Necrotizing enterocolitis and congenital heart disease: differences in management and prognosis

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Abstract

Objectives. Necrotizing enterocolitis (NEC) is a main cause of neonatal morbimortality. Gut prematurity and ischemia-reperfusion injury contribute to NEC and characterize two different scenarios: prematurity and congenital cardiopathy (CC). Our aim is to investigate whether CC worsens NEC gastrointestinal and general prognosis.

Materials and methods. NEC episodes from 2015-2023 were reviewed and classified into CC and non-CC. Patients with focal intestinal perforation were excluded. Data regarding NEC debut and management, surgical timing, intestinal segment involved and short-term outcomes were compared.

Results. Out of 205 neonates, 15 were excluded for unavailable records or uncertain diagnosis. 190 cases were included, 59 with CC. Comparing CC and non-CC, no significant differences were found in weight or age at diagnosis, or NEC stage. Hemodynamic (HD) shock [38.98% vs 24.43% ($p<0.05$)] and need for vasoactive support at debut were more frequent in CC patients [44.07% vs 23.66% ($p<0.05$)]. No differences were found regarding need for surgery at debut, length of resected intestine or segment affected or days on parenteral nutrition. CC conditioned longer hospital stay [110.8 ± 68.4 days vs 68.4 ± 44.6 ($p<0.05$)] and higher mortality [30.5 vs 11.5 ($p<0.05$)].

Conclusions. NEC in CC patients presents more HD instability at debut and worse global prognosis, probably due to inherent cardiovascular compromise, but need for surgery, type of intestinal involvement and short-term outcomes are similar to non-CC NEC.

Key Words: Enterocolitis, necrotizing; Infant, premature; Heart defects, congenital.

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Enterocolitis necrotizante y cardiopatías congénitas: diferencias en el manejo y el pronóstico

Resumen

Objetivos. La enterocolitis necrotizante (ECN) es una causa importante de morbimortalidad neonatal. La prematuridad intestinal y la lesión por isquemia-reperfusión contribuyen a la ECN, dando lugar a dos escenarios distintos: prematuridad y cardiopatía congénita (CC). Nuestro objetivo es investigar si la CC empeora el pronóstico general y gastrointestinal de la ECN.

Material y métodos. Se revisaron los episodios de ECN registrados en el período 2015-2023, y se clasificaron en CC y no-CC, excluyéndose a los pacientes con perforación intestinal focal. Se compararon los datos sobre el inicio y el manejo de la ECN, el tiempo operatorio, el segmento intestinal afectado, y los resultados a corto plazo.

Resultados. De los 205 neonatos, se excluyó a 15 por no disponerse de los historiales o por presentar un diagnóstico incierto. Se incluyeron 190 casos, 59 de ellos con CC. Al comparar el grupo CC con el no-CC, no se apreciaron diferencias significativas en términos de peso, edad en el momento del diagnóstico, o estadio de la ECN. El shock hemodinámico (HD) (38,98% frente a 24,43% ($p<0,05$)) y la necesidad de soporte vasoactivo al inicio fueron más frecuentes en los pacientes CC (44,07% frente a 23,66% ($p<0,05$)). No se hallaron diferencias en cuanto a la necesidad de cirugía al inicio, la longitud de intestino resecado, el segmento afectado o los días de alimentación parenteral. La CC conllevó una mayor estancia hospitalaria (110,8 ± 68,4 días frente a 68,4 ± 44,6 ($p<0,05$)) y una mayor mortalidad (30,5 frente a 11,5 ($p<0,05$)).

Conclusiones. En los pacientes CC, la ECN presenta una mayor inestabilidad HD al inicio y un peor pronóstico global, probablemente debido al compromiso cardiovascular inherente, mientras que la necesidad de cirugía, el tipo de afectación intestinal y los resultados a corto plazo son similares respecto a los pacientes no-CC.

Palabras Clave: Enterocolitis necrotizante; Prematuridad; Cardiopatía congenita.

INTRODUCTION

Necrotizing enterocolitis (NEC) is the most common neonatal gastrointestinal emergency[1], with devastating consequences on patients' morbidity, mortality and quality of

life[2]. It affects 5-7% preterm infants, especially those with very-low birthweight[3]. Improvement of neonatal care and novel treatments have allowed for survival rates of preterm and great preterm infants to rise, therefore increasing the incidence of NEC[2,3]. Pathogenesis is multifactorial, including gut prematurity, ischemia-reperfusion injury and abnormal gut bacterial overgrowth[2]. Congenital heart disease (CHD) is a known risk factor for NEC[1,4], with 1.6-9% of them developing NEC, in spite of being born full-term[3,5].

Consequently, two different entities have been proposed[2,6]: inflammatory NEC (iNEC, typical of preterm infants, 85-97% cases of NEC[5]) and cardiac NEC (cNEC, where the trigger is an ischemia-reperfusion injury). Evidence regarding this hypothesis is contradictory[5], and especially queries regarding NEC surgery remain unanswered[3]. The aim of our study is to analyze variables regarding NEC surgical and short-term outcomes in CHD and non-CHD patients in search of difference between the two.

MATERIALS AND METHODS

A retrospective analysis of all NEC cases over IIA according to Bell's modified staging[7] diagnosed at our neonatal ICU (NICU) from January 2015 to December 2023 was performed. The list of patients was obtained from codified diagnoses of "NEC" and from the Pediatric Surgery Unit databases. Patients were classified into CHD and non-CHD. As CHD was considered every cardiac anomaly that entailed any type of hemodynamic repercussion, including persistent ductus arteriosus (PDA). In this last case, a separate analysis was performed between surgically and pharmacologically treated PDA patients.

Focal intestinal perforation (FIP) is a form of ischemia-induced bowel wall damage, associated to persistent ductus arteriosus or NSAIDs, but lacking inflammation or necrosis[8]. It is considered a different entity to necrotizing enterocolitis[9], and was therefore excluded from the start. Also, after a quick review of patient records, those with rectorrhagia but uncertain NEC diagnosis (Bell's modified stage I[7]) were also excluded.

Data was recorded regarding patient identification, birth (gestational age and birth weight) and comorbidities. In cases with CHD, different anomalies were codified and registered, as well as the treatment they received and classification into cyanotic CHD (cCHD) or not (ncCHD). Variables were classified into those corresponding to the NEC episode (symptoms, physical exam, severity, radiological signs, need for hemodynamic support and microbiological analyses), NEC surgery (timing, length of resection, technique performed and reinterventions), postoperative period (start of enteral feeds, parenteral nutrition (PN) days) and discharge (age, weight, need for nutritional support and neurological status).

Statistical analysis was performed using Stata 13.1 software (StataCorp, College Station, TX). Variables are expressed as mean with standard deviation (continuous variables) or percentage (categorical variables). Student's t-test was used to compare continuous variables with a normal distribution and the Mann-Whitney U test was used for variables with a non-normal distribution. For categorical variables, Pearson's Chi-square test or Fisher's exact test was used. A value of $p<0.05$ was considered statistically significant.

Table 1. Demographic variables.

	CHD	*Non-CHD*	*p*
Preterm (%)	52 (88.14%)	121 (92.37%)	0.344
Birthweight (g)	1457.6±708.6	1457.6±944.8	0.653
Gestational age (weeks)	29.9±4.9	30.6±3.9	0.278

CHD: congenital heart disease. Preterm considered under 37 weeks' gestational age.

RESULTS

205 cases of NEC were treated at our center N-ICU from January 2015 to December 2023. Out of these 205 cases, 15 were excluded for unavailability of records or uncertain NEC diagnosis. From the 190 remaining cases, 59 presented CHD (31.05%) and 131 did not (68.95%). 91.05% cases in our series were preterm, with a similar percentage between both groups, and no significative differences were found regarding birthweight [1457.6±944.8g vs 1513.3±708.6 g ($p=0.653$)] (Table 1).

Out of the 54 CHDs, 31 were PDAs with hemodynamic repercussion. 22/31 were successfully managed with pharmacological treatment and 9/31 needed surgical correction. The second most frequents were pulmonary branch stenosis and transposition of great arteries, with 5 cases each, and there were 4 cases of aortic arch interruption. The remaining 12 cardiopathies presented in 2 or less cases (Table 2). 10 cases presented two simultaneous CHDs. Together, we recorded 8 cases of cyanotic CHD, 40 left-to-right shunts (31 of them PDAs), 8 right ventricle obstructions and 6 left ventricle obstruction.

Regarding the NEC episode, no significative differences were found between CHD and non-CHD cases in age at NEC debut [19.6±22.5 days vs 16.1±15.9 ($p=0.214$)] nor NEC stage according to Bell's staging[7]. NEC stage III was more frequent in non-CC patients, but not statistically significant [59.32% vs 70.22% stage II, 40.68% vs 29.77% stage III ($p=0.334$)]. CHD NEC patients presented more instability at debut in the form of hemodynamic shock [38.98% vs 24.43% ($p=0.041$)], with more need for vasoactive support during the acute episode [44.07% vs 23.66% ($p=0.005$)], being these differences statistically significant (Table 3).

Table 2. Congenital cardiopathies in our series.

Cardiopathy	*Nº of cases*
Patent ductus arteriosus with hemodynamic repercussion	31
Tetralogy of Fallot	2
Pulmonary branch and pulmonary valve stenosis	5
Transposition of the great arteries	5
Aortic arch interruption	4
Major aortopulmonary collateral arteries	1
Pulmonary atresia	2
Interauricular communication	1
Ventricular dysfunction, pericardial effusion	1
Aortic coarctation	2
Ebstein anomaly	1
Atrioventricular canal defect	2
Hypertrophic cardiomyopathy	1
Persistent fetal circulation	2
Congenital systemic-to-pulmonary shunt	1
Interventricular communication	2
Double outlet right ventricle	1

10 patients presented with 2 different simultaneous cardiopathies. Permeable foramen ovale was not considered a cardiopathy in itself and therefore excluded.

Table 3. NEC debut.

	CHD	*Non-CHD*	*p*
Age at NEC diagnosis (days)	19.6 ± 22.5	16 ± 15.9	0.214
Stage II (%)	35 (59.32%)	92 (70.22%)	0.334
Stage III (%)	24 (40.68%)	39 (29.77%)	
Hemodynamic shock at debut (%)	23 (38.98%)	32 (24.43%)	0.041
Need for HD suport (%)	26 (44.07%)	31 (23.66%)	0.005
Rx findings			
Pneumatosis intestinalis	42 (71.19%)	85 (64.89%)	0.393
Portal venous gas	8 (13.56%)	19 (14.50%)	0.863
Pneumoperitnoeum	2 (3.39%)	11 (8.4%)	0.206

CHD: congenital heart disease; HD: hemodynamic. Stages according to Bell's modified classification.

Table 4. NEC surgery.

	CHD	*Non-CHD*	*p*
Need for surgery (%)	21 (35.59%)	48 (36.64%)	0.889
Need for surgery at debut (%)	20 (33.89%)	45 (34.35%)	
Age at surgery (days)	24.8 ± 12.3	27.2 ± 19.6	0.703
Colonic segment involved			
Ascending colon	6 (54.55%)	13 (39.39%)	0.38
Descending colon	0 (0%)	1 (3.0%)	0.559
Ileo-cecal valve remaining	5 (45.45%)	17 (51.52%)	0.728

CHD: congenital heart disease. Colonic segment involved based on surgery reports.

Table 5. Outcomes.

	CHD	*Non-CHD*	*p*
Time on PN (days)	31.5 ± 65.3	30.76 ± 107.31	0.961
Age at discharge (days)	110.8 ± 68.4	68.4 ± 44.6	0.000
Mortality (%)	18 (30.5%)	15 (11.5%)	0.001

CHD: congenital heart disease; PN: parenteral nutrition. Mortality includes short- and long-term.

Regarding NEC surgery, no differences were found between the two groups in the need for emergent surgery (20% CHD vs 45% non-CHD), the length of resected bowel, the intestinal segment affected or the age [27.2 ± 19.65 vs 24.8 ± 12.31 (p = 0.703)] or weight at surgery (Table 4).

Regarding outcomes, a significant difference was found between CHD and non-CHD NEC regarding length of hospital stay [110.8 ± 68.4 días vs 68.4 ± 44.6 (p = 0.005)] and mortality [30.5 vs 11.5 (p = 0.001)]. Postoperative days on parenteral nutrition also showed no significant difference between groups (Table 5).

On secondary analysis, no differences were found in any of these parameters (NEC presentation, surgical variables or outcomes) between surgical and pharmacological PDA closure patients.

DISCUSSION

NEC is one of the most devastating gastrointestinal diseases in newborn and preterm infants[1,2]. The current consensus on NEC pathogenesis is a multifactorial combination of gut prematurity, bacterial overgrowth, and ischemia-reperfusion injury, which eventually leads to an exaggerated inflammatory response in the bowel and consequent tissue damage[2]. Two main groups of patients

are affected by NEC[2,6]: preterm (especially very low birth weight[3]) infants and full-term infants with CHD[3,5]. This has motivated the definition of two pathogenesis patterns or entities in NEC: inflammatory NEC (iNEC) and cardiac NEC (cNEC), respectively[2]. The pathogenesis hypothesis proposed for cardiac NEC consists of neutrophil activation through the interleukins released during ischemic injury due to mesenteric hypoperfusion[2], whether because of low cardiac output or because of diastolic steal, depending on the type of CHD[3,5]. The gut is particularly at risk of ischemia during the postoperative low cardiac output state because of the sensitivity of the splanchnic circulation to endogenous and exogenous catecholamines, and selective vasoconstriction effects of angiotensin[5]. Neutrophil activation together with the prematurity of the bowel immune system, unable to control the inflammatory response, leads to tissue damage. The intestinal flora can therefore invade intestinal tissue and access the blood stream, leading to sepsis and multiorgan failure[2].

In our series an important percentage of CHD patients were premature, in disagreement with the literature, that reports most CHD-NEC cases occurring in full-term and normal birthweight newborns[6,10,11]. This could be because preterm patients with persistent ductus arteriosus were included as CHD when hemodynamically significant. Even though pathogenesis hypotheses show different mechanisms leading to NEC, whether it they are clinically and surgically separate entities remains unclear. Klinke et al.[2] performed a retrospective analysis of surgical NEC patients with previous cardiac surgery or PDA treatment, analyzing also laboratory parameters and histological aspects. No difference on clinical or radiological signs was found other than regarding age at diagnosis, where cNEC patients were significantly older than iNEC patients[2]. Our study showed no difference regarding NEC severity (classified by Bell's staging criteria), symptoms or signs at debut between CHD and non-CHD, in agreement with the literature. In our series we also analyzed whether NEC debut was accompanied by hemodynamic instability, finding that CHD patients presented more often with shock and need for vasoactive drugs. This is most probably due to the basal hypoperfusion circulatory situation of these patients and their lower cardiac reserve in case of critical conditions, which is reflected in the higher overall in-hospital mortality in CHD newborns in comparison to non-CHD[12]. This was also explained by Cheng et al., who found a 57% mortality for CHD-NEC in comparison to a 20% for preterm NEC[13].

Few studies have specifically analyzed differences in the surgical techniques performed or need for surgery, but evidence suggests that severity is less in CHD infants, needing in less cases emergency surgery for bowel perforation or non-improvement of NEC with medical management[5,14]. Kessler et al.[15] also investigated gastrointestinal complications of NEC and found that CHD neonates do not have more complications than patients without CHD. In our analysis no difference was found regarding need for emergency surgery during the acute phase in both groups, contradicting Pickard et al.'s research[14]. Similarly, Bubberman et al.[16] found that the complication rates were comparable between both groups.

Also, in the group of surgery-related variables we studied the anatomic localization of the disease, under the hypothesis that hypoperfusion affects specially frontier areas between different vascular territories, as could be the splenic flexure or the sigmoid (Griffith's and Suddeck's points)[17]. Evidence in the literature shows no unanimous findings, with some studies showing more lesions in the colon[16] but not others[11]. Cozzi et al.[11] described how the location of gut necrosis in CHD and patients with normal cardiac anatomy was similar and in the small intestine. In other studies, Bubberman et al.[16], Diez et al.[18], and Giannone et al.[19] found most lesions of CHD-NEC in the colon. In our study we found no difference between small intestine or colon involvement, as well as between the affected segment of the colon. In fact, diffuse colonic involvement was also reported by Martos et al. as one of the differential traits between CHD NEC and isolated ileal damage in FIP[20].

Even though need for surgery may differ, morbidity and mortality have been found to be significantly higher in CHD patients with NEC. Maheshwari et al.[5] performed a systematic review of NEC associated with CHD, finding that even mild medical NEC impeded feeding and weight gain resulting in prolonged hospital stay. We also found a longer hospital stay in the CHD group, statistically significant in comparison to non-CHD NEC. Regarding mortality, Pickard et al.[14] performed a retrospective analysis of over 200 NEC cases comparing CHD and non-CHD patients, finding a higher survival rate in CHD patients, but this study has also shown to be heterogeneous in inclusion criteria and methodology, as explained by Kashif et al.[3]. In contraposition to Pickard's findings, Kessler et al.[15] found a higher overall mortality in CHD patients, only including in their study confirmed NEC cases (considered as Bell stage II or higher). Other studies have come to the same conclusion[3,11], also in agreement with our results, where mortality was significantly higher in the CHD group.

Limitations to our study are its retrospective nature, the consequent unavailability of some records, and the difference in sample size between CHD patients (59) and non-CHD (131), which could affect the statistical significance of our results. Further studies are needed to define surgical aspects of CHD and non-CHD NEC, as well as nutritional outcomes.

In conclusion, we found that there are no essential differences between CHD-NEC and non-CHD, suggesting that they may not be different entities. CHD-NEC does not present a higher need for surgery or worse short-term outcomes. Regarding surgical aspects, our evidence suggests that they also do not imply shorter resections or involve-

ment of different zones of the bowel. We did find that NEC in CHD patients presents more hemodynamic instability at debut and worse global prognosis, probably due to inherent cardiovascular compromise and a lower cardiac reserve.

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