The Origin of the Cerebral Palsies: Contribution of Population-Based Neuroimaging Data

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Abstract

Background Surveillance of cerebral palsy in Europe (SCPE) presents the first population-based results on neuroimaging findings in children with cerebral palsy (CP) using a magnetic resonance imaging classification system (MRICS).

Method MRIs of children with CP born between 1999 and 2009 from 18 European countries were analyzed. MRICS identifies patterns of brain pathology according to timing during brain development which was analyzed with respect to CP subtypes and gestational age.

Results MRIs or written reports from 3,818 children were available. The main clinical characteristics were similar to the 5,415 without such data. Most frequent was predominant white matter injury (49%), followed by predominant gray matter injury (21%). Maldevelopments were found in 11% of cases. Miscellaneous findings were present in 8.5% and normal findings in 10.6%. MRI patterns of children with unilateral spastic, bilateral spastic, and dyskinetic CP were mainly lesional (77, 71, and 59%, respectively), whereas children with ataxic CP had more maldevelopments, miscellaneous, and normal findings (25, 21, and 32%, respectively). In children born preterm, predominant white matter injury was most prevalent (80% in children born <32 weeks of gestation).

Conclusion Analysis of MRI in the European CP database identified CP as a mainly lesional condition on a large population basis, maldevelopments were relatively uncommon. An exception was ataxic CP. Children born preterm mostly presented with a lesion typical for their gestational age (GA) at birth. The decreasing prevalence of CP in this group suggests that progress in perinatal and neonatal medicine may lead to a reduction of these lesions.

Keywords
- magnetic resonance imaging
- classification
- cerebral palsy

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Introduction

SCPE (Surveillance of Cerebral Palsy in Europe) is a network of population-based cerebral palsy (CP) surveys and registers that extends across Europe. It was set up in 1998 to monitor trends in CP rate and provide a framework for collaborative research.[1] In a first step, harmonization of definitions with respect to clinical features was obtained and a classification based on neurological signs suggested. SCPE then set up a common database with harmonized data from population-based registries.[2] With these solid data, it was possible to monitor trends and prevalence over time and to show for the first time that the prevalence rate of CP is decreasing in Europe driven by a decrease in preterm CP.[3,4]

Magnetic resonance imaging (MRI) is abnormal in more than 80% of children with CP, disclosing the pathogenic pattern responsible for the CP, which is mainly lesional.[5–7] There is consensus on an international basis, that cerebral MRI is an important tool in the assessment of a child with CP. MRI is recommended as the first diagnostic step after medical history taking and neurological examination. To systematically collect MRI data on a population basis, SCPE developed a classification system for MRI findings to be used in CP registers (MRICS). A teaching tool to improve knowledge on MRI was elaborated (www.scpenetwork.eu; https://eu-rd-platform.jrc.ec.europa.eu; MRI chapter of the SCPE reference and training manual [RTM]). The MRICS was proven to be applicable by CP registers and reliable.[8] This paper presents the first population-based results on neuroimaging findings in children with cerebral palsy on a European level, using the MRICS.

Aims

- The primary aim of this study was to analyze MRI patterns with respect to CP subtypes, as well as to gestational age (GA), and birth weight (BW) groups with the hypotheses that (1) lesional patterns are predominant, (2) lesions typical for the early third trimester are predominant in preterm children with CP, (3) patterns indicating genetic or early pregnancy compromise are rare and observed mainly in term-born children, and (4) ataxic CP is different from other subtypes and shows mainly patterns indicating genetic or early pregnancy compromise and nonspecific or normal results. These hypotheses are based on results from smaller CP studies that already dealt with these issues.[5,7] The questions here were whether this holds true for a large population-based European dataset and whether neuroimaging data collected on such a large scale can give meaningful results.
- In addition, several questions referring to the representativeness and quality of data were addressed. Children with CP may be offered neuroimaging, mostly when severely affected or when uncommon etiologies are suspected. Thus, the analysis of patterns indicating specific pathology and timing may not be representative for the whole CP population. Therefore, children who had MRI were compared with those without with respect to CP subtype, severity of CP, and GA.
- SCPE recommends performing MRI in children with CP after the age of 2 years when myelination is completed. If MRI is performed earlier and findings are unspecific or normal, it is recommended to repeat imaging after the age of 2 years, as mild lesions might have been missed.[8] SCPE, therefore collects only the results from the latest imaging if several were performed. However, the latest MRI may have been done before 2 years of age. Therefore, we looked at whether nonspecific or normal findings were more prevalent in children with an early MRI.
- Cerebral palsy with a very mild motor impairment (gross motor function classification system [GMFCS] level I[9]) may represent a more nonspecific etiological group, especially if the rigorous neurological definition is not applied. We wanted to know whether, in these children with GMFCS I, nonspecific or normal findings were more often found than in children with more severe CP.

Methods

Participants

Information on children with CP was provided by population-based registers participating to the SCPE collaboration. Methods, definitions, and criteria used by participating registers are detailed in other publications.[1,2] Data of children with CP from birth years 1999 to 2009 were analyzed. We excluded children with a postneonatal cause for CP.

Studied Characteristics

The following characteristics for children with CP were analyzed: BW and GA, CP subtypes classified into unilateral and bilateral spastic CP, dyskinetic CP and ataxic CP, gross and fine motor impairment classified according to GMFCS and bimanual fine motor function (BFMF), intellectual impairment according to intelligence quotient (IQ) levels (here, $IQ > 50$ and ≤ 50 is addressed), visual impairment, hearing impairment, and epilepsy.

Data on MR Imaging

Only images performed postneonatally were considered, that is, when MRI was performed after the age of 4 weeks. The MRICS classifies (A) maldevelopments (A1, disorders of cortical formation; A2, other maldevelopments), (B) predominant white matter injury (B1, periventricular leukomalacia; B2, sequalae of intraventricular hemorrhage or periventricular hemorrhagic infarction; and B3, combination of B1 and B2), and (C) predominant grey matter injury (C1, basal ganglia/thalamus lesions; C2, corticosubcortical lesions only not covered under C3; and C3, arterial infarctions), as well as (D) miscellaneous, and (E) normal findings.[8] Examples of miscellaneous findings are cerebellar atrophy, cerebral atrophy, delayed myelination, ventriculomegaly not covered under B, hemorrhage not covered under B, brainstem lesions, and calcification. In the registers, either MRIs directly or written reports are classified, both of which have been validated.[8] In addition, the SCPE common database includes age at imaging and gives the option for clear text on MRI findings. Each register enters MRI according to MRICS, the data then are checked at each annual submission

by a group of three pediatric neurologists with specific expertise in MRI (K.H., V.H., and I.K.M.). In case of incongruity, additional information may be requested from the registers and the category corrected accordingly.

Data Analysis

Variables are presented as frequencies and percentages. Comparisons were performed using Chi-square test. The following comparisons were performed:

- Characteristics of children with MRI versus those without MRI. Children recorded as having had an MRI but without known results were included in the latter group.
- MRI patterns in children with imaging done before versus after 2 years of age.
- MRICS according to CP subtypes, BW, and GA groups.
- MRICS in children with GMFCS level I versus levels II to V.

Statistical analyses were performed using Stata Statistical software (version 10.0, Stata Corp., College Station, Texas, United States).

Results

Data from 20 registers across Europe for birth years 1999 to 2009 were used in these analyses. In 3,818 cases, a postneonatal MRI or written report was available and classified. 5,415 children had no data on MRI, this included 293 children recorded as having had a MRI but the results were not known.

Characteristics of children with MRI results and children without MRI results (►**Table 1**): clinically meaningful findings were the higher rates of missing values in the group without MRI results. Children with MRI were more often born at term (53.4 vs. 44.2%) or of normal BW (52.8 vs. 42.8%), but the distribution of CP subtypes was rather similar. Interestingly, children with milder impairment (GMFCS levels I and II and IQ > 50) were more frequent in the group with MRI than those without MRI, 59.3 and 60.1 versus 47.7 and 49.4%.

Age at postneonatal MRI (►**Table 2**): in 1,720 children (45%), MRI was performed before 2 years of age. Median age at MRI in this group was 12 months (interquartile range [IQR]: 8–16). In 1,859 children (48.7%), MRI was done at the age of 2 years or later. In 239 cases (6.3%), age at MRI was unknown. A similar percentage of children with miscellaneous findings were found in the group with MRI performed before 2 years versus after 2 years of age (8.9 vs. 8.3%). Normal findings were less frequently found in the group with MRI before 2 years of age compared with those performed after 2 years (7.5 vs. 13.4%).

Distribution of MRI patterns: is presented in ►**Fig. 1**. Nearly half of the children had a predominant white matter injury.

The distribution of imaging patterns in CP subtypes: is presented in ►**Fig. 2**. In children with unilateral spastic CP, predominant white matter injury was most prevalent (47.3%), followed by predominant gray matter injury in 30.1%. Maldevelopments, miscellaneous, and normal findings represented each less than 10%.

Table 1 Comparison of characteristics between children with an MRI result and children without MRI result

	Children with MRI result $n = 3,818$ (%)	Children without MRI result $n = 5,415$ (%)	*p*-Value
Gestational age <37 weeks	1,568 (41.1)	2,161 (39.9)	<0.001
Gestational age ≥37 weeks	2,039 (53.4)	2,392 (44.2)	
Unknown	211 (5.3)	862 (15.9)	
Birth weight < 2,500 g	1,556 (40.8)	2,144 (39.6)	<0.001
Birth weight ≥ 2,500 g	2,017 (52.8)	2,318 (42.8)	
Unknown	245 (6.4)	953 (17.6)	
CP subtype			
Bilateral spastic	1,930 (50.5)	2,793 (51.6)	<0.001
Unilateral spastic	1,320 (34.6)	1,692 (31.2)	
Dyskinetic	331 (8.7)	404 (7.5)	
Ataxic	154 (4.0)	184 (3.4)	
Unknown	83 (2.2)	342 (6.3)	
GMFCS III, IV, or V	1,469 (38.5)	1,964 (36.3)	<0.001
GMFCS I, II	2,264 (59.3)	2,585 (47.7)	
Unknown	85 (2.2)	866 (16.0)	
BFMF III, IV, or V	1,014 (26.6)	1,062 (19.6)	<0.001
BFMF I, II	1,778 (46.6)	1,798 (33.2)	
Unknown	1,026 (26.9)	2,555 (47.2)	
Severe intellectual impairment	1,119 (29.3)	1,328 (24.5)	<0.001
IQ > 50	2,295 (60.1)	2,674 (49.4)	
Unknown	404 (10.6)	1,413 (26.1)	
Epilepsy	1,395 (36.5)	1,569 (29.0)	<0.001
No epilepsy	2,269 (59.4)	2,882 (53.2)	
Unknown	154 (4.0)	964 (17.8)	
Known to have severe visual impairment	318 (8.3)	460 (8.5)	0.77
Known to have severe hearing impairment	104 (2.7)	121 (2.2)	0.13

Abbreviations: BFMF, bimanual fine motor function; CP, cerebral palsy; GMFCS, gross motor function classification system; IQ, intelligence quotient; MRI, magnetic resonance imaging.

Table 2 Distribution of MRI patterns according to age <2 versus ≥2 years, $p < 0.001$

	<2 years old $n = 1,720$	≥2 years old $n = 1,859$
A	212 (12.3)	180 (9.7)
B	789 (45.9)	958 (51.5)
C	437 (25.4)	317 (17.0)
D	153 (8.9)	155 (8.3)
E	129 (7.5)	249 (13.4)

Abbreviation: MRI, magnetic resonance imaging.

In children with bilateral spastic CP, predominant white matter injury was most common (58%), followed by predominant gray matter injury (13.4%). Maldevelopments and normal findings accounted for less than 11% each.

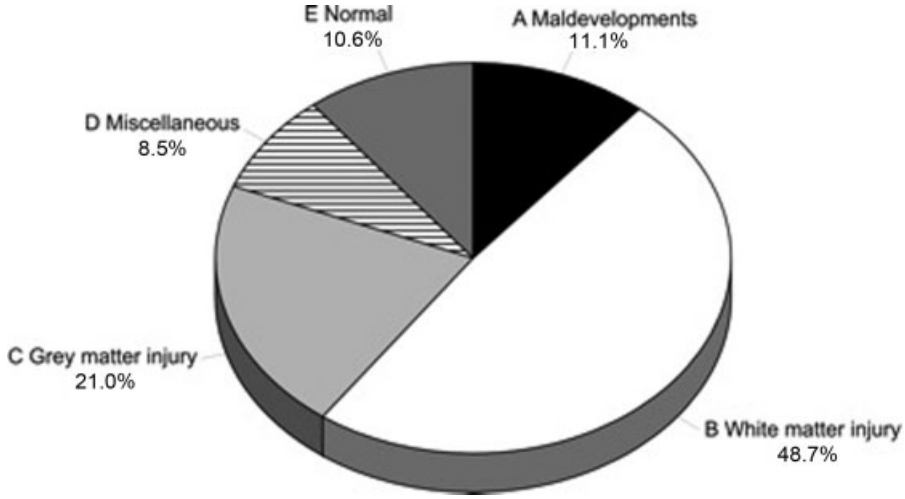

Fig. 1 Distribution of MRI patterns, $n = 3{,}818$ cases. MRI, magnetic resonance imaging.

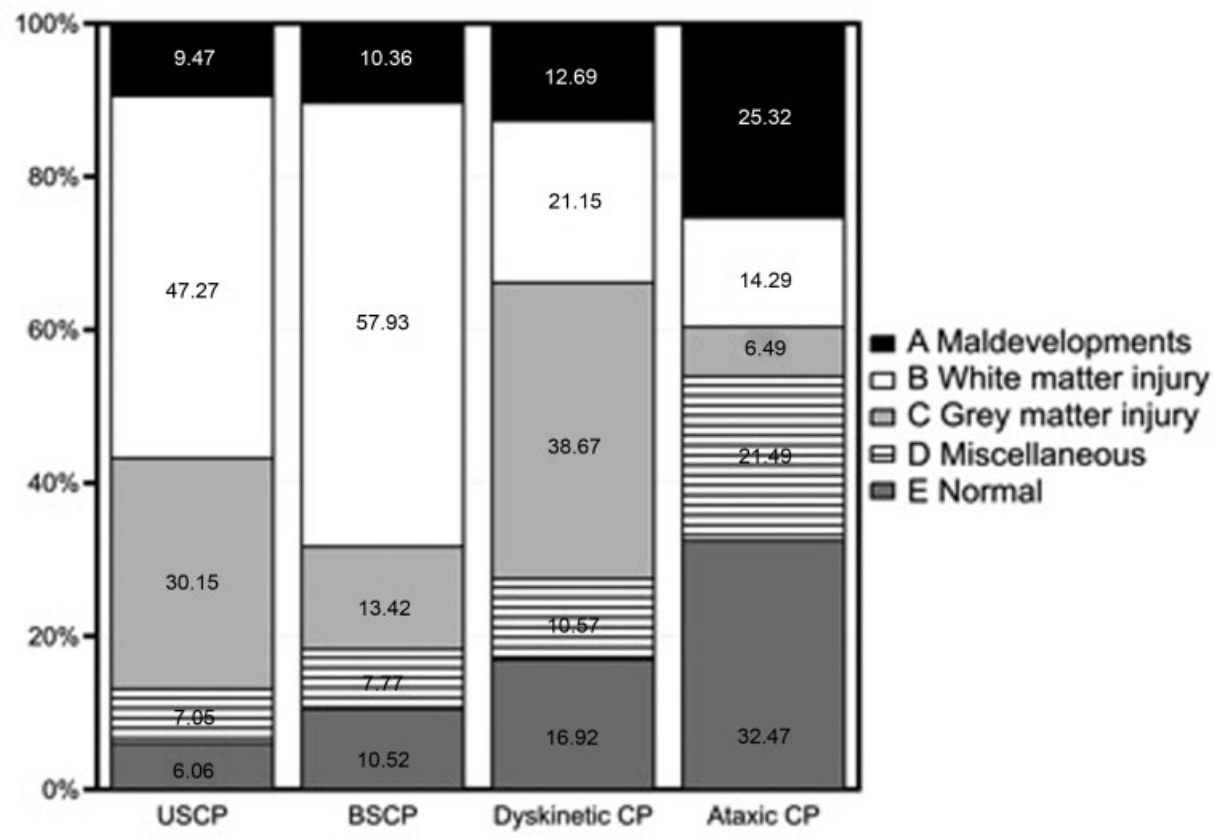

Fig. 2 Distribution of MRI patterns in CP subtypes; USCP (unilateral spastic CP) $n = 1{,}320$, BSCP (bilateral spastic CP) $n = 1{,}930$, dyskinetic CP $n = 331$, ataxic CP $n = 154$. CP, cerebral palsy; MRI, magnetic resonance imaging.

In children with dyskinetic CP, predominant gray matter injury was most common with 38.7%, while predominant white matter injury was found in 21.1%. Normal findings accounted for 17% of cases.

In the group of ataxic CP, normal findings were most frequent with 32.5%, followed by maldevelopments in 25.3%, and miscellaneous findings in 21.4%.

The distribution of imaging patterns in GA groups: is presented in ►**Fig. 3**. In children born preterm before 32 weeks of gestation, predominant white matter injury was most prevalent, seen in around 80%. With increasing gestational age, this pattern was seen less often and predominant gray matter injury increased. Similarly, there was an increasing percentage of maldevelopments, miscellaneous, and normal findings.

The distribution of imaging patterns in BW groups showed a similar distribution of MRI patterns (results not shown here).

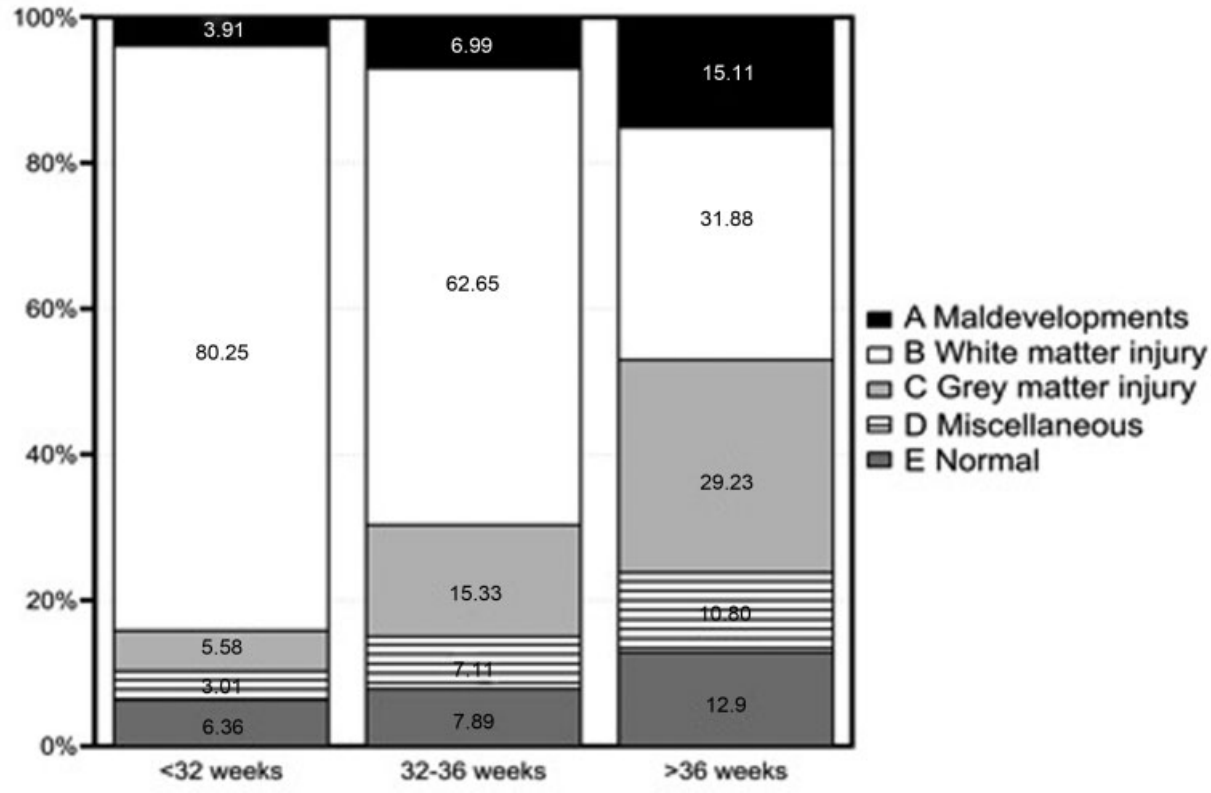

Fig. 3 Distribution of MRI patterns in gestational age groups. (<32 weeks: $n = 896$, 32–36 weeks: $n = 672$, >36 weeks: $n = 2{,}039$). MRI, magnetic resonance imaging.

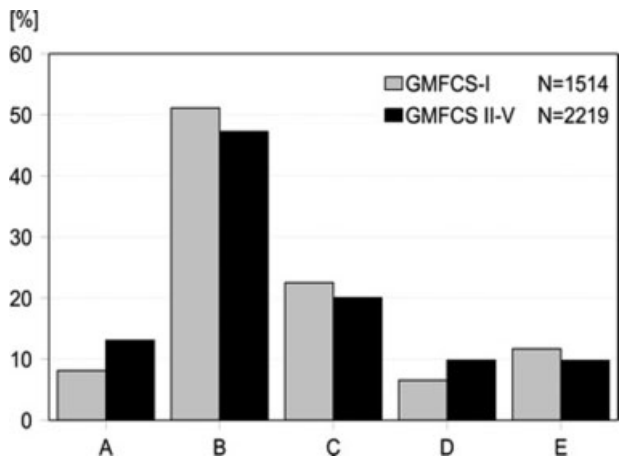

Fig. 4 Distribution of MRI patterns in GMFCS I versus II–V (A: maldevelopments, B: white matter injury, C: gray matter injury, D: miscellaneous, E: normal). GMFCS, gross motor function classification system; MRI, magnetic resonance imaging.

The distribution of MRI patterns in children with GMFCS I versus II to IV: is presented in ►**Fig. 4**. About 1,514 (40.6%) children with GMFCS level I and 2,219 (59.4%) with more severe motor impairment (GMFCS levels II–V) were compared. MRI patterns showed somewhat less maldevelopments and miscellaneous findings for the group with GMFCS I (8.1 and 6.5 vs. 13 and 9.7%). Normal findings were not much higher in the GMFCS I group (11.7%) than in the group with more severe motor impairment (9.8%).

Discussion

The effort of SCPE to harmonize language on CP has proven important not only for research purposes but also from a clinical point of view. Referring to CP according to SCPE standards means a condition which is clearly defined on the basis of phenomenology, subclassified according to neurological signs with severity reflected by functional scores. In this context, it was clear that neuroimaging was not considered a prerequisite for the diagnosis of CP. However, neuroimaging is often abnormal in children with CP, which helps to understand etiology or at least pathogenesis of the underlying brain disorder, and may also help to understand structure–function relationship.[10] However, this may not be available in all countries to the same extent. More importantly, a commonly agreed neuroimaging-based classification was missing.

As a step forward, SCPE developed a classification system for MRI findings to be prospectively used in registers, the MRICS, accompanied by a teaching tool to improve knowledge on MRI (www.scpenetwork.eu; https://eu-rd-platform.jrc.ec.europa.eu; MRI chapter RTM). MRICS was then validated before being used in the registers.[8]

In this paper, we present the first results on neuroimaging findings from the European database in children with CP born between 1999 and 2009, using the MRICS. MRI results were available in around 40% of children with CP. Main clinical characteristics were not very different between children with and without MRI. MRI was rather more often

performed in children born at term than in preterm born children (53 vs. 44%) which may be due to the fact that etiology is considered less clear in a child with CP born at term. Cranial ultrasound is often performed sequentially in preterm born children and gives also important information on brain compromise. Interestingly, children who had undergone an MRI had somewhat milder impairments (e.g., around 60% had an IQ > 50 vs. 50% in the group without MRI).

In the SCPE recommendations for when to perform an MRI, we suggest an age of two years and more, when ongoing myelination is less an issue. Also, an MRI considered as normal when done before two years of age, should be repeated, as especially mild gliosis indicating periventricular or basal ganglia/thalamic lesions might have been missed. In the data analyzed here, normal findings were found even less often when MRI had been done before 2 years of age. Thus, we consider our data presented here to be valid also from MRIs done during the first 2 years of life.

The hypothesis, that CP is mainly a lesional condition, was confirmed here on a large population basis. Predominant white matter injury (such as periventricular leucomalacia or sequelae of hemorrhage) and predominant grey matter injury (indicating hypoxia–ischemia, e.g., after asphyxia or neonatal encephalopathy or infarcts) accounted for 70% of all MRI patters in the 3,818 children. Brain maldevelopments, which may be due to genetic conditions but which can also be acquired during early pregnancy, only accounted for 11% of brain pathology.

When looking at CP subtypes, a lesional pathology was typical for children with spastic and dyskinetic CP, those with unilateral spastic CP showing a lesional pathology in nearly 80% followed by those with bilateral spastic CP and dyskinetic CP with around 70 and 60% each. Bilateral spastic CP is the typical CP type in a preterm born child,[4] which explains why predominant white matter injury was most prominent here, seen in nearly 60%. Dyskinetic CP occurs more often in the term-born child and is associated with deep gray matter lesions,[11,12] which are part of the predominant gray matter injuries, found here in nearly 40%.

Ataxic CP was an exception, with lesional pathology comparatively rare. It must be pointed out here, that cerebellar lesions typical for the extremely preterm child[13,14] are not specifically addressed in the MRICS, they are coded within the miscellaneous group. Whether they are to a large extent associated with ataxic CP is as yet not entirely clear, whereas their role for cognitive impairment has been clearly reported.[15] These data support the hypothesis that ataxic CP may pathophysiologically and etiologically be very different from other CP subtypes, showing mainly patterns indicating genetic or early pregnancy compromise, or nonspecific or normal results.

The results from the imaging patterns in GA groups give two important messages. First, maldevelopments were mostly found in term-born children with CP, indicating that an early compromise or genetic anomaly giving rise to a brain maldevelopment is rarely associated with preterm birth. Second, in preterm born children with CP predominant white matter injury, lesions typical for their GA at birth, were most prevalent. In children born <32 weeks of gestation, this was found in 80%. In the term-born group, lesions indicating a pathology typical for their GA at birth were found in only around 30%. In the European and also Australian CP registers, a decrease of CP prevalence in preterm born children has been consistently shown, leading in Europe to a decrease in overall CP prevalence.[3,4,16,17] Our data on neuroimaging findings may give an explanation as to why the prevalence of preterm children with CP can be influenced by progress in peri- and neonatal care, as lesions behind CP mostly have their origin in a period covering their GA at birth. In term-born children with CP, only around one-third have a lesion indicating an origin around birth, where quality and strategies of care may have an impact.

We were interested as to whether CP of different severities is characterized by different MRI patterns, and therefore analyzed MRI results in children with CP with GMFCS level I versus levels II to V. It is interesting that the differences were minor, somewhat more white matter lesions in children with GMFCS I and some more maldevelopments in those with more severe forms. This suggests that timing of a brain lesion/pathology is less a predictor for severity of motor impairment than its extent and exact topography. For our network it was especially reassuring to see that children with a CP of GMFCS level I were no more likely to have a normal MRI scan than those with more severe motor impairments, indicating that our classification on the basis of neurology is rigorous and reliable.

This is the very first analysis of neuroimaging findings in our network. We have not yet been able to look into subgroupings of the main pathological patterns that indicate different pathophysiology within the timing period, such as sequelae after bleeding versus periventricular leucomalacia in the B group or cortico-subcortical lesions versus basal ganglia thalamic lesions and stroke in the C group. Neither could we yet analyze uni- or bilaterality and different severities, which are part of the subclassification. With such additional parameters, more specific analysis with respect to pathophysiology and severity (also with respect to morphology–function relationship) could be addressed.

We would like to emphasize that the MRICS is primarily a classification system, which aims at characterizing brain pathology with respect to timing during brain development. The above-mentioned additional items go a step further into different pathophysiology within the same timing period and severity or extent of pathology. However, other systems aiming at even more detailed assessment of extent and topography of a lesion or maldevelopment could be used in addition, to quantify the findings.[18,19] We wanted to show here, however, that an approach on a population basis which refers not only to the analysis of the images themselves, but relies also on the classification of written medical records, is possible and gives meaningful results and can, hopefully, also be used in the future to illustrate changes over time.

Conflict of Interest
None declared.

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