Developmental Profiles of Infants with Hypoxic Ischaemic Encephalopathy (HIE) at a Tertiary Hospital in South Africa

Degree of Master of Medicine in Paediatrics

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DECLARATION

I, Ayanda Myaka-Gama (0602767Y), hereby declare that this research report is my own work. It is being submitted for the degree of Master of medicine in paediatrics in the University of the Witwatersrand. It has not been submitted before for any degree or examination at this or any other university.

Signature: 

Date: **18/10/2024**

DEDICATION

This research paper is dedicated to my husband, Simphiwe who has been a constant source of support and encouragement in life. This work is also dedicated to my parents and my sisters who have continually provided their moral, spiritual, emotional and financial support.

Above all, to Almighty God who always gives me strength to keep persevering.

ACKNOWLEDGEMENTS

I would like to express my gratitude and appreciation to my supervisors for their continued support, patience, motivation, and enthusiasm.

Developmental Profiles of Infants with Hypoxic Ischaemic Encephalopathy (HIE) at a Tertiary Hospital in South Africa

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Abstract

Background: Hypoxic ischaemic encephalopathy is one of the most common causes of neonatal death and severe neurological deficit in children.

Objectives: To describe the neurodevelopmental outcomes of infants with moderate and severe HIE at Chris Hani Baragwanath Academic Hospital (CHBAH) and the proportions with neurodevelopmental impairment (NDI) and neurological complications. To explore the effect of HIE severity and therapeutic hypothermia (TH) on the neurodevelopmental outcome.

Methods: A retrospective, descriptive study was conducted at CHBAH Neonatal Neurodevelopmental Clinic (NNDC). 239 infants with moderate and severe HIE, attending between 2015 and 2020, met the inclusion criteria. Neurodevelopmental outcomes were assessed using the Griffiths Mental Developmental Scales at 1 year. General Quotient scores were used to define NDI. Clinical and investigation criteria determined those with neurological complications.

Results: Of the 239 infants, 211 (88.3%) and 28 (11.7%) had moderate HIE and severe HIE, respectively. Cerebral palsy was diagnosed in 9.2% and NDI in 17.1% of the cohort. Severe HIE infants had significantly higher rates of NDI and CP, 50% (14) and 21.4% (6) respectively, as compared to moderate HIE infants, 12.7% (27) NDI and 7.6% (16) CP. One hundred and fifty-two (72%) moderate and 14 (50%) severe HIE infants received TH. Infants who received TH were less likely to have NDI (p=0.005), CP (p=0.002), epilepsy and visual impairment.

Conclusions: Neurodevelopmental outcomes compared favourably with other countries. Developmental scores were in the average range for the cohort with equivalent profiles across domains. Therapeutic hypothermia was associated with decreased CP and NDI in both groups.

Keywords: Neonates, asphyxia, therapeutic hypothermia, Griffiths Mental development Scales (GMDS), general quotient, subscales, neurodevelopmental impairment (NDI).

Contributions: AMG, SL, SM, FLN conceptualized the study. AMG collected data. AMG and KT analysed the data. AMG wrote the first draft. SL, SM, KT and FLN edited the subsequent drafts. All authors contributed to the final draft of the manuscript.

Abbreviations

ADHD: attention deficit hyperactivity disorder

AED: Antiepileptic Drugs

CHBAH: Chris Hani Baragwanath Academic Hospital

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital

CP: Cerebral Palsy

CT: Computed Tomography

DQ: Development Quotient

GDD: Global Developmental Delay

GMDS: Griffiths Mental Development Scales

GMFCS: Gross Motor Function Classification System

HI: Hearing impairment

HIC: High Income Countries

HIE: Hypoxic Ischaemic Encephalopathy

LMIC: Low and Middle Income Countries

MDT: Multidisciplinary Team

NDI: Neurodevelopmental impairment

NNDC: Neonatal Neurodevelopment clinic

TH: Therapeutic Hypothermia

TS: Thompson Score

Wits: University of the Witwatersrand

Presentations

1. Paediatric Research Day (2022)
2. Priorities in Perinatal Care (2023)
3. International Developmental Pediatrics Association Congress (2023)

Author Guidelines African Journal of Disability

Original Research Articles

An original research article needs to provide an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Submission status	open
Word limit	7000 words (excluding the abstract, tables, figures, graphs, and references)
Abstract	maximum: 250 words requires structural headings: Background, Objectives, Method, Results, Conclusion and Contribution
Main text	requires structural headings, refer to the full structure 'Ethical considerations' is a sub-section in the manuscript and must include: Name of the ethical review committee Study approval number Manner of consent (written, oral) for human participants Description of measures taken to maintain the confidentiality of data If the study was not human or animal research or the study was determined to be non-human subjects research or exempt, the authors must provide a statement with those details in this section.
References	60 or less, adhere to the **Harvard referencing style**
Tables, figures and graphs	7 or less, adhere to the Illustrations requirements found in the AOSIS House style guide
Formatting requirements	apply the guidelines located on the **Formatting requirements page** and the **AOSIS house style guide**
Compulsory supplementary file(s)	the **Authorship, disclosure statements, copyright, and license agreement form**, **Ethical Clearance/Waiver Documentation** and any other relevant form applicable to your submission
Ethical clearance/waiver documentation	evidence of ethical clearance for the study, such as the study approval letter or certificate from the Institutional Review Board (IRB), a waiver from the IRB et cetera

Introduction

Hypoxic ischaemic encephalopathy (HIE) is a heterogeneous syndrome characterized by neurologic dysfunction in an infant born at or beyond 35 weeks of gestation with failure to initiate and maintain respiration, manifested by reduced level of consciousness or seizures and often accompanied by depression of tone and reflexes (Coetzee, 2018). HIE is one of the commonest causes of neonatal mortality and severe neurological deficit in children and contributes to ever increasing medico-legal litigation (Bhorat et al., 2023). In low- and middle-income countries (LMIC), neonatal encephalopathy accounts for approximately 1 million deaths annually (Pauliah et al., 2013). Globally 287 000 infants with HIE were estimated to have died in 2010 (Lee et al., 2013). The incidence of HIE varies considerably, with the greatest burden occurring in Sub-Saharan Africa (14.9 per 1000 live births) and much lower rates (1.5 per 1000 live births) in high income countries (HIC) (Ballot et al., 2020). Charlotte Maxeke Johannesburg Academic hospital (CMJAH), a tertiary referral centre in South Africa, had HIE rates of 2.3 – 13.3 per 1000 live births in 2016 (Ballot et al., 2020). In 2011, Chris Hani Baragwanath Academic Hospital (CHBAH) reported the incidence to be 8.7-15.2 per 1000 live births (Bruckmann and Velaphi, 2015). Nakwa et al reported an incidence of 8.8/1000 live births with an overall mortality of 29% (Nakwa et al., 2023). More than 400 000 infants each year develop NDI after HIE. In 2010, about 233 000 infants survived with moderate or severe NDI (Lee., 2013).

The rate of mortality and the severity of neurodevelopmental impairment (NDI) correlates with the severity of HIE, using the Thompson score (Thompson et al., n.d.) and Sarnat scoring systems (Sarnat and Sarnat, 1976). Neurodevelopmental impairment includes cerebral palsy (CP), cognitive impairment, visual and hearing impairment, epilepsy, learning disabilities, autism, attention deficit hyperactivity disorder (ADHD) and subtle deficits affecting learning later in childhood (Azzopardi et al., 2014). Infants with mild HIE have been shown to have few motor or intellectual deficits at preschool age, while those with severe HIE are more heterogeneous in terms of outcomes, have higher mortality and rates of NDI (Van Handel et al., 2007). The risk of severe impairment in at least one domain is high after intrauterine and neonatal insults (Mwaniki et al., 2012).

Therapeutic hypothermia (TH) remains one of the most effective neuroprotective interventions available for HIE (Coetzee, 2018). Management with TH has been shown to improve survival and neurodevelopmental outcome at 18 months of age in infants with Stage 2 and Stage 3 encephalopathy (Mathew et al., 2022). This neuroprotective effect has been seen to persist at 6 to 7 years of age (Coetzee, 2018).

Very few studies have examined the developmental profiles of HIE infants. Stark et al. managed 30 HIE children from 3 months to 5 years at a secondary hospital in South Africa. Gross motor ability exceeded both cognitive and fine motor skills at 5 years of age (Stark et al., 2020). These findings are in contrast to research findings from HIC, where fine motor ability supersedes gross motor (Mc Guiness et al., 2012). It has been postulated that in less advantaged communities, children engage in more outdoor play as there is less access to formal schooling and technology (Stark et al., 2020). In this study children with mild HIE developed appropriately, while cerebral palsy was associated with severe HIE. Those infants with HIE and no major motor disability had an increased risk of long-term intellectual, verbal and motor deficits at 5 years of age (Stark et al., 2020). In this study, we aimed to describe the range of NDI and the developmental profiles at 1 year of age in infants with Stage 2 and 3 HIE who were managed with and without TH.

Methods

Design and objectives

This was a retrospective, descriptive study of the Neonatal Neurodevelopment Clinic (NNDC) database and records, at CHBAH, a tertiary academic hospital in Johannesburg South Africa. The primary objective was to document the Griffiths general and subscale quotients (GQ and SQ) and to determine the proportion with neurodevelopmental impairment, cerebral palsy, epilepsy, visual and hearing impairment, in one year old children attending the NNDC. The secondary objective was to compare the performance on the GMDS in those that were managed with therapeutic hypothermia and those that were not.

Setting

CHBAH has approximately 8000 caesarean section deliveries and 19000 live births annually. The NNDC was started in 2012 with the aim of monitoring all infants born or referred to this hospital with HIE. The clinic aims to detect developmental delay and neurological complications early and initiate interventions and parental education, to minimize disability. This multidisciplinary clinic comprises neonatologists, neurodevelopmental paediatricians, and allied professionals (physiotherapists, occupational and speech therapists). Infants are seen regularly from 6 weeks to 2 years of age. Standardized developmental testing takes place in all infants unless appointments are missed or in cases of acute illness or profound neurological impairment, where a formal assessment is not possible (43 infants were excluded for these reasons). The Infant Neuromotor Assessment is performed at 4-5 months of age and the GMDS at around 12 and 18- 24 months in all patients, by GMDS-certified neurodevelopmental specialists. Cranial ultrasounds are performed routinely during neonatal admission and repeated at the first clinic visit. CT Brain or MRI are ordered when clinically indicated. Hearing tests are also conducted during the neonatal admission but in cases where this did not occur, referral is made to audiologists. Hearing testing at this clinic involves initial Automated Auditory Brainstem Response (AABR) screening and Otoacoustic Emission (OAE) testing, followed by a Brainstem Auditory Evoked Response (BAER) if necessary.

Vision is assessed clinically and if there are signs of visual impairment such as nystagmus and impaired fixation and/or following, this results in patients being referred to St John's Eye Hospital and a computed tomography (CT) scan of the brain booked. At 2 years of age, children are either discharged or in the case of developmental concerns, referred to the appropriate specialist clinic for ongoing support. Patient records have been captured in an Excel database since 2012 and this is updated weekly by the head neurodevelopmental paediatrician.

Population and sample size

The population comprised all infants seen at NNDC over a 6-year period, between January 2015 and December 2020. There were 355 patients in total and this included infants with mild, stage 1 HIE (Figure 1). Severity of HIE with the Sarnat (Appendix 1) and Thompson scoring (Appendix 2) methods was assigned during the neonatal admission. Encephalopathy was graded based on the clinical presentation at birth, including seizures, level of consciousness, autonomic nervous

system instability, gross motor system functioning, and primitive reflexes. Sarnat stage 2 HIE was defined as moderate and stage 3 HIE as severe. Infants eligible for this study were those with moderate (stage 2) and severe (stage 3) HIE, birth weight ≥ 2000g, a GMDS assessment at 12 months of age and all CP infants (regardless of GMDS assessment). This resulted in 239 infants – 211 with moderate and 28 with severe HIE (Figure 1). This study aimed to measure the burden of NDI and neurological complications in those with moderate- to severe HIE.

CHBAH neonatal unit uses the TOBY criteria for determining eligibility for TH. The following TH exclusion criteria apply: no spontaneous respiratory effort after 30 minutes post-resuscitation, heart rate below 100 b/min at 20 minutes post-resuscitation, neonates who present beyond 6 hours post-delivery and those with major congenital abnormalities. Some infants may not have received TH due to these exclusion criteria or unavailability of TH equipment due to demand (Figure 1).

Outcome measures

Clinical examination was performed at every clinic visit with detailed documentation of neurological status, including evidence of epilepsy, cerebral palsy, visual or hearing impairment. Investigations and specialist referrals were conducted as previously described. Cerebral palsy was further categorized into subtypes (spastic, hypotonic, dyskinetic, and mixed) and formally diagnosed at 1 year.

In this study, a patient was considered to have epilepsy when recurrent non-febrile seizures had occurred outside of the neonatal period, and which required antiepileptic treatment. Visual impairment is diagnosed clinically and patients are referred to the ophthalmologist. Neuroimaging is requested to diagnose cortical visual impairment. Hearing impairment is defined as abnormal OAE or BAER either unilateral or bilateral.

Neurodevelopmental measures

The GMDS (0–2-year scale) 2nd edition (Extended Revised) was used to measure neurodevelopmental status. The test has been used routinely at this clinic since 2012, by GMDS-certified clinicians with many years of experience. It assesses children from birth to 2 years of age, providing an overall general developmental quotient (GQ) score and sub-quotient (SQ) scores in the 5 developmental subscales (A-E); Locomotor scale (Scale A), Personal-social scale

(Scale B), Hearing and Speech scale (Scale C), Eye and Hand Coordination scale (Scale D) and the Performance scale (Scale E) (14). The GMDS subscales were reported as general quotients, sub-quotient scores with, age equivalents and percentiles.

Neurodevelopmental impairment (NDI) was defined based on the general quotient scores and severity of NDI was assessed as mild, moderate or severe. A GQ score of >85 was classified as appropriate development, 80-84 mild NDI, 70-79 was moderate NDI and a score less than 70 (< -2 SD) severe NDI.

GMDS is used extensively in research settings in South Africa (Luiz et al., 2001, Amod et al., 2007, Jacklin & Cockcroft., 2013). Amod et al demonstrated that South African children similar to British counterparts with no difference in GQ scores (Amod et al., 2007). South African scores from different race and language groups, showed good correlation with the British normative values. Positive correlation has been shown between the GMDS (0-2 year) and the Bayley's Scales of Infant Development- II (BSID-II) (Cirelli et al., 2015); the general quotient (GQ) of the GMDS-ER correlated with scores on the Junior South African Individual Scales (JSAIS), as well as academic school performance in South African children (Laughton et al., 2010).

Data collection and analysis

The demographic data was extracted from neonatal files and the Asphyxia and Neonatal - REDCap Neonatal Databases. The GMDS data variables were extracted from the NNDC database. Data was analyzed using Statistica (version 13). Categorical variables were represented as frequencies and proportions. Continuous variables were reported as means and standard deviations or medians and interquartile ranges depending on the distribution of the data. Comparative statistics were performed to identify factors associated with an abnormal subscale/domain. A chi-square or Fischer exact test was done to compare categorical variables and Mann-Whitney U test for skewed continuous variables. A p-value of <0.05 was significant.

Ethical considerations

The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M220248). The Asphyxia database registry ethics number is M1511100 and

the Neonatal Redcap database number is M151196. Informed consent was waived as this was a retrospective study. Confidentiality was maintained by assigning a study number to the subjects.

Results

A total of 355 infant files were reviewed. One hundred and sixteen were excluded. (Details in figure 1). Two hundred and thirty-nine infants were included, 211 (88.3%) were stage 2 and 28 (11.7%) were stage 3. Therapeutic hypothermia was received by 166 (69.5%) infants, 152 were stage 2 and 14 were stage 3. Therefore, 72% of stage 2 and 50% of stage 3 infants received TH (Figure 1).

The mean gestational age and birth weight at delivery were 38.8 (±1.7) weeks and 3116g (±503.4), retrospectively. One hundred and thirty-nine infants (58.2%) were male and more than half of the infants 136 (56.9%) were delivered vaginally. Most infants (86.2%) were born to HIV negative mothers. There were significantly lower APGAR scores and higher Thompson scores (TS) in the stage 3 HIE group, in Table 1. A greater number of stage 2 HIE patients received TH ($p = 0.001$)

Neurodevelopmental impairment (NDI) was observed in 17.1% (41) of the whole cohort of which majority (63.4%) had severe NDI (GQ < 70), while 17.1% had moderate NDI (GQ 70-79). NDI occurred in 12.7% (27) of the stage 2 (22.2% mild, 22.2% moderate, and 55.6% severe NDI) and in 50% (14) of the stage 3 HIE group (14.3% mild, 7.1% moderate, and 78.6% severe) as shown in – Figure 2. The severity of NDI was not significantly different between the TH and non-TH groups; $p = 0.25$.

Just under half ($n = 20$; 48.8%) of those with NDI had not received TH (Table 2). Sixteen stage 2 NDI infants and 5 stage 3 received TH. Infants with stage 3 had higher rates of NDI than those with stage 2 [14(50%) vs 27 (12.8%); $p < 0.001$]. Infants with stage 3 who received TH had fewer NDI [5 (35.7%) vs 9 (64.3%); $p = 0.005$]. There were no significant differences in GQ and Griffith subscales between Sarnat stage 2 and 3 in those with NDI as shown in Table 2. NDI and CP were less frequent in the group that received TH compared to the group that did not, [NDI: 21 (12.1%) vs 20 (27.4%); $p = 0.005$ and CP: 9 (5.4%) vs 13 (17.8%); $p = 0.002$].

Twenty-two (9.2%) of the infants had CP, 16 (72.7%) Sarnat stage 2 and 6 (27.3%) stage 3. Eight (50%) with stage 2 received TH and only one (16.7%) infant with stage 3 received TH. More than a third (36.3%) of infants with CP had seizures, 6 (27.3%) were blind and 3 (18.7%) had hearing impairment. Out of the 9 CP patients that received TH; 2 (22.2%) were blind, 1 (11.1%) had hearing impairment and 4 (44.4%) had epilepsy.

There was a significantly higher percentage of infants with visual impairment, epilepsy, and cerebral palsy in the stage 3 group versus stage 2 HIE in Table 3. More than a fifth (21.4%) of stage 3 HIE infants were diagnosed with cerebral palsy; 21.4% had visual impairment and a quarter (25%) had epilepsy. Stage 2 infants had less complications with 7.5% diagnosed with CP, 0.9% visual impairment and 6.6% epilepsy.

Overall median GQ scores were within normal range for Sarnat stage 2 and 3 infants. However, stage 3 GQ scores [89.5 (69-105)] were significantly lower than stage 2 [(GQ 103 (95-109)], p=0.002). Stage 2 infants outperformed stage 3 infants in all domains. This difference was significant in all subscales, except in the language domain (subscale C) in Table 4. Therapeutic hypothermia resulted in significantly higher GQ ($p = 0.002$) and subscale scores in Sarnat stage 2 and 3 (data not shown). This effect was also clearly shown in the stage 3 group. Those that did not receive TH had median GQ and subscale scores in the severe NDI range (GQ 69 (43-100) vs 101 (83-107); $p = 0.02$) in Table 5.

Discussion

This study revealed that infants with stage 2 and stage 3 HIE followed up at CHBAH NNDC over a 6-year period, had NDI in 17.1% and CP in 9.2% at 1 year of age. Neurodevelopmental impairment was present in half of the stage 3 and in 12% of stage 2 HIE infants. Cerebral palsy was diagnosed in 21.4% of Stage 3 infants and in 7.6% of stage 2 infants. Epilepsy, visual impairment, lower APGAR scores and higher Thompson scores were also more frequent in the Stage 3 group. This is consistent with a large body of research globally which shows that the incidence of long-term disability is related to the severity of HIE.

Cochrane review in 2007 reported that as many as 80% of infants who survive severe HIE develop serious complications, 10-20% have moderate disabilities, and 10% are healthy. Among

the infants who survive moderate HIE, 30-50% may have serious long-term complications, and 10-20% have minor neurologic morbidities (Evans et al., 2007).

Reported rates of cerebral palsy following HIE vary but are generally around 10%-13% among survivors of moderate to severe encephalopathy in HIC, with dyskinetic CP and spastic quadriplegia being the most common subtypes. Rates of hearing loss are reported to be as high as 17.1% in those with other persistent neurological deficits. Up to 41% of infants with a diagnosis of HIE have an abnormality in some element of visual function in the first year of life. (Ahearne et al., 2016)

Mbatha et al. reported on a 32% impairment in 2-year-old infants that received TH at CHBAH and 6% showing impairment at 1 year of age (Mbatha et al., 2021). Studies have reported NDI rates between 34.3% to 36% in infants with stage 2 and 3 HIE (Carli et al., 2004; Kachhwaha et al., 2023). In Kathmandu, 45 % of the neonatal encephalopathy patients died in the neonatal period, 20% had NDI in survivors at 1 year, and a physical disability rate of 25% was predicted in those with moderate neonatal encephalopathy (Ellis et al., 1999). In Bangladesh, normal development and mild impairment were found in 21.6% of children, all of them having stage 1 or stage 2. Moderate and severe impairment was found in 33% and 25% cases respectively (Thayyil et al., 2021). In this study, more infants with stage 3 had NDI than those with stage 2. This is similar to a report in 2013 at CHBAH, by Sukha, where infants with stage 3 (100%) had significantly more developmental delay ($p = 0.01$) than those with stage 2 HIE (52%). More infants with stage 3 had both gross and fine motor delays (Sukka,2013).

The findings of this study support the use of TH as a neuroprotective strategy in both Stage 2 and stage 3 HIE. Therapeutic hypothermia was associated with fewer NDI ($p = 0.005$) and CP ($p = 0.002$) in these infants. General quotients and SQ median scores were significantly higher in those who received TH and particularly in the stage 3 group.

Many other studies have reported on the benefit of TH in reducing NDI. A systematic review by Matthew et al reported that TH reduces neurologic disability and cerebral palsy in infants with stage 2 and stage 3 (Mathew et al., 2022). A randomized clinical trial by Laptook resulted in a 76% probability of any reduction in death or disability and a 64% probability of at least 2% less death or disability (Laptook et al., 2017). Azzopardi et al. found that infants with HIE who

received TH had significant reductions in the risk of CP (21% vs 37%; p = 0.03) and that the frequency of moderate to severe disability was lower in the TH group (22% vs 37%; p = 0.03) (Azzopardi et al., 2014). Edwards et al. found that TH increased survival with normal neurological function and in survivors reduced the rates of severe disability (Edwards et al., 2010). Kachhwaha et al. found that 85.7% of the infants in the TH group were neurodevelopmentally normal. In the non-TH group, 15 (42.8%) were normal and 20 (57.2%) were having some neurodevelopmental abnormality (Kachhwaha et al., 2023). A study by Gano et al. reported that the proportion of patients with NDI at 12 months was significantly lower ($p < 0.05$) in the TH group (9.43%) than the non-TH group (36%) (Gano et al., 2014). Ellis et al found that majority with NDI had severe NDI and 78% of those children had CP (Ellis et al., 1999). In this study infants who received TH were less likely to develop NDI and CP. There were lower rates of CP as the moribund infants were excluded from receiving TH and the more severe infants died in the neonatal period.

General quotients and SQs were in the normal range for the group as a whole at 1 year. There were differences in all subscales except for subscale C in all group comparisons. Language testing at 12 months may be less sensitive than later testing as the 1st year milestones mostly relate to prelinguistic skills and communicative intent. It is during the 2nd year that the complexity of language, both vocabulary and receptive language, increase rapidly. There is a lexical spurt in vocabulary development at around 17 months (Serrat-Sellabona et al., 2021). Language delays, especially subtle deficits, are more likely to be to be detected the later standardized testing is performed. Items recorded on the GMDS at 12 months include understanding 1-2 single words, singing, observing the response to name and inhibitory words and some rely on maternal report. Mbatha et al. reported higher rates of NDI on GMDS testing at 18-24 months than at 12 months. Therefore, standardized testing at 2 years and beyond provides a deeper understanding of subtle deficits. Language is therefore unlikely to be a sensitive indicator of neurodevelopmental delay at 1 year of age using the GMDS. Specific standardized language tools should be considered for testing at 12 months in future studies.

A third of infants in the same institution with stage 2 and stage 3 who received TH had moderate to severe neurodevelopmental abnormality at 18-24 months, majority survived with mild or no disability at 2 years (Mbatha et al., 2021). These findings emphasise the importance of ongoing

developmental assessment beyond the first year of life. Normal scores on GMDS at 1 or 2 years do not always predict good outcome at 6 and 7 years. An abnormal score is very likely to be associated with poor performance at school age (Barnett et al., 2004). Early neurodevelopmental assessment at 1 and 2 years does not exclude cognitive, neurological or perceptual motor abnormalities at school age. The sensitivity values for the GMDS were slightly higher at 2 years than at 1 year (90% vs 76%) (Barnett et al., 2004). Knowledge of the outcome of this group of children is important because these subtle problems can affect later scholastic achievement and behavioural adjustment. Failure to identify such children in infancy results in a missed opportunity for early intervention which may help them cope better at home and at school (Barnett et al., 2004).

Conclusion

Neurodevelopmental impairment (NDI) and CP were observed in 17.1% (41) and 9.2% (22) of the cohort, which compares favourably with other countries. The GQ and SQ scores were in the average range for the cohort with equivalent profiles across the 5 domains. Therapeutic hypothermia and moderate HIE were associated with decreased CP and NDI. Neurodevelopmental assessments at 2 years and beyond are necessary to determine longer term outcomes and subtle deficits.

Strengths

This study investigated data which was collected over a 6-year period at the largest hospital in Sub-Saharan Africa. The sample was large and standardized GMDS testing was routinely performed in all patients, resulting in high quality data.

Limitations

This was a retrospective descriptive study and therefore could not evaluate causation. only associations. The severe HIE group had far smaller numbers than the moderate group; 50% had

NDI and 21.4% had CP. Though these results were encouraging when compared to other studies which report rates of NDI around 80% for severe HIE, they should be interpreted cautiously. These infants represent a small sample biased in that the most severe of the group had demised. They also had lower rates of TH in this group as compared to the moderate HIE sample. The infant GMDS at 12 months may not detect subtle language deficits and therefore, analysis at later ages or alternative standardized tools should be considered.

Acknowledgements

The Neonatal REDCap database and the Asphyxia database.

Funding: nil

Conflicts of interest: none

Figures and tables

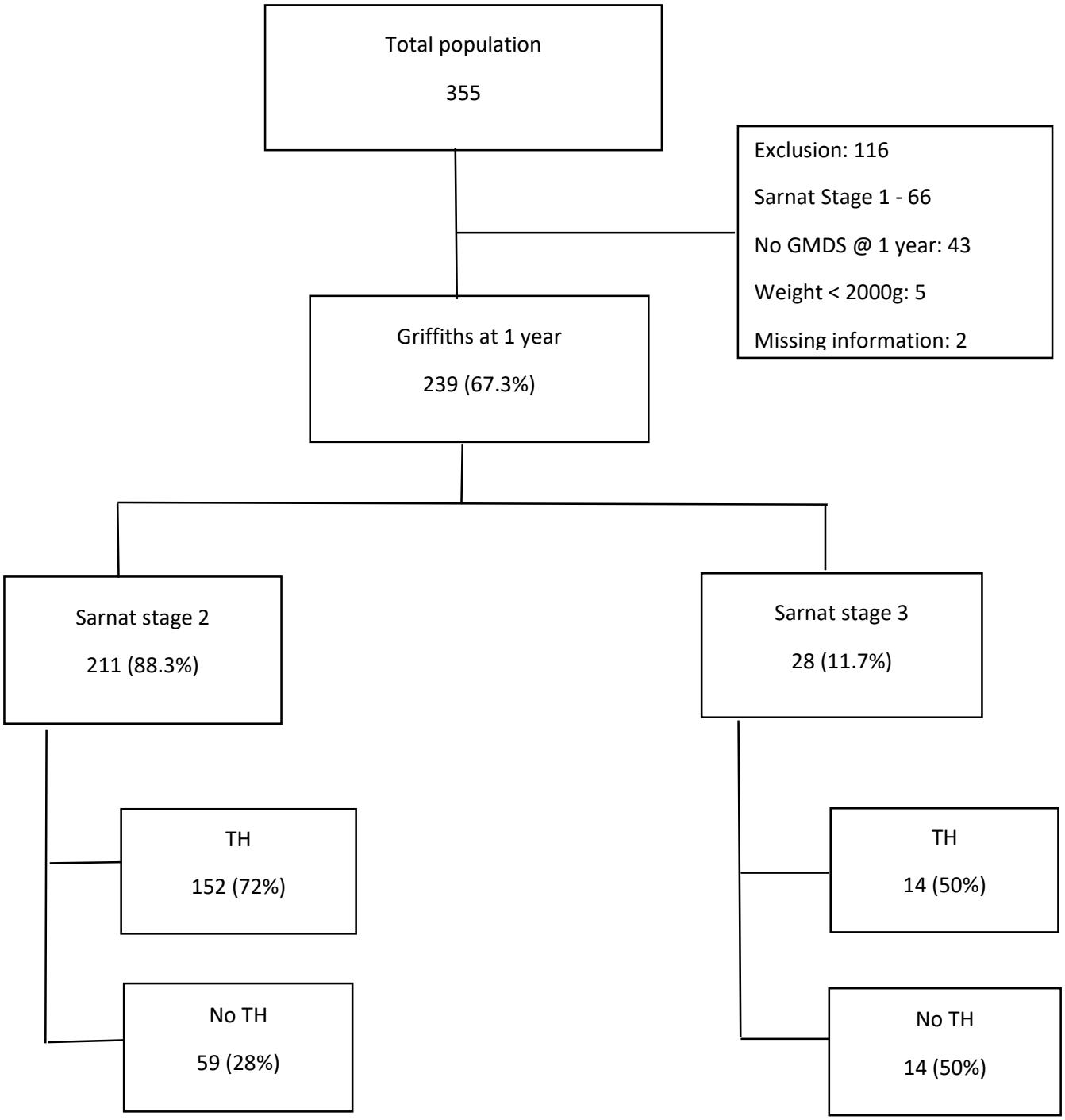

Figure 1: Flow diagram of infants included in the study

Table 1: Demographics of Infants with Moderate to Severe HIE

Variable	All N=239 N (%)	Stage 2 N=211 N (%)	Stage 3 N=28 N (%)	p-value
Gestational age* (weeks)	38.8 ±1.7	38.8 ±1.8	39.2 ±1.8	0.26
Birthweight* (grams)	3116 ±503.4	3112 ±485.6	3145 ±631.5	0.82
Mode of Delivery Caesarean Section	103 (43.1)	95 (45)	8 (28.6)	0.09
HIV unexposed	206 (86.2)	183 (86.7)	23 (82.1)	0.33
Male	139 (58.2)	122 (57.8)	17 (60.7)	0.46
Apgar at 1 minute#	3 (2 – 5)	3 (2 – 5)	2 (1 – 4)	0.001
Apgar at 5 minutes#	6 (5 - 7)	6 (5 – 7)	4 (3 – 5)	<0.001
Thompson score (admission)*	10 ±3.2	10 ±3.0	14.0 ±3.7	<0.001
Therapeutic hypothermia	166 (69.5)	152 (72)	14 (50)	0.01
Age at Griffiths* (months)	12.5 ±1.6	12.5 ±1.6	12.2 ±0.8	0.40

*** Mean (SD), # Median (IQR)**

Figure 2: Severity of neurodevelopmental impairment in Infants with Sarnat Stage 2 and 3

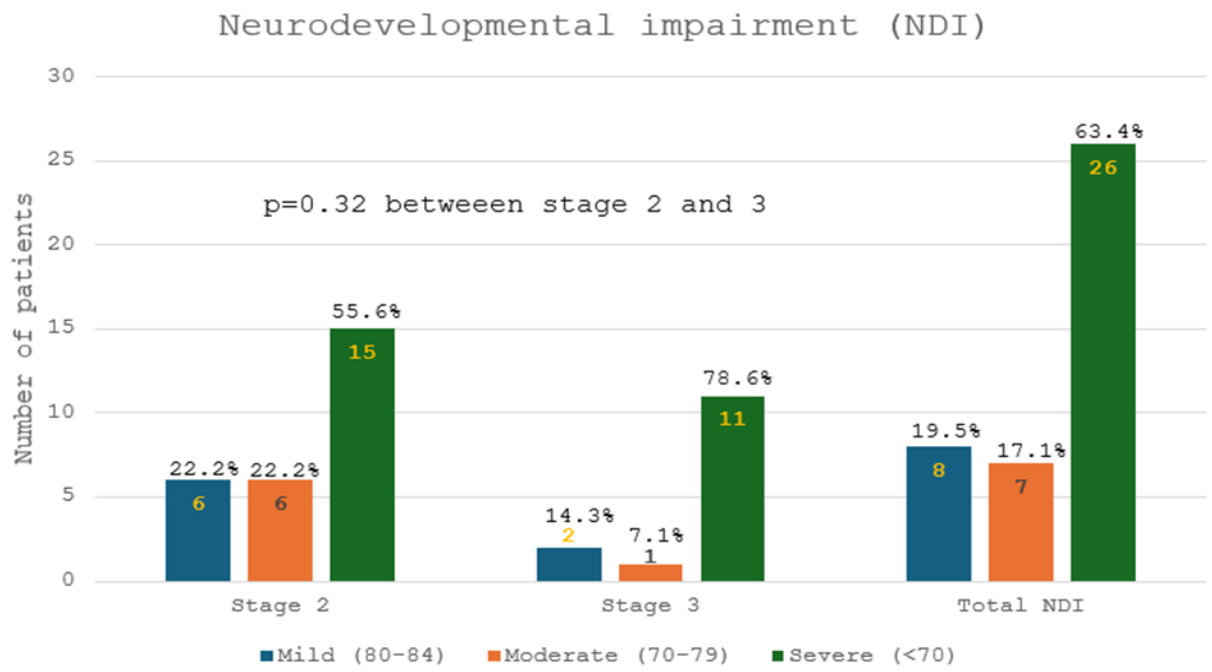

Table 2: Comparisons of TH, GQ and Subscales in Sarnat stages 2 and 3 infants with NDI

	NDI			
	All (stages 2 & 3) N = 41	**Sarnat Stage 2 n = 27**	**Sarnat Stage 3 n = 14**	**p-value**
TH	21 (51)	16 (59)	5 (36)	0.19
No TH	20 (49)	11 (41)	9 (64)	
	All (stages 2 & 3) n=36	**Sarnat Stage 2 n = 26**	**Sarnat Stage 3 n = 10**	
Subscale A (Locomotor)	52.5 (31-71)	55 (23-73)	52 (46-63)	0.90
Subscale B (Personal-Social)	60 (38-74.5)	61 (38-73)	54 (37.5-77)	0.71
Subscale C (Hearing and Language)	83 (49-92.5)	85 (50-93)	72 (48-92)	0.76
Subscale D (Eye, Hand Co-ordination)	56 (31.5-73)	60 (32-72)	51.5 (31-74)	0.68
Subscale E (Performance)	58.5 (31-78.5)	61.5 (33-73)	50 (29-83)	0.66

Table 3: Complications in Infants with Moderate to Severe HIE

Variable	All N=239 N (%)	Stage 2 N=211 N (%)	Stage 3 N=28 N (%)	p-value
Blind	8 (3.3)	2 (0.9)	6 (21.4)	<0.001
Hearing impairment	6 (3.1)	4 (1.9)	2 (7.1)	0.19
Epilepsy	21 (8.8)	14 (6.6)	7 (25)	0.005
Cerebral Palsy	22 (9.2)	16 (7.5)	6 (21.4)	0.02

Type of Cerebral Palsy (CP): Mixed CP-7, Spastic CP-4, Dystonic CP-2, Right hemiplegia-2, Unspecified-7

Table 4: Griffiths Subscale for Sarnat Stage 2 and Sarnat Stage 3

Variable	All N=232 Median (IQR)	Sarnat Stage 2 N=207 Median (IQR)	Sarnat Stage 3 N=25 Median (IQR)	p – value
Age at Griffiths	12 (12-13)	12 (12-13)	12.2 (12-12.5)	0.40
GQ	103 (93-109)	103 (95-109)	89.5 (69-105)	0.002
Subscale A (Locomotor)	101 (89-109)	101 (91-109	96 (55-104)	0.03
Subscale B (Personal-Social)	99 (87-105)	100 (89-105)	91 (60.5-103)	0.04
Subscale C (Hearing and Language)	107 (100-114)	107 (100-114)	107 (84-114)	0.48
Subscale D (Eye, Hand Co-ordination)	100 (89-111)	104 (90-111)	97 (56-106)	0.03
Subscale E (Performancce)	101 (90-109)	101 (92-110)	98 (61.5-104)	0.04

GQ General Quotient

Table 5: Griffiths Subscale for Sarnat Stage 3 for TH compared to Non-TH Infants

Variable	TH N=14 Median (IQR)	Non-TH N=14 Median (IQR)	p – value
Age at Griffiths	12.0 (12-13)	12.5 (12-13)	0.25
GQ	101 (83-107)	69 (43-100)	0.02
Subscale A	101 (77-109)	63 (46-97)	0.02
Subscale B	97 (89-105)	55 (37.5-99)	0.03
Subscale C	111 (103-115)	78 (48-110)	0.03
Subscale D	100 (95-106)	55 (31-106)	0.15
Subscale E	101 (84-106)	68 (29-101)	0.04

GQ General Quotient

APPENDIX 1

SARNAT CLASSIFICATION

Variables	Stage I (Mild)	Stage II (Moderate)	Stage III (Severe)
Consciousness	Hyperalert	Lethargic or obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular control			
a. Muscle tone	Normal	Mild hypotonia	Flaccid
b. Posture	Mild distal flexion	Strong distal Flexion	Intermittent decerebration
c. Stretch reflexes	Overactive	Overactive	Decreased or absent
Primitive reflexes			
a. Sucking	Weak	Weak or absent	Absent
b. Moro	Strong	Weak incomplete/strong	Absent
c. Tonic neck	Slight		Absent
Autonomic function			
a. Pupils	Dilated	Constricted	Variable, unequal
b. Heart rate	Tachycardia	Bradycardia	Variable

APPENDIX 2

THOMPSON SCORE

Sign	Score			
	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
Level of consciousness	Normal	Hyper alert, stare	Lethargic	Comatose
Fits	None	Infrequent <3/day	Frequent >2/day	
Posture	Normal	Fisting, cycling	Strong, distal flexion	Decerebrate
Moro-reflex	Normal	Partial	Absent	
Grasp-reflex	Normal	Poor	Absent	
Suck-reflex	Normal	Poor	Absent	
Respiratory pattern	Normal	Hyperventilation	Brief apnoea	IPPV (apnoea)
Fontanelle	Normal	Full, not tense	Tense	

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Protocol

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INTRODUCTION, BACKGROUND AND RATIONALE FOR THE STUDY

Nearly 140 million children per year are born worldwide, with 3.6 million neonatal deaths and 2.6 million still births (1). The WHO and UNICEF countdown report of 2015 estimated that neonatal deaths account for 45% of the 5.9 million child deaths that occurred in 2015 globally (2). The gap between low and middle income countries (LMIC) and high income countries (HIC) with regards to neonatal mortality still remains wide. A child born in LMIC is 14 times more likely to die during the first 28 days of life than a baby born in a HIC, with Sub-Saharan Africa and South East Asia being most affected (5).

Prematurity and hypoxic ischaemic encephalopathy (HIE) are responsible for most of these neonatal deaths, with HIE being a preventable cause of death. In LMIC, neonatal encephalopathy accounts for approximately 1 million deaths annually (8). Intrapartum hypoxia resulting in HIE is only one of the many causes of neonatal encephalopathy (6). There is no definitive test to make the diagnosis and therapeutic hypothermia (TH) remains the only neuroprotective strategy available for HIE (6).

The incidence of HIE varies considerably, with the greatest burden occurring in Sub-Saharan Africa (14.9 per 1000 live births) and much lower rates (1.5 per 1000 live births) in HIC. Previous studies done at Charlotte Maxeke Johannesburg Academic hospital (CMJAH), a tertiary referral centre in South Africa, have demonstrated HIE rates of 2.3 – 13.3 per 1000 live births (9). In a study done at Chris Hani Baragwanath Academic Hospital (CHBAH) the incidence was reported to be 8.7-15.2 per 1000 live births (5). The rate of HIE is likely to be considerably higher in rural areas, where home births are common and health facilities are often inaccessible and under-resourced. Insufficient and inadequately trained health care workers, high patient loads, scarce ambulance services and lack of operating theatres, all result in critical delays of

essential obstetric care, necessary to prevent both maternal and neonatal mortality and morbidity (9).

Neonatal HIE is one of the most common causes of severe neurological deficit in children (3). It is associated with a high risk of death or early neurodevelopmental impairment and contributes to ever increasing medico-legal litigation. Among survivors, cerebral palsy, functional disability, seizures and cognitive impairment often develop later in childhood. The cost of this condition to patients, their families and society is high. It is therefore important to prioritise interventions and management to reduce the incidence and complications of intrapartum hypoxia (4). A meta-analysis of 7 large randomised controlled trials has demonstrated that TH improves survival and neurodevelopmental outcome at 18 months of age in neonates with moderate or severe encephalopathy (6). TH initiated within 6 hours after birth for moderate or severe HIE reduced the outcome of death or disability at 18 months in multiple randomised clinical trials and improved outcome at 6 to 7 years (6). In 2015, the International Liaison Committee on Resuscitation (ILCOR) recommended that newly born infants, born at or near - term with evolving moderate to severe HIE should be offered therapeutic hypothermia (7). TH has been performed at CHBAH since 2011.

Many neonates survive major insults without any evidence of impairment because of the plasticity of the developing brain and improvements in medical care (8). However, in some neonates, insults can cause varying degrees of long term neurodevelopmental impairment. These impairments cause major socioeconomic burden, especially in resource-poor countries and mostly in the rural areas (8). Worldwide, 80% of the estimated 200 million children with physical and intellectual disability live in LMIC where implications for the health, well-being and life chances of affected individuals, families and communities are far-reaching (10). A systematic review of long-term neurodevelopmental outcome after intrauterine and neonatal insults showed 1 in 5 infants to be at risk of severe impairment in at least one domain. However, contributing

data from LMIC were scarce (1). A tertiary hospital in South Africa reported a prevalence of moderate to severe impairment of 33.3% after HIE using a comprehensive neurodevelopmental assessment at one year of age, albeit among a small cohort of 36 (10). Mbatha et al. reported on 38% impairment in neonates that were cooled at CHBAH and 6% showing impairment at 1 year of age (18).

Developmental tests have been used since the early 1930s as a valuable tool for assessing the development of infants and young children. The Griffiths Mental Developmental Scales (GMDS) was developed in the United Kingdom in 1954 by Ruth Griffiths who observed children in their natural environments while they were engaged in their everyday activities (11). The GMDS Infant Scales were revised in 1996. The scale assesses children from birth to 2 years of age, provides a general developmental quotient and subquotients in the 5 developmental subscales (A-E); Locomotor scale (Scale A), Personal-social scale (Scale B), Hearing and Speech scale (Scale C), Eye and Hand Coordination scale (Scale D) and the Performance scale (Scale E). Locomotor scale assesses gross motor skills like sitting, crawling, walking, running, jumping, throwing a ball, climbing stairs, etc. Personal-social scale assesses the child's proficiency in activities of daily living. Hearing and speech scale assesses the infant's language, expressive and receptive. Eye and hand scale assesses the child's fine motor skills and visual monitoring. The performance scale assesses the child's visuospatial skills (12). South African research has focused on the overall development of HIE children, and there is limited data on the domain-specific patterns of strengths and weaknesses in these children.

Griffiths scales were introduced to South Africa in 1977 and since then, there has been a pool of research done on the overall development profile of South African children, comparing the South African and British standardisation samples of the Griffiths Scales. South African infants performed significantly better on the eye-hand coordination and performance scales but significantly poorer on the personal-social scale relative to the

normative sample, suggesting differences between the developmental rate of the British and South African infants, with each culture appearing to support a distinct aspect of development (11). Based on the studies that have been reviewed from 1977 to 2005, South African and British children's overall performances were similar. A number of studies locally and internationally have suggested that the GMDS is a culture-fair measure applicable to a range of cultures tapping common experiences (13). Griffiths III is the latest version and it assesses children from birth to 6 years. GMDS-ER has been used at CHBAH since 2013.

A comprehensive review on outcomes in children with HIE showed that very few children with mild encephalopathy show neurological impairments or have developed severe mental or motor retardation at preschool age. In contrast, children with severe encephalopathy nearly always die or develop severe impairments (14). Children with moderate HIE form a more heterogeneous group with respect to outcome. Research shows varying rates of infant death and morbidity. Children with severe encephalopathy have high mortality and morbidity, such as cerebral palsy (CP), intellectual disability, epilepsy and in some cases sensorineural hearing loss or cortical visual impairment (14). In a study done in Bangladesh, 20% of neonates with HIE died before discharge and majority of those who died had severe HIE. Normal development and mild impairment were found in 21.6% of children, all of them having mild or moderate HIE. Moderate and severe impairment was found in 33% and 25% cases respectively. The most severely impaired domain was gross motor and the most common complication was seizures (15). In a study done in Uganda, the risk of neurodevelopmental impairments among survivors increased significantly with HIE severity and neonatal clinical seizures. Of the neonates with HIE, 29.3% had neurodevelopmental impairments and 10.3% had GDD without CP. Among those with CP, median development quotient (DQ) was 31.1, compared to 60 for those with GDD without CP. Spastic diplegia was the commonest type of CP (63.6%) and was frequently associated with dystonia. Of the HIE survivors, 16.4% either needed assistive devices for walking or were non-ambulant, 27% had seizures and were on medication and most had CP

(10). In a study done at a tertiary-level hospital in South Africa, a third of neonates with HIE II and III who received TH had moderate to severe neurodevelopmental abnormality at 18-24 months, majority survived with mild or no disability at 2 years. There was a statistical difference in developmental outcome at 12 months and at 18-24 months. Assessment at 12 months identified more patients with normal or mild disability than assessment at 18-24 months (18). In a study done by Stark et al, at a secondary hospital in South Africa, infants with mild HIE demonstrated normal development. Infants with moderate HIE who received TH had greater fine motor skills delays than gross motor skills when measured at 1 and 2 years. The South African result seems to be in contrast to HIC such as the United Kingdom where fine motor skills seems to be better developed than gross motor skills (16). Children from disadvantaged backgrounds are more likely to engage in unrestricted play in open spaces such as the streets of their communities. This kind of play combined with a lack of access to technology such as computers and video games, contributes to improved gross motor skills. In HIC, on long term follow up, it was found that children who sustained HIE without major disability had an increased risk of long-term intellectual, verbal and motor deficits at 5 years (16).

Based on the GMDS, a developmental quotient (DQ) of 85 and above is considered normal. Normal scores on Griffiths scales at 1 or 2 years do not always predict good outcome at 6 and 7 years. An abnormal score is very likely to be associated with poor performance at school age (17). Early neurodevelopmental assessment at 1 and 2 years does not exclude cognitive, neurological or perceptual motor abnormalities at school age. It was found that sensitivity values for the Griffiths test were slightly higher at 2 years than at 1 year (17). However, the differences in the sensitivity values were relatively small and the possibility that professional intervention might have influenced the outcome, since many children with evidence of abnormal development receive physiotherapy, occupational therapy and systematic training in test related activities (17). Knowledge of the outcome of this group of children is important because these subtle problems can affect later scholastic achievement and behavioural adjustment.

Failure to identify such children in infancy results in a missed opportunity for early intervention which may help them cope better at home and at school (17).

Chris Hani Baragwanath Academic Hospital is the largest hospital in South Africa and has a high burden of neonatal encephalopathy and HIE. Therapeutic hypothermia as an intervention was introduced in 2011 in the CHBAH neonatal unit. These neonates with HIE are followed up at a Neonatal Neurodevelopmental clinic (NNDC) up to 2 years of age. A GMDS test is performed at 2 time points; at 12 months and 18-24 months of chronological age. This study aims to report on the domain-specific profiles of the GMDS, so as to identify the “at risk” infants and streamline them into appropriate therapeutic programmes.

2.0 AIM OF THE STUDY

Research Question: What is the composite developmental outcome in infants with moderate to severe HIE (those who received TH and those who did not) followed up at the neonatal neurodevelopment clinic at one year.

3.0 OBJECTIVES OF THE STUDY

3.1 Primary objective

- To document the Griffiths general and subscale quotients in one year old children attending the Neonatal Neurodevelopmental Clinic (NNDC).
- To compare the subscale/domains in infants with moderate to severe HIE that had received therapeautic hypothermia with those who did not receive therapeautic hypothermia.

3.2 Secondary objectives

- To determine the prevalence of children who develop visual impairment, hearing impairment, cerebral palsy, seizures and epilepsy.
- To compare the APGAR scores, severity of the HIE stage with the abnormal subcale/domain.

4.0 RESEARCH ASSUMPTIONS:

The following abbreviations have been used in the documentation of the study:

CHBAH: Chris Hani Baragwanath Academic Hospital

CMJAH: charlotte Maxeke Johannesburg Academic Hospital

CP: Cerebral Palsy

DQ: Development Quotient

GDD: Global Developmental Delay

GMDS: Griffiths Mental Development Scales

GMFCS: Gross Motor Function Classification System

HIC: High Income Countries

HIE: Hypoxic Ischaemic Encephalopathy

LMIC: Low and Middle Income Countries

MDT: Multidisciplinary Team

SDG: Sustainable Developmental Goals

TH: Therapeutic Hypothermia

UNICEF: United Nations Children's Fund

WHO: World Health Organisation

Wits: University of the Witwatersrand

5.0 ETHICAL CONSIDERATIONS

The protocol will be submitted to the University of Witwatersrand Human Research Ethics Committee (HREC). Data will then be collected after approval from the Ethics committee. Informed consent will be waived as this is a retrospective study. Confidentiality will be maintained by assigning a study number to the subjects. The spreadsheet with the names and study number will be kept separately to the main spreadsheet and be linked by a study number. These datasheets will be password protected. Permission to conduct the study will be requested from the Head of Department of Paediatrics, Head of Division of Neonatology, and the CHBAH CEO.

6.0 RESEARCH METHODOLOGY

6.1 STUDY DESIGN

This study is a retrospective descriptive study.

6.2 STUDY POPULATION

All those infants who had moderate to severe encephalopathy who were followed-up at the neonatal neurodevelopmental clinic at CHBAH and had a GMDS at around 1 year of age, between 1 January 2015 and 31 December 2020.

Study setting:

The study will be conducted at CHBAH a tertiary academic hospital in Johannesburg South Africa. The Neonatal Neurodevelopmental Clinic takes place every Tuesday morning. There are neonatologists, neurodevelopmental paediatricians, and multidisciplinary allied professionals; speech therapists, occupational therapists, and physiotherapists. The infants are seen for the first visit at 6 weeks of chronological age and assessed by the paediatricians/neonatologists and MDT. The infant is referred for a cranial sonar and hearing test at the first visit. The infants are then followed up 3 monthly till 2 years of age. A developmental assessment with GMDS is undertaken at 12 months and again at 18-24 months of age. The GMDS assessment is performed by GMDS trained doctors. The GMDS subscales are reported as individual raw scores and an age equivalent. At 2 years of age, the children are either discharged from the follow up clinic or referred to specialist clinics dependent on the support required, e.g. cerebral palsy or neurodevelopmental clinic, physiotherapy, speech therapy or occupational therapy as required.

6.3 INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

- All children with moderate to severe HIE as neonates who had at least one GMDS assessment at 12 months of age.
- All children who had a diagnosis of CP whether a GMDS was done or not

Exclusion criteria:

- Neonates/ infants with missing information.

6.4 DATA COLLECTION

The demographic data will be extracted from neonatal files and a Redcap Neonatal Database. The GMDS subscales/domain scores will be extracted from an existing asphyxia clinic database. The data will be captured as per the datasheet (Appendix A). The data will be captured on an excel spreadsheet.

6.5 DATA ANALYSIS

The excel spreadsheet with the data will be exported onto a statistical package (Statistica 10.0). Descriptive statistics will be reported; continuous variables will be reported as means and standard or medians and interquartile ranges depending on whether the data is normally destributed. Comparative statistics will be performed to identify factors associated with an abnormal subscale/domain.

6.6 DEFINITIONS

- Visual impairment : lack of vision, unilateral or bilateral as assessed by the ophthalmologist or a computed tomography scan with cortical involvement in the occipital lobes.
- Cerebral palsy : permanent disorder of movement and posture due to a non-progressive insult to the developing brain -spastic quadriplegic, double hemiplegic, unilateral hemiplegic, dystonic/dyskinetic, spastic diplegic and hypotonic cerebral palsy ; GMFCS III, IV and V, and GMDS score < 70.
- Epilepsy : a patient with seizures on one or more antiepiletic drugs beyond the neonatal period.
- Hearing impairment : unilateral or bilateral hearing loss. Those assessed by the audiologist with a hearing loss of more than 41 decibels.
- Sarnat staging : defined as neonates with a use of the definitions in the neonatal protocol book – looking at clinical presentation i.e. encephalopathy, seizures, Thompson scores etc.

7.0 SIGNIFICANCE OF THE STUDY

A focus on early childhood development is crucial to achieving the Sustainable Development Goals, to ensure that all children have the opportunity to maximise their full potential and to improve life chances for themselves and their families. Understanding the developmental strengths and weaknesses of children with HIE may facilitate a more tailored approach to intervention strategies. Knowledge of these developmental profiles, in South African children is limited. This study hopes to address this and thereby add to our understanding of the morbidity associated with HIE in this tertiary hospital setting.

8.0 POTENTIAL LIMITATIONS

The limitations of this study are the retrospective nature of the study and the fact that there may be missing or incomplete data.

9.0 PROJECTED OUTLINE

9.1 GANTT CHART

	2021					2022							
	August	Sept	Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	July	Aug
Protocol	x	x	x	x									
Submission to post-grad committee					x	X							
Application for institutional permission					x	X							
Submission for ethics approval						X	x						
Data collection								x	x	x	x		
Data analysis											x	x	
Write-up											x	x	X
Submission												x	X

9.2 BUDGET FOR THE STUDY

Total budget is estimated at R520.

	Pages per document	**Total**
Printing of research report	Estimated at 60	R120
Binding of report	Estimated at 60	R400
Statistician consult	N/A	
TOTAL		R520

The cost of the study will be funded privately by the researcher.

9.3 PUBLICATION PLAN

The final report will be submitted to the University of Witwatersrand post graduate research office for assessment. The information will be disseminated in terms of presentation at conferences and research day and published in a journal.

10. APPENDICES

Appendix A

Perinatal asphyxia and Induced hypothermia data sheet

Maternal details:

1) Self – referral 2) Clinic Referral 3) Hospital referral

Booked: Yes/No Para: _____ Gravida: _____

HIV: _____ Gestation: _____ weeks

Baby's Details:

Study number: _____

Date of birth: _____

Gestational age: _____ Birth Weight: _____

Apgar score: 1'____ 5'____ 10'___

Mode of Delivery: 1) NVD 2) Breech 3) C/S 4) Forceps 5) Vacuum

Resuscitation: 1) BMV

2) Intubation

Ventilated: Yes/No

Sarnat classification: 1) HIE I 2) HIE II 3) HIE III

Induced Hypothermia: Yes/No

Thompsons score: _____

Seizures: Yes/No

Antiepilectic Drugs (AEDs): Yes/No

Follow-up at 6 weeks/3 months/6months/9 months/12 months/18 months/24 months

HC:_____cm

Seizures: Yes/No Anticonvulsants:Yes/No

Blind: Yes/No Feeding difficulties: Yes/No PEG: Yes/No

Hearing: Normal/Abnormal

Tone: increased/decreased/normal

Reflexes: increased/decreased/normal

Clonus: Yes/No Plantars: upgoing/downgoing

Nutrition: normal/ underweight/ severely malnaurished

Imaging:

Cranial sonar: yes/no _____ findings:

CTB/MRI: yes/no _____findings:

Complications:

Blind: Yes/No

Hearing impaired: Yes/No

CP: Yes/No

Type: Spastic-hemiplegic/ Diplegic/ Quadriplegic/ Dystonic/ Dyskinetic/ Hypotonic

Developmental Assessment

Griffiths: Yes/No 12 months/18 months/24 months

	12 months Raw Score	12 months General quotient
A.Locomotor		
B.Personal-Social		
C.Hearing and Language		
D. Eye Hand Co ordination		
E. Performance		
F. Practical Reasoning		
Total Raw Score		
Equivalent age		
Developmental quotient		

Developmental level: Appropriate/Delayed (score < 85)

Severity of developmental delay**:** mild/moderate/severe

Score 85 is appropriate

Score 80-84 (mild)

Score 70-79 (moderate)

Score < 70 (severe)

Outcome:

1. Discharge	
2. T/F CP Clinic	
3. T/F Neurodevelopmental Clinic	
4. T/F to allied professionals	
5. Lost to follow up	

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Ethics clearance certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr A Myaka-Gama

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220248

NAME: (Principal Investigator)	Dr A Myaka-Gama
DEPARTMENT:	School of Clinical Medicine Department of Paediatrics and Child Health Medical School University
PROJECT TITLE:	*Developmental profiles of infants with Hypoxic Ischaemic Encephalopathy at a tertiary hospital in South Africa*
DATE CONSIDERED:	2022/02/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Dr F Nakwa
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/04/20

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized 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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **February** and therefore reports and re-certification will be due in the month of **February** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator _____ Date _____

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