Review article

Indian Journal of Pathology: Research and Practice

Teratogenic Viruses

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Accepted on 29 July 2012

Abstract

Delivery and survival of a malformed baby is a painful challenge, not only for the baby but also for the parents, doctors and the society. Though etiology behind this is largely unknown, however infectious etiologies cannot be ruled out that include viral, parasitic and bacterial. In this review it has been focussed on viral infections in human that are associated with congenital malformation. Human cytomegalovirus, Rubella virus, Varicella-Zoster virus and Herpes-Simplex Virus are among the major culprits. Here different aspects i.e. mechanism behind the malformation, clinical features, laboratory diagnosis , management as well as prophylactic measures that could be taken to prevent them have been summarized with maximum emphasis on the laboratory diagnosis of individual viral agent. As malformation cannot be reverted every effort should be meant to prevent it. This can be done by routine screening of susceptible females who want to conceive or are pregnant.

Key words: *Congenital infection; Teratogenic; Viruses.*

Introduction

Teratogenecity means permanent developmental malformation, either structural or functional that occurs during the embryonic or fetal life.[1] There are several agents responsible for it. Among them majority are due to genetic, drugs, chemicals, infections etc. Approximately 25% of human developmental defects are genetic in origin, 2% - 3% due to drugs and rest 65 % are either unknown or due to combination of genetic and environmental causes.[1] Viruses, bacteria and parasites are among the major infectious agents.

Viral infections in pregnancy which are responsible for teratogenecity are Rubella virus, Human cytomegalovirus (CMV), Varicella Zoster virus (VZV), Herpes-Simplex virus (HSV).[2] Some uncommon viruses associated with teratogenecity are West-Nile virus, Venezuelan Equine Encephalitis virus and Lymphocytic Choriomeningitis virus.[3,4,5,6]

Delivery and survival of a malformed baby is a painful challenge, not only for the baby but also for the parents, doctors and the society. As malformation cannot be reverted every trial should be meant to prevent it. This can be done by routine screening of susceptible females who want to conceive or are pregnant.

Human cytomegalovirus

Human cytomegalovirus (CMV) is a double stranded DNA virus in *Herpesvirideae* family, genus *Cytomegalovirus* and it is the most common viral agent responsible for intrauterine infections.[7] In immunocompetent people it causes an infectious mononucleosis-like syndrome while in immunocompromised its consequences are serious. Besides this it plays a crucial role in susceptible pregnant females, where it causes congenital infection with fetal malformation.

Different serological surveys in different parts of India have shown 80% - 90 % prevalence of

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IgG antibodies in women of child bearing age. Risk of seroconversion during pregnancy is 2% - 2.5 %. Primary infections are transmitted more frequently (15% -50 %) and are more likely to cause fetal damage than recurrent infections (0.15% - 1%). Ninety percent of congenitally infected infants are asymptomatic at birth; 5% - 17 % of these develop sequelae in first 2 years of life. Among 10 % of the symptomatic newborns, 20% die and 90% of the survivors develop severe sequelae.[8]

Fetal transmission

Vertical transmission occurs from mother to fetus by hematogenous route. Primary infection of mother during first trimester results in fetal malformation. The classical tetrad of CMV is mental retardation, cerebral calcifications, microcephaly and chorioretinitis. The mechanisms of these congenital anomalies due to CMV infections are cell death, resultant ischemia from vasculitis. Structural fetal defects are common if infection occurs in the first trimester whereas functional abnormalities (i.e. hepatitis, thrombocytopenia and pneumonia) are common if infection occurs during late gestation.[9]

Laboratory diagnosis

(a) Diagnosis in pregnant females

It is difficult to diagnose CMV infection in antenatal women as it is mostly asymptomatic or subclinical. Hence laboratory testing is required for diagnosis. Since most of the patients have non-specific symptoms and signs, viral isolation, antigen and nucleic acid detection are not practically possible.

Antibody detection in serum is a very simple and practically feasible method. But IgM antibody can appear in both primary and reactivated CMV infections and can persist for extended periods after primary infection. Therefore, it is difficult to say if the infection has been acquired during the pregnancy or before. Also, occasional false positive results may be obtained due to factors like circulating rheumatoid factor or Epstein-Barr virus infections.[10,11] A four-fold rise in IgG antibody titre at 4 to 6 weeks interval is suggestive of a recent or recurrent infection. CMV IgG antibody avidity test is useful in diagnosing primary infection in which IgG antibodies produced have low affinity for the CMV antigens, whereas in reactivation or re-infection the antibodies have high affinity (avidity is expressed as avidity index, i.e. % of IgG bound to its antigens in presence of denaturizing agent, i.e. 6M urea; high avidity means past infections whereas low avidity means recent primary infection).[11] So, to diagnose primary infection, IgM antibody by capture ELISA (as chances of false positive are less compared to indirect ELISA) along with IgG avidity ELISA should be preferred whenever possible.

Blood can be used for viral culture either by conventional tube culture using human fibroblast cells and looking for cytopathic effect (CPE), i.e. enlarged, rounded, retractile cells in one week duration, or by shell vial culture using MRC-5 fibroblast cells which is a rapid assay where early viral antigens are detected by monoclonal antibodies within 24 hours without waiting for CPE.[12]

Viral antigens by pp65 in peripheral blood leukocytes may hasten diagnosis as they are positive earlier than culture.

Polymerase chain reaction (PCR) can also diagnose CMV infection by detecting viral DNA or mRNAs in blood. Based on published literature the most common targets for CMV PCR include glycoprotein B, the immediate early antigen, and US17 followed by pp65 and polymerase genes.[13] Both PCR and viral isolation techniques, however, do not differentiate between primary and recurrent/ reactivated infection. Routine maternal screening for primary CMV infection is not recommended as serial samples have to be taken to exclude seroconversion which is not cost effective.

(b) Fetal diagnosis in pregnant females

Prenatal diagnosis of CMV infection of fetus is best done by analysis of amniotic fluid for CMV DNA by PCR after 21 to 23 weeks of gestation. Hence, amniocentesis should be done after 21 weeks of gestation and at least 4 weeks

after maternal serological diagnosis. A single negative amniotic fluid test does not exclude intrauterine infection and a repeat test should be done 4 to 8 weeks later. Amniotic fluid can be used for viral culture. Ultrasound findings like microcephaly, ventriculomegaly, intracerebral calcifications and IUGR are found in those fetuses which are severely affected.[14]

Fetal blood culture has low sensitivity and hence is not recommended. Since fetus can synthesize IgM antibodies after 20 weeks of gestation, therefore cordocentesis is not justified.[14]

Routine antenatal fetal screening of CMV infection is not recommended as neither does it influence the management nor it is cost effective.

(c) Diagnosis in neonates

Diagnosis of congenital CMV infection in neonates is best done by PCR or viral culture from urine, saliva or cord blood in first 2 weeks of life.[14] Serum can be tested for IgM antibody. Testing saliva or oral fluids for CMV specific antibodies has been suggested as an noninvasive alternative to collection of blood.[15] Neonatal blood collected at birth and dried on paper (Guthrie cards) has been recently described for neonatal screening and for retrospective diagnosis in patients beyond the neonatal period with a clinical suspicion of congenital CMV infection.[15]

Management

Pregnant females with primary infection in first 20 weeks of gestation should be offered medical termination of pregnancy while expected management is done in those who are diagnosed after 20 weeks of gestation.[16] There is no therapy available to prevent the fetal damage, and pregnancy termination is the only alternative expectant management. However, CMV immune or hyperimmune globulin has been reported to prevent congenital CMV infection in infants of women with primary infection during pregnancy. Symptomatic neonates can be treated with Ganciclovir.[17]

Prevention

Infections are acquired by direct, close personal contacts with individuals who are shedding the virus. Hence, prevention of CMV infection in susceptible pregnant females can be done by informing them to remain away from all secretions i,e. urine, stool (pads) of small kids around them along with good personal hygiene giving maximum stress on handwashing. Barrier method of contraception should be encouraged. There is currently no vaccine available, but vaccination trials using CMV surface glycoprotein rather than live attenuated virus are currently being conducted. CMV can remain in latent state in various cells like endothelial cell, leukocytes; therefore, blood transfusion in pregnancy, if required, should be done with seronegative blood.[7]

For prevention of infection, healthcare personnel or daycare workers should be advised to maintain proper hygiene, frequent handwashing and taking universal precautions or change occupation. Hygiene and sanitation instructions can be given to all women irrespective of knowledge of their serostatus.

Rubella virus

It is a single stranded RNA virus that belongs to family *Togoviridae* and genus *Rubivirus*. It causes two types of infections: postnatal rubella (Rubella or German measles or 3-day measles), a mild infection characterized by rash, fever and lymphadenopathy in susceptible children and adults; whereas in susceptible pregnant females, it causes a serious fetal infection called congenital rubella syndrome (CRS) characterized by classical triad cataract, heart defects and deafness. Rubella virus is now recognized as the most potent infectious teratogenic agent yet identified.[18] N. McAlister Gregg an Australian ophthalmologist, first recognized the association between the virus and congenital anomaly i.e. cataracts in children delivered from pregnant females who had maternal rubella during gestation.[19]

Incidence of rubella has decreased over the past years due to advent of rubella vaccine; still, 10 % - 15 % of women in the child bearing age

lack protective antibodies and are susceptible to primary infection.[20]

Fetal transmission and pathogenesis

Hematogenous transmission can occur throughout pregnancy. Maternal rubella may lead to spontaneous abortion and congenital rubella syndrome (CRS) in early pregnancy and stillbirth in late pregnancy.

The fetal consequences relate directly to the gestational age at the time of maternal infection: infection in first 12 weeks of gestation carries 40% - 50 % risk of fetal infection with 100% risk of congenital abnormalities. During 13-16 weeks, risk of fetal infection is 30% - 35 % where deafness and retinopathy is found in 15 % and spontaneous abortion in 20%. Fetal infection after 16 weeks carries only 10% risk of fetal infection with normal development, but slight deafness and retinopathy may be anticipated.[21]

When rubella occurs in first 11 weeks of gestation, there is a high likelihood of birth defects whereas after 18 weeks birth defect is much lower. Congenital rubella virus infection (CRI) refers to infants born with rubella virus infection with or without birth defects. The pathogenesis of CRI leading to congenital rubella syndrome (CRS) is not well understood, but rubella virus infection early in gestation results in an altered immune response to the virus and altered organogenesis. This can be related to the following facts : (a) fetus can't synthesize IgM until about 20 weeks of gestation (b) cell -mediated immunity not developed till late in gestation (c) congenitally infected infants shed virus for long periods, have a slowly developing immune response to the virus and respond to particular rubella virus proteins differently than individuals with postnatal rubella.[18] Other mechanisms of teratogenecity are due to direct cellular destruction causing altered formation or function of developing tissues, blood vessel obliteration with hypoxic damage, chromosomal injury, immunopathologic damage to tissues, formation of antigen-antibody complexes with deposition into certain tissues and interference with cell mitosis. Organogenesis in fetus is affected in CRS cases, since specific organs are abnormal and other apparently normal organs have a reduced number of cells.[21] Reinfection with rubella virus can occur, but viremia is rare; reinfection of pregnant women poses low risk to the fetus.[18]

Laboratory Diagnosis

(a) Diagnosis in pregnant females

As disease caused by rubella virus is mild, many cases of postnatal rubella are subclinical and diagnosis on clinical ground may be difficult. Hence, diagnosis of rubella in mother can be done by serology i.e. ELISA for IgG and IgM antibodies. Demonstration of seroconversion is suggestive of rubella infection, i.e. four fold or greater rise in IgG titres in paired sera samples (acute and convalescent) taken at 2-3 weeks interval. Presence of rubella specific IgM also suggests acute infection. But it can also be positive in Human Parvovirus B-19 infection or even in cases of reinfection.[22,23] IgG avidity testing may help to differentiate recent from remote infection or Human Parvovirus B-19 infection. Therefore, for diagnosis of primary infection, serum IgM antibody should be done by capture IgM ELISA along with IgG avidity ELISA whenever possible. Regarding viral culture, different cell types can be used, i.e. Vero, BHK21, AGMK and RK13 cells but the primary problem encountered is that virus does not produce any CPE. So interference assays may be done by using lytic Enteroviruses i.e. Coxsackievirus A9 However these interference assays are very difficult to maintain, so virus growth from culture can be identified by RT-PCR, IFA, immunocolorimetric assays (ICA) to detect viral RNA or proteins.[24] However viral culture is time consuming, costly and difficult.

(b) Fetal diagnosis in pregnant females

Prenatal diagnosis of congenital rubella can be done by assessing amniotic fluid for RNA, antigen or culture for rubella virus. It may also be diagnosed by presence of specific IgM in fetal blood but this may not be detectable until 22 weeks of gestation.[23,25] Ultrasound can detect cerebral ventriculomegaly, intracranial

calcifications, cardiac malformations and fetal growth retardation and may supplement other tests.

(c) Diagnosis in neonates

Diagnosis of CRS can be done by detection of Rubella specific IgM in serum and postnatal persistence of Rubella specific IgG.[25,26] Viral isolation can be done by culture of urine, blood, stool or swab from pharynx.[25] Imaging studies for periventricular calcifications, leukomalacia or subependymal cystic lesions can be done. Early diagnosis of CRS facilitates appropriate medical intervention for specific disabilities and prompts implementation of infection control measures.

Management

Women coming for pre-conceptional counseling should be tested for rubella for IgG antibody in serum by ELISA. Those who are positive for IgG antibody are supposed to be immune whereas negative are assumed to be susceptible; so a live attenuated rubella vaccine, RA 27/3, single dose is administered subcutaneously with information to avoid conception for the next 28 days.[27] If, inadvertently, patient becomes pregnant before 28 days, abortion is not recommended because though there exists 1% -2 % risk of CRS theoretically, but, till date, no reports of CRS has been documented after inadvertent vaccine administration.[28]

Women on their first antenatal visit should undergo rubella testing in which serum IgG is assessed by ELISA. Those positive for IgG antibody are supposed to be immune whereas those negative are considered susceptible. These susceptible individuals should be followed routinely with immediate postpartum vaccination.

With evidence of primary infection during first trimester, mothers are offered medical termination of pregnancy, whereas during second trimester same is offered when there is evidence of fetal infection i.e. RT-PCR of amniotic fluid or viral culture are positive. Diagnosis during third trimester requires conservative management with fetal surveillance. There is no effective antiviral therapy available to reduce maternal viremia. Long-term follow-up should be done for developmental defects like sensorineural defects, mental retardation and endocrinological problems.

Post exposure prophylaxis with immunoglobulin does not prevent infection or viremia; therefore, not routinely recommended.

Prevention

Rubella can be prevented by universal MMR (Measles, Mumps and Rubella) vaccination of children at 15-18 months and selective vaccination of susceptible non-pregnant females in child bearing age by live attenuated Rubella vaccine RA 27/3 which is protective for 15 year in 95% individuals. However, as it is a live vaccine it should not be given in pregnancy.[29]

Infants with CRS, despite high titres of specific neutralizing antibodies, may excrete the virus from respiratory tract and urine until the age of 1 year-an important issue related to infection control in hospital and daycare settings.[26]

Varicella-zoster virus

Varicella Zoster virus (VZV) is a double stranded DNA virus in the family *Herpesvirideae*.[30] Primary infection with VZV causes varicella or chickenpox in children & adults, while reactivation causes shingles, a common infection among elderly. Primary infection in pregnant females is serious when it occurs during the first trimester because it causes fetal malformation known as fetal varicella syndrome (FVS), whereas at the time of delivery it is associated with increased morbidity and mortality, both in mother and fetus.

There is paucity of data regarding the burden of chickenpox infection in pregnant females in India. Primary VZV infection in pregnancy is uncommon (3/10,000 pregnancies) because 90% of antenatal population is seropositive for VZV

IgG antibodies due to infection acquired in childhood.[31]

Maternal infections

Chickenpox is manifested by numerous lesions in various stages of evolution: vesicles on an erythematous base, umbilicated vesicles, and crusts predominantly over trunk whereas shingles manifests as hemorrhagic vesicles and pustules on an erythematous base grouped in a dermatomal distribution.

Fetal transmission and clinical presentation

Maternal varicella infection in pregnancy can cause congenital varicella syndrome, characterized by cicatricial skin lesions, limb hypoplasia or paresis, microcephaly, and ophthalmic lesions. The risk depends on when the mother was infected: about 0.4% if in the first 12 weeks of pregnancy, increasing to 2% if between 13 and 20 weeks.[32] It is rare after 20 weeks of gestation.

It is a highly contagious infection transmitted by respiratory droplets, direct personal contacts with vesicular fluid, fomites. Varicella infection in pregnancy leads to placental infection with chronic villitis and varicella embryopathy showing the consequences of VZV infection of spinal ganglion cells of the developing nervous system, leading to unusual limb hypoplasia, cutaneous defects, and cicatricial skin scar. Esophageal dysfunction and hydroureter result from damage to the developing autonomic nervous system. Severe microcephaly with cortical atrophy and calcification follows intrauterine encephalitis and necrosis of brain parenchyma. In disseminated neonatal varicella, characteristic pathologic changes can be seen in lung, liver, brain, and other tissues in immunocompromised patients.[33]

Laboratory diagnosis

(a) Diagnosis in pregnant females

Diagnosis of chickenpox is clinical but confirmation can be done by laboratory testing. Viral DNA detection can be done by PCR (most sensitive method) from vesicular fluid. VZV DNA can also be detected from blood by PCR during active disease. Viral antigens (glycoprotein i.e. gE) can be detected from the lesions by using fluorescent monoclonal antibody (direct fluorescent antibody i.e. DFA staining) which is more sensitive than culture but less sensitive than PCR and its result can be obtained within 2 hours.[34] Viral culture is the most accurate method but it is associated with difficulty in recovery of the virus, is laborious and time consuming, i.e.it takes 7-10 days for CPE that consists of small foci of rounded and swollen cells which can be confirmed by PCR or monoclonal antibodies. Hence, it is not routinely practiced. Shell vial centrifugation cultures can provide result in 2-5 days and are more sensitive than conventional culture but less sensitive than PCR.[35] Cytological study can be done by Tzanck smear preparation for multinucleated giant cells which contain multiple eosinophilic intranuclear inclusions representing viral capsids. This test has low sensitivity and it cannot differentiate VZV from HSV ; however, it can complement other tests. VZV can be visualized by electron microscope but it cannot differentiate this virus from other members of *Herpesvirideae*.[36]

The results of serologic tests can be suggestive but are not definitively diagnostic of primary infection, i.e. IgM or four fold increase in IgG antibody in paired serum samples can be seen during primary infection but can also be observed during reactivation.[37] Method considered the gold standard for serologic testing is FAMA (fluorescent antibody to membrane antigen) test; however, ELISA tests are most frequently used by most laboratories as they are less laborious. Easier test likes Latex agglutination test kits are now commercially available.[38]

(b) Fetal diagnosis in pregnant females

FVS in fetus of a mother with primary infection can be suspected by ultrasound findings like limb deformity, microcephaly or hydrocephalous, soft tissue calcifications and IUGR. For confirmation of VZV infection; amniotic fluid can be tested by PCR (DNA).[25]

(c) Diagnosis in neonates

Diagnosis in newborns can be done using fluorescent antibody (FA) stain or PCR or culture of lesions.[25]

Management of chickenpox in pregnancy

Management of mother can be done by oral acyclovir (800 mg orally 5 times a day for 5-7 days), isolation and symptomatic treatment.[39]

If chickenpox occurs before 20 weeks of gestation mother should be informed about 0.4% - 2% risk of FVS. Serial ultrasound should be done at 16-20 weeks or 5 weeks after infection for any congenital malformation. And if evidence of malformations is found, termination of pregnancy should be offered. Varicella zoster immunoglobulin (VZIG) during pregnancy decreases the severity of infection.[40]

If primary infection occurs at term, then, if possible, delivery should be delayed till 5th day rash for the passive transfer of maternal IgG antibodies. If delivery occurs within this period or mother develops chickenpox 2 days after delivery, then VZIG should be given to newborn to decrease the severity of infection. If neonate develops clinical signs, acyclovir can be given. Breast feeding should be given unless there is evidence of active lesions on and around nipples in mother.[40]

Prevention

Non-immune, non-pregnant females should be assessed for their immunity either by asking their previous history of chickenpox or serum IgG antibody testing by ELISA. Those who are found to be susceptible should be vaccinated with a live attenuated vaccine derived from "Oka" strain. Since seroconversion after first dose is only 78%, second dose is given at 4-8 weeks interval that is associated with seroconversion in 99%. This immunity probably lasts for 10 years. Another vaccine called zoster vaccine is also available for prevention of shingles for elderly.[41]

In non-immune, pregnant females vaccination should not be given. They should be advised to avoid contacts with patients with chickenpox or shingles and to report immediately if exposure occurs.

In pregnant females with contact history with chickenpox, a careful history to confirm the exposure should be taken along with serological test for the immune status. With past history of chickenpox or positive IgG antibody testing, she should be assured safe, otherwise, VZIG should be administered with serial followup with postpartum vaccination.

All susceptible children should be vaccinated by "Oka" strain between 12-18 months to prevent chickenpox; to reduce the transmission to pregnant females, as human is the only reservoir.

Herpes simplex virus

Herpes simplex virus (HSV) is a double stranded DNA virus in family *Herpesvirideae*.[42] It has two serotypes, i.e. HSV-1 and HSV-2. It causes primary infection of skin and mucous membrane in those who get the infection for the first time; manifested either as herpes labialis or herpes genitalis. After a period of latency in neurons, reactivation of the virus can occur, particularly when immunity falls. It is the primary infection of the genital area, i.e. herpes genitalis,that is crucial in pregnant females, as it causes serious infection in neonates called neonatal herpes. Ninety percent of neonatal herpes is perinatally acquired, 5% - 8% is congenital, whereas rest is acquired postnatally. Seventy percent of neonatal HSV infection is caused by HSV-2 acquired by contact with infected genital secretions during delivery.[43] Though genital infection with HSV-2 is more common, primary HSV-1 is increasing in frequency. Transmission of HSV-1 occurs at a significantly higher rate than that of HSV-2. Therefore, pregnant women who present with HSV infection should undergo both a type-specific serologic assay and viral typing to identify those infants at higher risk for infection.[44]

Genital herpes is a sexually transmitted disease. Antibodies to HSV-2 start to appear during puberty and correlate with initiation of sexual activity. HSV-2 seroprevalence in antenatal clinics in India has been reported to

be 14% .[45] In females of child bearing age group, subclinical infection is found in 25% - 30% whereas 1% present with clinical disease, with the rate of asymptomatic shedding during pregnancy between 0.2 to 7.4 % and at the time of delivery 0.1 to 4 %.[46]

Maternal Genital Herpes

The typical clinical manifestations include unilateral or bilateral vesicular lesions, with an erythematous base, located in the area of the sacral dermatome (usually S2, S3) and which can, therefore, be on the genital skin or adjacent areas. They often evolve into pustules, then ulcerations, and finally, if on keratinized skin, crusted lesions. Although this is the classic presentation, atypical presentations are common, including minor erythema, fissures, pruritus and pain with minimal detectable signs. Some individuals will never show clinical manifestations but can be demonstrated to be episodically shedding virus.

Fetal transmission

At least four factors influence transmission of infection from mother to fetus. First, the type of maternal genital infection is crucial. The risk of transmission with maternal primary or first episode genital infection during the third trimester is 30% to 50% as compared with 3% or less with recurrent infection. In part, this reflects prolonged viral excretion during the third trimester of gestation as well as an inadequate transplacental antibody transfer. Second, the mother's HSV antibody status at delivery influences the severity of infection as well as the likelihood of transmission. Transplacental maternal neutralizing antibodies appear to have at least an ameliorative effect on acquisition of infection. Third, prolonged rupture of membranes (>6 hours) increases the risk of acquisition of virus. Fourth, use of fetal scalp monitors increase the risk of neonatal HSV infection.[47] Infection in-utero by hematogenous transmission is rare and may cause skin vesicles or scarring, retinitis or keratoconjuctivitis, microcephaly or hydrocephaly which presents at birth or 1-2 days after birth.[48]

Laboratory diagnosis

(a) Diagnosis in pregnant females

Diagnosis in mother is clinical and confirmed best by PCR of HSV DNA or viral culture from vesicular fluid or lesion scrapings from vulva, cervix and anal canal. Viral antigens can be detected by using fluorescent monoclonal antibody (DFA staining). Conventional viral culture (using mink lung cells or human diploid fibroblasts, i.e. MRC-5 cells for CPE characterized by cellular enlargement, rounding, cytoplasmic granulation by one week duration followed by complete destruction of monolayer) is laborious and time consuming, while shell vial culture is a rapid method which can give the report within 24 hours. Here, tissue culture vials are centrifuged to increase the viral attachment to cells and viral antigens can be detected by using antibodies without waiting for the cytopathic effect that takes extra time.

Because of extensive cross reactivity among structural proteins only IgG tests based on the type specific HSV gG (glycoprotein G) accurately distinguish HSV-1 and HSV-2. Type specific IgM tests are not available. FDA approved IgM tests decrease the time to detect seroconversion in new infections but cannot accurately distinguish new from established infections. Tests for HSV-2 antibody avidity which can discriminate accurately between first episode (low avidity) from recurrent (high avidity); are not commercially available. Cytology for the demonstration of intranuclear inclusion bodies and multinucleated giant cells can be done in scrapings taken from the base of lesions in Tzanck smear, but it has low sensitivity and it doesn't differentiate HSV from VZV but can supplement other tests.[49]

(b) Diagnosis in neonates

Typical neonatal infection is diagnosed by PCR, culture or FA stain of lesion.[25,50] PCR performed on CSF may help in detection of involvement of the central nervous system. PCR performed on blood may help in recognition of disseminated infection, in cases lacking cutaneous lesions. Rare cases of HSV acquired in utero may be recognized by detection of HSV-

specific IgM antibodies in blood sample obtained during first week of life.[25]

Management

Acyclovir is well tolerated during pregnancy and there is no clinical or laboratory evidence of maternal or fetal toxicity. Acyclovir 400 mg thrice a day for 7-10 days reduces the duration and severity of symptoms and decreases the duration of viral shedding. For women with recurrent infections during pregnancy, antiviral therapy is not recommended prior to 36 weeks.[51]

The high HSV-2 prevalence rate in pregnancy and low incidence of neonatal disease indicate that only a few infants are at risk of acquiring HSV. Cesarean section is therefore not warranted for all women with recurrent genital disease.[52]

Prevention

Susceptible pregnant females should be informed to keep themselves away from patients suffering from HSV infection. Prevention of genital herpes in pregnant women with no prior history can be attempted by use of condoms throughout pregnancy or avoiding sexual intercourse. Pregnant females with history of primary genital herpes during pregnancy should be administered acyclovir at 36th week of gestation to prevent recurrence during delivery. For pregnant females presenting with primary genital herpes around delivery, elective cesarean section should be undertaken to prevent neonatal herpes along with 7-10 days of acyclovir 400 mg thrice daily or valacyclovir 500-1000 mg twice daily.

Postnatal HSV transmission can be prevented by health education, i.e. keeping the baby away from all sources of contact that could be infectious. Breastfeeding should not be avoided till any vesicular lesions develop in breast. Symptomatic mother should wash her hands before touching baby. Infected healthcare workers and family members should not be allowed as they may transmit the infection to baby.

Development of an effective HSV vaccine would be the best approach for the prevention of HSV. However, there is no vaccine available yet. Clinical trials are ongoing.

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