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Grey matter brain injuries are common in Ugandan children with cerebral palsy suggesting a perinatal aetiology in full-term infants

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ABSTRACT

Aim: There is limited literature on brain imaging studies of children with cerebral palsy (CP) in low and middle income countries. We investigated neuroimaging patterns of children with CP attending a tertiary referral centre in Uganda to determine how they differed from studies reported from high income countries and their relationship with prenatal and postnatal factors.

Methods: Precontrast and postcontrast computed tomography (CT) scans of 78 CP children aged 2–12 years were conducted using a Philips MX 16-slice CT scanner. Two radiologists, blinded to the patient's clinical status, independently reviewed the scans.

Results: Abnormal CT scans were detected in 69% of the children sampled, with very few having primary white matter injuries (4%). Primary grey matter injuries (PGMI) (44%) and normal scans (31%) were most frequent. Children with a history of hospital admission following birth were three times more likely to have PGMI (odds ratio [OR] 2.8; 95% CI 1.1–7.1), suggesting a perinatal period with medical complications.

Conclusion: Brain imaging patterns in this group of CP children differed markedly from imaging studies reported from high income countries, suggesting a perinatal aetiology in full-term infants and reduced survival in preterm infants.

INTRODUCTION

Cerebral palsy (CP) describes a heterogeneous group of childhood-onset movement disorders attributed to a non-progressive brain lesion in the developing child's brain. It is often accompanied by sensory, cognitive and behavioural problems as well as comorbidities such as epilepsy (1). The cause is variable and encompasses several aetiological pathways and pathological mechanisms disturbing early brain development (2). In the last few decades, neuroimaging has become established as a useful tool for investigating children with CP. Neuroimaging may provide insights into the timing and aetiology of the insult (2,3). The brain pathology is also correlated to the phenotype, and early examinations may predict future clinical and functional development (4,5). Several studies have been performed in high income countries on clinical samples of children with CP (3,6,7) that show strong correlations between the neuroimaging findings with the clinical subtypes of CP. Examples of these correlations comprise primary white matter injuries (PWMI), also referred to as white matter damage of immaturity (3), that include periventricular leukomalacia and periventricular haemorrhage, seen in children with mild bilateral CP (spastic diplegia). Other correlations include focal infarcts in children with unilateral CP (spastic hemiplegia), and basal ganglia and thalamus damage in children with dystonic CP or severe bilateral CP (quadriplegia).

Abbreviations
CP, Cerebral palsy; CT, Computed tomography; MRI, Magnetic resonance imaging; OR, Odds ratio; PGMI, Primary grey matter injury; PWMI, Primary white matter injury.

Key notes

- Neuroimaging is a recommended investigation in cerebral palsy (CP) because it may provide information on the aetiology of the brain injury; however, there are hardly any studies from sub-Saharan Africa.
- We found more primary grey matter injuries with associated perinatal complications and fewer white matter injuries in our Ugandan CP children.
- Findings suggest differing aetiology of CP in preterm and full-term infants between sub-Saharan Africa and high income countries.

The distribution of the various subtypes of CP and the association of the neuroimaging pattern was confirmed in a big population-based study in Australia (8). This study also included prenatal and perinatal information, making it possible to find associations between risk factors and different neuroimaging patterns.

Only a limited number of neuroimaging studies have been performed on children with CP in low and middle income countries (9,10). In particular, studies from sub-Saharan Africa are rare (11), with hardly any information on the pattern of brain injury and its relation to aetiology or timing of the brain injury. Nor is there any information regarding the correlation of the pattern of brain injury with phenotype, motor function and comorbidities. Based on the results of clinical studies carried out from low and middle income countries (12,13), it is probable that the spectrum of children with CP from low and middle income countries differs from that of high income countries; for example, fewer preterm born children with CP and mild bilateral CP (diplegia) cases. It would therefore be expected that the neuroimaging pattern of the brain pathology differs as well with a smaller proportion of PWMI. This assumption was partly supported in a recent study on a clinical cohort of children with CP from Northern India (10). The authors reported 34% white matter abnormalities, which is less than the 43% reported in a Pan-European clinical sample (3), or the 45% in the Australian population-based study (8).

In this study, we describe the neuroimaging patterns in a clinical sample of children with CP and examine any associations with prenatal and postnatal risk factors described in detail in a previous report (13). In this study, we hypothesised that Ugandan children with CP would have markedly different neuroimaging patterns from those reported from studies from high income countries.

METHODS

Study setting

This neuroimaging study was part of a larger clinical study of 135 children with CP attending the paediatric CP clinic at Mulago National Referral Hospital in Kampala, Uganda. The study was conducted from September 2009 to August 2010 and included all children between the ages of two and 12 years, who were attending the paediatric CP clinic. They were screened for CP in a series of three steps described in detail in a previous report (13). The clinic has an attendance of approximately 400 children annually, with a catchment area covering the local and regional areas and extending throughout the country, and parts of neighbouring countries.

Study population

A group of 80 children with CP were recruited from the original CP cohort. Inclusion criteria included children aged between two and 12 years who had a diagnosis of CP made by the principal investigator (AK-M) trained in paediatric neurology; caregivers accepted an invitation to participate by giving written informed consent and returning to the clinic on the scheduled appointment date. The exclusion criteria were as follows: children with known allergies to the contrast medium, an inability to keep still in the computed tomography (CT) scanner despite sedation, or without a caregiver to provide the history of the child were excluded. Before obtaining consent from the caregivers, one of the authors (AK-M) explained to them the risks and benefits of the procedure. A flow diagram of recruitment and inclusion in the study is shown in Figure 1.

The study was conducted in keeping with the Declaration of Helsinki on research on human subjects. The use of sedation in these patients was justified as there was a clinical indication for these CT scans, in addition to ensuring that we realised the aim of the research project. Ethical approval of the study was granted by the Mulago Hospital Ethics Committee, the School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences and Uganda National Council of Sciences and Technology (Reference HS 628).

Study design

This was an observational cross-sectional study. Detailed information on recruitment, setting of CP diagnoses, assessing gross and fine motor function, gathering information about co-morbidities and demographic and clinical characteristics of the entire sample has been reported elsewhere (13). A comparison between this subsample and the subsample that did not undergo brain CT scan examination is shown in Table 1.

Study definitions

CP definition according to Rosenbaum et al. (1) was used. The CP classification tree of the Surveillance of Cerebral Palsy in Europe (SCPE) (14) was used so as to define the clinical subtypes: bilateral spastic, unilateral spastic, dyskinetic and ataxic.

The severity of the gross and fine motor impairment of each child was classified as mild, moderate or severe as previously described (13). The presence of comorbidities was obtained from caregiver interviews using a structured interview guide and a standard clinical examination conducted by the study medical doctor and principal investigator (13).

The prenatal period was defined as from the time of pregnancy until labour resulting in delivery. The postnatal period was defined as from birth until two years of age. Preterm birth was defined as less than 37 weeks of completed gestation.

Procedure of the brain CT imaging

The examination was performed with a Philips MX 16-slice CT scanner, 2010 Model (Philips Medical Systems, Best, the Netherlands). All metallic materials and intrusive clothing around the body were removed so as not to interfere with the clarity of the images. The brain was first scanned without contrast injection using a protocol of 3 mm slice thickness. An intravenous injection of 76% IOPAMIRO contrast medium then followed at a rate of 2 mL/kg of body weight, except in 12 children in whom

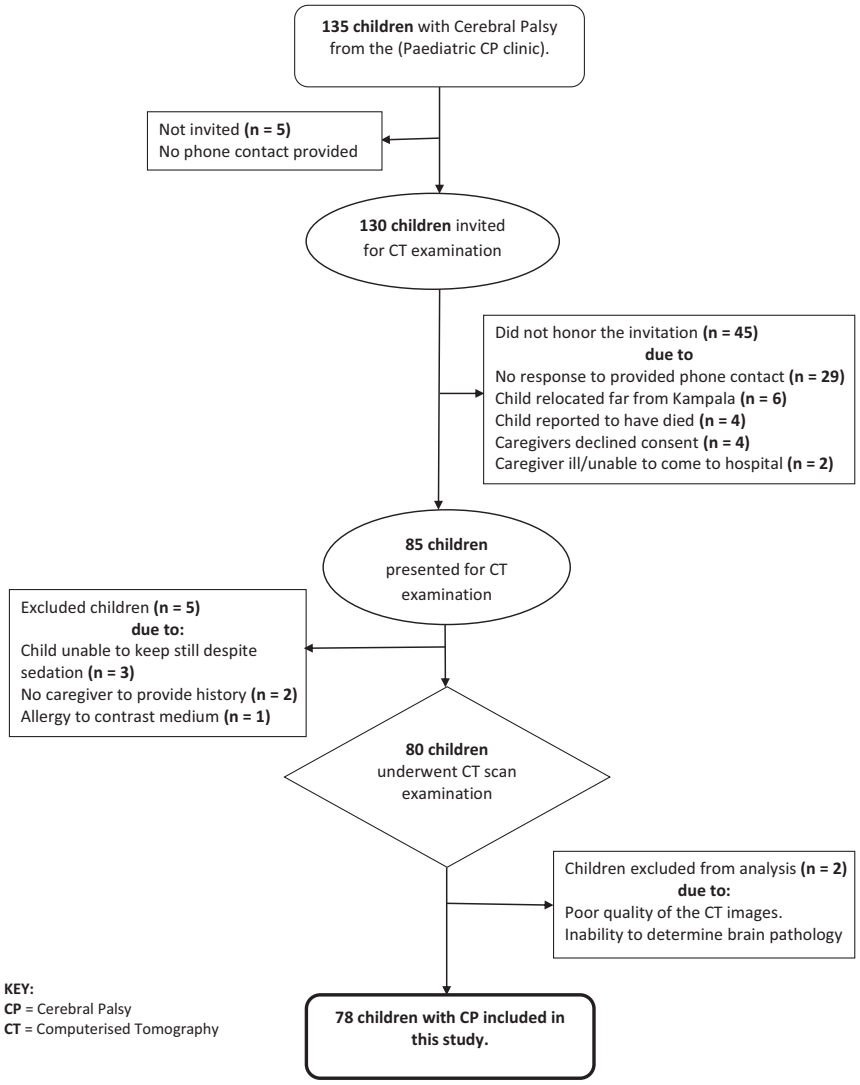

Figure 1 Flow chart showing the recruitment of the children that underwent computed tomography scan examination.

intravenous access was impossible. The brain scan was then repeated immediately after contrast injection using the same parameters for imaging. Sixty-two children required sedation with intravenous diazepam (0.2 mg/kg body weight). After the scan, the patient was observed for any signs of delayed allergic reaction to the contrast medium or effects of the sedation such as stridor, wheezing or airway obstruction.

To minimise or prevent respiratory, circulatory and further neurological compromise following the sedation, the CT scans were performed in the presence of the principal investigator (AK-M) trained in Advanced Paediatric Life Support. The anaesthetist on call was also a phone call away in case of any emergency requiring further expertise. None of the children exhibited any side effects to the sedation or contrast medium.

Two radiologists, each with over 20 years of radiological experience from working in tertiary hospitals, from Uganda (RKB) at Mulago National Referral Hospital and Sweden (OF) at Karolinska University Hospital independently reviewed the scans. The radiologists were blinded to the clinical and demographic characteristics of the children. In case of conflicting reports, one of the radiologists (OF) re-evaluated the images and communicated with (AK-M) before the final image pattern was established. The neuroimaging findings were categorised according to a classification system similar to that used in other studies (15) including the Pan-European Cerebral Palsy study (3) and the Australian population-based study (8) into six categories: (i) congenital malformations, (ii) primary white matter injury, (iii) primary grey matter injury, (iv) heterogeneous pattern (including a combination of both primary white and grey matter injuries), (v) focal cortical infarcts and (vi) normal. See Table S1 for further details of image characteristics.

Statistics

Data were checked for completeness, coded and analysed accordingly, using IBM SPSS Statistics software version

Table 1 Demographic and clinical characteristics of the children with cerebral palsy with computed tomography (CT) scan images (n = 78) compared with those with none (n = 57)

Characteristic	CP cases with analysed CT scan images (N = 78) N (%)	CP cases with no CT scan images (N = 57) N (%)	p-Value*
Gender of child			
Male	37 (47.4)	35 (61.4)	0.108
Age of child at assessment (years)			
Less than five years	58 (74.4)	34 (59.6)	0.070
Above five years	20 (25.6)	23 (40.4)	
Age of mother/caregiver (years)			
Below 20 years	7 (9.0)	13 (22.8)	0.025
Above 20 years	71 (91.0)	44 (77.2)	
Perinatal factors			
Birth order – second or later pregnancy	58 (74.4)	44 (77.2)	0.705
Birth in hospital/clinic	74 (94.9)	53 (93.0)	0.721†
Born at term	67 (85.9)	50 (87.7)	0.758
Singleton	73 (93.6)	56 (98.2)	0.401†
History of difficult delivery	52 (66.7)	35 (61.4)	0.528
History of infection in perinatal period	21 (26.9)	15 (26.3)	0.937
Admission in hospital after birth	34 (43.6)	19 (33.3)	0.228
Gross motor function level			
Mildly affected	18 (23.1)	16 (28.1)	0.017
Moderately affected	17 (21.8)	23 (40.4)	
Severely affected	43 (55.1)	18 (31.6)	
Fine motor Function level			
Mildly affected	28 (35.9)	24 (42.1)	0.023
Moderately affected	9 (11.5)	14 (24.6)	
Severely affected	41 (52.6)	19 (33.3)	
Type of cerebral palsy			
Bilateral Spastic	41 (52.6)	25 (43.9)	0.148
Unilateral Spastic	15 (19.2)	17 (29.8)	
Dyskinetic	6 (7.7)	9 (15.8)	
Ataxia	7 (9.0)	4 (7.0)	
Unclassifiable	9 (11.5)	2 (3.5)	
Comorbidity			
Signs of epilepsy	37 (47.4)	24 (42.1)	0.539
Signs of speech and language disorders	30 (38.5)	20 (35.1)	0.688
Signs of visual impairments	23 (29.5)	17 (29.8)	0.966
Signs of hearing impairments	14 (17.9)	7 (12.3)	0.369
Signs of behavioural disorders			
Signs of anxiety/depression	13 (16.7)	13 (22.8)	0.372
Signs of attention deficit/hyperactivity	27 (34.6)	19 (33.3)	0.877
Signs of learning disability	60 (76.9)	42 (73.7)	0.665
Signs of autism spectrum disorders	22 (28.2)	10 (17.5)	0.150

*p-Value for the chi-square test of independence.
†p-Value for Fisher's exact test.

22.0 (SPSS Inc., Chicago, IL, USA). The frequency distribution of the CP-clinical subtype and level of fine and gross motor function with respect to the different brain CT scan patterns was outlined as the first step.

We then determined the strength of association between the prenatal and postnatal factors and brain CT scan pattern by bivariate analysis using the Pearson chi-square test or Fisher's exact test. Our model was based on two outcomes, namely comparing all the children with grey matter injury (including focal infarcts) versus those with nongrey matter injury. Prenatal factors were those occurring during the prenatal period with the postnatal factors happening in the postnatal period. Results were presented as an odds ratio (OR) with corresponding 95% confidence intervals (95% CI). All p-values were two sided with a probability level of $p < 0.05$ considered statistically significant.

RESULTS

A total of 80 children from the original sample were subjected to brain CT scans and had their images analysed

by the two independent radiologists (RKB and OF). There were conflicting categorisation on nine examinations, for which final classification was made following discussion. Images from two children were excluded from further analysis due to suboptimal imaging with inconclusive findings, resulting in a study sample of 78 children with CP.

The demographic and clinical characteristics in the subgroup of 78 children were similar to the subsample of 57 children who did not undergo CT scan examination (Table 1). Notably, however, those who underwent brain CT scans were more likely to have severe levels of gross and fine motor dysfunction and have older caregivers ($p < 0.05$).

The median age at scanning was three years, two months with an interquartile range from two years, four months to five years, two months.

Brain CT scan images

Abnormalities were detected in 54/78 (69%) of the sample. Over half of the brain CT images showed a single abnormality 41/78 (53%); in 24/78 children (31%), there were no abnormalities, and in 13/78 children (17%), there was a combination of primary grey and white matter abnormalities, that is a heterogeneous injury pattern (Table 2).

Primary grey matter injury (PGMI) was the commonest neuroimaging pattern seen and was identified in 34 children (44%). These scans showed features of bilateral cortical and subcortical tissue damage of the cerebral hemispheres with loss of brain tissue and widened sulci (Fig. 2A). Twenty children with grey matter injury had bilateral spastic CP; seven had unilateral CP (with corresponding unilateral grey matter injury of the contralateral side); three children had ataxic CP; two had dyskinetic CP, and in two children with grey matter injury the type of CP could not be classified.

Normal CT scans were found in 34 children (31%). Twelve children (12) with normal imaging pattern had bilateral spastic CP, five children had unclassifiable forms of CP, three had ataxic CP, two had unilateral CP and two children with normal CT scan had a dyskinetic CP.

Heterogeneous injury, including both primary white and grey matter injuries, was found in 13 children (17%). These scans included extensive asymmetrical or symmetrical cerebral damage, small calcifications bilaterally in the periventricular area, dilatation of the ventricles and cystic formation (Fig. 2B). A heterogeneous imaging pattern was found in nine children with bilateral spastic CP, in two children with unilateral CP, in one child with dyskinetic CP and in one child with unclassifiable form.

Primary white matter injury (PWMI) was noted in three children. One had unilateral spastic CP, one had dyskinetic CP and in one the type could not be classified. The child with dyskinetic CP was born preterm. The exact gestation period was not clear but, according to the mother, the birth date was more than three weeks before the expected date of delivery (Fig. 2C).

Focal infarct was present in three children. The scans had features of neonatal stroke showing hemi-atrophy of one cerebral hemisphere with secondary dilatation of the cerebral sulci and ventricles (Fig. 2D). All the children had unilateral spastic CP with right hemiplegia in two children and left hemiplegia in one. Two of the children were females and both suffered from epilepsy.

One child was categorised as having a *congenital malformation*. This was a two-and-a-half-year-old boy who had microcephaly, corpus callosum agenesis and a Dandy Walker malformation. He had ataxic CP, mild gross motor impairment and bilateral squints.

Distribution of neuroimaging pattern by CP type and level of motor impairment

The distribution of the neuroimaging patterns by the different types of CP and in relation to the severity level of motor impairment is shown in Table 2. The three children with PWMI all had mild or moderate gross and fine motor impairments. PGMI were accompanied with severe gross and fine motor impairment in more than half (59%) of the children. Heterogeneous imaging pattern was

Table 2 Distribution of brain computed tomography (CT) scan neuroimaging pattern by cerebral palsy (CP) type and severity level of gross and fine motor impairment

	Congenital malformation	Primary white matter injury	Primary grey matter injury	Heterogeneous injury	Focal infarct	Normal CT scan
All CP types n = 78 (%)	1 (1.3)	3 (3.8)	34 (43.6)	13 (16.7)	3 (3.8)	24 (30.8)
Bilateral spastic n = 41 (%)	0 (0.0)	0 (0.0)	20 (48.7)	9 (22.0)	0 (0.0)	12 (29.3)
Unilateral spastic n = 15 (%)	0 (0.0)	1 (6.7)	7 (46.7)	2 (13.3)	3 (20.0)	2 (13.3)
Dyskinetic n = 6 (%)	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	0 (0.0)	2 (33.3)
Ataxic n = 7 (%)	1 (14.2)	0 (0.0)	3 (42.9)	0 (0.0)	0 (0.0)	3 (42.9)
Unclassifiable n = 9 (%)	0 (0.0)	1 (11.1)	2 (22.2)	1 (11.1)	0 (0.0)	5 (55.6)
Gross motor impairment						
Mild; n = 18	0 (0.0)	1 (33.3)	7 (20.6)	1 (7.7)	2 (66.7)	7 (29.2)
Moderate; n = 17	1 (100.0)	2 (66.7)	7 (20.6)	2 (15.4)	1 (33.3)	4 (16.7)
Severe; n = 43	0 (0.0)	0 (0.0)	20 (58.8)	10 (76.9)	0 (0.0)	13 (54.2)
Fine motor impairment						
Mild; n = 28	1 (100.0)	3 (100.0)	7 (20.6)	3 (23.1)	3 (100.0)	11 (45.8)
Moderate; n = 9	0 (0.0)	0 (0.0)	7 (20.6)	1 (7.7)	0 (0.0)	1 (4.2)
Severe; n = 41	0 (0.0)	0 (0.0)	20 (58.8)	9 (69.2)	0 (0.0)	12 (50.0)

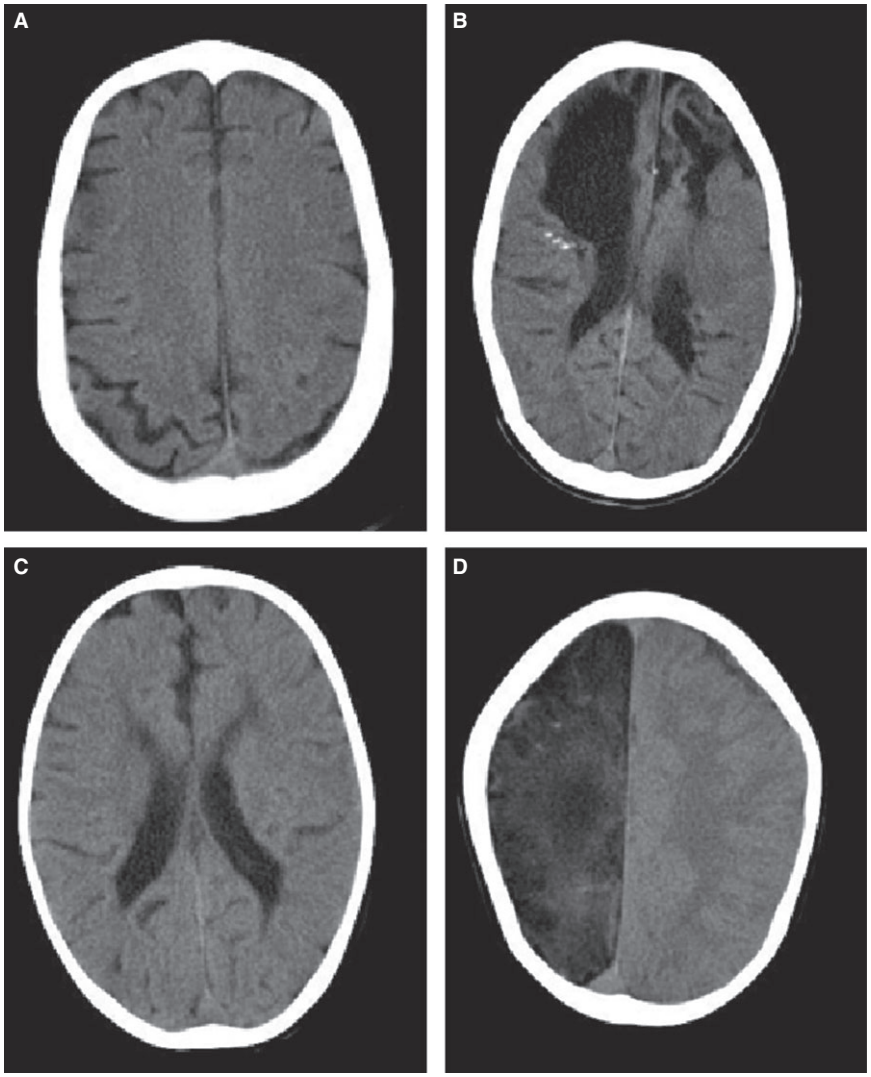

Figure 2 Examples of the computed tomography (CT) scan findings in the studied children with Cerebral palsy. (A) Primary grey matter injury. Precontrast CT scans of a four-year-two-months-old girl who presented with left unilateral spastic cerebral palsy (CP) and epilepsy. The cortical sulci are wider than normal, further supporting the diagnosis of diffuse cortical atrophy. Images show a very thick skull bone, which is indicative of arrested brain growth. The right sylvian fissure is wider, but no obvious focal brain lesion is evident. This child was on sodium valproate tablets for her epilepsy, and while some anti-epileptic drugs have been shown to interfere with bone mineral density, she had low serum magnesium levels, which could explain this thick skull. In addition, she had no features of malnutrition, had normal serum calcium and phosphate levels and did not have chronic iron deficiency anaemia. We were, however, not able to rule out sickle-cell anaemia or thalassaemia. (B) Heterogeneous white and grey matter damage. Precontrast CT scans of a nine-year-old boy who presented with bilateral spastic CP. Images show destructive lesions in both frontal lobes, more extensive on the right side. There is also extensive bilateral parietal damage with calcifications in the periventricular area, and cyst formation suggestive of end stage brain damage following an intrauterine infection with CMV or toxoplasmosis late during the third trimester. The child was born at home with the assistance of a traditional birth attendant. The mother denied any history of infection during pregnancy or after birth. (C) Primary white matter injury. Precontrast CT scans of a two-year-eight-months-old girl, born preterm (more than three weeks before expected date of delivery), who presented with dyskinetic CP, microcephaly and a bilateral talipes equinovarus deformity. Mother reported she had bleeding on several occasions throughout the pregnancy, a history of fever and infection in the 1st trimester. The child was admitted to hospital after birth for four days and managed for suspected infection and seizures. Images show signs of mild cerebral atrophy and severe loss of periventricular white matter. Grey matter close to trigone abuts the ventricular wall and slightly indents the ventricular wall. This appearance is very typical of white matter damage of Immaturity, previously known as periventricular leukomalacia – PVL. (D) Focal cortical infarction. Precontrast CT scans of a four-year-three-months-old girl who presented with left unilateral spastic CP. Images show total destruction of the entire right cerebral hemisphere with a normal left hemisphere suggestive of a probable late occlusion in the entire right carotid artery system. Note also the reduced size of the right hemicranium.

associated with severe gross and fine motor impairments in 10 of 13 children (77%), and half of the children with normal CT scans had severe gross and fine motor impairments. As previously mentioned, it is worth noting that the proportion of children with severe gross and fine motor impairments was larger in this subsample of 78 children compared to the subsample of 57 children who did not undergo CT scanning (Table 1).

Prenatal and postnatal factors associated with the neuroimaging patterns

Brain CT grey matter injury pattern versus nongrey matter injury

The association of the prenatal and postnatal factors with a grey matter injury pattern is presented in Table 3. In the bivariate analysis, only one postnatal factor was significant ($p < 0.05$). Children who had been admitted to hospital following birth were three times more likely to have primary grey matter injury than any of the other neuroimaging patterns [odds ratio (OR) 2.8; 95% CI 1.1–7.1; $p = 0.026$] (Table 3).

Among children with PGMI, 59% were admitted to hospital during the early postnatal period, 62% had a history of a delayed cry (after five minutes) following birth and 51% had feeding difficulties during the initial neonatal period.

Mothers with a prenatal history of bleeding in the 1st trimester were less likely to have PGMI ($p = 0.031$) (Table 3).

DISCUSSION

The main finding in the present study was that the distribution of neuroimaging patterns in a Ugandan clinical sample of children with CP differed markedly from that found in neuroimaging studies performed in high income

Table 3 Prenatal and postnatal factors associated with a grey matter injury versus a nongrey matter injury brain computed tomography (CT) scan pattern

	Brain CT scan pattern			
Variables	Grey matter injury N = 37 (%)	Nongrey matter injury N = 41 (%)	Unadjusted odds ratio (CI)	p-Value
Prenatal factors				
Infection 1st trimester				
Yes	16 (43.2)	18 (43.9)	0.9 (0.4–2.4)	0.953
No	21 (56.8)	23 (56.1)		
Bleeding 1st trimester				
Yes	1 (2.7)	8 (19.5)	0.1 (0.0–0.9)	0.031*
No	36 (97.3)	33 (80.5)		
Baby born at term				
Yes	35 (94.6)	32 (78.0)	4.9 (0.9–24.5)	0.051*
No	2 (5.4)	9 (22.0)		
Prolonged rupture of membranes more than 24 hours				
Yes	8 (21.6)	3 (7.3)	3.5 (0.8–14.3)	0.104*
No	29 (78.4)	38 (92.7)		
Duration of labour				
>24 hours	15 (40.5)	12 (29.3)	1.6 (0.4–4.6)	0.296
<24 hours	22 (59.5)	29 (70.7)		
Mode of delivery				
Normal	27 (73.0)	35 (85.4)	0.4 (0.1–1.4)	0.176
C-section/assisted	10 (27.0)	6 (14.6)		
Postnatal factors				
Baby cried after birth				
Delayed >five minutes	23 (62.2)	17 (41.5)	2.3 (0.9–5.8)	0.068
Immediately	14 (37.8)	24 (58.5)		
Infection neonatal period				
Yes	7 (18.9)	12 (29.3)	0.5 (0.2–1.6)	0.288
No	30 (81.1)	29 (70.7)		
Admission to hospital after birth				
Yes	21 (56.8)	13 (31.7)	2.8 (1.1–7.1)	0.026
No	16 (43.2)	28 (68.3)		
Delay in sitting without support				
Yes	18 (48.6)	13 (31.7)	2.0 (0.8–5.1)	0.127
No	19 (51.4)	28 (68.3)		
Symptomatic epilepsy				
Yes	16 (43.2)	25 (61.0)	0.5 (0.2–1.2)	0.117
No	21 (56.8)	16 (39.0)		
Ability to speak				
None	18 (48.6)	12 (29.3)	2.3 (0.9–5.8)	0.079
Verbal	19 (51.4)	29 (70.7)		

CI = Confidence interval.
*Fisher's exact test used.

countries. The most striking differences were fewer PWMI in this cohort (4%), compared with, for example, 43% PWMI in a Pan-European clinical cohort (3), or 31% PWMI in another clinic cohort from a tertiary-level university hospital in the United Arab Emirates by Gururaj et al. (16). In our sample, PGMI (including infarcts) was more common (47%) compared to 30% in Bax et al. (3), or 23% in Reid et al. (8). In addition, CT scans with no visible pathology were more common in our sample (31%) compared with other studies in low and middle income countries utilising similar methodology (11), or those from high income countries using magnetic resonance imaging (MRI) (3,8). These substantial differences can be due to several factors, such as variations in the general CP-clinical presentation including differences in aetiology and phenotypes, the method utilised in reporting the neuroimage abnormalities or the modality for neuroimaging employed, that is CT versus MRI scans. MRI is known to be better than CT at distinguishing between grey and white matter injuries and is more precise in identifying malformations (2).

White matter lesions are known to be most prevalent in children with CP born preterm. This type of brain injury is known to occur during foetal brain development (gestational week 24–34) (17) in contrast to injuries of the grey matter in the cerebral cortex and basal ganglia, which occur later in the foetal period and often in relation to birth (3). The difference of prevalence of white matter injuries compared with the CP cohorts of the European (43%) (3) and Australian studies (45%) (8) is, thus, in agreement, as more than half of the children were born preterm in those studies in contrast to only 14% (n = 11) of children in our cohort. The lower proportion of PWMI in our CP sample (4%) is, therefore, probably a result of fewer preterm born children developing CP in Uganda. In Uganda, the 'met need for emergency obstetric care' (which is the proportion of women with complications of pregnancy or childbirth who actually receive treatment) is only 14% (18,19), due to limited postnatal care in many facilities (20). It is likely that owing to the limited resources and capacity to handle emergency obstetric care (21), there is reduced survival of preterm born children in the general Ugandan population. The high neonatal mortality of 29 per 1000 live births in Uganda is dominated by infections (31%), birth asphyxia (27%) and preterm delivery complications (25%) which are largely preventable (22). In sub-Saharan Africa, preterm birth complications were the third leading cause of death (after malaria and pneumonia) in children younger than five years (23). Hence, the smaller proportion of white matter lesions and of preterm birth in our sample indicates that the aetiology of CP and the subsequent brain injuries are different from those seen in high income countries where a large proportion is due to preterm birth.

PGMI was the most common neuroimaging pattern observed in our sample. It can comprise damage of the cortical–subcortical grey matter, or deep grey matter, or both, and be with or without brain atrophy and accompanying widened sulci. The larger proportion of primary grey matter injuries in our cohort compared to those from high income countries, thus suggesting that CP in Uganda is more frequently caused by events occurring during the period around birth. This is supported by the significant association between PGMI and admission to hospital following birth. Whereas children who had had a delayed cry after birth were two times more likely to have a PGMI, this finding was not significant. The risk factors for having PGMI point to circumstances that may have affected the blood circulation, oxygenation or metabolism of the child's brain and thereby contributed to the brain injuries. Likewise, the brain injuries may have inflicted the health condition of the child and contributed to the admission to hospital. This observation is in line with Reid et al. (8) reporting that children with PGMI were more likely than those in the general population to be admitted in neonatal intensive care units. Several of the conditions resulting in grey matter injuries may be prevented by emergency obstetric and neonatal healthcare programs. However, as is shown by the European and Australian studies (3,8), a complete elimination of the grey matter injuries has not been realised in high income countries, and the number of full-term born children developing CP seems to be rather constant over time as has been shown in a long-term follow-up study in western Sweden (24).

Consequently, while there is great potential to reduce grey matter injuries in Uganda, a complete eradication is less likely, probably due to the interplay of other risk factors, such as genetic or metabolic factors. Although the literature from high income countries indicates that birth asphyxia plays a relatively minor role in CP aetiology (contributing 10–20% of CP cases) (25), the reverse is probably true in low resource settings (10). Our findings suggest that the aetiology of CP in our setting revolves around the perinatal period with children being subject to severe birth asphyxia, which necessitates respiratory support and observation for a period of time in a hospital environment. In future research, investigation of the underlying causes of the birth asphyxia in our setting needs to be explored. These findings also infer that if the conditions leading up to birth asphyxia could be prevented, for example by improvement of the emergency obstetric and neonatal care services (19), the number of children developing CP could be reduced.

An interesting indirect support for grey matter injuries occurring later in pregnancy or during birth is the finding that children of mothers who reported that they had had a history of bleeding in the 1st trimester were less likely to develop PGMI.

The frequency of normal CT scans was higher in this study compared with the European study (3) and the Australian study (8). In those studies, MRI was used rather than CT. The frequency was, however, similar to a study made of CP term children from other high income countries that found 27% having normal scans (26). There are components of destructive brain damage that is not well shown on CT scans such as gliosis. The improved sensitivity and spatial resolution with MRI scanning is also important for the detection of small but strategically placed injuries in

important motor areas of the brain. The improved sensitivity of MRI brings the number of normal brain imaging studies down to the level of around 10%, depending on the kind of clinical sample (27). It is, therefore, likely that there were unidentified lesions in our sample that could have been detected had MRI been used rather than CT scanning. It is also likely that the normal brain scans in some of these children may not have been a consequence of the reduced sensitivity of CT, but were probably due to unidentified genetic or metabolic disorders that could not be detected by any structural brain imaging method.

The basis of these suspicions stems from the finding that among the children with normal CT scans in our sample, half had severe gross and fine motor impairments, 29% had bilateral spastic CP and 56% had unclassifiable CP. These findings indicate that most children with normal CT scans had severe forms of CP. This is in agreement with Bax et al. (3), who reported that all degrees of severity of motor dysfunction were represented in the group of children with normal MRI scans. It is known that the cause of CP remains elusive in the majority of cases despite its being attributed to several foetal and perinatal risk factors. Our findings lend weight to the current debate that CP, like other neurodevelopmental disorders, is in some cases, probably caused by an interaction of multiple genetic and environmental risk factors, and may warrant that genetic or metabolic screening is performed in particular in CP cases with normal neuroimaging pattern (28).

Only one child was identified with a malformation in our study. This is unexpected considering that findings from other studies on children with CP from low and middle income countries have found higher rates (10,11). This might be due to several reasons, for example caregivers/parents keep these children away from medical support due to stigma related to the physical appearance, or that we had few preterm children in our cohort while children with malformations are more likely to be born preterm (8).

The subpopulation of children participating in this CT study had more severe levels of gross and fine motor impairment compared with the original population of 135 children with CP (13). The original sample was from a tertiary hospital, which already limits the possibility of estimating the prevalence of CP in the general population. The participation of proportionally more severe cases in this study biases the representation further. One may hypothesise that parents with children who have more severe forms of CP are more likely to keep hospital appointments, while the parents of children who are less severely affected are less obliged to return to hospital as they may not regard their child's problem as worthy of further investigation. Similar findings that support the caregiver's perception of illness severity being strongly associated with health care seeking have been noted in previous studies carried out in low and middle income countries (29,30).

The strength of this study, compared with previous studies from low and middle income countries (9–11), is that all children with CP were examined in order to define the CP type and to determine the severity level of the gross and fine motor impairment. Secondly, the neuroimaging patterns were independently evaluated by two experienced radiologists using internationally recognised standards to enable comparability across previous studies performed in high income countries. Thirdly, information on prenatal and postnatal events was obtained so as to explore possible aetiological associated factors. However, it is important to understand the limitations of the study as well. We used a clinical sample attending a tertiary health unit that is subject to selection bias, resulting in a lack of generalisability of the findings. We relied on self-reported answers from the caregivers, and these may have been subject to recall and reporting bias. Furthermore, we used CT scans that are less sensitive than MRI scans that are nowadays mostly used in high income countries. Finally, we used proxy variables for birth asphyxia on the basis of a history of admission to hospital after birth.

CONCLUSIONS

Primary grey matter injuries and normal CT scans were more common in this clinical sample of children with CP, compared with previous MRI studies from high income countries. In contrast, there were many fewer primary white matter injuries that are more commonly found in children born preterm. These results correspond to a different clinical presentation of CP types with more severe cases of bilateral spastic CP predominating. The aetiology of CP in Uganda seems to be more closely related to perinatal causes than preterm-related causes, as is seen in high income countries. Thus, the results suggest that prevention and emergency treatment of birth asphyxia may prevent brain injuries and development of CP, which may play a role in reducing the incidence of CP in Uganda.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Categories of CT scan neuroimaging pattern.