Normal Imaging in Patients with Cerebral Palsy: What Does It Tell Us?

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Objective To identify distinctive clinical features characterizing children with cerebral palsy (CP) and normal-appearing magnetic resonance imaging (MRI) findings.

Study design Using a population-based CP registry, the Registre de la Paralysie Cérébrale au Québec (Quebec Cerebral Palsy Registry), various antenatal, perinatal, and postnatal predictor variables, as well as current phenotype, were compared in patients with normal-appearing MRI findings and those with abnormal MRI findings.

Results Of the 213 patients evaluated, 126 (60%) had MRI imaging results available and were included in our analysis. Of these 126 patients, 90 (71%; 51 males, 39 females) had abnormal findings and 36 (29%; 17 males and 19 females) had normal-appearing findings. Compared with other CP variants, normal-appearing MRI was more prevalent ($P = .001$) in dyskinetic CP (72.7%; 8 of 11) and less prevalent ($P = .002$) in spastic hemiplegic CP (10%; 4 of 40). There were no significant differences between the 2 groups ($P > .05$) in terms of the prevalence of perinatal or postnatal clinical features or clinical outcomes. Furthermore, 42% (15 of 36) of the children with normal-appearing MRI exhibited a high degree of functional disability (Gross Motor Functional Classification System IV-V), compared with 33% (30 of 90) with abnormal MRI.

Conclusion No clinical features, except a higher prevalence of dyskinetic CP, was identified in the children with normal-appearing MRI. More refined imaging techniques may be needed to evaluate patients with normal-appearing MRI findings. Furthermore, genetic or functional, rather than gross structural lesions, may underlie the pathophysiology of CP in this cohort. Finally, the high proportion of substantial functional disability underscores the importance of continuous follow-up even in the absence of early structural abnormalities on imaging. *(J Pediatr 2013;162:369-74)*.

Estimated to occur at a frequency of 1.5-2.5 per 1000 live births, cerebral palsy (CP) remains the most common cause of physical disability in children.[1] This neurologic entity is characterized clinically by a nonprogressive motor impairment manifested by abnormal muscle tone, strength, posture, reflexes, and motor skills, presumably arising from an early insult to the developing immature brain in the prenatal, perinatal, or early postnatal period.[2] Children with CP have an increased prevalence of associated comorbidities, including intellectual disability (52%), epilepsy (45%), speech/language deficits (38%), vision impairment (28%), and hearing impairment (12%).[3]

Neuroimaging plays an important role in elucidating the timing of the injury and contributes to our understanding of the etiology and pathogenesis underlying CP.[4] According to practice guidelines issued in 2004 by the American Academy of Neurology and the Child Neurological Society, neuroimaging is recommended in the diagnostic evaluation of all children with CP.[3] Numerous studies have identified neuroimaging patterns that correlate not only with the timing of injury, but also with the CP subtype.[3,5,6] For example, whereas periventricular leukomalacia occurs more frequently in preterm infants and is correlated with spastic quadriplegic or diplegic CP,[7,8] spastic hemiplegic CP is observed more often in stroke survivors.[6,9] Other neuroimaging patterns have been identified as well.[10]

Although abnormalities on neuroimaging can be identified in the majority of children with CP, case series have consistently demonstrated that up to 32% of patients with CP can present with normal or nonspecific findings, especially those with ataxic or dyskinetic variants.[3] Little is known of the etiology and pathogenesis of CP in this cohort of patients. The aim of the present study was to use a population-based CP registry to identify clinical factors that differentiate patients with CP and normal or nonspecific neuroimaging findings from those with structural abnormalities, and thereby elucidate the pathophysiological mechanisms in this cohort of patients.

CP	Cerebral palsy
CT	Computed tomography
DTI	Diffusion tensor imaging
GMFCS	Gross Motor Functional Classification System
MRI	Magnetic resonance imaging
REPACQ	Registre de la Paralysie Cérébrale au Québec

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Methods

The study was conducted using data extracted from the Registre de la Paralysie Cérébrale au Québec (REPACQ; Quebec Cerebral Palsy Registry), a population-based registry that covers approximately one-half of the province's population and annual births and is operational in 6 of the 17 geographically defined regions of Quebec's administrative health and social services infrastructure (island of Montreal, Quebec City, Laurentians, Lanaudiere, Estrie, and Outaouais). Children are recruited into REPACQ through systematic surveys of pediatric rehabilitation and healthcare providers, which in Quebec are universally funded by the government and accessible to the entire population. Once cases are identified, parental consent is obtained, and a detailed review of the maternal medical and obstetric records as well as the child's neonatal, medical, and rehabilitation charts is conducted. These data are further supplemented by a standardized parental interview and physical examination of the child. More than 120 variables are collected for each enrolled patient. Local Ethics Board approval for case and data ascertainment was obtained from each participating institution. The Montreal Children's Hospital-McGill University Health Center research ethics board provided central ethical approval for data storage, analysis, and overall REPACQ operations.

To be enrolled in REPACQ, a child must be at least 2 years of age and meet the diagnostic criteria for CP, which include clinical diagnosis of a nonprogressive motor impairment resulting from a presumably early insult to the developing brain, which also could be associated with one or more deficits in other spheres of development, including cognitive disabilities, language impairment, seizure disorder, sensory (ie, auditory or visual) loss, musculoskeletal abnormalities, or behavioral difficulties.[11,12] Children with myelodysplasias or neuromuscular disorders are excluded from REPACQ. Objective evidence of neuromotor impairment, as manifested by abnormal muscle tone, strength, posture, reflexes, and/or motor skills, must be confirmed on physical examination by a pediatric neurologist, developmental pediatrician, or pediatric physiatrist. Further details on case identification, enrollment, and data collection methods are available elsewhere.[13,14]

For the purposes of this study, neuroimaging data were extracted for children with CP enrolled into REPACQ between 1999 and 2002 inclusively. At this time, case ascertainment is complete only for this birth cohort. Neuroimaging studies for all patients with CP in REPACQ are interpreted by university-based pediatric neuroradiologists and have been classified into 10 mutually exclusive categories: periventricular leukomalacia/white matter injury, cerebral malformation, cerebral vascular accident, deep gray matter injury, superficial gray matter injury, diffuse gray matter injury (both deep and superficial), intracranial hemorrhage, infection, nonspecific findings, and normal. Nonspecific findings reflect unclassifiable, and presumably nonpathological, changes on imaging, such as delayed myelination, widened Virchow-Robin spaces, and nonspecific ventricular enlargement. Further detailed definitions of these subcategories have been summarized previously.[6]

For the purposes of this study, only children who had undergone magnetic resonance imaging (MRI) were included in the analysis (n = 126 patients). Patients with only computed tomography (CT) findings were excluded (n = 87 patients). The 10 neuroimaging categories were split into 2 main groups: those with normal-appearing MRI (including both normal and nonspecific findings) and those with abnormal MRI (the other 8 categories). A comprehensive statistical comparison of various predictor variables in these 2 groups was then performed. Specifically, various clinical factors, including antepartum, intrapartum, postpartum, CP subtype, CP severity (as defined by the Gross Motor Functional Classification System [GMFCS]), and identified comorbid outcomes, were compared in an attempt to identify variables that can differentiate CP patients with normal-appearing MRI from those with abnormal MRI.

SPSS version 17 (IBM, Armonk, New York) was used for both database entry and statistical analysis. Simple descriptive statistics were used throughout. Possible statistical associations between categorical variables were evaluated using Pearson χ^2 analysis. The Fisher exact test was used when expected values were <5. When statistical significance was attained (P value $\leq .05$), regression and correlation analysis was performed.

Results

Between 1999 and 2002, a total of 301 patients with CP were enrolled into the population-based REPACQ. Of these, 213 patients (71%) had undergone either a CT or MRI imaging study as part of their investigative workup. Only those patients who were evaluated with MRI (126 of 213; 60%) were incorporated into this study cohort and included for further analysis. Within this cohort, the majority of patients had abnormal MRI findings (71%; 90 of 126), and 29% (36 of 126) had normal or nonspecific MRI findings. The latter, termed the group with normal-appearing MRI, comprised 14 patients (11.5%) with normal imaging findings and 22 patients (17.5%) with nonspecific findings.

There was a slight, nonsignificant ($P > .05$) preponderance of males in the abnormal MRI group (51 males and 39 females; 1.3:1) compared with the normal-appearing MRI group (17 males and 19 females; 1:1.1). Otherwise, there were no significant differences ($P > .05$) between the 2 groups with respect to the mean age of enrollment into REPACQ (normal-appearing, 44 $\pm$ 12.4 months vs abnormal, 43 $\pm$ 14.3 months) or in terms of the mean age at which MRI was done (16.9 $\pm$ 12.5 months vs 14.4 $\pm$ 12.5 months).

Distribution of neuroimaging findings across CP subtypes revealed a higher prevalence of normal-appearing MRI findings in patients with dyskinetic CP variants (72.7%; 8 of 11), followed by ataxic/hypotonic (42.9%; 3 of 7), spastic diplegic (40.9%; 9 of 22), spastic double-hemiplegic/quadriplegic