Aetiology and epidemiology of cerebral palsy

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Abstract

Cerebral palsy is a common and significant disorder of motor development, with an incidence of 2—2.5 per 1000 live births. Despite improvements in antenatal and perinatal care, there has been little change in the overall numbers of children developing cerebral palsy in the last 40 years. More extremely premature infants are surviving and have more severe forms of cerebral palsy. The common risk factors are prematurity, small-for-gestational age, multiple pregnancy, and maternal genitourinary infections. Many children have more than one risk factor for developing cerebral palsy and it is useful to consider causal pathways to cerebral palsy rather than singe causal events. Only by understanding the aetiology and epidemiology of cerebral palsy can programmes be developed to prevent cerebral palsy and plan health services to meet the needs of the affected children.

Keywords aetiology; asphyxia; cerebral palsy; children; epidemiology; maternal health; neonatal encephalopathy; prematurity

Cerebral Palsy is one of the commonest disorders of child development and potentially for the child has a major impact on quality of life and participation in society. Quality of life for the child's family is also affected with implications for parents being able to work, housing and care of a disabled young person through childhood into adult life. The condition also has a major impact on health, social and education services with increasing survival of more severely affected children.

Cerebral palsy is defined as follows:

> "Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems."

Therefore, the term CP can be used to describe a range of motor problems from the child who has a mild impairment in one limb that interferes with sporting activities to the motor difficulties of a child in a wheelchair who has no voluntary movement including speech. The second part of the definition is intended to draw our attention to the accompanying developmental and neurological disorders that may have a greater effect on quality of life than the motor problem. For example, the presence of epilepsy in a child with mild hemiplegic cerebral palsy significantly affects quality of life and independence in later childhood.

Understanding the aetiology of CP is of course crucial for developing strategies to prevent CP but I believe is also crucial in communicating with parents and children. Parents wish to know what went wrong with brain development or growth, and was there any preventable risk factor. Knowing the cause and, in particular, knowing the neuroanatomy from Magnetic Resonance Imaging of the brain allows an informed discussion with the family. Although the correlation between imaging abnormalities and clinical features is not always strong, it does permit some prediction of future progress and risk of accompanying disorders in the young child.

Understanding the epidemiology of CP is important for planning services for children and young people as well as informing preventative strategies through identification of risk factors and trends in prevalence and severity over time.

Epidemiology

Frequency of cerebral palsy

Prevalence is the number of children with cerebral palsy in a defined population at a given time, usually assessed by population surveys. Studies from various countries quote prevalence of 1.5—2.7 per 1000 children. Incidence is usually calculated as the number of children who develop cerebral palsy in a defined region divided by the number of neonatal survivors in that region.

Variation in frequency of CP between studies is due to a number of factors, including methods of ascertainment. It has been proposed that a severity measure of disability — the Lifestyle Assessment Score — be included in any population study so that only children with a significant developmental impairment are included. It tends to be children at the mild end of the spectrum (Gross Motor Function Classification System level I) who are missed in studies.

Some studies exclude children who have CP of postnatal aetiology, CP as part of a genetic or malformation syndrome, or children with CP who move in or out of the study area. Thus, study results may not be directly comparable.

Improvements in maternal health, better management of premature and difficult deliveries and improvements in neonatal care would have been expected to improve outcomes of pregnancy. Although there have been some changes in patterns of cerebral palsy in the last four decades in developed countries, there has been a disappointing lack of significant decrease in frequency of CP. The numbers of children with more severe forms of CP are increasing, mainly in the group born prematurely as a result of greater survival of these children to an age when CP can be diagnosed. The outcome for children born with lesser degrees of prematurity e.g. born at 28—32 weeks gestation is improving.

Improved survival

Even in the most severely affected young person — unable to lift their head up from the lying position, need for tube feeding, and profound learning difficulties — 50% will survive into the middle of their third decade. This is a result of better nutrition, more aggressive prevention and management of chest infections, and more recently, surgery for scoliosis. This is welcome as long as the increased years of survival are good quality of life years. It

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does mean that there are an increasing number of profoundly disabled young adults reliant on ageing parents, or a poorly funded community care service, and adult services who may not yet able to meet their needs.

Variations between countries

CP registers run under the auspices of European Collaboration of Cerebral Play Registers (SCPE) using similar methodology have similar rates of CP. Very detailed population studies where all children are regularly reviewed produce higher rates of up to 2.7 per 1000.

There is a relative lack of information from developing countries. Where health services are not well developed, it is likely that infants in poor condition at birth, severely premature or small for gestation age (SGA) will not survive and that there may be more postnatal cases caused by conditions such as meningitis, cerebral malaria or severe neonatal jaundice from G6PD deficiency or maternal rhesus isoimmunization.

The strongest risk factors for development of cerebral palsy are prematurity, low birth weight, twins or higher multiple births, and perinatal infection. Infants who are in poor condition at birth are also at higher risk although this is more likely to indicate that the child is ill rather than that this is the damaging event. These risk factors operate both independently and in conjunction with each other.

Variation with gestational age

Prematurity is a risk factor for developing cerebral palsy and the rate rises considerably with decreasing gestation age to odds risk of 70 if born before 32 weeks. If born before 26 weeks, 16–28% of children will develop CP. Even children born between 32 and 36 weeks gestation still have a higher odds risk of CP than those born after 36 weeks.

Birth weight

Birth weight is a risk factor for cerebral palsy independent of gestation age. The small for gestation age (SGA) infant is more likely to be damaged by hypoxic ischaemic events in labour. The symmetrically growth retarded neonate (underweight, short height, and low head circumference) is also at risk of developmental delay even in the absence of birth asphyxia. The large for gestational age infant also has a higher risk related to maternal diabetes and obstructed labour. The graph that illustrates the relationship between birth weight and subsequent development of cerebral palsy is J-shaped (Figure 1).

Socio-economic factors

Recent research from a large population study in Sweden shows that mothers in less affluent socio-economic groups have children more at risk of CP and the risk is 50% higher in least affluent group than in highest affluence group. Some but not all the increased risk is associated with perinatal variables such as prematurity and low Apgar scores. Other aetiological factors may be nutritional deficiencies and infections that cause damage to the placenta and predispose towards hypoxia in labour.

Multiple births

Twin and higher multiple births are strong risk factors for cerebral palsy. The risks rise with increasing number of infants and

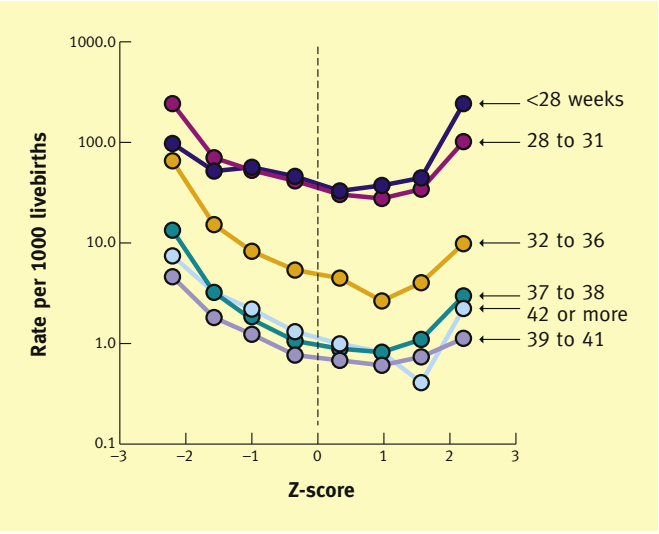


Figure 1 Prevalence of cerebral palsy by *Z* score of birth weight at different gestation ages (from Jarvis S, Glinianaia S, Blair E, Cerebral palsy and intrauterine growth, Clin Perinatal 33 (2006) 285–300 with permission).

are higher in identical twins. The risk are related to factors such as twin-to-twin transfusions, vascular anomalies of the placenta, death-in utero of a twin, prematurity, SGA, premature rupture of membranes and hypoxia during labour.

Twin and triplet pregnancies are more common in In-vitro Fertilization (IVF) programmes and there is some concern that certain techniques to improve IVF outcomes may predispose the infant to CP and other developmental disorders. The disappearing twin syndrome as a cause of cerebral palsy undoubtedly occurs but it is uncertain how common it is.

Classification of cerebral palsy

Severity of cerebral palsy

Severity is determined by the degree of functional motor impairment most often using the Gross Motor Function Classification System, derived from the child's score on the Gross Motor Function Measure. A number of different assessments of upper limb function have been developed, e.g. Manual Ability Classification Score, Adaptive Hand Skills etc. Alternatively a more global assessment of impact of cerebral palsy and associated difficulties can be made using measures such as Lifetime Assessment Questionnaire LAQ.

Topographical distribution of motor impairment

The traditional method of describing the topographical type of cerebral palsy is to use hemiplegia, diplegia and quadriplegia. Clinicians had difficulty agreeing what is severe diplegia and what is mild quadriplegia and differentiating between hemiplegia and asymmetric diplegia. Therefore it has been proposed by SCPE to use the terms symmetrical and asymmetrical cerebral palsy, to describe which limbs are predominantly affected and to describe if trunk and face are affected. With more children with cerebral palsy being investigated with MRI, it is apparent that different abnormalities on scan – malformation, periventricular leukomalacia (PVL), middle cerebral artery infarction – can each cause the various topographic and tone syndromes of CP.

Predominant tone abnormality

Similarly the traditional tone classification of dystonia, spasticity, chorea, and athetosis has been simplified to describing the predominant tone abnormality as:

- Spasticity
- Dystonia
- Dyskinesia
  - Chorea
  - Athetosis.

Classifying cerebral palsy by severity and topographical distribution does assist in predicting what associated impairments the child will have. Some of these impairments such as specific learning difficulties, or functional visual impairments may not become apparent until the child is in primary school and struggling with some aspects of learning.

Associated impairments may aggravate the symptoms of cerebral palsy and interventions for cerebral palsy may aggravate associated impairments.

- E.g. persistent focal seizures or electrical status epilepticus in sleep (ESES) can impair hand function or language skills in hemiplegic CP
- Baclofen or diazepam used in the management of spasticity may aggravate swallowing difficulties by increasing saliva production
- Use of spinal jackets to control progression of scoliosis in CP may aggravate gastro-oesophageal reflux and risk of aspiration pneumonia.

Aetiology

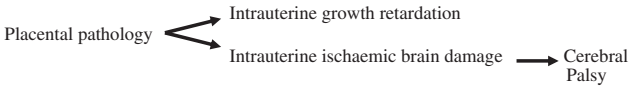
It is helpful to view causes of cerebral palsy in three broad groups:

- Brain damage
- Brain malformation
- Disorders of brain function without evidence of structural abnormality.

These are not mutually exclusive — in prenatal congenital cytomegalovirus infection, there can be evidence of malformation (a cortical migration disorder) and damage (gliosis and calcification).

All other factors associated with cerebral palsy are risk factors. Prematurity is not a cause of cerebral palsy but a strong risk factor.

It is useful to consider aetiology of CP as a sequence of causal factors occurring in series or in parallel that ultimately lead to a damaging event or events to the developing brain. Risk factors may play a variable role in the causal pathway different children. For example, a child born SGA is at higher risk of developing cerebral palsy.



I.e. the intrauterine growth retardation (IUGR) and the ischaemic event are both a result of placental pathology but the IUGR does not cause the CP.

In this example, the CP is a result of the IUGR (Figure 2).

As well as being part of the pathophysiology of brain insult, the IUGR may be part of protective mechanisms e.g. after an insult to the brain, the brain restricts somatic growth to preserve or divert energy to critical areas. This is an intriguing concept, as measures to improve foetal growth in these circumstances may further damage the foetus.

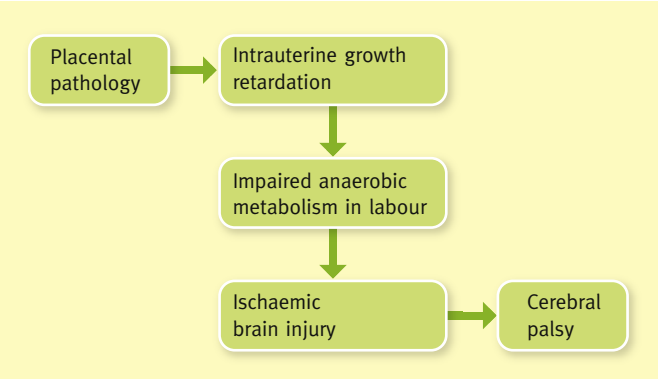


Figure 2 Causal pathway from placental pathology to cerebral palsy.

This concept of causal pathways is well described by Fiona Stanley and colleagues in Cerebral Palsies: Epidemiology & Causal Pathways (2000).

The cause of the brain damage in prematurity related cerebral palsy is often a combination of cytokine induced PVL and ischaemic damage complicated by later postnatal events such as intraventricular haemorrhage and hydrocephalus.

Timing of event

About 50% of children who have CP were born at 38—42 weeks gestation. However, the aetiological event or events did not necessarily happen at term.

When the damaging event occurred can be determined by obstetric history of adverse events, by monitoring of growth and behaviour of the foetus, and by how the infant is behaving at birth using parameters such as Apgar scores, blood gases and onset of neonatal encephalopathy. Ultrasound of the brain in the neonatal period and magnetic resonance imaging of the brain can also help identify timing and possible pathophysiological mechanisms of injury.

A multi-centre European study identified 610 children with CP from eight European centres born between 1996 and 1998, 350 of whom had MRI of the brain after the neonatal period. The results of the scans showed that the traditional association between topographical and tone classification and type of MRI abnormality e.g. diplegic CP is caused by PVL did not always hold true. (Figure 3).

The cytokine induced inflammatory damage and ischaemic damage of periventricular leukomalacia is not exclusively associated with diplegic CP. The sequence of events leading to this pathology usually affect the developing brain between 20 and 32 weeks gestation but do not necessarily lead to premature labour and prematurity. Mothers are more likely to give a history of problems during this time period in pregnancy such as vaginal bleeding or discharge and uterine contractions.

PVL may occur in a term infant with profound sepsis and in a young child treated with alpha-interferon for giant haemangioma. This suggests that there may be a dose-related cytokine effect with the 5—7 month foetus more susceptible than in an older foetus or child with a more mature brain.

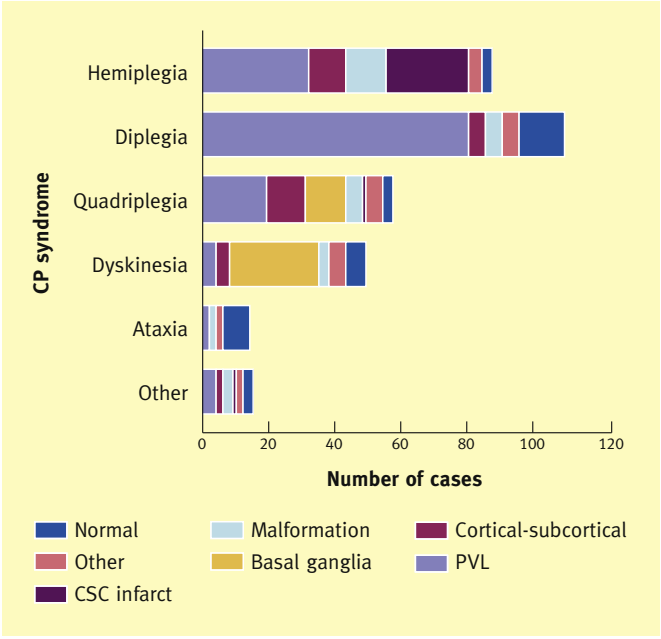


Figure 3 CP syndrome and MRI abnormality.

Acute intrapartum asphyxia

Birth asphyxia leading to neonatal encephalopathy and subsequent cerebral palsy (amongst other disorders of development) is often considered to be caused by damage occurring during labour and is the basis for many medical negligence claims. Only 2—10% of cases of CP are caused by intrapartum asphyxia. Measurable parameters such as CTG abnormalities and foetal blood gases and Apgar scores individually are poor predictors for subsequent development of CP. Are these measurable abnormalities in some pregnancies an indication that brain damage has already occurred? A significant number of pregnancies resulting in a term child with "birth asphyxia" have abnormal placental pathology causing foetal vascular obstruction. This is strongly associated with neurodisability in the term infant. Normal cord blood gases and abnormal placental pathology support an alternative diagnosis to acute intrapartum asphyxia.

A study from Scotland looked at post-mortems of brains of infants who died within 3 days of birth and had an illness that met the criteria for hypoxic ischaemic encephalopathy. 50% of these infants had pathological changes in the brains at post-mortem that must have predated the onset of labour e.g. cyst formation, calcification. Therefore, some foetuses are already damaged before they enter labour — a difficult labour of course may exacerbate the damage. Intervening to deliver the foetus may be too late to avoid brain damage.

In areas where Caesarean section rate have risen to 50% usually for social reasons, the incidence of CP has not dropped. Timing of an insult around term is not easy, unless there is a single witnessed obstetric catastrophe such as prolapsed umbilical cord.

Genetic factors — maternal, familial, foetal

There are rare Autosomal recessive syndromes that cause cerebral palsy, usually in association with microcephaly and learning difficulties. In families where more than one sibling has cerebral palsy, risk factors such as incompetent cervix with recurrent premature delivery, CMV infection, or multiple births may be found. To date, no single nucleotide polymorphism has been unidentified that increases susceptibility to cerebral palsy other than a mutation in a Prothrombin gene which confers a mildly increased risk of hemiplegic cerebral palsy.

Malformations

Up to 12% of children with CP in registers organized by SCPE have a brain malformation. Some malformations may be acquired e.g. ischaemic lesion in first or second trimester affecting cortical migration but some may have a genetic origin.

Genetic malformations — some of which are single gene disorders — may produce profound disorders of cortical migration such a lissencephaly. The child's severe motor disability may be overshadowed by intractable epilepsy, and the children tend to have global developmental delay. In some recognized gene disorders, antennal diagnosis is possible.

Less severe or focal malformation syndromes may be genetic disorders or due to acquired pathology e.g. first trimester cerebrovascular accident.

Cerebrovascular events

Cerebrovascular events affecting the developing brain in the first or second trimester can produce a migration disorder as can congenital cytomegalovirus infection. The motor disorder may be relatively mild and escape detection until well into childhood. Again, epilepsy may be problematic, and it is investigations into the cause of epilepsy that can reveal the structural abnormality of brain development.

Cerebrovascular events in the third trimester do not produce a disorder of cortical migration but a discrete infarct usually with gliosis.

In any cerebrovascular disorder in children — antenatal, perinatal or postnatal, it is worth considering underlying maternal, foetal or childhood thrombotic or haemorrhagic disorders — e.g. Factor V Leiden, Protein C or S deficiency. Although rare, they are risk factors for subsequent adverse events in the child and possibly other family members. The maternal antiphospholipid syndrome is a risk factor for placental thrombosis and may affect subsequent pregnancies.

Placental pathology

Other than the single catastrophic placental event such as retroplacental haemorrhage, there is no single placental pathology that is strongly associated with cerebral palsy. Rather, it is the extent of placental pathology that is important. The placenta has about 30% spare capacity. Once this spare capacity is used up, foetal growth will be affected. The three broad placental pathologies are:

- Abnormalities of vascular development
- Acquired inflammatory lesions
- Acquired degenerative lesion — usually thrombotic in nature.

Chronic inflammatory lesions in the placenta and membranes of premature infants are strongly associated with periventricular lesions and diplegic cerebral palsy. The link is likely to be cytokine (interleukins 1 and 6 and Tumour necrosis factor alpha) induced damage of developing oligodendrocyte which are dividing and migrating from 20 to 32 weeks of pregnancy.

Cytokine induced white matter damage is seen occasionally after neonatal meningitis in the term infant.

Maternal genitourinary tract infections during pregnancy increase the risk of cerebral palsy. The risk is higher with infections in the first and second trimester with increasing gestational age and birth weight being protective. Chlamydia, Trichomonas and urinary tract infections all increase the risk. Treatment of infections may increase the risk of CP, possible by enhancement of the cytokine response.

The causal pathway for maternal infection, cytokine induced damage and CP may be illustrated as follows (Figure 4):

Chorioamnionitis and inflammation of the umbilical cord are also risk factors for CP in the term and near term infant, increasing the risk of CP two-fold. They are strongly associated with quadriplegic CP rather then diplegic CP, and MRI of the brain is more likely to show lesion associated with hypoxic ischaemic damage rather than PVL.

Children with cerebral palsy and normal brain imaging

The group of children with cerebral palsy and normal MRI scan may have a genetic disorder or a slowly progressive disorder that has not yet declared itself. Children with a disorder of motor development and a recognized genetic condition such as Angelman syndrome have traditionally been excluded from the diagnosis of cerebral palsy. With time, it may be that this group of children will be reassigned to other diagnosis as they are discovered. If the child has a normal MRI scan and there is no history of an adverse antenatal, perinatal or postnatal event, consider metabolic and genetic investigations before giving a definitive diagnosis of cerebral palsy. The presence of other developmental disabilities such as visual impairment, deafness, or difficult epilepsy may give a clue as to underlying diagnosis.

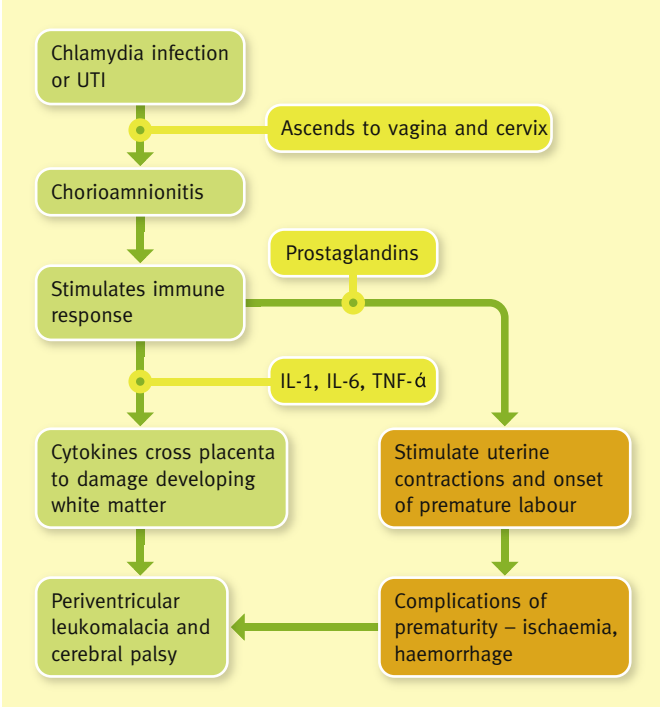


Figure 4 Causal pathways from maternal genitourinary infection to CP.

Disorders of Dopamine metabolism should always be considered as they may be treatable. E.g. Dopa-responsive dystonia caused by a mutation in GTP hydroxylase gene may present as a symmetrical CP with legs more affected than arms or dyskinetic CP and responds very well to Levodopa. Other disorders of dopamine metabolism may present with more severe CP syndromes with co morbidities and do not respond well to Levodopa.

Some factors may cause developmental difficulties without motor impairment or diagnoses of CP. Learning difficulties without motor impairment have been reported after hypoxic-ischaemic encephalopathy. Although these children would not be included in the diagnosis of cerebral palsy, they are an important group to include in outcome studies of neonatal interventions to improve prognosis.

Discussion

There have been changes in the epidemiology and aetiology of cerebral palsy in societies with advanced healthcare systems in the last four decades. Kernicterus for severe neonatal jaundice is now exceedingly rare, obstructed labour is prevented by planned Caesarean section, and congenital rubella infection and haemophilus meningitis have been significantly reduced by immunization programmes. Neonatal interventions such as cooling of the baby to reduce metabolic need in hypoxic ischaemic encephalopathy shows considerable promise in reducing the early neurodisability including CP associated with this syndrome. Antenatal steroids, surfactant and other neonatal interventions have considerably reduced mortality and morbidity including CP in premature infants.

However, more exceedingly premature and growth retarded babies are surviving and long term survival of profoundly disabled young people with cerebral palsy means that overall the prevalence remains similar to 40 years ago. Few children have a single antenatal or perinatal risk factor that predisposes them to CP other than a sudden unpredicted obstetric catastrophe. Most children will have multiple risk factors, some maternal, some foetal, some placental and some social. Therefore, it is important to consider causal pathways to cerebral palsy and to look how interventions at different stages in the pathway can improve outcomes of pregnancy.

I have not considered in detail postnatal acquired CP as it is a relatively unusual cause in developed countries. However, many cases are preventable. More could be done to reduce the frequency of head injuries in young children as a cause of CP, both accidental (road traffic accidents) and non-accidental injuries. Some countries have introduced regulations to fence off private swimming pools to prevent near drowning in young children. Meningococcal and haemophilus meningitis rates have decreased with advent of expanded immunization programmes. The introduction of malaria vaccine will hopefully reduce the neurological morbidity as well as the mortality caused by cerebral malaria.

The key areas to preventing cerebral palsy are:

- Prevention of premature delivery
- Ensuring adequate foetal nutrition
- Better understanding of placental function and detecting placental pathology antepartum

- Diagnosis and management of maternal genitourinary infection in pregnancy
- Identifying by maternal and foetal multimodal monitoring the foetus already in difficulties before the onset of irreversible brain damage
- Brain protection regimes in the neonatal period for the child showing signs of developing an encephalopathy. ◆

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