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Original Article

Predicting Comorbidities With Neuroimaging in Children With Cerebral Palsy

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ABSTRACT

A population-based registry was used to ascertain whether neuroimaging findings of children with cerebral palsy could predict the occurrence of certain comorbidities. Neuroimaging findings and comorbidities data were extracted from the Quebec Cerebral Palsy Registry for children born in a 4-year birth interval (1999-2002) covering half of the province's population. Neuroimaging studies were classified into 10 mutually exclusive categories (periventricular white matter injury/leukomalacia, cerebral malformation, cerebral vascular accident, deep gray matter injury, superficial gray matter injury, diffuse gray matter injury, intracranial hemorrhage, infection, nonspecific findings, and normal). Comorbidities studied included cortical blindness, severe auditory impairment, inability to communicate verbally, assisted feeding, and the presence of afebrile seizures in the prior 12 months. Neuroimaging results were available for a total of 213 children. Only deep gray matter injury (defined as signal abnormality or volume loss in subcortical gray matter, $n = 9$) was significantly ($P < 0.05$) linked with the occurrence of both the inability to communicate verbally ($n = 5$, 55.6% vs $n = 46$, 22.5%, $P = 0.04$) and with a higher mean number of comorbidities (1.67 vs 0.70, $P < 0.01$), and therefore with increased burden of comorbidities. These findings may improve our ability to prognosticate the outcome of children with cerebral palsy, enabling targeted early direct interventions.

Introduction

With a global incidence of between 2 and 2.5 per 1,000 live births, many children worldwide are faced with cerebral palsy [1-4]. By definition, affected individuals manifest early nonprogressive lesions to their developing central nervous system, reflected by signs of motor impairment that are cerebral in origin [5,6]. Cerebral palsy is recognized as the most prevalent cause of physical disability in children [1,4,5].

Beyond the inherent neuromotor impairments, various comorbid conditions can occur concomitantly in up to half of children with cerebral palsy [6]. These impairments, including seizure disorders, hearing and visual deficits, cognitive and attention disturbances, and speech and language disabilities, are not infrequently encountered, and as such, they have been included in most recent cerebral palsy consensus definitions [1,3,7-9]. These limitations may interfere with the individual's ability to function in daily life and lessen an individual's quality of life to a degree at times greater than the motor impairment component [5,6]. For many patients and their families, these co-occurring conditions can represent the disease's major burden.

The diagnosis of cerebral palsy is clinical and does not require ancillary tests to be performed. Cerebral palsy is a heterogeneous entity, and its causes are diverse. To assist in unraveling the specific cause for each individual child, the American Academy of Neurology and the Child Neurology Society have recommended since 2004 routine neuroimaging of cerebral palsy patients [2]. Specific patterns of neuroimaging findings in children with cerebral palsy were already previously found to be associated with gross motor severity (Gross Motor Function Classification System level) and neurologic subtype [4]. As a potential tool to determine predictive factors, recognizing neuroimaging patterns associated with the future development of one or more comorbid conditions would help in identifying at-risk individuals and implementing targeted, personalized early interventions.

We used a population-based registry to ascertain whether neuroimaging findings of a sample of children with cerebral palsy could predict the occurrence of certain associated comorbidities.

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Methods

Subjects were recruited through the Quebec Cerebral Palsy Registry (Registre de la paralysie cérébrale au Québec [REPACQ]). This population-based comprehensive registry was initially established in 1998 by a multidisciplinary collaboration of physicians and other health researchers. It became fully operational in 2004 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, Outaouais), covering about half of the province's population and annual births. Universal government-funded health and rehabilitation services are provided to the entire population of the province of Quebec through local specialized centers responsible for a specifically defined geographic region. Therefore, cases were identified through systematic surveys of these regionalized pediatric rehabilitation and medical service providers. Once a case was identified, consent for registry inscription was sought from the parents. For those who elected to participate in the registry, data were collected through a combination of parental (preferably maternal) systematic interview and direct review of the medical and rehabilitation charts of both the child and his or her mother. This data review was conducted by trained local research assistants according to standardized policies and procedures established by the registry. Data collection was supervised consistently by a single individual (L.D.), with a subset randomly selected for independent validation of accuracy. Ethical permission for the registry's establishment and implementation was obtained at the local host institution (McGill University Health Center) and each participating pediatric rehabilitation center. Over 120 variables were collected for each individual patient, as previously described [6,10,11].

To be included in the study, children had to be at least 2 years old and had to have received a diagnosis of cerebral palsy, which needed to comply with this most recent consensus definition: "a non-progressive early-onset motor impairment, presumably of cerebral origin, with or without concomitant developmental delays, cognitive limitations, language dysfunction, epilepsy, sensory (auditory or visual) deficit, orthopaedic disabilities, or behavioural issues" [2,9,12,13]. Diagnosis was made by a pediatric neurologist because this is required for referral to one of the regionalized rehabilitation and medical centers caring for children with cerebral palsy across Quebec. Signs and symptoms had to be present before the child's first birthday to be defined as early onset. Motor impairment, the sine qua non of diagnosis, was recognized at physical examination as an objective abnormality in tone, strength, posture, reflexes, and/or motor skills. When feasible, the diagnosis was confirmed when the patient reached 5 years of age. Patients with a neuromotor impairment resulting from a neuromuscular condition or myelodysplasia were excluded from diagnosis, as were individuals with genetic and metabolic disorders as established by Badawi et al., not satisfying a requisite nonprogressive underlying pathology [14].

Cases consisted of children with cerebral palsy born in a 4-year birth interval (1999-2002 inclusively) included in the registry. Data were extracted from the database regarding the neuroimaging findings and the presence and description of several comorbidities. Imaging studies were all interpreted by university-based pediatric neuroradiologists. Classification of the neuroimaging findings into 10 mutually exclusive neuroimaging 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) has been previously explicitly published and is summarized in Table 1 [4]. Five specific individual comorbidities were studied, as summarized in Table 2 [6]. These comorbidities were chosen because they can significantly affect the functional outcome of children with cerebral palsy, are common, and can be reliably ascertained by age 5; in addition, they were clearly documented in the registry. Lack of accessible psychiatric information and the young age of our subjects (between 2 and 5 years old) respectively precluded evaluation of coexisting behavioral and cognitive disabilities in this particular study.

Comparisons were made for the presence of each individual comorbidity between each neuroimaging category and any other scan result. Significance ($P \leq 0.05$, determined a priori) was evaluated by the Pearson chi-square test or the Fisher exact test when predicted values were less than 5. The mean number of comorbidities associated with each neuroimaging finding category was compared by the Student t test of means. All statistical analyses were performed by SPSS software (v. 16.0, SPSS, Chicago, IL).

Table 1. Definition of the mutually exclusive neuroimaging finding categories

Neuroimaging Finding	Definition
PVL/PVWMI	Abnormality or volume loss in the periventricular and/or deep white matter
Cerebral malformation	Includes cortical dysplasia, polymicrogyria, lissencephaly, pachygyria, heterotopias, schizencephaly, cerebellar hypoplasia or dysgenesis, holoprosencephaly, hydranencephaly, hydrocephalus, and agenesis of the corpus callosum
Cerebral vascular accident	Infarction in a specifically defined vascular territory
Deep brain GMI	Signal abnormality or volume loss in subcortical (i.e., basal ganglia and thalamus) gray matter structures
Superficial brain GMI	Signal abnormality or volume loss restricted to cortical gray matter structures, typically associated with an increase in ventricular volume
Diffuse GMI	Global/diffuse signal abnormality and/or volume loss involving the cortex/subcortex, deep gray matter, and subjacent white matter (i.e., ventricular enlargement)
Intracranial hemorrhage	Epidural, subdural, intracranial or intraparenchymal hemorrhage
Infection	Dystrophic, predominantly periventricular calcification with or without focal white matter destruction, and cerebral hypoplasia, in conjunction with a known positive serology
Nonspecific findings	Other unclassifiable changes on imaging (e.g., delayed myelination, widened Virchow-Robin spaces, nonspecific ventricular enlargement)
Normal	No abnormalities detected or noted

Abbreviations:
GMI = Gray matter injury
PVL = Periventricular leukomalacia
PVWMI = Periventricular leukomalacia white matter injury

Results

In total, 301 children with cerebral palsy born between 1999 and 2002 inclusively were included in the Quebec Cerebral Palsy Registry. Over the same 4-year interval, roughly 144,000 live births occurred in the same 6 of 17 geographically defined Quebec's administrative health and social service regions participating in the registry, yielding a crude prevalence rate of 2.08 per 1,000 live births. Among these cases, 242 parents consented to full registry inscription. Of these remaining subjects, 213 had available concurrent information on neuroimaging (126 brain magnetic resonance imaging [MRI] and 87 brain computed tomographic scan [CT scan]), and comorbidities and were therefore retained to comprise our study cohort. Although fewer cerebral malformations were detected with CT scans than with MRI ($\chi^2 = 8.994$, $P < 0.05$, df = 1)—specifically cerebral malformations and periventricular leukomalacia white matter injury—the imaging findings did not differ significantly between the imaging modalities used [4]. Of the 28 children with normal neuroimaging, 14 underwent MRI and 14 underwent CT scan. Of the 14 who had an MRI performed, only 1 had undergone a previous neonatal cranial ultrasound, which revealed only prominent cerebrospinal fluid spaces without any other abnormality. Of the 14 children with a normal CT scan and no MRI performed, 8 had a previous neonatal cranial ultrasound, 2 had grade 1 intraventricular hemorrhage, 4 had normal findings, 1 had cerebral edema, and 1 had a left frontal cystic lesion compatible with leukomalacia that then resolved on 2 subsequent cranial ultrasound studies. There were 91 female and 122 male subjects, and the participants were a median age of 42 months (mean 44 months, standard deviation 14 months, range 24-79 months) at the time of inscription to the registry. The distribution of neurologic subtypes was as follows: spastic quadriplegia 79 (37.1%), spastic hemiplegia 71 (33.3%), spastic diplegia 36 (16.9%), dyskinetic 15 (7.0%), other (i.e., ataxic-hypotonia, triplegia, monoplegia) 12 (5.6%). The distribution of Gross Motor Function Classification System levels was as follows: I 89 (41.8%), II18 (8.5%), III 28 (13.1%), IV 39 (18.3%), V 39 (18.3%). The individual comorbidity frequency distribution by each neuroimaging finding category is reported in Table 3. The mean number of comorbidities for each individual child is reported by each specific neuroimaging finding result in Table 4.

Comparing dichotomously the presence of each individual comorbidity between each neuroimaging finding category and any

Table 2. Definition of comorbidities

Comorbidity	Definition
Cortical blindness	As diagnosed by an ophthalmologist
Severe auditory impairment	≥70 dB bilateral hearing loss on audiometric testing requiring amplification
Inability to communicate verbally	Absence of specific words or recognizable vocabulary in the child's maternal language, regardless of possible etiology (i.e., motor or cognitive limitations)
Feeding via gavage	Use of a temporary or permanent artificial tube to administer the bulk of the child's nutrition internally
Afebrile seizures in the prior 12 months	Occurrence of afebrile seizures in the 12 months preceding Quebec Cerebral Palsy Registry inscription

other scan result as a whole, having a deep brain gray matter injury on neuroimaging was significantly associated with the inability to communicate verbally ($n = 5$, 55.6% vs $n = 46$, 22.5%, $P = 0.04$). All other neuroimaging finding categories failed to reach statistical significance. Similarly, when comparing the mean number of comorbidities experienced by children with each of the neuroimaging finding category, a deep brain gray matter injury neuroimaging finding was again significantly found to have a higher mean number of comorbidities than any other neuroimaging finding category as a whole (1.67 vs 0.70, $P < 0.01$). Analysis of the other neuroimaging finding categories did not yield any other results that reached statistical significance.

Discussion

The Quebec Cerebral Palsy Registry's crude prevalence for cerebral palsy of 2.08 children per 1,000 live births in its geographic area is comparable to previous reports of cerebral palsy prevalence in Western societies, allowing the Quebec Cerebral Palsy Registry to be considered reasonably complete in its identification of children with cerebral palsy in its geographic sector [1-3]. Likewise, the distribution of Gross Motor Function Classification System and neurologic subtype across our sample are similar to previous reports [15,16]. Therefore, our cohort constitutes a representative sample of the population of children with cerebral palsy.

Our Quebec Cerebral Palsy Registry population-based study revealed that children with cerebral palsy who were found to have signal abnormality or volume loss in the subcortical gray matter on their neuroimaging study were more likely to be unable to communicate verbally in comparison to children who had any other neuroimaging finding ($n = 5$, 55.6% vs $n = 46$, 22.5% respectively, $P = 0.04$). Initially conceptualized as a pure "motor regulatory" center, the basal ganglia has been demonstrated in recent studies to be a key component in various language functions, including phonology processing, language learning, semantic functions, and procedural memory involved in mental grammar [17-23]. According to a study by Moro et al., the left caudate nucleus appears to be activated with syntactic processing [21]. Booth et al., through dynamic causal modeling, found that the putamen exhibits unidirectional modulatory influence on the inferior frontal gyrus and the lateral temporal cortex, both cortical structures involved in phonologic processing [17]. Furthermore, a recent study that used [^{11}C] raclopride and positron emission tomography by Tettamanti et al. postulates that the striatal dopaminergic pathway is an essential component of human language, playing a fundamental role in grammatical processes involving the level of accuracy and speed of phonologic processing [22]. Through their complex connections, subcortical gray matter appears critical to the facilitation of language. It is therefore reasonable to suspect that verbal communication would be impaired with deep gray matter injury, as indicated by our results. Although the exact clinicoanatomic substrate has yet to be fully elucidated, our finding is consistent with recent functional evidence that verbal communication capacity and deep gray matter integrity are intertwined.

When comparing the mean number of comorbidities associated with each neuroimaging finding category, we again found an association with deep gray matter signal abnormality or volume loss. This particular neuroimaging finding category was found to have a higher mean number of comorbidities for any given patient with this scan result in comparison to children with any other scan result (1.67 vs 0.70 respectively, $P < 0.01$). Whether for language or many other higher cognitive functions, there is mounting evidence for the major role played by the subcortical gray matter in these functions [17-23]. With deep gray matter being a well-recognized integrator for wide-ranging numerous higher cerebral functions, lesions affecting this particular area of the brain can be expected to result in a higher mean number of comorbidities, as identified in our study, than lesions to regions exhibiting as critically important, but more specific, restricted roles.

Despite a large cohort of children with cerebral palsy, the number of individuals with each comorbidity was rather small for each neuroimaging finding category. Thus, these small numbers might have precluded our study from capturing a small effect, including the slightly surprising finding that the associations between the inability to communicate verbally and a higher mean number of comorbidities with deep gray matter injury were not similarly statistically significant for diffuse deep gray injury. Larger prospective studies would contribute to further elucidation of this question. Unfortunately, we did not have a central review of the neuroimaging studies to ensure the reliability of the different university-based pediatric neuroradiologists. Furthermore, our study did not allow

Table 3. Frequency of comorbidities distributed by neuroimaging finding

Neuroimaging Finding	Cortical Blindness ($n = 21$)	Severe Auditory Impairment ($n = 27$)	Inability to Communicate Verbally ($n = 51$)	Feeding via Gavage ($n = 18$)	Afebrile Seizure in the Prior 12 Months ($n = 38$)
PVL/PVWMI ($n = 41$)	3 (7.3%)	4 (9.8%)	5 (12.2%)	2 (4.9%)	6 (14.6%)
Cerebral malformation ($n = 24$)	4 (16.7%)	6 (25.0%)	8 (33.3%)	4 (16.7%)	5 (20.8%)
Cerebral vascular accident ($n = 25$)	3 (12.0%)	1 (4.0%)	3 (12.0%)	2 (8.0%)	8 (32.0%)
Deep brain GMI ($n = 9$)	2 (22.2%)	3 (33.3%)	5 (55.6%)	1 (11.1%)	4 (44.4%)
Superficial brain GMI ($n = 7$)	2 (28.6%)	1 (14.3%)	3 (42.9%)	2 (28.6%)	1 (14.3%)
Diffuse GMI ($n = 31$)	3 (9.7%)	4 (12.9%)	10 (32.3%)	2 (6.5%)	6 (19.4%)
Intracranial hemorrhage ($n = 5$)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infection ($n = 3$)	0 (0.0%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)
Nonspecific ($n = 40$)	2 (5.0%)	4 (10.0%)	10 (25.0%)	4 (10.0%)	5 (12.5%)
Normal ($n = 28$)	2 (7.1%)	3 (10.7%)	6 (21.4%)	1 (3.6%)	3 (10.7%)

Abbreviations:
GMI = Gray matter injury
PVL = Periventricular leukomalacia
PVWMI = Periventricular leukomalacia white matter injury

Table 4. Comorbidities (range 0-4) stratified by neuroimaging result

Neuroimaging Finding	Mean ± S.D.
PVL/PVWMI ($n = 41$)	0.49 ± 0.925
Cerebral malformation ($n = 24$)	1.13 ± 1.076
Cerebral vascular accident ($n = 25$)	0.68 ± 1.180
Deep brain GMI ($n = 9$)	1.67 ± 1.414
Superficial brain GMI $n = 7$)	1.29 ± 1.890
Diffuse GMI ($n = 31$)	0.81 ± 1.138
Intracranial hemorrhage ($n = 5$)	0.00 ± 0.000
Infection ($n = 3$)	0.67 ± 0.577
Nonspecific ($n = 40$)	0.63 ± 0.925
Normal ($n = 28$)	0.54 ± 0.916

Abbreviations:
GMI = Gray matter injury
PVL = Periventricular leukomalacia
PVWMI = Periventricular leukomalacia white matter injury

us to capture the entire spectrum of comorbidities associated with cerebral palsy. With our study designed to evaluate severe comorbidities, we included neither milder forms of these comorbidities nor all of the potential comorbidities that can arise in the context of cerebral palsy. As stated previously, our cohort was too young (ages 2-5 years) to permit reasonable and confident behavioral and cognitive assessments. Perhaps a follow-up study with more long-term assessments, including neuropsychologic evaluations, of the same children would provide us with the data necessary to complement our prediction of the occurrence of potential comorbidities. By using our design, we identified the children most in need, but we inherently underestimated the number of children who would certainly experience comorbidities and who would benefit from early intervention.

Scan results other than deep gray matter injury were not linked to any particular pattern of comorbidities, perhaps because of our classification of neuroimaging findings. Indeed, our participants' cerebral imaging contained a similar incidence of abnormalities in comparison to European, western Swedish, and Australian cohorts as previously reported [4,24-26]. We obtained a similar distribution to that found in the Swedish and Australian studies with the exception of slightly less periventricular white matter injury and a mild increase in nonspecific results [24,25]. In comparison to the European cohort, we obtained a higher frequency of cerebral vascular accidents and cerebral malformations [26]. However, because of variations between the classification schemes used in these different studies, it is difficult to determine whether the actual population differs. A different classification scheme could have altered the numbers included. Interestingly, children with a normal neuroimaging study were not less likely to have comorbidities. Their mean number of comorbidities was not significantly less than children with an abnormal neuroimaging finding. The same was found for children with a normal or nonspecific neuroimaging finding grouped together and compared to any other scan results as a group. This information might help us in guiding families about a possible falsely reassuring "normal" neuroimaging study.

Conclusion

Despite its limitations, our population-based study has demonstrated that one neuroimaging finding was found to correlate with both the presence of a specific comorbidity and a higher mean number of comorbidities: deep gray matter injury was linked with the inability to communicate verbally and was also associated with an increased overall burden of comorbidities. In combination with clinical history, sequential physical and functional evaluations, and other specialized investigations when appropriate, these findings improve our ability to prognosticate the outcome of children with cerebral palsy, thus permitting early direct interventions and providing an added benefit to the prior recommendation by the American Academy of Neurology and the Child Neurology Society of performing routine neuroimaging on all cerebral palsy patients [2]. Its potential widespread application coupled with studies like ours may ultimately lead to a better outcome for these individuals.

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