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Review Article

Neonatal Herpes Simplex Infection

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Maternal genital herpes is a sexually transmitted infection; asymptomatic in 70% of cases. Newborn babies usually catch the infection from maternal birth tract during delivery. Neonatal herpes simplex infection is a highly morbid and fatal dreadful infection. Though there have been great advances in diagnosis and management of this neonatal infection in last 3 decades, its morbidity continues to be high due to greater lag-time between symptoms and diagnosis. This delay is due to its non-specific presentation and lack of adequate awareness about the disease amongst the practising physicians. A high level of clinical suspicion is vital for early treatment initiation and better outcomes. Maternal education on safe sex practices, selective and elective caesarean surgery and prophylactic acyclovir for recurrent maternal herpes would diminish transmission and disease in newborn.

1. Introduction

Herpes (Greek for "creeping") is viral infection caused by herpes simplex virus type 1 or type 2 (HSV-1 or 2). Batignani first described herpetic infection in an infant with isolated ker ato-conjunctivitis [1]. Herpes can affect a newborn either through vertical transmission before or during labour, or due to direct contact with infected secretions from a patient in immediate postnatal period [2–4]. Its incidence varies widely worldwide from as low as 1 : 3200 births in USA to 1 : 60000 births in UK [4, 5]. The incidence has risen progressively in the past four decades [6]. Risk factors for neonatal herpes infection include prematurity, instrumentation (e.g., scalp electrodes), and presence of maternal primary genital herpes of cervix during delivery [7, 8]. If left untreated, it has a fatality rate of around 60% with poor neurologic outcomes in three-quarters of survivors [2, 5, 7, 9, 10]. Prompt antiviral therapy can avert a number of these deaths and minimise CNS damage [11]. But nonspecific presentation of this infection usually delays diagnosis [2]. An enhanced awareness amongst treating physicians about this serious neonatal illness could aid early pickup and treatment with improved outcomes.

2. Epidemiology

Genital herpes is a viral sexually transmitted infection caused by HSV-2 virus and rarely by HSV-1 virus [12]. 45 million people above 12 years in USA are infected with genital herpes, with 1.5 million new cases being diagnosed each year [13]. 5% of women in reproductive age give history of genital herpes. 2% of women acquire first infection during pregnancy. In majority, infection is asymptomatic and subclinical [14]. Less than 30% of them have circulating antibodies to HSV-2 virus. Less than 1/4th with positive serology are symptomatic [15]. Neonatal transmission rate is more than 40% with primary genital herpes infection in mother. In mothers with recurrent herpes and positive serology for HSV-2 virus, the transmission risk drops to 3%. Children born to mothers with first nonprimary infection have an intermediate risk [16–18]. Presence of specific HSV-1 antibodies does not protect against neonatal transmission [19]. Around 1500–2000 cases of neonatal herpes are diagnosed each year. Regional differences are noticed in prevalence of newborns with HSV-1 or HSV-2 types of infection [2, 6, 20].

3. Etiology

Herpes simplex virus is a neurotropic double-stranded DNA virus which belongs to Alphaherpesvirinae, a subfamily of Herpesviridae family [9]. It was taxonomized as herpes hominis virus in 1953 but somehow this name has not gained much general acceptance in the literature or practice [21]. The herpes simplex virus is of 2 types; HSV-1 and HSV-2. HSV-1 is responsible for most of orofacial lesions but it could also rarely cause genital disease. HSV-2 causes genital herpes infection. Both types have a roughly spherical central "core" of 750 Å diameter containing linear double-stranded DNA. Surrounding this core is the stable icosahedral capsid comprising of 162 capsomeres. Envelopes derived from host membrane encompass the capsid bringing the particle size to 1450–2000 Å. Some particles are "full" and complete; others are "empty" (without the core) while some are "naked" (with no envelope) [21]. The virus is neurovirulent. It propagates in neural tissue and has tendency towards latency. With physical and emotional stress, these dormant virions can get activated and cause disease [21].

4. Pathogenesis

Neonatal herpes is devastating to an infant. Most infection is acquired during intrapartum period. Some are caught *in utero* (congenital HSV) or postnatally through contact with oral or skin lesions. The latter may be from mother, adults including nursery personnel, or other babies [22]. Congenital HSV comprises 4% of neonatal herpes cases and is characterized by microcephaly, hydrocephalus, chorioretinitis, skin lesions, and visceral involvement [2]. Transplacental transmission or ascending infection from vagina or cervix either through intact amniotic membrane or due to leaks and reseals causes the infection. Histopathological examination of placenta can differentiate between these two modes of transmission [3]. Isolated cases have been reported in literature where herpes infection had spread from an infected breast lesion, HSV-1 infected breast milk and after traditional Jewish ritual of circumcision from the mouth sores of the infected *mohel* [23–26].

Skin and mucosal vesicular lesions are seen with neonatal herpes infection. There is viremia and since the virus has an affinity for the neural tissue, CNS involvement is an important component of the infection. Eye, liver, lungs, kidneys, adrenal glands, and so forth may be involved with formation of multinucleated giant cells or intranuclear inclusions in affected tissues.

5. Clinical Features

Early maternal genital infection leads to foetal wastage. Intrauterine growth retardation or prematurity often accompany maternal infection in late pregnancy. Newborns with congenital HSV infection have microcephaly, hydrocephalus, microphthalmia, chorioretinitis, intracranial calcifications, and vesicular mucocutaneous lesions. Infections acquired in antenatal or postnatal period may simulate neonatal sepsis. 33% of them present within 24 hours of birth and 61% in first week of life [9]. Depending on extent of infection, neonatal herpes can be categorised into three types: (1) skin, eye, and mouth (SEM) infections, (2) central nervous system involvement (encephalitis) which can include SEM, and (3) disseminated infection involving multiple organs such as liver, lungs, adrenals, brain, eye, kidneys, and fskin [5]. Non-specific symptoms such as fever or hypothermia, lethargy, poor feeding, and irritability may be seen with or without mucocutaneous lesions [2, 27, 28]. By the time diagnosis is made, many infants have progressed to severe disease and have developed complications. Focal or generalized seizures, hepatitis, pneumonitis, eye inflammations, gastrointestinal, and adrenal involvement may be seen. Dendritic eye ulcers, chorioretinitis, or acute necrotizing retinitis may be seen [27, 29]. Herpes-virus-induced dense congenital cataract of right eye in an 18-month-old infant has been reported in literature [30]. Bleeding diathesis, liver failure, coma, respiratory distress, and shock are usually seen in end-stage severe infections. Localised infections are more likely to be HSV-1 and central or disseminated infections due to HSV-2 virus [20]. Long-term complications such as sfeizures, psychomotor retardation, spasticity, blindness, and learning disabilities are often seen in survivors [2, 27].

6. Diagnosis

Neonatal herpes has a variable presentation and it may simulate other neonatal infective conditions. The treating paediatrician should always consider neonatal herpes in the differential diagnosis in a newborn that is brought with history of lethargy, irritability, fever or hypothermia, and skin vesicles with or without neurologic symptoms. Diagnosis requires a high degree of clinical suspicion especially because maternal history of genital herpes is usually not forthcoming. This should be especially considered when bacterial cultures at 48 hours are negative. Early initiation of specific therapy averts death and minimises neurologic damage [2].

Tzanck smear made from scrapings from skin or mucosal vesicles is a quick office test for confirmation of diagnosis of herpes infection. Wright, Giemsa, or Papanicolaou stained smears show characteristic multinucleated giant cells or intranuclear inclusion bodies. This test is only 60% as sensitive as viral culture, and it also cannot differentiate between herpes simplex virus and varicella-zoster infection [31]. Direct fluorescent-antibody (DFA) technique using mouse monoclonal antibody to detect HSV antigen scores better and has a sensitivity and specificity of 74 and 85%, respectively, when compared with viral culture test [32]. Isolation of virus in tissue culture is current "gold standard" confirmatory test for herpes infection. Blood, cerebrospinal fluid, urine, nasopharynx, eye secretions, and vesicular fluid can be cultured. HSV causes discernible typical cytopathic changes in a variety of cell culture lines and most specimens can be identified within 48–96 hours. The sensitivity of this test is higher in early vesicular stage as compared to ulcerative stage. It is also more sensitive for primary maternal lesions and in immunocompromised patients [33–35]. A negative test means that the virus was not isolated, but it

does not rule out presence of the virus. It may be falsely negative when actively replicating virus is less in sample, or when sample transport has been under suboptimum conditions [36]. HSV DNA analysis by polymerase chain reaction (PCR) is useful in such conditions. It also gives accurate results when sample is taken from an old lesion and from an asymptomatic patient. It is 25% more sensitive than viral isolation by culture. Refrigeration is not required for transport of sample for HSV PCR [37–39]. It has higher yield in herpes encephalitis [40, 41], and can also quantify viral load [42]. Restriction endonuclease analysis of viral DNA allows subtyping of infection into HSV type 1 or HSV type 2 and differentiation of various strains of the subtypes. This is useful for epidemiologic purposes, for prediction of recurrence of the infection, and for identification common source outbreaks of HSV [43, 44]. Detection of antibodies against HSV-1 or HSV-2 in serum has limited usefulness in neonatal herpes. HSV IgM is seen in acute stage. HSV IgG comes up later but its determination may be unable to differentiate maternal transfer of antibody from that produced by newborn due to infection in self. A fourfold rise in HSV IgG titre in acute and convalescent sera proves current infection in baby. Recurrent infection in mother, however, may not show this fourfold rise [43, 45, 46]. Cerebrospinal fluid examination in neonatal herpes with neurologic signs reveals lymphocytic pleocytosis with increased proteins with or without decreased glucose. Viral cultures and PCR for HSV DNA of CSF are usually positive. Infants with SEM have only 24% chance to have positive HSV DNA in their CSF [43]. Persistence of HSV DNA at the end of antiviral treatment is associated with poor prognosis [47]. Computed tomography of brain is found to be abnormal in 67% of infected babies. The abnormalities include parenchymal attenuation abnormalities, parenchymal atrophy, parenchymal contrast enhancement, leptomeningeal contrast enhancement, extra-axial fluid collection, and parenchymal calcifications [48]. MRI brain is quite often abnormal in neonatal herpes. Areas of hyperdensity and hemorrhage characterise CNS herpes. EEG abnormalities are detected in 100% of neonatal HSV encephalitis. These include focal epileptiform discharges, burst suppression, focal electrographic seizures, focal suppression, and diffuse slowing [48]. The unique multifocal or quasiperiodic pattern of HSV encephalitis decreases with early appropriate treatment [49, 50]. Additional tests that may be needed when baby is sick include arterial blood gas analysis, complete blood count, coagulation studies, electrolyte estimation, liver function tests, and kidney function tests [2].

7. Management

All newborns suspected to have or diagnosed with neonatal herpes should be started immediately on an effective and safe antiviral drug. 5-iodo-2-deoxyuridine (idoxuridine, IDU), cytosine arabinoside, adenine arabinoside, and acyclovir have been studied for their role and safety in neonatal herpes. These antiviral drugs inhibit DNA synthesis and hence virion replication. The effect is more marked with early treatment [51]. Herrman found inhibition of herpes simplex virus plaques in cell cultures with IDU [52]. Use of IDU ameliorates herpes symptoms [53–55]. 1-β-D-arabinofuranosyl-cytosine hydrochloride (cytosine arabinoside or CA or ara-C) was studied later and found to aid early recovery in herpes keratitis [56, 57]. In neonatal herpes, cytosine arabinoside is used in dose of 40–160 mg/m^2/day as continuous intravenous infusion for 4–6 days. It can also be used intrathecally in herpes encephalitis [58]. Vidarabine (adenine arabinoside or ara-A) in dosage of 10–20 mg/kg/day as a 12 hour continuous infusion for 10–14 days helped to decrease mortality in CNS and disseminated herpes from 74% to 38%. 50% of infants on vidarabine were normal at 1 year of age compared to 17% in control group [59–61]. Stepping up dosage to 30 mg/kg, however, did not improve survival or decrease morbidity [62]. Acyclovir is current antiviral recommended for neonatal herpes infection. It is more effective, safer, and easier to administer than vidarabine [10, 63]. Suggested dose is 60 mg/kg/day in three divided doses intravenously as 1-hour infusion for 14 days for SEM disease and 21 days for central nervous system or disseminated disease [2]. This high dose significantly improves survival. Also patients on high-dose acyclovir are 6.6 times more likely to be normal at 12 months of age when compared with those on standard dose of 30 mg/kg/day. There may be some transient neutropenia with this high dose but no serious adverse sequelae have been reported [64, 65]. Twice weekly serial absolute neutrophil count (ANC) estimation throughout this high-dose acyclovir course is advised. Decreasing acyclovir dosage or administration of granulocyte colony stimulating factor should be considered if low ANC count is prolonged. Transient renal insufficiency is likely due to crystallisation of acyclovir in renal parenchyma. This can be averted by proper hydration and acyclovir administration slowly over 1 hour [5]. All patients with CNS HSV involvement require repeat lumbar puncture at end of acyclovir therapy to document PCR negativity and end-of-therapy CSF indices. Acyclovir should only be ceased once PCR is negative [43, 66]. HSV elimination from CNS is better with continuous intravenous infusion of acyclovir in neonatal encephalitis [67]. A recent study has also revealed that after the 14/21 parenteral acyclovir therapy, acyclovir suppression at 300 mg/square meter per dose orally three times a day for 6 months causes significant improvement in the neurological outcome in children with CNS disease [68]. Famciclovir and valacyclovir are two newly marketed antiviral drugs. They have better absorption and need less frequent dosing. Though pharmacokinetically superior to acyclovir, they offer no clinical advantage over acyclovir. Controlled studies in children are lacking and hence they are at present not recommended for neonatal HSV infection [5]. Viral resistance to nucleoside analogues have been reported. The duration of disease before antiviral is initiated is significantly correlated with morbidity and mortality [2, 69]. A sick infant may need additional vigorous supportive care in form of intravenous fluids, alimentation, seizure control, coma care, respiratory support, blood transfusions, clotting abnormalities correction, and so forth [5]. Careful hydration and renal function monitoring is vital. Topical antiviral drug

with systemic acyclovir is used for herpetic keratitis. IDU was found to be effective in 80–90% of cases [53, 70, 71]. However, deep-rooted, chronic or resistant infections respond better to topical ara-C, trifluorothymidine, vidarabine, or steroids with IDU [56, 72–76]. Debridement with or without interferon therapy may be needed to hasten healing. Newer antiviral eye drops and ointments for herpes include acyclovir and ganciclovir. Acyclovir cream for skin vesicles is also available. Monthly immunoglobulin therapy decreased recurrence, severity, and duration of lesions in genital herpes [77, 78]. Though not recommended as standard treatment, Whitley extrapolated these findings and proposed HSV human monoclonal antibody or hyperimmune immunoglobulin as concomitant therapy for neonatal-disseminated HSV infection [79]. Production of monoclonal antibodies targeted against glycoprotein B or D of HSV virus is still in experimental stage. When successful, these could be used as adjuvant therapy in neonatal herpes infection [80].

8. Prognosis

Untreated neonatal herpes is associated with high mortality and morbidity. Fatality is high in disseminated and CNS herpes. With treatment, overall mortality has come down drastically and also the number of normal survivors has increased from 30 to 85%. Prognosis depends on disease extent and treatment efficacy. Early diagnosis and initiation of specific therapy improves outcome.

9. Prevention

Efforts directed towards prevention of neonatal herpes are minimally beneficial. Universal screening of mothers during pregnancy with serial viral cultures or type-specific serology has not been shown to be cost-effective. Most mothers with great risk of vertical transmission are in fact asymptomatic. Also, viral shedding is intermittent and weekly cultures may miss significant numbers of viral-shedding mothers. Herpes serology may diagnose mothers with past infection but the transmission rates in them are lower. It is therefore best practice to question mothers during prenatal visits about history of genital herpes in self or their sexual partner. Examine for signs of genital herpes. Educate mothers with recurrent genital herpes on safe sex practices. Risk of neonatal infection from mothers with primary or active genital herpes near term can be minimised with caesarean section. This is useful for up to 4–6 hours after amniotic membrane rupture. Scalp electrodes which increase neonatal transmission risk should be avoided in high-risk cases. Suppressive acyclovir can be tried but decrease in transmission rate is modest [81, 82]. Patients with active HSV mouth or skin ulcers should avoid contact with newborn babies. HSV vaccination trials are ongoing. HSV-2 gD subunit vaccine adjuvanted with alum combined with 3-deacylated monophosphoryl lipid A has demonstrated promising results [83]. A high degree of suspicion of herpes simplex infection in a sick newborn must be maintained. Empiric initiation of antiviral therapy should be considered in suspected cases.

10. Conclusions

To summarise, neonatal herpes simplex infection is a highly morbid and mortal condition. Though survival has improved, neurological disabilities due to it are still high. In spite of many advances at the diagnostic and therapeutic front, this disease continues to scourge newborns due to low index of suspicion and longer diagnostic and treatment lag-time. Hence, what is more vital is to detect and treat the illness early. This can be achieved through enhancing awareness amongst the physicians about the early symptoms and signs of the disease. Also attempts to diminish transmission from mother to child would be highly beneficial.

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