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Infection and Predisposing Factors in Neonatal Necrotising Enterocolitis

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Summary

Okolo AA, Omene JA and Odita JC. Infection and Predisposing Factors in Neonatal Necrotising Enterocolitis. *Nigerian Journal of Paediatrics* **1982; 9: 91.** A prospective study of 61 cases of neonatal necrotising enterocolitis (NEC) admitted to the special care baby unit, UBTH, over a four-year period (1978–1981) is presented. The peak period of its occurrence was between May and October. The overall prevalence was 20.9 per thousand admissions. The mean birthweight of the subjects was 1770 gm (range, 850–3700 gm), while the mean gestational age was 34 weeks (range, 27–44 weeks). NEC was diagnosed within the 1st week of life in 38 (62%) infants (range, 1–28 days). Infections, asphyxia and respiratory distress were the predisposing factors in the development of NEC. *Salmonella G* and *Staphylococcus aureus* which were the main pathogens isolated in two recent epidemics of septicaemia and diarrhoea in the unit were not associated with the development of NEC. The mortality rate was 80%.

Introduction

Neonatal necrotising enterocolitis (NEC) is a major cause of morbidity and mortality in neonatal intensive care units. A recent study suggests that the disease may occur in as much as 5–15% of stressed preterm infants.[1] The mortality from the disease is high and its morbidity during convalescence is protracted. The precise aetiology and pathogenesis of the disease remain controversial. Among the various pathogenic theories, gastro-intestinal tract ischaemia and consequent mucosal damage which permits bacterial invasion of the bowel wall, have been the most widely accepted.[2] The predisposing risk factors related to this theory are birth asphyxia,[3] umbilical vessel catheterisation,[4] respiratory distress syndrome,[5] haemodynamic disturbances during exchange blood transfusion[6] and polycythaemia.[7]

Epidemics of NEC have been observed in clusters or in association with specific pathogens by various investigators.[8-10] The present prospective study was undertaken in an attempt to identify any infectious agents associated with recent epidemics of NEC in our neonatal unit.

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Furthermore, seasonal variations in incidence of the disease and other predisposing factors would be documented.

Materials and Methods

All the patients admitted to the Special Care Baby Unit (SCBU), University of Benin Teaching Hospital (UBTH), between January, 1978 and December, 1981 were cared for by AAO and JAO. Suspected cases of NEC were closely monitored and relevant data documented. In addition, two or three matched controls were selected for each infant with NEC. These controls had no associated gastrointestinal tract problem or congenital abnormality. They were admitted immediately before or after each infant with NEC. The controls were matched in respect of birthweight and gestational age with infants who developed NEC, but no attempt was made to match the controls and infants with NEC for any other illness.

Samples of blood, cerebrospinal fluid and stool, umbilical catheter tips and swabs of orifices of all patients with suspected infection or NEC were cultured for bacteria. The diagnosis of NEC was based on the clinical and radiological signs as previously described.[11] In a few cases, the diagnosis was confirmed at autopsy by the histological findings of coagulation necrosis and minimal cellular infiltrates.

Management was mainly medical. After the diagnosis of NEC was made, oral feeds were discontinued and parenteral cloxacillin (100 mg/kg/day) and gentamycin (5mg/kg/day) were administered. Oral gentamycin, 10mg/kg/day, was instilled through the nasogastric tube, four-hourly. Patients were maintained on 5% dextrose intravenously with appropriate electrolyte replacement. Indwelling nasogastric tube was left *in situ* for gastric decompression.

One patient with perforation underwent surgery, but died subsequently in the post-operative period.

Results

During the four-year period, 61 cases of NEC were encountered. Infants with NEC were similar to the controls in respect of birthweight and gestational age (Table I). Infection occurred in only 26 (19%) of the 140 controls. In contrast, 38 (62%) infants with NEC had intercurrent infection. This difference was statistically significant ($P < 0.001$). Of these 38 infants, eight had proven septicaemia; nine infants had bronchopneumonia; three had meningitis and nine had omphalitis. Diarrhoeal disorder was present in five cases, while enteropathogenic *E. Coli* was isolated from the stools in three cases. One infant had neonatal hepatitis syndrome.

Asphyxia was a significant finding in 33 (54%) of the 61 patients with NEC and in 24 (17%) of the 140 controls ($p < 0.001$). Eight of the asphyxiated infants were intubated and ventilated in the delivery room. Respiratory distress preceded NEC in 20 (33%) infants, nine of whom had respiratory distress syndrome.

Umbilical venous catheterization had been undertaken in 12 (20%) of the 61 infants prior to the development of NEC. Similarly, 26 (19%) of the 140 controls had been catheterized. The characteristic features of the patients are shown in Table II. It will be observed that 45 of the 61 infants were preterm, while 16 (26.7%) were full term infants. The age of onset of NEC varied, ranging between the first day of life and the 28th day. Thirty-eight (62%) infants presented in the 1st week of life. One preterm infant with associated congenital heart defect and intractable heart failure presented on the 28th day of life.

TABLE I

Clinical Features in 61 Infants with NEC and in 140 Controls

Feature	*Infants with NEC* $n = 61$	*Controls* $n = 140$	X^2	*P*
Birthweight (gm, mean ± SD)	1770 ± 133	1884 ± 81		
Gestation (wk, mean ± SD)	34·2 ± 5·9	34·24 ± 4·2		
Sex ratio (Male : Female)	0.9 : 1	1.6 : 1		
Infection	38(62)	26(19)	25·5	< 0.001
Birth Asphyxia	33(54)	24(17)	20.4	< 0.001
Respiratory distress	20(33)	20(14)	7·337	< 0.01
PROM 24 hrs	10(16)	14(10)	1.47	NS
Umbilical vessel catheterisation	12(20)	26(19)		NS
Hypoglycaemia	8(13)	12(9)		NS
Hypothermia	3(5)	9(6)		NS

Figures in parentheses represent the percentage of the total
n = No of subjects
NS = Not Significant
PROM = Premature rupture of membrane

TABLE II

Features of 61 Patients with NEC

Feature	*No. of Cases*	% *of Cases*
Full term infants	16	26.2
Post term infants	2	3·3
Preterm AGA infants	38	62.3
Preterm SGA infants	5	8.2
Referred cases	30	49·2
Born within UBTH	31	50.8

AGA = Adequate for Gestational Age
SGA = Small for Gestational Age

The antecedent neonatal history in the 61 patients is presented in Table III. In a majority of the cases, multiple factors were present.

The clinical features of NEC (Table IV) revealed that abdominal distension, followed by blody stools and gastric retention were the commonest. Table V summarizes the annual incidence of NEC in the population studied. Two pertinent observations were made: (*a*) NEC was more common in very low birthweight (VLBW) infant (< 1500g), (*b*) the incidence of this clinical entity among the VLBW infants was highest during the period, 1980–1981, when compared with 1978–1979. This increase was statistically significant ($p < 0.001$).

TABLE III

Antecedent Neonatal History in 61 Infants with NEC

History	*No. of Cases*	% *of Cases*
Infection	38	62.3
Birth asphyxia	33	54.0
Respiratory distress	20	32.8
Umbilical venous catherterisation	12	19.7
PROM 24 hrs	10	16.4
Hypoglycaemia	8	13.1
Hypothermia	3	4.9
Exchange blood transfusion	2	3.3
Persistent ductus arteriosus	2	3.3
Anaemia (PCV = 35%)	2	3.3
Trisomy 21	1	1.6
Neonatal seizures	1	1.6

PROM = Premature rupture of membrane

TABLE IV

Clinical Features in 61 Infants with NEC

Feature	*No. of Cases*	% *of Cases*
Abdominal distension	54	88.5
Bloody stools	18	29.5
Gastric retention	15	24.6
Apnoea	15	24.6
Lethargy	12	19.7
Bilious vomiting	11	18.0
Haematochezia	11	18.0
Temperature instability	8	13.1
Jaundice	8	13.1
Peri-umbilical erythema or echymosis	6	9.8
Greyish cyanosis and toxaemia	5	8.2
Sclerema	4	6.6
Abdominal tenderness	3	4.9
Grunting respiration	2	3.3

TABLE V

Annual Incidence of NEC

	Year			
	1978	1979	1980	1981
Total admissions	776	744	699	693
Admissions delivered in UBTH	546	447	398	479
Admissions referred to UBTH	230	297	301	214
Total patients with NEC	8	6	26	21
Incidence/1000 total admissions	10.3	8.1	37.2	30.3
Patients born within UBTH	4	2	14	11
Patients referred to UBTH	4	4	12	10
Total admissions (BW < 1500g)	68	84	103	87
Patients with NEC (BW < 1500g)	3	3	13	9
Incidence/1000 admissions of infants (BW < 1500g)	44.1	35.7	126.2	103.4
Overall prevalence	20.9/1000 admissions			

The Figure illustrates the clustering of NEC cases. Seventy-two per cent occurred during the months of May through October. The observed variation in incidence corresponds with the rainy season when the relative humidity is high.

In an attempt to identify an aetiological infectious factor, isolates from 25 infants with septicaemia and five others with infective diarrhoea during two periods of epidemics of septicaemia and diarrhoea respectively, in 1981, were studied. These were compared with isolates from six infants who developed NEC during the corresponding period in the unit. *Staph. aureus* (8) and *Klebsiella* organisms (8) were the predominant isolates from blood during the septicaemic epidemics and *Salmonella G* was responsible for the epidemic diarrhoea as shown in Table VI. Neither of the last two organisms was isolated from the blood and stool cultures of the six patients with NEC during the periods of epidemics.

Fig. Monthly incidence of NEC during the study period, January 1978–December 1981.

TABLE VI

Organisms Isolated from 25 Infants with Septicaemia and/or Diarrhoea

Blood		Stools	
Organism	*No. of Cases*	*Organism*	*No. of Cases*
Staph. aureus	8	Salmonella G	5
Klebsiella	8		
E. Coli	4		
Pseudomonas	2		
Salmonella G	2		
Salmonella C	1		
Staph. albus	1		
Proteus	1		
Total	27		5

Discussion

The present study has confirmed that factors which cause hypoxia or ischaemia of the bowel wall are involved in the pathogenesis of NEC. Birth asphyxia, a significant predisposing factor of NEC in the present study, is a known cause of redistribution of blood flow from the intestines to the vital organs.[12 13] Similarly, the incidence of respiratory distress and respiratory distress syndrome was significantly higher in infants with NEC than in the controls.

The study failed to implicate umbilical venous catheterisation as an important determinant in the pathogenesis of NEC in our institution. This contrasts with the findings of Bunton *et al.*[3] A recent study[14] from our unit showed that umbilical venous catheterisation in excess of 48 hours, significantly increased the risk of bacterial colonisation thus suggesting that umbilical catheters be removed within 24 to 48 hours. It is therefore possible that the lack of association between umbilical catheterisation and NEC observed in the present study may be related to our deliberate policy of removing umbilical vessel catheters within 24 hours.

The precise aetiology of NEC remains elusive. It has been attributed to both infectious and non-infectious causes. Virnig and Reynolds[9] have also implicated intra-uterine infection. Infection was a more frequent finding in our study population than in the control group although we were unable to identify any transmissible bacterial pathogen. This finding agrees with that of Virnig and Reynolds[9] in which no identifiable transmissable viral or bacterial agent was found. In contrast, Stein *et al*[10] reported on 11 preterm infants who developed NEC in an epidemic of gastroenteritis and *Salmonella* infection in their preterm nursery. It should be noted that the five cases of *Salmonella G* diarrhoea which occurred during the epidemics in our Unit were not associated with the development of NEC.

It has been suggested that *E. Coli* plays a secondary role in the pathogenesis of NEC. Circulatory disturbances resulting in ischaemia of gut and bowel wall necrosis would permit bacterial invasion by normal gut flora.[9] Virnig and Reynolds[9] have therefore, concluded that altered intestinal resistance to invasion may play a direct role.

The incidence of NEC was highest in our unit in 1980 and 1981. A possible explanation for this trend may be due to increased admission of high risk infants weighing 1500gm or less who had many adverse predisposing perinatal factors.

There was a seasonal variation in the incidence of the disease in the present study, the incidence being highest during the humid months of May through October. To our knowledge, seasonal variation in the incidence of NEC has not been reported previously.

Contrary to previously held view that NEC was exclusively a disease of preterm infants, in the present study, it occurred in 16 term infants who had almost identical risk factors as the preterm babies namely: birth asphyxia, respiratory

distress from meconium aspiration and infections. This finding confirms the work of Polin and associates[15] who emphasised that NEC can occur in term infants in whom specific conditions are present. Contrary to their findings however, none of our term infants had congenital heart disease. The two cases of persistent ductus arteriosus associated with intractable heart failure occurred in preterm infants. The occurrence of this disease in term infants with identical risk factors as in preterm infants emphasises the concept that NEC is a disease entity that can develop in any infant in whom specific predisposing conditions are present rather than a disease entity peculiar to the preterm infant with a single aetiological factor.

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