Clinical and MRI Correlates of Cerebral Palsy
The European Cerebral Palsy Study

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T his article reports on the European Cerebral Palsy Study, carried out in 8 centers in Europe, including North West London and North East London, England; Edinburgh, Scotland; Lisbon, Portugal; Dublin, Ireland; Stockholm, Sweden; Tubingen, Germany; and Helsinki, Finland. The study investigated the correlates of cerebral palsy (CP) in a population sample and compared clinical findings with information available from magnetic resonance imaging (MRI) brain studies. The aim was that this study would help in understanding where potential preventive strategies could be targeted.

METHODS

A population of children with CP who were born between 1996 and 1999 was examined at each center. They were identified from a geographic area surrounding each center with 25,000 live births per year. According to the usual reported rates of CP of about 2 per 1000 live births, it was predicted that each center would recruit approximately 100 children during the study period. Ethical permission and written informed parental consent were obtained in all centers.

A standard clinical examination was devised largely based on the work of Grether et al., with reference to Ingram and Crothers and Paine. Cerebral palsy was defined as a group of nonprogressive motor disorders of movement and posture due to a defect or lesion of the developing brain. Children were recruited after the age of 2 years, when the diagnosis of CP can be firmly substantiated.

Lead clinicians involved in the study were highly experienced in the care and assessment of children with CP and, nonprogressive motor disorders of movement and posture due to a defect or lesion of the developing brain. Children were recruited after the age of 2 years, when the diagnosis of CP can be firmly substantiated.

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when possible, these clinicians examined the study children within their centers. To alleviate potential interobserver and intraobserver error, we optimized the validity and reliability of the examination by using a training video highlighting points that might present difficulties. Further training was offered by 3 key investigators, who visited satellite centers participating in the examination of a number of the children recruited to the study. Direct reliability studies on the coding of the physical examination were not possible due to the complexity of the cases and the multicenter format. Therefore, clinical characteristics were analyzed to profile the expected clinical pattern. Outliers from the usual pattern of findings were reviewed in liaison with the local clinician to check for any errors in coding.

An interview questionnaire with the parents provided information about family history and prenatal, pregnancy, and birth information. Hospital obstetric notes were sought to verify birth data given by parents and to collect extra information on the birth and neonatal period. The results of genetic and metabolic investigations were recorded when performed. In total, more than 300 items of information were requested for each child.

A very important component was the MRI brain scan. Various articles have reported findings from studies on children with selected types of CP, including bilateral spastic CP and hemiplegia, and types of MRI pattern, such as periventricular leukomalacia (PVL). However, we are unaware of any studies reporting MRI findings in a large CP population including all of the clinical subtypes. Cranial MRI is a standard diagnostic procedure safe to use in children.

We sought MRI scans taken at 18 months of age or later. Magnetic resonance imaging reports from the participating centers were often brief and difficult to compare, so each scan in the study was assessed jointly by 2 study members (O.F. and I.K.-M.) using a standardized scoring system developed for this study. Studies were carried out in line with the local protocols for pediatric patients available in all institutions. The sequences used were developed in association with the radiologists from the participating centers and were chosen for optimal information at minimum total time in the MRI camera. Each scan was assessed blindly to both the local MRI report and clinical findings.

Simple descriptive statistics are used throughout the article. χ² Tests were used to assess the statistical significance of associations between categorical variables. Case-control data were not collected because of staffing limitations. SPSS software, version 14.0 (SPSS Inc, Chicago, Ill) was used to analyze data.

**RESULTS**

In total, 585 children with CP were identified as eligible to participate in the study and 431 of these children were recruited and assessed. Of the children in the study, 61.9% were male.

Of the 154 children who were not recruited, 55 parents did not consent to the participation of their child, 21 families moved away before inclusion, 7 failed to attend appointments, 7 children died before inclusion, and 11 families could not be contacted. A further 53 children did not have a reason for noninclusion recorded. Information about the type of CP was available for 49 of the 154 children, and for this group, there was no significant difference compared with the children included in the study.

Only 1 center achieved the target of identifying 100 children with CP. Four possible reasons for the failure to reach the anticipated numbers are (1) failure of identification; (2) that the birth population sample was actually smaller than originally anticipated; (3) that centers were not accessing the entire population with CP in their area; and (4) that there had been some genuine decline in the rate of CP. As a consequence of 1 or more of these factors, our sample is smaller than expected. The most likely explanation is that there was some underidentification of mild cases in most centers because of the organization of services and methods of identification. There is no real evidence from the study that the lower numbers reflect a decrease in the 2-per-1000 live birth rate for CP.

**Prenatal Findings**

A striking finding from the mothers’ history was that 39.5% (158 of 400) reported an infection during the pregnancy. Specifically, 19.2% of the mothers reported a urinary tract infection during the pregnancy and 15.5% of women reported taking antibiotics during the pregnancy. Two of the study team independently reviewed the infection data recorded and it was agreed that 29.6% had a “significant” infection (excluding cases of common colds, coughs, etc).

Fifty-one children (12%) were known to be from a multiple pregnancy, with 48 from a twin pregnancy and 3 from a triplet pregnancy. This compares with a population rate of multiple pregnancy of about 1.5%. In some instances, both twins had CP and were in the study (4 pairs), and in 13 others, their twin had previously died (7 in utero and 6 during or after birth). Among children from multiple pregnancies, 12 (24%) were from pregnancies after infertility treatment compared with 12 (3.4%) of the singleton pregnancies in the study.

**Perinatal Findings**

More than half of the children (n=235 [54.5%]) were born at term. Forty-seven (10.9%) were very low-gestational-age infants (<28 weeks), 69 (16%) were born between 28 and 31 weeks, and 79 (18.3%) were born between 32 and 36 weeks of gestation (FIGURE 1). The numbers in the very low-gestational-age group are so small that any variation in the rates of CP in this group would not drastically affect the overall numbers of children with CP.

Among the study children, 19.1% were small for gestational age (birth weight <10th percentile), with similar rates occurring in all gestational age groups. However the actual number of infants who were small for gestational
age was higher in the term group (n=44) than in the preterm group (n=31). In the group born at less than 28 weeks, 16.3% were large for gestational age, whereas children in the other groups were just over the expected 10% rate (10.6%-11.1%). These data were calculated for all children in the study using the Child Growth Foundation growth charts.10

Emergency cesarean deliveries were performed in 32.3% of births, whereas 44.8% of the children were born by standard vaginal delivery. Of the rest, 7% were delivered by planned cesarean delivery, 4.2% by Ventouse extraction, 6.1% by forceps, and 2.3% were breech. The delivery method was not recorded for 3.5%.

Seventy percent of children were admitted to the special care infant unit after birth. Figure 2 shows the length of time spent in the special care infant unit according to the gestational age at birth. A total of 43.7% of children born at term were kept in the unit for 5 or more days and, therefore, presumed to be regarded by the attending clinician as “significantly ill” in the neonatal period. At the children’s discharge from the special care infant unit, 47.3% of the parents report that they were unaware that there was any concern about their child. The parents of children with more severe CP were more likely to have been told about the possibility of brain damage (Pearson $\chi^2=26.256; P<.001$).

**Clinical Findings**

On completion of the physical examination, the clinician was asked to record the topographical nature of the condition (hemiplegia, diplegia, quadriplegia, or other) and the nature of the CP (spastic, dystonic, choreoathetoid, or ataxia). The functional severity was graded as mild, moderate, or severe (TABLE 1).

At the time of original examination, the children ranged in age from 12 to 91 months, with a mean age of 46 months (9 children were seen at <23 months). Where children were assessed before the age of 3 years, a request was made to reassess at a later date to confirm the diagnosis of CP and note any changes in presentation. Selected variables from the physical examination are shown in TABLE 2 illustrating some clinical differences between the spastic CP subtypes.

During the period of data collection, there has been further validation of the Gross Motor Function Classification System in CP. To compare our coding of functional severity to this scale, a subsample of 36 randomly selected children were retrospectively recoded to the 1 through 5 scores in the Gross Motor Function Classification System. There was strong correspondence between the data ($\kappa=0.583; P<.001$), with 1 being mild, 2 and 3 being moderate, and 4 and 5 being severe.

Many children also have clinical findings not related to motor disorder, and failure to include this in any definition and classification of CP has recently been emphasized.12 In total, 28% of the children had epilepsy; the rate was highest (50%) among the quadriplegia group and lowest (16%) in children with diplegia. Communication problems were present in 58% of the total group—highest in the dyskinesia and quadriplegia groups and lowest in the diplegia and hemiplegia groups.

Vision is difficult to assess clinically in young children, but it was recorded that 31% of the children with hemiplegia, 38% of the children with...
diplegia, and 64% of those with quadriplegia had visual abnormalities of some kind. About 7% of the children had a hearing problem reported.

**MRI Findings**

Among children with clinical evaluation, 351 (81.4%) had a brain MRI scan assessed for the study. The ages at which the scans were taken ranged from 1 to 87 months, with a mean age of 38 months. Scans taken before the age of 18 months were only accepted for the study if the type of pathology was obvious and renewed imaging was not expected to provide further information; eg, in malformations or extensive posthemorrhagic periventricular destruction. The scans were grouped according to the primary pattern of damage (Table 3).

The MRI scans showed that white-matter damage of immaturity (WMDI, including PVL) was the most common finding (42.5%), followed by basal ganglia lesions (12.8%), cortical/subcortical lesions (9.4%), malformations (9.1%), focal infarcts (7.4%), and miscellaneous lesions (7.1%). Normal MRI findings were present in 11.7%.

**White-Matter Damage of Immaturity**

White-matter damage of immaturity included PVL and periventricular hemorrhage. White-matter damage of immaturity was found in 71.3% of the children with diplegia (n=87), 34.1% of those with hemiplegia (n=31), and 35.1% of those with quadriplegia (n=20). This type of damage is thought to occur before about 34 weeks of gestation, although 25% of the WMDI group were born at term.

**Basal Ganglia Damage**

Basal ganglia and thalamic damage was mainly associated with dystonic CP, which accounted for 75.6% (n=34) of the basal ganglia group. Occasionally, this type of damage was seen in children with spastic quadriplegia (n=7) and diplegia (n=4). There were no children with hemiplegia. Figure 3B shows an image at the level of thalamus and basal ganglia in a child with dystonic CP. Figure 3B also shows an image of the same child at the level of the parietal lobes.

**Focal Infarct**

Focal cortical infarcts were almost exclusively related to a clinical diagnosis of hemiplegia (n=25), with 1 child diagnosed as having quadriplegia. Among children with hemiplegia, 27.5% were found to have a focal infarct. Figure 3C shows an example of a child with hand-dominated left hemiplegia who probably had an embolus in the right middle cerebral artery.

**Cortical/Subcortical Damage**

This group included children with multicystic encephalomalacia and other cortical lesions. Eleven children (33%) had a watershed pattern of damage. All CP types apart from ataxia were represented in this group.

**Malformations**

Thirty-two children were found to have malformations. These were most common in the hemiplegia group (n=12) but were found across all clinical subtypes.

Six of the malformations were thought to be a result of specific in utero infections, such as cytomegalovirus, which can be identified on MRI by the specific distribution of calcifications.13 Other types of malformation included lissencephaly, polymicrogyria, schizencephaly, and cortical dysplasia. Figure 3D shows an image of a child with cytomegalovirus infection who clinically has spastic quadriplegia and extensive dysplasia involving large parts of both parietal lobes.
Miscellaneous
Twenty-five children (7.1%) had findings on the scans that did not fit into the aforementioned groups and were labeled “miscellaneous.” They were found across all clinical CP subtypes and were often accompanied by high rates of other problems, such as epilepsy and visual problems. Some of these children may have unidentified genetic abnormalities.

Normal MRI
Forty-one of the children (11.7%) had normal MRI results. They were distributed across all clinical CP subtype groups, although they did make up more than half of the group with ataxia (n=8). Sixty-one percent of the children had mild and 17% had severe functional severity. There may be genetic defects among this group.

Figure 3. Examples of Magnetic Resonance Imaging Scans From the European Cerebral Palsy Study

A. Normal T2-weighted axial image from a child aged 4 years 8 months shown for comparison. B. Left, Mild posterior periventricular white-matter damage in a child aged 5 years 4 months with mild diplegia. Two T2-weighted axial images show increased signal (black arrowheads) in the periventricular white matter extending posteriorly into the central white matter of the occipital lobes. Right, Severe bilateral, symmetrical periventricular leukomalacia in a child aged 5 years 6 months with quadriplegia. A T2-weighted axial image shows almost total absence of central white matter. Gray matter extends to the ventricular wall, which is irregular. Small amounts of white matter remain in the frontal lobes (yellow arrowheads) This tissue has abnormally high signal. White matter with abnormal signal is also seen in the lower aspects of the corona radiata (black arrowheads).

C. Basal Ganglia Lesions
T2-weighted axial images from a child aged 18 months with basal ganglia lesions and dyskinetic cerebral palsy. The left image shows reduction in volume and increased signal in the posterior third of the putamen (yellow arrowhead) and increased signal in a location corresponding to the inferolateral nucleus of the thalamus (black arrowhead). The lesions are symmetrical. No other abnormalities are noted. The right image, at the level of the parietal lobe, shows increased signal bilaterally in cortical structures anterior and posterior to the central sulcus (white arrowhead). These areas correspond to the sensory and motor cortex.

D. Focal Cortical Infarct
T2-weighted axial image at the level of the lateral ventricles from a child aged 5 years 9 months with a focal cortical infarct and hand-dominant left hemiplegia. The right hemicranium is significantly smaller than the left because of reduced volume of the right cerebral hemisphere. The right lateral ventricle is large secondary to the small volume of the hemisphere. There is a focal defect corresponding to large parts of the hemisphere supplied from the right middle cerebral artery. The defect includes thalamus and the basal ganglia, which are smaller than normal. This child probably had an embolus in the right middle cerebral artery.

E. Cerebral Dysplasia
Coronal T2-weighted image from a child aged 3 years 6 months with dysplasia of both parietal lobes after cytomegalovirus infection and spastic quadriplegia. Note the thick cortex and irregular surface indicating polymicrogyria. Signal abnormalities were present throughout most supratentorial white matter, some seen here in the centrum semiovale (black arrowhead) and in the lower temporal lobes (yellow arrowhead).
Abnormal MRI

Figure 5 indicates the distribution of pathologic MRI findings in 2 groups, those born before 34 weeks of gestational age and those born at or after 34 weeks.

In summary, the MRI findings relate both to the clinical description of the child and the severity of the condition. The timing of the lesion might help to define which events might have caused the CP.

COMMENT

Not only do MRI scans help reveal the pathologic basis of the condition, but also, the findings have strong correlations with clinical findings. This may be useful in helping parents, clinicians, and others involved in the care of children with CP to understand the nature of the children's condition and to predict their needs in the future. Therefore, all children with CP should have an MRI scan.

Our study has some important implications in relationship to possible malpractice suits. The scans can be reviewed in relationship to the pathologic findings to determine which might have been caused by some event during the delivery.

Among infants born before 34 weeks, the great majority had white-matter damage. This is often thought to be caused by obstetric malpractice, but there is little evidence for this. As pointed out by Nelson,14 changes in obstetric practice over the last 20 years and the development of overall neonatal care during the same period have had little effect on the rate of CP. Rather, predisposing factors that include genetic factors, nutritional factors, and infections during pregnancy and before the onset of premature labor lead to placental damage developing throughout the pregnancy.15 These factors predispose the infant to an increased risk of hypoxic ischemic episodes, leading to white-matter damage. By the time this occurs, the event has reached a stage at which it cannot be affected by interventions. This may lead to premature birth and concerns about the infant. In other instances, no event is noted by the mother or her attendants, and the child is born at term with established white-matter damage. Interventions around the time of either of these events will not affect the outcome. In their sophisticated study of stillbirths16 and early neonatal deaths17 in Scotland, Becher et al conclude that “the findings in this study support the notion that the birth of a compromised 'asphyxiated' encephalopathic infant is not necessarily the result of a mismanaged labour nor the lack of vigilance in pregnancy.”

In our study, 54 children with white-matter damage were born after 34 weeks. These, together with the 32 children with malformations, again indicative of earlier cerebral damage, would not have been affected by perinatal processes.

Of the other groups, focal infarcts are clearly not caused by obstetric events, and the 25 infants in the miscellaneous group included some infections. In the 41 children with normal MRI results, some infants probably had genetic causes for their CP, but when there is no evident lesion in the cerebral cortex, it is hard to conceive of an obstetric cause.

This leaves 70 children with either cortical/subcortical damage or basal ganglia damage born after 34 weeks of gestational age. Thus, in our study, only 19.9% of a population with CP might be considered on the basis of their MRI scan as having a possibility of some type of obstetric mishap as the cause of their brain damage.

The data on the method of delivery in this group show that 26% of mothers had emergency cesarean deliveries, indicating that the obstetrician was well aware that the infant was in difficulty. Although a proportion of these may have had difficulties due to some obstetric inattention, many would not, and it seems likely that the proportion of infants who might have had damage because of obstetric malpractice within the CP population is therefore low.

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This study has once again emphasized the great importance of infections occurring in mothers during pregnancy. Most study centers had no access to normative data on this topic. The closest comparable population data on the incidence of urinary tract infection during pregnancy that we were able to access were through the St Mary’s Maternity Information System. This database has information available on 74,838 live births in the 2-year period matching our study’s, collected from maternity units in the North West Thames region of London. Our finding that 19.2% of mothers reported a urinary tract infection during the pregnancy compares with the rate of clinically diagnosed urinary tract infection during pregnancy in the general population of the St Mary’s Maternity Information System of 2.9.

The results appear to show a raised rate of infection. This finding is also supported by the case-control study of Neufeld et al, in which maternal infection was a risk factor for CP in both term and preterm infants. Wu et al also reported a significantly increased rate of infection in children born with CP at or near term, in which 14% of the mothers had had chorioamnionitis compared with 4% of controls.

While there is a legitimate concern about overprescription of antibiotics, there should be no question that treating infections during pregnancy is a potential area for prevention. A systematic approach to identifying and treating maternal infections needs to be developed, as emphasized by Nelson.

Twin pregnancies are another potential area for prevention of CP. Multiple pregnancies, including pregnancies after infertility treatment, should be monitored closely, especially when other risk factors are present.

Because of the lack of warning to parents at discharge from special care infant units about the risks of potential problems, delay in diagnosis and referral to an appropriate service was common. These findings suggest that at discharge from the hospital, better arrangements should be made for the follow-up of these children, particularly as there is a possibility that further brain damage might occur after birth from, for example, nutritional effects. The recognition of maternal and child genetic factors in thrombophilia leading to stroke is an area in which early identification could perhaps lead to prevention.

Finally, perhaps 10% of this population of children with CP might have unidentified genetic or metabolic disorders.

We think it is not unreasonable to assume that with increased awareness of possible preventive measures, over the next decade the rate of CP could be reduced substantially, thus reducing the burden on families and saving tremendous sums of money for health services.

Author Contributions: Dr Bax had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bax, Flodmark.

Acquisition of data: Bax, Tydeman, Flodmark.

Analysis and interpretation of data: Bax, Tydeman, Flodmark.

Drafting of the manuscript: Bax, Flodmark.

Critical revision of the manuscript for important intellectual content: Bax, Tydeman, Flodmark.

Statistical analysis: Bax, Tydeman, Flodmark.

Obtained funding: Bax.

Administrative, technical, or material support: Tydeman, Flodmark.

Study supervision: Bax.

Financial Disclosures: None reported.

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Funding/Support: Ongoing funding for this study is provided by the Castang Foundation, having been initiated by the Little Foundation.

Role of the Sponsor: The funders had no role in the design, collection, analysis, and interpretation of data; in the writing of the report; or in the preparation, review, or decision to submit the manuscript for publication.

Acknowledgment: We thank all those who have helped to make this research possible, especially the children, the parents, and the families who allowed their information to be used. We also thank the numerous clinicians and staff involved in the care of these children who generously gave their time and efforts to help with the study. Statistical advice was provided by Ian Plewis, MSc, Institute of Education, University of London. Additional advice was supplied by Paul Eunson, MBChB, FRCPCH, Royal Hospital for Sick Children, Edinburgh, and Lucinda Carr, MD, MBChB, FRCPCH, Great Ormond Street Hospital for Children NHS Trust.

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