The epidemiology and causes of cerebral palsy

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Cerebral palsy is the commonest physical disability in childhood, occurring in 2.0 to 2.5 per 1000 live births. Although the total number of children with cerebral palsy has remained stable or increased slightly since 1970, there has been a consistent rise in the proportion of cerebral palsy associated with preterm and very preterm births. Known causes of cerebral palsy – whether prenatal, perinatal or postnatal – must be distinguished from risk factors or associations. Much is known about such risk factors which, alone or in combination, may indirectly result in cerebral palsy. Causes and risk factors implicated in cerebral palsy are discussed in detail, together with directions for future research.  

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Epidemiology Studies from Western Australia (Stanley and Watson 1992), Sweden (Hagberg et al 1993), the United Kingdom (MacGillivray and Campbell 1995, Pharoah et al 1987) and the United States (Murphy et al 1993) have reported cerebral palsy rates of between 2.0 and 2.5 per 1,000 live births. While the total number of children with cerebral palsy has remained stable (Pharoah et al 1990, Stanley and Watson 1992) or increased since 1970 (Hagberg et al 1993, MacGillivray and Campbell 1995, Murphy et al 1993), there has been a consistent rise in the risk of cerebral palsy associated with preterm and very preterm infants (Hagberg et al 1993, MacGillivray and Campbell 1995, Murphy et al 1993, Pharoah et al 1996, Stanley and Watson 1992). The overall increase in cerebral palsy reflects the increased survival rates of these infants (Mutch et al 1992, Paneth 1993, Pharoah et al 1996, Stanley and Watson 1992).

There have been radical changes in our understanding of aetiological factors over the last 20 years. In 1862, Little reported that abnormal birth was a possible factor in spastic cerebral palsy. Although he was aware of other causes, his writings were interpreted to mean that abnormal birth was the primary cause of spastic cerebral palsy. There was no recognition of Freud’s converse view that intrauterine developmental abnormality was responsible (Scherzer and Tscharnuter 1982). For over 100 years, most cases of cerebral palsy were thought to be caused by asphyxia during either labour or the perinatal period (Blair and Stanley 1988, Paneth 1986). Prevalence rates of cerebral palsy were used as outcome measures of obstetric practice and neonatal care and it was expected that improvement in these areas would result in lower rates of cerebral palsy (Stanley and Blair 1991, Torfs et al 1990). As a result, there was increased use of interventions such as electronic foetal monitoring and caesarean section. However, the role of perinatal asphyxia in the aetiology of cerebral palsy was challenged when the stillbirth and neonatal death rates declined but the cerebral palsy rate remained constant (Emond et al 1989, Stanley and Blair 1991, Stanley and Waton 1988).

Current research suggests that perinatal asphyxia accounts for between 6% and 8% of cerebral palsy (Blair and Stanley 1988, Naeye et al 1989, Yudkin et al 1995). However, even in this group, there may be other underlying causes making infants at risk for perinatal asphyxia and, in most children, prevention is not possible (Australian and New Zealand Perinatal Societies 1995). Prenatal events are thought to be responsible for approximately 75% of all cases of cerebral palsy although it is usually impossible to determine the nature and the exact timing of the damaging event. Estimates of the proportion of cases with postnatally acquired cerebral palsy range between 10% (Holm 1982) and 18% (Pharoah et al 1989). The current trend is to assume a prenatal cause in the absence of clear evidence for a perinatal or postnatal cause (Gaffney et al 1994, Holm 1982, Palmer et al 1995).

Research Prospective studies to determine risk factors across populations are costly and difficult when only two per thousand of all pregnancies will result in a child with cerebral palsy. Most research has involved retrospective studies where obstetric and perinatal histories of groups of children with cerebral palsy are compared with controls without cerebral palsy. Attempts are then made to identify prenatal and perinatal exposures common to children with cerebral palsy. Natural events have provided evidence of prenatal determinants of cerebral palsy on rare occasions.
For example, between 1953 and 1960, an epidemic of cerebral palsy was noted in children born to families eating fish contaminated by methyl mercury in Minamata Bay in Japan and an epidemic consisting of a triad of spasticity, deafness and intellectual disability in Papua New Guinea during the early 1960s was caused by lack of iodine early in pregnancy (Stanley 1997).

**Known causes of cerebral palsy**

It is helpful to classify the known causes according to the timing of the brain insult, whether prenatal, perinatal or postnatal.

**Antenatal causes of cerebral palsy** Among the important known causes of cerebral palsy are congenital brain malformations including malformations of cortical development. Modern imaging techniques enable more children with these conditions to be identified (Krageloh-Mann et al 1995, Steinitz et al 1993, Truwit et al 1992), and knowledge about the cortical dysplasias, of which some have a genetic basis, is increasing rapidly (Dobyns and Truwit 1995). Congenital malformations in general are strongly associated with cerebral palsy (Blair and Stanley 1993a, Croen et al 2001, Nelson and Ellenberg 1985 and 1986, Palmer et al 1995, Torfs et al 1990) and children with congenital brain malformations also have more anomalies outside of the central nervous system (Coorssen et al 1991).

Other known antenatal causes of cerebral palsy are vascular events demonstrated by brain imaging (for example, middle cerebral artery occlusion), and maternal infections during the first and second trimesters of pregnancy (rubella, cytomegalovirus, toxoplasmosis). Less common causes of cerebral palsy include metabolic disorders, maternal ingestion of toxins and rare genetic syndromes.

**Perinatal causes** Problems during labour and delivery Obstetric emergencies such as obstructed labour, antepartum haemorrhage or cord prolapse may compromise the foetus causing hypoxia, but essential criteria must be fulfilled before cerebral palsy can be attributed to the acute intrapartum episode. These criteria are metabolic acidosis in foetal scalp, umbilical cord arterial or very early neonatal blood samples (pH < 7.00 and base deficit ≥ 12 mmol/L); early onset of severe or moderate neonatal encephalopathy in infants of ≥ 34 weeks gestation; and cerebral palsy of the spastic quadriplegic or dyskinetic type (MacLennan 1999).

Neonatal encephalopathy is a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal levels of consciousness and often, seizures (Nelson and Leviton 1991). Children with cerebral palsy who have a history of neonatal encephalopathy are more likely to have had signs of intrapartum hypoxia such as meconium staining of the amniotic fluid, and to have a more severe form of cerebral palsy, than those without neonatal encephalopathy (Gaffney et al 1994). However, there may be no evidence of perinatal asphyxia in a significant percentage of children with neonatal encephalopathy (Badawi et al 1998). In a systematic study, cerebral palsy was more strongly associated with Sarnat Grade III than with Sarnat Grade II encephalopathy, using a grading system of 0 to III (Van de Riet et al 1999).

**Neonatal problems** Severe hypoglycaemia, untreated jaundice and severe neonatal infection may be responsible for cerebral palsy.

**Post-neonatally acquired cerebral palsy** Infection and injuries are responsible for most cases of post-neonatally acquired cerebral palsy in developed countries. The introduction of new vaccines will hopefully decrease the numbers of children with meningitis and subsequent neurological sequelae. Accidental injuries such as motor vehicle accidents and near-drowning episodes, and non-accidental injuries may result in cerebral palsy. Other causes of post-neonatally acquired cerebral palsy include apparent life-threatening events, cerebrovascular accidents and following surgery for congenital malformations. Meningitis, sepsicaemia and other conditions such as malaria remain extremely important causes of cerebral palsy in developing countries.

**Risk factors and their role in the genesis of cerebral palsy**

It is important to distinguish between associations or risk factors and known causes. For some children who have cerebral palsy, there appears to be no single event but rather, a sequence of events, responsible for the motor damage. This has led to the concept of “causal pathways” – a sequence of interdependent events that culminate in disease (Stanley et al 2000). A large body of information is available about possible associations and risk factors. Some of these factors are found in infants of all gestations, whilst others are only associated with either full term or premature infants. Multiple pregnancies also have some unique associations.

Risk factors may be present before and during pregnancy, during labour and birth, and in the period shortly after birth.

**Risk factors before pregnancy** Maternal factors Delayed onset of menstruation, irregular menstruation or long intermenstrual intervals are associated with an increased risk of cerebral palsy (Torfs et al 1990). An unusually short or long interval between pregnancies has also been described as an antecedent of cerebral palsy (Pinto-Martin et al 1998, Torfs et al 1990). Two studies have found that low social class is associated with cerebral palsy in children with normal birth weight (Dolk et al 2001, Dowding and Barry 1990).

Parity of three or more was a factor in a study of preterm infants (Topp et al 1997). Several researchers have reported a relationship between cerebral palsy and previous foetal deaths (Nelson and Ellenberg 1986, Powell et al 1988).
A range of maternal medical conditions is associated with cerebral palsy. These include intellectual disability (Nelson and Ellenberg 1986), seizures (Nelson and Ellenberg 1986) and thyroid disease (Blair and Stanley 1993b, Nelson and Ellenberg 1986).

**Paternal and sibling factors** Paternal and sibling factors are rarely reported. Advanced paternal age is more frequent in those with athetoid/dystonic cerebral palsy (Fletcher and Foley 1993). Motor deficit in a sibling has been reported as an association with cerebral palsy in the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke (NCPP) (Nelson and Ellenberg 1986).

**Risk factors during pregnancy** Pre-eclampsia is associated with an increased risk of cerebral palsy in term infants (Collins and Paneth 1998), but this association does not seem to exist in preterm infants (Murphy et al 1995, Spinillo et al 1998a). It has been suggested that pre-eclampsia may lead to a release of catecholamines in preterm infants, which accelerates foetal maturation (Amiel-Tison and Pettigrew 1991) but care is needed in comparing rates in infants of the same gestation, given that pre-eclampsia itself can be directly responsible for preterm births. Alternatively, the presence of pre-eclampsia may result in elective preterm delivery, avoiding the inflammatory responses of spontaneous preterm labours with all their associated problems such as infection and precipitate delivery (Stanley et al 2000).

 Whilst maternal trauma in pregnancy has been implicated as a possible cause of cerebral palsy, this issue is not resolved (Gilles et al 1996). The rate of cerebral palsy was increased in children whose mothers received thyroid hormone or oestrogen in pregnancy in the NCPP (Nelson and Ellenberg 1985).

Antepartum haemorrhage is associated with mortality, cerebral palsy and white matter damage in preterm infants but if cases are compared with controls born at the same gestation, antepartum haemorrhage is found to increase the risk of cerebral palsy associated with preterm birth, but not to add any further risk (Stanley et al 2000).

Two mutations have been identified that predispose heterozygous carriers to venous thrombosis. One is a mutation localised to the Factor V gene (Factor V Leiden mutation, VL) and is the most common cause of familial thrombosis. The second is the gene for prothrombin. The carrier frequency in caucasian men is 5.5% and in caucasian women is 4.8% (Ridker et al 1997). A report of three babies with hemiplegic cerebral palsy who were heterozygous for the Factor V Leiden mutation (Thoramensen et al 1997) has prompted current research in this area. In the three cases reported, there was a suggestion that placental thrombosis, or neonatal stroke, may have occurred and resulted in hemiplegia. There appears to be an association between inflammatory mediators and markers of autoimmune and coagulation disorders with cerebral palsy (Nelson et al 1998a).

**Multiple pregnancy** The increased risk of both mortality and cerebral palsy in multiple births has been known for many years. Multiple pregnancies are associated with preterm delivery, poor intrauterine growth, birth defects and intrapartum complications. However the increased risk to twins of cerebral palsy is not entirely explained by their increased risk of prematurity and low birth weight (Williams et al 1996).

In monochorionic twin pregnancies, death of one twin is recognised as being an important risk factor for the surviving co-twin having cerebral palsy. The death of one twin may impair the neurological development of the survivor throughout gestation (Pharoah and Cooke 1997). Meta-analysis of four studies has demonstrated that the antenatal death of a co-twin is associated with a six-fold increase in rate of cerebral palsy per twin confinement, or an 11-fold increase in rate per child (Stanley et al 2000). The live-born co-twin of a foetus that died in utero is at increased risk of cerebral impairment, the overall risk being 20% (Pharoah and Adi 2000).

**Risk factors during labour** Major events likely to cause perinatal asphyxia include prolapsed cord, massive intrapartum haemorrhage, prolonged or traumatic delivery due to cephalopelvic disproportion or abnormal presentation, a large baby with shoulder dystocia and maternal shock from a variety of causes (Stanley et al 2000).

Other reported associations with cerebral palsy include prolonged second stage of labour (Powell et al 1988), emergency caesarean section (Powell et al 1988), premature separation of the placenta (Torfs et al 1990) and abnormal foetal position (Torfs et al 1990). In considering these factors, it is important to remember that it may not be the event itself that is the causal factor, but rather that the event is simply associated with one or more true causal factors.

Substantial evidence has recently emerged that intrauterine exposure to infection, particularly chorioamnionitis, in the latter stages of pregnancy and during labour, is a strong risk factor for cerebral palsy, particularly in term infants (Murphy et al 1995, Nelson and Willoughby 2000, Polivka et al 1997, Walstab et al 2002). Furthermore, infants of normal birth weight born to infected women were more often hypotensive, needed intubation, had neonatal seizures and a clinical diagnosis of hypoxic-ischaemic encephalopathy (Grether and Nelson 1997). In a meta-analysis of studies that addressed the association between clinical and histological chorioamnionitis and cerebral palsy or periventricular leukomalacia in both preterm and full term infants (Wu and Colford 2000), chorioamnionitis was found to be a risk factor for both cerebral palsy and periventricular leukomalacia. More information is needed about the role of infection in the perinatal period and this is an area of active research.

Other associations with cerebral palsy include prolonged rupture of the membranes in infants of all gestations (Nelson and Ellenberg 1985) and in preterm babies...
Neonatal seizures
Risk factors in the newborn period
(Moster et al 2001).

It has been suggested that magnesium sulphate, given for severe pre-eclampsia, is a protective factor in the development of cerebral palsy in preterm infants (Nelson and Grether 1995, Schendel et al 1996). Several multicentre randomised trials are in progress.

Risk factors at birth The availability of neonatal intensive care units and high technology diagnostic procedures has led to the increased survival of premature infants, in some of whom cerebral palsy later becomes apparent. Fertility treatments, including in vitro fertilisation, have also increased the number of premature children being delivered. Cerebral palsy risk increases with decreasing birth weight (Hagberg et al 1993, Murphy et al 1995, Stanley and Watson 1992, Torfs et al 1990). Of all children on the Western Australian Cerebral Palsy Register born 1986-1992, 34.7% and 24.8% respectively were born before 37 weeks and 33 weeks (Stanley et al 2000). Birth weight is dependent on both gestational age at delivery and intrauterine growth.

The risk of cerebral palsy increases with decreasing age at delivery, and the length of gestation is the strongest determinant of cerebral palsy (Stanley et al 2000). Poor intrauterine growth also increases the risk of cerebral palsy (Blair and Stanley 1990, Uvebrandt and Hagberg 1992), particularly in the moderately preterm (Stanley et al 2000). It is not a major risk factor in very preterm infants (Murphy et al 1995, Topp et al 1997).

The increasing numbers of low birthweight infants with cerebral palsy may be due to their survival and subsequent development of brain damage from complications of their immaturity such as intraventricular haemorrhage. Alternatively, these children may be damaged before birth and the same influences that damaged them may also have been the cause of their preterm birth.

Low placental weight (Torfs et al 1990) and low Apgar scores are strongly associated with cerebral palsy (Van de Riet et al 1999). Children with scores of 0 to 3 at five minutes had an 81-fold increased risk of cerebral palsy (Moster et al 2001).

Risk factors in the newborn period Neonatal seizures (Powell et al 1988, Torfs et al 1990), sepsis (Blair and Stanley 1993a) and respiratory disease are associated with cerebral palsy (Powell et al 1988). Reported risk factors in the preterm infant include patent ductus arteriosus, hypotension, blood transfusion, prolonged ventilation, pneumothorax, sepsis, hyponatremia, total parenteral nutrition, seizures, and parenchymal damage with appreciable ventricular dilatation detected by cerebral ultrasound (Murphy et al 1997). Neonatal seizures, in particular, are strongly associated with the risk of cerebral palsy (Murphy et al 1997, Torfs et al 1990).

Role of brain imaging
Brain imaging, particularly magnetic resonance imaging, can provide evidence about the timing of adverse events. For example, cortical dysplasias date from early in pregnancy, around the 12th to 20th week of gestation, periventricular leukomalacia occurs between the 28th and 34th week, and term infants with perinatal asphyxia have cortical and subcortical gliosis and atrophy in the parasagittal watershed areas (Barkovitch and Truwit 1990).

Whilst periventricular leukomalacia is a strong predictor of cerebral palsy in preterm infants, it is also found in infants born at term, suggesting that the adverse event occurred well before delivery. Factors that cause periventricular leukomalacia may provide information as to possible causes of cerebral palsy (Kuban and Leviton 1994, Spinillo et al 1998b).

The future
More information about the causes of cerebral palsy is likely to come from further exploration of the role of infection in the perinatal period, investigations of the role of coagulation and inflammatory factors and the use of sophisticated brain imaging. By classifying the various types of cerebral palsy according to their clinical features, it may be possible to determine factors unique to particular motor disorders and to infants born at different gestations. Ongoing research about both risk factors and causes involved in cerebral palsy will be an essential first step in the important goal of developing strategies for prevention.

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