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Viral infections of the developing nervous system

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Both clinical and experimental studies indicate that viruses can interact with the developing nervous system to produce a spectrum of neurological damage and brain malformations. Following infection of the pregnant woman, virus may indirectly or directly involve the fetus. Direct involvement is generally due to transplacental passage of the virus and invasion of fetal tissue. Resultant disease is determined by a variety of virus-host factors, including the developmental stage of the fetus at the time it is infected, the neural cell populations which are susceptible to infection, the consequent virus-infected cell interactions, and the mechanism and timing of viral clearance. There is a growing list of human viruses which injure the developing nervous system. There are also several experimental models in which congenital viral infections have been shown to result in a variety of brain malformations but with no evidence of the prior infection remaining at the time of birth.

Key words: congenital viral infection / fetus / brain malformations / developing nervous system

AN INCREASING NUMBER of viruses are recognized as capable of causing intrauterine or perinatal infection with consequent damage to the developing human nervous system (Table 1).¹ Infection of the fetus or neonate may be fatal, may produce a spectrum of fixed or progressive neurological damage or may have no apparent consequences. Both virus and host factors determine the outcome of a congenital infection. All the viruses listed in Table 1 produce obvious inflammatory neuropathological changes consistent with an infectious process. There are also a number of animal models in which viral infection of the fetus results in congenital anomalies of the nervous system, reminiscent of human defects that are generally considered to be genetic, toxic or vascular in nature.^{1,2} Here I consider the pathogenic mechanisms involved in a congenital infection, highlight several experimental models which may have particular relevance for human birth defects

and cover briefly the human viruses which are known to have major effects on the developing nervous system.

Pathogenic mechanisms

A maternal viral infection may have adverse consequences for the fetus even though it does not lead to viral invasion of the fetus. Severe maternal systemic illness can result in fetal death. Smallpox epidemics, for example, were historically associated with high rates of abortion even though virus did not appear to infect fetal tissue.² The placenta is known to act as a partial barrier to viral transmission and maternal infection with associated viremia may lead only to placental infection without fetal involvement. But because the placenta serves an important nutritional role for the fetus, a significant placentitis will result in intrauterine growth retardation. Maternal virus may also directly invade fetal tissue through one of four possible routes: (1) a maternal viremia with virus crossing the placental barrier to enter the fetal blood system or amniotic fluid; (2) extension of infection from the adjacent cervical-amniotic region; (3) infection of germinal cells; or (4) genetic transmission of viral genome.

Most congenital infections involve the first mechanism, which requires that the virus produce a maternal viremia of sufficient magnitude and duration to penetrate the placenta. The placenta is formed by the chorion, an outer embryonic fetal membrane, and the decidua, which is part of the uterine mucosal coat. By 12 weeks of gestation, maternal blood flows through the trophoblastic cell layer into intervillous spaces, into which fetal blood vessels covered by a trophoblast layer also extend, so that the fetal and maternal blood system are almost contiguous. Any virus which infects and crosses these membranes will enter the fetal system. Penetration of the chorionic plate and amniotic membranes by mechanisms such as phagocytosis or infiltration of infected cells will also shed virus directly into fetal tissue. The second category includes certain perinatal infections, such as those caused by herpes simplex virus (HSV), which typically occur during parturition as

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Table 1. Viruses which damage the human developing nervous system

Agents	Time of infection	Sequelae
Major Agents		
Cytomegalovirus	Intrauterine (especially first half of pregnancy)	Cerebral calcifications, focal encephalitis and periependymitis, hearing loss, mental retardation, microcephaly, motor abnormalities, neuronal migration defects, psychomotor retardation, seizures
Herpes simplex virus (type I 20%; type II 80%)	Perinatal (rarely intrauterine)	Necrotizing encephalitis, microcephaly
Human immunodeficiency virus-type I	Intrauterine (rarely perinatal)	Progressive subacute encephalitis with brain atrophy, developmental delay, dementia, motor deficits
Rubella	Intrauterine (especially first trimester)	Behavioral disturbances, chronic encephalitis, hearing loss, meningo-encephalitis, mental retardation, microcephaly, motor deficits
Minor Agents		
Arboviruses	Intrauterine (late)	Encephalitis
Coxsackie B viruses	Perinatal (?late intrauterine)	Encephalitis with myocarditis
Human parvovirus B19	Intrauterine	Fetal hydrops, intrauterine death (10%)
Polioviruses	Intrauterine (late)	Paralytic polio
Varicella zoster virus	Intrauterine (first half)	Cicatricial scar, encephalomyeloradiculitis, limb hypoplasia

Adapted from Johnson (1988).¹

the infant passes through an infected birth canal. The third and fourth mechanisms are known to occur in animals but have not been documented to occur in humans. Lymphocytic choriomeningitis virus (LCM) infects germinal epithelium in the ovary and ovum of the mouse and can be passed to offspring.³ Murine leukemia virus can be transmitted in provirus form, integrated into the parental chromosome.⁴

The fetal immune system is immature and cannot mount a normal defense. The only maternal antibodies which cross the placenta are immunoglobulin G (IgG, preferentially the IgG₁ subclass), which bind to Fc receptors on the trophoblast membrane, beginning in the first trimester. Specific fetal IgG and IgM are not made before 20 weeks gestation. Once virus infects the fetus, it generally disseminates freely to tissues including the nervous system. Several factors determine the sequelae of viral infection of the developing nervous system: the developmental stage of fetal brain; the cell populations vulnerable to infection; the effect of the virus on these cell populations; and viral clearance from fetal brain. The fetal nervous system has a predetermined

ontogenic development (Table 2),⁵ so that the timing of viral infection is often crucial with regard to neurological sequelae. A prime example is rubella infection, which, during the first 2 months of gestation, generally produces severe and multiple teratogenic defects; during the first 4 months of gestation it often produces fetal brain damage but after this period neurological disturbances are rare. Fetal cells may also differ in their susceptibility to virus invasion, so that infection by different viruses will give distinct patterns of neurological disease. Once virus infects a cell there are three possible outcomes: cell death, cell transformation, or persistent infection which may or may not alter cell function. Functional changes can be so subtle as to be undetectable. For example, MHV-3, a mouse corona virus, causes a persistent infection of fetal neurons and astrocytes *in vitro*. Although the virus has no obvious effect on these cells, it does alter the neuronal uptake of neurotransmitter and the affinity of glial membrane receptors.⁶ All of the major viruses which infect the human fetus result in a persistent infection, and inability to clear virus explains

Table 2. Ontogenic development of the human nervous system

Event	Gestation time	Associated defects
Neural tube formation	3-4 weeks	Anencephaly, encephalocele, tube closure defects
Prosencephalon cleavage	5-6 weeks	Holoprosencephaly
Neuronal proliferation	2-4 months	Microcephaly
Cell migration	3-5 months	Schizencephaly, lissencephaly, pachygyria, polymicrogyria, neuronal heterotopias
Organization	6 months-years postnatal	Mental retardation
Myelination	birth-years postnatal	Hypomyelination syndromes

Adapted from Volpe (1987).⁵

the high frequency of sequelae after birth with cytomegalovirus (CMV), human immunodeficiency virus (HIV-1) and rubella.

Once virus infects the developing nervous system, there are several possible mechanisms for damage: virus may cause a diffuse encephalitis with inflammation and necrosis; altered embryogenesis due to involvement of specific cell populations; mitotic inhibition with interruption of cell growth and division; or chromosomal damage. There is evidence for the first three mechanisms in human congenital infections. Although chromosomal damage can be induced *in vitro* by viruses,⁷ it has not been proven to happen *in vivo*.

Animal models

Viral infection has been shown to result in congenital malformations of the nervous system in a number of experimental and natural animal models (Table 3).^{1,2} Developmental abnormalities include cerebellar hypoplasia, encephalocele, cerebral cavitory defects, hypomyelination, hydrocephalus and neural tube defects. Unlike congenital infection of the human nervous system, in these animal models the nervous system typically lacks inflammatory neuropathology or persistent virus at the time of birth. Such models have caused speculation that certain human congenital defects which are currently considered secondary to genetic, toxic or vascular insults may actually prove to be sequelae of congenital infection.

A hypoplastic cerebellum may result following congenital infection with several different viruses in a number of species. Both rat parvovirus and LCM will cause selective infection and subsequent destruction of the rapidly-dividing external germinal cell layer of the cerebellum. The mechanism of cell

destruction after cell infection differs for the two viruses: rat parvovirus produces cell lysis but LCM leads to an immune-mediated attack on infected cells. The final result of infection by the two viruses is, however, the same: loss of a crucial cell population within the developing nervous system. These are cells that normally migrate postnatally to form the granular layer of the cerebellum. Their prenatal destruction results in a number of gross and microscopic cerebellar anomalies, including hypoplasia, abnormal folia and abnormal synaptic organization. Although there are associated inflammatory changes at the time of acute infection, all traces of the virus are subsequently cleared. The investigators studying rat parvovirus noted that the congenital malformation was identical to that found in a neurological disorder of kittens known as spontaneous ataxia. For years this disorder was believed to be an autosomal recessive neurodegenerative disease, but subsequent studies confirmed that it was indeed due to congenital infection with feline panleukemia virus.⁸

Bluetongue virus provides an excellent example for the importance of the timing of fetal infection on consequent damage.² It causes a selective acute infection of subventricular germinal cells in the forebrain of fetal sheep and cows. These are the cells which subsequently migrate to form the neurons and glia throughout the cerebral hemispheres. Once germinal cells are infected, virus spreads to involve nearby cortex, dentate gyrus and olfactory bulbs. The congenital infection results in forebrain cavitory lesions which mimic human hydranencephaly and porencephaly, but the lesions are time-dependent. Viral infection during the first trimester, when there are large numbers of germinal cells, results in massive necrosis and cavitation resembling hydranencephaly. Second trimester infection, when there are fewer target cells, results in more limited focal cavitations

Table 3. Experimental and natural animal models for congenital malformations

Defect	Agent	Species
Cerebellar anomalies	Arenaviruses (lymphocytic choriomeningitis, Tamiami virus)	Mouse, rat
	Parvoviruses (feline panleukemia, minute, rat virus)	Cat, ferret, hamster, mouse, rat
	Togaviruses (border disease, bovine viral diarrhea, hog cholera virus)	Cow, pig, sheep
Encephalocele	Togavirus (St Louis encephalitis virus)	Mouse
Forebrain cavitory defects (hydranencephaly; porencephaly)	Bunyaviruses (akabane, Rift Valley fever virus)	Cow, Sheep
	Orbivirus (bluetongue virus) Togaviruses (border disease, bovine viral diarrhea, Venezuelan equine encephalitis, Wesselsbron virus)	Cow, sheep Monkey, sheep
Hypomyelination	Togaviruses (border disease, bovine diarrhea, hog cholera virus)	Pig, sheep
Hydrocephalus (non-communicating; communicating)	Paramyxoviruses (canine parainfluenza, mumps, mutant measles, Newcastle disease, parainfluenza, pneumonia mouse, respiratory syncytia virus)	Dog, hamster, monkey, mouse
	Poxvirus (vaccinia)	Cat
	Orthomyxovirus (influenza)	Hamster, mouse, monkey
	Reovirus (type I)	Ferret, hamster, mouse, rat
Neural tube defects	Togaviruses (Ross River, St Louis encephalitis virus)	Mouse
	Myxoviruses (influenza, Newcastle disease virus)	Chick embryo

From Johnson (1988).¹

resembling porencephaly. Third trimester infections produce only scattered microscopic changes without gross abnormalities.

Pregnant ewes infected with border disease virus, a natural infection of sheep, were noted to give birth to calves with diffuse hypomyelination in the brain. Although the precise mechanism for this viral-induced myelin abnormality is unknown, ultrastructural studies have suggested that the virus interferes with normal oligodendrocyte differentiation.²

Hydrocephalus can be produced by infecting fetal animals with a variety of viruses.² Mumps virus inoculated into suckling hamsters selectively infects the ependymal cells lining the ventricles and choroid plexi. The associated acute inflammatory reaction clears within two weeks but subsequently the aqueduct becomes obstructed, blocking the flow of cerebrospinal fluid

and non-communicating hydrocephalus develops, with no trace of the prior mumps virus infection. It is of interest that in humans aqueductal stenosis and hydrocephalus have sometimes been noted weeks to years after childhood mumps infection. The neonatal and adult nervous systems may have different pathological reactions to ependymal destruction.² The immature brain appears much less likely to show permanent reactive changes. Influenza infection of fetal and neonatal mouse brain results in abnormalities identical to those produced by mumps. Virus infects and destroys ependymal cells but is then cleared, leaving only normal brain tissue surrounding the stenosed aqueduct. In contrast, influenza infection of the adult mouse brain also produces an aqueductal stenosis, but the abnormal area is surrounded by reactive gliosis as a marker of the earlier infection.

Different viruses, infecting different cell populations of the developing nervous system, may result in identical malformations. Influenza and Newcastle disease virus produce a similar neural tube defect in chick embryos, leading to abnormal neural tube flexion and closure, collapse of the primitive brain and death of the embryo. However, the viruses infect different cell populations. Experimental inoculation with influenza leads to infection of chorionic and amnionic membranes, non-neural ectoderm and focal areas of the primitive gut and myocardium;⁹ neural organogenesis is altered even though infection involves noncontiguous extraneural tissue. Newcastle disease virus, a natural infection of chick embryos, in contrast directly disrupts organogenesis by infecting caudal neural tube cells.¹⁰

Human infections

Viral infections of the developing human nervous system may result in damage from inflammatory-mediated destructive changes as well as disruption of normal ontogenic development. The consequent neurological picture may therefore vary widely. Four viruses account for the majority of perinatal infections (Table 1): CMV, HIV-1 and rubella cause intra-uterine infections which become persistent; HSV typically causes perinatal infection, although there are rare cases of congenital viral transmission with resultant microcephaly.¹¹

CMV infects 1% of all newborn babies and is the most common congenital viral infection.¹² It is also the most common infectious cause of mental retardation. A primary infection of the mother will transmit virus to approximately 40% of fetuses. Recurrent maternal infections also have a high transmission rate¹³ but maternal immunity is able to moderate viral virulence, since fetal damage is almost always associated with a primary infection. Only 10% of infected infants have clinically apparent disease at birth but half have the severe cytomegalic inclusion disease characterised by a severe disseminated infection including liver, spleen and CNS. Another 5-15% eventually develop neurological abnormalities including hearing loss, mental retardation, microcephaly and motor defects. CMV infects periependymal neurons and glia of the developing brain and necrotic periependymal tissue may subsequently calcify to give a typical periventricular pattern. The virus generally produces a microcephaly with neuronal migration defects, particularly polymicrogyria.¹⁴ Severe destructive changes can lead to more severe brain abnormalities,

including porencephalic cysts, cerebellar hypoplasia, aqueductal stenosis and hydrocephalus.

Approximately 80% of HSV perinatal infections involve type 2 (genital) virus, with the remainder due to type 1.¹⁵ Perinatal infections almost always result in clinically apparent disease. HSV can cause a disseminated fulminating infection of the neonate with diffuse brain involvement and an 85% mortality rate if untreated, but infection may be localized to brain, with a mortality rate of 50% if untreated. Unlike adult HSV encephalitis, where damage is limited to orbitofrontal and anterior temporal regions, neonatal HSV encephalitis leads to diffuse inflammatory and destructive brain damage.

HIV-1, the retrovirus which causes AIDS, is now recognized to produce a devastating perinatal infection.¹⁶ The World Health Organization estimates that 10 million children may be infected worldwide by the year 2000, most through intrauterine infection. The transmission rate of virus from mother to fetus may be as high as 40%. Factors which seem to increase this risk include absence of maternal antibodies against the envelope glycoprotein, gp 120,¹⁷ which are directed against peptides from the hypervariable V3 loop. Transmission also appears more likely when the mother has a symptomatic infection. Placental invasion with spread to the fetus occurs as early as 8 weeks gestation¹⁸ and HIV-1 probably invades the fetal brain early by a similar route to that in infected adults, by way of virus-infected monocytes/macrophages (see Tillman and Wigdahl, this issue³¹). Congenital infection results in developmental delays, cognitive impairment, acquired microcephaly and bilateral corticospinal tract abnormalities. Consistent with persistent infection and reminiscent of the adult syndrome of AIDS-dementia complex, these children show a progressive encephalopathy. Pathologically there is brain atrophy, a subacute encephalitis in deep white and gray matter, deep white-matter gliosis and sometimes a calcific vasculopathy involving the basal ganglia region. The encephalopathy may also show a more static, fixed, or 'plateau' stage. HIV-1 is readily detectable in the brains of children with progressive disease¹⁹ and antigen is usually found in monocytes/macrophages or multinucleated giant cells, which are thought to be infected macrophages that have undergone syncytial formation. Antigen is less commonly found in cells consistent with endothelium. Children with a stable course of disease have little or no detectable viral antigen in brain, suggesting that active infection is responsible for

ongoing nervous system damage. This is supported by studies which have correlated HIV-1 p24 antigen expression in cerebrospinal fluid with progressive disease.²⁰ Just as is true for infected adults, it is not known how HIV-1 disrupts nervous system function in infected children but both direct and indirect mechanisms are likely to be at work. Although children who are congenitally infected may remain asymptomatic for years,²¹ this is distinctly unusual; generally children progress to AIDS more rapidly than adults and over half of infected children die by the age of three.²²

Rubella was the first virus recognized to damage the developing human nervous system. In 1941 Gregg, an Australian ophthalmologist, described a cluster of infants with congenital cataracts.²³ They also had microcephaly, low birth weights and congenital heart disease. The one feature in common was that the mothers had all had rubella early in pregnancy and Gregg postulated that the infection may have resulted in developmental arrest. Rubella produces placentitis with intrauterine growth retardation.²⁴ The virus spreads widely in the fetus to infect many organs but only a limited number of cells are infected per tissue. Within the brain, rubella causes vascular abnormalities, with focal areas of parenchymal and perivascular necrosis;²⁵ inflammatory changes are variable. Rubella infection results in reduced numbers of cells and smaller than normal organs, including brain. The precise mechanisms by which rubella produces fetal teratogenesis are unknown but they appear to involve direct viral effects. *In vitro*, persistent rubella infection of human embryonic cells alters their response to growth substances, such as epidermal growth factor, and decreases their synthesis of collagen.²⁶ The timing of fetal infection with rubella is crucial: infection early (during organogenesis) results in severe heart, brain and eye malformations which typify the congenital rubella syndrome; with later fetal infections, the infant may shed virus for months to years but is otherwise healthy. It is not known why virus persists following fetal infection but it may relate to immune disturbances.²⁵ Congenitally infected infants show impaired cell-mediated immune responses to rubella and a qualitatively different humoral response. They often lack antibodies to the C protein and show deficient antibody response to the E2 protein of rubella. Such children frequently have persistent rubella-specific circulating immune complexes.

Other viruses rarely cause perinatal infection with damage to the nervous system. Arboviruses and

coxsackie B viruses have produced congenital infections with encephalitis.^{27,28} Maternal infection with human parvovirus B19, which infects late erythroid precursor cells, may result in fetal death or severe fetal anemia, congestive heart failure and generalized edema (fetal hydrops).²⁹ Polioviruses in late gestation have been associated with congenital polio. Varicella zoster infection during pregnancy has produced a severe necrotizing encephalomyeloradiculitis involving the fetal nervous system, with hypoplastic limbs and cicatricial scarring.³⁰

Problems for the future

Despite the advances offered by molecular biology, improved diagnostic techniques and vaccination programs, viral infections of the developing human nervous system continue to be a problem. The problem may soon be a critical one, since there is likely to be an epidemic of children infected *in utero* with HIV-1, with resultant neurological morbidity and death unparalleled by other congenital infections. The factors which determine viral transmission to the fetus, and the pathogenic mechanisms involved in consequent nervous system damage, are not well understood. Effective antiviral treatments for almost all these agents are lacking. In addition, experimental models have clearly indicated that a wide array of noninflammatory congenital birth defects may result from viral infection of the fetus. There are several issues that need to be clarified in future studies. These include defining the precise risk to the fetus following a maternal infection; identifying the entire spectrum of developmental brain damage in the human produced by virus infections; defining the mechanisms by which a given virus disrupts and damages the developing nervous system; developing safe techniques to permit reliable early antenatal diagnosis of a fetal infection; devising effective treatment strategies to block transmission of virus from mother to fetus, as well as to prevent damage once such infection has occurred; and developing effective vaccination programs ultimately to abolish these infections.

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