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Research Article

Feeding Intolerance in Newborns

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Abstract

Introduction: Feeding intolerance defined as the inability to digest enteral feedings, and is associated with increased gastric residuals, abdominal distension and/or regurgitations. Recently, we observed in our neonatal intensive care unit, a tendency for feeding intolerance in relation to origin.

Aim: To evaluate whether feeding intolerance is more prevalent in African Israelis newborns (AIN) versus other Israelis newborns (OIN) origin.

Methods: A retrospective case control study based on medical records between 2014 and 2016. The groups included 50 AIN and 100 OIN.

Results: The AIN had significantly higher prevalence of feeding intolerance in (34%) compared to OIN (15%) (p=0.007). Moreover, feeding intolerance symptoms were higher in the AIN group compared to the OIN group; gastric residual volume more than 50% (24% vs 10%, p=0.014) regurgitations (76% vs 50%, p=0.002), vomiting (44% vs 10%, p=0.046), and two days without defecation (10% vs 2%, p=0.029). Mother's own milk feeding was more prevalent in the AIN group.

There were no differences between the two groups in the prevalence of necrotizing enterocolitis, intestinal perforation, or milk allergy.

Conclusion: Feeding intolerance was more prevalent in AIN versus OIN. Our research results can be used as a basis for future studies on this population of newborns with feeding intolerances, examining the use of hypoallergenic formulas as a rescue treatment or as a first-line treatment for the initial infancy period.

Keywords: Feeding intolerance, Hydrolyzed protein formula, Milk allergy, Newborns, Origin

Abbreviations: CMA: Cow's Milk Allergy; DHM: Donor Human Milk; FI: Feeding Intolerance; GRV: Gastric Residual Volume; HPF: Hydrolyzed Protein Formula; MOM: Mother Own Milk; NEC: Necrotizing Enterocolitis; NICU: Neonatal Intensive Care Unit; SIP: Spontaneous Intestinal Perforation; VLBW: Very Low Birth Weight (<1500gr)

Background

Feeding intolerance (FI), defined as the inability to digest enteral feedings, presents as gastric residual volume (GRV) of more than 50%, abdominal distension and/or regurgitations [1]. The most common cause of feeding intolerance is low gut motility due to prematurity. Other pathophysiological mechanisms are possibly related to enzymatic digestion, hormonal responses, bacterial colonization, and local immunity [2]. FI often seen in newborns

admitted to the neonatal intensive care unit (NICU) and can lead to enteral feed cessation, impaired nutrients supply, unnecessary blood tests and abdominal x-rays, to potential hospital-acquired infections due to a central inserted catheter and to long-term parenteral nutrition [2].

Mother's own milk (MOM) is the best feeding choice for both term and preterm infants. MOM's unique composition of digestive enzymes, growth factors, hormones, and prebiotics, offers clear benefits for the immature gastrointestinal functions and protective effects against gut microbiota alterations [2-4]. Moreover, there is evidence that a human milk-based diet is associated with better feeding tolerance in very-low-birthweight (VLBW) infants [5].

Preterm formulas that contain intact proteins are indicated for enteral feeding of preterm infants when sufficient MOM and donor human milk (DHM) are not available [6]. Hydrolyzed protein formulas (HPFs) have been shown to accelerate gastric emptying, increase stool frequency and reduce the time to full enteral feeds in preterm infants [7]. In addition, HPFs have been tested as an alternative strategy in treating FI in VLBW infants compared to standard preterm formulas and were shown to be beneficial [8]. However, formulas used in these studies were lactose free making it impossible to separate the effects of the hydrolyzed protein from other changes in the formula composition [9,10].

Former studies have found differences in lactose intolerance in newborns of African origin versus other origin newborns [11-19]. Recently, we observed in our NICU, a tendency for FI in African Israelis newborns (AIN) compared to other Israelis newborns (OIN). Therefore, we aimed to evaluate whether feeding intolerance is more prevalent in AIN versus OIN origin that were formula-fed (>20% of daily volume) during their first week of life.

Methods

This is a retrospective case control study, based on the analysis of data collected from medical records of term and preterm infants admitted to Kaplan Medical Center's (KMC) NICU between January 2014 and December 2016. The study group included 50 AIN and 100 OIN as controls. A match was made between the preterm infants in the two groups based on birth week (± 1-2 weeks) and birth weight (± 100-200 grams). Exclusion criteria included: death or discharge before the age of three days, congenital malformation, or asphyxia. We also excluded newborns that were exclusively MOM-fed (>80% of daily volume) [20]. Collected data included demographic data, anthropometric parameters, morbidities, medical treatments and feeding intolerance parameters (GRV, regurgitations, vomiting, frequency of stool), type of feeding (MOM versus formula and type of formula).

The KMC NICU follows a feeding protocol (appendix) based on the European Society for Paediatric Gastroenterology, Hepatology and Nutrition's (ESPHAGAN) recommendations of parenteral and enteral nutrition [21]. The feeding protocol was not changed during the study observation period. There was no change in senior physician or dietitian. The sample size was calculated according to 50% frequency of FI in AIN and 16% frequency in OIN with 80% power and a significance level of $p<0.05$. The sample size was calculated to be 34 AIN and 68 OIN. Based on this data we included 50 AIN and 100 OIN. The study was approved by the Ethics Committee of KMC (0175-17-KMC).

Definitions

FI was defined by gastric residuals (GR), with or without regurgitations, vomiting, abdominal distention, low frequency of defecation and the disruption of the patient's feeding plan [1]. Necrotizing enterocolitis (NEC) was defined according to the BELL criteria [22]. Cow's milk allergy (CMA) was clinically defined by a. bloody stools without pathological laboratory or imagery findings except for eosinophilia or anemia in complete blood counts, and b. both negative stool cultures and viral pathogens in polymerase chain reactions and c. clinical improvement with the elimination of cow's milk protein from the diet [23]. Spontaneous intestinal perforation (SIP) was defined as a neonate presenting typical clinical features of the disease (abdominal distension) with radiologically confirmed pneumoperitoneum, without radiographic evidence of NEC and when surgical data was available, SIP was confirmed when there was presence of isolated focal intestinal perforations surrounded by a normal-appearing bowel [24].

Statistical Analysis

Data is presented as median (range) or percentages. Continuous variables between the various study groups were tested for normality by a Shapiro-Wilk test and when abnormal distributions were found, non-parametric tests were performed. The Mann-Whitney test was performed to compare the two groups. Pearson chi-square tests were used for the relationship between two categorical variables. P values <0.05 were considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, software version 25, Chicago, IL, USA).

Results

The study population consisted of 50 AIN and 100 OIN. There were no significant statistical differences between two groups in infant characteristics including anthropometric parameters or neonatal comorbidities (Table 1).

Table 1: Infant characteristics.

Infant Characteristics	AIN (n=50)	OIN (n=100)	P-value
Gender (Male)	22 (44)	60 (60)	0.09
Gestational age (week) †	34 (26.5-42)	34 (26-42)	0.65
Birth weight (g) †	1743 (700-3875)	1782 (618-3720)	0.65
Appropriate for gestational age	35(70)	71(71)	0.89
Small for gestational age	15(30)	29(29)	0.89
Intra uterine growth restriction	10(20)	26(26)	0.41
Intra ventricular hemorrhage	3(6)	5(5)	0.35
Bronchopulmonary dysplasia	5(10)	15(15)	0.39
Mechanical ventilation	11(22)	16(16)	0.36
Assisted ventilation	15(30)	26(26)	0.6
Oxygen supplementation	18(36)	39(39)	0.72
Patent ductus arteriosus	9(18)	13(13)	0.41
Sepsis	1(2)	1(1)	0.44
Inotropic treatment	3(6)	1(1)	0.07
Blood products	4(8)	8(8)	1

Number (%), Pearson chi-square tests p values.

†Median (range), Mann-Whitney test p values.

We found that the AIN group had significantly higher prevalence of FI compared to the OIN group (17/50, 34% vs 15/100, 15%, p=0.007). Moreover, the FI symptoms were higher in the AIN group compared to the OIN group; GRV more than 50% (12/50, 24% vs 10/100, 10%, p=0.014) regurgitations (38/50, 76% vs 50/100, 50%, p=0.002), vomiting (11/50, 44% vs 10/100, 10%, p=0.046), and two days without defecation (5/50, 10% vs 2/100, 2%, p=0.029).There were no differences in the prevalence of NEC, intestinal perforation, or CMA between the two groups (Table 2). MOM feeding (any volume) was more prevalent in the AIN group in the first week of life (12% vs 3% p=0.03), with 88% of the AIN and 97% of the OIN being formula-fed exclusively (>80% of daily volume) in the first week of life.

Table 2: FI Symptoms, FI, and Other Gastrointestinal Morbidities.

FI symptoms	AIN		OIN		P-value
	n	%	n	%	
FI	17	34	15	15	0.007‡
GRV more than 50%	12	44	10	22	0.014‡
Regurgitations	38	76	50	50	0.002‡
Vomiting	11	22	10	10	0.046‡
Two days without defecation	5	10	2	2	0.029‡
Suspected cow's milk allergy	2	4	1	1	0.2
NEC	0	0	1	1	0.47
SIP	1	2	0	0	0.15

Number (%), Pearson chi-square tests, p-values.

‡Statistically significant difference.

OIN with FI had higher rates of other neonatal comorbidities and respiratory support compared to OIN without FI. This association was not found in the AIN group (Table 3). The prevalence of changing the cow's milk intact protein-based formula to HPFs was higher in the AIN group compared to the OIN group (14/50, 28% vs 8/100, 8%, respectively, p=0.001). The prevalence of clinical improvement in FI after formula change was higher in the AIN group, though not statistically significant (12/14 86% vs 5/8 62%, p=0.21). The weight at discharge was significantly lower in the AIN group than in the OIN group (2349±476g vs 2479±473g, respectively, p=0.036).

Table 3: Association between FI and Comorbidities.

	AIN with FI (n=15)		P-value	OIN with FI (n=14)		P-value
	Yes	No		Yes	No	
Suspected cow's milk allergy	1(7)	14(93)	0.16	1(7)	13(93)	0.015‡
Bronchopulmonary dysplasia	2(13)	13(86)	0.76	5(36)	9(64)	0.015‡
Intraventricular hemorrhage Ⅱ	1(7)	14(93)	0.69	2(14)	12(86)	0.040‡
Patent ductus arteriosus	4(27)	11(73)	0.29	6(43)	8(57)	<0.001‡
Mechanical ventilation	5(33)	10(67)	0.22	5(36)	9(64)	0.025‡
Assisted ventilation	4(27)	11(73)	0.45	8(57)	6(43)	0.003‡
Supplemented oxygen	6(40)	9(60)	0.89	10(72)	4(28)	0.006‡
Bloody stool	2(13)	13 (86)	0.04‡	2(14)	12(86)	0.009‡

Number (%), Pearson chi-square tests, p-values.

‡Statistically significant difference.

Discussion

Our retrospective case control study demonstrated that FI is more prevalent in AIN compared to OIN. There is evidence that human-milk-based diet is associated with better feeding tolerance in VLBW infants [5]. We aimed to study FI in AIN versus OIN that were formula-fed during their first week of life, as a basis for a future study investigating HPFs as a rescue or as a first line feeding in AIN not receiving MOM. Although MOM feeding in the first week of life was more prevalent in the AIN group, they still had a higher rate of FI. These results might indicate that the origin of the newborns may play a role in the presence of feeding intolerance.

Furthermore, there were no differences in comorbidities in the two groups. The discharged weight of the AIN group was significantly lower than the OIN group. We assume that lower weight is secondary to the higher rate of FI as abnormal weight gain is a known complication of FI [2].

OIN with FI had higher rates of other neonatal comorbidities and respiratory support compared to OIN without FI. This suggests that FI might be secondary to other morbidities in the OIN group. This association was not found in the AIN group.

We speculate that FI is associated with an intrinsic factor in the AIN group, such as lactose intolerance or differences in genetics and/or the microbiome. The higher prevalence of clinical improvement in AIN given HPFs compared to OIN also supports this hypothesis, as HPFs are also lactose free unlike MOM that contains lactose [25]. There were several studies in the 1960s and 1970s suggesting a higher prevalence of lactose intolerance in African descent infants [10-18]. These studies included children over one year old. They theorized that there is a genetic tendency of lactose intolerance in this ethnic decent. Another theory suggested that this is an acquired tendency, secondary to low consumption of milk products. Another theoretical explanation is differences in the microbiome between the two ethnic groups. Recently, Yuan et al. found that the gut microbiota composition of preterm infants diagnosed with feeding intolerance was significantly different than that of preterm infants without feeding intolerance. They suggest that the abundance of Klebsiella may cause feeding intolerance [26].

Limitations

The main limitation of the study relates to its retrospective design and a relatively small study group number. Additionally, FI is a clinical diagnosis with an equivocal definition, which can be confused with other clinical diagnosis.

Conclusion

FI was more prevalent in AIN versus the OIN group. The origin of the newborn may be another factor that influences the development of FI. Early identification of risk factors for FI may help to suit better nutritional therapy. To the best of our knowledge, this is the first study examining this issue. Further studies are needed to determine whether the difference is due to lactase deficiency or microbiome variability.

Individualized Contributions

Dr Calanit Hershkovich–Shporen was responsible for the conceptualization, methodology, investigation, validation, original draft preparation. Ms Lilach Hofi was responsible for conceptualization, methodology and writing-review and editing. Dr Alona Khodajev was responsible for data curation.Pro. Orna Flidel-Rimon was responsible methodology, writing-review, and editing.

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Conflict of Interest

None.

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