

Neurological Outcome of Symptomatic Neonatal Hypoglycaemia in Term Infants without Other Risk Factors for Global Brain Injury

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Abstract

Aim: We are aiming to examine the outcome among patients with history of symptomatic neonatal hypoglycaemia (NH) in the absence of other risk factors for global brain injury.

Methods: All patients were term and appropriate for gestational age infants without pregnancy, obstetric or neonatal complications, anomalies, endocrine disorders, and whose birth weight and Apgar score were within reference range. The data recorded after comprehensive retrospective review of medical reports including neonatal discharge summary, community assessments, ophthalmology, paediatric medical notes and laboratory results. 849 neonatal electronic records of new-born with symptomatic NH were identified. The final eligible cohort comprised 93 patients.

Results: 2/93 (2.1%) patients had NH related brain injury and adverse neurological outcome. Both patients attended our emergency department from home with neonatal seizure and symptomatic NH. The remaining 91/93 (97.8%) had favourable outcome, and were admitted from the labour ward and none of them had neonatal seizure.

Interpretation

Symptomatic NH alone could cause adverse neurological outcomes with neonatal seizure and admissions from community are poor prognostic factors.

What this paper ads

- Symptomatic neonatal hypoglycaemia in the absence of other risk factors for global brain injury has an incidence of 1.9% among healthy term infants.
- Neonatal hypoglycaemia alone can cause severe neurological sequelae
- Neonatal seizure and prior discharge from hospital are poor prognostic factors.

Keywords: Hypoglycaemia; Infants; Brain Injury

Abbreviations

NR: Not Recorded; CS: Caesarean Section; NVD: Normal Vaginal Delivery; VD: Ventouse Delivery; FD: Forceps Delivery; NH- Neonatal Hypoglycaemia; NICU: Neonatal Intensive Care Unit

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Introduction

Neonatal hypoglycemia is a well-recognized cause of neurological adverse outcomes including epilepsy, cerebral palsy, neurodevelopmental delay, specific learning difficulties and autonomic dysregulation [1-6]. Hypoglycemic brain injury is well reported in the literature and it could be related to the combination of NH with other risk factors suggesting a likely more global insult [7-11]. Lack of strict selective criteria for patients and controlling of risk factors of global brain injury, make it difficult to interpret whether the neurological morbidities and / or brain injury resulted directly from NH per se.

To date studies on NH include infants with other medical conditions such as metabolic disorders, central nervous system infection or hypoxic ischemic encephalopathy. Parents of newborn infants with NH first and foremost want to be told about the prognosis when their child is admitted to the NICU.

Our study's emphasis is on clinically pertinent outcomes of NH such as epilepsy, specific learning difficulty, visual impairment, hearing loss and developmental delay. Other studies to date have looked at hypoglycaemia but not separated from other risk factors that may also cause brain injury. Therefore, the main objective of our study was to evaluate the long-term outcome in patients with a history of symptomatic NH with no other risk factors of global brain insult.

Method

Study Design

The study design was a retrospective cohort study of patients with a history of symptomatic NH. The study period is 6 years from January 2008 and January 2014. During the study period, there were 6411 new born infants who were admitted to our neonatal intensive care unit (NICU). In view of the retrospective anonymous analysis, consent of parents or individual patients and ethical approval for research analysis was therefore, not considered necessary [12,13]. This study was carried out in accordance with policies by the Audit Department at Barking, Havering and Redbridge University NHS Trust (BHRUT).

Local service

BHRUT is a major centre where neonatal and paediatric service is delivered by neonatologists and paediatricians with a range of special interests. The service delivers care to approximately 200 000 young people under the age of 18 years with a birth rate of about 80000/annum. The local service is closely linked to other providers including tertiary paediatric neurology units, tertiary neonatal units and three local community teams. There are regular weekly neurodevelopment clinics delivered by neonatologists with interest in neurodevelopment. Our neuro-radiology and electrophysiology departments deliver almost all the brain imaging and EEG procedures respectively.

Definitions

Hypoglycaemia was defined as plasma glucose level < 2.6 mmol / l. Capillary blood glucose was measured with a point of care glucose meter as a rapid screening. Hypoglycemia was confirmed by true laboratory measurement of venous blood glucose prior to administration of intravenous fluid. Neonatal period was defined in this study from birth to one month. Due to the retrospective collection of data, it was exceptionally difficult to define the exact time of onset of NH. Therefore, in this study, we analysed data on the basis of the clinical age at which NH was confirmed. Age of each patient at the end of the study was calculated up to the last community and / or hospital follow-up. Symptomatic NH was defined as low blood glucose (as stated above) and the presence of one or more symptoms. Symptoms included poor feeding, jitteriness or irritability, hypothermia, respiratory distress (e.g. tachypnoea, grunting), and seizures. Diagnosis of neonatal sepsis or congenital intrauterine infections was excluded through review of the laboratory reports on culture / viral serology of blood and / or cerebrospinal fluid (CSF). Neonatal stroke, brain anomalies and intracranial haemorrhage were excluded, if suspected, on the basis of

brain magnetic resonant imaging (MRI). Inborn errors of metabolism were excluded, if suspected, on the basis of appropriate metabolic work - up. In our study, we preferred the term ‘favourable’ outcome instead of good outcome.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were: (1) gestational age of at least 37 weeks; and (2) symptomatic NH. To remove potential risk factors of brain injury the following exclusion criteria were applied: birth weight of < 2.5 kg or > 4.5 kg; 5 minute Apgar score below seven, maternal use of drugs and medications with risk for the new-born, maternal illnesses; and major pregnancy complications (e.g. Rh incompatibility; gestational diabetes; gestational hypertension; moderate to severe anaemia). Additionally, those with any of the following were also excluded: (1) birth defects; (2) birth asphyxia; (3) dysmorphic features; (4) intracranial haemorrhage, (5) neonatal stroke, (6) proven neonatal infection; (7) inborn errors of metabolism; (8) congenital heart diseases; or (9) endocrine disorders. Also, exclusion criteria were insufficient or inaccessible medical records. Table 1 shows main reasons of exclusion.

Reasons	Number of patients
Gestation age < 37 weeks	518
Birth weight < 2.5kg	90
Birth weight > 4.5 kg	20
Birth asphyxia	30
Infants of diabetic mother	28
Neonatal infection	21
Congenital heart disease	17
Meconium aspiration syndrome	13
Dysmorphic features/ chromosomal abnormalities	8
Hyperinsulinism	3
Intestinal obstruction	3
Necrotising enterocolitis	3
Spontaneous intracranial haemorrhage	1
Pneumothorax	1

Table 1: Reasons for exclusion.

Data collection

The study was conducted in three practical steps. First, we searched our neonatal electronic database using ‘neonate’, ‘hypoglycaemia’ as search terms. Secondly, medical records were retrieved and comprehensively examined by at least two of the authors. After application of our inclusion / exclusion criteria 93/849 (10.95%) patients met all study eligibility. In the final step, eligible patients suspected of having adverse outcome were reviewed in our paediatric assessment unit (Figure 1).

Data collected from multiple sources including neonatal discharge summaries, hospital paediatric medical records, community and ophthalmology reports, and laboratory reports in particular electro-encephalography (EEG) and brain imaging. The medical records were read and reviewed manually. Data comprised demographic factors, clinical variables and laboratory data, with particular emphasis on age at onset of symptoms, age at the confirmation of NH, first obtained blood glucose level, duration of NH prior to normalisation of BG, and neonatal seizures. Extensive perinatal data including age, sex, ethnicity/race, gestational age, birth weight and mode of delivery were collected.

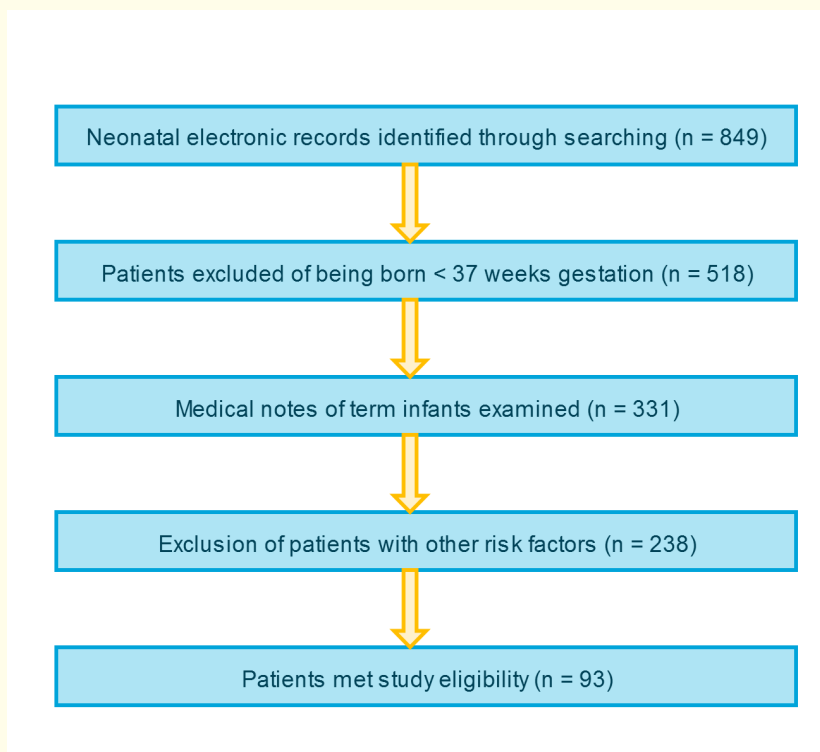


Figure 1: Study selection process.

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There was a session about the review process to ensure that each reviewer went through a uniform process. Appropriate summary statistics were calculated for all variables that expressed in numbers and percentiles.

In this study, outcome measures included survival or death of the patient, requirement of mechanical ventilation, history of neonatal seizures, and development of epilepsy, visual impairment, hearing loss, neurodevelopmental delay, specific learning difficulties, abnormal head growth and brain injury as evident by brain MRI. Epileptic seizure was classified into tonic, clonic, tonic/clonic, myoclonic, spasms, and atonic seizures. Neonatal non-motor seizures and / or neonatal subtle seizures can be difficult to detect, and therefore, not included unless it was clearly documented in the medical notes. Detailed classification of epilepsy syndromes was beyond the scope of our study.

Results

Neonatal data

There were 6114 admissions (4898 term infants and 1216 preterm infants) to our neonatal unit during the study period. Of these, we

were able to identify 93 eligible patients. There were 62 males (66%) and 31 females (34%). Race and ethnicity in our cohort included White European (n = 48), Africans (n = 12); and Asians (n = 27). Race and ethnicity was not recorded in the remaining 6 patients. Regarding mode of delivery there were lower segment caesarean section (n = 46); normal vaginal delivery (n = 32), Suction delivery (n = 10), and forceps delivery (n = 5). Average birth weight was 3.2 kg (range = 2.52 – 4.2 kg). Average gestational age was 38+7 weeks (range 37 – 41+5). Age at which NH was confirmed was 2 hours or less (n=13; 14%), > 2 to 24 hours (n = 63, 67%), > 24 to 48 hours (n = 12, 13%), and > 48 hours (n = 5, 5%). First recorded blood glucose was less than 1 mmol/l (n = 19, 20%), 1-2 mmol/l (n = 54, 57.5%), and > 2 to < 2.6 mmol/l (n = 20, 21.5%).

All patients were symptomatic and required admission to our unit. Predominant symptom were poor feeding (n = 51, 55%), breathing difficulties (n = 24, 26%), jitteriness (n = 10, 11%), hypothermia (n = 5, 5%), cyanosis (n = 1, 1%), and seizure (n = 2, 2%). Table 2 illustrates demographics and clinical characteristics among patients with first blood glucose of < 2 mmol/l in contrast with blood glucose of > 2 mmol/l. Table 3 shows demographics and clinical characteristics among patients with onset of NH under the age of 48 hours in contrast with NH at 48 hours of age or after.

Variables	BG < 2 mmol/l n = 68	BG = 2 - < 2.6 mmol/ l n = 25
Gender		
Males	47 (69%)	15 (59%)
Females	21 (31%)	10 (41%)
Ethnicity		
Caucasians - White	35 (52%)	13 (52%)
Ethnic groups	28 (42%)	9 (33%)
Others	0	2 (7.5%)
Not recorded	5 (6%)	1 (7.5%)
Mode of delivery		
NVD	23 (34%)	9 (37%)
Instrumental delivery	45 (66%)	16 (37%)
CS	33 (48%)	13 (52%)
VD	7 (11%)	3 (11%)
FD	5 (7%)	0
Age at onset of NH		
2 hrs or less	19 (28%)	4 (15%)
> 2 to 24hrs	34 (51%)	19 (70%)
> 24hrs	15 (21%)	2 (15%)

Table 2: Characteristics of patients according to the level of first recorded blood glucose (mmol/l).

In our entire cohort, we were able to confidently identify 2/93 (2%) patients with poor outcome. We describe in brief the case history of each of these two patients.

Patients	< 48 hours n = 86	48 hours or more n=7
Gender		
Males	55 (65%)	6 (78%)
Females	31 (35%)	1 (22%)
Race		
White Caucasians	44 (%)	4 (67%)
Ethnic groups	35 (41%)	2 (22%)
Others	2 (2.5%)	0
Not recorded	5 (6%)	1 (11%)
Mode of delivery		
CS	44 (51%)	2 (28.5%)
NVD	30 (35%)	2 (28.5%)
VD	9 (10.5%)	1 (11%)
FD	3 (3.5%)	2 (22%)
First blood glucose		
< 1 mmol/l	17 (%)	3 (33.5%)
1 to < 2 mmol/l	43 (52.5%)	2 (42%)
2 to < 2.6 mmol/l	25 (28%)	2 (22%)
Neonatal seizures	0	2* (22%)
NH - home*	0	2* (22%)
Follow up outcome		
Favourable	86 (100%)	7 (78%)
Poor	0	2 (22%)

Table 3: Characteristics of patients according to the clinical age of onset of NH. Abbreviations: *: patients arrived to our emergency department from community.

Case 1

The patient is a 4-year-old male born at 42+3 weeks gestation by caesarean section because of failure to progress following normal pregnancy. He was the first child of non - consanguineous parents from Sri Lanka with a birth weight of 3400g, and had an uneventful perinatal course. Apgar scores were 8 at 1 minute, 9 at 5 minutes and 10 at 10 minutes. He needed no resuscitation. There was no history of maternal abuse of street drugs. Whilst establishing normal breast feeding he was discharged home on day one after normal neonatal check.

The patient presented to our emergency department from home at the age of 60 hours (day 3 of life). History was obtained from the parents via a Tamil interpreter. Further history revealed that he was feeding poorly, he had not established full breast feeding, was not sucking well on the breast for approximately 24 hours and he had not fed for at least fifteen hours. The parents also noticed a few intermittent short lasting jerks but they were not sure how long they lasted or when they first started. At physical examination, he was floppy, pale, and afebrile. His vital signs were stable although oxygen saturation was 88% on air. Examination of chest, cardiovascular system and abdomen was unremarkable. Body weight was 3100g. During examination, he was noticed to have a few twitches which later progressed to recurrent generalised tonic clonic seizures lasting 1 to 3 minutes. First laboratory blood glucose was 0.6 mmol/l. Urine examination

was normal but with a trace of ketones. Blood gases were normal. Investigations including blood culture, viral serology (e.g. PCR – HSV), and metabolic profile were arranged prior to commencement of any form of treatment. Hypoglycaemia was corrected with a bolus of 10% dextrose and he was commenced on intravenous antibiotics and acyclovir. He was kept on intravenous infusion of 10% dextrose and subsequent blood levels of glucose remained normal (> 3.4 mmol/l). Seizures continued to occur despite intravenous phenobarbitone and midazolam. In view of this, he received pyridoxine, biotin and folic acid.

On day 4, although he was clinically stable, but continued to have intermittent generalised twitching and stiffness which were well controlled after commencement of clonazepam. From day 5 and onward, he had no more seizures and was haemodynamically stable. Repeated pre-feed blood glucose remained normal. Hospital follow up was arranged with further community and ophthalmology input. He remained in our neonatal unit for 30 days. He was discharged home on phenobarbitone and carbamazepine.

Magnetic resonance imaging (MRI) brain showed generalised brain swelling with extensive cortical oedema affecting both cerebral hemispheres predominantly affecting the parieto-occipital regions but extending to the frontal region particularly on the left. Inter-ictal EEG showed multiple focal epileptiform discharges over both hemispheres maximally over the fronto-central and parietotemporal regions. Electrodiagnostic testing showed normal electroretinograms but poor visual evoked potentials – consistent with the diagnosis of cortical visual impairment. Metabolic work – up included blood lactate, ammonia, aminoacids, acyl-carnitine profile, biotinidase, vitamin B6, cortisol, growth hormone, insulin, electrolytes, liver function, and urine organic acids was non-conclusive. Bacterial cultures for blood and cerebro-spinal fluid were negative. Viral serology (e.g. PCR for HSV) was negative.

Final follow up at the age of 51 months showed no purposeful hand movement, severe intellectual disability, cortical visual impairment, microcephaly (below 0.4 centile), four limb dyskinetic body movement disorder with central hypotonia and epilepsy. Video fluoroscopy showed severe oro-pharyngeal dysphagia and he needed percutaneous endoscopic gastrostomy for feeding.

We were able to identify three seizure types. First seizure type consisted of tonic spasms that begin with eyelids flickering and lasting for about lasting 10 seconds. These seizures tend to cluster and are worse in the morning. Second seizure type entailed head drops with body drop forward with associated loss of tone. These episodes last for 2 to 3 seconds. Third seizure type consisted of myoclonic jerks of upper limbs bilaterally occurring at least three times a day. His seizures were independent of external stimuli but it could be precipitated or triggered by fever and febrile illnesses. There were no startle responses. Few antiepileptic medications were tried. Follow up for about 18 months showed that the patient's seizures remained poorly controlled and the patient continued having tonic clonic seizures, myoclonic jerks and absence seizures particularly during febrile illnesses. A combination of Sodium Valproate and Levetiracetam resulted in much better, but not complete, control of his seizures.

Case 2

The patient is a 3-year-male born at 37+6 gestations by forceps delivery following normal pregnancy. He was the first child of non-consanguineous Indian parents with a birth weight of 2790g, and had an uneventful perinatal course. There was no history of maternal abuse of street drugs. Apgar scores were 10 at 1 minute, 10 at 5 minutes and 10 at 10 minutes, and he needed no resuscitation. After establishing normal breast feeding he was discharged home on day two.

He presented to our emergency department from home on day 5. History revealed that he was not feeding well for 3 days. The parents noticed from day 2, he was jaundiced and commented on twitching episodes of his body and other episodes when his eyes rolled downwards with high-pitched screams. On arrival to our emergency department, he manifested with intermittent tonic clonic seizures lasting 2 to 3 minutes. On physical examination, he was unwell, afebrile, pale, jaundice and appeared to have obviously lost weight (body weight = 2220g; weight loss of 20%). Examination of chest, abdomen and the cardiovascular system was unremarkable. A blood glucose level was carried out immediately and was 0.6 mmol. Vascular access was obtained and lumbar puncture performed. Blood and cerebrospinal fluid

were sent for metabolic screen, cultures, viral serology, PCR for herpes simplex virus, blood gases, and other base line investigations. 10% dextrose bolus was given and he was immediately commenced on intravenous antibiotics, Acyclovir and maintenance fluid. Repeated blood glucose, within 15 minutes, was 2.3 mmol/l. He was given another intravenous bolus of 10% dextrose. Subsequent glucose levels were normal. Seizures improved, but not completely, after intravenous loading doses of phenobarbitone and phenytoin. He required brief mechanical ventilation for approximately 8 hours. He completed a 7- day course of intravenous antibiotic and Acyclovir. He remained stable and maintained normal levels of blood glucose. He was discharged from our NICU on day 14 fully fed on milk formula by bottle.

MRI brain showed global cerebral volume loss with focal parenchymal loss and abnormal signal involving the parietal and occipital lobes bilaterally, along with severe changes frontally and ulegyria. Standard inter-ictal EEG showed no abnormal electrical discharges. Basic metabolic screen was unremarkable. Bacterial cultures for blood and CSF were negative. Blood and CSF viral PCR screen for herpes simplex, cytomegalovirus, Epstein virus, Enterovirus, and herpes zoster were negative. Metabolic work – up included blood lactate, ammonia, aminoacids, acyl-carnitine profile, electrolytes, liver function and urine organic acids was non-conclusive. Head circumference was 39 cm (< 0.4 centile) at the age of 6 months. Formal ophthalmological examination showed normal ocular structures and vision.

At the age of 36 months, he was able to walk but with difficulties and has tendency to fall intermittently while walking. He has trouble stepping down from the curbs and stepping up a curb when crossing the road. He was unable to put the painting brush in the pot he had to be helped, and he was unable to put on his shoelaces without help. He used zips but with difficulty and unable to do up buttons. He made many meaningful words but few full sentences. Formal ophthalmological examination showed normal ocular structures and vision.

Final follow – up at the age of 59 months, revealed mild motor developmental delay, behavioural issues, attention deficit, hyperactivity, specific learning difficulties, and head circumference of 45.5 cm (HC remained along the 0.4th percentile). He was not recognised to have a hearing impairment or visual problems. He attended a mainstream school but required one to one educational support. He had no further epileptic seizure and he was not on regular anti-epileptic medications for 4 years.

Discussion

In this study, we report on the long-term outcome of NH among 93 children who had no other risk factors of global brain injury. In this cohort, patients were term infants born without pregnancy, obstetric or neonatal complications, anomalies, endocrine disorders, and whose birth weight and Apgar score were within reference range. Other studies have looked at infants with NH and excluded some risk factors of global brain injury such as birth asphyxia and prematurity [3]. To the best of our knowledge, no study with similar objectives and design has hitherto been published.

The key clinically important messages from this study were that NH in its own can cause severe neurological morbidities, and that neonatal seizure at presentation with onset of NH in the community is associated with poor outcome. In the literature, there is no clear evidence to suggest if NH related outcome is due to hypoglycaemia or other causes. We also report that symptomatic NH occurred at a rate of 1.9% (93/4898) among all admissions of term infants during the study period. Other studies reported an incidence of NH ranges from 1 to 3% and much higher incidence has been reported in high risk groups [14]. We also found considerable association regarding gender. There was a predominance of male patients (66.5% [n = 62male] compared with female patients (33.5% [n = 31]). Regarding mode of delivery, we found the prevalence of NH was higher among those delivered by caesarean sections (49.5% [n = 46]) versus normal vaginal delivery (34.5% [n = 32]). Regarding presenting neurological symptoms of NH, we did not find that jitteriness is a risk for adverse neurological sequelae, as we checked the medical records of all patients (11% [n = 10]) with jitteriness and we found no documented evidence to suggest t adverse neurological outcome.

Another marked observation in the present study was among patients with favourable outcome, age at onset of NH and the level of BG prior to management did not considerably differ from those among the two patients with neurological sequelae. Even though the age at

clinical onset of NH was somewhat uncertain in some patients, an average time from assumed debut of clinical symptoms to diagnosis and management of NH was estimated to be 16.4 hours (range = 0.5 to 120 hours). Excluding the two patients with poor outcome, 7/92 (7.6%) patients presented with clinical symptoms for 48 hours or more and 68/92 (74%) patients presented with blood glucose of less than 2 mmol/l. Interestingly, all these patients had symptomatic NH prior to discharge from the labour ward, but made an excellent recovery and were discharged home.

We were able to identify only two out of the 93 patients who had developed neurological morbidities. We are unable to exactly delineate why these two patients in particular did so poorly but it is clear that both patients attended our emergency department from home with neonatal seizure and severe symptomatic NH. These two patients have been reviewed regularly up to the age of 49 and 51 months respectively. One patient has global developmental delay, spastic quadriplegia, visual impairment, hearing loss, microcephaly and refractor symptomatic epilepsy. The other patient has motor developmental delay, language / speech delay, specific learning difficulties, behavioural changes, attention deficit hyperactivity. This patient was seizure free for the last four years and had normal EEG. Neurological adverse outcome of NH has a wide range of conditions including epilepsy, global neurodevelopmental delay, cerebral palsy, specific learning difficulties, autonomic dysregulation, and developmental conditions such as attention deficit hyperactivity disorder [1-6]. Current literature describes seizure semiology and epilepsy types among patients who had NH although most of these studies are retrospective studies or small case series from specialized centres and did not exclude other risk factors of global brain injury [2,4,6]. A recent study evaluating the electro-clinical features of epilepsy secondary to NH, showed variable seizure manifestations and course of epilepsy after NH with occipital refractory and symptomatic generalized epilepsies [4] Although epilepsy is more frequent among those with NH, in our cohort, the frequency of childhood epilepsy was 1/93 (1.1%). This could be explained on the basis that our cohort was not a heterogeneous group as prematurity, meningitis; birth asphyxia; neonatal stroke and intracranial haemorrhage, maternal abuse of street drugs and brain anomalies have had no effect on the long-term outcome. However, the incidence of non-convulsive status epilepticus among these two patients is unknown to us as EEG was only arranged for motor seizures.

Literature reported a well-recognised pattern of brain injury among infants with NH. Involvement of the parietal and occipital cortices and sub-cortical white matter lesion are characteristic of NH [7-11]. Brain injury detected by MRI has been reported among hypoglycemic symptomatic infants, although there is no available data that defines the glucose concentration or the duration of hypoglycemia associated with damage. The pathogenesis of NH related brain injury could be either a reduction in glucose leads to increased cerebral blood flow, or the occipital axonal growth and synaptogenesis in neonates require higher glucose supply, and / or the combination of both mechanisms. In our study, brain imaging of both children showed bilateral symmetrical changes in the parieto-occipital lobes. There is also ulegyria (case 2) which is a recognised finding of HIE in term infants but in the clinical context are more likely to represent damage secondary to NH.

It is clear to us that neonatal seizure, in our study, is a key predictor of NH - related outcome. Neonatal seizure is known to be associated with adverse neurological outcome [15,16], although, the outcome depends on the underlying cause with a poorer outcome among those with hypoxic ischaemic encephalopathy [17-20]. In our cohort, the incidence of neonatal seizure among those with NH was 1.5 % (2/93). This is lower than previously reported in the literature [11-15]. This could be explained on the basis that our cohort of patients differed substantially to those of other studies. Studies showed that the incidence of neonatal seizure varies between 0.15 and 3.5 per 1000 live births with a higher incidence among preterm infants with hypoxic ischaemic encephalopathy, intracranial haemorrhage and neonatal stroke [17-20].

Limitations

We recognised several limitations of this study. The retrospective nature of the study has limited our ability to examine fully the data, information was initially gathered from the electronic records, the precise time of onset of NH and its duration prior to management was

somewhat uncertain, almost all neonates had no EEG, diagnosis of neonatal seizure was made on clinical observation alone and many of our patients had no formal neurodevelopmental assessment.

Particular strengths of this study are data documented in structured clinic letters, strict study eligibility, and there is a well-established network with neonatologists, ophthalmologists and community and acute paediatric teams. However, the duration of clinical symptoms had to be extrapolated from the medical records based on time of onset of clinical symptoms as reported by the parents or the carers and approximated to the nearest hours of age. The medical records were carefully examined to provide some assurance regarding the duration of NH. Furthermore, the need for formal neurodevelopmental assessment of our patients relies on the decision made by the responsible neonatologist in charge of each individual. Importantly, we checked thoroughly the inpatient hospital records, paediatric emergency department data, community records and the neonatal discharge summary, and we found no information suggesting that any of the 91 patients had required attendance at the hospital or community for neurological or neurodevelopmental problems thereby suggesting that these patients had no adverse neurological problems. Furthermore, data were not prospectively collected for the purpose of research and we can only extract data which are sensibly dependable and we recognise methodological issues relating to the study design which limit result interpretation and do not allow testing of current pathophysiological hypotheses. The question of transient low blood glucose concentrations cannot be directly addressed satisfactorily.

Conclusion

Our findings widen our understanding of the spectrum of NH and indicate that NH in the absence of other risk factors for global brain injury can cause neurological adverse outcome in particular among infants with onset of NH in community and a history of neonatal seizures. Education of the parents/carers and health professional remains an important strategy to avoid such unwanted consequence. Long-term outcome studies with a prospective design and more neuropsychological evaluation are needed to determine that patients who had NH with no history of neonatal seizure usually have more favourable outcome. Such research should also emphasis on the effect of specific variables and in particular socio-economic factors (e.g. parental education).

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Author Contributions

Mas Ahmed: study design, data collection, data analysis, data interpretation, writing manuscript

R Begley: data analysis, data interpretation, writing manuscript

B Rafique: data collection, literature review, writing manuscript

JO Davies: data collection, literature review, writing manuscript

Khalid Hussain: comments and writing manuscript

Conflict of Interest

The authors declare that they have no conflict of interest.

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