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Short-term feeding outcomes after neonatal brain injury

ABSTRACT

Background

Although brain injury is known to be associated with feeding outcomes in preterm and unwell neonates, these groups are frequently excluded from studies of neonatal feeding development. This paper aims to identify the short-term feeding outcomes of infants with neonatal brain injury.

Methods

A retrospective cohort analysis was undertaken to ascertain the incidence of feeding disorders (full/partial tube feeding at 40 weeks) among infants with brain injury admitted to a UK neonatal unit between 2013-2017.

Results

202 surviving infants with neonatal brain injury were included in the study. Feeding disorders were common among infants with brain injury (preterm 34%, term 34%) compared to infants without significant neurological comorbidities (preterm 9%, term 3%). The likelihood of feeding disorders increased with injury severity.

Conclusions

All infants with neonatal brain injury should have access to specialist feeding therapist to maximise their feeding potential and provide support to families.

Keywords: neonatology, infant, feeding disorders, deglutition disorders, brain injuries, brain diseases, intraventricular haemorrhage, hypoxic ischaemic encephalopathy, cerebrovascular accident, neurological rehabilitation

INTRODUCTION

Brain injuries occur during or soon after birth in 5.19 per 1000 live births in England (Gale et al., 2018). The impact of these brain injuries on infant health and neurodevelopment is dependent on a range of factors, including the type and severity of injury and the gestational age at which the injury occurs. Brain injuries in preterm infants typically result from haemorrhage, most commonly intraventricular haemorrhage (IVH) stemming from the germinal matrix (Gale et al., 2018; Webster, 2020). In term infants, the most common form of brain injury is hypoxic ischaemic encephalopathy (HIE) (Gale et al., 2018). Other causes of neonatal brain injury affecting both term and preterm infant include infections of the central nervous system, non-IVH forms of intracranial haemorrhage (ICH), and stroke (Gale et al., 2018). Areas known to be damaged by neonatal brain injury include the cortex, basal ganglia and thalamus, brain stem, subcortical white matter, and the cerebellum (Bano et al., 2017; Fumagalli et al., 2015; Inder et al., 2018; Jeong et al., 2016; Rutherford et al., 2010; Tam et al., 2011). These are areas of vital importance to the control of feeding and swallowing (Ahn & Musso, 2018; Kashou et al., 2017; Mourão et al., 2017). It is therefore unsurprising that brain injury is one of several important predictors of feeding outcomes in infants admitted to a neonatal unit (Edney et al., 2019; Harding et al., 2012, 2015; Hawdon et al., 2000).

There is increasing recognition that early therapy interventions can capitalise on the potential for neuroplastic change and improve outcomes for infants at risk of neurodisability (DeMaster et al., 2019; Hutchon et al., 2019; Khurana et al., 2020; Kolb & Gibb, 2011; Morgan et al., 2013). Such interventions may improve feeding outcomes for infants with neonatal brain injuries; however, this group is typically excluded from studies of neonatal feeding development and feeding interventions. This exclusion has resulted in a lack of understanding about neonatal feeding disorders specific to neurological impairment, hindering intervention development and clinical practice. The most detailed studies in this area have focused on HIE and stroke and provide evidence that neonatal brain injury can result in impaired oral motor skills and pharyngeal swallow function, reduced opportunities for consistent oral practice and associated motor learning, and prolonged reliance on tube feeding (Barkat-Masih et al., 2010; Harding et al., 2015; Krüger et al., 2019; Martinez-Biarge et al., 2012). However, comparison of the feeding disorders reported in these groups is hampered by a lack of agreed definitions, differences in the methods used to measure outcomes, and limited descriptions of the severity, characteristics, and associated physiology of the feeding disorder.

A consensus definition statement and conceptual framework has been published that identifies the medical, nutritional, feeding skill, and psychosocial aspects of oral intake disturbance that define a paediatric feeding disorder (Goday et al., 2019). Use of such a framework in neonatal brain injury research would clarify which types of brain injury are most associated with feeding disorders, what pathophysiology underlies these

disorders, and how these disorders impact on infants and their families. These data, in reliable form, are needed to develop appropriate interventions that target the specific feeding and swallowing disorders experienced by these groups.

This study aims to identify the incidence and types of brain injuries experienced by infants admitted to a Level 3 neonatal unit (including intensive care, high dependency, and special care) and the feeding outcomes of neonates with brain injuries at 40 weeks corrected age and at discharge. The findings of this study will be used to inform targeted intervention development and studies of intervention effectiveness.

METHODS

Design

Retrospective cohort study.

Setting

A Level 3 Neonatal Unit in an acute hospital in north-west England.

Sample

Data were collected for all infants admitted to the neonatal unit from 1st January 2013 to 31st December 2017 who experienced HIE, IVH, ICH, PVL, stroke, or central nervous system infection prior to or during their admission. Infants were excluded if data regarding gestational age at birth, diagnostic group, or feeding outcome were not available. Infants with diagnoses in addition to brain injury were included. Comparative data for term and preterm infants admitted to the neonatal unit with no significant

neurological co-morbidities were obtained via a previously collected dataset of admissions to the same unit. Infants in the comparison cohort were admitted from 1st January 2015 to 30th June 2015, a six-month period occurring in the middle of the five-year brain injury data collection timeframe. The comparison cohort was obtained via secondary analysis of previously reported data (Edney et al., 2019) and included infants with IVH of grades I-II but no other brain injuries or neurological conditions.

Data collection

Data were collected from BadgerNet, a patient data management system that is routinely used to record clinical information for all infants in neonatal units within the United Kingdom. The data include diagnoses, procedures, clinical reports, and a daily nursing record from which it is possible to determine progression from parental feeds to gavage feeds to full oral feeding. Discharge reports and daily notes were used to determine gestational age at birth, type of brain injury, and whether the infant was fully oral feed by 40 weeks corrected age and at discharge. For infants with IVH and HIE, severity scores were allocated by their treating doctor according to standard criteria (Papile et al., 1978; Sarnat & Sarnat, 1976). BadgerNet discharge reports and daily notes were used to obtain gestational age at birth, medical history, and feeding outcomes for the term and preterm non-brain injured comparison groups. Methods for the comparative study are described in detail elsewhere (Edney et al., 2019).

Gestational age at birth was categorised according to World Health Organisation definitions: term (>37 weeks), moderate to late preterm (32-36+6 weeks); very

preterm, (28-31+6 weeks); or extremely preterm (<28 weeks) (Quinn et al., 2016). Feeding outcomes were categorised as the presence or absence of a feeding disorder, and the presence or absence of tube feeding at discharge. A feeding disorder was defined as inability to achieve full oral feeding by 40 weeks corrected age (due date), or by discharge home if this occurred earlier than 40 weeks, or by one-week chronological age if born at or over 39 weeks. This definition represents a need for tube feeding beyond what may be expected for gestational age and acute illness and therefore reflects Goday et al.'s (2019) consensus definition of feeding disorder. To preserve anonymity, a detailed analysis of other co-morbidities and reasons for prolonged tube feeding was not undertaken.

Analysis

Counts and proportions were calculated for each type of brain injury, severity level (HIE and IVH only), and feeding outcome. Odds ratios for risk of feeding disorders were calculated by comparing feeding outcomes for infants with IVH (grades III-IV) and HIE (all grades) to the outcomes of term and preterm infants admitted to the same neonatal unit without significant neurological comorbidities. Odds ratios for IVH grades I-II could not be calculated due to the inclusion of these mild brain injuries in the comparison cohort. Odds ratios for other brain injury types were not calculated due to the small number of cases in each category.

Ethical considerations

The study design and procedures were approved by North East - Tyne & Wear South Research Ethics Committee (Approval number: 19/NE/0273). The data utilised were routinely collected and were gathered retrospectively and in anonymous coded format by a member of the clinical team. Parent/guardian consent was not sought to prevent the need for collection of personal data and for reasons of practicality. As only one site was included and data was collected by a member of the clinical team, these methods were approved without the need for confidentiality advisory group approval procedures.

RESULTS

Sample

After removal of duplicates, 2499 infants were admitted to the unit during the 5-year study period and screened for inclusions. A total of 202 infants with brain injury were identified and included in the study (8% of admissions). Brain injury types included: IVH (53%), HIE (30%), infection (7%), stroke (3.5%), multiple brain injury types (3%), PVL (2%), and ICH (1.5%). IVH, PVL, and ICH occurred only in preterm infants, while HIE and stroke tended to affect term born infants (Table 1). Data from 110 preterm and 99 term infants admitted to the same neonatal unit without significant neurological comorbidities were also included in the study (Table 2).

Feeding outcomes

Of the 135 preterm infants with brain injury, 46 (34%) had feeding disorder, and 23 of the 67 term infants had a feeding disorder (34%). Feeding disorders were more

common among infants with neonatal brain injury (Table 3) than infants admitted to the neonatal unit without neurological comorbidities (Table 4). In infants with IVH and HIE, feeding disorders became more likely with increasing injury severity. Infants with Grade 1 HIE had four times the odds of having a feeding disorder when compared to term infants admitted to the neonatal unit with no neurological co-morbidities, though this did not reach statistical significance (odds ratio = 4.00, 95% CI = 0.76 to 21.07, $p = 0.102$), and odds were 30 times as high for Grade 2 HIE (odds ratio = 29.71, 95% CI = 7.51 to 117.52, $p < 0.0001$). Although the sample number was small, all infants with Grade 3 HIE had feeding disorders. For this group, the odds of feeding disorder was significantly greater than the term-born comparison cohort (odds ratio = 358.43, 95% CI = 16.67 to 7704.55, $p = 0.0002$) and only one of the six infants achieved full oral feeding prior to discharge. Infants with Grade III-IV IVH had 12 times the odds of having a feeding disorder when compared to preterm infants admitted to the neonatal unit without significant neurological co-morbidities (odds ratio = 12.14, 95% CI = 4.65 to 31.74, $p < 0.0001$). Although odds ratios for Grade I-II IVH could not be calculated due to infants with mild IVH already being included in the comparison group, it is interesting to note that 23% of the cohort of infants with Grade I-II IVH experienced feeding disorders compared to only 9% in the comparison preterm cohort.

Table 1: Sample characteristics by gestational age at birth in weeks (infants with brain injury)

	<28 **n (%)**	**28-31^{+6}** **n (%)**	**32-36^{+6}** **n (%)**	**37+** **n (%)**	**TOTAL** **n**
IVH Grade I-II	41 (53)	29 (38)	7 (9)	0	77
IVH Grade III-IV	21 (68)	8 (26)	2 (6)	0	31
Total IVH	**62 (57)**	**37 (34)**	**9 (8)**	**0**	**108**
HIE Grade 1	0	3 (11)	2 (7)	22 (81)	27
HIE Grade 2	0	1 (4)	1 (4)	25 (93)	27
HIE Grade 3	0	0	2 (33)	4 (67)	6
Total HIE	**0**	**4 (7)**	**5 (8)**	**51 (85)**	**60**
Infection	**1 (7)**	**3 (21)**	**2 (14)**	**8 (57)**	**14**
Stroke	**0**	**0**	**0**	**7 (100)**	**7**
Multiple injuries	**3 (50)**	**2 (33)**	**0**	**1 (17)**	**6**
PVL	**1 (25)**	**2 (50)**	**1 (25)**	**0**	**4**
ICH	**1 (33)**	**0**	**2 (67)**	**0**	**3**

TOTAL	**68 (34)**	**48 (24)**	**19 (9)**	**67 (33)**	**202**

Table 2: Sample characteristics by gestational age at birth in weeks (comparison cohort: neonatal admissions with no significant neurological comorbidities)

	<28 **n (%)**	**28-31^{+6}** **n (%)**	**32-36^{+6}** **n (%)**	**37+** **n (%)**	**TOTAL** **n**
Preterm comparison	**19 (17)**	**20 (18)**	**71 (65)**		**110**
Term-born comparison				**99 (100)**	**99**

Table 3: Feeding outcomes (neonatal admissions with brain injury)

	No feeding disorder n (%)	**Feeding disorder n (%)**	**Feeding disorder + tube fed at discharge n (%)**	**Total**
IVH Grade I-II	59 (77)	18 (23)	6 (8)	77
IVH Grade III-IV	14 (45)	17 (55)	5 (16)	31
Total IVH	**73 (68)**	**35 (32)**	**11 (10)**	**108**
HIE Grade 1	24 (89)	3 (11)	0	27
HIE Grade 2	14 (52)	13 (48)	1 (4)	27
HIE Grade 3	0	6 (100)	5 (83)	6
Total HIE	**38 (63)**	**22 (37)**	**6 (10)**	**60**
Infection	**11 (79)**	**3 (21)**	**0**	**14**
Stroke	**5 (71)**	**2 (29)**	**0**	**7**
Multiple injuries	**2 (33)**	**4 (67)**	**1 (17)**	**6**
PVL	**2 (50)**	**2 (50)**	**1 (25)**	**4**

ICH	**2 (67)**	**1 (33)**	**1 (33)**	**3**
TOTAL	**133 (66)**	**69 (34)**	**20 (10)**	**202**

Table 4: Feeding outcomes (comparison cohort: neonatal admissions with no brain injury)

	No feeding disorder n (%)	**Feeding disorder n (%)**	**Feeding disorder + tube fed at discharge n (%)**	**Total**
Term	**96 (97)**	**3 (3)**	**0**	**99**
Preterm	**100 (91)**	**10 (9)**	**1 (1)**	**110**

DISCUSSION

In this study, infants with neonatal brain injury were found to be at increased risk of being partially or fully reliant on non-oral nutrition at 40 weeks corrected age and at discharge when compared to preterm or unwell term infants without significant neurological co-morbidities. It is interesting to note the trend towards higher risk of feeding disorders in infants with milder forms of brain injury. This is in keeping with an increasing body of literature suggesting that milder forms of intraventricular haemorrhage and hypoxic ischaemic encephalopathy may not be as benign as previously thought, with studies demonstrating increased rates of cerebral palsy, neurosensory impairment, neuromotor impairment, cognitive impairment,

behavioural difficulties, and other neurodevelopmental disabilities in these groups (Bolisetty et al., 2014; Finder et al., 2020; Hayes et al., 2018; Hollebrandse et al., 2020; Mukerji et al., 2015; Pfahl et al., 2018; Reiss et al., 2019). Potential mechanisms for the influence of lower grade IVH on neurodevelopmental outcomes include their negative impact on neural migration, injuries to the caudate nucleus and the destruction of cells destined for the subcortical structures, white matter injury and hypomyelination, and impaired cerebellar development (Bolisetty et al., 2014; Briana & Malamitsi-Puchner, 2019; Jeong et al., 2016; Volpe, 2019). In brain injuries related to the less severe categories of hypoxic ischaemic encephalopathy, worsened neurodevelopmental outcomes may be due to white matter injuries and watershed infarcts affecting the cortex and white matter (Annink et al., 2020; Bano et al., 2017).

Studies of feeding outcomes in the more commonly researched forms of neonatal brain injury (e.g. HIE) have typically agreed that these infants are at high risk of feeding disorders; however, findings have been inconsistent. One reason for this is the varied terminology used, with feeding disorder or feeding difficulty being used as a non-specific label for what can represent a myriad of motor and sensory impairments affecting the pre-oral, oral, pharyngeal, and oesophageal phases of feeding. The definition of feeding disorder used in this study is ongoing tube feeding beyond what would be expected for gestational age and acute illness. This is consistent with the consensus definition of feeding disorder recently published by Goday et al. (2019) and provides a platform on which to further build knowledge of the natural history of feeding problems in children with a history of neonatal brain injury. Another problem

within the existing evidence base is a lack of focus on the most common types of brain injury. Previous studies of feeding outcomes following IVH have focused on term IVH (which is rare) (Afsharkhas et al., 2015; Chaoying et al., 1999; Jocelyn & Casiro, 1992) and IVH complicated by hydrocephalus (Gigi et al., 2019). Our study demonstrates that IVH, by far the most common type of neonatal brain injury affecting preterm infants, is associated with an increased likelihood of feeding disorders. This relationship warrants further research.

Our study has several limitations. Sample sizes were relatively small, particularly for rarer causes of neonatal brain injury, and sampling was restricted to one neonatal unit. Non-neurological comorbidities impacting on oral feeding progression, such as chronic lung disease, being small for gestational age, and feeding milestones on the journey to full oral feeding could not be collected in this study due to the need to preserve anonymity. The identifier for feeding disorders used in this study (full or partial tube feeding at 40 weeks corrected age and at discharge) is not sensitive to the reasons for feeding disorders, and not all infants requiring tube feeding have difficulties with oral feeding. For example, infants with cardiac conditions may require tube feeding due to increased calorie requirements rather than delayed or disordered oral feeding skills. Although prematurity and many non-neurological co-morbidities impact on feeding development in infants admitted to a neonatal unit (Edney et al., 2019; Giannì et al., 2015), the increasing incidence of feeding disorders with increasing injury severity seen in this study suggests an independent relationship between brain injury and feeding outcomes. It is recognised that, although the comparison cohorts of preterm

and term-born infants without neurological co-morbidities were admitted to the same neonatal unit during an overlapping time frame, the comparison data came from a six-month period in the middle of five-year study period and this comparative analysis is therefore limited by non-contemporaneous data sets. Additionally, comparison groups are not directly analogous in term of key characteristics. For example, infants born under 28 weeks gestation age made up 53% of the IVH Grade I-II group but only 17% the preterm comparison group, a factor that may have influenced feeding outcomes. However, the comparison cohorts were likely to have been affected by many of the same consequences of prematurity, medical complications, and neonatal care as their brain-injured peers and our study supports the need for further research into the links between neonatal brain injury severity and worsened feeding outcomes.

Despite limitations, the findings in this study provide evidence that infants with neonatal brain injury should be considered at high risk for feeding disorders. Feeding disorders are associated with choking risk, respiratory illness, long-term tube feeding, feeding aversions, and poor growth and nutrition and associated negative effects on neurodevelopment in infancy (Andrew et al., 2018; Arvedson, 2013; Dabydeen et al., 2008; Dodrill, 2014; Sullivan et al., 2000; Tutor & Gosa, 2012). Additionally, children with feeding disorders and their families experience altered bonding opportunities, disrupted family life, reduced social participation, increased stress and anxiety, and reduced quality of life (Adams et al., 1999; Azios et al., 2016; Dodrill, 2014; Hawdon et al., 2000; Hewetson & Singh, 2009; Nelson et al., 2015; Sullivan et al., 2000). Given these consequences, neonatal feeding disorders need to be skilfully approached. Input

from specialist feeding therapists can minimise the risk of negative feeding outcomes, maximise oral feeding potential, and support families to understand, anticipate, and manage feeding disorders during and following admission to the neonatal unit. Future research should include the influence of milder types of brain injury on feeding outcomes, identifying the natural history and pathophysiology of feeding problems experienced within each brain injury type, and identifying the best methods of preventing and treating feeding problems following neonatal brain injury.

CONCLUSIONS

Neonatal brain injury of all types and severity levels can increase the risk of feeding disorders in the neonatal phase, preventing progression to full oral feeding and prolonging admission to the neonatal unit. Access to specialist feeding therapists should be made available to all infants with neonatal brain injury to maximise the infants feeding potential and support their families, while on the neonatal unit and after discharge.

Conflicts of interest:

The authors declare that there is no conflict of interest in publishing this paper.

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