Infections of the Developing Brain

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The brain, spinal cord, and their coverings may be subjected to a spectrum of infectious processes with significant effects on central nervous system (CNS) structure and neurologic function. Although there are hundreds of infectious agents that can infect the CNS, the type of pathologic alterations caused by these organisms is relatively limited. Recognition of the patterns of pathology creates the essence of the differential diagnosis of images using different modalities. This review emphasizes the pathogenesis of infection leading to particular patterns of pathology.

Pathogenesis of Infection

The mechanism of infection is different for viruses, bacteria, fungi, and parasites. Viruses tend to produce a rather selective necrosis of cell types in contrast to the nonselective necrosis of tissue characteristic of other organisms such as bacteria, fungi, and parasites. The nature of this process is similar through fetal, neonatal, and childhood infections.

If an organism can get into the CNS, it can infect it. Most infectious organisms reach the CNS through the blood stream following an infection at some other site. However, direct spread may also occur from sinus tracts, skull fractures, and adjacent sinus or middle ear infection. The site of entry into the CNS may relate to the localization of pathology.

Once in the CNS, the infectious agent may cause a nonselective necrosis of tissue (Table 1). The character of the inflammation depends on the size of the agent, the host's ability to react to the organism, and the length of time the process has been evolving. Bacteria and some fungi pass easily into the microcirculation of the CNS and readily infect the leptomeninges. Tuberculosis with meningitis is uncommon in North America but does occur, often as part of miliary tuberculosis. Fungi such as *Candida* cause focal necrosis in the area around the microcirculation, producing microabscesses.

The pathogenesis of parasitic infection is more complicated and individualized for the specific parasite. For example, the definitive host for *Toxoplasma gondii* is cats. Their excretion of oocysts allows a fecal-oral pathway of spread to man and to intermediate hosts such as cattle, sheep, and pigs. In the intermediate host, infection leaves viable cysts, which through inadequately cooked meat, may infect man.

The ingestion of cysts of oocysts allows trophozoites to emerge and burrow in the intestinal mucosa and spread through the blood to infect virtually any organ of the body. Placental infection can also occur if the mother acquires toxoplasmosis during pregnancy.

Understanding the mechanisms by which viruses gain entry into the CNS and infect the different cellular components of the CNS enable the establishment of basic insight into the pathologic basis for the radiologic appearances of viral infection in the CNS.

Viruses such as rabies and perhaps herpes simplex and varicella-zoster can enter the CNS through a neural pathway (1): axons, perineural lymphatics, endoneurial space, Schwann cells. For example, herpes simplex may enter through the olfactory mucosa and olfactory nerves. However, most viral CNS infections are established

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TABLE 1: Nonselective necrosis of tissue

	Immature Tissue	Mature Tissue
Organism	Toxoplasmosis	Bacteria, fungi, parasites
Pathology	± Calcification	± Cysts
	± Cysts	± Abscesses
	± Hydranencephaly	± Infarction
	± Porencephaly	± Calcification
		± Astrogliosis (scar)

through a hematogenous route with viruses growing at some extraneural site, establishing a viremia, and then coursing from blood to brain or blood to cerebrospinal fluid (CSF). Virus can spread across the blood-brain barrier by infecting endothelial cells, by pinocytotic vesicular transport, and by infected leukocytes.

Viruses are obligate intracellular parasites so they must attach to a receptor on the cell surface, enter the cell, and multiply within the cell. Viruses depending on receptors available to them have a degree of specificity unmatched by other infectious agents. Different cells within the brain have different receptor sites and different capacities to produce and release virus. Cells in the CNS are variably susceptible to viruses: anterior horn cells (polio and Coxsackie), neurons (rabies), oligodendroglia (papova virus), all CNS cells including endothelial cells (herpes simplex), immature/undifferentiated cells (rubella) (Table 2).

In the developing child, organisms have individual preferences for infection at specific stages of development. For example, cytomegalovirus (CMV), rubella, and toxoplasmosis infect the fetus, whereas herpes simplex targets the neonate and older child (2). The consequences of any infection are carried as sequelae to the next age: CMV in the fetus may interfere with neuronal migration producing polymicrogyria, but the polymicrogyria may not be apparent until some later time in childhood. The consequences of the organized purulent exudate in meningitis may be hydrocephalus occurring weeks or months after the acute event. In the following discussion, pathology patterns are described according to developmental epoch: fetal, neonatal, childhood (Table 3).

Fetal Infection

The prerequisite to fetal infection is involvement of the mother, although the infection is often inapparent in the mother. Viruses can reach the fetus by a hematogenous route across the placenta or by an ascending infection through the birth canal. For the fetus to become infected, the maternal viremia must be sufficiently severe to allow passage through the placenta. The effects of virus in the fetus depend on the stage of development and on what cells are susceptible to infection. Specific and nonspecific cellular immune responses also modify the pathologic effects of the virus. Rubella appears to have an antimitotic effect that interferes with cell multiplication. This may explain the micrencephaly described as part of the rubella syndrome. CMV encephalitis early in development may leave few markers of the inflammatory process, producing lesions that resemble malformations: hydranencephaly, porencephaly, polymicrogyria. Toxoplasmosis is asymptomatic in the mother, but produces tragic results in the fetus. Other organisms, particularly viruses, have been implicated in brain malformations, some of these examples are based on animal models and some on specific case studies (3).

Rubella

Infection of the fetus with rubella occurs in utero by transplacental passage of virus. Although once a devastating condition of the infant, widespread rubella immunization has dramatically diminished its frequency. The effects of rubella on the developing fetus were clearly documented in 1941 by Greg (4). In symptomatic infections, viremia may be present in 85% of patients. In a pregnant women, the fetus can be infected at any time during gestation. The timing of the infection is related to the degree of pathology in the infant. Fucillo and Sever (5) found congenital lesions in 50% of fetuses infected at 1 month of gestation, 22% of those infected in the second month of gestation, and 7% of those infected between 3 and 5 months gestation. Some infants appear normal at birth, but continue to excrete virus. The pathogenesis of rubella infection probably involves both a cytolytic effect and an inhibition of mitoses of the immature undifferentiated cells.

The rubella syndrome (2) is usually associated with infection during the first trimester and consists of a wide spectrum of abnormalities: cataracts, glaucoma, chorioretinitis, microphthalmia, cardiac malformations, micrencephaly, deafness. In the neonatal period, there may be transient meningoencephalitis, thrombocytopenia, hepatosplenomegaly, and lymphadenopathy. The

TABLE 2: Selective necrosis of cells

Cell type	Ependymal cell	Neuron	Oligodendroglia	Endothelial cell	Immature cell
Organism	Mumps	Herpes simplex Rabies Poliomyelitis Enterovirus Herpes zoster	PML SSPE Rubella HIV	Herpes simplex	CMV Rubella
Pathology	Hydrocephalus	Astrogliosis	Demyelination	Infarction/hemorrhage ± Calcium	Micrencephaly Polymicrogyria Hydranencephaly Porencephaly ± Calcium

TABLE 3: Pathology patterns according to age

	Fetus	Neonate	Child
Sequellae of previous infection		Hydranencephaly Porencephaly Polymicrogyria Neuronal heterotopia Microcephaly Calcification Hydrocephalus Cystic change Astrogliosis (scar)	Calcification Hydrocephalus Cystic change Astrogliosis (scar) Cerebral atrophy
Acute infection	Meningoencephalitis Infarction/hemorrhage Necrosis Meningeal exudate	Meningoencephalitis Infarction/hemorrhage Necrosis Meningeal exudate	Meningoencephalitis Infarction/hemorrhage Necrosis Meningeal exudate Demyelination

neuropathology of rubella is characterized by an inflammatory reaction (meningoencephalitis), vasculopathy with associated ischemia, necrosis, micrencephaly, and delayed myelination (6–8). Meningoencephalitis consists of inflammatory cells in the meninges and perivascular spaces. A characteristic feature of rubella is vasculopathy with involvement of leptomeningeal and parenchymal vessels. In the vessel walls are focal areas of destruction with disruption of elastica and mineral deposition. Microcalcification is prominent in and around blood vessels. Small perivascular areas of parenchymal necrosis are most prominent in the centrum ovale, corpus callosum, and basal ganglia.

Micrencephaly does not appear to be due to a destructive process but rather is related to rubella inhibition of progenitor cell multiplication with insufficient generation of neurons and astroglia. Impaired myelination may also be due to insufficient production of oligodendroglia (8).

Cytomegalovirus

CMV is the most common and serious fetal infection. Although 1% of all newborns have serologic evidence of CMV infection, only 1%–5% of these have CMV disease (8). Of those with CMV disease, 20% develop mental retardation or deafness. Postnatal primary infection is usually not clinically manifest but has been associated with monocucleosis syndrome, post-transfusion fever, and systemic disease in immunosuppressed patients. Maternal infection is significant; 5% of pregnant women excrete CMV in the urine. Of the pregnant women with infection, 40% of their offspring will become infected (2, 8, 9). The fetus may be infected by a primary maternal exposure or by a maternal reinfection from latent CMV.

Neonates with CMV disease have hepatomegaly, splenomegaly, jaundice, petechiae, cerebral involvement (psychomotor retardation), chorio-

retinitis, and deafness. In the CSF, there is a pleocytosis and an elevated level of protein. As a result of CMV disease, there may be micrencephaly, cerebral calcification, seizures, mental retardation, deafness, and death. Only 15% of infants with CMV disease are normal (2, 8, 9). Most infants with fetal CMV disease appear normal at birth, but neurologic deficits become apparent as mental retardation and auditory impairment (10).

Infection during the first and second trimester is associated with frequent CNS involvement. Destruction of tissue is multifocal, associated with calcification and often severe inflammatory changes. The target cells are the immature cells present in the germinal matrix region. Necrosis of these regions and subsequent calcification explains the prominent periventricular localization for the calcification. The identification of inclusion bodies may depend on the stage of the disease, as well as the severity of the infection. Associated with early infection have been aberrations of neuronal migration, including polymicrogyria and neuronal heterotopia. Hydranencephaly, porencephaly, and micrencephaly have also been reported as consequences of CMV infection (11). Particularly convincing evidence has been the identification of CMV inclusions around some porencephalic cysts. Infection in early gestation interferes with neuronal migration, whereas later infections produce encephaloclastic lesions of hydranencephaly and porencephaly. Although periventricular infection is found in more than half the cases, other sites of involvement include the cerebral cortex, white matter, cerebellum, brain stem, and spinal cord. Microscopically, cytomegaly with intranuclear and intracytoplasmic inclusions is identified in a variety of cell types, including astrocytes, microglia, ependyma, leptomeningeal cells, endothelial cells, and occasionally neurons. The infection is characterized by microglial nodules, with cytomegalic cells often in the periphery of these nodules.

During parturitional infection, the CNS is rarely involved. When it is affected, there is not evident periventricular predilection, but the histology will indicate microglial nodules with identifiable cytomegalic cells. Mineralization is not apparent in such infections. CMV infection in the neonatal period from infected breast milk or blood transfusion is rarely associated with CNS involvement and, when the CNS is infected, there is no periventricular predilection. Since 1% of newborns excrete CMV and 10% of these have CNS signs and symptoms, CMV continues to be a significant cause of neurologic impairment.

Toxoplasmosis

Toxoplasmosis is probably second to CMV in terms of clinical significance. As with CMV, the fetus is affected by transplacental mechanisms; however, toxoplasma infection is more easily identified in infected newborns than is CMV. The effects on the fetus are often devastating, presumably due to defective cellular defenses, especially phagocytosis. Transplacental infection results in significant involvement of the CNS in 50% of the fetuses who are infected (2, 12, 13).

Toxoplasmosis infection tends to be multifocal and random without prominent periventricular localization, although granular ependymitis is common (Fig. 1). The infection causes necrosis but has no effect on neuronal migration, in contrast to the effect that CMV has on the developing brain. The necrotizing granulomatous infection is associated with numerous giant cells, eosinophils, and toxoplasmosis organisms. Toxoplasma confined to cysts produces no inflammatory response. Release of toxoplasma from the cysts causes an intense inflammatory reaction. The consequences of toxoplasmosis infection are serious and often become apparent in the neonatal period.

Neonatal Infections

Intrauterine infections are frequently severe and destructive. However, their effects on the

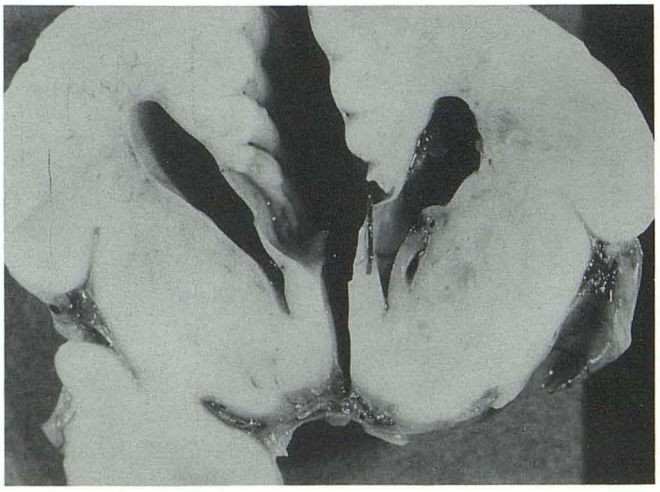


Fig. 1. Toxoplasmosis. Acute fetal infection. Multifocal CNS involvement with prominent periventricular necrosis.

infants are usually not manifest until the neonatal or childhood period. In this section, the consequences of intrauterine infection are discussed followed by a description of acute infections occurring in the neonatal period.

Consequences of Intrauterine Infection

In a child who survives an intrauterine infection, a spectrum of abnormalities may be found in the CNS. Some of these, such as subtle cortical dysplasias, are not manifest grossly or by imaging and require detailed microscopic examination. Other consequences of fetal infection may include hydranencephaly, porencephaly, polymicrogyria, neuronal heterotopia, micrencephaly, hydrocephalus, and cerebral calcification.

CNS infection by toxoplasmosis or CMV early in gestation causes large areas of destruction. Infection very early in development produces hydranencephaly (Fig. 2). If the infection is more localized and occurs later in gestation, a focal area of necrosis will eventually manifest as porencephaly. Micrencephaly may be caused by extensive focal destruction, such as that seen with toxoplasmosis or CMV. Interference with neuronal migration may produce grossly evident polymicrogyria (Fig. 3) and neuronal heterotopia (Fig. 4). In rubella infection, a direct effect on immature cells may interfere with their multiplication, resulting in micrencephaly. Infection by any organism involving the cerebral aqueduct can cause ependymal disruption and gliosis with aqueductal stenosis and hydrocephalus.

CMV, toxoplasmosis, and rubella can all produce calcification. The calcium is deposited in the necrotic foci in the brain. CMV infection tends to localize to the germinal matrix immediately surrounding the ventricles, so the calcification is characteristically periventricular. Toxoplasmosis, on the other hand, does not necessarily have a periventricular predilection and may cause a multifocal necrosis with deposition of calcium in many areas of the brain. The calcification in rubella is subtle. Often it is not apparent except under the microscope, especially in relationship to blood vessels. This suggests that an underlying vasculopathy accounts for the calcification.

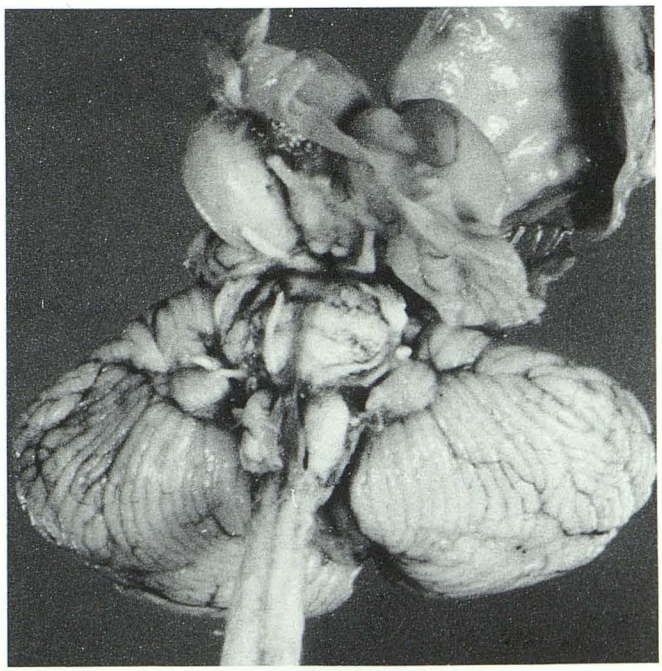


Fig. 2. Hydranencephaly. Neonate with intrauterine infection. Thin cerebral mantle disintegrated upon brain removal. Small remnants of cortex remain.

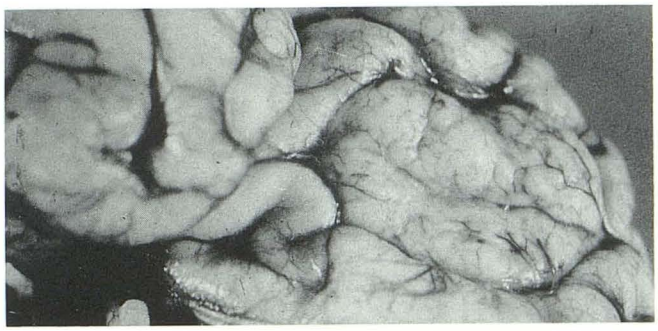


Fig. 3. Focal polymicrogyria. Neonate with intrauterine infection.

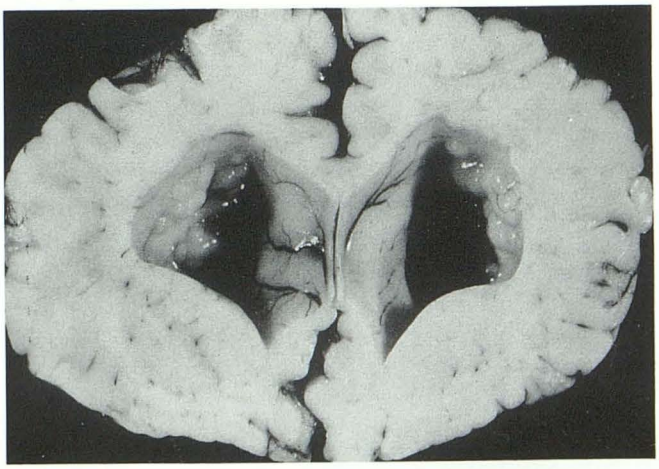


Fig. 4. Periventricular neuronal heterotopia. Neonate with intrauterine infection.

Acute Infection

An infant may have an entirely normal gestational period but acquire an infection during or shortly after birth. CMV and toxoplasmosis infections in late gestation may also manifest in the neonatal period.

In the neonate, the most significant acute viral infection is herpes simplex encephalitis. Varicella-zoster virus and the enteroviruses also effect the neonate. Neonatal leptomeningitis remains a condition often associated with devastating neurologic outcome. Cerebral abscesses are uncommon in the neonate. Other infections include disseminated candidiasis with CNS involvement.

Herpes simplex. Disseminated infection of the newborn can occur with both type I and type II herpes simplex virus, but over 75% of these infections are related to the type II or genital strains (14). Infection is rare in the fetal period, although there are case reports of infants with micrencephaly and intracranial calcification in whom herpes simplex virus is recovered from CSF and urine (15). The rarity of early infection may be explained by the severe destructive effects of this virus in the infant, producing spontaneous abortions rather than malformed or infected CNS. The most common infections are parturitional, ascending infections as a result of infected mothers (16). The mothers may not have any signs or symptoms of infection at the time of delivery but many have a history of herpes simplex. It is thought that the infants become infected through direct contact of the infant's skin, eyes, or oral cavity with herpetic lesions in the cervix or vagina. Postnatal infection is uncommon but can occur from mothers with oral herpetic lesions, from other adults such as hospital personnel, or from other infants. The devastating infection in the young infant may be due to defective macrophage function or to impaired production of anti-herpes antibody.

The neuropathology in herpes simplex infection is variable depending on the time of gestational infection and the viral dosage (17). In early gestation, the infection produces a spectrum of changes that may be severe encephaloclastic lesions or minor focal calcifications. Acute neonatal infections are associated with diffuse brain involvement without the localization to the orbitotemporal lobes characteristic of older children. Microscopically, there are microglial nodules with intranuclear inclusion-bearing cells. All cells of the nervous system may be infected. The predilection for endothelial cells results in vascular thrombosis and hemorrhagic infarction. The nonacute form of herpes simplex encephalitis is associated with astrogliosis and multifocal grey and white matter involvement with cystic infarction and demyelination. This may lead to a multicystic encephalomalacia (17).

Varicella-zoster. Varicella-zoster virus may pass through the placenta during late gestation, infecting the infant and producing characteristic skin lesions of chicken pox and/or shingles. Varicella-zoster infection of the fetus is associated with a discrete acute attack and not with chronic shedding of the virus as occurs with CMV and rubella. Autopsy studies have shown a severe necrotizing encephalomyelitis with prominent myelitis involving anterior horn cells and dorsal root ganglia. These children have also had chorioretinitis, cataracts, microphthalmia, and optic atrophy.

Perinatal infection is uncommon but varicella infection will develop in about one quarter of infants born to mothers with varicella during the last month of pregnancy. The brain is rarely involved (18). Herpes zoster in the mother has not been implicated in fetal infection or damage.

Enteroviruses. Enteroviruses, particularly the Coxsackie B viruses, may produce an acute neonatal infection with myocarditis and encephalitis (19). However, intrauterine infections with enteroviruses have not been associated with CNS disease or malformations. The enterovirus infection usually occurs in late summer and early fall and often is spread from the parents to the infant. It is thought that the infant is particularly susceptible due to a poor production of interferon or to presence of age-related receptors for the enterovirus. Pathologically, a microscopic meningoencephalitis occurs with a high frequency of microglial nodules and perivascular cuffing in the inferior olivary nuclei and the ventral horns of the spinal cord.

Neonatal meningitis. In the neonate, bacterial infections of the CNS are common, especially leptomeningitis (20, 21). The most commonly encountered organism is group B streptococcus, followed by *Escherichia coli*, *Listeria monocytogenes*, and others (*Staphylococcus*, *Proteus*, *Pseudomonas*). Factors involved in the pathogenesis of neonatal meningitis relate to delivery (maternal urinary tract or genital infection, prolonged rupture of membranes), immaturity (deficiencies

of cellular and humoral immunity), and environment (aerosols, catheters, inhalation therapy equipment).

The characteristic feature of neonatal bacterial meningitis is a widely dispersed purulent exudate (Fig. 5) and prominent ventriculitis (Fig. 6). The ventricular exudate covers the choroid plexus and disrupts the ependymal lining. As an extension of the arachnoid inflammation, phlebitis and arteritis frequently develop. Acute infarction, often hemorrhagic, follows venous thrombosis (Fig. 7). Significant cerebral edema is characteristic of the acute stage of neonatal bacterial meningitis, although herniation of the hippocampal unci or cerebellar tonsils is uncommon. Subdural effusions are rare in the neonate.

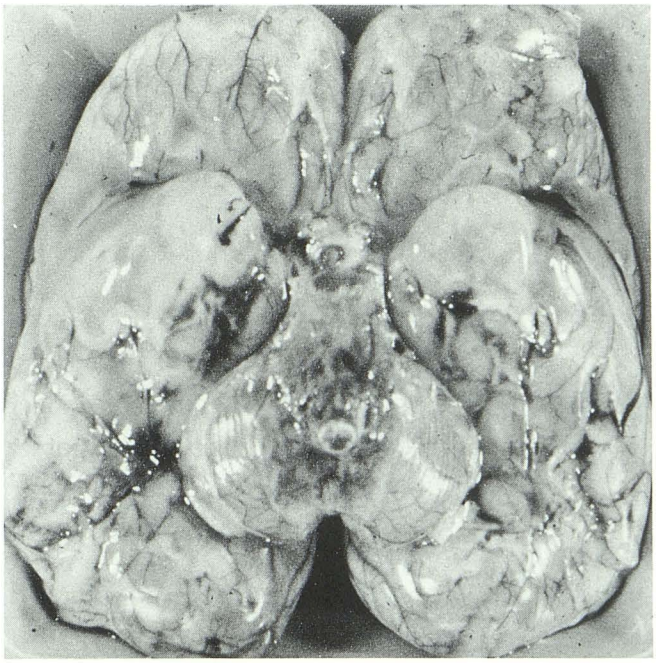


Fig. 5. Acute *Escherichia coli* leptomeningitis in neonate with extensive thick purulent exudate covering brain.

Cerebral abscess. Most brain abscesses in the neonate occur as a complication of bacterial meningitis (22–24) but some have been reported with no detectable meningitis. The organisms implicated are *Citrobacter*, *Proteus*, *Pseudomonas*, *Serratia*, and *Staphylococcus aureus*. It is suspected that a vasculitis and thrombosis may be the initiating factor, followed by cerebral infarction and infection from a bacteremia. In the neonate, abscesses tend to be large, lack good capsule formation, and be located in the cerebral hemispheres.

Disseminated fungal infection. Disseminated fungal infections are uncommon but, when identified, *Candida albicans* is usually the culprit (25). The CNS is involved in two thirds of cases of systemic candidiasis in premature infants. The predisposing factors in the infant include poor nutritional status, prolonged use of indwelling vascular catheters, or prior use of broad spectrum antibiotics.

The neuropathology consists of multifocal microabscesses (Fig. 8*A*) that are associated microscopically with microglial cells, giant cells, and myceliate forms of *Candida* (Fig. 8*B*). All parts of the CNS are involved with no apparent areas of predilection.

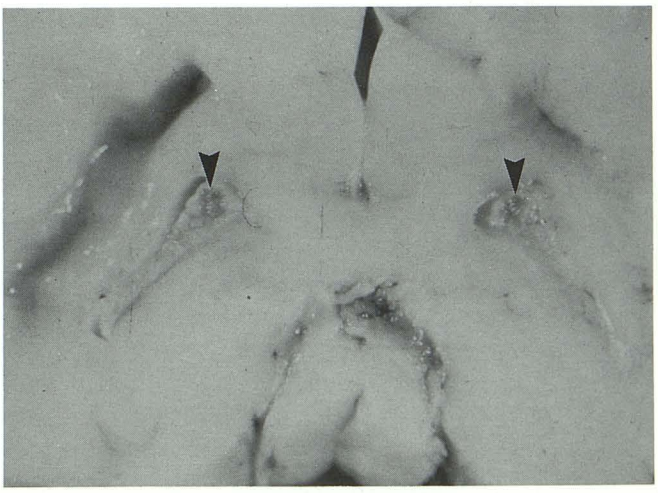


Fig. 6. Acute *Escherichia coli* ventriculitis in neonate with intraventricular purulent exudate (*arrowheads*).

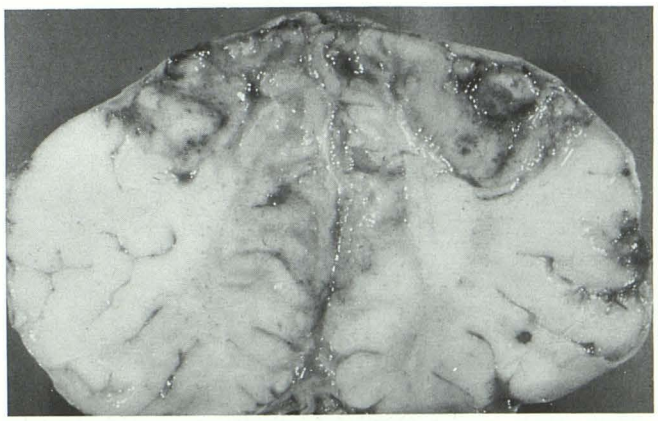
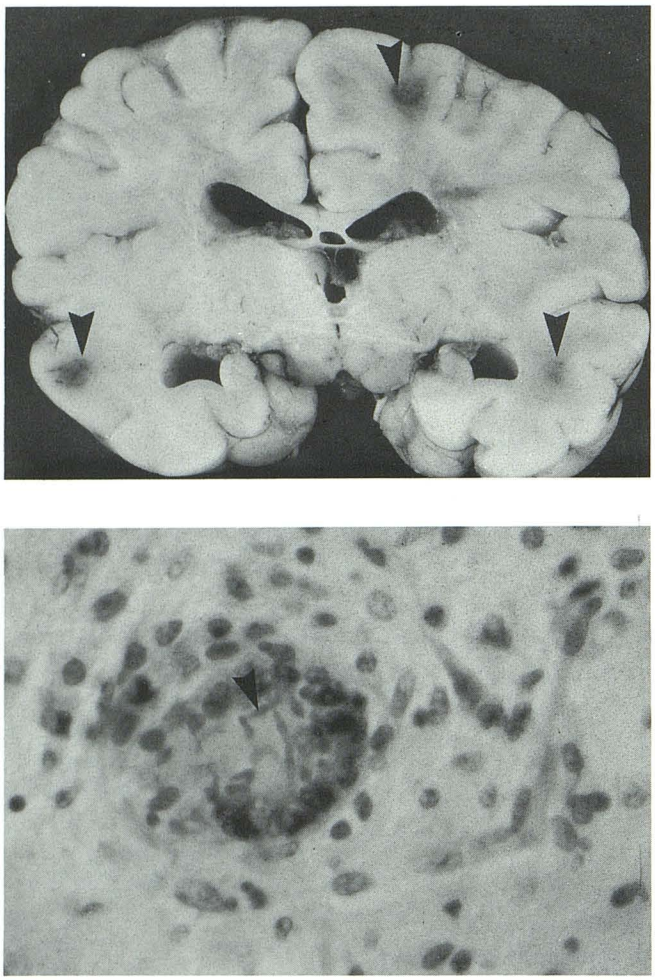


Fig. 7. Acute β hemolytic streptococcal leptomeningitis in neonate with superior saggital sinus thrombosis, hemorrhagic infarction, and incipient abscess formation.



B

Fig. 8. *Candida albicans. A*, Multifocal hemorrhagic microabscess (*arrowheads). B*, showing myceliate forms of fungus (*arrows*).

Childhood Infection

In childhood, the consequences of previous fetal and neonatal infection may become manifest. The sequelae of fetal infections have been discussed in the section on neonatal infection. The consequences of neonatal infection in terms of patterns of pathology and selected comments on acute infections in childhood are presented in this section.

Consequences of Neonatal Infection

As a result of neonatal infection mainly due to bacterial meningitis and viral meningoencephalitis, patterns of gross neuropathology can be identified (26, 27). These include cystic change from old necrosis or infarction, cerebral atrophy, hydrocephalus, calcification and focal atrophy (astrogliosis).

Cystic change in the brain is the result of necrosis. The necrosis may be the consequence of the direct damage to the neuropil or it may be secondary to ischemia, producing infarction. In most infections, the striking destructive cystic residue is the result of vasculitis affecting vessels of widely different caliber. In bacterial meningitis, infection may involve the arteries or veins; most commonly, it is a thrombophlebitis that occludes draining veins with large areas of infarction (Fig. 9). There may be a hemorrhagic component to the infarction, or the necrotic areas, particularly in neonates, may become secondarily infected with incipient abscess formation. The areas of cystic change (infarction) may be multiple, producing multicystic encephalomalacia. Fibrous organization of the purulent exudate in the leptomeninges (Fig. 10) obstructs flow of CSF to the superior sagittal sinus, producing hydrocephalus. However, ventricular dilation also results from cerebral atrophy and necrosis, making it sometimes difficult to distinguish from hydrocephalus. Leptomeningeal fibrosis may also compromise cranial nerve function. Residua of ventriculitis may include loculated cysts with intraventricular septation, ependymal disruption, and periventricular necrosis (Fig. 11).

In meningoencephalitis due to herpes simplex, the virus infects capillary endothelial cells with consequent thrombosis and multiple areas of infarction. These may coalesce to produce larger areas of tissue loss (Fig. 12). Most other viral encephalitides do not infect endothelial cells. For

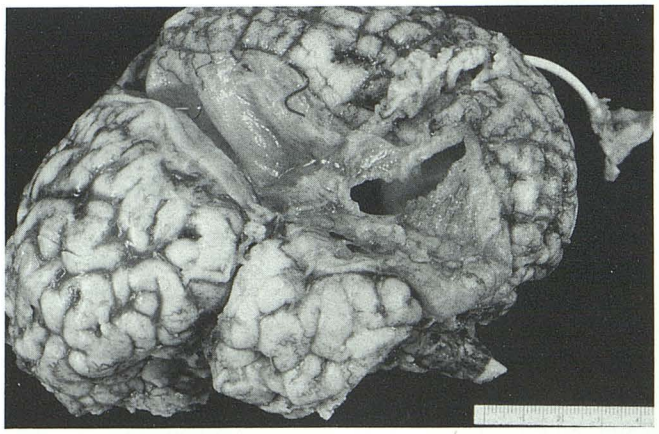


Fig. 9. The consequences of neonatal meningitis include a large cystic cerebral infarction involving frontal and temporal lobes. Note ventriculo-peritoneal shunt.

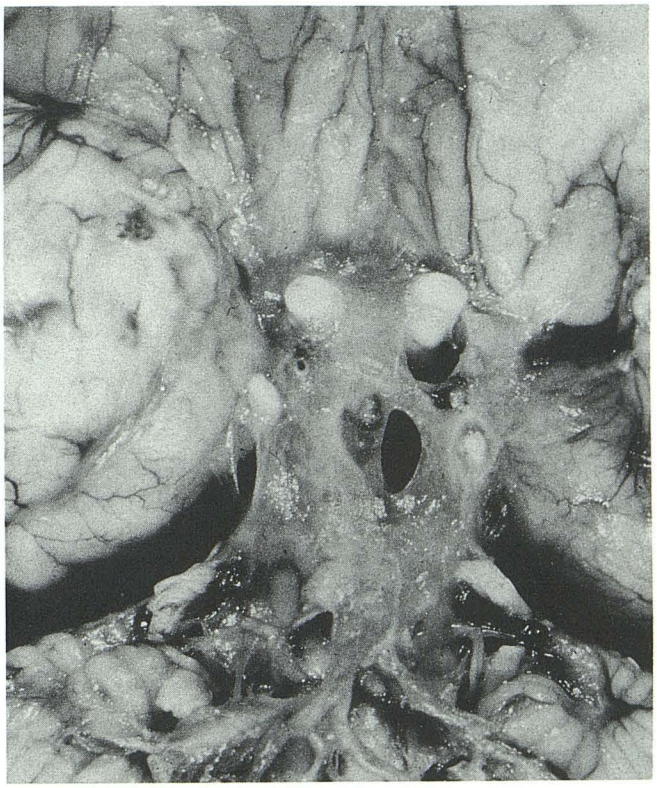


Fig. 10. Fibrosis of leptomeninges developing as a consequence of neonatal meningitis.

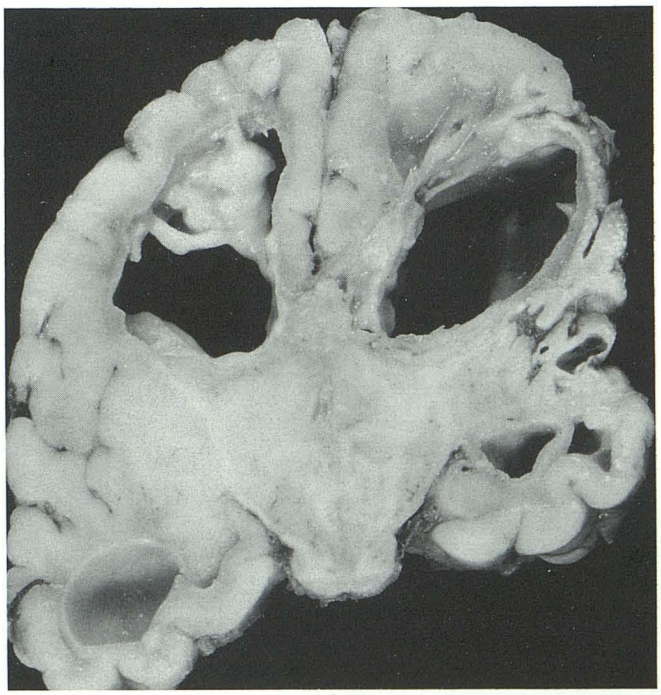


Fig. 11. In this coronal section, the sequelae of neonatal meningitis and ventriculitis are present: hydrocephalus, intraventricular loculation of purulent material, periventricular disruption with necrosis, and adjacent (right) gyral atrophy.

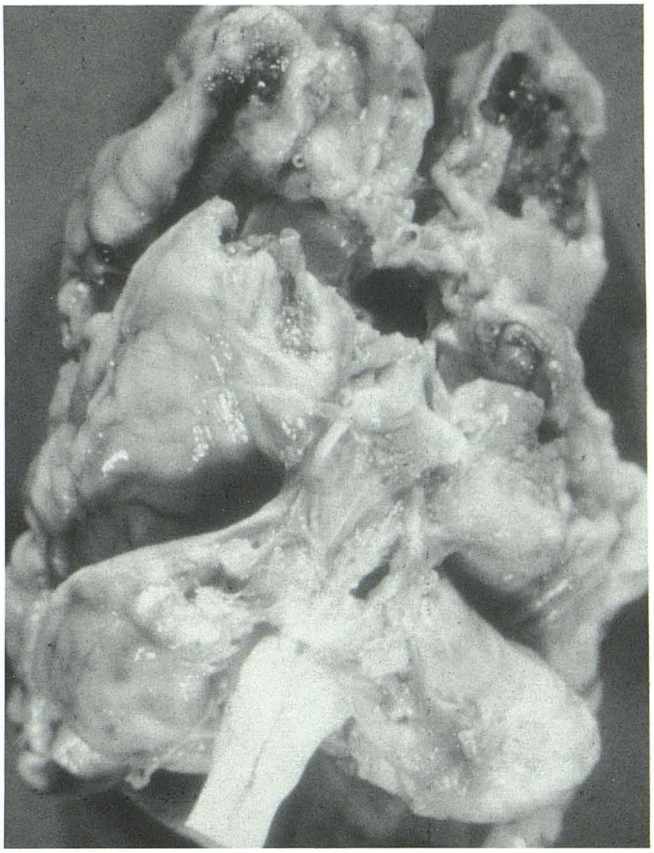


Fig. 12. Extensive cerebral infarction as a result of neonatal herpes simplex type II encephalitis.

example, Coxsackie virus produces microscopic foci of neuronal loss and astrogliosis, but no tissue necrosis and no gross brain abnormality.

However, extensive encephalitis with neuronal loss and astrogliosis may produce diffuse cerebral atrophy without evidence of focal cystic destruction. Bacterial meningitis and septicemia may also be associated with systemic hypotension and secondary hypoxic damage to the brain with neuronal loss and astrogliosis, with or without cerebral atrophy.

Acute infections

Acute infections in childhood involve bacterial meningitis, encephalitis, cerebral abscess, herpes simplex, and acquired immune deficiency syndrome (AIDS). Cerebral cysts with or without calcification may also be identified. Viral infection in childhood may target the oligodendroglial cells and produce a striking demyelinating picture: progressive multifocal leukoencephalopathy (PML) and subacute sclerosing panencephalitis

(SSPE). PML is exceedingly rare in childhood, whereas SSPE tends to be confined to childhood.

Bacterial meningitis. Bacteria gain entry to the intracranial cavity from blood or from primary infection in the nasopharynx, sinuses, middle ear, or cardiopulmonary system, or through traumatic or congenital breeches of the skull. Most cases of purulent meningitis occur in children less than 5 years of age and are caused by *Streptococcus pneumoniae*, *Hemophilus influenza*, and *Neisseria meningitis*. The pathology of meningitis consists of purulent leptomeningeal exudate. The distribution of the exudate is variable and is not helpful in terms of predicting the organism causing the meningitis (Fig. 13). When the exudate is minimal, the purulent exudate tends to accumulate along the margin of the subarachnoid veins. Acutely, there may be cerebral edema presumably caused by the cytotoxic effects of bacterial toxin. In association with the infected CSF, there may be mild ventriculitis with denudation of the ependymal surface.

The complications associated with meningitis are less common in the child than in the neonate, but do occur. Vasculitis and thrombosis are late complications that lead to cerebral infarction, neurologic signs, and seizures. As the leptomeningeal exudate becomes organized, it may involve the cranial nerves. The subarachnoid fibrosis may also obstruct CSF flow and produce hydrocephalus. Early diagnosis with appropriate antibiotic therapy reduces the likelihood of these complications.

Cerebral abscess. Cerebral abscesses are infrequent in infancy but are found in older children, particularly in preadolescents. They occur in children with congenital heart disease and right-to-left shunting, otitis media, or paranasal sinus infections. The organisms that cause abscesses include *S. aureus*, streptococci, gram-negative bacteria, anaerobes, and others such as *Nocardia*, *Mycobacteria tuberculosis*, and fungi.

The cerebrum is the commonest site for abscesses usually occurring in the frontal and parietal lobes. About 15% of abscesses are multiple. In the early stages of development, an abscess is associated with an area of necrosis surrounded by granulation tissue, a layer of fibrosis, and an outer rim of astrogliosis. Complications of abscess include increased intracranial pressure due to edema and mass effect created by purulent material and reaction, resulting in eventual herniation, medullary compression, and possibly respiratory arrest (Fig. 14). Abscesses may rupture into the subarachnoid space and produce a toxic purulent meningitis. Uncommonly, infection may

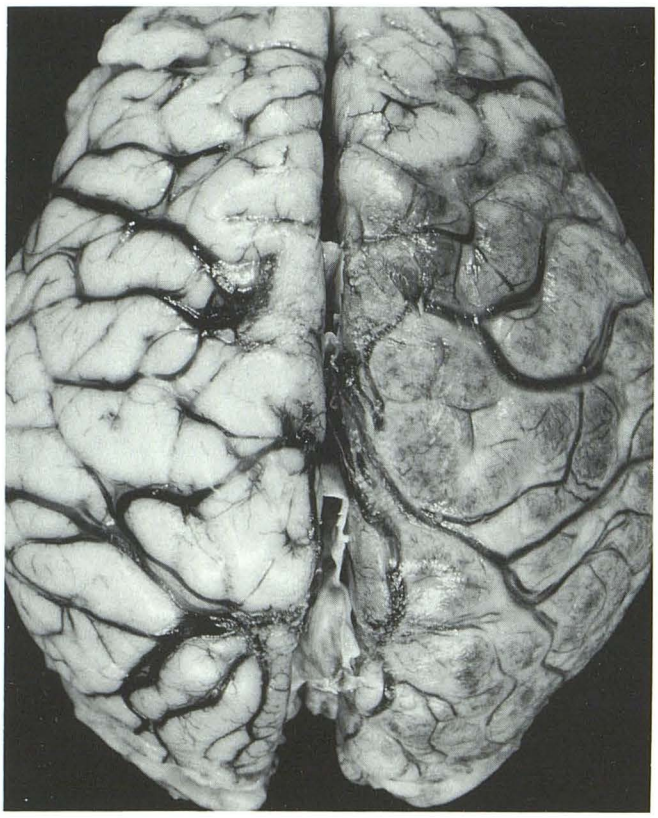


Fig. 13. *Hemophilus influenzae* meningitis with focal purulent exudate over the right hemisphere and associated hemorrhagic infarction.

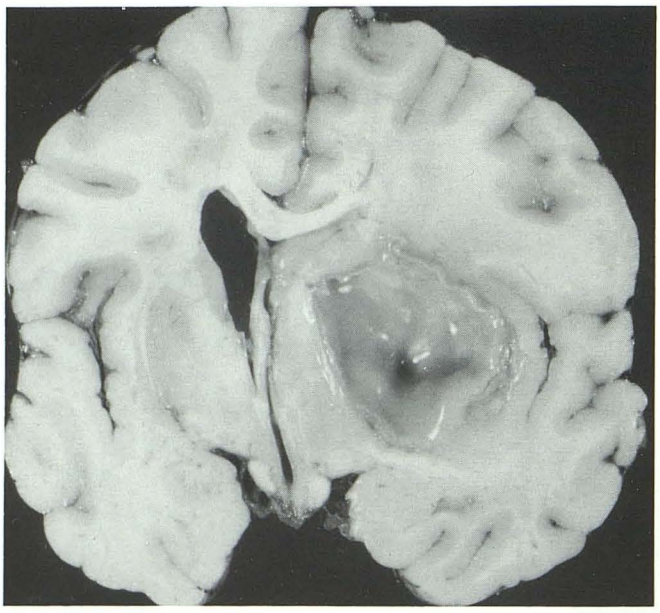


Fig. 14. Cerebral abscess with mass effect.

occur in the subdural space (empyema) as a primary infection, or as a complication of infection elsewhere. Spinal epidural infections also occur in children. In our experience, tuberculosis and syphilis are uncommon causes of bacterial CNS infection in children in Toronto.

Herpes simplex encephalitis. Although herpes simplex type I is a frequent isolate from the oropharynx, only rarely does it cause meningoencephalitis (2). Type I virus is spread by salivary or respiratory contact. During the primary infection, virus is likely transported up to sensory nerve fibers to lie latent in sensory ganglia. Reactivation (labial herpes or cold sores) may occur with or without symptoms and may be due to many nonspecific events or diseases. Meningoencephalitis may result from primary infection, reinfection, or activation of latent infection.

In contrast to the diffuse encephalitis occurring in the neonate with herpes simplex II infection, the encephalitis of type I infection is often localized to the fronto-temporal region and is strikingly unilateral (Fig. 15). The localization may be related to the route of virus entry into CNS via the trigeminal ganglia (reactivation) or olfactory nerve (primary infection) (2).

The encephalitis in children and neonates is microscopically similar.

Acquired immune deficiency syndrome. AIDS is a fatal disease that destroys the immune system (28, 29, 30). Human immunodeficiency virus (HIV) infects T_4 helper cells, the major component of the immune system, allowing the occurrence of secondary infections (*Pneumocystis carinii*, CMV, *Candida*, herpes simplex), and neoplasia (Kaposi's sarcoma, lymphoma). AIDS occurs in children whose mothers developed AIDS before, during, or after birth, or after receiving blood products containing HIV. In children, the findings in AIDS are different than in adults, in that opportunistic infections are less frequent and the signs and symptoms are more related to the direct effects of primary retroviral encephalitis. The neuropathologic observations include decreased brain weight, glial, and microglial nodules in the basal ganglia, pons, and white matter, and characteristic multinucleated cells. Perivascular calcification has been reported to particularly prominent in the putamen and globus pallidus. There may be areas of perivascular accumulation of inflammatory cells and a subtle focal demyelination. Clinically, these children appear to have a progressive spastic quadriplegia. The occurrence of seizures is rare, presumably due to lack of cortical involvement by inflammatory infiltrate. It is thought that the dementia is due to subcortical pathologic alteration.

Demyelinating disorders. White matter can be damaged by infarction secondary to vasculitis in bacterial meningitis and in the necrosis associated with herpes simplex encephalitis. In these conditions, however, selective demyelination is uncommon. The target cell in demyelinating disorders is the oligodendrogliocyte. Some viruses such as papovavirus, measles, and probably HIV selectively infect and destroy oligodendroglia and produce demyelination.

Papovavirus infection causes PML in immunocompromised hosts and is extremely rare in children (Fig. 16). In contrast, SSPE more commonly occurs in children and is caused by a defective measles virus. Measles immunization programs have significantly reduced its incidence.

Fig. 15. Acute herpes simplex type I encephalitis with generalized cerebral edema and congestion and swelling of temporal lobe (*right*).

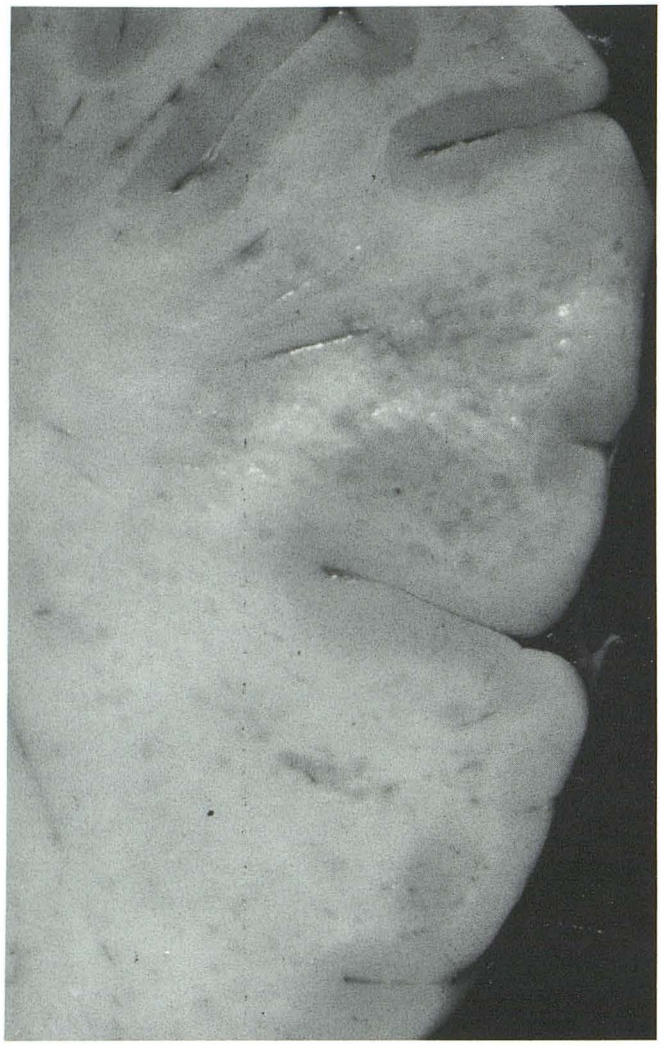


Fig. 16. Progressive multifocal leukoencephalopathy with focal grey areas in the white matter, representing multifocal demyelination.

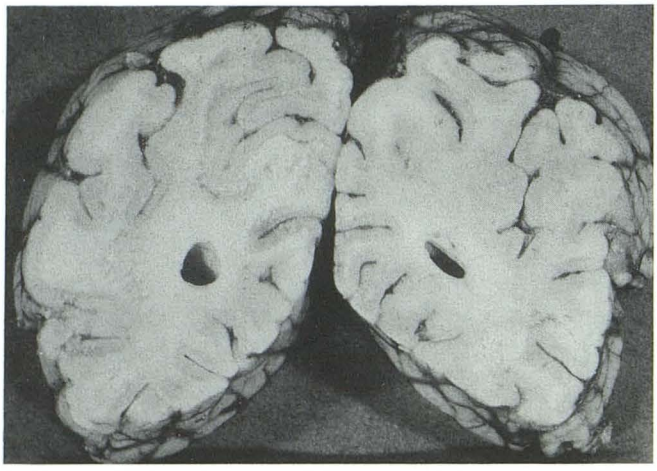


Fig. 17. Subacute sclerosing panencephalitis. In the occipital lobes, extensive demyelination tends to follow the cortical ribbon.

SSPE is characterized by behavioral problems and decline in school performance, followed over months by disturbed motor function (myoclonic jerks), and eventually a stuporous rigid state. Pathologically, demyelination is prominent in the posterior cerebral hemispheres, with less involvement of frontal lobes, brain stem, cerebellum, and spinal cord (Fig. 17) (31). Symmetrical enlargement of ventricles may be seen. The occasional sparing of the subcortical arcuate fibers and involvement of occipital lobes resembles the pattern of demyelination found in adrenoleukodystrophy.

Conclusions

The spectrum of infectious diseases that can affect the nervous system is broad. Genetic changes in the natural evolution of viruses produce new strains and surprising clinical syndromes such as those described with HIV infection. Medical intervention with new antibiotics and immunization programs alters the incidence and character of infectious diseases. In the adult, the immune response is fully mature and host reaction is more nearly stereotypical. In the developing infant, however, many aspects of the host are in flux. Not only are the cellular and humoral components of the host immune system maturing from fetal to infant stages of development but the target organ, the CNS, is also undergoing profound alteration, creating a changing population of susceptible cells. As a consequence of these complexities, the patterns of pathology produced by infectious agents in the developing nervous system can be difficult to interpret. They often require a close correlation of observations from clinical, radiologic, and pathologic areas of expertise.

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