Stroke in newborn infants

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The few days before and after birth are a time of special risk for stroke in both mother and infant, probably related to activation of coagulation mechanisms in this critical period. Arterial ischaemic stroke around the time of birth is recognised in about one in 4000 full-term infants, and may present with neurological and systemic signs in the newborn. Neonatal seizures are most commonly the clinical finding that triggers assessment. In other children, perinatal stroke is recognised only retrospectively, with emerging hemiparesis or seizures after the early months of life. Risk factors for perinatal stroke include hereditary or acquired thrombophilias and environmental factors. Perinatal stroke underlies an important share of congenital hemiplegic cerebral palsy, and probably some spastic quadriplegic cerebral palsy and seizure disorders. There is much to be learned about the natural history of perinatal stroke, and there are as yet no evidence-based strategies for prevention or treatment.

Stroke is the third most common cause of death in adults in the developed world, and an important cause of mortality and chronic neurological morbidity in children. Many strokes in children happen in the perinatal period, soon before birth or within the month after.

Risk of ischaemic stroke in the mother also increases near the time of birth,[1,2] and is 34 times more common in the 2 days before and 1 day after delivery than earlier in pregnancy or in the non-pregnant state.[2] The heightened vulnerability to ischaemic stroke in both mother and child, and also to thromboses in non-cerebral sites[3–5] is probably related to activation of coagulant mechanisms by parturition,[6,7] presumably an evolutionary adaptation to lessen the risk of haemorrhage at this crucial time.

Improvements in and the increasing availability of neuroimaging have increased the diagnosis of perinatal stroke. The result has been an increasing awareness of stroke as part of the differential diagnoses in newborns and infants with neurological symptoms.

Residues of focal cerebral infarction are a common finding in neuroimaging studies of older children with congenital hemiplegic cerebral palsy. Perinatal stroke is probably not a new syndrome: in 1892, Sir William Osler described 15 children with congenital hemiparesis[8] and 5 years later Sigmund Freud added another 61 to the records.[9] In many of these children there was no obvious antecedent trauma or infection; current experience suggests that many had perinatal strokes. This review will consider arterial ischaemic stroke in the fetus and neonate, with focus on its frequency, clinical presentation, assessment, management, and outcome.

Definition

Perinatal ischaemic stroke is a cerebrovascular event around the time of birth with pathological or radiological evidence of focal arterial infarction. Haemorrhagic lesions, generalised ischaemic lesions involving arterial border zones, and cerebral venous thromboses are not discussed in this review. Most studies have combined both perinatal (from 28 weeks into the pregnancy to 7 days old) and neonatal (under 28 days old) events. As currently understood, perinatal stroke is chiefly, although not exclusively,[10] a disorder of term or near-term infants. Early reports of perinatal stroke defined cases based on autopsy criteria,[11] while recent series have based diagnoses on neuroimaging criteria including CT and MRI.

Incidence

Most population-based studies of paediatric stroke have excluded the first months or first year of life, and many studies of perinatal systemic thromboembolic events have excluded stroke. Ultrasonography, the neuroimaging modality in most general use in the neonatal nursery, is not a sensitive indicator of perinatal stroke.[12] Early imaging studies may be unrevealing in neonates with cerebral infarction,[13] and early hospital discharge may preclude in-hospital diagnosis of perinatal stroke in infants not symptomatic in the earliest days of life. Hence, the incidence of perinatal stroke has been difficult to determine.

As recognised in the neonatal period, symptomatic perinatal stroke occurs in about one in 4000 term neonates.[14] Ischaemic stroke after the first month of life occurs with an annual incidence rate of about one in 30 000 children.[15]

No information is available on the frequency of perinatal strokes that were asymptomatic in the nursery period and were diagnosed later. Unless followed by disability leading to neuroimaging in later months or years, such strokes remain unrecognised. Racial and gender differences have been identified for paediatric stroke, but such information is not available for perinatal stroke.

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Clinical presentation

Perinatal stroke recognised in the neonatal period

Some newborns with perinatal stroke have neurological or general illness leading to neuroimaging and thereby to the identification of the perinatal stroke. Neonatal seizures are most commonly the clinical finding that triggers assessment, but in autopsy studies of infants who had ischaemic cerebral infarcts, neonatal seizures were noted in 25–40%.[11,16] Many neonatal seizures in infants with arterial stroke are focal and may occur in the absence of other signs of neonatal encephalopathy—such as abnormalities of tone or feeding, or depressed level of alertness.[17] The infant may thus be apparently well between seizures. Systemic signs, if present, are nonspecific and sometimes subtle and include hypotonia, lethargy, or apnoea.[18,19]

Some neonates with perinatal stroke are more seriously ill. Whether severity of illness is related to the extent or recentness of cerebral or extracerebral thrombosis is unclear. Among children with perinatal strokes who later had moderate or severe cerebral palsy, low Apgar scores and other signs interpreted to indicate "birth asphyxia" or "hypoxic-ischaemic encephalopathy" were common.[20] Differential diagnosis of neonatal neurological depression and seizures, and recognition of perinatal stroke, rest chiefly on neuroimaging evidence of focal infarction. The distinction between focal ischaemic injuries versus other cerebral pathologies is important because of the implications for understanding of pathogenesis and direction of workup.

Whether outcome is worse in infants with perinatal strokes in whom neonatal depression is severe and accompanied by other signs of neonatal encephalopathy is not established but is plausible. To date, studies have included no infants with notably low 5 min Apgar scores or very low pH, and few with unfavourable long-term outcome.[19,21]

Perinatal stroke diagnosed retrospectively

In some infants not thought to be neurologically ill as neonates, perinatal stroke may be diagnosed in later months after presentation with asymmetry of reach and grasp, failure to reach developmental milestones, or post-neonatal seizures.[22] Even severe congenital hemiparesis is seldom diagnosed in the newborn period.[23] A specialised motor examination may identify affected infants early,[24] but emerging hemiparesis is rarely detected until the development of voluntary motor activity in the middle of the first year of life.

Perinatal stroke is probably under-recognised: one newborn infant had an MRI as a control individual in a study of perinatal stroke and was found to have had a stroke.[25]

Retrospective diagnosis of perinatal stroke depends on neuroimaging findings. Asymmetry of skull volume and thickness may be seen on plain skull films and the finding of lesser breadth of thumbnail beds on the affected side may provide a hint on physical diagnosis.

In perinatal stroke diagnosed in the newborn, neurological outcome is not always unfavourable. In contrast, retrospectively diagnosed perinatal stroke is recognised because of the presence of the abnormal neurological findings that led to imaging; if moderate or severe at the time of recognition, these abnormal findings commonly persist.[26] At present, whether perinatal stroke diagnosed acutely and that diagnosed retrospectively are different in time of occurrence, cause, or pattern of injury is unclear.

Pathophysiology

Clot formation is influenced, as Virchow pointed out almost 150 years ago,[27] by hypercoagulable blood constituents, injury to vessel walls, and stasis of blood flow. All these may be relevant in perinatal stroke. Many factors that are associated with risk of stroke in older children, and some factors associated with stroke in adults, are also relevant in the perinatal period. In addition, there are risk factors unique to this developmental stage.

Features of the perinatal period that influence coagulation status include the presence of fetal haemoglobin, fetal proteins, and a high haematocrit and blood viscosity. Concentrations of procoagulant and anticoagulant proteins change with gestational and postnatal age, with activation of coagulation in both fetus and mother near the time of birth.[6] Placental infections can also interact with coagulation. Maternal and placental microbiology, and the associated clinical and placental histological manifestations, vary according to gestational age and the immune status of mother and infant.

The mechanisms by which ischaemic stroke occurs in the perinatal period include thromboembolism from an intracranial or extracranial vessel, or the heart or placenta. Commonly the source is undetermined,[28] but a placental origin is suspected in many.

Most perinatal strokes occur in the territory of the middle cerebral artery. There is a predominance of left-hemisphere lesions, which may be caused by haemodynamic differences from a patent ductus arteriosus,[29] or a more direct route involving the left common carotid. The distribution of cerebral infarction differs somewhat with gestational age—preterm infants tend to have multifocal lesions[11] involving the cortical or lenticulostriate branches of the middle cerebral artery, whereas full-term infants tend to have occlusions of the main branch.[30]

Risk factors

Risk factors for perinatal stroke have been assessed on limited evidence from selected case series and case reports. Epidemiological investigations of infants with perinatal stroke have observed an association with maternal and placental disorders, perinatal asphyxia, blood disorders, cardiac disorders, infection, trauma, and drugs. More than one risk factor is identified in many cases (panel 1).

Maternal disorders

Pregnancy is itself an important risk factor for maternal thrombosis.[31] Although some changes in pregnancy—such as increases in blood volume—decrease the procoagulant tendency, the net change is prothrombotic. During pregnancy, protein S and activated protein C ratios are low, while thrombin generation, protein C, von Willebrand

factor, factor VIII, factor V, and fibrinogen concentrations are high.[32–36] Old maternal age, infection, obesity, personal or family history of thromboembolic events, surgery (including surgical delivery), dehydration or shock of any origin, and prolonged bed rest are additional risk factors for maternal thrombosis.[37,38] Bed rest is prescribed in nearly 20% of pregnancies,[39] but neither it nor other environmental factors—such as maternal obesity, mode of delivery, maternal smoking, or migraine and its treatment—have been investigated as potential risk factors for perinatal stroke.

Women with inherited or acquired thrombophilias are predisposed to complications of pregnancy including middle trimester pregnancy loss, placental abruption, severe fetal growth restriction beginning in the middle trimester, and early severe pre-eclampsia.[37,40–43] Such coagulation abnormalities may predispose to thrombosis at the maternal side of the placenta, where maternal uterine spiral arteries perfuse the fetal villous vessels in an area of low pressure. Coagulation abnormalities inherited from either parent may lead to thrombosis on the fetal side of the placenta, and may be a source of emboli that can bypass the hepatic and pulmonary circulation via the patent foramen ovale and travel to the fetal brain.

Acquired coagulation disorders, such as antiphospholipid antibodies, can also predispose to perinatal stroke. Phospholipids are involved in the activation of protein C and the coagulation pathway. Lupus anticoagulant, anticardiolipin, and β2-glycoprotein-1 antibodies are directed against anticoagulant proteins, and affect normal coagulation.[44] People with high concentrations of antibodies against phospholipid are at a high risk of arterial and venous thrombosis, recurrent pregnancy loss, intrauterine death, and placental thrombosis.[45] Since 1992,[46] there have been several reported cases of perinatal stroke associated with high concentrations of phospholipid antibodies in the mother or infant.[47] Stroke in the infant may occur years before a diagnosis of antiphospholipid syndrome is made in the mother.[48–50]Antiphospholipid antibodies may affect the fetus either by transport of antibodies across the placenta, by thrombotic or other alteration in the placenta that impedes transport across that vital organ, or direct involvement of the fetus.

Use of cocaine by the mother causes vasoconstriction and can result in placental abruption or perinatal stroke.[51,52] Authors of one study observed that 17% of full-term infants born to cocaine abusers had evidence of cortical infarction.[53]

Placental disorders

The placenta is a highly vascular organ with areas of low flow and has its own mechanisms to regulate haemostasis.[54] In pathological states the placenta may be a source of embolisation to the fetal brain. Maternal and fetal factors that affect placental function can lead to pregnancy complications and perinatal stroke. However, in many cases, the placenta is not examined in detail or is not available for examination when infants become symptomatic in the neonatal period.

The combination of low blood flow and the presence of chorioamnionitis may contribute to the risk of thrombosis

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Panel 1. Risk factors for perinatal stroke

Cardiac disorders
Congenital heart disease
Patent ductus arteriosus
Pulmonary valve atresia

Blood, homocysteine, and lipid disorders
Polycythaemia
Disseminated intravascular coagulopathy
Factor-V Leiden mutation
Protein-S deficiency
Protein-C deficiency
Prothrombin mutation
Homocysteine
Lipoprotein (a)
Factor VIII

Infectious disorders
CNS infection
Systemic infection

Maternal disorders
Autoimmune disorders
Coagulation disorders
Anticardiolipin antibodies
Twin to twin transfusion syndrome
In utero cocaine exposure
Infection

Placental disorders
Placental thrombosis
Placental abruption
Placental infection
Fetomaternal haemorrhage

Vasculopathy
Vascular maldevelopment

Trauma and catheterisation

Birth asphyxia

Dehydration

Extracorporeal membrane oxygenation

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in the placenta, and is associated with a high risk of pregnancy complications.[55–57] Abnormalities of placental blood flow are documented in the placentas of thrombophilic women[58] and are a plausible basis for abnormalities sometimes noted on electronic fetal monitoring in these women.[59] In children with early strokes, mother and child may both have thrombophilias, the same or (if inheritance is from the father) different mutations, and may thereby injure both maternal and fetal placental vasculatures.[60]

An association has been observed between placental abnormalities and fetal or neonatal stroke in studies of stillborn infants and children with cerebral palsy.[61,62] Reports linking placental lesions with cerebral palsy in full-term infants come largely from review of cases for litigation. In this selected source, thrombotic lesions in the fetal circulation of the placenta were commonly observed.[63] The combination of acute and chronic lesions in the placenta seemed to be most strongly related to neurological outcome.[64]

History
Maternal medical history
Pregnancy disorders
Birth history (labour, delivery, and complications)
Family history of neurological disorders
Family history of thrombosis

Imaging Studies
Diffusion-weighted MRI and MRA
CT if MRI unavailable
Ultrasound if CT or MRI unavailable
Echocardiogram

Laboratory Studies

Blood tests
Blood-cell count
Ratio of prothrombin time to partial thromboplastin time
Protein-C activity
Protein-S activity
Antithrombin activity
Phospholipid antibodies
Cardiolipin antibodies
Homocysteine
Lipoprotein (a)
Plasminogen
Fibrinogen

Genetic tests
Factor V Leiden mutation
Prothrombin 20210G→A mutation
MTHFR mutation

Urine tests
Toxicology screen
Organic and amino acids

Additional studies
EEG
Placental pathology
Maternal testing for coagulation disorders

Birth asphyxia

Signs interpreted to indicate birth asphyxia might be either a result or a cause of prenatal stroke. Early reports of infants with perinatal stroke included a history of birth asphyxia in most of these infants,[65-67] but this has not been confirmed in more recent studies. In a study of full-term infants with cerebral infarction, there was no significant difference between cases and controls in pregnancy complications, intrauterine heart rate monitoring, and mode of delivery, umbilical artery pH, or Apgar score at 5 min.[21]

Blood and metabolic disorders

The association between blood and metabolic disorders and perinatal stroke has been based on small series from referral centres. Blood disorders associated with stroke in neonates include polycythaemia, protein-C deficiency, prothrombin 20210A mutation, and the factor V Leiden (fVL) mutation.[68,69] Multiple factors are associated with high risk of thrombosis.[70] Other factors related to coagulation, fibrinolysis, endothelial activation, and other potentially relevant processes await exploration.

Polycythaemia leads to hyperviscocity and has been reported in association with neonatal stroke.[71–73] The fVL mutation, a dominantly inherited coagulation abnormality, has been found in association with cerebral arterial and venous disorders in neonates and children.[74] The fVL mutation is the most common inherited cause of thrombosis in white people. Alone, the fVL mutation does not greatly increase risk, but its presence can interact with other genetic and environmental factors that increase risk. Infants with stroke associated with the fVL mutation typically develop symptoms within the first months of life and only if additional endogenous or exogenous risk factors for thrombosis are present.[74]

High concentrations of lipoprotein (a) are associated with perinatal and childhood stroke.[69,75] One study in children revealed an association between mutation of *MTHFR* and paediatric stroke,[75] whereas other studies in neonates and children were either underpowered or failed to show an association.[69,76]

Thrombophilias may predispose to recurrent seizure disorders via the occurrence of perinatal stroke. The Lennox-Gastaut syndrome was observed in three children with porencephaly, two with the fVL mutation, and one with protein-C deficiency.[77] Infantile spasms have been described in a child heterozygous for both the fVL mutation and the mutated *MTHFR*.[78] There are reports of an association of anticardiolipin antibody with benign infantile convulsions[79] and of antiphospholipid antibodies with epilepsies in elderly patients.

There has not yet been a systematic exploration of seizure disorders in a representative group of children with perinatal stroke or of thrombophilias in patients with epilepsy. The possibility that disorders of coagulation and their consequences might underlie a proportion of the mysterious syndromes of malignant epilepsy in childhood seems worthy of investigation.

Cardiac disorders

Intracardiac thrombi can embolise to the brain. Several cardiac disorders, and procedures for their diagnosis and repair, have been reported with stroke in neonates and children.[80–83] Stroke in infants with congenital heart disease is probably related to the specific underlying abnormality, the diagnostic and surgical procedures used, and associated genetic or acquired factors that predispose to thrombosis. Silent infarction may occur; neuroimaging studies showed asymptomatic neurological damage in infants who had cardiac surgery for congenital heart disease.[84]

Infectious disorders

Perinatal stroke has been reported as a complication of meningitis,[85] disseminated intravascular coagulation, and sepsis.[11,86] Infection leads to a hypercoagulable state. During serious infection, there is a rapid destruction of protein C and antithrombin III, both of which normally inhibit coagulation. Infection also produces endothelial injury and a release of inflammatory cytokines, which lead to the downregulation of thrombomodulin and upregulation of tissue factor.
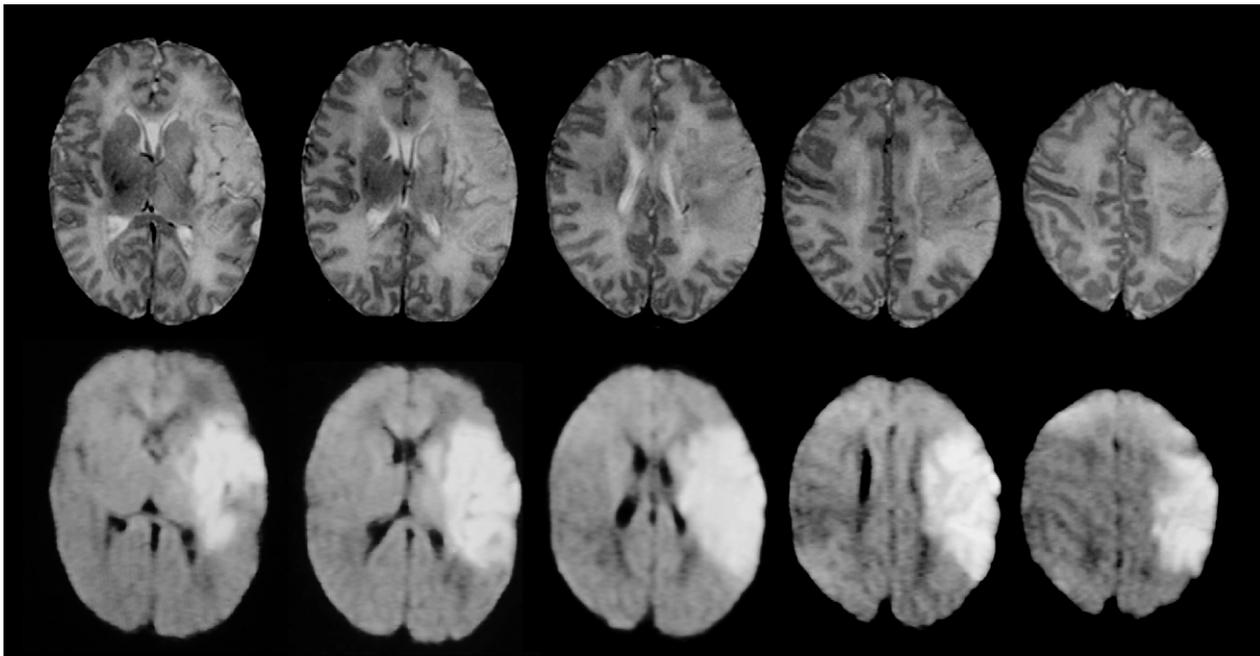
Figure 1. Axial T2 (TR 3500/TE 120; top) and diffusion-weighted MRI (b=1000; bottom) images of 5-day-old infant with left middle cerebral artery stroke.

Trauma, surgery, and catheters

Intravascular catheters and trauma are associated with increased risk of venous and arterial thrombosis including neonatal stroke.[87–90] Inherited risk factors may increase susceptibility to environmentally triggered thrombosis.[91] There has been no investigation of whether obstetric trauma caused by forceps or vacuum extraction is related to infant stroke risk.

A relatively large percentage of children with strokes were delivered by caesarean section. The reason for surgical delivery may be abnormalities on electronic fetal monitoring (noted in the presence of antiphospholipid antibodies[59] and inherited coagulation disorders), which may be caused by abnormalities of the placental vasculature. Surgery is in general a risk factor for thrombosis, caesarean delivery being associated with a risk of stroke three to four times higher than normal in the mother.[92] Whether, and under what circumstances, surgical delivery influences the risk of perinatal stroke has not been investigated.

Interactions of risk factors

Inflammation is not rare in placenta and can tip the balance toward coagulation. Multiple risk factors, both gene–gene and gene–environment interactions, and probably maternal plus fetal risk factors, may act synergistically to increase risk. The clinician's job is not finished once he or she has identified a mutation predisposing to thrombosis in an affected child; the combinations of factors that interact to produce thromboemboli in the fetal or newborn cerebral circulation must be investigated.

Assessment and neuroimaging

The assessment of neonatal patients with stroke should include a detailed history with questions regarding maternal disorders, pregnancy disorders (pre-eclampsia, history of fetal loss, placental abruption, haemorrhage), birth history, placental pathology, and family histories of neurological disorders, premature vascular disease (early myocardial infarction or stroke, deep venous thrombosis), and haematological disease (panel 2).[93]

Cranial imaging procedures for neonatal stroke include MRI, CT, and ultrasonography. Conventional T1-weighted and T2-weighted MRI with diffusion-weighted imaging is
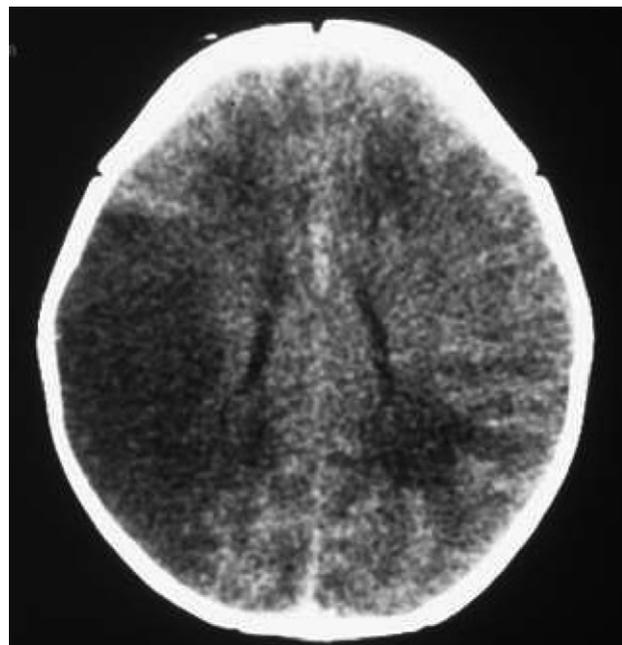

Figure 2. CT image of 1-day-old child diagnosed with right middle cerebral artery stroke.
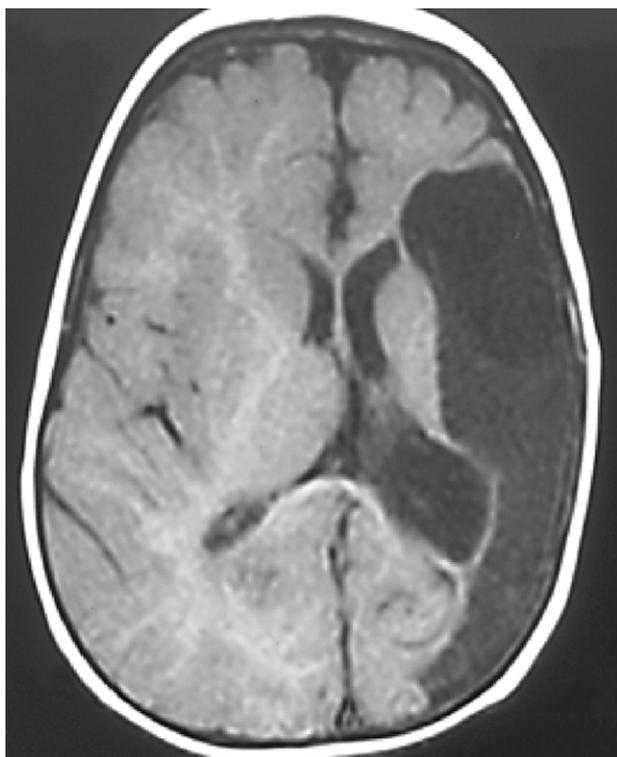
Figure 3. Axial MRI of 9-month-old child with evidence of perinatal stroke. Note the skull asymmetry as well as the large porencephalic cyst.

the current test of choice as it is particularly sensitive to detection of early infarction even when standard techniques do not detect abnormalities (figure 1). Magnetic resonance angiography is also useful for the detection of occlusion and hypoplastic vessels.[94] If MRI is unavailable or not possible for a sick newborn, CT or ultrasonography should be considered. Radiological criteria for perinatal stroke have included CT evidence of focal hypodensity (figure 2), focal hypodensity with intraparenchymal haemorrhage, hyperdensity of the grey matter associated with white-matter lucency and cortical or central volume loss or porencephalic lesions (figure 3), and MRI evidence of acute or remote focal infarction.[66]

EEG is useful for prognosis and should be done in the first 24 h, as some neonates with stroke will have seizures early in the postnatal period, between 12 h and 72 h.[21]

The usefulness of cerebral blood flow studies in perinatal stroke has not been established. Although a few small series have identified asymmetric flow velocities in neonates with middle cerebral artery infarctions, further studies are needed to guide therapy and determine prognosis.[67,95,96] Conventional cerebral angiography has been recommended in special situations for ischaemic stroke in children, but requires further study in neonates.[97]

Further diagnostic studies should focus on risk factors for neonatal stroke; and they should assess metabolic and coagulation tests, cardiac imaging, urine toxicology screening, lumbar puncture and EEG. Maternal testing for coagulation abnormalities should be considered. Because the numbers of phospholipid antibodies in the mother vary over

time and disappear in the infant if they were passively acquired, it is useful to test for these antibodies early and again later.

Assessment of the placenta by an experienced pathologist is an important part of understanding the pathophysiology of perinatal stroke, of value both in research and in clinical settings. Thrombosis in the placenta, especially if coexistent with inflammatory changes is among the "clinically silent" processes often present in the placentas of children whose neurological outcome is unfavourable.[98]

An early diagnosis of perinatal stroke can direct the remainder of the assessment and the removal of environmental risk factors by correction of dehydration, treatment of infection, or minimising the use of intravascular catheters. A complete assessment can provide information useful in determining recurrence risk.[99,100]

Management

Few studies and no randomised trials have addressed the issue of treatment, either acutely or for primary or secondary prevention of perinatal stroke. On the basis of adult and animal studies, infection, fever, and seizures should be treated aggressively. The recurrence risk for neonatal stroke is low in the first year and it is unclear whether long-term medical therapy is useful. Further studies are needed to determine the best treatment for neonatal stroke and whether prophylactic measures in pregnant women with thrombophilia can prevent perinatal stroke.

The identification of a perinatal stroke and the underlying pathogenetic mechanisms may have implications for subsequent pregnancies of the mother and for health of other family members. For affected infants, testing of prothrombotic factors is clearly desirable for purposes of research and to provide an informed basis for prognosis. These tests should include those for a wide range of environmental factors in addition to genetic and acquired thrombophilias. Except for research purposes, there is no consensus as to whether the screening of family members of children who have had a stroke is useful. Recent reviews have discussed counselling in the presence of venous thromboembolism in pregnant and non-pregnant adults.[101] No review has discussed counselling and screening for the family of the child with perinatal stroke.

A potential downside of screening is possible difficulty in obtaining insurance or employment. It has been suggested[102] that relatives of a child with a stroke, whether they are screened or not, should behave as if they themselves have a propensity to thrombosis. They should inform their physicians of their family history of thrombosis, so that this information is available in the event of trauma, surgery, prolonged immobilisation, or cancer. It also seems reasonable that they should refrain from activities that increase the risk of thrombosis—including tobacco use, lengthy sitting or standing without interspersed exercise, prolonged dehydration, and oral contraceptives.

Outcome

The outcome after neonatal stroke varies among studies because of differences in functional measures, stroke type,
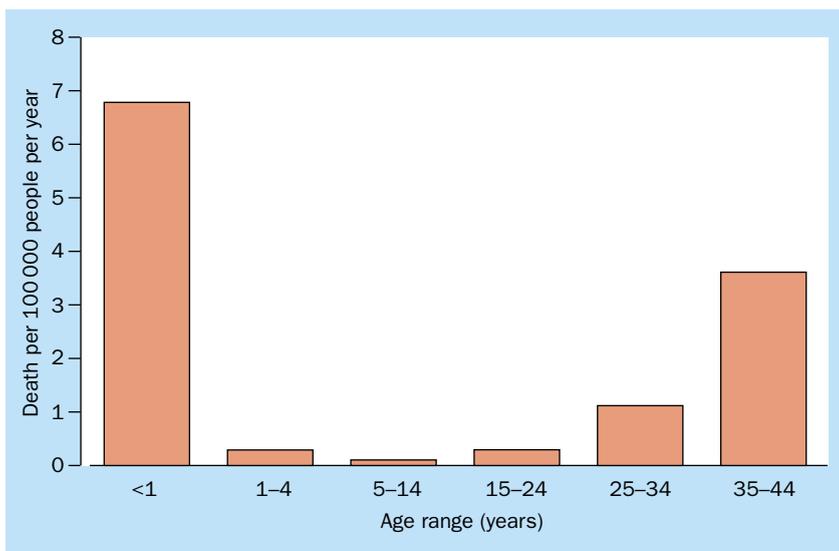
Figure 4. Mortality rates for ischaemic stroke in the USA.

length of follow-up, and clinical sample studied. Outcome measures used include gross and fine motor development, visual, speech and language function, IQ and behaviour abnormalities, and recurrent seizures. Children with perinatal stroke are typically diagnosed with congenital hemiplegic cerebral palsy, and it seems likely that bilateral lesions cause some spastic quadriplegic cerebral palsy.

On the basis of a review of epidemiological studies of perinatal stroke over the last 30 years, 40% of infants with perinatal stroke were later neurologically normal, 57% were neurologically or cognitively abnormal, and 3% died.[14] A similar review by de Vries and Levene[103] concluded that over half of children with neonatal stroke were clinically normal by 12–18 months of age.

The infant mortality rate is the number of deaths that occur in children less than one year of age divided by the total number of live births for that year. Most infant deaths occur in the first 28 days (neonatal mortality). The US infant mortality for years 1995–98 due to stroke (ICD-9 CM,[104] excluding perinatal intraventricular haemorrhage and periventricular leucomalacia) was 5·3 per 100 000 and neonate mortality was 3·5 per 100 000 live births per year.[105] In the National Hospital Discharge Survey, from 1980 through 1998, for infants less than 30 days of age, the in-hospital mortality for neonatal stroke was 10·1%.

The death rate from ischaemic stroke is much higher in the year after birth than during childhood and for the remainder of the first half-century of life (figure 4).[106] Unlike childhood deaths from intracerebral or subarachnoid haemorrhage, deaths from ischaemic stroke have not declined over recent decades.[107] As judged by both incidence and mortality data, then, it is likely that the perinatal period is the most common time of occurrence for ischaemic stroke in childhood, as it is for thrombosis in other organs.[4,108]

EEG and neuroimaging give important information on long-term prognosis. A study by Mercuri and co-workers[109] of 24 infants with perinatal stroke revealed an association between early EEG and MRI abnormalities and motor outcome after 15 months. Infants with an abnormal background on EEG in the first week and infants with combined involvement of the internal capsule, basal ganglia, and cortex developed hemiplegia. There was no association between adverse prenatal and perinatal factors and long-term outcome.

Imaging studies have been less predictive of later cognitive function. A recent case-control study of children with perinatal unilateral brain damage found no significant difference between patients and uninjured children in clinically significant behavioural or emotional problems.[110]

Although no direct comparison studies exist, the long-term outcome and recurrence-rate after perinatal stroke seem to be better than in older children and adults. Data from the Canadian Pediatric Ischaemic Stroke Registry, which includes 402 children with arterial ischaemic stroke and 160 children with sinus thrombosis, revealed that 27% of children were neurologically normal, 61% were abnormal, 21·6% had recurrences of stroke, and 12% died by the outcome evaluation period.[111] Further studies are needed to determine whether the relatively good outcome in neonatal stroke is related to plasticity of the term neonatal brain, retention of connections, modifications in function, or type and location of ischaemic injuries.

Perinatal stroke is different

Perinatal stroke shares many features with strokes occurring later in childhood or indeed in adult years; however, there are also important differences. The neonatal coagulation system is immature and more susceptible to clot formation. The fetus with a stroke is, and the newborn recently was, attached to the mother and a placenta, and pathology arising in these may be relevant to stroke in the infant. The placenta interface is a unique environment with its own regulation of coagulant mechanisms.[54,57]

Many factors associated with arterial thrombotic events in the newborn, such as the fVL and prothrombin mutations, are chiefly associated with venous disease rather than arterial disease in adults. In children, coexisting infection, specific or not, seems to predispose to arterial stroke; whereas, in adults venous thromboembolic disease is affected much less by inflammation. Even the volume of blood that can be withdrawn for laboratory assessment in newborns can complicate some diagnostic assays.

Many medical specialties—including obstetrics, neonatology, haematology, neuroradiology, placental pathology, child neurology, and epidemiology—are involved in the study of children with perinatal stroke. The different points of view of these various specialists contribute to differences in what they see. For example, obstetricians aware of thrombophilic mutations in their pregnant patients may

feel that risk to the fetus is low, whereas paediatric neurologists or epidemiologists studying antecedents in children with neurological disability may find perinatal stroke and coagulation disorders to be present in appreciable proportions of these children. Similarly, intrauterine growth restriction is not common in progeny of women with coagulation mutations, but among infants with growth restriction and unfavourable outcome, thrombophilic mutations may be among important causes. Neither the prospective view starting with fairly low-risk individuals nor the retrospective view looking backward from the occurrence of adverse neurological outcomes is false, but both are partial views. Only when a study has been done in a population of known denominator, with good ascertainment of perinatal stroke, extensive evaluation of risk factors, and determination of long-term outcome, will a complete picture emerge.

Conclusion

In the study of perinatal stroke, much is uncertain—including the best case definition for neonatal and for delayed diagnosis, neuroimaging criteria for different procedures at different ages, what haematological tests are best at what ages, and whether effective safe preventive treatment is feasible. We still have no evidence-based approach to prevention or management.

The care of children with perinatal stroke is dispersed over several medical specialties. Obstetricians care for women with thromboembolic disease in pregnancy, but the large obstetric research on this topic seldom discusses the effect of the disorder or its treatment on the fetus or infant. Neonatologists care for sick newborns whose outcome is

generally good, whereas paediatricians or neurologists see the older infant or child with fixed disability. The clinicians involved in the care of children with clinical disorders due to thrombi in extracerebral organs are different to those involved with cerebral infarctions. Rarely do representatives of all the relevant specialties discuss with one another patient care or study development in perinatal stroke, as will be necessary for the setting up of studies that have a hope of answering some of the many questions that remain.

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