Aspects in the neurological localization of intrapartum infections

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ABSTRACT

There are many infectious diseases that the newborn can acquire during the passage through the birth canal. Since the evolution of the medical world, the transmission risk during childbirth has declined severely but it’s not non-existent. We included several studies discussing the most important infections that can be transmitted intrapartum and that can have neurological outcomes. These studies have proven a correlation between newborn intrapartum infections and neurological disorders, as well as long-term neurological sequelae in some cases.

Keywords: intrapartum infections, neurologic outcome, group B Streptococcus, Ureaplasma, Herpes simplex virus

INTRODUCTION

Infectious pathology is common in newborns, the risk being higher with lower gestational age. Such infections can be acquired antenatally, during birth or postnatally. Perinatal infections, transmitted from the genital tract of the mother to the newborn, can be done by colonization with pathogens and prolonged membrane rupture (more than 18 hours) [1]. The placenta actively carries maternal IgG antibodies, although effective levels for all species do not occur until later in pregnancy and it doesn’t include the transport of IgM antibodies [2].

There are many infections that can affect the newborn during pregnancy. Due to the fact that newborns lack the typical microbial flora of non-pathogenic organisms and have an underdeveloped immune system, their bodies are quickly colonized by organisms from the mother’s genital canal and their surroundings [3].

In this review, we presented the most important germs that can be transmitted intrapartum and that can generate unfavorable neurological outcomes: Group B Streptococcus, Herpes Simplex Virus, Ureaplasma, Enteroviruses, Gonococcus, Cytomegalovirus and SARS-CoV-2.

GROUP B STREPTOCOCCUS INFECTION

Group B Streptococcus (GBS) represents a bacterium that most often causes invasive infections in newborns [4]. It is commonly found in the genital and gastrointestinal tract and colonization among pregnant women is usually asymptomatic [5].

The reported incidence in pregnant women usually varies between 15% to 40%, however, a lower incidence was reported, during recent studies, in some Eastern European countries (Romania 6.2%, Bulgaria 7.8%, Moldova 5.9%) and Israel 3% [6]. However, some studies estimate that the official number of cases in some countries might be underreported, the real values being higher [7]. From 1993, in the next fifteen years, the incidence of early-onset GBS disease has met a decline of 83.5 percent [8].

During pregnancy, the fetus can acquire a GBS infection due to an intraamniotic infection, rupture of membranes and also during the passage through the birth canal [5].

The major cause of neonatal and infant meningitis and sepsis is Group B Streptococcus. GBS infection in neonates manifests as either early-onset disease (EOD), in the first week of life or late-onset illness (LOD), between 7 and 90 days of life. LOD can be trans-
mitted vertically and horizontally from the community and nosocomial sources, while EOD is commonly associated with GBS in the mother’s birth canal and transmission during childbirth [7]. The bacterial meningeal inflammation can have some neurologic repercussions such as disruption of the blood-brain barrier (cerebral edema), brain parenchymal inflammation (cerebritis) and impaired cerebrospinal fluid circulation culminating in hydrocephalus. Little is known about the impact of bacterial meningitis on the cerebral blood supply and the subsequent ischemic stroke.

In a study from Germany published in 2010, Hernandez et al. present the evolution of eight neonates (50% females and 1 preterm newborn) who were diagnosed with GBS meningitis. At approximately 8 days of life, the neonates developed fever, seizures, poor feeding and lethargy. Every newborn was scanned using MRI within the 3rd and 14th day of the hospital admission and they concluded that 7 of the 8 neonates had modifications on the MRI. The MRIs described a deep pattern of arterial ischemic stroke in some territories affecting the thalamus, deep white matter and basal ganglia; 6 of the 8 neonates were diagnosed with superficial cortical infarction. Large artery ischemic stroke was not observed. The follow-up MRI showed chronic injury modification such as hydrocephalus and atrophy in the affected structures [9].

24 months after, Hernandez et al. studied the neurological outcomes of all the infants and discovered that 6 of the 7 children presented neurologic impairment such as cerebral palsy (86%), global development delays (71%), language deficit (86%), hydrocephalus (57%), epilepsy (29%) and visual impairment (29%) [9].

Another study from China, published by Chang et al., documented 166 children of different ages, admitted to a hospital between 1986 and 2001. The infants presented with bacterial meningitis with a different etiology and they discovered that less than 10% of all patients developed cerebral infarction [10].

Fluegge et al. documented 347 and 360 infants with invasive infection with group B Streptococcus admitted between 2001-2003 in Germany. The most frequent complication for EOD was sepsis alone, at about 80.1%. However, they found in 13.6% of cases an association of sepsis with meningitis, and only 2.3% of cases presented meningitis. Between 85% and 92% of the patients with EOD developed symptoms in the first 24-48 hours of life. On the other hand, patients with LOD had a much higher rate of developing meningitis (61.8% compared with 16% in EOD) or had neurologic symptoms (32.4% compared with 15.4% in EOD). At the time of the release from the hospital, because of the GBS infection, 50 of the 347 infants (13.8%) presented sequelae, the most common being hydrocephalus (14 cases) or hydrocephalus combined with cerebral seizures (11 cases). Other types of infant sequelae are represented by microcephalus, retinopathy, defective hearing, intracerebral abscess, muscular hypotension and one case of cerebral palsy. Overall mortality was 4.3% and there was no difference in mortality between EOD and LOD [7].

Levent et al., documented in a retrospective review 53 infants born at more than 36 weeks of gestation, hospitalized between 1998 and 2006 in Texas and diagnosed with group B Streptococcus meningitis. LOD was more prevalent than EOD (43 cases and 6 cases). The most frequent symptoms at admission were irritability, lethargy, respiratory distress, seizures, fever and poor feeding. The infants received antibiotic therapy for an average of 21 days. At discharge, 50% of the patients with EOD and 17% of the patients with LOD presented neurological impairments most common being persistent seizures and hypertonicity. Other outcomes were prevalent in the LOD and include hypotonia, clonus, dysphagia, ptosis, cortical blindness and hearing loss. There were no deaths in the EOD group and only 3 infants died in the LOD group [8].

**HERPES SIMPLEX VIRUS (HSV)**

Herpes simplex is a DNA double-stranded virus with two known types: HSV-1 and HSV-2 [11]. The incidence of HSV in neonates has been estimated between 1 in every 3200 to 10000 live births. There have been documented three forms of this disease which are: the skin/eye/mouth form, the disseminated and the central nervous system form [12].

The most common way of transmission to the neonate is during childbirth (85% incidence), when the virus shedding is present either asymptomatic or symptomatic on the reproductive tract [13]. The risk for neonatal infection is also impacted by the mode of delivery or by the rupture duration of the membranes [14].

Almost 30% of neonatal infections with HSV will develop into a central nervous system disease. Clinical manifestations include lethargy, seizures, tremors, bulging fontanelle, irritability, poor feeding [11]. Even when receiving acyclovir treatment, almost 50% of the patients infected with HSV in the central nervous system develop neurologic impairment [12]. Untreated, the outcomes can worsen, leading to death with a rate between 30 and 80 percent [15].

In a retrospective study, Vossough et al., followed 12 patients with herpes simplex virus type 2 encephalitis. A total of 24 CT and 22 MRIs were performed on the patients over 38 months. Early in the disease’s course, the CT and MRI images showed only mild abnormalities or were normal. After a while, the dis-
ease evolved as multifocal in 67% of the patients and in the others was only limited to the cerebellum and brainstem or temporal lobes [16].

Okanishi et al. reviewed, in another retrospective study, 13 neonates that were admitted in the hospital with the diagnosis of isolated HSV encephalitis. The main symptoms were fever (57%), lethargy (23%), seizures (38%) and poor feeding (8%). They performed MRI and DWI (diffusion-weighted imaging) scans separated in 4-time points. Superficial cerebral lesions were discovered by all scans at less than 7 days after the onset. There were also found deep cerebral lesions which all coincided with the superficial ones. All the patients affected by the bilateral deep cerebral lesions showed severely delayed outcomes of motor functions and IQ/DQ scores [17].

A prospective study, between 2000 and 2003 in Canada by Kropp et al., reported 58 neonates infected with Herpes simplex virus (the incidence was 5.9 per 100000 live births). The majority (62.5%) were diagnosed with HSV-1, whereas the rest (37.5%) were typed as HSV-2. The majority of the HSV infections were localized (59.6%), involving mostly the skin (>90%) and disseminated infections were discovered in 18% of the patients. 22.8% of the patients had central nervous system disease and the total fatality rate was 15.5%. At the 2-month follow-up, 24.1% of the infants displayed neurological sequelae, mostly in HSV-2 infections, but also in disseminated or central nervous system infections. Also, there were highlighted some developmental delays in motor function, language, and social development, certain infants developed seizures, microcephaly, hydrocephaly and blindness [18].

UREAPLASMA INFECTION

Ureaplasma belonging to the Mycoplasmataceae family, represents a bacterium that contains two species capable of infecting the human: Ureaplasma urealyticum and Ureaplasma parvum. Ureaplasma species are commonly found in the lower genital tracts of sexually active women, with colonization rates ranging from 40% to 80%. Vertical transfer to the baby is frequent, especially in preterm neonates weighing less than 1000g [11], and in general, the transmission rate ranges between 18% and 88% [19].

The neonate can get infected through several mechanisms including exposure of the fetus to the ascending intrauterine infection, passage through the infected birth canal and hematogenous dissemination. Ureaplasma urealyticum meningitis affecting the newborn was first documented in 1986 and since then several researches showed that Ureaplasma urealyticum can cause invasive disorders such as bacteremia, pneumonia and central nervous system infection [20].

A case report from 2013, published by Marao et al., describes a 7-day-old neonate that was diagnosed with Ureaplasma urealyticum meningitis. The disease manifested with fever, seizures as well as apneic episodes requiring intubation. The doctors performed brain magnetic resonance imaging which displayed multifocal subdural collections that caused a mass effect and hydrocephalus. Another brain MRI was performed after 6 weeks of treatment which showed complete normalization of the previous abnormalities [21].

Zhan et al. (2021), affirms that Ureaplasma parvum meningitis is very rare in neonates. There have been only 6 reported cases in the English literature. In this study, Zhan et al., presents a neonate that after 5 days from birth developed fever and later seizures and tight fontanel. A brain MRI was performed by the doctors and which revealed a subdural hemorrhage on the right parietal temporal lobe and on the occipital lobe. A later MRI showed right cerebral hemisphere atrophy with cortical necrosis. Before discharging they performed an ultrasound that showed an enlargement of lateral ventricles. After 5 months, the infant has developed normally without any neurological complications [19].

A similar case was reported by Wang et al. in 2019, where an 11 days old infant was admitted with fever and hypotonia. The MRI showed a mild expansion of the right lateral ventricle and ventriculitis without any bleeding or abscess. After 6 months, the follow-up MRI revealed the resolution of the previous complications and after 18 months the infant developed normally without any neurological impairment [22].

CYTOMEGALOVIRUS

Human cytomegalovirus (CMV), is a herpesvirus family DNA virus, also known as human herpesvirus 5. In the United States, CMV is one the most frequent pathogens that produce congenital infections, with an incidence between 0.5 and 1.3 percent of all newborns [11] and worldwide the incidence is about 1 percent [23].

The neonate can get infected from the mother transplacentally causing congenital infection, during the passage through the birth canal and through breast milk [24]. Pass et al. affirms that the neonate infected with CMV through breast milk and during birth will not get central nervous system sequelae compared with congenital infections [24].

Women who are positive for CMV antibodies will more likely develop cervicovaginal shedding of the virus. A study of women who were tested for vaginal shedding while pregnant and did not breastfeed after birth revealed that 50% of the newborns were infected with CMV. Furthermore, women who are al-
ready infected with HIV are more likely to acquire an active CMV infection with vaginal and cervical shedding [24].

**ENTEROVIRUSES**

Enteroviruses are RNA viruses belonging to the Picornaviridae family. It has been found that neonates are more severely affected by enteroviruses compared to older children. The most common infection at neonates are non-polio enterovirus infections that usually manifests with poor feeding, irritability, lethargy, and fever with or without a rash and can occasionally lead to sepsis, hepatitis, myocarditis and meningoencephalitis [25].

The most common mechanism of neonatal infection with enteroviruses (63%) is realized via direct contact of the newborn with maternal fluids such as stool, blood or vaginal secretions during delivery. There have been some isolated cases of transmission via breast milk [25-27]. On the other hand, breastfeeding was found, in a study from Sadaharju et al., to be a good protective factor against symptomatic enterovirus infections because of the existence of neutralizing antibodies [28].

Morris et al. documented 5 neonates in the United States, infected with enterovirus, most likely perinatally, with ages ranging from 3 to 10 days. 3 of the 5 neonates were diagnosed with meningitis or meningoencephalitis. However, only one child was developmentally delayed by the age of 9 months and had increased tonus in his left leg, the rest following normal development [29]. Many Echoviruses and Coxsackie virus B1-B5 have been mostly associated with neonatal cases of enteroviral meningoencephalitis [30].

Other studies have shown that long-term sequelae caused by neonatal enteroviral infection are rare, however, patients that developed enteroviral meningitis or encephalitis had some persisting neurological deficits such as seizures, language disorders, learning difficulties and spasticity [27].

**GONOCOCCAL INFECTIONS**

Gonococcal infections are the most commonly spread through sexual contact and are caused by gram-negative diplococcus Neisseria gonorrhoeae [31].

In the United States, the reported incidence per 100,000 people is around 171.9 gonorrhea cases, compared to Spain where the reported incidence is around 13.89 cases per 100,000 individuals [32,33]. The probability of perinatal gonorrhea transfer from the mother to the newborn is between 30% and 40% [34].

Gonococcal infection is commonly acquired by newborns during delivery via contact with the mother’s infected cervix. However, an intrauterine infection can also happen before delivery, after the membranes have ruptured [35].

The most prevalent clinical symptom (accounting for 80% of the cases) of neonatal disease is neonatal conjunctivitis [11]. The manifestation debuts in two to five days after delivery [32].

Disseminated disease is a rare manifestation of a perinatally exposed newborn to gonococcal infection, with an incidence of less than 1 percent. The most frequent form of manifestation is septic arthritis. Other manifestations are rare and include sepsis and meningitis [36]. Fever, lethargy, vomiting, agitation and poor feeding are common presenting signs and symptoms. Cerebrospinal fluid should be evaluated if there is a suspicion of systemic gonococcal infection [35].

In the present day, meningitis caused by gonococcal infection is very rare, due to preventive measures that are enforced to diagnose and treat during pregnancy. In the current literature, meningitis is only referenced as a complication of the gonococcal infection and there are very few documented cases.

In 1933, Bradford et al. documents thoroughly a newborn diagnosed with conjunctivitis which later developed into meningitis. The diagnosis was confirmed at 18 days of life by a lumbar puncture. The infant further developed convulsions and died at 41 days of life. It’s not certain if the neonate received any antibiotic treatment [37].

**SARS-COV-2**

Globally, an increasing number of pregnant women have been diagnosed with COVID-19 and during gestation, intrapartum or early postnatal period, the neonate can get infected from the mother. World Health Organization reported in 5 case reports that SARS-CoV-2 is rarely present in vaginal swabs. However, SARS-CoV-2 RNA shedding can be present in the stools of infected persons. The neonate can get infected from the birth canal or vulva through contaminated fecal matter. On the other hand, distinguishing between the moment of infection (postnatal or perinatal) is rather difficult [38]. A recent review estimates that the intrapartum or congenital transmission rate is around 39% and the postpartum transmission rate is around 15% [39].

The most common manifestation in neonates is respiratory distress, others being asymptomatic and some others manifesting gastrointestinal symptoms. There were documented certain neurological symptoms such as lethargy, hypotonia, apnea, irritability and seizures in 26.4% of the studied neonates [40]. Fragoso et al., described a case of a male term neo-
nate who was diagnosed with severe encephalitis with brain edema. He tested COVID-19 positive in his third day of life, but he was released home because he did not have any symptoms. After a couple of days, the neonate presents left arm focal to bilateral clonic seizures, lethargy and hypotonia [41]. They postulated that the neurologic symptoms, including cytotoxic cerebral edema and refractory seizures, were produced by the infection paired with the matching immune response in the neonate reported here [41].

There are few studies that report the neurologic outcome of SARS-CoV-2-infected neonates and the reported number of cases might be underestimated. More studies are needed to be able to conclude the long-term neurologic outcome.

CONCLUSIONS

The current literature has shown a correlation between neonatal intrapartum infections and neurologic disorders and in some cases long-term neurologic impairments. The most common prevention methods of intrapartum infections are represented by the introduction of prophylaxis guidelines, prenatal screening of the mother with early detection of infections and adequate treatment according to the implied infectious pathogens. Furthermore, generated costs by these prevention methods are much lower compared to the costs of prolonged hospitalization of the newborn together with the costs of neurological follow-ups and treatments of the child.

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REFERENCES


