ORIGINAL ARTICLE

Prevalence and pathogenesis of congenital anomalies in cerebral palsy

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Background: It has been hypothesised that cerebral palsy (CP) and other congenital anomalies are attributable to feto–fetal transfusion problems in a monochorionic multiple gestation. Thus more than one organ could be compromised leading to the coexistence of two or more anomalies in a fetus. Such anomalies in a singleton birth may be attributable to early demise of the co-conceptus as a vanishing twin.

Aim: To determine whether the coexistence of congenital anomalies and CP is greater than a chance finding by comparing the prevalence of congenital anomalies in children with CP with that in the general population of children.

Methods: A population-based register of children with CP born in 1966–1991 in the counties of Merseyside and Cheshire, UK, comprised the index population. Coexisting congenital anomalies were recorded. For comparison the population prevalence of congenital anomalies was obtained from eight congenital malformation registers in the UK.

Results: Children with CP were found to have highly significant increases in risk for microcephaly, isolated hydrocephaly, congenital anomalies of the eye, congenital cardiac anomalies, cleft lip and/or palate and congenital dislocation of the hips and talipes ($p<0.001$) and atresias of the oesophagus ($p<0.001$) and intestines ($p<0.01$). The relative risks ranged from 3.1 (95% CI 1.9 to 4.8; $p<0.001$) for congenital malformations of the cardiac septa to 116.09 (95% CI 84.0 to 162.3; $p<0.001$) for microcephaly.

Conclusions: Congenital anomalies in children with CP are found much more frequently than expected by chance. A common pathogenic mechanism may account for the coexistence of disparate congenital anomalies. A hypothesis is proposed for such a common pathogenic mechanism.

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One of several proposed classifications of cerebral palsy (CP) is determined by the presumed timing of cerebral impairment, which may be prenatal, perinatal or post-perinatal. Currently it is thought that approximately 10–20% of CP is post-perinatal[1–3] and 10–20% is perinatal due to hypoxic-ischaemic damage.[4–6] The remaining 70% is considered to be prenatal in origin. Part of the evidence supporting a prenatal aetiology is the observation that congenital anomalies are more frequently found in children with CP than in the general population, with odds ratios ranging from 2.6 to 8.6.[7–10] Although these studies supported a prenatal aetiology, the increased risk of congenital anomalies in children with CP in these studies pertained to congenital anomalies in general rather than to specific anomalies. Furthermore, possible pathogenic mechanisms linking the coexistence of congenital anomaly and CP were not considered.

The hypothesis that some types of congenital heart disease were the result of haemodynamic instability in a twin monochorionic conception with one twin failing to survive was proposed several years ago.[11] This hypothesis was subsequently extended with the proposal that a considerable proportion of several other congenital anomalies and CP of prenatal origin have the same pathogenesis, and that these congenital anomalies in singletons may be explained by early, unrecognised or unrecorded loss of a conceptus in a monochorionic monozygous twin conception.[12]

Many congenital anomalies have a recognised pathogenesis that is not common to the pathogenesis of CP, such as some chromosomal or gene abnormalities, environmental teratogens and nutritional deficiencies. If some congenital anomalies, including prenatal CP, are the result of a common pathogenic mechanism, associations of specific anomalies and CP need to be examined.

The study reported here aimed to determine what congenital anomalies coexist with CP more frequently than would be found by chance by comparing the prevalence of organ-specific congenital anomalies in children with CP with that in the general population of children. Coexistence of CP with other congenital anomalies would support the hypothesis that there may be a common pathogenic mechanism and pathogenic pathways could be formulated.

METHOD

The Merseyside Cerebral Palsy Register has maintained a record of all children with CP in the counties of Merseyside and Cheshire, UK, and all those born in 1966–1991 comprise the cohort for this study. Case ascertainment of CP for these years is virtually complete, and the method of ascertainment of cases has been described previously.[13] The neonatal and paediatric hospital and community child health records of all children on the register have been extracted for details of any coexisting congenital anomaly. For those children who died, the Office for National Statistics provided draft copies of the death certificate for medical research. This allowed congenital anomalies recorded as a cause of death to be noted.

All congenital anomalies were coded according to the Q rubric of the International Classification of Diseases, Revision 10 (ICD-10, 1989). Microcephaly, hydrocephaly, dislocation of the hip and talipes were coded as congenital anomalies only if they were noted antenatally or at the time of birth. ICD-10 code Q03 includes only isolated congenital hydrocephalus and excludes those that occur with a neural tube defect.

For comparison, data from the eight UK congenital anomaly registers contributing to EUROCAT covering the period

Abbreviation: CP, cerebral palsy

1991–2003 were obtained from the EUROCAT website.[14] In calculating prevalence, the EUROCAT registries use total births (stillbirths + live births) as the denominator. As the CP cases were all live births, prevalence comparisons should be determined using number of live births for the EUROCAT data. As this was not available, an estimated 10 000 stillbirths was obtained by assuming a stillbirth rate of 5–6/1000 total births for the UK over the time of the EUROCAT registry data. This was subtracted from total births to give the estimated number of livebirths. The adjusted population prevalence used the estimated population live births (population total births – estimated population stillbirths) as denominator. The adjusted relative risk compared the prevalence of congenital anomalies in CP with the adjusted population prevalence. The denominator number of live births is so large that only a marginal difference is made to adjusted relative risk, whether 5000 or 20 000 stillbirths are subtracted from total births.

The EUROCAT registries do not record congenital dislocation of the hip or talipes. Population comparison data for these abnormalities (Q65 Congenital deformities of the hip and Q66 Congenital deformities of feet) were provided by the Office for National Statistics for England and Wales 2000–2004. This allowed the relative risk for specific ICD-10 groups of congenital anomalies in children with CP to be determined.

Statistics

Relative risks were calculated using EPIinfo (Centers for Disease Control and Prevention, Atlanta, Georgia, USA). Where the number in a cell was <5, the Fisher exact two-tailed test was applied. To calculate the adjusted population prevalence, the denominator was obtained by subtracting estimated population from population total births. Adjusted relative risks compared prevalence of congenital anomalies in CP with adjusted population prevalence.

RESULTS

A total of 2262 children on the Mersey CP Register were born in 1966–1991, nine of whom had missing data on whether or not a congenital anomaly was present. Thus, 2253 children comprised the data for further analysis. Among the 2253 cases, 248 had a congenital anomaly (183 children with one, 50 with two and 15 with three recorded anomalies), a prevalence of 11.0% (95% CI 9.7% to 12.4%). This is greatly in excess of the prevalence observed in the EUROCAT registries (range 1.4% to 4.1%).

Children with CP who were recorded as having congenital deformities of the hips or feet at the time of birth were at high risk of these abnormalities compared with notified national prevalence rates (table 1). All those coded within ICD-10 rubric Q65 had either unilateral or bilateral dislocation of the hip. Similarly, those coded as having a deformity of the feet (Q66) had unilateral or bilateral talipes.

The most striking increases in risk were for microcephaly (Q02) and hydrocephaly (Q03). As these anomalies were evident at birth or had been diagnosed antenatally, they indicate that the cerebral impairment in these children had been sustained prenatally. The children with CP were at over nine times greater risk of congenital anomalies of the eyes. The eight cases shown in table 2 comprised four with coloboma, three with bilateral congenital cataracts and one with unilateral cataract and a retinal abnormality. Colobomas are the result of failure of the embryological fissure to fuse. Other failures of fusion manifest as anomalies of cleft lip and palate. These also were significantly more prevalent in children with CP than in the general population (table 2; $p<0.001$).

A congenital cardiac anomaly was recorded in 52 of the 2253 children with CP. Among the 52 children with cardiac anomalies, 43 had one, 6 had two and 3 each had three congenital cardiac anomalies. In two of the 52 children, the congenital cardiac anomaly was associated with Down syndrome. There was over a fivefold increased risk of a congenital cardiac anomaly in a child with CP compared with the general population. This increased risk was not limited to a particular subgroup but was found in all subgroups of cardiac anomaly (table 2; $p<0.001$). Highly significant increases in risk were also found for gut atresias and oesophageal atresia with or without tracheo-oesophageal fistula (table 2; $p<0.01$ and $p<0.001$, respectively).

Thus a range of disparate congenital anomalies were found consistently to be significantly more prevalent in children with CP than in the general population.

DISCUSSION

It is recognised that there is a higher prevalence of congenital anomalies in children with CP than in the general population. However, previous studies have examined the generality rather than specific groups of congenital anomaly.[7–10] The observation has been used to support a prenatal pathogenesis in the majority of children with CP but a pathogenic mechanism that explains the coexistence of CP and congenital anomalies has not been postulated.

The increased risk of congenital dislocation of the hip and talipes in children with CP is probably explained by the muscular weakness that is characteristic of CP affecting in utero positioning of the limbs. Similarly, the excess risk observed for microcephaly and hydrocephaly is the direct consequence of the prenatally acquired cerebral impairment that may be manifest clinically as CP. The coexistence of these anomalies with CP confirm that the cerebral impairment occurs during fetal development. It has been proposed that the form of cerebral impairment may vary depending on the timing of feto–fetal transfusion episodes. The damage to the brain may lead to neuronal migration abnormalities, porencephaly, multicystic encephalopathy, subcortical leucomalacia and other cerebral pathologies.[12] Some of these pathologies may manifest clinically as CP, other clinical manifestations may not present with motor disability and will not be diagnosed as CP.

Table 1 Comparison of population prevalence of congenital dislocation of hip and deformities of feet with prevalence in children with cerebral palsy (CP)

		Mersey CP register n = 2253		England and Wales 2000–2004 n = 3 056 387		
ICD-10 rubric	Congenital anomaly	Number	Prevalence/ 10 000 CP	Number	Prevalence/ 10 000 live births	CP: population relative risk (95% CI)
Q65	Congenital deformities of hip	27	119.8	888	2.9	41.7 (22.8 to 62.2)*
Q66	Congenital deformities of feet	31	137.6	3384	11.0	12.4 (8.8 to 17.7)*

Comparison of the prevalence of other congenital anomalies in the general population and children with CP are shown in table 2.
*$p<0.001$.

Table 2 Comparison of population prevalence of congenital anomalies with prevalence in children with cerebral palsy (CP)

		Mersey CP register n = 2253		UK Congenital anomaly registers n = 1852085 total births (adjusted n = 1842085 live births)				
ICD-10 Q rubric	Congenital anomaly	Number	Prevalence/ 10 000 CP	Number	Prevalence/ 10 000 total births	Prevalence range/ 10 000 total births†	Adjusted prevalence/10 000 live births	CP: population relative risk (95% CI)
Q02	Microcephaly	40	177.5	280	1.5	0.5 to 4.6	1.5	116.09 (84.0 to 162.3)**
Q03	Congenital hydrocephaly (without neural tube defect)	29	128.7	342	1.8	1.4 to 3.5	1.9	69.4 (47.6 to 101.2)**
Q11–Q14	Congenital anomalies of the eye	8	35.5	707	3.8	1.1 to 15.9	3.8	9.3 (4.6 to 18.6)**
Q20	Congenital malformation of cardiac chambers and connections	8	35.5	892	4.8	1.6 to 7.3	4.8	7.3 (3.7 to 14.7)**
Q21	Congenital malformation of cardiac septa	18	79.9	4830	26.1	10.4 to 79.3	26.2	3.1 (1.9 to 4.8)**
Q22	Congenital malformations of pulmonary and tricuspid valves	5	22.2	139	0.8	0.4 to 1.3	0.8	29.4 (10.7 to 74.6)**
Q23	Congenital malformations of aortic and mitral valves	3	13.3	450	2.4	1.8 to 6.1	2.4	5.5 (1.8 to 17.0)*
Q24	Other congenital malformations of heart	1	4.4	Not available				
Q25+Q26	Congenital malformations of great arteries and veins	14	62.2	1950	10.6	4.6 to 30.2	10.6	5.9 (3.5 to 9.9)**
Q20–Q26	All congenital cardiac anomalies	52	230.8	7417	40.0	17.4 to 108.3	40.3	5.7 (4.4 to 7.5)**
Q35–Q37	Cleft lip ± cleft palate	13	57.7	2539	13.7	10.5 to 17.0	13.8	4.2 (2.4 to 7.2)**
Q39	Congenital malformations of the oesophagus	5	22.2	442	2.4	1.7 to 3.1	2.4	9.3 (3.8 to 22.3)**
Q41+Q42	Congenital absence, atresia and stenosis of small or large intestine	4	17.8	656	3.5	1.5 to 6.0	3.6	5.0 (1.9 to 13.3)*

*p<0.01; **p<0.001.
†The range of prevalence per 10 000 total births gives the lowest and highest values recorded by the eight UK congenital anomaly registers contributing to EUROCAT.

Some of the children with CP who have other congenital anomalies may have had surgical correction of the latter. It is possible that adverse events during the surgical procedure may result in postnatally acquired CP. Coexisting congenital cardiac abnormalities, particularly those with right to left shunts and polycythaemia will be at heightened risk. However, this mechanism cannot be evoked for the majority of congenital anomalies, including those cardiac anomalies that were not surgically corrected.

The coexistence of so many disparate congenital anomalies with CP suggests that there is probably a common pathogenic mechanism. Intrauterine infection has been implicated as a pathogenic mechanism for CP.[15–17] However, correlation between markers of intrauterine infection and CP should not be inferred as being causal. It is possible that the presence of the remains of a vanished twin predisposes to infection occurring. Perinatal exposure to neurotropic viruses has also been found to be associated with preterm delivery and CP.[18] However, evidence of perinatal exposure neither accounts for CP of prenatal origin neither does it provide a satisfactory explanation of the coexistence of CP with a disparate group of congenital anomalies.

An alternative pathogenic mechanism for CP relates to the role of twinning, specifically monochorionic twinning. Death of one twin late in gestation is recognised as being a significant risk factor for CP.[19–24] It has been hypothesised that early loss as a ''vanishing'' twin may be causal of prenatally acquired CP in apparently singleton infants.[25] This hypothesis has been extended to include monochorionic twinning in the pathogenesis of many congenital anomalies.[12]

While the underlying basis for the hypothesis is monochorionicity in a twin conception, the specific pathogenic pathway for different congenital anomalies may vary. Figure 1 adapts a proposed pathogenic classification of congenital cardiovascular malformations.[26] Some anomalies of organ laterality, such as partial or complete situs inversus, atrial isomerism and the heterotaxias—for example, the asplenia/polysplenia syndromes—may be attributable to an abnormality at the time of zygote division. Although cardiac anomalies are most frequently reported among the heterotaxias, extracardiac anomalies of midline fusion such as cleft palate frequently coexist with the cardiac anomaly.[27] Laterality abnormalities are a feature of twinning. They are more common in mono- than dizygous twins[28] and conjoined twins are at particularly high risk.[29]

Neural crest cells and their migration during embryonic development have an important role in the development of the heart. Perturbation of this process may give rise to abnormalities of conotruncal septation, tetralogy of Fallot and transposition of the great vessels.[26 30] Furthermore, inadequate migration or proliferation of neural crest ectomesenchyme may affect closure of the facial clefts. Similarly, neuronal migration abnormalities produce serious cerebral malformations, many of which are clinically manifest as CP. Twin–twin haemodynamic instability could have a role in a variety of congenital abnormalities attributable to anomalies of neural crest or neuronal migration.

Blood flow and haemodynamic forces also influence the early embryonic development of the heart.[31] Disturbance of the laminar blood flow within the primitive cardiac tube results in hypoplasia of some structures and chambers of the heart with reciprocal enlargement of contralateral structures.[26] Other congenital anomalies such as intestinal atresias, oesophageal atresia with or without tracheo-oesophageal fistula and renal agenesis also may be attributable to haemodynamic factors affecting embryonic organ development.

The increased prevalence of congenital anomalies in children with CP may be an underestimate. Post-mortem examination of

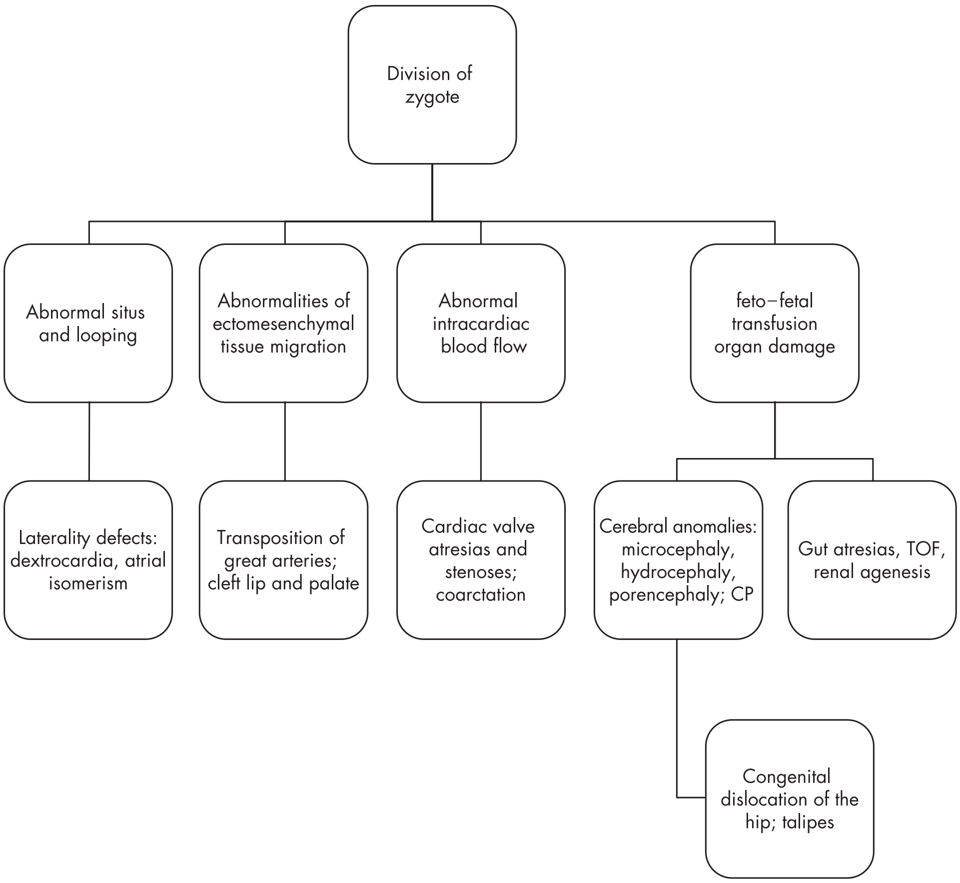

Figure 1 Pathogenic pathways for cerebral palsy (CP) and congenital anomalies. TOF, tetralogy of Fallot.

a stillbirth or infant who has succumbed to a congenital anomaly may have only a cursory examination of the brain and major cerebral pathology may be missed. Such infants will not have survived long enough to have CP or other clinical manifestation of cerebral impairment recognised. A detailed post-mortem examination of the brain will allow the underestimate of the coexistence of cerebral impairment and other congenital anomalies to be quantified.

Gene and chromosomal defects and environmental teratogens are undoubtedly responsible for many congenital anomalies. Nevertheless, most anomalies are of unknown aetiology. The coexistence of CP with a wide variety of other congenital anomalies suggests a common pathogenic mechanism that may be distinct from genetic or teratogenic influences. A monochorionic twin conception, with its common placental vasculature and potential for perturbation of inter-fetal haemodynamics, provides a plausible explanation for such a common pathogenic mechanism. If haemodynamic perturbation is causal of the CP and congenital anomaly in one fetus, reciprocal lethal damage to the co-fetus is highly probable, resulting in its early loss as a vanishing twin.

To test the hypothesis, ultrasound diagnosis very early in gestation is needed. This may be achieved, fortuitously, by following up women who present very early in gestation for a variety of reasons. Those women who present with a threatened miscarriage, but subsequently deliver a singleton infant, are of particular relevance as the miscarriage may be the vanishing twin. Alternatively a resource intensive study with subsequent long-term follow up could be designed, inviting women to have an ultrasound examination as soon as pregnancy is suspected.

What is already known on this topic

- The cerebral impairment that presents clinically as cerebral palsy occurs prenatally in most cases
- Children with cerebral palsy are at higher risk of other congenital anomalies but the level of risk and the specificity of congenital anomalies are unclear.

What this study adds

- Highly increased relative risks for specific congenital anomalies in children with cerebral palsy are reported.
- The pathogenesis and possible pathogenic pathways linking cerebral palsy and congenital anomalies are postulated.

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