Congenital non-central nervous system malformations in cerebral palsy: a distinct subset?

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This article is commented on by Kirby on pages 677–678 of this issue.

PUBLICATION DATA
Accepted for publication 4th March 2012.
Published online 12th May 2012.

ABBREVIATION
REPACQ Registre de la paralysie cérébrale au Québec (Quebec Cerebral Palsy Register)

AIM The aim of this article was to identify and contrast the subset of children with cerebral palsy (CP) and non-central nervous system (CNS) congenital malformations with children with CP but no coexisting non-CNS congenital malformations.
METHOD A population-based regional comprehensive CP registry was used to identify children with CP who had non-CNS congenital malformations (*n*=34; 19 males, 15 females; 22 classified as Gross Motor Function Classification System [GMFCS] levels I–III, 12 as GMFCS level IV or V). Their clinical features were then compared with other children with CP without non-CNS congenital malformations (*n*=207; 115 males, 92 females; 138 classified as GMFCS levels I–III, 69 as GMFCS level IV or V).
RESULTS Children with CP and non-CNS congenital malformations did not differ from those without in terms of neurological subtype distribution or functional severity, as measured by the GMFCS. Also, there was no association with previous maternal infections (i.e. toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus 2 [TORCH]), maternal fever, use of illicit substances, asphyxia, neonatal encephalopathy, intraventricular haemorrhage, or septicaemia. The incidence of comorbidities such as convulsions, communication difficulties, gavage feeding, cortical blindness, and auditory impairment was not higher in this subgroup.
INTERPRETATION The incidence of congenital non-CNS malformations among children with CP is appreciable. Children with these non-CNS malformations do not appear to differ from other children with CP regarding neurological subtype, functional severity, and comorbidities, or maternal or obstetrical factors. Thus, the specific presence of a non-CNS congenital malformation does not appear to assist the practitioner in the management or understanding of a child's CP.

Cerebral palsy (CP) remains a significant cause of motor impairment in childhood,[1] affecting 0.15 to 0.25% of children (i.e. 1.5–2.5/1000 live births).[2] CP is a neuromotor disability that originates from an anomaly and/or damage to the motor regions of the brain, leading to the early onset of observable motor dysfunction.[3,4] CP can also be associated with non-motor impairments and disorders such as epilepsy, difficulties with feeding and communication, vision and hearing loss, cognitive disability, behavioural disturbances, and orthopaedic difficulties.[5,6]

The aetiology of CP can be divided into two broad categories: (1) congenital anomalies/dysgenesis of the brain and (2) acquired brain injury. Congenital brain anomalies have been shown to be associated with low birthweight, low gestational age, and prenatal infections. Brain injury can be acquired following prenatal or birth ischaemia/asphyxia, central nervous system (CNS) trauma, haemorrhage, stroke, or infection.[5]

The objective of this study was to use a regional population-based registry to compare risk factors, clinical presentation, and associated comorbidities of children with CP with an associated non-CNS congenital malformation with those without. The non-CNS congenital malformations were evaluated as a group as well as by subtype. This subgroup of individuals can then be better characterized by establishing whether there are clinical differences between children with CP with and without associated non-CNS congenital anomalies. The use of a registry permits the study of CP in a relatively unbiased way.

METHOD

The data for this study were obtained from the Quebec Cerebral Palsy Registry (Registre de la paralysie cérébrale au Québec [REPACQ]), which was established in 1998 and became operational in 2004. REPACQ is a population-based registry including children born between 1999 and 2002 in 6 of the 17 geographically distinct administrative health and social service regions of Quebec (Estrie, island of Montreal, Lanaudière, Laurentians, Outaouais, and Quebec City) that represents approximately half of the province's population and annual births. Patients requiring rehabilitation after a diagnosis of CP

 DOI: 10.1111/j.1469-8749.2012.04309.x

by a paediatric subspecialist (neurologist, developmental paediatrician, or physiatrist) are treated in specialized centres in their specific geographic region as defined and proscribed by provincial healthcare policy.

In order to recruit cases for this registry, systematic surveys of regionalized paediatric rehabilitation centres and healthcare professionals involved in the care of children with CP were employed. To be eligible, children had to be over the age of 2 years and qualify for the recent consensus definition of CP as a non-progressive motor impairment of early onset, presumably cerebral in origin, which may or may not be associated with developmental delays, cognitive disability, language impairment, epilepsy, sensory (i.e. auditory or visual) loss, orthopaedic abnormalities, or behavioural difficulties.[7,8] A recognized motor impairment required objective documentation of abnormalities in tone, muscle strength, posture, reflexes, and motor skills on examination for diagnosis. Non-progressive referred to the underlying pathological process and not apparent clinical manifestations. Genetic and metabolic disorders were considered for inclusion or exclusion as per Badawi et al.[9] Early onset meant that signs and symptoms, but not necessarily a diagnosis, were evident before 1 year of age. When possible, the diagnosis of CP was confirmed at 5 years of age.

Parents or guardians were asked to consent to participation in the registry once their child met the eligibility criteria. A secure computerized database was established using information regarding over 120 variables for each participating child. Data were obtained according to standardized protocols and procedures established by the registry by trained local research assistants. Data were acquired through a combination of a parental (preferably maternal) interview and a review of both the mother's and child's medical health records. The provincial host institution, McGill University Health Centre, and each participating centre granted ethics approval for the registry. The data collection was consistently supervised by a registry coordinator with a subset of data randomly selected for validation of accuracy. Previous publications are available for further information regarding the REPACQ registry format and methodology.[10–12]

Non-CNS congenital malformations were divided into five categories: cardiovascular, musculoskeletal, genitourinary, gastrointestinal, ophthalmological, and multiple (elements of two or more of the previous categories). Cardiovascular malformations included transposition of the great vessels, cardiomegaly, pulmonary stenosis, ventricular septal defect, atrial septal defect, patent ductus arteriosus, heart murmur, heart hypoplasia, aortic arch hypoplasia, bicuspid aortic valve, patent foramen ovale, and cardiomyopathy. Musculoskeletal malformations included congenital talipes equinovarus, arthrogryposis, feet malformation, vertebral anomalies, phalanges amputation, syndactyly, rib abnormalities, and hip dysplasia. Genitourinary malformations included hypospadias, vesico-urethral reflux, clitoral hypertrophy, congenital anomaly of the urinary tract, ectopic kidney, and sexual (genitalia) ambiguity. Gastrointestinal malformations included intestinal malrotation, cleft palate, oesophageal atresia, congenital anomaly of the intestines, gastrochisis, and bilateral inguinal hernia. Ophthalmological malformations included macular hypoplasia and microphthalmia.

What this paper adds

- Children with CP with non-CNS malformations do not appear to differ from other children with CP regarding neurological subtype, functional severity and comorbidities, or maternal or obstetrical antecedent factors.

The severity of the motor impairment and the neurological and functional subtype were ascertained in order to obtain a more comprehensive picture of the patients' profiles. The following categories were used for neurological subtyping: spasticity (symmetrical or asymmetrical increased resistance to velocity-dependent muscle stretch) – quadriplegic (all four extremities involved), hemiplegic (restricted to one side of the body), and diplegic (usually involving both lower extremities without appreciable upper limb involvement). Dystonia and choreoathetosis were the major impairments in dyskinetic CP. Finally, ataxic–hypotonic CP corresponded to hypotonia and a lack of smooth coordination of voluntary muscle contractions in the absence of spasticity. The mixed subtype refers to any combination of spasticity and dyskinesia.[5,12]

The Gross Motor Function Classification System (GMFCS) was used to assign functional status. The GMFCS is a validated[13–15] five-level scale, developed by Palisano et al.[16] in the late 1990s, that assesses the severity of gross motor impairment from the most able (level I) to the least able (level V).[17] Independent ambulation without (levels I and II) or with (level III) assistance can be reliably differentiated from non-ambulation (levels IV and V) using this approach. This was either extracted from the chart or assigned based on the information available.

Several comorbidities were studied, such as cortical blindness (determined by an ophthalmologist), substantial auditory impairment (bilateral hearing loss on audiometric testing of 70 dB or greater necessitating amplification), non-verbal communication difficulties (absence of specific words or recognizable vocabulary in the child's maternal language, regardless of whether evident cognitive limitations were present), gavage feeding status (use of a temporary or permanent artificial tube to administer nourishment of the child), and coexisting convulsions (occurrence of afebrile seizures in the past year preceding registry inscription). The evaluation of a possible cognitive disability was not carried out because of the young age of the children (between 2y and 5y), which made reliable consistent assessment difficult. Furthermore, data regarding concurrent behavioural disorders were not collected because of the lack of consistent access to psychiatric information.[12]

Certain maternal and obstetrical factors were studied, such as TORCH infections (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus 2), maternal fever during pregnancy, use of substances including alcohol, cigarettes, and illicit drugs, possible perinatal depression as indicated by an Apgar score of less than 5 at 5 minutes, neonatal encephalopathy, septicaemia, and intraventricular haemorrhage grades 1 to 4.

The data obtained are presented from a descriptive perspective as the number of children with CP overall was insufficient

to adequately power a detailed statistical comparison over the large number of variables available.

RESULTS

In the six administrative regions defined by REPACQ, 301 children with CP were identified who were born over the period spanning 1999 to 2002 inclusive. In the same time period and regions, there were roughly 144 000 live births, indicating an approximate prevalence of 2.09 per 1000 live births, which is around the median for CP prevalence estimates in developed countries. Existing information on the presence or absence of non-cerebral congenital malformations was available for 241 of these children. These individuals constitute the present study cohort.

Of these 241 children (107 [44%] females; 134 [56%] males), 34 (14%) were diagnosed with a coexisting non-CNS congenital malformation. Characteristics of the children with or without a concurrent non-CNS congenital malformation are summarized in Table I. As for comorbidities in the children with non-CNS congenital malformations, four had cortical blindness, six had an auditory impairment, 23 had communication difficulties, three had a need for gavage feeding, and six had convulsions in the past year.

Table I: Characteristics of children with cerebral palsy (CP) with or without coexisting non-cerebral congenital malformations

Variable	Non-cerebral congenital malformation, *n*	No non-cerebral congenital malformation, *n* (%)
Total	34	207 (86)
Sex		
Female	15	92 (44)
Male	19	115 (56)
Type of pregnancy		
Twin	4	23 (11)
Gestational category		
<37wks (preterm)	19	86 (42)
>37wks (term)	15	118 (58)
Categorical birthweight		
<2500g	19	73 (36)
>2500g	15	131 (64)
Requiring admission to NICU		
Yes	29	128 (62)
No	5	77 (38)
Comorbidities		
Cortical blindness	4	19 (9)
Auditory impairment	6	22 (11)
Communication difficulties	23	134 (65)
Gavage feeding	3	15 (7)
Convulsions in the past year	6	35 (17)
Neurological subtype		
Quadriplegia/dyskinesia	17	83 (40)
Diplegia/hemiplegia/other	17	124 (60)
GMFCS levels		
I–III	22	138 (67)
IV–V	12	69 (33)
Causations of CP		
Asphyxia	6	31 (16)
Neonatal encephalopathy	10	57 (28)
IVH	5	14 (16)
Septicaemia	3	6 (3)
Substance abuse	15	98 (48)
Maternal fever	3	20 (10)
TORCH infections	0	15 (7)

NICU, neonatal intensive care unit; GMFCS, Gross Motor Function Classification System; IVH, intraventricular haemorrhage; TORCH, toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus 2.

Table II: Subtypes of non-cerebral congenital malformations (*n*=34)

Congenital malformation category	Frequency, *n*
Cardiovascular	23
Musculoskeletal	9
Genitourinary	6
Gastrointestinal	5
Ophthalmological	2
Multiple	8

Children with non-CNS congenital malformations were divided into two broad neurological subtypes: half were of the quadriplegic/dyskinetic subtype, and half were of the diplegic/hemiplegic/other subtype. The distribution of GMFCS levels was as follows: 22 were classified as being independently ambulant (levels I–III) and 12 as non-ambulant (levels IV–V).

When all non-CNS congenital malformations were grouped as one variable (Table I), there were no apparent differences for neurological subtype, GMFCS scoring, and associated comorbidities such as cortical blindness, auditory impairment, communication difficulties, gavage feeding, and seizures in the past year. There was no association between congenital malformations and previous maternal infections (TORCH, maternal fever, use of substances such as alcohol, tobacco, or illicit drugs, possible asphyxia, neonatal encephalopathy, intraventricular haemorrhage, and septicaemia). Of note, patients with non-CNS congenital malformations were of lower birthweight and had a greater need for neonatal intensive care. The various comparisons undertaken are summarized in Table I.

Non-CNS congenital malformation subtypes were then analysed to identify associations with the different variables. Of the 34 children with non-cerebral congenital malformations, 23 had a cardiovascular malformation, nine (26%) musculoskeletal, six genitourinary, five gastrointestinal, two ophthalmological, and eight multiple. The precise breakdown can be found in Table II.

DISCUSSION

Congenital malformations are reported in a higher proportion in children with CP than in the general population of children.[18–21] A study based on the CP Register and the Birth Defect Registry of Western Australia reported that 15.8% of children with CP had non-CNS anomalies.[19] Pharaoh[21] demonstrated an increase in eye anomalies, cardiac anomalies, cleft lip and/or palate, congenital dislocation of the hip and talipes, and atresias of the oesophagus and intestines in children with CP. Garne et al.[20] reported an increase in cardiac anomalies, facial clefts, and limb and skeletal anomalies in children with CP, using data from 11 CP registers for the period 1976 to 1996. Of note though, studies of non-CNS anomalies remain rare because of small sample sizes.[18]

The REPACQ probably represents a true complete ascertainment of children with CP as the 2.09 CP cases per 1000 live births of the REPACQ is consistent with the 1.5 to 2.5 of 1000 live births range found in the literature for regions comparable in profile to Quebec.[4] Using the REPACQ, permits bringing together of large numbers to give greater credance for the analysis of the different variables. A more unbiased, representative, and reliable view can be found by the use of a population-based registry over a traditional convenience sample. Often, convenience studies are a biased ascertainment as they include individuals who require greater attention from available medical and support systems, and thus represent the most severe cases of CP.[10] On the other hand, the use of registries permits extensive data compilation regarding prevalence, diagnostic trends, classification, and outcomes of all patients regardless of their precise CP profile.

Several studies have demonstrated an association between CP and congenital anomalies.[18–21] Different hypotheses are postulated for this linkage. One theory is that congenital non-CNS malformations and CP are a result of the same maternal cause.[18] However, when non-CNS congenital malformations are taken as an entity, there seems to be no association with specific, different, easily identifiable maternal or obstetrical factors such as possible asphyxia, neonatal encephalopathy, intraventricular haemorrhage, septicaemia, substance abuse, maternal fever, or TORCH infections.

Also, the presence of non-CNS congenital malformations in children with CP was not associated in our sample with an increased severity of CP. When the functional subtypes were grouped as spastic quadriplegic/dyskinetic versus other (spastic diplegia, spastic hemiplegia, ataxic, and other), and when the GMFCS categories were grouped as ambulant (levels I–III) and non-ambulant (levels IV and V), there was no difference between those with and without a concurrent non-CNS congenital malformation. Additionally, non-CNS congenital malformations do not correlate with an apparent increase in various associated comorbidities such as cortical blindness, auditory impairment, communication difficulties, gavage feeding, and seizures in the previous year.

However, the presence of non-CNS congenital malformations, although not associated with the functional or neuro-logical severity of CP, nor with comorbidities or maternal or obstetric factors, appear to be correlated with low birthweight and neonatal intensive care hospitalization, thus suggesting an antenatal origin. Birth defects are associated with a substantial morbidity rate and high hospitalization charges. A population-based study by Yoon et al.[22] demonstrated that infants with congenital anomalies and genetic diseases account for the greatest proportion of infant hospitalizations, as well as hospitalizations that are the most costly and of the longest duration. This was also suggested by a 2007 Centers for Disease Control and Prevention report.[23] As for birthweight, many studies demonstrate a statistical association between birth defects and low birthweight.[24,25] In a large prospective multicentre study by Dolan et al.,[24] after controlling for many confounding factors, including shared risk factors and pregnancy complications, a live-born single fetus with a birth defect was 3.6 times more likely than those without a defect to have a birthweight of less than 2500g.[24]

Non-CNS congenital malformations are relatively common among children with CP. Children with such non-CNS malformations do not appear to differ from other children with CP regarding neurological subtype, functional severity, and comorbidities, or maternal or obstetric factors. Thus, the specific presence of a non-CNS congenital malformation does not appear to assist the practitioner in the management or understanding of a child's CP.

This study's limitations include the fact that the method of ascertaining whether any particular child had a non-CNS congenital malformation was non-direct, being achieved through reviewing the medical file or questioning of the parent. Furthermore, based on the number of children available, the study was insufficiently powered to analyse data from a statistical perspective, and thus the study is descriptive in nature. Finally, there are substantial differences between the absolute number of children with and without a non-CNS congenital malformation.

ACKNOWLEDGEMENTS

The authors are grateful for the support of the Montreal Children's Hospital Foundation during the writing of this manuscript. Alba Rinaldi provided the necessary secretarial assistance. Anna Radzioch provided the necessary data analysis assistance. All authors contributed extensively to the work presented in this paper. REPACQ is presently funded by NeuroDevNet NCE. It was originally funded by the Fonds de recherche Santé Québec (FRSQ).

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