Magnetic resonance imaging findings and the clinical characteristics of children with cerebral palsy at a public sector hospital in Gauteng South Africa

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Abstract:

Background.

Cerebral palsy (CP) is a common cause of physical impairment in children. Brain MRI can define different neuropathological patterns of brain injury in CP. There is limited data available on the MRI findings of children with CP in Africa.

Objective.

To describe the clinical characteristics, risk factors and MRI findings of children with CP attending a developmental clinic at a tertiary hospital in South Africa. To assess possible associations between the clinical characteristics and pathogenic neuroimaging patterns.

Methods.

This was a retrospective cross-sectional study. The cohort of 112 children were identified from the clinic's REDcap® database.

Clinical information was obtained from the existing medical records of the patients. Findings from the brain MRI reports were classified according to the MRI classification system (MRICS) for CP. The MRI reports were rated independently by two study investigators.

Descriptive analysis was conducted.

Results

A total of 112 patient files and MRI brain reports were reviewed. Spastic cerebral palsy was the most common type of CP (n=75%). The most common perinatal risk factors included prematurity (31%) and low-birth weight (28%). Nineteen (17%) children acquired CP after the neonatal period. CP sub-type showed a significant association with functional motor impairment classified as GMFCS, $p < 0.001$.

Predominant grey matter injury (PGMI) was the most common pathogenic MRI pattern identified (30%).

The radiological findings (MRICS) had a significant association with both the CP sub-type ($p<0.005$) and functional impairment according to GMFCS ($p<0.001$).

Conclusion

Standardized classification of neuro-imaging findings can assist in defining the pathogenesis and clinical manifestations of CP.

Introduction

Cerebral palsy (CP) is one of the most common causes of significant physical impairment in children world-wide with an estimated prevalence of 2-10 per 1000 live births in Africa.[1-2]

To date CP remains a clinical diagnosis.[1]Although neuroimaging is not a prerequisite for the diagnosis of CP, it assists in determining the onset of the brain insult and possible aetiology.[1, 3-5] Both the American Academy of Neurology (AAN) and the 2017 NICE guidelines recommend that neuroimaging should be done if the aetiology of CP is unknown, MRI is the preferred diagnostic modality. [6-7] MRI at term gestation has also proven to be useful in predicting CP in high-risk patients such as premature infants with a sensitivity range of 86-100% and specificity range of 87-97%.[4]

Neuroimaging assists in defining different neuropathological patterns including congenital malformations and various destructive lesions of white and grey matter.[3,5-6] In a review by Krägeloh-Mann and Horber, the incidence of these pathogenic patterns was periventricular white matter injury (56%), deep grey matter injury (18%) and congenital malformations (9%).[5]

Research has demonstrated an association between structural brain lesions and the CP motor subtype. [8-10] A systematic review by Franki et al. published in 2020 concluded that more research is required to establish the relationship between structural brain pathology and functional outcome in CP.[11]

Inconsistent use of terminology and radiological descriptions makes it difficult to compare research findings.[3] As a result, the Surveillance of Cerebral Palsy in Europe (SCPE) network developed a classification system for neuroimaging findings in CP. The MRI classification system for children diagnosed with CP (MRICS) was developed by integrating classification systems used in previous research and harmonizing terminology used in these different classifications. It is based on pathogenic neuroimaging patterns that are related to the timing of brain compromise and are mainly qualitative in nature. The MRICS has been proven to be a useful and reliable tool. It can be applied by looking at the images directly or by scoring the radiology report, and importantly, the user does not need to be a trained radiologist.[12] The goal of the MRICS is to establish a common language when describing MRI findings in individuals with cerebral palsy.

Although it is postulated that CP is more prevalent in Africa with a larger proportion of more severely disabled children compared to high-income (HI) countries, data is limited. [2,13] There are very few MRI-studies reporting the neuroimaging findings of children with CP in Africa.

In the present study we described the clinical characteristics, risk factors and functional impairment of a cohort of patients diagnosed with CP attending a developmental clinic at a tertiary hospital in South Africa. Pathogenic imaging patterns described on the MRI reports of the cohort were classified according to the MRICS and possible associations between the clinical characteristics and pathogenic neuroimaging patterns were examined.

Methods

Study design and setting

A retrospective, cross-sectional study was conducted on a cohort of patients with CP attending a developmental clinic at a Gauteng tertiary academic hospital in South Africa. Data was collected from the time-period February 2016 to December 2019.

Study population

Currently, all patient information is captured electronically onto a Redcap database at the developmental clinic. The cohort included children over the age of two years, with a diagnosis of CP on the REDcap® database who had an MRI brain scan report available on the hospital PACS (Picture Archiving Communication System). A definitive diagnosis of CP can usually be made after the age of two years as the clinical picture may vary prior to this age, making the diagnosis challenging. [14] Ethical approval for the study was obtained from the University of the Witwatersrand, Johannesburg, South Africa. (Reference M1911112)

Measurements

Demographic information and medical history were obtained from the existing medical records of the patients. The 2006 consensus definition by Rosenbaum *et. al* was used to define CP.[1] The most recent clinical assessment documented in the medical records was used to describe the clinical profile of the patients. CP motor subtypes were classified based on the predominant motor disorder and anatomic distribution as spastic hemiplegia, spastic diplegia, spastic quadriplegia, dyskinetic, ataxic, or mixed CP. Clinical assessments were conducted by both developmental paediatricians and generalists with extensive experience in neurodevelopmental conditions.

Although literature describes multiple risk factors for CP in the prenatal, peri and post -natal period, we only included risk factors that could be identified retrospectively with certainty .[15-16] Prematurity was defined as birth before 37 weeks of completed gestation and extreme prematurity as birth before 28 weeks of gestation.[17] Low birth weight (LBW) was defined as a weight of less than 2500g at birth, very low birth weight (VLBW) as a weight of less than 1500g at birth and extremely low birthweight (ELBW) a weight of less than 1000g at birth.[17] Neonatal seizures were defined as seizures occurring in the first 28 days of life. Maternal HIV status was captured as positive/ negative/ unknown. Bilirubin encephalopathy was captured if the neonate had jaundice requiring exchange transfusion in the first three weeks of life. Post-neonatal adverse events were defined as a brain injury that occurred in a previously well-child after 28 days of life and included, traumatic brain injury, status epilepticus and meningitis.

CP functional impairment was based on the documented assessment of self-initiated movement abilities and classified according to the gross motor function classification scale (GMFCS) developed by Palisano et al.[18] This ordinal scale stratifies individuals with CP into 5 categories, with I being the most able, to V the least able to mobilize independently. The GMFCS was further stratified into GMFCS I-II, patients able to ambulate independently and GMFCS III-V, patients requiring assistive devices for mobility.

MRI reports obtained during routine care of the patients were accessed from the hospital radiology department PACS system. All the reports were anonymized. The MRI classification system (MRICS) for children with cerebral palsy developed by the SCPE network was used to classify the report findings.[12] The reports were viewed and scored independently by two investigators, both paediatricians. In cases with discrepant findings consensus was obtained through discussion with a third investigator who is also a paediatrician. The predominant pattern of injury that was most likely to have caused the CP was recorded as per the SCPE network recommendations. Pathogenic patterns identified in the reports were categorized into one of 5 headline levels (A, B, C, D, E) and if possible, at subgroup level as seen in **Table 1.** [12]

Statistical analysis

Descriptive statistics included medians and interquartile ranges for non-parametric distributed continuous variables and percentages for categorical variables. Interrater agreement was calculated using the kappa-statistic measure for two unique raters. Inferential statistics were performed by

means of contingency tables chi-square, Fisher's exact and Likelihood-ratio (LR) chi-squared test. One-way ANOVA was performed using the Kruskal-Wallis test for non-parametric data for more than two groups, or the Mann-Whitney test when two groups were compared. Statistical significance was set at $p<0.05$. All analyses were done using Stata 16.1 (Statacorp, Texas, USA)

Results

A total of 112 patient files and MRI brain reports were reviewed. There were 68 males and the median age at the time of the chart review was five years. **Table 2** describes the demographic information and characteristics of the cohort.

Perinatal findings

Among the infants born prematurely, 40% (14/35) were LBW, 17% (6/35) were VLBW and 6% (2/35) were ELBW. Four children were part of a multiple pregnancy and were born prematurely.

Risk factors

The most common risk factors identified for CP were prematurity (n=35, 31%) and low birth weight (n=31, 28%). Among the 19 children who acquired CP after the neonatal period, 11 (58%) had status epilepticus, 6 (32%) had meningitis and 4 (21%) had a head injury. One child had both meningitis and status epilepticus and another both status epilepticus and a head injury. Maternal HIV status was documented in 94 (84%) patients and 26 (23%) infants were born to mothers with HIV.

Clinical findings

Spastic cerebral palsy was the most common type of CP (n=74, 67%). The distribution of the functional motor impairment, GMFCS I-V and the CP subtypes is shown in **Table 3.** The association between the CP sub-types and GMFCS was significant (overall contingency table LR $Chi^2 = 79.8$, $p < 0.001$).

MRI findings

Almost one third of the brain MRIs were done before the age of two years (**Figure 1**), and of those four were reported normal. The ages at which the scans were done ranged from a minimum of 7.7 months to a maximum of 13 years with a median age of 3 years (IQR=3.5). A consultant radiologist reviewed the scans in 96% of cases.

The MRI reports were rated independently by two study investigators. The interrater agreement between the first and the second investigator was 78,1% (κ=0.7486, Z=21.65, p<0.001).

The distribution of MRICS categories in GA groups is presented in **figure 2**. Seventy-six percent of the patients (n=25) with PGMI were born at term. PWMI was also reported in more infants born at term (53%, n=16).

Seven cases (6%) had two pathogenic patterns and the investigators were unable to distinguish the predominant pattern based on the imaging report and clinical findings. All seven cases were both subcategories B1 (periventricular leukomalacia) and C1 (Basal ganglia/thalamus lesions), of those, six cases had mixed CP and one spastic quadriplegia. These cases were categorised separately as heterogeneous.

Predominant grey matter injury

PGMI was the most common MRI finding, of these patients, half of the cases presented with cortico-subcortical lesions (17/33, 52%) and 39% (13/33) had basal ganglia/thalamus lesions. Arterial infarctions were reported in only 3 patients. Neonatal seizures were statistically significantly more common in PGMI cases in proportion to other MRICS classifications (n=15, 60%) with a LR Chi^2 contribution = 21.3 (Overall contingency table model, LR=21.3, p < 0.002).

Predominant white matter injury

PWMI was the second most common imaging pattern reported in 27% (n=30) of cases. Ninety percent of these cases (n=27) had peri-ventricular leukomalacia reported as the most prominent finding. The largest proportion of infants born to HIV positive mothers (n=8, 32%) had MRI findings with predominant white matter injury.

Miscellaneous

Miscellaneous findings, including, cerebral and cerebellar atrophy, ventriculomegaly, brainstem lesions and calcifications were reported in (n=16, 14%) of cases. Almost two thirds of cases with miscellaneous findings were born at term (n=10, 63%) and had a normal birthweight (n=10, 63%) recorded.

Normal

Fifteen of the children (13.4%) had normal MRI results. Most were born at term (n=11, 73%) with normal birth weight (n=9, 60%).

Maldevelopments

Eleven of the children (10 %) had maldevelopments. Thirty six percent (n=4) were disorders of cortical formation.

Distribution of neuroimaging classification by CP subtype and level of motor impairment

There was a significant correlation between pathogenic patterns described on the MRI reports and the clinical CP subtype (LR Chi^2 contribution 47.3, $P < 0.004$). Children with PWMI on MRI were more likely to have spastic diplegia (LR Chi^2 contribution =9.7) whereas children with PGMI were more likely to present with dyskinetic CP (LR Chi^2 contribution =10.8).

MRI findings also had a significant correlation with functional motor impairment (GMFCS). Children with PGMI were more likely to be severely affected GMFCS IV-V (LR Chi^2 contribution = 16.3, $p < 0.001$).

The proportion of CP subtypes and functional impairment stratified into GMFCS I-II and GMFCS III-V in relation to the MRI classification is shown in **Table 4.**

Discussion

In this study we described the MRI findings according to the MRICS of children with CP attending a Developmental Clinic at a tertiary hospital in Johannesburg, SA. To our knowledge this is the first description of pathogenic MRI patterns, according to the MRICS, in a group of children with CP in Africa. A systematic review published by Donald et al. in 2014 indicated that previous CP studies from Africa had assessed primarily prevalence and aetiology. Donald et al. concluded that CP in Africa is more prevalent and has different aetiologies compared to high-income (HI) countries, with birth asphyxia, kernicterus, and neonatal infections most reported.[2] However, large gaps in the knowledge of CP in Africa remain.

The AAN recommends the use of MRI over Computerised Tomography (CT) to investigate CP, as the overall yield was found to be 89%.[5] Of the 112 MRI reports reviewed, imaging abnormalities were detected in 88% of the children. This is comparable with three population-

based studies from North America, Europe, and Australia, which reported an incidence of 86-89% imaging abnormalities in their patients.[9-10,19] A recent systematic review on structural neuroimaging in CP by Franki et al., reported 94% of patients as having MRI imaging abnormalities suggesting that better imaging quality has led to improved identification of brain lesions.[11]

In our cohort all CP subtypes were represented with the largest proportion (67%) having spastic cerebral palsy. Most brain lesions reported in the cohort were PGMI (n=33, 30%), followed by PWMI (n =30, 27%). The incidence of brain maldevelopments has been consistent between several studies ranging between 9.1-11.1%.[3,5,9-10,19] Similarly, 9.8% (n=11) maldevelopments was identified in our cohort.

Although the African literature on neuroimaging and CP is limited, a study done at a referral hospital in Uganda, Africa, also identified more PGMI (44%) in their cohort of children with CP.[20] CT imaging was utilized in this study which is known to have a poorer detection of white matter injury, therefore making a direct comparison to our findings challenging.[6,20] Evidence from HI countries indicate a much higher rate of PWMI, with 49% reported by Horber et al. and 19-45%, by Reid et al.[9,19] The population characteristics, associated risk factors for CP and imaging technique must be considered as an explanation for the neuroimaging differences between high- and low-income countries.

Interestingly, it was also noted that more than half (n=16, 53%) of PWMI was evident in term-born children in our cohort. Although this is not an uncommon finding the incidence reported in other cohorts is lower, ranging between 12-37%.[5,9-10,19,21] This type of lesion is usually associated with early third trimester brain injury and prematurity.[3,5,9,22] Intra-amniotic infection and inflammation are two mechanisms which have shown causality between the intra-uterine process and PVL in animal models.[16] This might indicate that some term born infants may have had an earlier brain insult which could be related to intra-uterine infection/inflammation. Rates of communicable diseases in Africa such as HIV/AIDS, tuberculosis, and malaria are the highest in the world. [23] It is also reported that adolescent girls and young women in Sub-Saharan-Africa have up to six times higher rates of HIV infection compared to male peers. [24] Although we could not show a significant association between maternal HIV infection and the MRICS findings, further

research may assist in explaining the unique profile of children with CP in Africa compared to HI countries.

In our present cohort, 31% of the children (n=35) were born prematurely. In comparison two cross-sectional studies from Benin in West Africa, and Uganda in East Africa indicated prematurity as a risk factor in only 7% and 13% respectively of their CP cohorts.[25-26] A recent population-based study on the clinical features and aetiology of CP in Nigeria published in 2020, reported premature birth in 8% of their cohort.[27]

Although the present analysis indicated a higher rate of prematurity (31%), it is less compared to the Pan- European cohort reported by Horber et al. (41%) and the systematic review by Franki et al., (44%). [11,19] The higher proportion of PGMI in our cohort as well as elsewhere in Africa is likely related to the poor survival of premature infants in Africa, as well as the relative under-representation of premature infants in our cohort. [2,28] Birth asphyxia and bilirubin encephalopathy, commonly reported aetiologies of CP in other African cohorts possibly also contribute to more PGMI findings in the literature.[13] Bilirubin encephalopathy is an important preventable cause of CP and a major cause of death and disability in low-income and middle-income countries.[29] Bilirubin encephalopathy was identified in 8% of our study participants.

Another important preventable factor contributing to the incidence of CP in Africa is post-neonatal complications. The 2020 population-based study from Nigeria indicated 36% post-neonatal risk factors in their cohort, with malaria with seizures accounting for 72% of the cases.[27] Post-neonatal complications were identified in 17% of our study participants, which was similar to the findings from Benin (17%) and Uganda (18%).[25-26] Malaria and seizures contributed to the post-neonatal complications in both these countries. It was noted that the upper age limit for acquiring post neonatal brain injury was not indicated in all the studies and this might affect the incidence in different populations.

We found a significant correlation between the radiological findings and both the CP-subtype ($p < 0.005$) and functional impairment according to GMFCS ($p < 0.001$). Further research would be needed to determine the relationship between specific brain lesions and fine motor impairment. As

indicated in the review article by Franki et al., a representative cohort of patients with possibly better imaging techniques are needed to confirm these results.[11]

The study-investigators in this study reported no difficulty in applying the MRICS to rate the radiological reports. The interrater reliability (κ) in our study was 0.78, which was similar to the original interrater reliability exercise for rating of the imaging reports (0.81).[12]

We identified seven cases with heterogeneous imaging findings where the predominant pattern was not clear in the report. All seven patients were severely affected with mixed CP and it is likely that both white and grey matter injury contributed to clinical picture. Large population- based studies would be required to also incorporate imaging findings at sub-group levels of the MRICS.

Study strengths and limitations

The strength of this study is that the imaging modality of choice, MRI, was used to assess pathogenic brain imaging patterns in CP according to the MRICS, a validated classification system, therefore, allowing better comparison with other CP cohorts. It also enabled us to delineate the relative contribution of PWMI and maldevelopments which is often not well visualized on CT brain imaging in our group of patients.

The study has several limitations. The patient cohort was identified at tertiary hospital-based specialist clinic and only patients with an MRI scan were included. It therefore introduced selection as well as sample bias. MRI is a costly investigation that is primarily available in tertiary centres in South Africa. It is usually reserved for patients with an unclear diagnosis, possibly explaining the relative underrepresentation of premature infants in our group of patients. Clinical information was obtained by retrospective chart review and some data was not well documented in the medical records. Although most of the MRI reports were reviewed by a qualified radiologist there were 4 reports which were not verified by a consultant due to staff constraints. Another limitation was that one third of the images (n=36, 32%) were done before the age of 2 years when brain myelination is not yet complete, therefore, subtle white matter injury, might have been missed.

Future directions

Future directions would include assessing the reliability of our rating of the MRI reports with ratings of the brain images according to the MRICS by paediatric radiologists. An editorial by Katangwe et al in 2020 advocated the need to establish a South African CP registry to collect quality data that can inform evidence-based care and preventative strategies for CP in South Africa.[30] The use of clear definitions and validated classification systems in CP will have an important role in establishing such a registry.

Conclusion

In conclusion CP is a common condition with multiple well described risk factors. However, the aetiology and pathogenesis often remain elusive despite thorough history and clinical examination. Brain MRI can assist to identify the pathogenic brain lesion and guide further investigation. Classifying the clinical and MRI findings according to validated classification systems has benefits for both individual patients and at population-level. We found a significant association between the radiological findings and clinical profile of our patient cohort which could assist in determining the risk of future disability and prognosis. The standardized classification of the brain lesions reported on MRI allowed us to compare our findings to international data. MRI findings can assist us to better understand the aetiology of CP in the African context and improve measures to prevent this important condition.

Declaration. The research for this study was done in partial fulfilment of the requirements for CN's master's degree from the University of the Witwatersrand.

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Author contributions**.** CN was responsible for collection of data, analysis of results and writing up of the article. CN, JB and HT were responsible for the study design, application of the MRICS to the study data and editing of the article. PM was responsible for statistics, analysis of results and editing of the article.

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Conflict of interest. None declared.

Table 1. MRI classification system for CP (MRICS) proposed by the Surveillance of Cerebral Palsy in Europe Network.[12]

A. Maldevelopments
    A.1. Disorders of cortical formation (proliferation and/or migration and/or organization)
    A.2. Other maldevelopments (examples: holoprosencephaly, Dandy Walker malformation, corpus callosum agenesis and cerebellar hypoplasia)
B. Predominant white matter injury
    B.1. PVL (mild/moderate/severe)
    B.2. Sequelae of IVH or periventricular haemorrhagic infarction
    B.3. Combination of PVL and IVH sequelae
C. Predominant grey matter injury
    C.1. Basal ganglia/thalamus lesions (mild/moderate/severe)
    C.2. Cortico-subcortical lesions only (watershed lesions in parasagittal distribution/ multi-cystic encephalomacia not covered under C3
    C.3. Arterial infarctions (middle cerebral artery/other)
D. Miscellaneous (examples: cerebellar atrophy, cerebral atrophy, delayed myelination, ventriculomegaly not covered under B, haemorrhage not covered under B, brainstem lesions, calcifications)
E. Normal

PVL, periventricular leukomalacia. IVH, intraventricular haemorrhage

Table 2 Demographics and characteristics of the study cohort (**N=112**)

	N	%
Age at time of chart review (years)		
2-3	14	13
3-5	43	38
>5	55	49
Sex		
Male	68	61
Gestation at Birth		
Term	77	69
GA 34-37 weeks	16	14
GA 28-34 weeks	15	13
GA <28 weeks	4	4
Multiple gestation		
Twins	5	5
Mode of delivery		
Vaginal delivery	73	65
Caesarean section	37	33
Assisted delivery	2	2
Birth weight		
Normal	69	62
Low birth weight	31	28
- Very-low birth weight	6	5
- Extreme low birth weight	2	1.8
Unknown (Not in records)	12	11
Perinatal risk factors		
Prematurity	35	31
Low birth weight	31	28
Maternal HIV infection	26	23
Neonatal seizures	25	22
Bilirubin encephalopathy	9	8
Post-neonatal risk factors		
Status epilepticus	11	10
Meningitis	6	5
Head injury	4	4
Cerebral palsy motor types		
Spastic hemiplegia	28	25
Mixed CP	24	21
Spastic diplegia	23	21
Spastic quadriplegia	23	21
Dyskinetic CP	11	10
Ataxic	3	3

GA, gestational age

Table 3. Distribution of GMFCS impairments in the different CP subtypes.

		GMFCS				
CP subtype		I	II	III	IV	V
Spastic Hemiplegia	n	5	20	3	0	0
n = 28 (25%)	%	18	71	11	0	0
Mixed CP	n	2	3	3	9	7
n = 24 (21%)	%	8	13	13	38	29
Spastic quadriplegia	n	0	3	3	8	9
n = 23 (21%)	%	0	13	13	35	39
Spastic diplegia	n	5	9	7	1	1
n = 23 (20%)	%	22	39	30	4	4
Dyskinetic CP	n	1	3	0	5	2
n = 11 (10%)	%	9	27	0	46	18
Ataxic CP	n	0	1	2	0	0
n = 3 (3%)	%	0	33	67	0	0

CP, Cerebral Palsy; GMFCS, Gross Motor Function Classification Scale

Figure 1: Number of children per age category that underwent MRI.

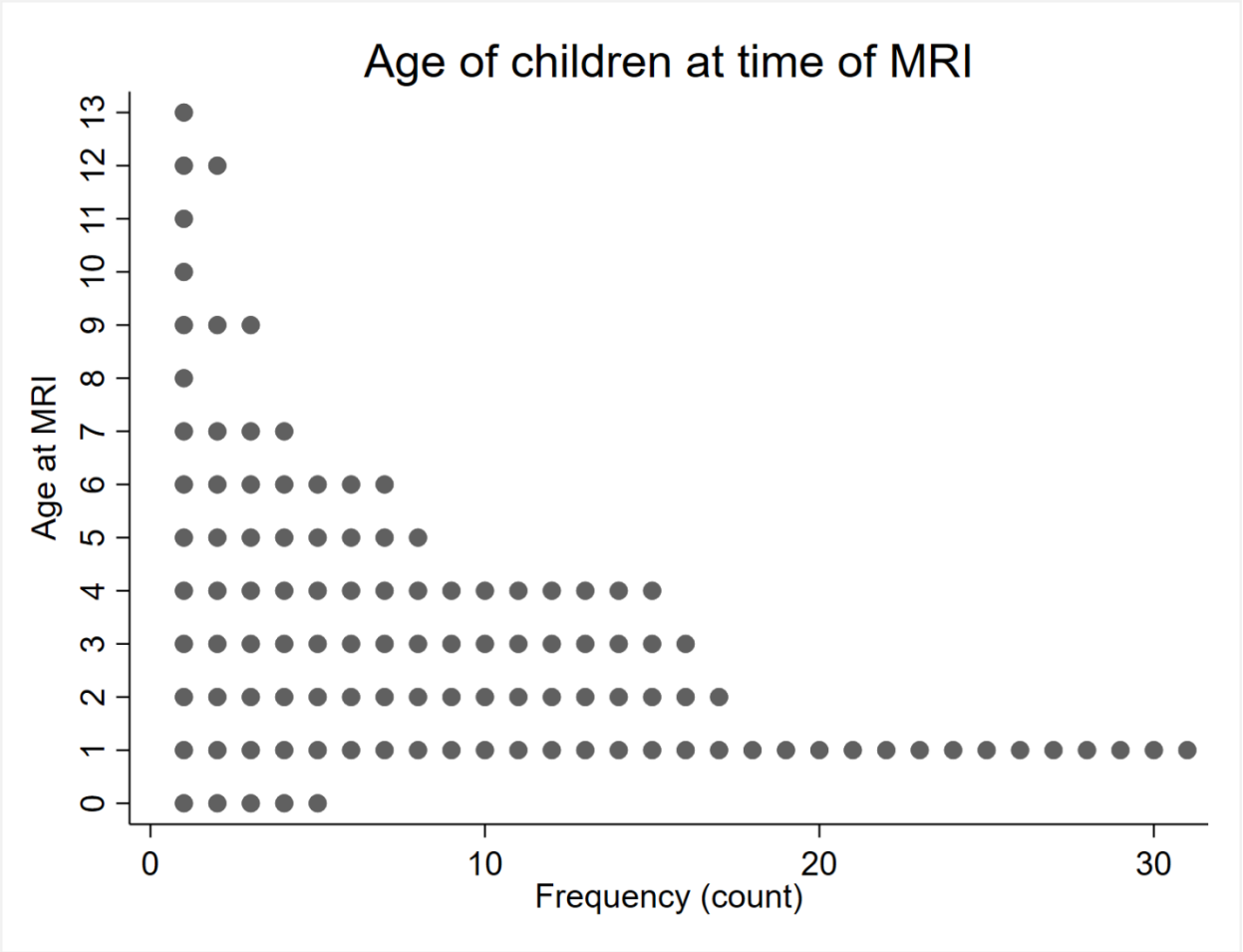

Figure 2. The distribution of the MRICS categories in infants born at term (>37 weeks) and prematurely (<37 weeks). N=112

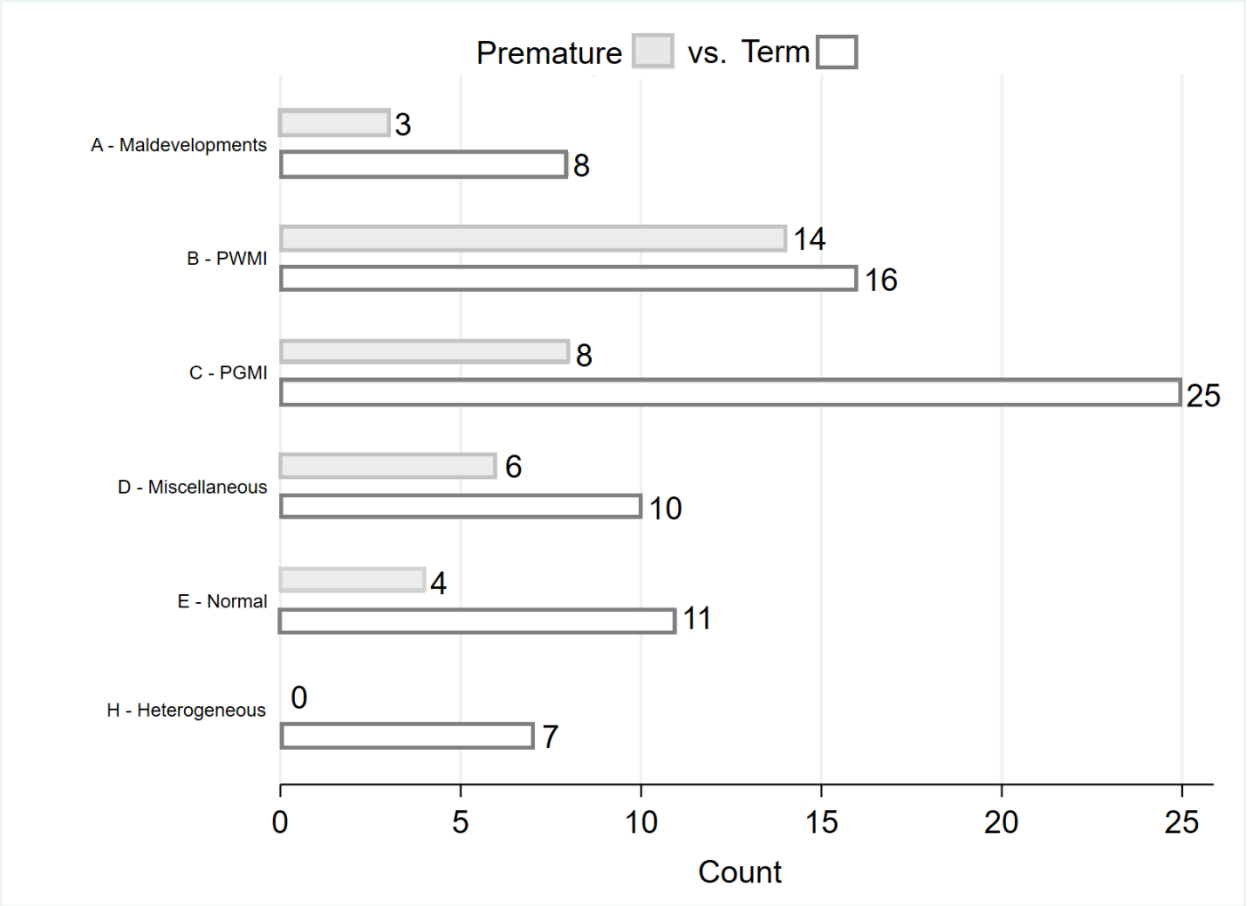

Table 4. CP subtypes and functional impairment in relation to MRICS patterns.

CP Subtypes		**MRICS**					
		A	B	C	D	E	Hetero geneous
Spastic hemiplegia n=28	n %	2 7	9 32	9 32	6 22	2 7	0
Mixed CP n=24	n %	1 4	3 13	8 33	3 13	3 13	6 25
Spastic quadriplegia n=23	n %	3 13	5 22	7 30	5 22	2 9	1 4
Spastic Diplegia n=23	n %	3 13	10 44	1 4	2 9	7 30	0
Dyskinetic CP N=11	n %	1 9	2 18	7 64	0	1 9	0
Ataxic CP n= 3	n %	1 33	1 33	1 33	0	0	0
GMFCS Subcategories							
I – II n = 52	n %	4 8	16 31	11 21	11 21	10 19	0
III – V n = 60	n %	7 12	14 23	22 37	5 8	5 8	7 12
A = Maldevelopments; B = Predominant White Matter Injury; C = Predominant Grey Matter Injury; D = Miscellaneous; E = Normal							

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