A Descriptive Study of MRI Findings of Children with Suspected Hypoxic Ischaemic Injury at a Tertiary Academic Hospital in Johannesburg, South Africa

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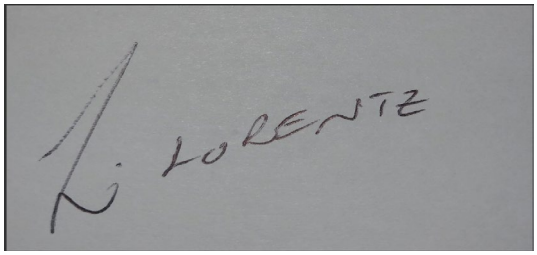
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology.

Johannesburg, May 2024

Declaration

I, Liam Lorentz, declare that this research report is my original work. The submission is for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not previously been submitted for any degree or examination at this or any other University.



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On this 2nd day of May 2024

Abstract

Background: Hypoxic ischaemic brain injury and its clinical sequalae present a global health burden. MRI is the imaging modality of choice to investigate hypoxic ischaemic injury. As there is limited data from low and middle-income countries describing MRI findings of children with suspected hypoxic ischaemic brain injury, we describe the MRI findings of children with suspected hypoxic ischaemic brain injury in a resource-limited setting.

Materials and methods: MRI studies performed for children under the age of 15 years, with clinically suspected hypoxic ischaemic injury were retrospectively evaluated over a 2-year period. A simplified MRI classification of injury, with a final, majority consensus reading was used at the data analysis phase. The 3 readers were blinded to each other and all clinical details, except for age. All clinical information available at the time of MRI was collated by the principal investigator, who was not an imaging reader.

Results A total of 128 MRI studies were evaluated. MRI evidence of hypoxic ischaemic injury was found in 42.2% of children. Normal MRI findings were present in 41 (32.0%) children; and punctate periventricular white matter injuries in 19.5%, watershed injury in 3.1%, central injury in 10.2% and diffuse injury in 23.4% of MRI studies. Preterm infants more commonly demonstrated periventricular white matter injury.

Conclusion: Periventricular white matter pattern of injury was the most common type in premature infants, congruent with international cohorts. Despite the majority of children with suspected hypoxic ischaemic injury being imaged beyond the infant period, MRI findings may have implications for medicolegal recourse.

Acknowledgements

- My sincerest gratitude to my supervisor: Professor Nasreen Mahomed, your guidance and expertise have made this project possible. Thank you for your endless support, encouragement and resilience in adversity.

- Ms. Maryn Viljoen for assistance with statistical analysis.

Submission Format

This research report, for the purposes of Master in Medicine, Department of Radiology has been drafted in the *Submissible Format* as per the University of the Witwatersrand guidelines.

The original research article is written in the manuscript style required by the journal entitled *Wits Journal of Clinical Medicine* with the intention to publish.

Requirements outlined by *Wits Journal of Clinical Medicine* for original research include:

- Word count: 5000
- Unlimited tables and figures
- Structured abstract: 250 words.
    - Background
    - Key methods
    - Main results
    - Conclusion
- Headings:
    - Introduction
    - Materials and methods
    - Results
    - Discussion
    - Conclusion
- Tables and figures to be submitted separately.
- Referencing style: *Vancouver styling*
- Font: Times New Roman was used, size 12. 1.5 line spacing.
- The article manuscript was written using British English

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List of Tables

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List of abbreviations

ADC – Apparent diffusion coefficient

CD – Compact disc

CP – Cerebral palsy

CT – Computed tomography

CMJAH – Charlotte Maxeke Johannesburg Academic Hospital

DICOM – Digital imaging and communication in medicine

DWI – Diffusion weighted imaging

FLAIR – Fluid attenuation inversion recovery

GRE – Gradient echo imaging

HIE – Hypoxic ischaemic encephalopathy

HII – Hypoxic ischaemic injury

MR – Magnetic resonance

MRI – Magnetic resonance imaging

MRS – Magnetic resonance spectroscopy

NE – Neonatal encephalopathy

pH – Potential of Hydrogen

RT – Repetition time

SNR – Signal to noise ratio

Study Protocol

A Descriptive Study of the Magnetic Resonance Imaging Findings of Hypoxic Ischaemic Injury at a Tertiary Academic Hospital

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Table of Contents (Protocol)

1. Background Literature Analysis and Critique

1.1. Introduction

Neonatal encephalopathy (NE) describes a clinically defined syndrome of neurological dysfunction in the neonatal period (1). Clinical manifestations include: abnormal respiration or altered tone, reflexes, altered consciousness and the development of seizures (1). There are no universal definitions for NE and the subgroup hypoxic ischaemic encephalopathy (HIE) making the estimation of incidence and identification of risk factors challenging (2). It is suggested that NE be used as a general term for the clinical manifestation of altered neonatal brain function with heterogeneous aetiologies, and HIE is considered a subset of NE cases where there is evidence of a recent, typically intrapartum, hypoxic-ischaemic cause for NE (1, 3). Other causes for NE include: infectious diseases, metabolic and congenital disorders, perinatal stroke and birth trauma (1, 4, 5).

Encephalopathy occurring secondary to hypoxic ischaemic injury (HII) typically manifests in the early neonatal period, however, with delayed onset encephalopathy (after days to weeks following delivery) metabolic and infectious causes should be considered (4). Hypoxic ischaemic injury is a significant cause of death and permanent neurologic deficit in children (1, 4, 5).

1.2. Epidemiology

An estimate of HIE incidence from three population based studies carried out from 1980 is 1.5 per 1000 live births; it should be noted, however, that these data are from the United Kingdom, Australian and Swedish populations and notably, a spectrum of definitions for HIE were used for each study (2). Current literature describes two methods for HIE estimation: population based studies and hospital based estimates (2). There is controversy regarding

comparing the two estimates in that the hospital based estimates are generally significantly higher than their population based counterparts; with one Nigerian estimate of a hospital based study being as prevalent as 26.2 per 1000 live births (2). Reasons for the discordance includes: several hospital based studies being carried out decades before population based studies, with a higher detection rate in an in-hospital neonatal group as well as a referral bias (2). Improvements in neonatal referral and asphyxia management have also influenced the epidemiology and consequently, realistic comparisons are suboptimal (6).

Approximately double the number of cases of NE in the developing world, compared to the developed world are attributed to hypoxic ischaemic injury, 60% and 30% of cases, respectively (2). The incidence of hypoxic ischaemic injury is more prevalent in preterm neonates. Approximately half of all cerebral palsy cases occur in preterm infants (4, 5).

At present, there is limited data, specifically population-based studies on the incidence of HIE in Sub-Saharan Africa. A South African hospital-based study, in 2009 found an incidence of 8.3 per 1000 live births (7). In 2002, a population-based study in the Southern Cape Peninsula described mild HIE in 3.6 per 1000 live births and moderate to severe HIE in 1.7 per 1000 live births (7).

1.3. Hypoxic ischaemic injury pathophysiology

The pathological mechanisms of HII include: altered cerebral blood flow and decreased blood oxygenation (5). Inefficient, anaerobic oxidation ensues, resulting in energy depletion, acidosis, the release of inflammatory mediators and production of free radicals (5). Severe energy depletion leads to the development of necrosis and cell death, where apoptosis results from lesser degrees of energy depletion (4, 5).

1.4. Magnetic resonance imaging in hypoxic ischaemic injury

MRI is recognised as an important tool in identifying the aetiology of NE and in predicting long-term neurologic outcomes (1, 4, 5, 8). MRI of the newborn brain has gained popularity in clinical practice due to its sensitive and accurate depiction of the developing neurologic system and furthermore, its lack of ionising radiation (4, 5). Computed Tomography (CT), although widely available, is not the imaging modality of choice in the setting of HII due to its lack of myelination depiction in the paediatric brain and furthermore, its reliance on ionising radiation for image production (5). Where MRI is not readily available, CT may depict a predominant pattern of injury; however, an accurate assessment of HII is not possible and the sensitivity and specificity are significantly lower when compared to MRI (9). Despite the advantages and advances of cranial ultrasound; there is limited evidence for prescribing its routine use in the encephalopathic, term neonate (1). Cranial ultrasound may be normal even in the setting of severe HII; however, it can demonstrate intracranial haemorrhage (germinal matrix haemorrhages), albeit at a lower sensitivity when compared with susceptibility weighted imaging at MR (5, 9). CT and cranial ultrasound may be useful modalities for specific indications, particularly in the depiction of intracranial haemorrhage (9).

Hypoxic ischaemic injury is the most prevalent aetiology of NE and has characteristic MRI findings depending on the severity and duration of injury as well as the degree of brain maturation (4, 5). Perinatal clinical characteristics, including low APGAR scores, the necessity for resuscitation, altered cord arterial pH, systemic organ dysfunction and respiratory failure are indicators in the diagnosis of HII (5). Neonates treated with therapeutic hypothermia characteristically demonstrate a reduced severity of injury with the deep grey

nuclei in the setting of HII (4, 5). Documentation of therapeutic hypothermia is critical as well as the interval between the expected hypoxic-ischaemic event and the MR study as this will influence the distribution and pattern of injury (5).

MRI with diffusion weighted imaging (DWI) is the most sensitive modality for detecting HII, when imaged in the early neonatal period, with or without hypothermia treatment (4, 5). There is, however, controversy regarding imaging during the first week of life (early imaging) as it may underestimate the extent of injury (4, 5, 8).

MRI with T1 weighted imaging is superior for myelination detection in infants less than 6 months old and is helpful in depicting subacute haemorrhage in the internal capsule and deep grey nuclei (4). T2 weighted imaging provides excellent differentiation between grey and white matter, providing identification of abnormalities in the deep and cortical grey matter and white matter with high signal intensity (4). Susceptibility weighted sequences assist in demonstrating haemorrhage and differentiating it from an ischaemic insult (4).

MRI findings of the premature neonate with hypoxic ischaemic injury will demonstrate white matter injury in the periventricular and watershed zones (4). In term neonates, however, HII typically affects the subcortical white matter and the perirolandic cortex (4, 5). In severe HII, the susceptible brain regions include those which demonstrate increased metabolic demand and a greater volume of myelination (4). In preterm neonates, these areas include: the thalamus, anterior portion of the vermis and posterior brainstem. In comparison, those areas affected in term neonates are the sensorimotor cortex, lateral aspect of the thalamus, globus pallidus, posterior portion of the putamen, hippocampus and brainstem (4). Milder forms of hypoperfusion cause redistribution of cerebral blood flow and result in injury in the

watershed areas (4, 10). In preterm neonates, mild to moderate HII can cause germinal matrix haemorrhage with or without periventricular leukomalacia (4). Cerebellar haemorrhages may also occur in very low birth weight neonates (4, 5).

White matter injury of prematurity, including periventricular leukomalacia is characterised by foci of necrosis in the periventricular and deep white matter (4). Periventricular leukomalacia typically affects the ventricular trigones and the foramina of Monro – representing watershed areas in the premature neurological system (4). Mild to moderate HII in term neonates commonly causes injury to the watershed areas, subcortical white matter and the parasagittal cortex. The posterior cranial structures and deep grey matter nuclei are typically spared (4).

1.5. Limitations

The use of MRI in HII has been widely appraised. Three review articles: Shroff et al., Chau et al. and Krishan et al. published in 2010, 2014 and 2016 respectively, critically outline the latest advancements in MR technology and the imaging protocols and evaluation of infants with HII. Importantly, these summative publications review literature and data from predominantly North America and Europe – a developed nation bias, likely secondary to a lack of developing nation, notably African data. This presents possible caveats in that not only is the proposed study sample, but also the technology and imaging protocols used to evaluate the sample that of a developing country and not typical of that used in the established reviews.

Charon et el described findings from a single center of retrospective French data. Despite a small sample size (n=33) and data spanning 4 years, there was good to excellent inter-reader agreement for early and late MRI findings of infants with clinical moderate to severe HIE,

using Cohen's Kappa coefficient. Preterm infants (less than 36 weeks gestation) and infants less than 1800g were excluded from the sample as well as infants whose MRI demonstrated neonatal stroke. The exclusion of premature infants results in a small sample size as the majority of HII and the development of cerebral palsy is in this population group. MRI studies were all performed on a 1.5T (Tesla) magnet on day 4 and day 11 of life as per facility protocol. Two paediatric neuroradiologists, blinded to clinical details, outcome and each other, interpreted the imaging. Disputes were resolved by consensus and not by a third party. A simplified reporting template was used; classifying findings into normal, punctate periventricular white matter injuries, watershed, central and diffuse patterns.

1.6. MRI correlation with clinical findings in the setting of hypoxic ischaemic injury

Demonstration of hypoxic ischaemic injury with MRI provides insight into the neurologic outcome of children with cerebral palsy (11). Up to 90% of children with cerebral palsy have abnormal findings on brain MRI which can be categorised into white matter injury and focal infarct, cortical and subcortical lesions and deep grey nuclei injury including the basal ganglia and thalamus (11).

Infants with injuries in the basal ganglia and thalamus typically manifest with impaired motor and postural function, disordered mobility and cognitive impairment (12). Generally, the outcomes of children with injuries secondary to hypoxic-ischaemic insult located in the deep grey matter and posterior limb of the internal capsule are poor (4, 10, 12). There is a significant correlation between the degree of grey matter injury and the extent of motor deficit when imaged during and following the neonatal period, providing crucial clinical impairment prognostication (10-12).

Krageloh-Mann et al. described deep grey matter findings in 17 children, while the later published Choi et al. described findings in a larger population size; 69 infants (11, 12). Martinez-Biarge et al. described clinical manifestations of white matter injuries of 84 infants with HIE and normal deep grey nuclei from 1992 until 2007; and established that the prevalence of cerebral palsy was lower in infants with selective white matter injury; however other neurologic deficits were more common, including: global developmental delay, communication and behavior problems, visual impairment and seizures (10). The study took place over more than a decade and as a result published data using 1, 1.5 and 3T MRI findings for different infants, with no meaningful difference in white matter injury findings between the magnet strengths. Notably, Martinez-Biarge et al. data excluded preterm infants and those who had received therapeutic hypothermia treatment. All three of the described publications; Choi et al., Krageloh-Mann et al. and Martinez-Biarge et al. discuss data spanning years to decades; they are all retrospective in nature with a wide range of sample sizes.

Table 1– Background literature – pertinent findings			
Author	Year published	Sample size	Pertinent findings
Chau V et al	2014	Review article	Typical patterns of brain injury have been recognised on MR imaging. Specific patterns of injury correlate with clinical manifestations and long term neurologic deficits. Acute, profound asphyxia is evident by the *basal nuclei pattern* of injury, which involves the deep grey nuclei and perirolandic cortex predominantly. The predominant watershed pattern of injury involves the parasagittal white matter, watershed vascular territories and in severe injury, may extent into the cortical grey matter The *total pattern* demonstrates maximal injury to both the basal nuclei and watershed areas. Importance of diffusion weighted imaging with hypoxic ischaemic lesions demonstrating restricted diffusion, the injury may be underestimated if performed within the first day of life.
Kurinczuk JJ et al	2010	Best practice	The incidence of NE ranges from 2.0 to 6.0 per 1000 live births.

		guideline. Multicenter	The incidence of HIE ranges from 1.0 to 8.0 per 1000 live births. The lack of universal definitions for NE and HIE results in suboptimal comparisons.
Shroff MM et al	2010	Review article	MRI is the most sensitive modality for evaluating HII. Injury identified in the posterior limb of the internal capsule is a predictor of abnormal outcome in full term infants. Abnormalities demonstrated on DWI peak at 3-5 days after the hypoxic ischaemic injury, which normalise thereafter. The pattern of injury differs depending on three distinct factors: brain maturity at the time of the insult as well as the severity and duration of the insult. In the premature brain: severe hypoxic ischaemia typically affects the thalamus, anterior vermis and posterior brainstem. Involvement of the deep grey nuclei, hippocampus, cerebellum and corticospinal tracts are occasionally

			demonstrated. Injury to the basal ganglia is typically less extensive than that of the thalamus. With mild to moderate HII, findings include: germinal matrix haemorrhage with or without periventricular white matter injury. In the term neonate, mild to moderate HII results in abnormalities in the watershed areas. The interval between the hypoxic ischaemic insult and the MRI examination will affect the neuroimaging characteristics.
Krishan P et al	2016	Review article	Severe HII in the premature brain demonstrates a typical pattern of deep grey nuclei, posterior brainstem and cerebellar vermis involvement. Less commonly there is involvement of the hippocampal formation, corticospinal tracts and the cerebellar hemispheres. Germinal matrix haemorrhage and periventricular white matter injury are associated with mild to moderate HII in preterm infants. In term infants, severe hypoxic ischaemic injury typically affects ventrolateral

			thalamus, posterior putamen, perirolandic cortex and corticospinal tracts. Mild to moderate injury is usually demonstrated by watershed zone: parasagittal and subcortical white matter abnormal signal, and typically spares the deep grey matter, brainstem and cerebellum. Abnormal signal within the posterior limb of the internal capsule is a useful indication of adverse outcomes.
Horn AR et al	2013	110 infants	South African data: September 2008 to March 2009. The incidence of HIE varies from 2.3 to 4.3 per 1 000 live births, depending on specific criterion used. Mild HIE ranged from 0.4 to 1.3 and moderate to severe HIE ranged from 1.5 to 3.7 per 1 000 live births. Consensus definitions for HIE are required for accurate, meaningful comparisons.
Charon V et al	2015	33 infants	MRI with diffusion weighted imaging (DWI) is the most sensitive modality for detecting HII when imaged in the early neonatal period. There is controversy regarding imaging during the first week of life (early imaging) as it may underestimate the extent of the injury.

			For neonates with moderate or severe HIE and therapeutic hypothermia, the early and late MRI findings were concordant.
Merhar S et al	2016	Review article	MRI has superior sensitivity and specificity in depicting the pattern and severity of HII when compared to CT and cranial ultrasound. In the absence of MRI, CT and cranial ultrasound may be a useful imaging modality, particularly in the setting of intracranial haemorrhage.
Martinez-Biarge M et al	2012	84 infants	There is concordance between the degree of deep grey matter injury and the extent of motor deficit.
Choi JY et al	2016	69 children	The severity of injury depicted on MRI is associated with the extent of gross motor, mobility and communication dysfunction and intellectual impairments and can reliably predict the severity of impairment.
Krageloh-Mann I et al	2002	17 children	Injury within the deep grey nuclei impairs motor and postural function, locomotion and cognition. Children with deep grey nuclei injuries typically have poor neurologic outcomes.

2. Rationale

At present, there is a paucity of published literature describing the epidemiology of HII in South Africa and furthermore, there is limited data on HII MRI findings in children with suspected HII. The incidence of HIE in South Africa, as estimated by a hospital based study is 8.3 per 1000 live births (7). Population-based data from 2002 indicate and incidence of 3.6 and 1.7 per 1000 live births of mild and moderate to severe HIE respectively (7). Evaluation of MRI studies can assist in the clinical prognostication of South African children affected by HII. The proposed study will evaluate MRI data over a two year period of children with clinically suspected HII. Correlates will be established between clinical presentation and MRI findings.

3. Aim

To describe the MRI findings of children with suspected hypoxic ischaemic injury at Charlotte Maxeke Johannesburg Academic Hospital.

4. Study Objectives

1. To describe the clinical information provided at the time of the MRI study of children with suspected hypoxic ischaemic injury at a tertiary, academic hospital in Johannesburg.
2. Describe the MRI findings in subjects with suspected hypoxic ischaemic injury.

5. Methods

This is a retrospective study of paediatric brain MRI examinations with clinical evidence of hypoxic ischaemic injury which were conducted at Charlotte Maxeke Johannesburg Academic Hospital. All MRI studies were acquired using the institution's 1.5T Siemens Syngo system.

5.1. Population to be studied

Inclusion criteria

- MRI examinations performed for children younger than 15 years of age during the period: January 1st, 2014 to December 31st, 2015.
- MRI examinations performed for children where the indication was for:
    - Suspected HIE or hypoxic ischaemic injury, including poor condition at birth: APGAR score (≤5), major resuscitation at birth, neonatal encephalopathy, altered level of consciousness
    - Cerebral palsy
    - Delayed milestones
    - Seizures
    - Cognitive or visual impairment.
    - Focal neurological deficit, including tone, motor, reflexes, speech, feeding and movement abnormalities.

Exclusion criteria

- MRI examinations for children where the clinical history indicated:
    - Congenital neurological anomalies
    - Central nervous system tumours
    - Chromosomal abnormalities

- Neurocutaneous syndromes
- Head trauma

5.2. Data collection

Included MRI studies will be assigned a *study number* to ensure anonymity. The MRI DICOM files will be copied onto a CD and thereafter will be identified by the *study number*. Clinical parameters collected from the MRI request form as provided by the referring clinician in each case include:

a. Gestational age at delivery
b. Method of best gestational age estimate
c. Birth weight
d. Mode of delivery
e. Gender
f. Age at MRI study
g. One, five and ten minute APGAR score allocated and resuscitation effort
h. Neurologic deficit
i. Manifestations of hypoxic ischaemic injury

5.3. MRI analysis

The included MRI examinations will be evaluated by three, individual paediatric radiologists (NM. HM, TP). The imaging readers' field of practice and experience is within South Africa. The imaging readers will be blinded to the patient's name, clinical details and tp each other. The raw MRI data will be in DICOM format; the imaging readers will interoperate the MRI study with the use of a DICOM-reader of their choice, which allows for multiplane reformatting. Where the DICOM-reader used is not OSIRX, mention will be made thereof.

A 2 out of 3-consensus reading will be employed during the MRI data analysis phase.

The imaging readers will have access to the study number and the age of the child, at the time of the MRI to correlate appropriate myelination milestones, while evaluating the MRI examination. Imaging readers will have access to: Further clinical details will be collated to the MRI evaluation, by the primary investigator who will not be involved in the imaging evaluation process.

Table 2

Simplified MRI pattern of injury classification (8):

Pattern	**Criteria**
Normal	No signal abnormality in the entire brain.
Punctate periventricular white matter injuries	Punctate or small, confluent periventricular (<1cm) white matter signal abnormalities.
Watershed	White matter (except punctate periventricular) or cortical signal abnormalities in the intravascular boundary zones, without central or diffuse pattern criteria.
Central	Signal abnormalities in at least one of the following regions: lentiform nucleus, caudate nucleus, thalamus, perirolandic cortex, cerebral peduncle or hippocampus, without diffuse pattern criteria.
Diffuse/mixed	Diffuse white matter signal abnormalities involving at least four lobes or cortical injuries involving more than the perirolandic cortex or watershed cortex, or watershed and central pattern criteria.

A reference manual with examples of each injury type will be provided to the imaging readers.

The imaging readers will be briefed with the contents of the following review article to facilitate with the precision of abnormal signal findings in paediatric brain MRI:

Krishnan P, Shroff M. Neuroimaging in Neonatal Hypoxic Ischemic Encephalopathy. Indian J Pediatr. 2016;83(9):995-1002.

The magnetic resonance myelination tables as described in the below article will be used to facilitate precision of magnetic resonance studies. Similarly, examples of normal myelination in children for a range of ages will be included.

Welker KM, Patton A. Assessment of normal myelination with magnetic resonance imaging. Semin Neurol. 2012;32(1):15-28

An image checklist, *Appendix I*, will be employed by the imaging readers to evaluate the MRI examinations.

5.4. Role of Primary Investigator

The principal investigator will be responsible for:

- Auditing MRI examinations for the study period and identifying those which qualify for the 'inclusion criteria'
- Transcribing the MRIs into DICOM and readable format
- Anonymising the MRI studies.
- Collating clinical details supplied at the time of MRI request using *Appendix II.*
- Preparation of DICOM for the imaging readers with the *Imaging checklist*.
- Collate MRI findings into an Excel spreadsheet in preparation for data analysis.
- Data analysis

5.5. Data Analysis

Data from the ‘image checklist' and ‘data capturing sheet' will be captured electronically in Microsoft Excel by the researcher. Statistical analysis using SAS Version 9.2 will be performed. Descriptive statistics, namely frequencies and percentages, will be calculated for categorical data. Means and standard deviations or medians and percentiles will be calculated for numerical data. Clinical characteristics between the different hypoxic ischaemic injury categories will be compared using the appropriate tests (χ^2, Fisher exact test for categorical data and Mann–Whitney or Kruskal–Wallis test for continuous data). A Multiple longitudinal regression model using an adjusted odds ratio will be used to compare the MRI findings with the specified clinical parameters. A significance level (*p*-value) of less than 0.05 was used.

6. Ethics

This proposal was submitted to the University of the Witwatersrand Human Research Ethics Committee. The intended study is retrospective and anonymous and consequently, informed consent for the use of clinical information is not mandatory. Permission to access the necessary records and data will be obtained from the Chief Executive Officer of the Charlotte Maxeke Johannesburg Academic Hospital and the Head of Department of Radiology at the same facility.

Patient anonymity will be ensured with the use of the ‘study number' system as outlined in ‘methods.' Only the primary investigator will have access to patient names and identifying numbers. The three imaging readers will have access to the study identified only with the study number and the patient's age at the time of imaging.

University of the Witwatersrand ethics clearance certificate, Appendix III

7. Timing

	October to December 2016	May/June 2017	July to November 2017	January to October 2018	October to December 2018	Early 2019
Literature Review and Protocol Development						
Submission to Postgraduate Research Committee						
Submission to Ethics Committee						
Data Collection						
Data Analysis						
Write up of Research Report						
Review of Research Report						
Submission of Research Report						

8. Funding

All costs incurred will be at the expense of the investigator.

9. Limitations

As a retrospective review, a paucity of relevant details from MRI records as well as restrictions in storage systems may restrict the collection of a complete set of data. Any data omissions will be noted.

10. Definition of terms

Neonatal encephalopathy: clinical manifestation of disordered neonatal brain function (4).

Hypoxic ischaemic injury: any brain impairment caused by inefficient oxygenation and blood flow (5).

Hypoxic ischaemic encephalopathy: condition that is diagnosed with specific clinical findings of profound acidosis, a poor APGAR score (0-3) at birth, seizure, coma, hypotonia and multiorgan dysfunction (5).

APGAR: medical assessment of a newborn's overall health. APGAR scores that fall below a certain level necessitate medical attention and possible resuscitation intervention.

Cerebral palsy: a group of non-progressive, but permanent disorders that occur early in life and are characterised by impairment of movements and posture with or without cognitive deficits (1).

Term neonate: neonate born at more than 37 completed weeks gestation.

Preterm neonate: neonate born at less than 37 completed weeks gestation.

Infant: subject where chronological age is less than 12 months.

Child/children: subject where chronological age is between 12 months and 18 years.

11. References

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12. Appendices

Appendix I

Imaging checklist for imaging readers

Please indicate your Imaging Reader number	**1**	**2**	**3**

Study Number:

Patient age at time of MR: _____ months OR _____years

A	**MRI Sequences**

1	T1	☐
2	T2	☐
3	FLAIR	☐
4	DWI	☐
5	GRE	☐
6	Post contrast	☐
7	MRS	☐

B	**MRI Pattern**

	Pattern	**Criteria**	
1	Normal	No signal abnormality in the entire brain	☐
2	Punctate periventricular white matter injuries	Punctate or small confluent periventricular <1cm white matter signal abnormalities	☐
3	Watershed	White matter (except punctate periventricular) or cortical signal abnormalities in the intravascular boundary zones, without central or diffuse pattern criteria	☐
4	Central	Signal abnormalities in at least one of the following regions: lentiform nucleus, caudate nucleus, thalamus, perirolandic cortex, cerebral peduncle or hippocampus without diffuse pattern criteria	☐
5	Diffuse	Diffuse white matter signal abnormalities involving at least 4 lobes or cortical injuries involving more than the perirolandic cortex or watershed cortex, or watershed AND central criteria	☐

C	**Germinal Matrix Haemorrhage**

1	No haemorrhage	□
2	Limited to subependymal matrix	□
3	Extending into ventricular system <50%, without acute ventriculomegaly	□
4	>50% of ventricular area or acute ventriculomegaly	□
5	Grade 1,2 or 3 and extension into the brain parenchyma	□

D Hippocampus

1	Normal	□
2	Abnormal (descriptor)	□

E Cerebellum

1	Normal	□
2	Abnormal	□

F Ventriculomegaly

1	Nil	□
2	Present	□

G Posterior Fossa

1	Normal	□
2	Abnormal (descriptor)	□

H Intra-axial lesion

1	Nil	□
2	Present	□

I Sella

1	Normal	□
2	Abnormal	□

J Other findings

Appendix II

Data capturing sheet
Study Number:____

A	Gestational age at delivery (weeks)															
B	Referral from															
C	Most accurate gestational age	1	Sure dates	2	Early sonar	3	Late sonar	4	Ballard score	5	SFH	6	Not specified			
D	Birth weight (grams)															
E	Mode of delivery	1	NVD	2	CS	3	Assisted	4	Not specified							
F	Gender	1	Male	2	Female											
G	Age at MR	1	0-14d	2	15-28d	3	29d-2mo	4	3-4mo	5	5-6mo	6	7-12mo	7	13-24mo	8	>24mo
H	1 Min APGAR	1	8-10	2	6-7	3	4-5	4	<4	5	Not specified					
I	5 Min APGAR	1	8-10	2	6-7	3	4-5	4	<4	5	Not specified					
J	10 Min APGAR	1	8-10	2	6-7	3	4-5	4	<4	5	Not specified					
K	Resuscitation required at birth	1	Yes	2	No	3	Not specified									
L	Therapeutic hypothermia	1	Yes	2	No	3	Not specified									
M	Neurological deficit	1	Tone	2	Reflexes	3	Consciousness	4	Respiration	5	Seizures	6	Combination	7	Not specified		
N	Clinical HIE	1	Mild	2	Moderate	3	Severe	4	Not specified							

Appendix III – University of the Witwatersrand ethics clearance certificate

R14/49 Dr Liam Lorentz

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170516

NAME: (Principal Investigator)	Dr Liam Lorentz
DEPARTMENT:	Radiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Descriptive Study of the Magnetic Resonance Imaging Findings of Hypoxic Ischaemic Injury at a Tertiary Academic Hospital
DATE CONSIDERED:	26/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Nasreen Mahomed
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/07/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review May and will therefore be due in the month of May each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

LORENTZ

Principal Investigator Signature

21/07/2017

Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Article for submission

1. Title page

MRI findings of children with suspected hypoxic ischaemic injury at a Tertiary Academic Hospital in Johannesburg, South Africa

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2. Abstract

Background: Hypoxic ischaemic brain injury and its clinical sequalae present a global health burden. MRI is the imaging modality of choice to investigate hypoxic ischaemic injury. As there is limited data from low and middle-income countries describing MRI findings of children with suspected hypoxic ischaemic brain injury, we describe the MRI findings of children with suspected hypoxic ischaemic brain injury in a resource-limited setting.

Materials and methods: MRI studies performed for children under the age of 15 years, with clinically suspected hypoxic ischaemic injury were retrospectively evaluated over a 2-year period. A simplified MRI classification of injury, with a final, majority consensus reading was used at the data analysis phase. The 3 readers were blinded to each other and all clinical details, except for age. All clinical information available at the time of MRI was collated by the principal investigator, who was not an imaging reader.

Results A total of 128 MRI studies were evaluated. MRI evidence of hypoxic ischaemic injury was found in 42.2% of children. Normal MRI findings were present in 41 (32.0%) children; and punctate periventricular white matter injuries in 19.5%, watershed injury in 3.1%, central injury in 10.2% and diffuse injury in 23.4% of MRI studies. Preterm infants more commonly demonstrated periventricular white matter injury.

Conclusion: Periventricular white matter pattern of injury was the most common type in premature infants, congruent with international cohorts. Despite the majority of children with suspected hypoxic ischaemic injury being imaged beyond the infant period, MRI findings may have implications for medicolegal recourse.

Keywords: Neuroradiology, hypoxic ischaemic brain injury, cerebral palsy, MRI

3. Introduction

Hypoxic ischaemic injury (HII) is characterized by altered cerebral blood flow and decreased oxygenation resulting in neurologic dysfunction. (1) Clinical manifestations of hypoxic ischaemic injury range from neonatal encephalopathy to seizure disorders and cerebral palsy in older children. (1-3) HII and its clinical sequelae present a global health burden with significant morbidity and mortality in neonates, infants and older children. (4, 5) Magnetic resonance imaging (MRI) is recognized as the gold standard in identifying the aetiology of neonatal encephalopathy, identifying patterns of HII and a diagnostic tool for predicting long term neurologic outcomes. (1, 2, 6, 7)

HII is one of the most prevalent aetiologies of cerebral palsy (CP). (3, 8-11) In low- and middle-income countries, including South Africa, the estimated prevalence of CP is reported in up to 15.2 per 1000 live births, and between 1.4 to 4 per 1000 births in high-income nations. (10, 12, 13) MRI is suggested for children with CP after the age of 2 years to obviate the difficulty in interpreting developing myelination and reduce the risk of missing milder injuries. (14, 15) MRI abnormalities may be seen in up to 85 to 95% of children with CP, despite 25 to 50% of children with CP having a normal perinatal history and absence of neurological signs in the neonatal period. (7, 8, 14, 16, 17)

At present, there is limited published data from low and middle-income countries describing the imaging findings of HII and cerebral palsy in children using MRI. (7, 18) In 2015 a verified analysis of licensed South African diagnostic imaging equipment detailed the disparaging shortage of specialized radiology services, including MRI in the state health sector. (19) In the same year, Johannesburg had 0.3 MRI facilities per million population. Consequently, children in our setting, are imaged following the neonatal period once the diagnosis of developmental delay or cerebral palsy has been established clinically. The surging epidemic of medicolegal action in the setting of birth asphyxia, HII and CP afflicts a growing number of medical service providers. MRI remains an invaluable tool in the assessment of such cases and guiding legislative recourse. Thus, this study aimed to identify the MRI findings in children with suspected HII in a South African population.

4. Materials and methods

MRI examinations, performed at Charlotte Maxeke Johannesburg Academic Hospital, in Johannesburg, South Africa for children with clinical suspicion of HII, including CP, were retrieved and evaluated. All the MRI studies were acquired using the institution's 1.5T Siemens Syngo system, paediatric brain MRI protocol, including Diffusion Weighted Imaging (DWI). A retrospective analysis was performed for the study period January 2014 to January 2016, wherein137 children were eligible for inclusion. All children younger than 15 years of age who had undergone a MRI brain examination were included where the clinical indication was for: suspected HIE, poor condition or resuscitation at birth, neonatal encephalopathy or altered level of consciousness, cerebral palsy, delayed milestones, seizures, cognitive or visual impairment and focal neurological deficit, including tone, motor, reflex, speech, feeding and movement abnormalities. Exclusion criteria included those with known congenital neurological anomalies, central nervous system tumours, chromosomal abnormalities, neurocutaneous syndromes, head trauma and instances of MRI demonstrating solely congenital structural abnormalities. Prematurity, low birth weight and therapeutic hypothermia were not exclusion criteria.

Included MRI studies were evaluated by three radiologists, (NM, TP, HM) with a minimum of 4-years' experience reading paediatric MRI brain studies within the South African setting. The imaging readers were blinded to the clinical details (except the age of the child at the time of the MRI to correlate with appropriate milestones) and blinded to each other's imaging findings. Clinical parameters available at the time of the MRI were captured by LL who was not involved in the imaging reading process.

A simplified MRI injury pattern *(Table 1)* described by Charon et al. for neonatal HII and which previously demonstrated good to excellent inter-reader variability was used for MRI evaluation. (20) The imaging readers received a prototype manual outlining specific MRI patterns of injury and included examples of each injury type at various ages of imaging. Standardized myelination tables and graphic examples were referenced to facilitate MRI evaluation precision. A final MRI evaluation was computed using a majority consensus

reading (2 out of 3 readers). The study was approved by the University of the Witwatersrand Human Research Ethics Committee.

Statistical analysis using SAS Version 9.2 was performed. Descriptive statistics were calculated for categorical data. Clinical characteristics between the different HII categories were compared using Chi-squared Test. A significance level p-value < 0.05 was used. Inter-reader variability was evaluated using Randolph's Free-marginal multi-rater Kappa.

5. Results

Of the 137 children evaluated, 63.3% were male. The range of children's ages at the time of the MRI study was 22 days to 12 years, with a mean age of 15 months. One child (0.8%) had an MRI in the neonatal period. Almost half (46.9%) of children were older than 2 years at the time of MRI.

The mode of delivery was available in only 5 children (3.9%); 3 of the 5 (60.0%) children delivered by normal vaginal delivery and 2 of the five (40%) children by Caesarian section. 16 (12.5%) children were documented to have received resuscitation at birth; however, specific details of the events were not available. Perinatal resuscitation data was not available for 109 (85.2%) children.

Children with neurological deficits commonly manifested with a combination of deficits (n=46; 35.9%), including tone abnormalities with comorbid seizures. Description of developmental delay was inconsistent; however, a combination of developmental delay (speech and motor) was most frequently observed, n=35 (27.3%). Among the children with clinical HIE, 3 out of 5 were classified as severe, *Supplementary Table 1*. Details pertaining to therapeutic hypothermia were not available in the MRI referral, consequently all included MRIs were interpreted with the presumption that this intervention had not been administered.

MRI DICOM data was available for 128 (93.4%) children. Examples of MRI injury pattern types are demonstrated with FLAIR and T2-weighted imaging in *Figure 1*. A normal MRI

from our sample is included for comparison. Complete reader discordance (deficient two out of three majority reading) occurred in 2 of the MRI cases. MRI evidence of HII was present in 54 (42.2%) of MRI studies and 41 (32.0%) children had entirely normal MRI studies, *Supplementary Fig 1*.

For miscellaneous MRI findings, including ventriculomegaly, cerebellum, sella and hippocampal evaluations, Kappa values indicate near-perfect inter-reader agreement. The inter-reader Free-marginal Kappa value for the MRI pattern of injury was 0.30, *Table 2*.
In children with MRI features compatible with HII, 25 (19.5%) and 30 (23.4%) demonstrated punctate periventricular white matter injuries and diffuse patterns respectively. Watershed and central patterns of injury represented a smaller proportion and included 4 (3.1%) and 13 (10.3%) of evaluated MRI studies, *Supplementary Figure2.*

All of the MRI studies which demonstrated ventriculomegaly had some degree of corpus callosum thinning. Corpus callosum dysgenesis was present in 1 (0.8%) MRI without associated ventriculomegaly.

Children with documented gestational age <36 weeks demonstrated a spectrum of MRI patterns of injury. Punctate periventricular white matter injuries were the commonest in this group, as noted in 9 (34.6%, p=0.2677) children. The only child with a documented birth weight <1000g was found to have a punctate periventricular pattern of injury. Similarly, children with birth weights between 1000 and 2500g were commonly found to have a periventricular white matter pattern of injury, n=4 (36.4%).

6. Discussion

In the setting of HII, MRI is a reliable biomarker and provides invaluable insight into the possible causation of neurological deficit and furthermore has the potential to predict specific clinical manifestations. (17, 20) MRI classification of HII patterns of injury is the current neuroimaging practice, facilitating standardized lexicon and common understanding between imagers and referrers. (21) The current study demonstrates a

spectrum of MRI patterns of injury in children with suspected HII in a South African population.

Our study reiterates the predominant pattern of periventricular white matter injury in premature infants as described previously in the literature. (17, 20) Conversely, all the children in our study with documented gestational age ≥ 36 weeks demonstrated neither punctate periventricular nor watershed patterns of injury, thus providing prognostic implications for premature infants and their term counterparts and their expected relative neurologic deficits. Published literature describes a significant correlation of the severity of central grey nuclei injury with the severity of CP, specifically motor deficits. (22, 23)

The high cost and limited availability of MRI in the South African state health system is evident in this cohort, where almost half the study cohort were imaged beyond the infant period. State health resources remain deficient with a high disease burden of HIV, TB, non-communicable diseases and trauma. (19) This is compounded by the exponential rise in litigation claims relating to HII and CP, invariably resulting in an irreparable cycle of limited funds, access to adequate neuroimaging and inability of the state to confidently defend such cases without radiological evidence. (11, 21) The imbalance of MRI availability is detailed by Kabongo et al where in Gauteng province in 2015, there were 46-fold more MRI facilities in the private sector and interestingly 30-fold and 70-fold more in the United Kingdom and Organisation of Economic Cooperation and Development (OECD) during the same period respectively. (19) This wide discrepancy in access and demand of advanced imaging will further challenge any anticipated state healthcare reform.

Almost a third (32%) of MRIs in our study were normal and 26% were abnormal without evidence of HII. The relevance of these two groups, combined making up greater than 50%, is paramount in providing sufficient proof to mitigate potential malpractice claims and refuting HII. This is despite the delayed median imaging time from suspected age of injury. Similar inferences were described by Elsingergy et al in a review of 1 620 MRIs of South African children with CP involved in medicolegal cases, where the median interval of suspected injury to imaging was six years. Their study established an MRI diagnosis in 92%, but only 76% of cases of CP demonstrated MRI evidence of HII and 31% were either non-HII findings or preterm pattern of HII which can be successfully defended in

malpractice suites. (8) The greater percentage of abnormal MRIs (92% vs 68%) and those consistent with HII (76% vs 42%) in Elsingergy et al analysis, compared to our cohort is explained by selection bias; in our study the inclusion criteria were expanded to include any child suspected of HII, including the subset of CP.

Inter-reader free-marginal agreement for MRI pattern of injury was poor with a Kappa value of 0.3. Possible explanations include subjectivity of the MRI pattern of injury classification with the potential overlap of pattern types, specifically punctate periventricular white matter injuries and watershed patterns. Improved inter reader agreement may in the future be established with comprehensive injury pattern reference guides including a range of children ages. Standardized referral templates for suspected HII MRI studies will facilitate clinical contextualization.

7. Conclusion

Hypoxic ischaemic injury and cerebral palsy continue to cause significant morbidity in the South African paediatric population. In this study, we describe a spectrum of MRI injuries in children with suspected hypoxic ischaemic injury. Periventricular white matter pattern of injury was the most common type in premature infants, congruent with international cohorts. Despite the limited availability of MRI in the state health sector, delayed neuroimaging in the setting of suspected HII may provide pivotal evidence of causation. We recommend future studies with robust, standardized clinical criteria and a validated MRI injury reporting scale.

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9. Legend of figures

Figure 1: Examples of MRI pattern of hypoxic ischaemic injury

Supplementary Figure 1: Categorical findings of MRI studies

Supplementary Figure 2: Demonstration of children's age at time of MRI and pattern of injury

10. Tables and Figures

Table 1

Description of simplified criteria used for MRI pattern of injury evaluation as described by Charon (20)

Pattern	**Criteria**
Normal	No signal abnormality in the entire brain.
Punctate periventricular white matter injuries	Punctate or small, confluent periventricular (<1cm) white matter signal abnormalities.
Watershed	White matter (except punctate periventricular) or cortical signal abnormalities in the intravascular boundary zones, without central or diffuse pattern criteria.
Central	Signal abnormalities in at least one of the following regions: lentiform nucleus, caudate nucleus, thalamus, perirolandic cortex, cerebral peduncle or hippocampus, without diffuse pattern criteria.
Diffuse/mixed	Diffuse white matter signal abnormalities involving at least four lobes or cortical injuries involving more than the perirolandic cortex or watershed cortex, or watershed and central pattern criteria.

Table 2

Description of final MRI findings with inter-reader Free-marginal Kappa
n=128

Finding	Frequency (%)	Inter-reader Free-marginal Kappa
MRI pattern of injury		0.30
No majority reading	2 (1.6)	
None	54 (42.2)	
Punctate periventricular white matter injuries	25 (19.5)	
Watershed	4 (3.1)	
Central	13 (10.2)	
Diffuse	30 (23.4)	
Germinal Matrix Haemorrhage		0.90
No haemorrhage	122 (95.3)	
Limited to subependymal matrix	4 (3.1)	
Extending into the ventricular system, without acute ventriculomegaly	1 (0.8)	
>50% ventricular area or acute ventriculomegaly	1 (0.8)	
Germinal matrix haemorrhage with extension into the brain parenchyma	0 (0.0)	
Hippocampus		0.90
Normal	117 (91.4)	
Volume loss	11 (8.6)	
Cerebellum		0.82
Normal	127 (99.2)	
Focal calcifications	1 (0.8)	
Ventriculomegaly		0.94
None	80 (62.5)	
Present	48 (37.5)	
Posterior fossa		0.55
Normal	127 (99.2)	
Mega cisterna magna	1 (0.8)	
Focal intra-axial lesions		0.93
None	127 (99.2)	
Present	1 (0.8)	
Sella		0.93
Normal	128 (100)	
Miscellaneous findings		
No majority reading for specific finding	16 (12.5)	
None	103 (80.4)	
Periventricular calcifications	1 (0.8)	
White matter cysts	2 (1.6)	
Corpus callosum dysgenesis	1 (0.8)	
Hydrocephalus	3 (2.3)	
Subdural effusions	2 (1.6)	

Supplementary Table 1

Clinical characteristics available at the time of MRI examination
n=128

Characteristic	**Frequency (%)**
Male	81 (63.3)
Female	47 (36.7)
Age at time of MRI	
0-14 days	0 (0.0)
15-28 days	1 (0.8)
28 days to 6 months	11 (8.6)
6 months 1 day to 12 months	25 (19.5)
12 months 1 day to 24 months	31 (24.2)
Older than 24 months	60 (46.9)
Gestational age at delivery	
Premature (<36 completed weeks)	26 (20.3)
Term (≥36 completed weeks)	6 (4.7)
Not stated	96 (75.0)
Birth weight at delivery	
<1000g	1 (0.8)
1000-2500g	11 (8.6)
2501-3500g	3 (2.3)
>3500g	0 (0.0)
Not stated	113 (88.3)
Resuscitation required at birth	
Yes	16 (12.5)
No	3 (2.3)
Not stated	109 (85.2)
Neurological deficit	
Tone abnormalities	34 (26.6)
Reflex abnormalities	1 (0.8)
Seizures	12 (9.4)
Multiple deficits	46 (35.9)
None	4 (3.1)
Not stated	31 (24.2)
Developmental delay	
None	48 (37.5)
Present, specific deficit not described	30 (23.4)
Motor	8 (6.3)
Speech	5 (3.9)
Combination	35 (27.3)
Not stated	2 (1.6)
Clinical HIE	
Mild	1 (0.8)
Moderate	1 (0.8)
Severe	3 (2.3)
Not stated	123 (96.1)
Origin of referral	
Internal referral (CMJAH)	101 (78.9)
Rahima Moosa Mother and Child Hospital	20 (15.6)
South Rand Hospital	2 (1.6)
Chris Hani Baragwanath Academic Hospital	4 (3.1)
Edenvale Hospital	1 (0.8)

Supplementary Table 2

Results in context

	Current Study	Elsingergy et al. 2021	Mahlaba et al. 2020	Charon et al. 2015	Aggarwal et al. 2013	Martinez-Biarge et al. 2012	Bax et al. 2006	Krageloh-Mann et al. 2002
Study Period	2 years	Medicolegal database	1 year	2 years, 8 months	2 years	15 years	3 years	8 years
Sample size	137	1620	145	33	98	84	585	17
Region of study	South Africa	South Africa	South Africa	France	India	United Kingdom	Europe	Germany
Age at MRI	Neonates, infants and children less than 15 years Mean age: 15 months	0-18 years	3 months to 18 years *6 children imaged with MRI	Neonates	2-12 years	Neonates	18 months and older	Older than 12 months
Specific exclusions	Chromosomal abnormalities, head trauma, neurocutaneous syndromes, previously investigated congenital neurologic malformations	Duplicated reports Inadequate MRI quality – motion artifact	Children with syndrome and chromosomal abnormalities Children suspected with a progressive disorder	Gestational age <36weeks Birth weight <1800g Neonates that did not have early and late MRI Congenital malformations, compressive airway and neonatal stroke	None	Metabolic disorders, congenital malformation/infection, genetic abnormality or treatment with hypothermia	MRI at age less than 18 months	No specific exclusions, however, MRI needed to have basal ganglia and thalamic abnormalities
Number of normal MRI studies	41 (32.0%)	132 (8%)	Not specifically stated. 11 had normal imaging	Early MRI: 16 (48%) Late MRI: 14 (43%)	4 (4.3%)	Normal or mildly abnormal: 28 (33.5%)	11.7%	Not applicable
Pertinent findings	Majority of children imaged beyond 24 months Spectrum of MRI pattern of HII Predominant periventricular white matter injury in preterm infants	CP medicolegal database 6 year median age to imaging 76% of MRI diagnosis due to HII, 15% with preterm pattern of HII	*mixed imaging US, CT, MRI (n=6) Periventricular white matter lesions in 54% Combination of findings: deep grey matter nuclei, cortical, parasagittal, middle cerebral artery infarcts.	Neonates with moderate or severe HIE who received therapeutic hypothermia, early and late MRI findings were consistent	No correlation between the types of CP and gestation. Weak correlation between injury type detected on MRI and clinical presentation of CP	White matter injury is the predominant finding in premature infants Low prevalence of motor impairment and development of CP with isolated white matter injury Infants who developed CP had more diffuse white matter injury.	Periventricular white matter injury/hemorrhage is associated with prematurity CP with diplegia was most commonly associated with white matter damage of prematurity Deep grey nuclei injury was associated with dystonic CP Focal infarct resulted in hemiplegia Malformations were present in 32 children	Injury to the basal ganglia and thalamus impairs motor and postural function, locomotion and cognition. Neurologic outcomes of children with deep grey nuclei injuries are poor.

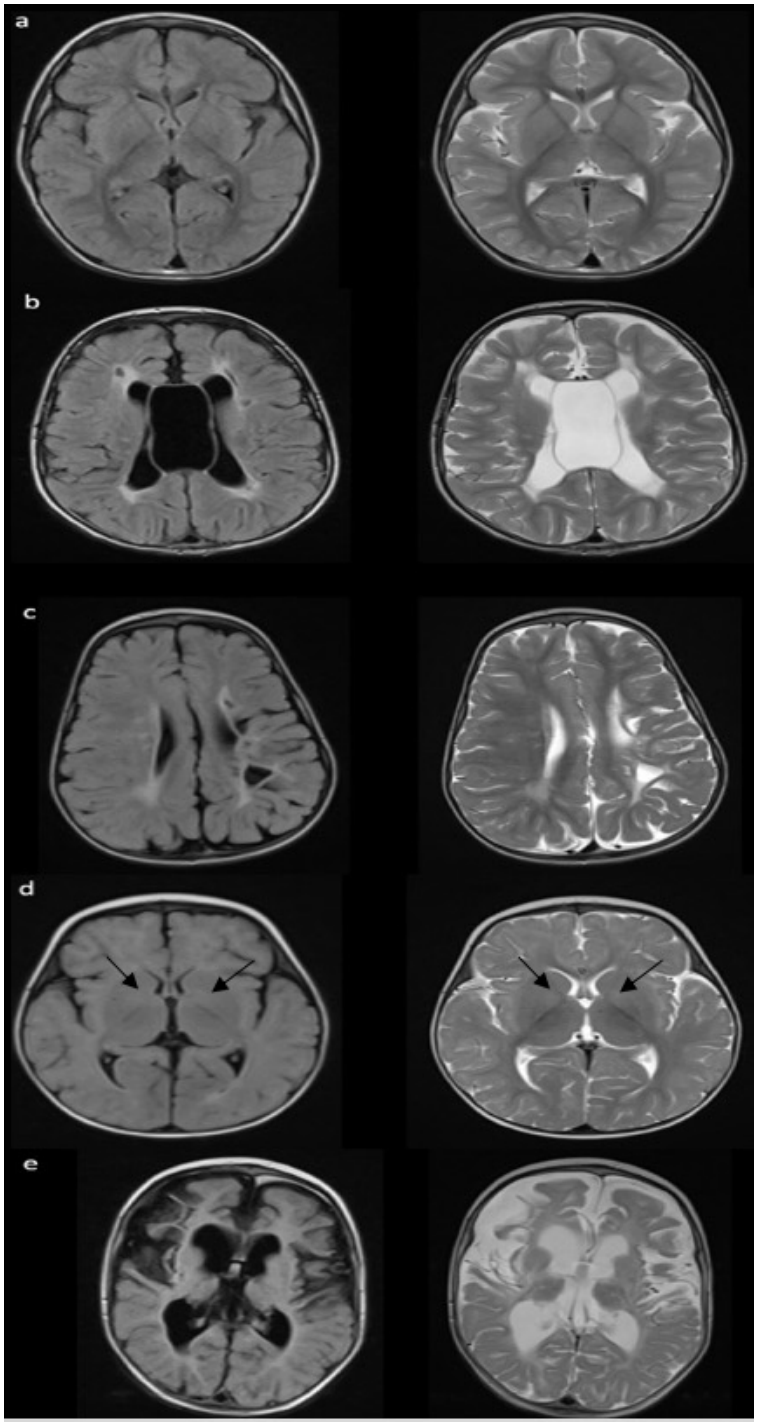
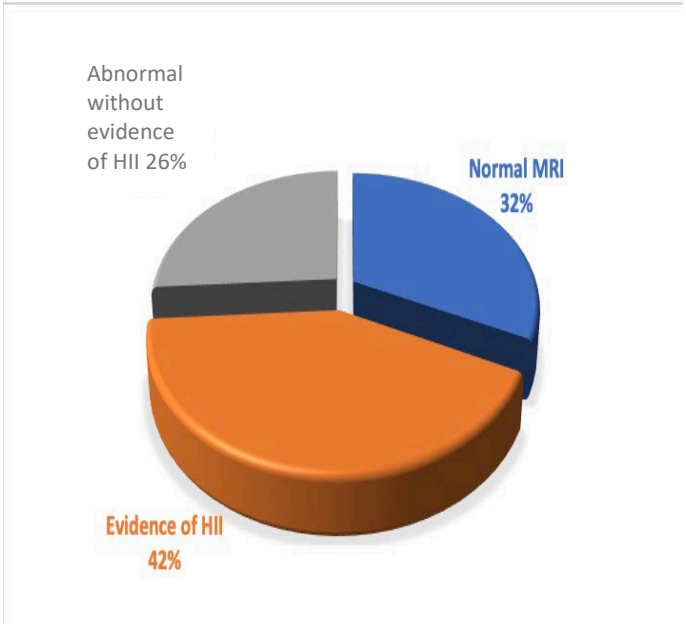
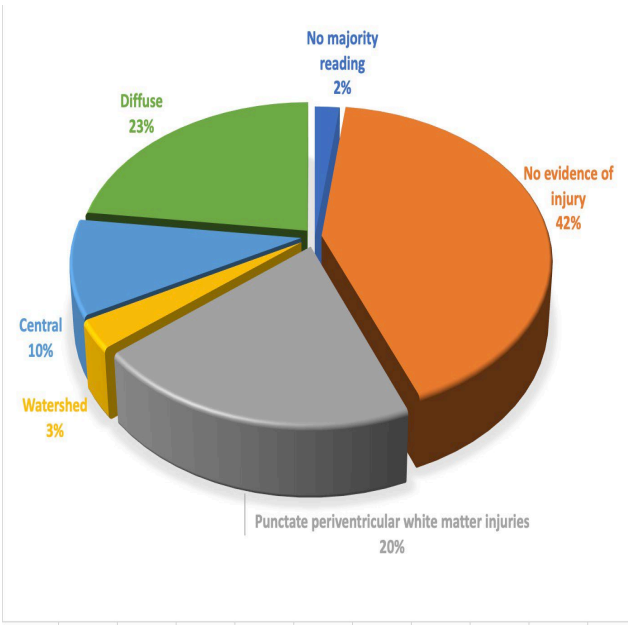


Figure 1
Examples of MRI pattern of hypoxic ischaemic injury with FLAIR (left) and T2-weighted imaging (right). **a** No identifiable injury, for comparison in a 3-year old child. **b** Punctate periventricular pattern in a 4-year old child. **c** Watershed pattern in a 2-year old child. **d** Central pattern in a 2-month old child, black arrows indicate symmetrical hyperintensity within the globus pallidi. **e** Diffuse/mixed pattern in a 6-month old child.

Supplementary Figure 1

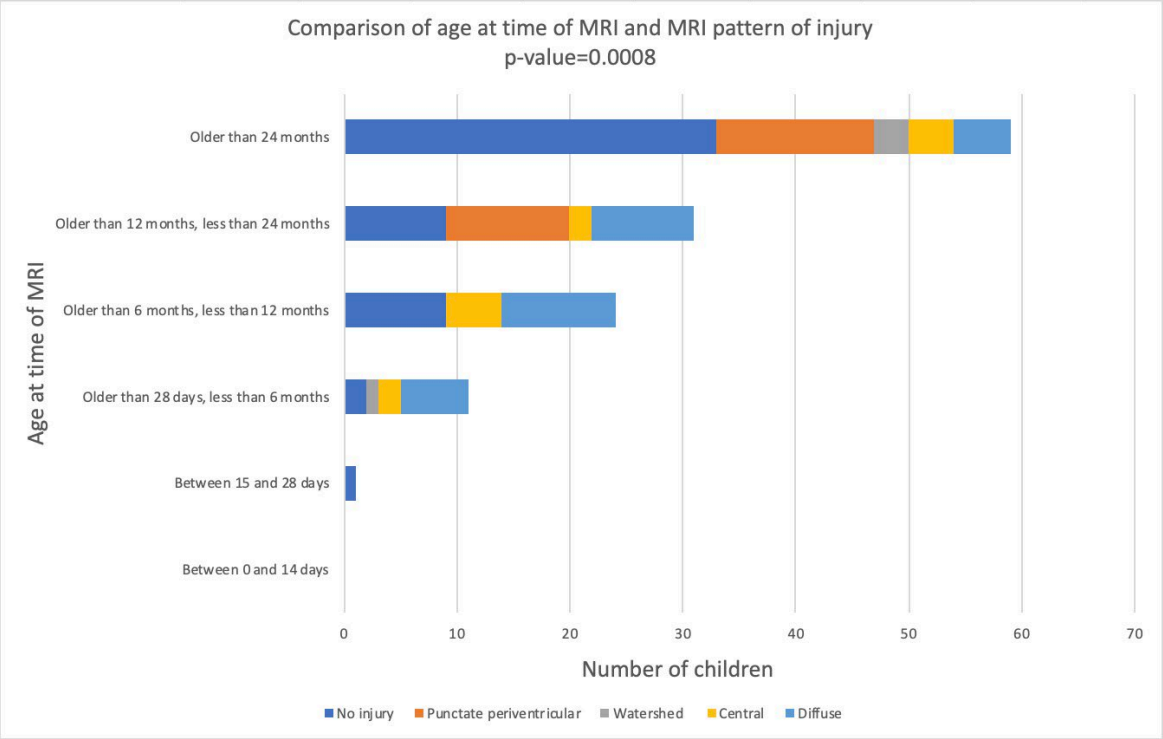
Categorical findings of MRI studies.





Supplementary Figure 2

Demonstration of children's age at time of MRI and pattern of injury. Majority of children were imaged beyond the age of 2 years



Appendix A – Turn It In Report Protocol

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ORIGINALITY REPORT

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Appendix C – Published manuscript

Wits Journal of Clinical Medicine, 2023, 5(1) 31–40

http://dx.doi.org/10.18772/26180197.2023.v5n1a5

Wits Journal of Clinical Medicine, 2023, 5(1) 31–40 http://dx.doi.org/10.18772/26180197.2023.v5n1a5

Research Article

MRI findings of children with suspected hypoxic ischaemic injury at a Tertiary Academic Hospital in Johannesburg, South Africa

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Abstract

Background: Hypoxic ischaemic brain injury and its clinical sequalae present a global health burden. MRI is the imaging modality of choice to investigate hypoxic ischaemic injury. As there is limited data from low and middle-income countries describing MRI findings of children with suspected hypoxic ischaemic brain injury, we describe the MRI findings of children with suspected hypoxic ischaemic brain injury in a resource-limited setting.

Materials and methods: MRI studies performed for children under the age of 15 years, with clinically suspected hypoxic ischaemic injury were retrospectively evaluated over a 2-year period. A simplified MRI classification of injury, with a final, majority consensus reading was used at the data analysis phase. The 3 readers were blinded to each other and all clinical details, except for age. All clinical information available at the time of MRI was collated by the principal investigator, who was not an imaging reader.

Results: A total of 128 MRI studies were evaluated. MRI evidence of hypoxic ischaemic injury was found in 42.2% of children. Normal MRI findings were present in 41 (32.0%) children; and punctate periventricular white matter injuries in 19.5%, watershed injury in 3.1%, central injury in 10.2% and diffuse injury in 23.4% of MRI studies. Preterm infants more commonly demonstrated periventricular white matter injury.

Conclusion: Periventricular white matter pattern of injury was the most common type in premature infants, congruent with international cohorts. Despite the majority of children with suspected hypoxic ischaemic injury being imaged beyond the infant period, MRI findings may have implications for medicolegal recourse.

Keywords: Neuroradiology, hypoxic ischaemic brain injury, cerebral palsy, MRI

INTRODUCTION

Hypoxic ischaemic injury (HII) is characterized by altered cerebral blood flow and decreased oxygenation resulting in neurologic dysfunction.(1) Clinical manifestations of hypoxic ischaemic injury range from neonatal encephalopathy to seizure disorders and cerebral palsy in older children.(1–3) HII and its clinical sequelae present a global health burden with significant morbidity and mortality in neonates, infants and older children.(4,5) Magnetic resonance imaging (MRI) is recognized as the gold standard in identifying the aetiology of neonatal encephalopathy, identifying patterns of HII and a diagnostic tool for predicting long term neurologic outcomes.(1,2,6,7)

HII is one of the most prevalent aetiologies of cerebral palsy (CP).(3,8–11) In low- and middle-income countries, including South Africa, the estimated prevalence of CP is reported in up to 15.2 per 1000 live births, and between 1.4 and 4 per 1000 births in high-income nations.(10,12,13) MRI is suggested for children with CP after the age of 2 years to obviate the difficulty in interpreting developing myelination and reduce the risk of missing milder injuries.(14,15) MRI abnormalities may be seen in up to 85% to 95% of children with CP, despite 25% to 50% of children with CP having a normal perinatal history and absence of neurological signs in the neonatal period.(7,8,14,16,17)

At present, there is limited published data from low and middle-income countries describing the imaging findings of HII and cerebral palsy in children using MRI.(7,18)

In 2015 a verified analysis of licensed South African diagnostic imaging equipment detailed the disparaging shortage of specialized radiology services, including MRI in the state health sector.(19) In the same year, Johannesburg had 0.3 MRI facilities per million population. Consequently, children in our setting, are imaged following the neonatal period once the diagnosis of developmental delay or cerebral palsy has been established clinically. The surging epidemic of medicolegal action in the setting of birth asphyxia, HII and CP afflicts a growing number of medical service providers. MRI remains an invaluable tool in the assessment of such cases and guiding legislative recourse. Thus,

this study aimed to identify the MRI findings in children with suspected HII in a South African population.

MATERIALS AND METHODS

MRI examinations, performed at Charlotte Maxeke Johannesburg Academic Hospital, in Johannesburg, South Africa for children with clinical suspicion of HII, including CP, were retrieved and evaluated. All the MRI studies were acquired using the institution's 1.5T Siemens Syngo system, paediatric brain MRI protocol, including Diffusion Weighted Imaging (DWI). A retrospective analysis was performed for the study period January 2014 to January 2016, wherein137 children were eligible for inclusion. All children younger than 15 years of age who had undergone a MRI brain examination were included where the clinical indication was for: suspected HIE, poor condition or resuscitation at birth, neonatal encephalopathy or altered level of consciousness, cerebral palsy, delayed milestones, seizures, cognitive or visual impairment and focal neurological deficit, including tone, motor, reflex, speech, feeding and movement abnormalities. Exclusion criteria included those with known congenital neurological anomalies, central nervous system tumours, chromosomal abnormalities, neurocutaneous syndromes, head trauma and instances of MRI demonstrating solely congenital structural abnormalities. Prematurity, low birth weight and therapeutic hypothermia were not exclusion criteria.

Included MRI studies were evaluated by three radiologists, (NM, TP, HM) with a minimum of 4-years' experience reading paediatric MRI brain studies within the South African setting. The imaging readers were blinded to the clinical details (except the age of the child at the time of the MRI to correlate with appropriate milestones) and blinded to each other's imaging findings. Clinical parameters available at the time of the MRI were captured by an individual (LL), who was not involved in the imaging reading process.

A simplified MRI injury pattern *(Table 1)* described by Charon et al. for neonatal HII and which previously demonstrated good to excellent inter-reader variability was used for MRI evaluation.(20) The imaging readers received a prototype manual outlining specific MRI patterns of injury and included examples of each injury type at various ages of imaging. Standardized myelination tables and graphic examples were referenced to facilitate MRI evaluation precision. A final MRI evaluation was computed using a majority consensus reading (2 out of 3 readers). The study was approved by the University of the Witwatersrand Human Research Ethics Committee.

Statistical analysis using SAS Version 9.2 was performed. Descriptive statistics were calculated for categorical data. Clinical characteristics between the different HII categories were compared using Chi-squared Test. A significance level p-value < 0.05 was used. Inter-reader variability was evaluated using Randolph's Free-marginal multi-rater Kappa.

RESULTS

Of the 137 children evaluated, 63.3% were male. The range of children's ages at the time of the MRI study was 22 days to 12 years, with a mean age of 15 months. One child (0.8%) had an MRI in the neonatal period. Almost half (46.9%) of children were older than 2 years at the time of MRI.

The mode of delivery was available in only 5 children (3.9%); 3 of the 5 (60.0%) children delivered by normal vaginal delivery and 2 of the five (40%) children by Caesarian section. 16 (12.5%) children were documented to have received resuscitation at birth; however, specific details of the events were not available. Perinatal resuscitation data was not available for 109 (85.2%) children.

Children with neurological deficits commonly manifested with a combination of deficits (n=46; 35.9%), including tone abnormalities with comorbid seizures. Description of developmental delay was inconsistent; however, a combination of developmental delay (speech and motor) was most frequently observed, n=35 (27.3%). Among the children with clinical HIE, 3 out of 5 were classified as severe, *Supplementary Table 1*. Details pertaining to therapeutic hypothermia were not available in the

Table 1. Description of simplified criteria used for MRI pattern of injury evaluation as described by Charon (20)

Pattern	Criteria
Normal	No signal abnormality in the entire brain.
Punctate periventricular white matter injuries	Punctate or small, confluent periventricular (<1 cm) white matter signal abnormalities.
Watershed	White matter (except punctate periventricular) or cortical signal abnormalities in the intravascular boundary zones, without central or diffuse pattern criteria.
Central	Signal abnormalities in at least one of the following regions: lentiform nucleus, caudate nucleus, thalamus, perirolandic cortex, cerebral peduncle or hippocampus, without diffuse pattern criteria.
Diffuse/mixed	Diffuse white matter signal abnormalities involving at least four lobes or cortical injuries involving more than the perirolandic cortex or watershed cortex, or watershed and central pattern criteria.

Supplementary Table 1. Clinical characteristics available at the time of MRI examination **n = 128**

Characteristic	Frequency (%)
Male	81 (63.3)
Female	47 (36.7)
Age at time of MRI	
0–14 days	0 (0.0)
15–28 days	1 (0.8)
28 days to 6 months	11 (8.6)
6 months 1 day to 12 months	25 (19.5)
12 months 1 day to 24 months	31 (24.2)
Older than 24 months	60 (46.9)
Gestational age at delivery	
Premature (<36 completed weeks)	26 (20.3)
Term (≥36 completed weeks)	6 (4.7)
Not stated	96 (75.0)
Birth weight at delivery	
<1000 g	1 (0.8)
1000–2500 g	11 (8.6)
2501–3500 g	3 (2.3)
>3500 g	0 (0.0)
Not stated	113 (88.3)
Resuscitation required at birth	
Yes	16 (12.5)
No	3 (2.3)
Not stated	109 (85.2)
Neurological deficit	
Tone abnormalities	34 (26.6)
Reflex abnormalities	1 (0.8)
Seizures	12 (9.4)
Multiple deficits	46 (35.9)
None	4 (3.1)
Not stated	31 (24.2)
Developmental delay	
None	48 (37.5)
Present, specific deficit not described	30 (23.4)
Motor	8 (6.3)
Speech	5 (3.9)
Combination	35 (27.3)
Not stated	2 (1.6)
Clinical HIE	
Mild	1 (0.8)
Moderate	1 (0.8)
Severe	3 (2.3)
Not stated	123 (96.1)
Origin of referral	
Internal referral (CMJAH)	101 (78.9)
Rahima Moosa Mother and Child Hospital	20 (15.6)
South Rand Hospital	2 (1.6)
Chris Hani Baragwanath Academic Hospital	4 (3.1)
Edenvale Hospital	1 (0.8)

MRI referral, consequently all included MRIs were interpreted with the presumption that this intervention had not been administered.

MRI DICOM data was available for 128 (93.4%) children. Examples of MRI injury pattern types are demonstrated with FLAIR and T2-weighted imaging in *Figure 1*. A normal MRI from our sample is included for comparison. Complete reader discordance (deficient two out of three majority reading) occurred in 2 of the MRI cases.

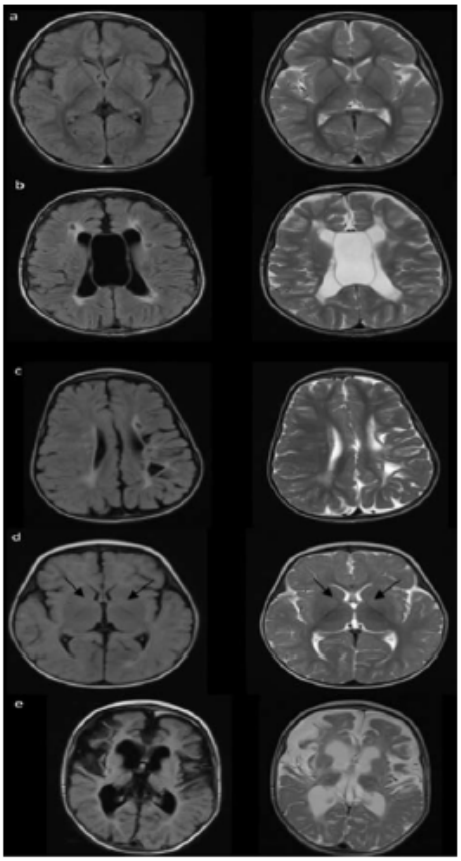
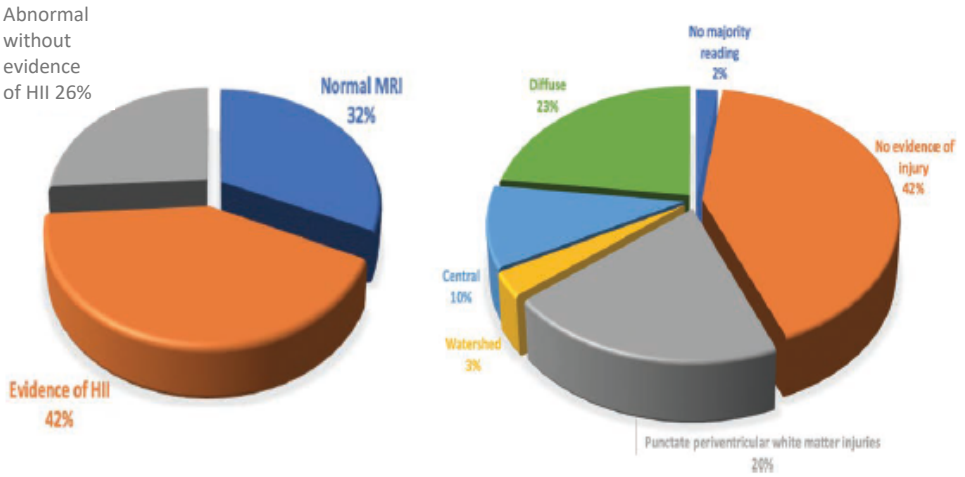


Figure 1. Examples of MRI pattern of hypoxic ischaemic injury with FLAIR (left) and T2-weighted imaging (right). **a** No identifiable injury, for comparison in a 3-year old child. **b** Punctate periventricular pattern in a 4-year old child. **c** Watershed pattern in a 2-year old child. **d** Central pattern in a 2-month old child, black arrows indicate symmetrical hyperintensity within the globus pallidi. **e** Diffuse/mixed pattern in a 6-month old child

Supplementary Figure 1. Categorical findings of MRI studies



MRI evidence of HII was present in 54 (42.2%) of MRI studies and 41 (32.0%) children had entirely normal MRI studies, *Supplementary Fig. 1*.

For miscellaneous MRI findings, including ventriculomegaly, cerebellum, sella and hippocampal evaluations, Kappa values indicate near-perfect inter-reader agreement.

The inter-reader Free-marginal Kappa value for the MRI pattern of injury was 0.30, *Table 2*.

In children with MRI features compatible with HII, 25 (19.5%) and 30 (23.4%) demonstrated punctate periventricular white matter injuries and diffuse patterns respectively. Watershed and central patterns of injury represented a smaller proportion and included 4 (3.1%) and 13 (10.3%) of evaluated MRI studies, *Supplementary Figure 2*.

All of the MRI studies which demonstrated ventriculomegaly had some degree of corpus callosum thinning. Corpus callosum dysgenesis was present in 1 (0.8%) MRI without associated ventriculomegaly.

Children with documented gestational age <36 weeks demonstrated a spectrum of MRI patterns of injury. Punctate periventricular white matter injuries were the commonest in this group, as noted in 9 (34.6%, p=0.2677) children. The only child with a documented birth weight <1000 g was found to have a punctate periventricular pattern of injury. Similarly, children with birth weights between 1000 and 2500 g were commonly found to have a periventricular white matter pattern of injury, n=4 (36.4%).

DISCUSSION

In the setting of HII, MRI is a reliable biomarker and provides invaluable insight into the possible causation of neurological deficit and furthermore has the potential to predict specific clinical manifestations.(17,20) MRI classification of HII patterns of injury is the current neuroimaging practice, facilitating standardized lexicon and common understanding between imagers and referrers.(21) The current study demonstrates a spectrum of MRI patterns of injury in children with suspected HII in a South African population.

Our study reiterates the predominant pattern of periventricular white matter injury in premature infants as described previously in the literature.(17,20) Conversely, all the children in our study with documented gestational age ≥ 36 weeks demonstrated neither punctate periventricular nor watershed patterns of injury, thus providing prognostic implications for premature infants and their term counterparts and their expected relative neurologic deficits. Published literature describes a significant correlation of the severity of central grey nuclei injury with the severity of CP, specifically motor deficits.(22,23)

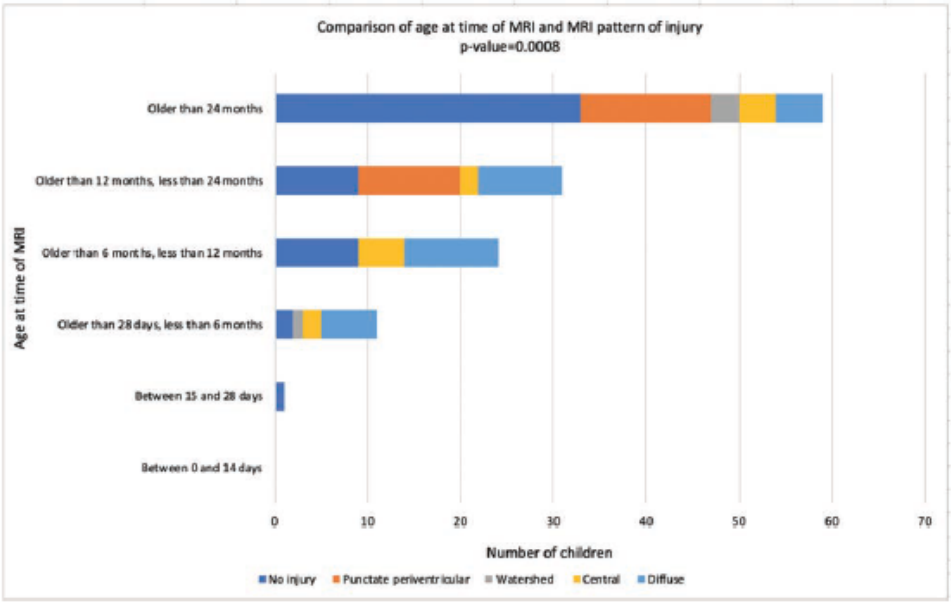
The high cost and limited availability of MRI in the South African state health system is evident in this cohort, where almost half the study cohort were imaged beyond the infant period. State health resources remain deficient with a high disease burden of HIV, TB, non-communicable diseases and trauma.(19) This is compounded by the exponential rise in litigation claims relating to HII and CP, invariably resulting in an irreparable cycle of limited funds, access to adequate neuroimaging and inability of the state to confidently defend such cases without radiological evidence.(11,21) The imbalance of MRI availability is detailed by Kabongo et al where in Gauteng province in 2015, there were 46-fold more MRI facilities in the private sector

Table 2. Description of final MRI findings with inter-reader Free-marginal Kappa **n = 128**

Finding	Frequency (%)	Inter-reader Free-marginal Kappa
MRI pattern of injury		0.30
No majority reading	2 (1.6)	
None	54 (42.2)	
Punctate periventricular white matter injuries	25 (19.5)	
Watershed	4 (3.1)	
Central	13 (10.2)	
Diffuse	30 (23.4)	
Germinal Matrix Haemorrhage		0.90
No haemorrhage	122 (95.3)	
Limited to subependymal matrix	4 (3.1)	
Extending into the ventricular system, without acute ventriculomegaly	1 (0.8)	
>50% ventricular area or acute ventriculomegaly	1 (0.8)	
Germinal matrix haemorrhage with extension into the brain parenchyma	0 (0.0)	
Hippocampus		0.90
Normal	117 (91.4)	
Volume loss	11 (8.6)	
Cerebellum		0.82
Normal	127 (99.2)	
Focal calcifications	1 (0.8)	
Ventriculomegaly		0.94
None	80 (62.5)	
Present	48 (37.5)	
Posterior fossa		0.55
Normal	127 (99.2)	
Mega cisterna magna	1 (0.8)	
Focal intra-axial lesions		0.93
None	127 (99.2)	
Present	1 (0.8)	
Sella		0.93
Normal	128 (100)	
Miscellaneous findings		
No majority reading for specific finding	16 (12.5)	
None	103 (80.4)	
Periventricular calcifications	1 (0.8)	
White matter cysts	2 (1.6)	
Corpus callosum dysgenesis	1 (0.8)	
Hydrocephalus	3 (2.3)	
Subdural effusions	2 (1.6)	

and interestingly 30-fold and 70-fold more in the United Kingdom and Organisation of Economic Cooperation and Development (OECD) during the same period respectively.(19) This wide discrepancy in access and demand of advanced imaging will further challenge any anticipated state healthcare reform. Almost a third (32%) of MRIs in our study were normal and 26% were abnormal without evidence of HII. The relevance of these two groups, combined making up greater than 50%, is paramount in providing sufficient proof to mitigate potential malpractice claims and refuting HII. This is despite the delayed median imaging time from suspected age of injury. Similar inferences were described by Elsingergy et al in a review of 1620 MRIs of South African children with CP involved in medicolegal cases, where the median interval of suspected injury to imaging was six years. Their study established an MRI diagnosis in 92%, but only 76% of cases of CP demonstrated MRI evidence of HII and 31% were either non-HII findings or preterm pattern of HII which can be successfully defended in malpractice suites.(8) The greater

Supplementary Figure 2. Demonstration of children's age at time of MRI and pattern of injury. Majority of children were imaged beyond the age of 2 years



percentage of abnormal MRIs (92% vs 68%) and those consistent with HII (76% vs 42%) in Elsingergy et al analysis, compared to our cohort is explained by selection bias; in our study the inclusion criteria were expanded to include any child suspected of HII, including the subset of CP.

Inter-reader free-marginal agreement for MRI pattern of injury was poor with a Kappa value of 0.3. Possible explanations include subjectivity of the MRI pattern of injury classification with the potential overlap of pattern types, specifically punctate periventricular white matter injuries and watershed patterns. Improved inter reader agreement may in the future be established with comprehensive injury pattern reference guides including a range of children ages. Standardized referral templates for suspected HII MRI studies will facilitate clinical contextualization.

LIMITATIONS

Limitations of our study include an incomplete clinical data set, specifically gestational age, birth weight, perinatal adverse events and standardized clinical assessment. The explanation for this is multifactorial; where more than 20% of children were referred for MRI from a satellite hospital and majority of children were imaged at older than 24 months and perinatal details were incomplete. Despite a positive correlation in our study of premature infants and periventricular white matter injuries as described in the international literature, accurate perinatal data could have improved significance of our findings.

Assessment of HII in the neonatal period and imaging of the sequalae of possible HII in older children illustrates a dichotomy of disease. Our study had a single child imaged in the neonatal period and highlights the local resource deficit regarding pediatric MRI.

CONCLUSION

Hypoxic ischaemic injury and cerebral palsy continue to cause significant morbidity in the South African paediatric population. In this study, we describe a spectrum of MRI injuries in children with suspected hypoxic ischaemic injury. Periventricular white matter pattern of injury was the most common type in premature infants, congruent with international cohorts. Despite the limited availability of MRI in the state health sector, delayed neuroimaging in the setting of suspected HII may provide pivotal evidence of causation. We recommend future studies with robust, standardized clinical criteria and a validated MRI injury reporting scale.

Supplementary Table 2

	Current Study	Elsingergy et al. 2021	Mahlaba et al. 2020	Charon et al. 2015	Aggarwal et al. 2013	Martinez-Biarge et al. 2012	Bax et al. 2006	Krageloh-Mann et al. 2002
Study Period	2 years	Medicolegal database	1 year	2 years, 8 months	2 years	15 years	3 years	8 years
Sample size	137	1620	145	33	98	84	585	17
Region of study	South Africa	South Africa	South Africa	France	India	United Kingdom	Europe	Germany
Age at MRI	Neonates, infants and children less than 15 years Mean age: 15 months	0–18 years	3 months to 18 years *6 children imaged with MRI	Neonates	2–12 years	Neonates	18 months and older	Older than 12 months
Specific exclusions	Chromosomal abnormalities, head trauma, neurocutaneous syndromes, previously investigated congenital neurologic malformations	Duplicated reports Inadequate MRI quality – motion artifact	Children with syndrome and chromosomal abnormalities Children suspected with a progressive disorder	Gestational age <36 weeks Birth weight < 1800 g Neonates that did not have early and late MRI Congenital malformations, compressive airway and neonatal stroke	None	Metabolic disorders, congenital malformation/infection, genetic abnormality or treatment with hypothermia	MRI at age less than 18 months	No specific exclusions, however, MRI needed to have basal ganglia and thalamic abnormalities
Number of normal MRI studies	41 (32.0%)	132 (8%)	Not specifically stated. 11 had normal imaging	Early MRI: 16 (48%) Late MRI: 14 (43%)	4 (4.3%)	Normal or mildly abnormal: 28 (33.5%)	11.7%	Not applicable

	Current Study	Elsingergy et al. 2021	Mahlaba et al. 2020	Charon et al. 2015	Aggarwal et al. 2013	Martinez-Biarge et al. 2012	Bax et al. 2006	Krageloh-Mann et al. 2002
Pertinent findings	Majority of children imaged beyond 24 months Spectrum of MRI pattern of HII Predominant periventricular white matter injury in preterm infants	CP medicolegal database 6 year median age to imaging 76% of MRI diagnosis due to HII, 15% with preterm pattern of HII	*mixed imaging US, CT, MRI (n=6) Periventricular white matter lesions in 54% Combination of findings: deep grey matter nuclei, cortical, parasagittal, middle cerebral artery infarcts.	Neonates with moderate or severe HIE who received therapeutic hypothermia, early and late MRI findings were consistent	No correlation between the types of CP and gestation. Weak correlation between injury type detected on MRI and clinical presentation of CP	White matter injury is the predominant finding in premature infants Low prevalence of motor impairment and development of CP with isolated white matter injury Infants who developed CP had more diffuse white matter injury.	Periventricular white matter injury/hemorrhage is associated with prematurity CP with diplegia was most commonly associated with white matter damage of prematurity Deep grey nuclei injury was associated with dystonic CP Focal infarct resulted in hemiplegia Malformations were present in 32 children	Injury to the basal ganglia and thalamus impairs motor and postural function, locomotion and cognition. Neurologic outcomes of children with deep grey nuclei injuries are poor.

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