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Perinatal Viral Infections

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In comparison to older children and adults, neonates are immunologically incompetent. They are susceptible to infections caused by a variety of microorganisms, including bacteria, fungi and viruses. These infectious agents may be acquired by neonates either prenatally, during the intrapartum period or postnatally. The purpose of this review is to emphasize the potential impact of viral infections contracted by neonates at the time of delivery or within the neonatal period. The viruses reviewed include the herpes group of viruses (cytomegalovirus, herpes simplex viruses and varicella-zoster virus), type B hepatitis virus, human immunodeficiency virus, respiratory viruses, enteroviruses, rotavirus and human papilloma virus. For each virus the potential sources and incidence of the infection, the common manifestations of the illness, and possible means of prevention and therapy are discussed. Although infections caused by bacteria tend to be more clinically dramatic and more immediately life-threatening, it is emphasized that infections caused by viruses are common and associated with substantial long-term morbidity. Perinatal viral infections need to be recognized as early in life as possible so that their natural history can be more completely defined and any possible intervention made.

Neonates are susceptible to infections caused by a wide variety of microorganisms. They are immunologically incompetent hosts with specific defects rendering them more susceptible to viral infections. Delayed production of or response to interferon has been observed (1, 2). Lymphocytes and monocytes from neonates have reduced natural killer cytotoxicity (3, 4) and neonatal T-lymphocyte proliferation to viral antigens is diminished compared to that of adult cells (5). Viral-specific humoral immunity (antibody) present at birth is completely dependent upon passive transfer from the mother. If a mother experiences a primary viral infection around the time of delivery, the neonate may not have received any specific passive protection.

The sources of perinatally acquired viral infections include the transplacental route (e.g. cytomegalovirus), the maternal genital tract (e.g. cytomegalovirus, hepatitis B virus, papillomaviruses and herpes simplex virus), the maternal gastrointestinal tract (e.g. enteroviruses), breast milk (e.g. cytomegalovirus and hepatitis B virus), and nosocomial sources. Predominant among the nosocomial sources are contact with infected hospital personnel (e.g. respiratory viruses, varicella-zoster virus and herpes simplex virus) and blood transfusions (e.g. cytomegalovirus and human immunodeficiency virus).

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In general, more consideration is given to the possibility of bacterial rather than viral infections in neonates who become ill in the first few days of life. Although bacterial infections tend to be more dramatic and are associated with more immediate morbidity and mortality than viral infections, the overall incidence of perinatal viral infections is greater and their long-term consequences are substantial. The goal of this review is to underscore the impact of viral infections acquired by neonates at the time of delivery or within the immediate neonatal period.

Cytomegalovirus

Cytomegalovirus (CMV) is the most common viral cause of congenital infections. World-wide, the incidence of congenital CMV infection ranges from 0.2–2.2 % of all live births (6). At most, only 10 % of congenitally infected neonates are symptomatic at birth. These infants often have devastating manifestations including prematurity, low birth weight, microcephaly, chorioretinitis, hepatosplenomegaly and thrombocytopenia (7). In addition, their long-term prognosis is almost universally extremely poor (8). Of the 90 % of the infants infected with CMV in utero who are asymptomatic at birth, 5–15 % manifest late effects, including sensorineural hearing loss, subnormal intelligence, behavioral disorders and subtle neurologic findings (9, 10). However, the majority of cases of cytomegalovirus infection in infants are acquired in the perinatal period.

Sources and Incidence

The most important sources of perinatal CMV infections are the maternal genital tract at the time of delivery, breast milk and blood transfusions. Only rarely have other sources of infection, such as nosocomial transmission from another neonate, been described (11). The diagnostic distinction between congenital and perinatal CMV infection is based upon urine viral cultures obtained during the first weeks of life. If a urine culture obtained during the first 2 to 4 weeks of life is positive for CMV, a congenital infection is diagnosed. If the first urine culture is negative but subsequent cultures are positive, a perinatally acquired infection is presumed. The distinction between congenital and perinatal CMV infections has prognostic significance in terms of immediate and long-term sequelae.

A maternally derived CMV infection can only be acquired from a mother who has been infected with CMV; antibody to CMV will be present in her serum. The maternal infection may have occurred in the distant past with CMV excretion resulting from endogenous reactivation of latent virus, although it appears that perinatal acquisition is more frequent among infants born to women who have had primary infection during the pregnancy. In a recent study, 61 % of 23 neonates who did not contract CMV in utero from mothers experiencing a primary CMV infection during gestation were infected in the perinatal period (12). Perinatal CMV infections have not been associated with maternal CMV shedding from the pharynx or urinary tract (13). It has been estimated that 10 % of seropositive American women excrete CMV from the genital tract at delivery (14). Approximately 50 % of infants who are not breast-fed and who are born to women with virus in their genital tracts at delivery will acquire CMV, with onset of viral excretion between 3 and 9 weeks of age (15, 16). Thus, if the seropositivity rate for CMV in a given population is 50 %, 2.5 infants born to 100 women from that population will contract CMV at the time of delivery. About 30 % of infants nursed by seropositive mothers contract a CMV infection, viruria usually developing between 4 and 12 weeks of age (13, 17, 18). Thus, if the seropositivity rate for CMV in a given population is 50 % and 50 % of the women breast feed, 7.5 infants born to 100 women from that population will contract CMV from breast milk. Transmission has been observed even more commonly from mothers who are viruric (17) or lacturic (18) and if breast feeding is continued for at least one month (18). CMV infection rates in infants are highest in countries with high rates of CMV seropositivity and of breast feeding (13).

The most important non-maternal source of perinatally-acquired CMV infections is blood transfusions (19, 20). The first suggestion that neonatal CMV infection could be acquired by blood transfusion was made by McCracken et al. (21). Subsequently, many epidemiologic reports have confirmed the association between blood product administration and the development of neonatal CMV infections (20). In a recent report transfusion transmission of CMV to neonates was proved using the technique of restriction endonuclease analysis to demonstrate the identity of CMV from a blood donor and two infected neonates (22). For a blood product to cause CMV infection it must have been obtained from a donor infected with CMV. These "infectious" donors (unless acutely infected) are usually CMV seropositive and the virus is transmitted, after reactivation, from its latent state. We have shown that blood derived from seronegative donors failed to transmit infection to any of 90 infants born to seronegative mothers. In contrast, 13.5 % of 74 infants of seronegative mothers who received blood from seropositive donors contracted CMV (19). Infants born to seropositive mothers appear to be less at risk of acquiring a CMV infection from seropositive blood products. This is presumably related to the protective effect of passively acquired CMV antibody in these infants. In addition, if an infant born to a seropositive mother contracts a CMV infection, it is very difficult to determine whether the infection has been acquired from the mother or from the blood product transfusions.

The risk of acquiring a transfusion-related CMV infection has been shown to be directly related to the volume of blood received. In our population of infants born to seronegative mothers, none of 33 infants who received less than 50 ml of red blood cells contracted CMV infection compared with an infection rate of 24 % (10 of 41) who received more than 50 ml (19). This relationship between volume of blood received and risk of infection also has been demonstrated in studies conducted by Adler (20). The risk of acquiring a transfusion-related CMV infection is inversely related to the birth weight of the neonate (20, 23–25). The incidence of transfusion-acquired CMV infection in low birth weight infants has been estimated to be 10–30 % (20). In contrast, transfusion-related infections in infants of normal birth weight are quite unusual.

Manifestations

Maternally derived perinatal CMV infections occurring in infants born near term may be associated with short-term morbidity. In one recent study, 7 of 21 (33 %) infants who acquired CMV postnatally developed symptoms, in temporal association with CMV viruria, which included some combination of hepatosplenomegaly, lymphadenopathy, anemia, atypical lymphocytosis, rash and pneumonitis (26). Other reports also have noted the importance of postnatally acquired CMV as a cause of pneumonia in young infants (27, 28). The collaborative study

conducted by Stagno et al. (28) identified CMV in 20 % of 104 infants hospitalized between 1 and 3 months of age with pneumonitis. Chronic viruria in term infants who acquire CMV postnatally has also often been observed (15, 18). However, long-term morbidity is uncommon. All of the 21 postnatally infected infants described by Kumar et al. (29) had normal physical, neurologic, audiologic and ophthalmologic assessements at one year of age. Psychometric testing of 17 of the 21 revealed a mean IQ of 107 (26, 29). Similarly, follow-up of twenty-one term infants with maternally derived perinatal CMV infections cared for at another institution failed to identify long-term sequelae (30). One study has reported a long-term consequence of CMV infections in postnatally infected term infants (31). This study, conducted in Finland, found that 18 % of these children had delays in language development. However, this conclusion was based upon a Denver Development Screening Test performed at approximately two years of age. Audiometric testing was not performed and other potentially confounding variables such as maternal age and educational level were not evaluated. One of the reasons for the general lack of symptoms in infants born near term may be the presence of transplacentally acquired CMV antibody.

Prematurely born infants are at higher risk for symptomatic CMV infections. They do not receive as much transplacental CMV antibody and the antibody that they do receive disappears more rapidly through catabolism and iatrogenic blood loss than in infants born near term (32). Symptoms attributed to maternally derived CMV infections in these infants have included hepatosplenomegaly, thrombocytopenia, neutropenia and pulmonary morbidity as manifest by prolonged oxygen requirement (32). Symptomatic infection appears to be especially likely in those premature infants who begin excreting CMV before seven weeks of age (32). Long-term sequelae in these infants included moderately abnormal EEGs (17 %) and severe handicaps (DQ < 70, severe neuromuscular impairment, or profound loss of vision or hearing) in 14 % (30). These late sequelae were also more likely in premature infants who had early excretion of CMV (< 8 weeks).

Given the possible protective role of passive antibody, it is not surprising that perinatally-acquired CMV infections are more common and more severe if acquired from a non-maternal source by infants born to seronegative mothers. Such non-maternal sources include banked breast milk obtained from seropositive women or blood products obtained from seropositive donors. Most of the data evaluating the consequences of these infections has been derived from studies concerning transfusion related CMV. Morbidity associated with these infections has been almost exclusively in infants with birth weights < 1250–1500 g (19, 20, 24, 25, 33). These infants often have multiple-organ dysfunction (respiratory, cardiovascular and neurologic) compounding their CMV infection. This multiplicity of problems also makes it very difficult to determine how much of their morbidity is CMV related and how much is related to other causes. With this important reservation, disease attributed to transfusion-related CMV infections has ranged from mild self-limited illness to death. In some series up to 50 % of premature neonates acquiring a transfusion-related CMV infection may have severe illness or die (19, 20). Symptoms have included a "septic" appearance with a peculiar gray pallor and fever, pneumonia, apnea, respiratory deterioration, hepatosplenomegaly, chorioretinitis and encephalitis. Laboratory findings have variably included both an atypical and absolute lymphocytosis, leukopenia, thrombocytopenia, anemia, liver enzyme elevation, and hypoalbuminemia. Many of these findings are similar to those observed in infants infected in utero as a result of a maternal primary infection (7, 12). This is not surprising; newborn premature infants are comparable in many ways to the fetus in late gestation. Hence, an infection acquired by a premature infant born to a seronegative mother may have the same consequences as a congenitally acquired infection.

Prevention

Cytomegalovirus infections acquired by neonates from the maternal birth canal cannot be prevented. Those acquired from maternal breast milk could be prevented by prohibiting breast feeding if a mother is known to be CMV seropositive. It is probable however that the benefits of breast feeding outweigh the risk of acquiring a symptomatic CMV infection from this source. Breast feeding infants of seronegative mothers with milk derived from seropositive women is more likely to cause a symptomatic CMV, especially in prematurely born infants. Therefore, this practice should perhaps be discouraged. The highest risk circumstance for transmission of a CMV infection is created by administering blood products derived from CMV seropositive donors to CMV seronegative premature infants. These transfusion-related infections can be prevented by administering blood products derived from seronegative donors only (19). Preliminary evidence also suggests that these infections can be prevented by using frozen deglycerolized packed red blood cells (34, 35). Processing blood products in this way effectively removes viable leukocytes, the cells in which CMV is presumed to be latent. Saline washing of red blood cells, which results in only an 89 % reduction in white blood cells, is ineffective in preventing transfusion-acquired CMV infections in neonates (36).

Herpes Simplex Virus

Neonatal infection with herpes simplex virus (HSV) can be caused by either HSV-1 or HSV-2. Although some cases of intrauterine infection with HSV have been described, most of the serious HSV infections in infants result from perinatal infection. The infants who have acquired HSV in utero are usually identified by the appearance of widespread cutaneous HSV lesions at birth, often accompanied by evidence of intrauterine infection of the central nervous system, including microcephaly with cerebral atrophy and chorioretinitis (37). Most of these infants survive but exhibit profound psychomotor retardation as a consequence of intrauterine encephalitis. The risk factors for intrauterine HSV infection have not been determined. Affected infants have been born to mothers with both primary and recurrent HSV infection during pregnancy and to mothers with no prior history of symptomatic HSV infection (38). Fortunately, given the prevalence of HSV in the general population, this manifestation of neonatal HSV infection is very rare.

Sources and Incidence

Although both HSV-1 and HSV-2 can cause serious neonatal HSV, most affected infants have HSV-2 infection (39). The analysis of infants with perinatal HSV infection demonstrates that as many as 70 % of these infants are born to mothers with no history of symptomatic HSV disease (40). In most cases, asymptomatic HSV excretion in the maternal genital tract at the time of delivery is the probable source of infection of the newborn. Asymptomatic HSV excretion can follow maternal genital HSV infection at some time in the past, i.e. as the result of reactivation of latent virus, or it may represent acute primary genital herpes in the mother. The attack rate of HSV infection in the infant is probably much lower for infants whose mothers are experiencing recurrent HSV at delivery because of the relatively lower virus inoculum and the localization of viral replication to external genital sites. Neutralizing HSV antibodies are also present in the amniotic fluid of these women. Their infants have transplacentally acquired serum HSV antibodies which can mediate virus neutralization as well as antibody dependent cellular cytotoxicity (4, 41). The theoretical maximum attack rate was less than 8 % based upon a study of 34 infants born to mothers with known recurrent genital herpes, who were inadvertently exposed to HSV by vaginal delivery (42). In contrast, the attack rate among infants born to mothers with primary genital herpes at delivery is estimated to be 50 %. Primary genital herpes in women is associated with a high frequency of viral infection of the cervix and prolonged excretion of HSV in high titers (43). The interval required for the production of neutralizing HSV antibodies following primary herpes is often 7 to 14 days. The infant of the mother who develops primary genital herpes late in gestation may be delivered prior to the transplacental transmission of protective HSV antibodies. In any case, passive antibody protection against HSV is not complete, as illustrated by the fact that HSV infection does occur among infants of mothers with recurrent genital herpes.

The transmission of HSV to the neonate exposed to a non-maternal source of the virus has also been documented (44). In the few cases that have been investigated, the infant was born to a susceptible mother, therefore having no passive antibodies against HSV, and was cared for within the first few days of life by a father or grandmother with recurrent herpes labialis. This circumstance probably occurs very rarely because most infants have acquired HSV-1 specific antibodies transplacentally and the chance and duration of direct contact with the lesion is limited. Nosocomial transmission of HSV from infant to infant has occurred in neonatal nurseries.

Manifestations

The early diagnosis of neonatal herpes is critical because both acyclvoir and vidarabine are effective antiviral drugs for this disease (45). Perinatal HSV infections in infants usually present after the first 24 to 48 hours of life. The mucocutaneous form of the infection is recognizable by the vesicular appearance of the lesions, which may occur as a single lesion or cluster of lesions on the skin or scalp or involving the mucous membranes of the eye or mouth. Infection may begin around a fetal scalp monitor site. Conjunctivitis is not unusual in this form of neonatal herpes but the extensive stomatitis of primary HSV as seen in older children is rare. The mucocutaneous lesions can be difficult to distinguish from staphylococcal or other types of rash by clinical appearance, but must be identified as herpetic as soon as possible to allow early antiviral therapy. Direct immunofluorescence of a lesion scraping using HSV antibodies provides the most rapid and specific method of diagnosis; the Tzanck smear is not sufficiently reliable to rule out this potentially life-threatening infection of the newborn. Viral culture of the lesions should be done to confirm the immunofluorescence result and is usually positive within 2 to 4 days. Without early treatment, more than 75 % of these infants will have progression of the disease to the disseminated or encephalitic forms of neonatal herpes (39).

Unfortunately, many infants who have perinatal herpes infection present with disseminated or central nervous system disease without any mucocutaneous lesions at the onset of the illness (46). Infants with disseminated herpes usually have fever and signs indistinguishable from bacterial sepsis in the newborn

within the first 7 to 10 days of life. The infection progresses rapidly with severe hepatitis, thrombocytopenia and bleeding diathesis as well as pneumonia and encephalitis. HSV can be isolated from the oropharynx of the infant, from blood and occasionally from the cerebrospinal fluid; examination of the mother may reveal signs of primary genital herpes. Some infants develop cutaneous herpetic lesions in the course of the illness from which the virus can be isolated. Disseminated neonatal herpes has a mortality rate of greater than 70 % if untreated. Because of the fulminant course of the infection in many of these infants, the mortality rate approaches 50 % even with acyclovir or vidarabine therapy (45).

Herpes encephalitis usually occurs in infants from ten days to four weeks of age. The symptoms include fever, lethargy and poor feeding, followed within 24 to 48 hours by the onset of seizures (39, 46). The seizures are typically focal and unilateral initially and then become generalized. Apnea or periodic breathing is a prominent sign. The cerebrospinal fluid can be normal immediately after the onset of symptoms but usually shows a mild pleocytosis (20–100 cells) and elevated protein (> 100); the glucose may be normal or slightly low (20–30). Computerized tomography brain scan may be normal or show diffuse enhancement. In contrast to older children and adults with HSV-1 encephalitis, infants rarely have the classic temporal lobe lesion identifiable by CT scan; the EEG is also diffusely abnormal. Neonatal herpes encephalitis is caused by HSV-2 and causes a very extensive tissue necrosis of brain which is often far-advanced when the diagnosis is made. At the present time the early diagnosis of most cases requires brain biopsy unless the infant has mucocutaneous lesions. HSV has not been isolated from the CSF of these infants except late in the clinical course in a few cases. Antiviral treatment of these infants reduces the mortality rate and lessens the risk of severe sequelae among survivors. A few infants present with a meningitic form of central nervous system infection, have positive CSF cultures and respond well to antiviral therapy.

Serologic assays are rarely useful for the diagnosis of neonatal herpes. The cord blood HSV antibody titer is not helpful because the majority of newborn infants have passive HSV antibodies due to prior maternal infection with HSV-1 or HSV-2 or both. A negative titer does not rule out herpes because the infant may have acquired the infection as a result of primary maternal HSV or from a non-maternal source (41). None of the standard assays for HSV antibodies can distinguish between HSV-1 and HSV-2 nor is there a reliable method for HSV IgM detection. In addition, the IgM response of infants with proven HSV occurs very late or not at all (41).

Prevention

Preventing the exposure of infants to HSV is a goal which has been difficult to achieve. Since most neonatal disease is caused by HSV-2 acquired from maternal genital infection at the time of delivery, the first problem is to identify women who may have active genital HSV at the onset of labor. If the mother has obvious genital herpes lesions, the risk to the infant can be reduced significantly by cesarean delivery prior to or within a few hours after rupture of the membranes. However, women with a history of recurrent genital herpes have intermittent asymptomatic shedding of the virus in the genital tract. Approximately 1–2 % of these women will have HSV excretion at the time of delivery (47). Because of the brief duration of episodes of asymptomatic shedding, antepartum cultures failed to predict the risk of exposure of the infant at delivery even when the culture was obtained within a week before the onset of labor. Nevertheless, the low attack rate for infection among infants exposed to recurrent maternal HSV combined with the low risk that asymptomatic shedding will actually be present at delivery, makes it unreasonable to recommend cesarean delivery for every woman with a past history of genital herpes.

The fact that the majority of mothers of infants with neonatal herpes have no history of genital herpes means that the prevention of neonatal infection cannot focus only upon pregnancies known to be complicated by maternal herpes. The reasons for this absence of maternal history include the occurrence of past HSV-2 infection which was asymptomatic and not associated with clinically obvious recurrences and the onset of primary genital HSV late in gestation (48). The detection of primary infection present at the onset of labor requires careful examination of all women in labor for herpetic lesions, regardless of past history.

At the present time there is no standard serologic method for identifying women who may have had silent genital HSV-2 infection. In the United States, research serologic techniques which can detect antibodies to the HSV-2 specific glycoprotein gG have demonstrated that about 30 % of women have had past HSV-2 infection (49). Because of these problems, studies are in progress to determine whether HSV cultures should be obtained routinely from all women at the time of delivery. The hypothesis of this strategy is that exposed infants could be monitored carefully and treated immediately if signs of neonatal HSV infection occur.

Varicella Zoster Virus

Varicella-zoster virus (VZV) is an unusual cause of perinatal infection in the USA and Europe because more than 90 % of women of childbearing age who

live in temperate climates have had varicella in childhood. In addition to perinatal infection, maternal varicella can cause the congenital varicella syndrome. This syndrome is a unique constellation of anomalies present at birth in fewer than 5 % of infants born to mothers who have had varicella during pregnancy. Most cases have followed maternal infection in the first trimester (50, 51). Affected infants have characteristic cicatricial cutaneous scars, limb atrophy, rudimentary digits, chorioretinitis, microcephaly and other obvious defects (52). Death in infancy is common because of autonomic disorders, especially severe gastroesophageal reflux which causes recurrent aspiration pneumonia. A few otherwise asymptomatic infants with intrauterine exposure to VZV have immunologic evidence of VZV infection and some develop uncomplicated herpes zoster during infancy (50). Herpes zoster, which is due to reactivation of latent VZV, occurs during pregnancy, but has not been associated with the classic features of the congenital varicella syndrome.

Sources and Incidence

Infants born to mothers who acquire varicella late in gestation may develop clinical signs of varicella. If the maternal infection occurs in the last few weeks of pregnancy, the infant may be asymptomatic or may have cutaneous varicella lesions at or shortly after birth. These infants rarely develop complications from the infection whereas infants who are born within four days after or 48 hours before the onset of maternal varicella are at risk for fatal varicella. Among cases summarized by Myer et al. (53) the attack rate for perinatal infection under these circumstances was approximately 20 % and the incidence of fatal infection was 30 %. These infants are delivered prior to the transmission of maternal VZV antibodies across the placenta; they become infected with VZV either transplacentally, as a consequence of maternal viremia, or by exposure to maternal cutaneous lesions at delivery or in the perinatal period.

Infants who are exposed to varicella in non-maternal contacts rarely develop severe varicella. Although other children in the household may have varicella, the infant is usually protected by transplacentally acquired VZV antibodies (54). The infant whose mother has never had varicella may be the exception but this circumstance, like maternal varicella during pregnancy, is rare because of the high prevalence of VZV immunity among adult women. High-risk, hospitalized infants have occasionally developed varicella after nosocomial exposure to a care person with varicella (55).

Infants whose mothers develop herpes zoster late in pregnancy or immediately postpartum are not at risk for serious illness. The primary concern in these cases arises when the zosteriform eruption is in the lumbosacral dermatomes since the rash is caused by herpes simplex in as many as 15 % of patients with apparent herpes zoster in this distribution.

Manifestations

Infants at risk for serious varicella are well until after the first 5 to 10 days of age (53). The infection begins with the typical cutaneous exanthem. The diagnosis is usually obvious because of the characteristic vesicular lesions and the recognition of recent maternal varicella. The clinical diagnosis can be confirmed by viral culture of the lesions or by direct immunofluorescence stain of cells from the base of the cutaneous lesion using VZV specific antibody. Progressive cutaneous infection is associated with life-threatening illness resulting from VZV pneumonia, encephalitis, hepatitis and bleeding diathesis. Varicella in these infants resembles disseminated varicella in other immunocompromised populations. Perinatal VZV infection in infants in the group identified as high-risk, i.e. those with a late onset of symptoms, who were born to mothers with illness beginning four days before or within 48 hours after delivery, should be treated with intravenous acyclovir. Although clinical experience with acyclovir treatment of infants with perinatal varicella is lacking the drug prevents progressive VZV infection among other immunodeficient patients (56).

Prevention

Passive antibody administration, given as varicella-zoster immunoglobulin (VZIG), is recommended for infants with perinatal exposure to maternal varicella. Immunoglobulin should be given to the infant immediately after birth if the mother has acute varicella with onset less than four days before delivery or if the mother develops varicella within 48 hours. There is no evidence to suggest that the fetus can be protected by the administration of VZIG to the susceptible pregnant woman who has been exposed to VZV. Nevertheless, VZIG prophylaxis should be considered if the mother is proved to be susceptible by a sensitive serologic test for VZV antibodies, such as immunofluorescence or ELISA, in order to modify the severity of the maternal infection. VZIG prophylaxis should be given within 72 to 96 hours after the exposure. No intervention is required for infants exposed to maternal herpes zoster.

Hepatitis Viruses

Most of the morbidity of viral hepatitis in the newborn period is a consequence of hepatitis B. Hepatitis A is usually asymptomatic and non-A, non-B hepatitis has not been an important problem in newborns.

Sources and Incidence

Most neonates who become infected with hepatitis B virus acquire their infections from mothers who are chronic asymptomatic carriers of the virus and can be identified serologically by their chronic antigenemia (HBsAg positive). This spread from mothers to their infants is termed vertical transmission. Transmission may occur transplacentally, at the time of delivery, or shortly after delivery. However, it is clear that most infections are acquired at the time of delivery as a result of swallowing maternal blood. The gastric contents of over 95 % of infants born to chronic carrier mothers contain HBsAg (57). The risk of vertical transmission of hepatitis B is geographically very variable and, depending on the prevalence of chronic surface antigenemia. For example, in Taiwan, where the prevalence of HBsAg is 5–20 %, the frequency of vertical transmission is 40 % (58). This strikingly high frequency of transmission has also been observed in some Asian and African populations where the prevalence of HBsAg also is high. In contrast, rates of vertical transmission from asymptomatic HBsAg carrier mothers is generally unusual in countries with a low prevalence of chronic HBsAg carriers. For example, in Pakistan where chronic HBsAg carriage rates are approximately 1.5 %, the vertical transmission rate is < 4 % (59). In the USA the frequency of vertical transmission also appears to be low, one study showing that only 1 of 21 infants born to HBsAg-positive mothers became positive for HBsAg (60).

The HBsAg titer also seems to be predictive of the risk of vertical transmission from women who are chronic carriers of HBsAg. Taiwanese infants had an over 90 % risk of becoming infected if their mothers had a prenatal complement fixation titer of $> 1:64$ for HBsAg (58). A high incidence of vertical transmission of HBsAg has been noted in Japan, despite a prevalence of HBsAg in the general population of only 2.2 %. In one study, eight of eleven infants born to chronic HBsAg carrier mothers developed HBsAg on follow-uo (61). HBsAg, as determined by an immune adherence hemagglutination method had been present in high titers ($> 1:512$) in maternal serum.

Another factor which correlates positively with the risk of vertical transmission from mothers who are chronic carriers of HBsAg is the presence of e antigen (HBeAg) in the maternal blood. In studies conducted in Japan and Taiwan, 85–100 % of infants born to mothers who were positive for HBeAg became chronic carriers of HBsAg (62, 63). The presence of HBeAg was a better indicator of infectivity than was the titer of HBsAg. It was originally suggested that antibody to HBeAg (anti-HBeAg) prevented vertical transmission. However, several case reports have now documented vertical transmission from chronic HBsAg-positive women who are also positive for anti-HBeAg (64). The infants described in one of these reports actually developed severe acute icteric hepatitis (65).

Hepatitis B can also be transmitted from mothers with acute hepatitis B in pregnancy or in the early postpartum period. In a study conducted in the USA 18 of 43 (42 %) infants became positive for HBsAg after being born to mothers who had acute hepatitis B during gestation or within two months postpartum (66). It was subsequently demonstrated that the risk of vertical transmission was high (76 %) if the maternal infection had occurred in the third trimester or early in the postpartum period and low (10 %) if it had occurred in the first two trimesters (67). Vertical transmission from a mother with acute hepatitis B seems to occur at the time of delivery. This conclusion is derived from the observation that neonates are usually HBsAg-negative at birth but become HBsAg-positive between 4 to 12 weeks of age (67, 68).

Transmission by breast feeding is another possible mode of maternal-neonatal spread. HBsAg has been detected frequently in breast milk (57, 69). It is quite likely that transmission by breast milk does occur but, because infection is much more likely to occur from exposure to antigen during birth, its relative contribution is neglibible. The decision to encourage or discourage breast feeding by HBsAg-positive mothers therefore should be individualized.

Manifestations

Most infants who acquire HBsAg as a result of vertical transmission become chronic carriers of HBsAg (66). The majority are asymptomatic at the time of their seroconversion and remain asymptomatic throughout childhood. Most infants do not become positive for HBsAg until around three months of age. This period corresponds to the incubation period of hepatitis B and further supports the supposition that there is contact with the virus at the time of delivery rather than transplacental passage. Some studies have noted a high incidence of cord blood seropositivity but contamination with maternal blood cannot be established. The study conducted in Taiwan showed that 21 of 103 infants born to HBsAg carrier mothers had a positive cord blood sample (59). Sixteen of the 21 infants who had cord blood samples positive for HBsAg remained chronically positive for HBsAg.

When hepatitis does develop in infants born to HBsAg-positive mothers, it is usually mild. Jaundice may or may not be evident and transaminase elevation is variable but usually transient (67). Biopsies obtained from infants with chronic antigenemia often reveal evidence of chronic hepatitis (70). Ten year follow-up studies have revealed periodic increases in liver enzymes, hepatomegaly and/or spider angiomas in some of these infants (71). A condition that seems to

be associated with HBsAg-positive neonatal hepatitis is congenital alpha 1-antitrypsin deficiency (72).

Severe and even fatal hepatitis with onset between 1 and 3 months of age is an uncommon but well described complication of hepatitis B infections in neonates (73–75). These forms of hepatitis appear to be more common in infants born to chronic carrier mothers than in infants born to mothers who have had acute hepatitis late in pregnancy or the post-partum perioid (74). Successive children can be infected from a chronic HBsAg-positive mother. In one report six children born consecutively over 22 years to a chronically infected mother contracted hepatitis (76). In four of these children the disease had a fatal course. Immune-complex mediated manifestations of chronic hepatitis B infections including glomerulonephritis, arthritis and vasculitis have been well described in adults. These manifestations have not yet been observed in infants with neonatal hepatitis caused by hepatitis B virus. Infants born to mothers who contract their hepatitis B infection during gestation have an increased incidence of prematurity (35 %) and low birth weight, irrespective of whether the infant contracts hepatitis B (67).

The single most important consequence of neonatal hepatitis B infection is the establishment of chronic antigenemia as a prelude to the development of cirrhosis and ultimately primary hepatocellular carcinoma (HCC) in later life. In those areas of the world that have a high incidence of HCC, vertical transmission of hepatitis B from carrier mothers to infants occurs more frequently than in those areas that have a low incidence. In addition, between 37 and 90 % of patients with HCC are HBsAg-positive; a figure tenfold greater than that in matched controls living in the same areas (77). In studies conducted in Senegal, West Africa where HCC is a major cause of hospitalization in young men, mothers of patients with HCC have been found to be positive for HBsAg four times more frequently than their fathers (78). This finding suggests that the virus was acquired vertically from the mother.

Prevention

It is now firmly established that vertical transmission of hepatitis B is preventable in the majority of instances using hyperimmune globulin directed against hepatitis B virus (HBIG) and the inactivated vaccine against hepatitis B. The major impact of a prevention program will be on the world-wide incidence of HCC, a malignancy with a high fatality rate. Prevention of severe and fatal cases of neonatal hepatitis B infections is obviously another goal, but the frequency of these infections is low. For any prevention program to be effective the at-risk population must first be identified. Screening of pregnant women who may be positive for HBsAg is therefore of paramount importance. Pregnant women who are likely to be HBsAg-positive include women of Asian, Pacific Island or Alaskan Eskimo descent and women born in Haiti or sub-Saharan Africa. Other women at high risk for chronic hepatitis B infection for whom screening is indicated include those with a history of acute or chronic liver disease, those employed or treated in a hemodalysis unit, those employed or resident in an institution for the mentally retarded, those rejected as blood donors, those who have had frequent blood transfusions or occupational exposure to blood in medical-dental settings, those who have household contact with a chronic carrier of HBsAg, those with mutiple episodes of venereal disease, or those who use percutaneously administered illicit drugs.

If one of these mothers is found to be positive for HBsAg, her infant should receive both passive and active immunization against hepatitis B. Passive immunization needs to be given as soon after birth as is possible. Preparation should be made to inject 0.5 ml of HBIG in the delivery room. Whereas administration of HBIG within seven days of birth was originally found to be unsuccessful in reducing vertical transmission, administration within 30 hours of birth (usually within 30 minutes) was successful (79). Although every effort must be made to give HBIG in the delivery room, if a mother is not identified as being positive until after this time, it still should be administered to the neonate. Some reduction in vertical transmission may still be possible. Passive protection against hepatitis B is effective for only a limited time, therefore if this is the sole form of immunoprophylaxis, successive doses must be administered (80). In addition to HBIG, it is now recommended that exposed infants should receive three 10 μg doses of the plasma-derived, urea, formalin and pepsin inactivated hepatitis B vaccine. The first dose can be given at a separate site at the same time as HBIG or it may be delayed until later in the first week of life. The second and third doses should be administered at 1 and 6 months of age. At least one month after the third dose of vaccine, infants should be tested for HBsAg and antibody to HBsAg, to determine the outcome of immunoprophylaxis. A randomized, double-blind controlled trial conducted in China has clearly demonstrated the enhanced efficacy of combined passive and active immunization over passive immunization alone (81). Passive immunization alone had an efficacy of approximately 71 % whereas passive-active immunization had an efficacy of almost 94 % (81). Infants had been followed up for a minimum of nine months at the time this study was published. A study being conducted in New York City, San Francisco and Los Angeles also shows that passive-active immunization reduces the chronic carrier rate to 10–12 % (82). Findings of another

large randomized study conducted in Hong Kong supported the high efficacy of the combined vaccination approach and failed to demonstrate a significant advantage of multiple doses as opposed to a single dose of immunoglobulin (83). The dose of vaccine used in this study was only 3 μg. Infants had been followed up for at least six months at the time of analysis. Whereas declining antibody is evident in infants who receive passive immunization alone, combined passive and active immunization is associated with rising antibody levels and presumably more lasting protection (84). With the means now at hand, every effort must be made to prevent the perinatal acquisition of hepatitis B and its consequent long-term sequelae.

Human Immunodeficiency Virus

The acquired immunodeficiency syndrome (AIDS) is caused by a human retrovirus, recently named human immunodeficiency virus (HIV). The current epidemic which began in the USA among homosexual men and intravenous drug abusers in New York City, San Francisco and Los Angeles is now being recognized in children. Children most at risk for this devastating illness include hemophiliacs, recipients of blood or blood products obtained from donors infected with HIV, and infants born to mothers infected with HIV.

Sources and Incidence

The two most important potential sources of HIV acquired in the perinatal period are horizontal transmission from infected blood or blood products and vertical transmission from infected mothers. The first two reports of possible transfusion-related AIDS occurring in infants as a result of blood product receipt in the perinatal period appeared in 1983 (85, 86). Interestingly, the infant in one of these reports who received multiple blood transfusions in the neonatal intensive care unit first developed transfusion-associated CMV at 11 weeks of age and subsequently developed evidence of AIDS (86). One of the six donors of blood products received by this infant eventually developed many features of AIDS. The most recent report of perinatally-acquired, transfusion-related AIDS described the clinical outcome of nine newborns who were infected by plasma transfusion from a single donor (87). The observation that all nine infants developed laboratory and/or clinical evidence of AIDS or AIDS-related complex (ARC) supported the notion that neonates have an increased susceptibility to HIV infection. Based upon epidemiologic data, previous estimates indicated that the incidence of transfusion-associated AIDS was six fold higher in infants than in adults (88).

Transmission of HIV by transfusions of blood or blood products accounted for only 18 % of the 217 pediatric cases of AIDS reported to the United States Centers for Disease Control (CDC) as of 1 December 1985. Seventy-six percent of the reported cases had as their only risk factor a mother belonging to a group with increased prevalence of HIV infection (89). The high risk groups to which these mothers belonged included those who have used illicit drugs intravenously, those born in countries where heterosexual transmission of HIV is thought to play a major role (e.g. Haiti and Africa), those who have engaged in prostitution, and those who are or have been sexual partners of intravenous drug abusers, bisexual men, men with hemophilia, men who were born in countries where heterosexual transmission of HIV is thought to play a major role, or men otherwise known to be infected with HIV. Of all these high risk groups, the most important numerically appears to be illicit drug use. In one report 76 % of 59 infants with presumed vertically transmitted AIDS had one or both parents who were abusers of intravenous drugs (90). It is believed that vertical transmission of HIV occurs transplacentally during pregnancy, during labor and delivery as a result of contact with contaminated blood or body fluids, or perhaps shortly after birth. Postpartum acquisition of HIV has been attributed to an infected blood product received by a mother who breast-fed the child for six weeks (91). HIV has been isolated from the breast milk of infected mothers (92).

Although perinatal transmission of HIV is not inevitable, the rate of such transmission from infected mothers to their offspring appears to be high. In one study of 20 infants born to mothers who had already had one child with AIDS, 65 % of these subsequent infants had serologic and/or clinical evidence of HIV infection several months after birth (93).

Manifestations

Most children with AIDS contracted in the perinatal period develop clinical manifestations of their immunodeficiency during the first year of life. However, the longest latency period reported to date is 5 1/2 years (94). The most consistent clinical features of infants who contract AIDS are chronic interstitial pneumonitis, hepatosplenomegaly and failure to thrive. Other frequent abnormalities include diffuse adenopathy, protracted or recurrent diarrhea, persistent thrush, thrombocytopenia and a wide spectrum of infections (95, 96). Patients born to infected mothers are frequently small for gestational age. Infectious agents frequently isolated from infants with AIDS include opportunistic organisms such as *Candida* spp., *Pneumocystis carinii* and *Mycobacteria avium*, and viruses such as CMV, HSV, VZV and EBV (95). In contrast to adult patients with AIDS,

pyogenic infections such as otitis media, sinusitis, pneumonia and septicemia are also common in children with AIDS (97). The most frequent bacterial pathogens isolated include *Streptococcus pneumoniae, Haemophilus influenzae* type b and *Salmonella* spp. (97, 98).

Immunologic evaluation of infants with AIDS usually reveals a normal complete blood count, a decrease in the T helper lymphocytes resulting in a reversal of the ratio of T helper cells (OKT8+, Leu3+) to T suppressor cells (OKT4+, Leu2+), reduced proliferation of mononuclear cells following stimulation with non-specific and specific mitogens, and cutaneous energy to delayed hypersensitivity antigens (95, 98). Most infants with AIDS also have demonstrable B cell abnormalities. They often have polyclonal elevation of their immunoglobulins and do not respond to specific antigenic challenge with appropriate antibody increases (99, 100). T cell function tends to deteriorate later in children than in adults whereas B cell function tends to deteriorate earlier (95, 98).

Given the correct clinical circumstances and laboratory findings, the diagnosis of AIDS is confirmed by the presence of serum antibody to HIV and/or the isolation of HIV from body fluids or tissues. The prognosis of children with AIDS is a bleak as that of adults with AIDS. In a recent study of 64 cases of AIDS in children, of which 59 were presumed to be vertically transmitted, the median survival time from the time of diagnosis was slightly less than three months (90). Seventy-five per cent of the children were dead within one year of diagnosis.

Prevention

Since most cases of AIDS acquired in the perinatal period result from exposure to infected parents, prevention of AIDS in adults should prevent cases in children as well. Counselling services and testing for antibody to HIV should be offered to pregnant women and women who may become pregnant if they are members of any of the AIDS high-risk groups as defined above. Women identified as being infected with HIV should be encouraged to consider postponing pregnancy until more is known about the risk of vertical transmission of HIV. Infected women already pregnant should be made aware of the seemingly high rate of vertical transmission and the high likelihood of manifest disease in their offspring. It must be emphasized to these women that the available data has substantial limitations. A decision as to whether to undergo a therapeutic abortion then must be made. If the decision is to continue the pregnancy, these infected women should be advised against breastfeeding to avoid postnatal transmission to a child who may have escaped infection. The exposed child should receive frequent follow-up evaluations to determine whether or not infection with HIV has ensued and to diagnose and treat promptly any diseases that might be secondary to infection with HIV (89).

Transfusion-related, perinatally acquired AIDS has been a problem of much less magnitude in comparison with vertical transmission of HIV. In addition, the current policy of screening all blood and blood product donors for antibody to HIV and excluding all seropositive donors should virtually eliminate the risk of perinatal transfusion-related infections. Nevertheless, constant scrutiny of the requirements of each neonate for transfusions should be encouraged. Unnecessary transfusions should be eliminated.

Respiratory Viruses

Sporadic cases of infection and epidemics caused by respiratory viruses have been reported in neonatal intensive care units. The two agents most commonly implicated have been respiratory syncytial virus (RSV) and influenza A virus. Their recognition is important because of the introduction of a new antiviral agent, ribavirin, along with reliable methods for rapid viral diagnosis, e.g., direct immunofluorescence or ELISA antigen detection. Ribavirin, when administered by aerosolization, has demonstrated some effectiveness in young children and adults against both RSV and influenza virus infections (101). Its ultimate role in the management of these infections is still being defined.

Sources and Incidence

The number of reports of neonatal RSV infections exceed the number of reports of neonatal influenza infections (102). Most of the infections have not been traced to maternal sources, but rather have been presumed to result from exposure to infected hospital personnel or visitors from the community (103–105). Nosocomial outbreaks have then sometimes ensued (103–109). Two recent neonatal outbreaks were interesting in that there were two concurrently circulating respiratory viruses, RSV with rhinovirus in one (110) and RSV with parainfluenza virus type 3 in the other (111). Although the total number of reports of neonatal infections caused by the respiratory viruses is limited, they most certainly underestimate the true magnitude of the problem. Hospital infection control personnel tend to seek out and investigate neonatal outbreaks of bacterial or fungal disease, whereas less attention is given to respiratory viral disease. It is only through careful monitoring of neonates during the respiratory virus season that the prevalence of infection will be determined and appropriate interventions made.

Manifestations

Symptoms of infections in newborns caused by the respiratory viruses are often non-specific, especially

in infants less than three weeks of age at the onset of their infection (109). The illness is usually mild and self-limited. Fever is variably present. Occasionally neonatal infections are severe, mimicking bacterial sepsis (103, 112). Fatalities attributed to these viruses have been reported (109). Infants who appear to be at the highest risk for severe infections are those with underlying bronchopulmonary dysplasia or cyanotic congenital heart disease (113). When respiratory symptoms are evident, they are more often of an upper respiratory type than a lower respiratory type. In several reports, apnea has been a manifestation associated with RSV infections (114, 115). Risk factors for the development of apnea in RSV infected infants include premature birth and a young postnatal age (115).

Prevention

As already noted, most neonates seem to acquire their respiratory viral infections from infected visitors or hospital personnel. The nosocomial outbreaks which have been described are presumed to involve the spread of virus from patient to patient through hospital personnel. Therefore, in order to reduce the risk of neonatal infections, strict visiting regulations must be enforced during community epidemics of respiratory illness and all personnel with manifestations of a respiratory viral infection should be excluded from direct patient contact. Also, whenever feasible, infected infants should be isolated in a single room and cared for by a nurse who does not have to care for other neonates. The spread of RSV appears to be by close contact with infectious secretions through direct inoculation of large droplets or contaminated hands (116, 117). Thus careful handwashing should be stressed. Infectivity is greater if virus is inoculated into the nose or eyes, and less if inoculated into the mouth (118). It is not surprising therefore that the use of masks and gowns by hospital personnel does not effectively reduce nosocomial spread of RSV (119). However, preliminary evidence does support the effectiveness of eye-nose goggles (120).

Enteroviruses

The non-polio enteroviruses of the ECHO and Coxsackie groups cause annual epidemics during the summer and fall in temperate climates. The enteroviruses exist as many antigenically distinct serotypes so that individuals of all age groups become infected during community outbreaks. Intrauterine infection can occur, as shown by the presence of symptomatic Coxsackie myocarditis at birth in a few cases, but most neonatal enteroviral infections are acquired in the perinatal period (121, 122).

Source and Incidence

Infants born during an epidemic may be exposed because of maternal infection at the time of delivery (123). The enteric viruses are excreted in feces for several weeks after the acute infection so that maternal transmission to the infant can occur without recent maternal illness. Maternal enteroviral infection is rarely recognized because the symptoms are nonspecific, except for such findings as herpangina or hand-foot-mouth syndrome; adult infection is also often asymptomatic. Infants are also exposed to enteroviruses by non-maternal contacts. Nursery outbreaks of enteroviral infection have been reported with many ECHO virus serotypes as well as Coxsackie A and B (124, 125). In a prospective study Jenista et al. found that 12.8 % of newborns discharged during a typical enterovirus season became infected (126).

Manifestations

Many case reports emphasize the morbidity and mortality associated with perinatal enteroviral infection. However, the prospective study by Jenista et al. proved that most infected infants remained asymptomatic (126). Twenty-one percent of these infants were hospitalized with symptoms of fever and lethargy which resolved without complications. The usual interval to onset of symptoms caused by perinatal enteroviral infection is 3 to 5 days (121). As reported by Lake et al., most infants with neonatal enteroviral infection do not have the risk factors associated with bacterial sepsis, i.e. prematurity, premature rupture of membranes and maternal obstetrical complications, but 59 % of the mothers of these infants had had a febrile illness within ten days before delivery (127). Unless viral cultures are obtained, these infants are often considered to have bacterial sepsis with negative bacterial cultures. ECHO or Coxsackie viruses were cultured from 41 % of infants under two months of age who were hospitalized for suspected sepsis whereas bacterial pathogens were isolated in only 18 % (128). The enteroviruses are cultured from feces most reliably and may be present in oropharyngeal secretions; ECHO viruses can be isolated from CSF in the absence of pleocytosis. A serologic diagnosis can be made in retrospect for Coxsackie serotypes; the multiple serotypes of ECHO viruses makes serologic testing very difficult.

The life-threatening manifestations of perinatal enteroviral infection include meningoencephalitis, hepatitis and myocarditis (129). Typical signs of infection among infants with severe illness include fever, lethargy, irritability, seizures, rash, abdominal distension, hepatomegaly and jaundice (124, 127). The rashes associated with enteroviral infection are usually punctate, maculopapular and erythematous

but can be quite variable and are not diagnostic. Infants presenting with fever and lethargy may have no abnormal findings but liver function tests may be elevated at admission. The cerebrospinal fluid may show mild pleocytosis, slightly elevated protein and normal glucose.

The highest risk of fatal infection is associated with fulminant hepatitis in infants with ECHO viral infection and with myocarditis in cases of Coxsackie infection (122). Modlin found that severe hepatitis was fatal in 83 % of infants with perinatal ECHO virus infection while 19 % of those with meningoencephalitis died (121). In addition, his analysis of the reported nursery outbreaks revealed that five of six infants who had acquired infection from their mothers died whereas the mortality rate among secondary cases in the nurseries was 3 of 24 (12 %). Fatal ECHO 11 infection was associated with undetectable neutralizing antibody against the virus in cord blood from four infants while seven infants who were infected with the same strain but were not ill, had titers from 1:20 to 1:320 (123). Most fatal enteroviral disease is now caused by various ECHO virus serotypes. ECHO 11 serotype has been a particularly common cause of nursery outbreaks between 1956 and 1982. Neonatal Coxsackie B outbreaks occurred in 1961, 1967 and 1972 but have been uncommon since then although sporadic severe disease continues to be diagnosed (122).

Prevention

Neonatal enteroviral infection as a consequence of maternal infection during community outbreaks cannot be prevented in most cases. Enteroviral infection should be considered among the causes of maternal fever during these periods so that delivery can be delayed if possible. Careful handwashing and limiting the number of people having direct contact with newborn infants should reduce the risk of infection from non-maternal sources during seasonal epidemics. The possibility of nosocomial infection must be considered if hospitalized infants have symptoms consistent with enteroviral disease during such periods. Viral cultures should be taken from these patients to determine whether infection control measures, such as cohorting of infants, need to be initiated. Low passive antibody titers in severely affected infants suggests that immunoprophylaxis with antibodies against the relevant enteroviral serotype might be effective. However, immunoglobulin did not appear to modify the attack rate or symptoms of ECHO 11 infection in a recent nursery outbreak (130).

Rotavirus

Sources and Incidence

Rotaviruses and other enteric viruses, such as astrovirus, calicivirus, coronavirus and minirotavirus, cause asymptomatic infection or diarrheal disease in newborns. Among these, the rotaviruses, which have worldwide prevalence, are the most common pathogens in neonatal viral gastroenteritis (131). The observation that rotavirus can be isolated from infants on the first day of life suggests that most infection is transmitted from the mother at the time of delivery. Depending upon the prevalence of rotaviral infections in the community, the rates of excretion among newborns range from 0–50 %. Excretion is not associated with any identifiable risk factors. All four of the major rotaviral serotypes have been associated with perinatal infection (132).

Manifestations

While rotavirus infection in newborns is widespread, most infants from whom the virus has been isolated are asymptomatic or have transient, mild diarrhea. The diarrhea is watery and is not associated with blood or mucous (133). In contrast, older infants from 6 to 24 months of age are much more likely to develop severe diarrhea requiring hospitalization (134). Rotaviruses do not cause direct infection of other organs; other symptoms of severe disease are a consequence of dehydration and electrolyte losses. One serious outbreak of necrotizing enterocolitis has been described in which symptomatic high-risk newborns were infected with rotavirus (135). Rotaviruses replicate poorly in tissue culture. The presence of rotavirus in feces can be demonstrated by electron microscopy and by enzyme immunoassay or latex agglutination for antigen detection (131). The antigen detection methods are reliable in symptomatic patients because of the high titers of virus present in stool. However, when used to test neonates for asymptomatic infection, ELISA methods may produce false positive results (136).

Prevention

Since rotaviral infection in newborns is usually mild, attempts to prevent perinatal infection could have adverse effects in postponing the initial rotaviral infection to later infancy when the clinical consequences are more significant. In a prospective study, Bishop et al. found that infection of newborns with one rotaviral strain did not prevent subsequent reinfection but infants who had perinatal rotavirus infection did not develop severe diarrhea due to rotaviruses during the first three years of life (137). The role of breastfeeding in preventing perinatal rotavirus infection remains controversial (138, 139). Breastfed infants may be protected from the more

severe symptoms of gastrointestinal infection by maternal antibodies to rotavirus present in breast milk. Recently, important progress has been made in developing effective rotaviral vaccines. Initial studies with the RIT 4237 live attenuated bovine rotavirus vaccine showed a vaccine protection rate of 82 % in infants vaccinated just before a rotavirus epidemic (140). However, vaccine-induced immunity is not likely to prevent rotaviral infection in the immediate perinatal period and is also probably not necessary.

Human Papilloma Virus

Source and Incidence

Human papillomaviruses have been identified as the cause of condyloma acuminata (genital warts) and cervical condylomata (141). This group of viruses is now recognized as among the most common sexually transmissible agents. Although HPV cannot be isolated in tissue culture, recent investigations using cloned viral DNA probes, as developed by zur Hausen, suggest that HPV DNA sequences are present in cervical cells from 2.2 % of women (142). Infection of the infant is presumed to be due to maternal-infant transmission at delivery. The frequency with which asymptomatic infection occurs among infants of infected women is uncertain. In a recent study foreskins from three of 70 infants were positive for HPV DNA of virus types which have been found in genital condylomata, i.e. HPV-6 and HPV-16 (143). This study suggests a relatively high rate of perinatal exposure to HPV but the potential for false positive results with hybridization methods and the lack of a confirmatory method must be recognized in these early efforts to investigate perinatal infection with HPV.

Manifestations

Despite the difficulty of laboratory detection of HPV, the epidemiologic evidence provides strong support for the association of maternal HPV infection with the occurrence of laryngeal papillomatosis in infants and young children. Quick et al. found that 21 of 31 mothers of children with laryngeal papillomata had a history of genital warts during pregnancy or at delivery (144). The detection of HPV DNA sequences of the same viral types in papilloma tissue resected from patients with laryngeal papillomatosis confirms the epidemiologic evidence of maternal-infant transmission (145). The interval to the onset of clinical symptoms in infants with laryngeal papillomatosis is variable, as is the rapidity with which the disease progresses. The primary symptom in these infants is respiratory difficulty caused by airway obstruction. In the most severe from of the disease, lung parenchymal involvement ensues. In addition to laryngeal disease, a few infants have been described who developed condyloma acuminata after birth to mothers with genital warts (146).

Prevention

Until the route of infection and the frequency with which exposure to maternal HPV causes neonatal infection have been determined, preventive measures to protect infants from HPV cannot be established. Cervical and genital tract HPV infection appears to be quite common in the USA and Europe, including a high rate of asymptomatic maternal infection. Nevertheless, juvenile laryngeal papillomatosis is an exceedingly rare disease. While cesarean delivery might prevent the exposure of infants of women with condyloma acuminata to HPV, this approach cannot be supported by specific data concerning the risk to the infant.

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