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Predictive and diagnostic value of serum intestinal fatty acid binding protein in neonatal necrotizing enterocolitis (case series)

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HIGHLIGHTS

- This prospective study was performed on preterm neonates selected from the Neonatal Intensive Care Units (NICUs) of the Pediatric Department at Benha University hospital and Benha children hospital.
- The 1st values of IFABP taken within birth showed that mean serum IFABP concentrations of study group were higher than that of the control group. The 2nd values of serum IFABP taken at start of feeding showed that mean IFABP concentrations of study group were higher in comparison with IFABP at birth. In the 3rd values of serum IFABP taken at time of diagnosing NEC showed that mean serum IFABP concentrations of study group were higher than the control group.
- In the 4th values of serum IFABP taken one week after diagnosing NEC showed that the mean serum IFABP concentrations of the study group became significantly decreased in comparison with IFABP at time of diagnosis in stage 1 and 2.

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ABSTRACT

Objectives: In this study, we aimed to investigate the value of serum intestinal fatty acid binding protein (I-FABP) in early diagnosis and predicting the severity of Necrotizing enterocolitis (NEC).
Methods: This prospective study was performed on 160 preterm neonates ageing less than 35 weeks and weighting less than 2000 gm selected from the Neonatal Intensive Care Units (NICUs) of the Pediatric Department at Benha University hospital and Benha children hospital to evaluate which of them will develop NEC, after follow-up these neonates were divided into two groups: Group one compromised eighteen preterm neonates with symptoms and signs of NEC. Group two compromised ten preterm neonates as a control group. All participants were subjected to full clinical examination, abdominal X-ray and serum I-FABP.
Results: The 1st values of IFABP taken at birth showed that mean serum IFABP concentrations of the study group were higher than that of the control group. The 2nd values of serum IFABP taken at the start of feeding showed that mean IFABP concentrations of the study group were higher in comparison with IFABP at birth. In the 3rd values of serum, IFABP taken at the time of diagnosing NEC showed that mean serum IFABP concentrations of the study group were higher than the control group. In the 4th values of serum, IFABP taken one week after diagnosing NEC showed that the mean serum IFABP concentrations of the study group became significantly decreased in comparison with IFABP at the time of diagnosis in stage 1 and 2.
Conclusions: Serial measurements of serum I-FABP levels may be a useful marker for early diagnosis and prediction of disease severity in NEC.

1. Introduction

Necrotizing enterocolitis (NEC) is a severe neonatal gastrointestinal disease with high morbidity and mortality (20%–40%), characterised by inflammation and intestinal cell damage [1]. NEC

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results from a combination of several factors, including genetic predisposition, intestinal immaturity, excessive intestinal inflammatory response, and inappropriate microbial colonisation [2].

NEC is characterised histopathologically, by intestinal coagulate or ischemic necrosis starting at the mucosa and extending into the sub mucosa and muscularis externa [3]. Early symptoms of necrotizing enterocolitis (NEC) are often non-specific, such as abdominal distension, bloody stools, or gastric retention [4].

Early identification of those patients who will eventually develop definite NEC remains challenging, primarily because current laboratory and radiology tests lack sufficient discriminative power [5].

Intestinal fatty acid binding protein (I-FABP) is a small cytoplasmic protein located in small intestinal enterocytes involved in the uptake and transport of polar lipids such as fatty acids from the small-bowel lumen [6]. (I-FABP) was investigated as a measure of enterocyte damage and candidate biomarker of NEC, Upon the death of the enterocyte, its cytoplasmic contents are released into the circulation, and rise in plasma I-FABP concentration has been demonstrated both in animal models [7] and in preterm infants with NEC [8].

Furthermore, the use of serum I-FABP concentration in early diagnosis and prediction of the extent of NEC among infants with abdominal signs has been demonstrated [9].

The aim of this study was to determine the usefulness of serum IFABP in early diagnosis and prediction of severity of NEC in preterm infants.

2. Subjects and methods

2.1. Subjects

This case series study was conducted on preterm infants selected from the Neonatal Intensive Care Units (NICUs) of the Pediatric Department at Benha University hospital and Benha children hospital during the period from June 2016 untill december 2016. Approval of the study protocol by Ethical Scientific Committee of Benha University was obtained and informed consent was obtained from the parents before enrollment in the study. 160 preterm neonates ageing less than 35 weeks and weighting less than 2000 gm were included in this study to evaluate which of them will develop NEC, after follow-up 18 of them developed NEC and still present in our study until the last samples were obtained from them. These neonates were diagnosed and classified according to Bell's Staging for NEC [4].

- The 18 preterm neonates who developed NEC were defined as a **group I**. These neonates were diagnosed and classified according to Bell's Staging for NEC. Stage one included ten neonates, Stage two included five neonates, and Stage three included three neonates.
- 10 of preterm infants who didn't develop NEC were taken as control group these neonates were defined as **group II**.

The patients group was under the following inclusion and exclusion criteria.

2.1.1. Inclusion criteria

Preterm infant aged thirty-five weeks or less, of both sex.

2.1.2. Exclusion criteria

Newborns with any congenital anomalies, an inborn error of metabolism, fatal chromosomal defect and full-term infants were excluded from this study.

2.2. Methods

All neonates incorporated in this study were subjected to the following:

Full history taking, full clinical examination, abdominal x-ray and laboratory investigations including Complete blood count (CBC), and Serum I-FABP by Human I-FABP commercially available ELISA Kits.

The laboratory investigations included:

2.2.1. Blood sampling

Five millilitres of venous blood were withdrawn under aseptic precautions and distributed as follows:

a- Two millilitres whole blood was put in EDTA vacutainer (violet cap) and mixed up & down gently which was used to measure CBC.

b Three millilitres plain test tubes without anticoagulant. The plain tubes were left till coagulation. After coagulation, samples were centrifuged (at 1500 rpm for fifteen minutes). The separated serum was used for the assay of **I-FABP** at the following four-time points for study group: a) 1st twenty-four hours of birth b) at the start of feeding, c) at diagnosis of NEC d) within one week after. And two-time points for control group: a) 1st twenty-four hours of birth, b) at the time of diagnosis of NEC.

2.2.2. Routine laboratory investigations

CBC was done for all samples using a fully automated cell counter (**Sysmex 5, Xs 800**).

2.2.3. Specific laboratory investigations

Serum intestinal fatty acid binding protein (IFABP): was measured using human ELISA (sandwich technique) kits provided by SUN RED, China. (catalogue No. 201-12-1542) with assay range (0.3–80 ng/ml) and Sensitivity: 0.156 ng/ml.

2.2.4. Principles of serum I-FABP test

The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human intestinal fatty acid binding protein (iFABP) in samples.Intestinal fatty acid binding protein (iFABP) was added to monoclonal antibody Enzyme well which is pre-coated with Human intestinal fatty acid binding protein (iFABP) monoclonal antibody, incubation; then, intestinal fatty acid binding protein (iFABP) antibodies labeled with biotin, was added and combined with Streptavidin-HRP to form immune complex; then incubation and washing again to remove the uncombined enzyme. Then Chromogen Solution A, B were added, the colour of the liquid changes into the blue, and at the effect of acid, the colour finally becomes yellow which was read after 30 min at 450 nm with a Best 2000 (Top diagnostic) microplate reader (Inova Diagnostics, California, USA). The chroma of colour and the concentration of the Human Substance intestinal fatty acid binding protein (iFABP) of the sample were positively correlated.

3. Statistical analysis

The collected data were tabulated and analysed using SPSS version 16 software (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages using Chi-square test (X2) or Fisher's exact test (FET) for their analysis. Quantitative data were tested for normality using Shapiro-Wilks test assuming normality at $P > 0.05$, using Student “t”, for normally distributed variables, or Man-Whitney U test, Kruskal-Wallis test and Spearman's correlation coefficient (rho) if not normally distributed. ROC curve was used to detect the cut-off value of I-FABP level with optimum sensitivity and specificity in the

prediction of NEC. The accepted level of significance in this work was stated at 0.05 ($P < 0.05$ was considered significant).

4. Results

160 preterm neonates ageing less than 35 weeks and weighting less than 2000 gm were included in this study to evaluate which of them will develop NEC. After follow-up 18 of them developed NEC and still present in our study until the last samples were obtained from them. These neonates were diagnosed and classified according to Bell's Staging for NEC.

- The 18 preterm neonates who developed NEC were defined as a **group I**.
- 10 of preterm infants who didn't develop NEC were taken as control group these neonates were defined as **group II**. (Table 1). The remaining neonates, some of them died, others referred and excluded from our study.

Our study showed gastric residuals to be an indicator for premature infants developing NEC. About 88.9% of the patients in the present work had gastric residual and 44.4% of patients with bloody residual.

Regarding radiologic finding, in the present study the intestinal dilatation was seen in 9 (50.0%) neonates, dilated fixed loops in 6 (33.33%) neonates and pneumoperitoneum in 3 (16.7%) neonates, with a significant statistical difference ($p < 0.001$).

CBC was done to all cases and showed no statistical difference in WBCs, a significant statistical decrease in haemoglobin concentration ($p = 0.006$) in the patient group (10.35 ± 1.28 vs 12.20 ± 1.44) and a highly significant statistical decrease in platelet count ($p < 0.001$). (97.83 ± 45.47 vs 227.80 ± 49.44) (Table 3).

Regarding serum IFABP values; Comparing between Group I and Group II as regarding serum IFABP level at birth and at diagnosis show a high significant statistical increase in its level in the patient group ($p < 0.001$). (Table 2).

Regarding serum IFABP according to Bell's staging at the time of diagnosis of NEC, we found that mean serum IFABP stage 2 is significantly higher than stage 1 and mean serum IFABP in stage 3 is significantly higher than stage 1 and 2. Also, we found that serum I-FABP levels were decreased from the onset of the disease to 1 week after in stage 1 and 2 and slightly decreased in stage 3. (Table 3).

To define Validity and predictivity of I-FABP level in the prediction of NEC, subjects were analysed by ROC curve analysis. Area under curve (AUC) value was 0.99, 95% Cut-off point of I-FABP for prediction of NEC is estimated to be ≥**7.75** ng/ml at birth with sensitivity 94.4% and specificity of 100%. While at the cut-off point of I-FABP for prediction of NEC is estimated to be ≥**37.95** ng/ml at diagnosis with sensitivity 100% and specificity of 100%. (Fig. 1a). Also plotting ROC curve for serum I-FABP in the detection of NEC stage at diagnosis of NEC is estimated to be ≥**131.8** ng/ml with 90% sensitivity and 100% specificity. (Fig. 1b).

Table 1
Comparing the studied groups regarding Gestational age and anthropometric measures.

Variable	Study group (N = 18)		Control group (N = 10)		St."t"	P
	Mean	±SD	Mean	±SD		
Gestational age (wk)	32.1	1.71	32.7	1.94	0.83	0.41 (NS)
Weight (gm)	1427.7	290.64	1495.0	258.68	0.61	0.54 (NS)
Length (cm)	49.8	0.90	49.9	0.99	0.03	0.97 (NS)
HC (cm)	34.5	0.78	34.4	0.84	0.49	0.62 (NS)

HC:Head Circumference.

Table 3
Serum IFABP levels according to Bell's staging.

Group	n.	IFABP at diagnosis (ng/ml)			KWT	P
		Mean	± SD	Range		
Stage 1	10	115.71	35.99	70.8–198.6	13.1	0.001 (HS)
Stage 2	5	290.16*	90.49	133.4–347.7		
Stage 3	3	641.86*†	19.02	620.1–655.3		
		IFABP 1 w after NEC (ng/ml)				
Stage 1	10	19.19	3.69	12.3–25.4	13.2	0.001 (HS)
Stage 2	5	37.48	15.03	23.3–60.3		
Stage 3	3	571.53*†	27.97	550.2–603.2		

KWT: Krauskall Wallis test.
*→Significant in comparison with stage 1.
†→Significant in comparison with stage 2.

5. Discussion

Necrotizing Enterocolitis (NEC) is the most serious gastrointestinal disorder to occur in the premature infants. The incidence of NEC varies from 0.5 to 5 infants per 1000 live births with a mortality rate of 10–50% [10].

Because NEC is characterised by loss of bowel wall integrity, intestinal fatty acid-binding protein (I-FABP) is one of the more promising biomarkers. This small cytosolic protein, located mainly in enterocytes of the small intestine, is released into the blood stream after cell disruption [11]. While several studies investigated the discriminative power of I-FABP for NEC at the onset of disease, no study evaluated changes in I-FABP levels during its development. As NEC is often a progressive disease, consecutive measurements might offer more detailed information about the disease course than a single measurement at first symptoms [12]. Our aim was to determine the usefulness of serum intestinal fatty acid binding protein (I- FABP) in early diagnosis and prediction of severity of necrotizing enterocolitis (NEC).

Regarding gestational age distribution in our patients the mean gestational age was 32.3 ± 1.8 weeks this is in agreement with Luig and Lui [13], who confirmed that prematurity is the most important risk factor for the development of NEC because 95% 0f NEC cases occur in preterm infants. Premature babies are predisposed to develop NEC because of the immature mucosal barrier and immature response in addition to impaired circulatory dynamics and gastrointestinal motility. These are thought to make premature neonates at high risk for NEC higher than normal full term babies [14]. Regarding Weight: in our study the weight ranged from 1000 to 2000 g with mean 1451.8 ± 276.7 g, in the study done by Aydemir

Table 2
Comparing the studied groups regarding IFABP (ng/mL) level.

Variable	Patient group (N = 18)			Control group (N = 10)			Z of MWU test	P
	Mean	±SD	Range	Mean	±SD	Range		
IFABP at birth	11.76	4.09	7.6–25.1	3.12	1.44	1.1–4.9	4.32	<0.001 (HS)
IFABP at diagnosis	251.86	202.07	70.8–655.3	3.16	1.33	1.2–5.1	4.31	<0.001 (HS)

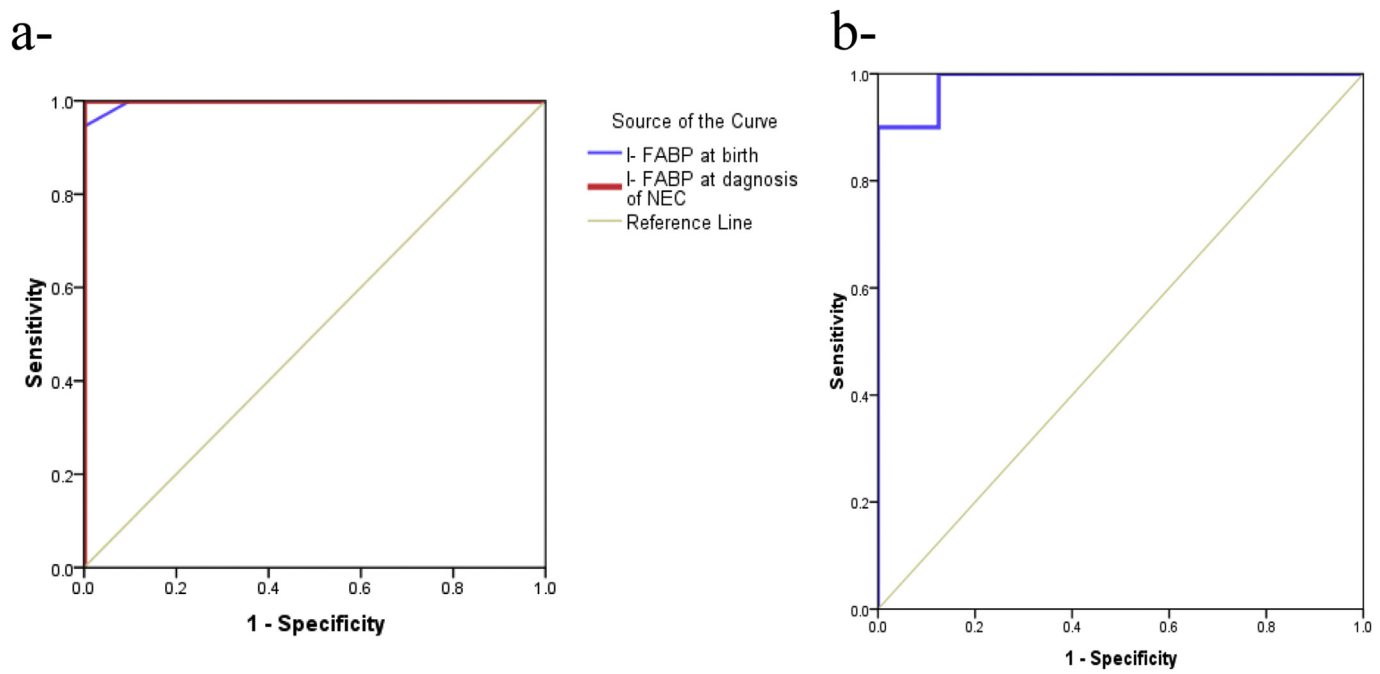

Fig. 1. a-Roc curve for accuracy of I-FABP level in prediction and diagnosis of NE at birth and at diagnosis of NEC. b- Roc curve to detect accuracy of I-FABP level in detection of NEC stage.

et al. [12] they found that the mean weight was 1298 ± 238 g in their cases, in another study done by Guthmann et al. [8] the mean weight was 1298.7 ± 572.5 g in neonates who developed NEC. Regarding sex: 9 were males (50.0%) and 9 were females (50%) with a male to female ratio 1:1. In contrast to our results, McGuire et al. [15] Reported that male gender is one of perinatal risk factors for NEC. In our study clinical presentation of NEC shows signs of feeding intolerance (abdominal distension – gastric residuals – occult blood in stools) and neurological signs (lethargy – weak reflexes). This was in agreement with the study by Buch et al. [16].

CBC was done to all cases and showed thrombocytopenia in group I and normal platelet count in group II with a significant statistical decrease in group I. This was in agreement with the previous study done by Hallstrom et al. [5] who reported that thrombocytopenia is a common laboratory finding in patients with proven NEC. Another laboratory finding in our study is anaemia, the median haemoglobin level is 10.35 ± 1.28 in group I, and compared with group II we found that neonates of group II have higher haemoglobin level.

In our study, Regarding serum IFABP values; The 1st values of IFABP taken within 1st 24 h of birth showed that the mean serum IFABP concentrations of study group were 11.76 ± 4.09 (ng/ml) that was stylistically significant higher than that of the control group 3.12 ± 1.1 (ng/ml), this was in agreement with the previous study by Schurink et al. [17] who reported that mean serum IFABP concentration 24 h after birth was 8.6 (ng/ml).

The 2nd values of IFABP taken at the start of feeding showed that the mean IFABP concentrations of the study group were 29.24 ng/ml, which are statistically significant higher in comparison with IFABP at birth. Early and reliable diagnosis of NEC is important to offer opportunities for early intervention, our results succeeded in early diagnosis and prediction of NEC. This was in agreement with the previous study by Gregory et al. [18], who illustrated that within 7 days before NEC, IFABP > 13.3 (ng/mL) would predict NEC with 60% sensitivity and 78% specificity.

The 3rd values of serum IFABP took at time of diagnosing NEC showed that the mean serum IFABP concentrations of control group were 3.16 ± 1 (ng/ml) and that of the study group were 251.86 ± 200.07 (ng/ml), also it is significantly higher in comparison with IFABP at birth and at the start of feeding. Our results demonstrated that I-FABP had diagnostic and prognostic properties. This was in agreement with the previous study by Ng et al. [19] who showed that I-FABP is a potentially useful biomarker for differentiating between NEC and control patients with suspected clinical sepsis or NEC. Similar to our results, they found significantly higher I-FABP levels in NEC infants than in control group. Recently, in a study comparing I-FABP with other potential markers, Benkoe et al. [20] reported too that I-FABP concentrations were significantly higher in NEC infants compared with controls.

The 4th values of serum IFABP taken one week after diagnosing NEC showed that the mean serum IFABP concentrations of the study group were 116.32 ng/ml which became decreased in comparison with IFABP at the time of diagnosis. This was in agreement with the previous study by Stepan et al. [21] who found that serum I-FABP taken 7–10 days after NEC, at the last day of antibiotic treatment was 20 ng/ml the continuous sampling showed that serum I-FABP levels decrease during the therapy.

Regarding serum IFABP according to Bell's staging at the time of diagnosis of NEC, we found that mean serum IFABP in stage 1 was 115.71 ± 35.99 ng/ml, mean serum IFABP in stage 2 was 290.16 ± 90.49 and mean serum IFABP in stage 3 was 641.86 ± 19.02 (ng/ml). This was in agreement with the study done by Aydemir et al. [12] who reported that the mean serum I-FABP concentrations of stage1 at 24 h of NEC was 112.5 ± 84.2, mean serum I-FABP concentrations of stage 2 was 269.4 ± 269.8 and mean serum IFABP in stage 3 was 317.4 ± 365.3 (ng/ml). In the study done by Edelson et al. [22] found that I-FABP concentrations at the onset of symptoms significantly higher in stage 3 (median 112.5 ng/ml) compared to stages 2. In contrast to our results, they could not detect I-FABP in infants (stage 1) NEC.

We found significantly higher levels of serum I-FABP in infants with stages 2 and 3 NEC compared to stage 1 NEC with a sensitivity

of 90% and a specificity of 100%. Furthermore, we demonstrated that significantly higher I-FABP values 1 week after disease are related to the severity of NEC. Higher serum I-FABP levels 1 week after NEC were found in infants with stage 3 NEC compared with stage 1 or 2 NEC. Serum I-FABP level was gradually decreased from the onset of the disease to 1 week in stage 1 and stage 2 NEC and slightly decreased in stage 3.

We plotted a ROC curve for serum I-FABP as a marker for prediction of NEC with 94.4% sensitivity and 100% specificity. Also, we found serum I-FABP had 100% sensitivity and 100% specificity as a marker for diagnosis NEC.

Also plotting ROC curve for serum I-FABP in the detection of NEC stage which revealed a cutoff value of serum I-FABP $\geq$131.8 (ng/ml) at diagnosis of NEC with 90% sensitivity and 100% specificity.

6. Conclusion

Serum I-FABP levels are increased in preterm neonates with NEC in comparison to age-matched controls; also serum I-FABP levels are increased according to the severity of NEC. So serial measurements of serum I-FABP levels may be a useful marker for early diagnosis and prediction of disease severity in NEC.

Ethical approval

Approval of the study protocol by Ethical Scientific Committee of Benha University was obtained.

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Author contribution

Omima M. Abdel-HaiE:, data collections, writing.
Eman G. Behiry: data collections, data analysis, writing.
Enas S. Ahmad, data collections, data analysis, writing.
Effat H. Assar: data collections.

Conflicts of interest

No conflict of interest.

Guarantor

Eman G. Behiry. Clinical pathology Department, Benha University.

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