K, Kuzushima K, Hanada N, Shibata M, Morishima T. Relapse of herpes simplex encephalitis in children. Pediatrics 1992 May;89(5 Pt 1): 891–4.
[6] Ito Y, Kimura H, Yabuta Y, Ando Y, Murakami T, Shiomizu M, et al. Excacerbation of herpes simplex encephalitis after successful treatment with acyclovir. Clin Infect Dis 2000;30(1):185–7.
[7] Mandyala H, Atagnostakis D, Koutsouvitis P, Siahosidou T, Yourokoudos S. Late recurrence of herpes simplex virus meningoencephalitis in two infants. Eur J Pediatr 2001 Dec 18;160(12):732–5.
[8] Bonkowsky JL. Herpes simplex virus central nervous system relapse during treatment of infantile spasms with corticosteroids. Pediatr Neurosurg 2001;34(2):75–8.
[9] Alonso-Vanegas MA, Quintero-López E, Martínez-Albarrán AA, Moreira-Holgain JC. Recurrent herpes simplex virus encephalitis after neurologic surgery. World Neurosurg 2016 May;89:731. e1–5.
[10] Kneen R, Michael BD, Menson E, Mehta B, Easton A, Hemingway C, et al. Management of suspected viral encephalitis in children - association of british neurologists and british paediatric allergy, immunology and infection group national guidelines. J Infect 2012;64(5):449–77.
Abel L, Plancoulaine S, Jouanguy E, Zhang SY, Mahfoufi N, Nicolas N, et al. Age-dependent mendelian predisposition to herpes simplex virus type 1 encephalitis in childhood. J Pediatr 2010;157(4).

Fisahn C, Tkachenko L, Moisi M, Rostad S, Umem R, Zwillman ME, et al. Herpes simplex encephalitis of the parietal lobe: a rare presentation. A case report. Cureus 2016;8(9).

Whitley RJ, Kimberlin DW. Herpes simplex: encephalitis children and adolescents. Semin Pediatr Infect Dis 2005 Jan;16(1):17–23.

Modi S, Mahajan A, Bhaveya D, Varelas P, Mitias P. Burden of herpes simplex virus encephalitis in the United States. J Neurol 2017;264(6):1204–8.

Whitley R, Kimberlin DW, Prober CG. Pathogenesis and disease [internet].

Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, et al. TLR3 deficiency in patients with herpes simplex encephalitis. J Exp Med 2010 Sep 24;213(3):400–11.

Modi S, Jouanguy E, Ou Y-H, Lorenzo L, Klaudel-Dreszl M, Pauwels E, et al. Heterozygous TRK1 mutations impair TLR3 immunity and underlie herpes simplex encephalitis of childhood. J Exp Med 2012 Aug 27;209(9):1567–82.

Andersen LI, Mark N, Reinert LS, Kofod-Olsen E, Narita R, Jørgensen SE, et al. Functional IRF3 deficiency in a patient with herpes simplex encephalitis. J Exp Med 2015 Aug 24;212(9):1371–9.

Zhang SY, Jouanguy E, Al-Hajjar S, Fiesschi C, Al-Mohsen IZ, Al-Jumaah S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 2003 Mar;33(3):388–91.

Chappier A, Wynn RF, Jouanguy E, Filipe-Santos O, Zhang S, Feinberg J, et al. Human complete Stat-1 deficiency is associated with defective type I and II IFN responses in vitro but immunity to some low virulence viruses in vivo. J Immunol 2006 Apr 15;176(8):5078–83.

Sancho-Shimizu V, Perez de Diego R, Lorenzo L, Hohwani R, Alangari A, Israelsson E, et al. Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF deficiency. J Clin Invest 2011 Dec 1;121(12):4889–902.

Zhang S, Chappier A, Yang K, Bustamante J, Puel A, Picard C, et al. Inborn errors of RNA lariat metabolism in humans with brainstem viral infection. Cell 2018 Feb;172(5):952–65, e18.

Rosenzweig SD, Holland SM. Defects in the interferon-gamma and interleukin-12 pathways. Immunol Rev 2005 Feb;203(1):38–49.

Modi S, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, et al. TLR3 deficiency leads to impaired CD40-dependent IL-12 production. J Exp Med 2006 Jul 10;203(7):1151–60.

Picard C, et al. Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. Immunity 2010 Sep 24;33(3):400–11.

Herren M, Ciancaneli M, Ou Y-H, Lorenzo L, Klaudel-Dreszl M, Pauwels E, et al. Heterozygous TRK1 mutations impair TLR3 immunity and underlie herpes simplex encephalitis of childhood. J Exp Med 2012 Aug 27;209(9):1567–82.

Andersen LI, Mark N, Reinert LS, Kofod-Olsen E, Narita R, Jørgensen SE, et al. Functional IRF3 deficiency in a patient with herpes simplex encephalitis. J Exp Med 2015 Aug 24;212(9):1371–9.

Dupuis S, Jouanguy E, Al-Hajjar S, Fiesschi C, Al-Mohsen IZ, Al-Jumaah S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 2003 Mar;33(3):388–91.

Chappier A, Wynn RF, Jouanguy E, Filipe-Santos O, Zhang S, Feinberg J, et al. Human complete Stat-1 deficiency is associated with defective type I and II IFN responses in vitro but immunity to some low virulence viruses in vivo. J Immunol 2006 Apr 15;176(8):5078–83.

Sancho-Shimizu V, Pérez de Diego R, Lorenzo L, Hohwani R, Alangari A, Israelsson E, et al. Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF deficiency. J Clin Invest 2011 Dec 1;121(12):4889–902.

Zhang S, Chappier A, Yang K, Bustamante J, Puel A, Picard C, et al. Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-a/b, IFN-g, and IFN-I in host defense. Immunol Rev 2008;226:29–40.

Lafaille FG, Pessach IM, Zhang S-Y, Ciancaneli MJ, Herman M, Abhyankar A, et al. Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. Nature 2012 Nov 29;491(7426):769–73.

Mook-Kanamori B, Van De Beek D, Wijdicks EFM. Herpes simplex encephalitis with normal initial cerebrospina I fluid examination. J Am Geriatr Soc 2009 Aug;57(8):1514–5.

Davis R, Jeffery K, Atkins BL. Hypoglycemia in herpes simplex encephalitis. Clin Infect Dis 2004 May 15;38(10):1506–7.

Binnicker MJ, Espy MJ, Irish CL. Rapid and direct detection of herpes simplex virus in cerebrospinal fluid by use of a commercial real-time PCR assay. J Clin Microbiol 2014 Dec 1;52(12):4361–2.

Bhullar SS, Chandak NH, Babetti NN, Paribot HJ, Tao GM, Daginawala HF, et al. Diagnosis of herpes simplex encephalitis by ELISA using antipeptide antibodies against type-common epitopes of glycoprotein B of herpes simplex viruses. J Immunasssay Immunochem 2016 May 3;37(3):217–27.

Gaunt JW, Whitley RJ. Herpes simplex encephalitis: an update. Curr Infect Dis Rep 2017 Mar 1;19(3):13.

Takemura AM, Horiuchi K, Kaji T, Kohyama S, Sakata I, Kusano S. MRI findings of recurrent herpes simplex encephalitis in an infant. Pediatr Radiol 2003 Dec;33(11):811–17.