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THE SIGNIFICANCE OF ZINC, COPPER AND MAGNESIUM LEVELS OF MATERNAL, CORD AND NEWBORNS' SERA IN HYPERBILIRUBINEMIA OF UNKNOWN ETIOLOGY*

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Hyperbilirubinemia of unknown origin in newborn babies is encountered frequently in our country[1]. Hyperbilirubinemia of obscure origin in the newborn is found frequently also in the Eastern and Middle Eastern countries and among the Eskimos[2,3]. Since hyperbilirubinemia above a certain level may lead to kernicterus, it is the duty of pediatricians to protect babies from its toxic and residual effects. It is of the utmost importance in the field of preventive medicine to carry out research to determine the etiology of hyperbilirubinemia of unknown origin that is so often seen in our country.

In 1972 the findings of Tunçer et al[4] pointed out for the first time the relation between magnesium deficiency and hyperbilirubinemia and have added a new dimension to this problem. In recent years the ability to measure with great sensitivity zinc (Zn), copper (Cu), and magnesium (Mg) levels in many given fluids and tissues with the aid of atomic absorption spectrophotometers[5] has led to the possibility of studying in greater detail the relationship between magnesium deficiency and hyperbilirubinemia. In the present study in addition to the magnesium level, zinc and copper levels were also studied in maternal, cord and infants' sera.

The purpose of this study is to determine the influence of zinc, copper and magnesium levels on hyperbilirubinemia of unknown origin in the newborn infant.

Material and Methods

The study was carried out in two parts, in the Department of Obstetrics of Hacettepe University Hospital and the Newborn Ward of Hacettepe Children's Hospital.

Part I

For the determination of zinc, copper and magnesium levels, 66 maternal and cord sera were obtained at the time of delivery by using special test tubes demineralized

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with nitric acid. Screening of blood group, Coombs' test and glucose-6-phosphate dehydrogenase (G-6-PD) was also carried out in the newborns to exclude blood group incompatibilities and enzyme deficiency. For bilirubin determination in this group capillary blood was drawn from the heels of neonates 48 hours after delivery.

Part II

In 30 babies admitted to the hospital with hyperbilirubinemia of unknown etiology, determination of zinc, copper and magnesium levels was carried out before performing exchange transfusions.

Information concerning the prenatal, natal and postnatal period of the neonates was obtained from the charts in the department and from the families and recorded on the survey records. Blood group incompatibilities, G-6-PD deficiency and the other possible causes known to lead to hyperbilirubinemia were excluded.

A control group of 30 babies who did not have hyperbilirubinemia in the early neonatal period was chosen, with gestational age, sex, age, birthweight, type of delivery and Hb levels comparable to those who had hyperbilirubinemia.

Measurement of zinc, copper and magnesium levels.

Sera obtained from the mothers, cord blood and babies were kept at −20° C until the trace elements were determined by using an atomic absorption spectrophotometer.

Findings

Results were analyzed as follows:

Part I

The data were evaluated according to the 48-hour serum bilirubin levels of the babies. Those whose bilirubin levels were above or below 8 mg/dl were classified as icteric or non-icteric babies, respectively.

a) Maternal sera values:

Zinc levels of maternal sera in icteric babies were found to be significantly lower than those of 40 mothers whose babies were non-icteric ($p < 0.05$, Table I).

Magnesium and copper levels in the maternal sera in icteric babies were not statistically different from non-icteric babies. Zinc, copper and magnesium levels in the maternal sera are summarized in Table I.

b) Cord sera values:

Zinc, copper and magnesium levels in the cord sera are indicated in Table II.

TABLE I

The Mean Levels of Zinc, Copper and Magnesium of Maternal Sera in Icteric and Non-Icteric Infants (μgr/dl)*

	Zn	Cu	Mg
Icteric infants	45.69 ± .82	226.26 ± .75	1067.2 ± 53.7
Non-icteric infants	60.25 ± 3.89	221.30 ± 10.59	1117.6 ± 38.7
	$p < 0.05$	$p > 0.05$	$p > 0.05$

* Mean ± $S\bar{X}$.

TABLE II

The Mean Levels of Zinc, Copper and Magnesium of Cord Sera in Icteric and Non-Icteric Infants (μgr/dl)*

	Zn	Cu	Mg
Icteric infants	53.19 ± 3.44	82.9 ± 4.10	945.0 ± 50.3
Non-icteric infants	62.60 ± 2.92	85.35 ± 6.68	1182.0 ± 47.9
	$p < 0.05$	$p > 0.05$	$p < 0.05$

* Mean ± $S\bar{X}$.

Cord sera mean zinc and magnesium levels of icteric babies were significantly lower than those of non-icteric babies ($p < 0.05$, Table II). Differences in the copper levels of the two groups were not statistically significant.

Part II

Determination of zinc, copper, and magnesium levels in babies with hyperbilirubinemia referred for exchange transfusion: Pre-exchange sera zinc and magnesium levels of 30 newborns with hyperbilirubinemia of obscure origin were found to be significantly lower than those of the 30 control infants who were age-, sex-, and

birthweight-matched ($p < 0.05$). Differences in the mean copper levels were not found to be statistically significant in the two groups. Values of pre-exchange serum samples are indicated in Table III.

TABLE III

The Mean Levels of Zinc, Copper and Magnesium of Pre-Exchange Sera in Newborns (μ/gr/dl)*

	Zn	Cu	Mg
Pre-exchange sera n = 30	53.20 ± 5.45	99.23 ± 5.24	1118.2 ± 66.0
Control n = 30	71.60 ± 1.24	96.13 ± 10.51	1282.6 ± 30.5
	$p < 0.05$	$p > 0.05$	$p < 0.05$

* Mean ± $S\bar{X}$.

Discussion

Hyperbilirubinemia of the newborn has been of great interest to pediatricians for more than 30 years[6-8]. As a result of these efforts the major causes and effective preventive measures to protect babies from hyperbilirubinemia and its consequences have been determined.

In recent years breast milk hyperbilirubinemia[9,10], phenolic detergent usage[11], and oxytocin administration to the mother for inducing labor[12,13] have also been found to be causes of hyperbilirubinemia.

Hyperbilirubinemia of unknown origin is encountered with great frequency in Turkey[2], and 4 to 5 exchange transfusions are still performed every day at the Hacettepe Children's Hospital. Unfortunately, many babies do not arrive at the hospital during the early stages of the disease, and exchange transfusion then cannot prevent their disablement due to brain damage related to kernicterus. These facts indicate that protection of these babies is essential. In countries such as Turkey[1] and in the Far East[2,3] where hyperbilirubinemia of unknown origin is so often encountered, in is necessary to consider some environmental factors which can play a role in hyperbilirubinemia.

In 1972 Tunçer et al[4] had pointed out that magnesium levels were low in the maternal and cord blood of the newborn with increased bilirubin. Chvapil et al[14,15] proved

that zinc prevents the lipid depolarization of the cell membrane and hypozincemia may modulate the erythrocyte membrane. Zinc and magnesium are very important as co-factors in the numerous enzyme systems and play a big role in the synthesis of nucleic acids. Furthermore magnesium is essential in the maintenance of ribosomes, which are responsible for enzyme synthesis [16]. Therefore it can be proposed as a hypothesis that deficiency of zinc would cause structural defects in the erythrocyte membranes, resulting in hemolysis. Moreover, it can be stated that deficiency of magnesium along with that of zinc could cause insufficient synthesis of the enzymes that play a role in the bilirubin metabolism, especially the Y and Z proteins, and as a result could lead to indirect hyperbilirubinemia.

Zinc is found in abundance in protein-rich foods such as fish and meat. Phytates (inositol hexophosphates), which constitute an important part of grain cereals and vegetables, unite to form complexes with zinc and inhibit its absorption [17]. Due to nutritional habits in our country, mainly carbohydrates and vegetables are consumed. A diet low in protein may lead to zinc deficiency, and this is reflected in the newborn baby.

Zinc can pass through the placenta in both directions and it has been found that cord blood zinc levels are somewhat higher than those of maternal levels, which corresponds to our findings [18]. It has been shown that the zinc levels of Turkish pregnant women decrease as pregnancy advances [19]. It has been indicated as well that hypozincemia during pregnancy would be more obvious in women with poor nutrition.

Magnesium is absorbed especially in the small intestines. It is believed that vitamin D is essential for maximum absorption of magnesium [20]. In Türkey and other developing countries it is known that pregnant women who have nutritional deficiencies in their diets fail to obtain sufficient amounts of vitamin D. This results in vitamin D deficiency which may manifest itself as congenital rickets in their infants [21]. Therefore it can be expected than vitamin D deficiency during pregnancy may cause hypomagnesemia in the woman and, eventually, in the newborn.

In the present study both the zinc and magnesium levels in the maternal and cord sera of icteric babies were found to be low. In addition to these findings in pre-exchange sera, zinc and magnesium levels of 30 newborns were significantly low. These findings are good support for the idea that hypozincemia is related in some way to neonatal hyperbilirubinemia of obscure origin. Low levels of zinc and magnesium encountered in mothers and neonates due to insufficient and unbalanced nutrition in Turkey might be among the causes of hyperbilirubinemia of unknown origin in the newborn. The etiology of hyperbilirubinemia of this type turns out to be a community problem.

It is an established fact that numerous factors play a role in bilirubin metabolism. Therefore, at the moment the above-mentioned statements must be taken as a hypothesis, the validity of which can only be proven by more detailed future studies.

Summary

Zinc, copper and magnesium levels were determined in the sera of mothers and the umbilical cords of 66 newborn babies to shed light on the causes of hyperbilirubinemia of unknown etiolgy of the newborn, encountered frequently in Turkey. Grouping the babies according to their bilirubin levels at 48 hours of age, zinc and magnesium were found to be significantly low in those in whom bilirubin levels were over 8 mg/dl.

The zinc and magnesium levels were also low in the sera of another group of 30 neonates in whom hyperbilirubinemia was high enough to necessitate exchange transfusion, when compared with a control group. Since zinc and magnesium are found mostly in proteins, hyperbilirubinemia of unknown etiology is believed to be due to nutritional disorders. The significance of zinc and magnesium deficiency in bilirubin metabolism is discussed.

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