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

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Background. Cerebral palsy (CP) is a common cause of physical impairment in children. Brain magnetic resonance imaging (MRI) can define different neuropathological patterns of brain injury in CP. There are limited data available on 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; and to assess possible associations between the clinical characteristics and pathogenic neuro-imaging patterns.
Methods. This was a retrospective cross-sectional study. The cohort of 112 children was identified from the clinic's REDcap database. Clinical information was obtained from existing medical records of the patients. Findings from brain MRI reports were classified according to the MRI classification system (MRICS) for CP. The MRI reports were rated independently by two study investigators. A descriptive analysis was conducted.
Results. A total of 112 patient files and MRI brain reports were reviewed. Spastic CP was the most common type of CP (n=75%). The most common perinatal risk factors included prematurity (31%) and low birthweight (28%). Nineteen (17%) children acquired CP after the neonatal period. CP sub-type showed a significant association with functional motor impairment classified as per the gross motor function classification system (GMFCS), p<0.001. Predominant grey matter injury (PGMI) was the most common pathogenic MRI pattern identified (30%). The radiological findings (per MRICS) had a significant association with both the CP sub-type (p<0.005) and functional impairment according to the GMFCS (p<0.001).
Conclusion. Standardised classification of neuro-imaging findings can assist in defining the pathogenesis and clinical manifestations of CP.

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Cerebral palsy (CP) is one of the most common causes of significant physical impairment in children worldwide, with an estimated prevalence of 2 - 10 per 1 000 live births in Africa.[1,2]

To date, CP remains a clinical diagnosis.[1]Although neuro-imaging 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 neuro-imaging should be done if the aetiology of CP is unknown. Magnetic resonance imaging (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]

Neuro-imaging 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.*[11] published in 2020 concluded that more research is required to establish the relationship between structural brain pathology and functional outcome in CP.

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 neuro-imaging findings in CP. The MRI classification system for children diagnosed with CP (MRICS) was developed by integrating classification systems used in previous research and harmonising terminology used in these different classifications. It is based on pathogenic neuro-imaging 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 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 CP.

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

In the present study, we describe 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 in the MRI reports of the cohort were classified according to the MRICS and possible associations between the clinical characteristics and pathogenic neuro-imaging 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 were collected from the time-period of 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, and who had an MRI brain scan report available on the hospital picture archiving communication system (PACS). 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] Ethics approval for the study was obtained from the University of the Witwatersrand's Human Research Ethics Committee (ref. no. 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.*[1] was used to define CP. 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, and dyskinetic, ataxic or mixed CP. Clinical assessments were conducted by both developmental paediatricians and generalists with extensive experience in neurodevelopmental conditions.

Although the literature describes multiple risk factors for CP in the prenatal, peri- and postnatal periods, 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' gestation.[17] Low birthweight (LBW) was defined as weight <2 500 g at birth, very low birthweight (VLBW) as weight <1 500 g at birth, and extremely low birthweight (ELBW) as weight <1 000 g 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 five categories, with I being the most able, to V, the least able, to mobilise 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 reports were anonymised. The MRI classification system (MRICS) for children with CP developed by the SCPE network was used to classify 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 was 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 categorised into one of five headline levels (A, B, C, D, E) and, if possible, at subgroup level as shown 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 tests. 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., 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.

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 organisation)
  - 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.

Risk factors

The most common risk factors identified for CP were prematurity (*n*=35, 31%) and low birthweight (*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 CP 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 subtypes and GMFCS was significant (overall contingency table LR chi-squared=79.8, $p<0.001$).

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)
GA at birth, weeks	
Term	77 (69)
34 – 37	16 (14)
28 – 34	15 (13)
<28	4 (4)
Multiple gestation	
Twins	5 (5)
Mode of delivery	
Vaginal	73 (65)
Caesarean section	37 (33)
Assisted delivery	2 (2)
Birthweight	
Normal	69 (62)
Low	31(28)
Very low	6 (5)
Extremely low	2 (1.8)
Unknown (not recorded)	12 (11)
Perinatal risk factors	
Prematurity	35 (31)
Low birthweight	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)
CP 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; CP = cerebral palsy.

MRI findings

Almost one-third of the brain MRIs were done before the age of two years (Fig. 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 (interquartile range (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 Fig. 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 patients presented with cortico-subcortical lesions (*n*=17/33, 52%) and 39% (*n*=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-squared 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 periventricular 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.

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

CP subtype		GMFCS				
		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 (20%)	%	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.

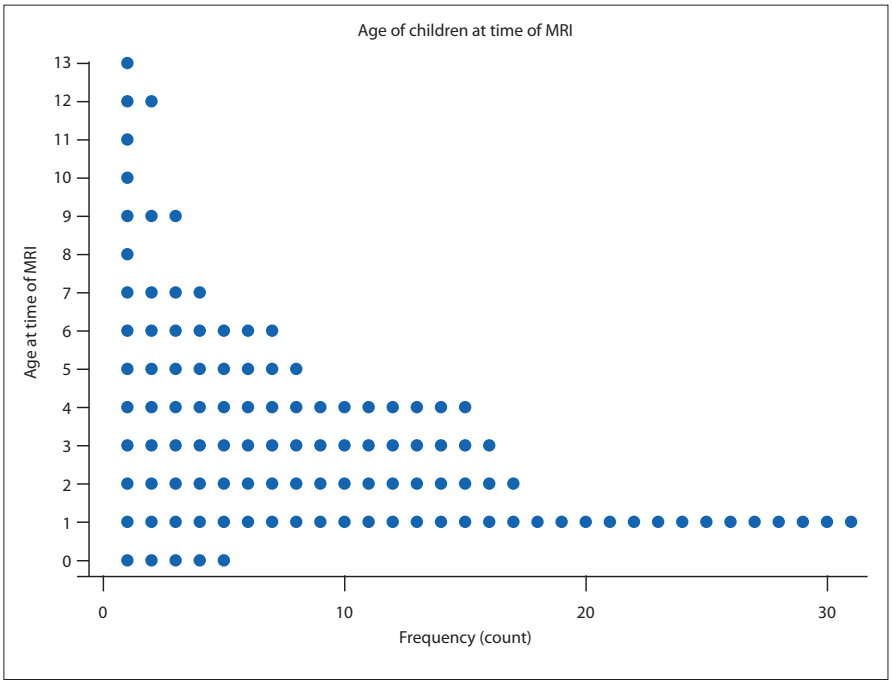

Fig. 1. Number of children per age category who underwent MRI.

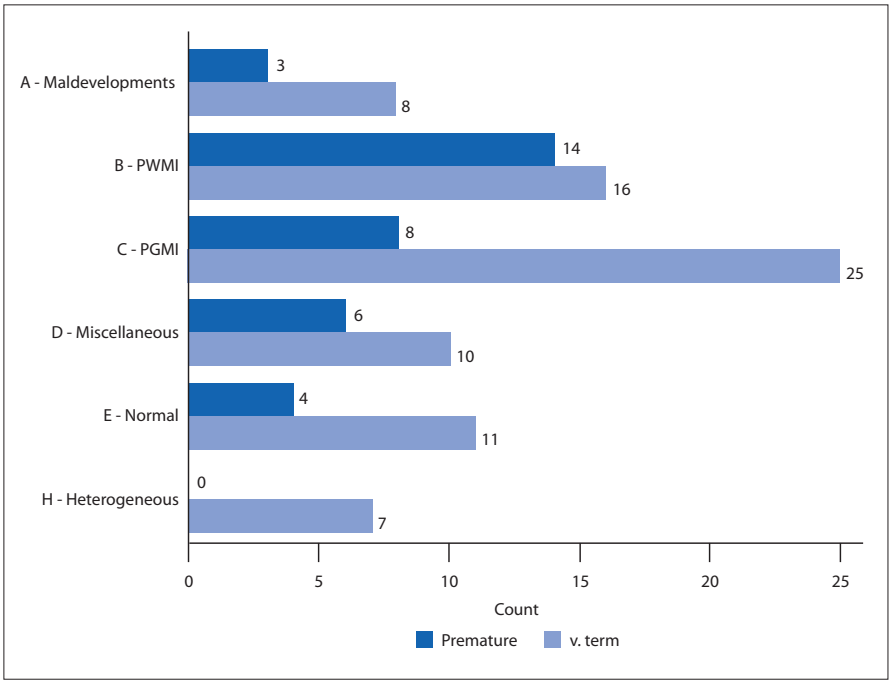

Fig. 2. Distribution of MRCIS categories in infants born at term (>37 weeks) and prematurely (<37 weeks), N=*112.*

Miscellaneous

Miscellaneous findings, including cerebral and cerebellar atrophy, ventriculomegaly, brainstem lesions and calcifications were reported in 16 (14%) of cases. Almost two-thirds of patients 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 birthweight (*n*=9, 60%).

Maldevelopments

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

Distribution of neuro-imaging classification by CP subtype and level of motor impairment

There was a significant correlation between pathogenic patterns described on MRI reports and the clinical CP subtype (LR *chi-squared* contribution 47.3, $p<0.004$). Children with PWMI on MRI were more likely to have spastic diplegia (LR chi-squared contribution=9.7) whereas children with PGMI were more likely to present with dyskinetic CP (LR chi-squared 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-squared 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 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, South Africa. 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.*[2] in 2014 indicated that previous CP studies from Africa had assessed primarily prevalence and aetiology. Donald *et al.*[2] concluded that CP in Africa was more prevalent and had different aetiologies compared with high-income (HI) countries, with birth asphyxia, kernicterus and neonatal infections most reported. 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 neuro-imaging in CP by Franki *et al.*[11] reported 94% of patients as having MRI imaging abnormalities suggesting that better imaging quality has led to improved identification of brain lesions.

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

		MRICS					
CP subtypes		**A**	**B**	**C**	**D**	**E**	**Heterogeneous**
Spastic hemiplegia	*n*	2	9	9	6	2	0
n=28	%	7	32	32	22	7	
Mixed CP	*n*	1	3	8	3	3	6
n=24	%	4	13	33	13	13	25
Spastic quadriplegia	*n*	3	5	7	5	2	1
n=23	%	13	22	30	22	9	4
Spastic diplegia	*n*	3	10	1	2	7	0
n=23	%	13	44	4	9	30	
Dyskinetic CP	*n*	1	2	7	0	1	0
n=11	%	9	18	64		9	
Ataxic CP	*n*	1	1	1	0	0	0
n=3	%	33	33	33			
GMFCS subcategories							
I - II	*n*	4	16	11	11	10	0
n=52	%	8	31	21	21	19	
III - V	*n*	7	14	22	5	5	7
n=60	%	12	23	37	8	8	12

A = maldevelopments; B = predominant white matter injury; C = predominant grey matter injury; D = miscellaneous; E = normal.
MRICS = MRI classification system; CP = cerebral palsy; GMFCS = gross motor function classification scale.

In our cohort, all CP subtypes were represented, with the largest proportion (67%) having spastic CP. The majority of 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% and 11.1%.[3,5,9,10,19] Similarly, 9.8% (*n*=11) maldevelopments were identified in our cohort.

Although the African literature on neuro-imaging and CP is limited, a study done at a referral hospital in Uganda also identified more PGMI (44%) in their cohort of children with CP.[20] CT imaging was utilised 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.*[19] and 19 - 45%, by Reid *et al.*[9] The population characteristics, associated risk factors for CP and imaging technique must be considered as an explanation for the neuro-imaging 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% and 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] which may 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 with 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 with 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 in comparison with the Pan-European cohort reported by Horber *et al.*[19] (41%) and the systematic review by Franki *et al.* (44%).[11] The higher proportion of PGMI in our cohort as well as elsewhere in Africa is probably 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.*,[11] a representative cohort of patients with possibly better imaging techniques are needed to confirm these results.

The study investigators in the present 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 the 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 are often not well visualised on CT brain imaging in our group of patients.

The study has several limitations. The patient cohort was identified at tertiary hospital-based specialist clinics, 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 were not well documented in the medical records. Although most of the MRI reports were reviewed by a qualified radiologist, there were four reports which were not verified by a consultant owing to staff constraints. Another limitation was that one-third of the images (n=36, 32%) were done before the age of two years, when brain myelination is not yet complete, and 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.*[30] 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. The use of clear definitions and validated classification systems in CP will have an important role in establishing such a registry.

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 profiles of our patient cohort which could assist in determining the risk of future disability and prognosis. The standardised classification of the brain lesions reported on MRI allowed us to compare our findings with 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.

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