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Acute phase proteins in "small for dates" babies II. Haptoglobin, transferrin, alpha-1-feto protein, alpha-1-acid glycoprotein and caeruloplasmin levels

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Summary

Haptoglobin, transferrin, alpha -1- feto-protein (AFP), alpha-1-acid glycoprotein (AAGP) and caeruloplasmin levels were estimated in 14 "small for dates" (SFD) and 31 "appropriate for dates" (AFD) babies by the single radial immunodiffusion method. The mean caeruloplasmin levels was observed to be significantly reduced in the SFD babies when compared with the AFD babies (t =3.4582, P <0.02). None of the other 4 acute phase proteins showed any significant differences in mean concentration between the SFD babies and the controls. The diminished caeruloplasmin levels observed in SFD babies agrees with previous reports in post-natal undernutrition. Our findings of no significant differences in the other 4 acute phase proteins between SFD and AFD babies are however at variance with previous observations of elevated levels of AFP, haptoglobin and AAGP and reduced levels of transferrin in malnourished infants.

Resume

Nous avons evalue les niveaux d'haptoglobine, de transferine, d'alpha-1 fetoproteine (AFP), d'alpha-1 glycoproteine acide (AGPA), ou AAGP en aglais et de caeruloplasmine dans 14 bebes "petis pour leur age" (PPLA, ou SFD en anglais) et 31 bebes "normaux pour leur age" (NPLA, ou AFD en anglais) en utilisant la methode d'immunodiffusion unique radiale.

Nous avons constate que le niveau moyen de caeruloplasmine chez les bebes PPLA est bien inferieur a celui des bebes NPLA (t =3.4582, P <0.02).

Nous n'avons treuve aucune difference majeure entre les concentrations moyennes des 4 autres proteines de phase aigue des bebes PPLA et celles des bebes controles.

Le niveau reduit de caeruloplasmine observe chez les bebes PPLA est an accord avec des comptes-rendus anterieurs de recherche sur la sous-nutrition post-natale.

Par centre, notre observation qu'il n'y a aucune difference majeure entre les concentrations moyennes des 4 proteines de phase aigue chez les bebes PPLA et les bebes NPLA est en desaccord avec des observations anterieures faisant etat de niveaux eleves d'AFP, d'hapto-globine et de AGPA, et de niveaux reduits de transferine chez les nourissons mal-nourris.

Introduction

There are at least 10 different plasma proteins which behave as acute phase reactants in diseases. These include haptoglobin, transferrin, alpha-1-feto-protein (AFP), alpha-1-acid glycoprotein (AAGP) and caeruloplasmin. Others are alpha-1-antitrypsin (AAT), alpha-2-macroglobulin (AMG), C-reactive protein (CRP), fibrinogen and third component of complement (C3). Most of these proteins are elevated in infections, after surgical trauma and in most inflammatory conditions[1].

Striking similarities exist between post-natal malnutrition and foetal growth retardation such as the loss of subcutaneous fat, presence of dry skin and hypoglycaemia [2-4]. In addition, both groups are known to have impaired immune mechanism [5-9] and are therefore highly prone to frequent infections and death [10,11]. Though there are several reports on the levels of acute phase proteins in post-natal undernutrition, not much is reported in foetal growth retardation.

In a previous investigation we determined the concentrations of three of the acute phase proteins - AAT, AMG and GRP in intra uterine growth retardation and compared the findings with previous reports in post-natal undernutrition [12]. In the present study the levels of five other acute phase proteins are assessed in foetal growth retardation and their values compared with previous assessment in post-natal malnutrition.

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Materials and methods

Estimation of the acute phase proteins was performed on cord sera obtained from 14 consecutive "small for dates" (SFD) and 41 "appropriate for dates" (AFD) babies. The latter served as controls. The babies were delivered at the University College Hospital, Ibadan, Catholic Hospital,Oluyoro, Ibadan and the Wesley Guild Hospital, Ilesha. Babies who had congenital malformations, septicaemia or those who were delivered following prolonged labour and/or prolonged rupture of the foetal membranes were excluded from the study. An intra uterine growth chart for Nigeria [13] was used to assess intra uterine growth among babies in this study. A baby was considered to be SFD if the birth weight was lower than two standard deviations (2SD) of the mean birth weight for his or her gestation.

The level of each of five acute phase proteins was measured using commercially prepared immunoplates (Behring Institute, West Germany) by the single radial immunodiffusion method as previously described [12,14,15].

Results

The mean (± ISD) haptoglobin levels in SFD babies was (65.5 ± 39.03mg/dl) (Table 1). This was found to be similar in concentration with that of the AFD babies (48.3 ± 30.97 mg/dl). There was also no significant difference between the mean levels of serum transferrin in the SFD babies when compared with the AFD babies ($t = 0.3138$, $P > 0.2$) as shown in Table 2. The mean alpha-1-fetoprotein (AFP) concentration was slightly but insignificantly higher in the SFD babies (107.8 ± 84.7 mg/dl) than in the AFD babies (90.6 ± 53.5 mg/dl). There is a wide scatter in values in both groups of babies (Table 3) and this may be responsible for our observation of no significant differences as shown in Table 3. The AAGP mean levels in SFD babies was also found to be similar to findings in AFD — Figure 1 ($t = 0.371$, $P > 0.2$). The only acute phase protein which showed any significant difference between the SFD and AFD babies is caeruloplasmin (Figure 2). The mean level in the SFD babies was significantly less than in the AFD babies ($t = 3.4582$, $P > 0.02$).

Discussion

We observed similarities between SFD and AFD babies in the levels of 4 of the acute phase proteins investigated. Depressed levels of caeruloplasmin were demonstrated in the blood of SFD babies. Significantly lowered caeruloplasmin concentration was also reported in cord blood of pre-term infants by Haga [16]. Pre-term infants are vulnerable to copper deficiency because of their small copper store at birth [17]. Our present findings suggests that this is probably true also of SFD babies. The exact physiological role of caeruloplasmin is still not clearly understood. Apart from its role in iron metabolism [18], it seems to be involved in copper transport in plasma [19] and also acts as an acute phase reactant [20]. SFD and pre-term infants have diminished capacity for protein synthesis [21]. Impaired synthesis of caeruloplasmin is a possible explanation of the low levels recorded. Ones *et al* [22] demonstrated diminished levels of caeruloplasmin in the blood of children with protein calorie malnutrition (PCM). The findings in PCM may be related to diminishing synthesis of caeruloplasmin which may also contribute to the low levels.

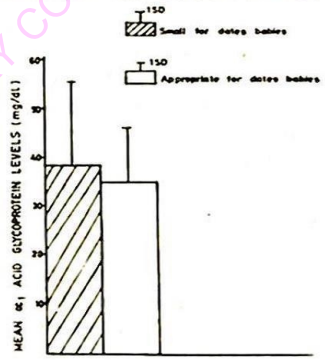

Figure 1: Mean (± ISD) alpha-1-acid glycoprotein levels (mg/dl) in "small for dates" (SFD) and "appropriate for dates" (AFD) babies.

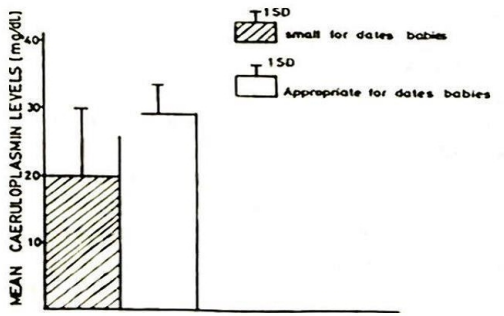

Figure 2: Mean (± ISD) caeruloplasmin levels (mg/dl) in "small for dates" (SFD) and "appropriate for dates" (AFD) babies.

Table 1 Mean (±ISD) haptoglobin levels (mg/dl) in "small for dates" (SFD) and "appropriate for dates" (AFD) babies.

	n	Mean	ISD
"Small for dates (SFD) babies	14	65.5	39.03
"Appropriate for dates" (AFD) babies	31	48.3	30.97

SFD compared with AFD, $t = 1.4550$, $P < 0.2$ (ns)

Table 2 Mean (±ISD) transferrin levels (mg/dl) in "small for dates" (SFD) and "appropriate for dates" (AFD) babies.

	n	Mean	ISD
"Small for dates (SFD) babies	14	235.9	27.8
"Appropriate for dates" (AFD) babies	31	238.8	30.6

SFD compared with AFD, $t = 0.3138$, $P > 0.2$ (ns)

Table 3 Mean alpha-1-fetoprotein concentration (mg/dl) in "small for dates" (SFD) and "appropriate for dates" (AFD) babies.

	n	Mean	ISD
"Small for dates (SFD) babies	14	107.8	84.7
"Appropriate for dates" (AFD) babies	31	90.8	53.5

SFD compared with AFD, $t = 0.6994$, $P > 0.2$ (ns)

We observed no significant differences in the AFP levels between the controls and the SFD babies. AFP is synthesized by the foetal liver and yolk sac [23]. In human pregnancy serum AFP reaches peak levels in foetal blood at about 14th week of gestation and declines rapidly thereafter until about 15 months of life [24] when only trace amounts are detectable in sera of man [25]. Following such observation of decrease in AFP with increasing gestational age, pre-term infants with a weight appropriate for their gestational age should have higher level of AFP than full term small for gestational age babies. Our results of similar levels of AFP in SFD and AFD babies in this study and the observations of Bergstrand *et al* [26] of elevated AFP in premature than in full term infants is in agreement with the findings of Terrenato *et al* [24]. Chandra & Bhujwala [27] however observed elevated AFP in 11 of 17 foetally growth retarded infants. In some pathological conditions there have been reports of association between elevated AFP and impaired immune responses. These conditions include prenatal and postnatal malnutrition [27], pyridoxine deficiency [28], ataxia telangiectasia [29] and in Indian childhood cirrhosis [30]. In addition AFP has been shown to exert suppressive effect on immune responses both *in vivo* and *in vitro* [31,32].

Other acute phase proteins whose levels were observed to be similar in SFD and AFD babies in this study include haptoglobin, AAGP and transferrin. No studies to date has investigated levels of haptoglobin in SFD babies. In post-natal malnutrition the reports are not consistent. While Schelp *et al* [33] reported no significant difference in the haptoglobin levels, Razban *et al* [34] reported elevated levels of haptoglobin in malnourished children. There are also no previous reports on the AAGP levels in SFD babies. Investigations carried out in children with marasmus

and kwashiorkor showed elevated levels of AAGP [33]. Raised levels of this protein are known to be associated with acute infections [35,36]. Our findings will suggest that factors known to raise AAGP such as acute infections are probably not present in these babies at the time of study.

Our observation of normal levels of transferrin in SFD babies is at variance with the findings of markedly reduced concentration of this protein in the blood of malnourished infants by several workers [22,33,34]. Serum transferrin plays an important role in the transportation of serum iron. Under normal conditions most of the iron is bound to transferrin leaving only a very small concentration of free iron. Also, iron requiring bacteria have been shown to grow more readily in sera containing excess of free iron caused by over saturation of available transferrin than in sera which contain all the iron bound to transferrin [37]. Diminished transferrin levels in malnourished children may be one of the major causes of their high morbidity and mortality rates. SFD may be expected to metabolize transferrin as AFD babies.

In summary, the present study shows that it is only in caeruloplasmin that findings in SFD of diminished mean concentration is in line with the previous observations of reduced levels in preterm [16] and malnourished infants [22]. With regards to AFP, haptoglobin and AAGP, there are no significant differences between SFD and AFD babies. This is at variance with the observations of elevated levels in postnatal undernourished infants [27,33,34]. Our demonstration of adequate levels of transferrin in SFD babies does not also agree with the report of markedly reduced levels in malnourished children [22,33,34]. Like in our previous report [12] the present study suggests that though the SFD babies and malnourished infants share some common physical and immunological defects, they do not have similar concentrations of most of the acute phase proteins.

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