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Original Research Article

Thyroid hormone status in children with protein energy malnutrition a hospital based case control study

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ABSTRACT

Background: WHO estimates that about half of all deaths, occurring among children aged less than five years in the developing countries, can be attributed to malnutrition. In malnourished children various endocrinal changes are noted. There is reduced synthesis of plasma proteins that affects secretion and metabolism of thyroid hormone. The present study has been conducted to study the effect of protein energy malnutrition (PEM) on thyroid hormone and plasma protein levels; and to find correlation between thyroid hormones and plasma protein levels in PEM children.
Methods: A cross sectional hospital based case-control study was carried out in tertiary care hospital of Northern India. 50 children with PEM, and equal number of age and sex matched healthy controls (1-5 years) were included in the study. Detailed clinical assessment of nutritional status followed by anthropometric measurement was recorded in a predesigned performa. The cases were categorized into moderate and severe malnutrition as per WHO classification (weight for height). Free Triiodothyronine (fT3), free Thyroxine (fT4), thyroid stimulating hormone (TSH), serum total protein and serum albumin were estimated. The parameters were compared among cases and controls using appropriate statistical tool.
Results: Mean hemoglobin, serum protein, serum albumin, fT3, fT4 and TSH levels were significantly low in case group, when compared to the control group ($p < 0.001$).The levels of biochemical variables, decreases as the severity of malnutrition increases. The difference within the cases (moderate and severe malnutrition) was also found to be statistically significant ($p < 0.001$).
Conclusions: PEM is associated with decrease level of thyroid hormone levels and were positively correlated with serum total protein and albumin levels. The decrease level of thyroid hormone may have a contributory role in retarded growth and development.

Keywords: Free triiodothyronine, Free thyroxine, Protein energy malnutrition, Thyroid stimulating hormone

INTRODUCTION

Globally protein energy malnutrition continues to be a major health burden in developing countries. The WHO estimates that nearly half of all deaths, occurring among children aged less than five years in the developing countries, can be attributed to malnutrition.[1] As per NFHS-3 report the prevalence of underweight, stunting and wasting in children under five year of age in India was 43%, 48% and 20% respectively.[2] In PEM various endocrinal changes may be noted like decrease in growth hormone, normal or increase in adrenocortical activity and decrease in thyroid hormone. These changes are associated with reduced synthesis of plasma proteins which affects secretion and metabolism of these hormones. The manifestations of PEM include retarded growth rate and limited weight gain with delayed skeletal maturation which may be mediated by alterations in

thyroid hormone status in these children. Most of the studies done earlier have compared total triiodothyronine (TT3), total thyroxine (TT4) and thyroid stimulating hormone (TSH) levels in PEM and healthy children.

There is limited data and studies available regarding the free triiodothyronine (FT3) and free thyroxine (FT4) levels in children with PEM (WHO classification) compared to healthy children. The present study has been conducted to study the effect of PEM onthyroid hormone status and to see the correlation between thyroid hormones and serum total proteins and albumin.

METHODS

A cross sectional hospital based case-control study was carried out in the department of paediatrics and biochemistry at 800 bedded tertiary care hospital MMIMSR Haryana during the period November 2014 to September 2016. Approval was taken from the college ethical committee prior to the start of the study. Fifty children with PEM as per WHO classification and equal number of age and sex matched healthy controls in the age group 1-5 years were included in the study. The children were enrolled in the study after taking the informed written consent from their parents. Detailed clinical assessment of nutritional status followed by anthropometric measurement (weight, height/length, mid arm circumference and head circumference) was recorded in a predesigned proforma. The cases were categorized into moderate malnutrition (z-score between -2SD and -3SD) and severe malnutrition (z-score below -3 SD) as per WHO classification (weight for height).

Inclusion criteria

- Children aged 1-5 years having PEM as per WHO Classification of PEM (weight for height).

Exclusion criteria

- Children suffering from endocrine and metabolic disorders.
- Children suffering from chronic infection like Tuberculosis, Urinary tract infection.
- Children suffering from malabsorption syndrome (celiac disease), protein losing enteropathy, nephrotic syndrome.
- Children with major congenital anomalies.
- Children with chronic liver and kidney diseases.
- Children on chronic medication.

Under aseptic condition 3 ml blood was collected in two test tubes one containing EDTA and the other a plain test tube. The EDTA containing blood was used for hemoglobin estimation.

The blood collected in a plain test tube without anticoagulant was centrifuged and the serum obtained was used to estimate fT3, fT4, TSH, total proteins and albumin. The Calbiotech, Inc. (CBI) fT3, fT4 and TSH Streptavidin ELISA kit is to be used for the quantitative measurement of fT3, fT4 and TSH in human serum respectively. Serum total proteins level was estimated by Biuret method. Serum albumin estimated by Bromocrisol green dye method (BCG). The complete hemogram was done by auto analyser. Data were analyzed in terms of frequencies, contingency coefficient, coefficient test (cross tab), student T test, Chi - Square test, one way ANOVA test and Pearsons correlation test. All the statistical methods were performed through SPSS for windows version 16, p value of < 0.05 was considered statistically significant. Microsoft word and Excel (2007) were used to generate figures and tables.

RESULTS

A total of 100 children in the age group between 1 and 5 years were included in the study. 50 children were malnourished (cases) and 50 children were healthy (controls). The distribution of cases as per WHO classification is shown below (Figure 1). In our study most of the cases were of severe malnutrition. Among the cases 32 (64%) children and in the control group 28 (56%) children were males.

The mean age of cases was 31.1 months and the mean age of controls was 33.1 months. The mean weight of cases was 7.98 kg and of control was 13.96 kg, mean length/height of cases were 80.5 cm and those of control were 93.6 cm, mean MAC of cases were 11.6 cm and control were 13.9 cm. (Table 1). The mean of anthropometric parameters i.e. weight, height or length, mid arm circumference and head circumference of the cases were significantly less than those from controls.

Pallor was present in 76 % of cases and in only 28 % of controls. The mean haemoglobin in cases was 8.8 ± 2.2 gm/dl and control was 10.7 ± 1.6 gm/d. The difference in haemoglobin level between the cases and controls were statistically significant ($p<0.001$).

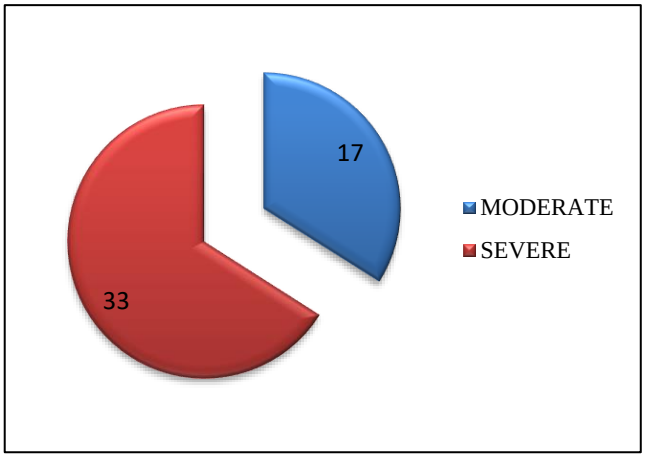

Figure 1: Distribution of cases (n = 50) according to who classification of PEM (weight for height).

The mean value of fT3, fT4 and the TSH in the malnourished group was 2.1 pg/ml, 1.2 ng/dl and 1.3 mIU/ml while of the control group was 4.9 pg/ml, 1.9 ng/dl and 4.5 mIU/ml respectively. The mean value fT3, fT4 and the TSH of the cases were significantly lower than the control group and was statistically significant ($p<0.001$). The mean serum total protein and albumin in the cases was 5.9 gm/dl and 3.4 gm/dl while in controls the total protein and albumin was 6.9 gm/dl and 4.6 gm/dl respectively. The difference in the two groups (cases and controls) was statistically significant.(Table 2).

Table 1: Age and anthropometric parameters in cases and controls.

Parameters	Cases (n = 50)	Control (n = 50)	t-value	P-value
	Mean±SD			
Age (months)	31.1±16.9	33.1±18.1	0.571	0.569
Weight (kg)	7.98±2.22	13.96±3.81	9.691	0.001***
Height/length(cm)	80.5±11.2	93.6±13.1	5.264	0.001***
MAUC (cm)	11.6± 0.9	13.9±0.9	3.909	0.001***
HC (cm)	46.1±2.2	47.8±2.1	12.568	0.001***

T-test;***highly significant MAUC-mid arm circumference, HC- head circumference

Table 2: Laboratory parameters of cases and controls.

PARAMETERS	Cases (n = 50)	Control(n = 50)	t-test	P value
	Mean±SD			
Hb(g/dl)	8.8±2.2	10.7±1.6	14.68	<0.001
fT_3 (pg/ml)	2.1±0.9	4.9±1.1	14.68	0.001***
fT_4 (ng/dl)	1.2± 0.3	1.9±0.3	10.76	0.001***
TSH (mIU/ml)	1.3±0.5	4.5±0.8	23.11	0.001***
Total protein(gm/d)	5.9±0.9	6.9 0.5	6.42	<0.001***
Serum albumin(gm/dl)	3.4±0.6	4.6±0.4	11.7	<0.001***

***Highly significant; t-test , Hb- haemoglobin, fT3- free Triiodothyronine, fT4- free Thyroxine, TSH- Thyroid stimulating hormone.

Table 3: Laboratory parameter of moderate and severe malnutrition children.

Parameters	Moderate malnutrition	Severe malnutrition		
	Mean±SD		t- value	P value
Hb (g/dl)	10.4±1.5	7.9±2.1	4.33	<0.002***
fT_3 (pg/ml)	2.6±1.1	1.8±0.5	3.51	0.001***
fT_4 (ng/dl)	1.4±0.4	1.1±0.2	3.75	0.001***
TSH (mIU/ml)	1.6±0.6	1.1±0.3	4.04	0.001***
Total protein(gm/d)	6.6±1.03	5.5±0.5	5.04	<0.001***
Serum albumin(gm/dl)	3.8±0.6	3.2±0.5	3.3	<0.002***

*** Highly significant; t-test, Hb- haemoglobin, fT3 - free Triiodothyronine, fT4 - free Thyroxine, TSH- Thyroid stimulating hormone.

Table 4: Correlation between thyroid hormone (fT3, fT4 and TSH) and serum total protein and albumin in cases.

Parameters	Total protein (gm/dl)		S.Albumin (gm/dl)	
	r	p-value	r	p-value
fT_3(pg/ml)	0.795	0.001***	0.576	0.001***
fT_4 (ng/dl)	0.794	0.001***	0.558	0.001***
TSH (mIU/ml)	0.759	0.001***	0.586	0.001***

r- Pearson's correlation coefficient; *** highly significant, fT 3- free Triiodothyronine, fT4 - free Thyroxine, TSH- Thyroid stimulating hormone.

The mean values of fT3, fT4 and TSH of the children with moderate malnutrition was 2.6 pg/ml, 1.4 ng/dl and 1.6 mIU/ml respectively while in the children with severe malnutrition was 1.8 pg/ml, 1.1 ng/dl and 1.1 mIU/ml respectively. The mean value was lower in cases of severe malnutrition in comparision to moderate malnutrition and was statistically significant ($p<0.001$) The mean haemoglobin, total protein, serum protein, fT3,

fT4 and TSH showed significant decrease with increase in severity of malnutrition (p value < 0.05) (Table 3)

On applying Pearson´s correlation coefficient to identify correlation between thyroid hormones with total serum protein and serum albumin, it was observed that mean i.e. fT3, fT4 and TSH had a statistically significant positive correlation with serum total protein and albumin (Table 4).

DISCUSSION

Globally Protein energy malnutrition continues to be a major health burden in developing countries. PEM is a multisystem disease and involves almost all organs of the body. PEM is associated with a decrease in the synthesis of serum proteins which has an indirect or direct effect on hormones levels in our body. The study was conducted to know the thyroid status of children with moderate and severe malnutrition and the correlation of thyroid hormone with serum total protein and albumin.

A total of 100 children in the age group between 1 and 5 years were included in the study. 50 children were malnourished (cases) and 50 children were healthy (controls). The ratio of male to female in the study was 3:2. Both the cases and the control were age and sex matched. In our study most of the children (both cases and controls) belong to class 3 and class 4 of the socio economic status as per modified Kuppuswamy scale.

The mean hemoglobin level of the cases was significantly lower than those of controls similar to that seen in study done by Adegbusi HS et al and Sandeep et al.[3,4] The low values of hemoglobin in PEM children was probably due to concomitant deficiency of iron, vitamins and micronutrients.

In our study it was observed that the mean value of serum fT3 was significantly lower (p value <0.001) in cases when compared to control group (Table 1). Among the cases mean fT3 value in children with severe malnutrition was significantly less (p <0.001) than children with moderate malnutrition (Table 2). The result of our study were similar to that seen in other studies. In the study done by Shaheen B et al. the mean fT3 value in cases was 1.5 pg/ml±0.3 and in controls was 2.3 pg/ml±0.5 (one - way ANOVA; p <0.0001) while in study conducted by Shahjadi S et al. mean fT3 value in cases divided into two groups marasmus group and kwashiorkor group were 3.16±0.30 pmol/L and 3.10±0.26 pmol/L respectively and control group was 6.46±0.76 pmol/L (unpaired Student 't' test; p<0.001).[5,6] There was a significant decrease in the mean fT3 values in PEM patients in the study done by Shahjadi S et al. when compared to control group but there was no statistically significant difference within subgroups of cases.[6]

In present study it was observed that mean value of serum fT4 was significantly lower (p <0.001) in cases when compared to control group (Table 1). Among the cases mean fT4 value in children with severe malnutrition was less than children with moderate malnutrition (Table 2). The difference between the two groups of cases was found to be statistically significant (p<0.001). In the study conducted by Shaheen B et al, the mean fT4 value in cases was 1.42ng/ml ± 0.31 and in controls was 1.66ng/dl ± 0.39 (one –way ANOVA; p<0.0001).[5]

The low level of fT3 in PEM children is due to low binding proteins, impaired thyroxine monodeiodinisation in liver which lead to decrease peripheral conversion of T4 to T3 and elevated corticosteroids level which is mostly seen in children with malnutrition and the steroids tends to inhibit 5´deiodinase system and the low level of fT4 in children can be due to fall in thyroid secretion rate, depletion of reserves and the failure of adaptive mechanism.[6,7] After thyroid hormones binding proteins decreases, free thyroxine levels also fall and that explains altered fT3 and fT4 in cases with PEM.[8]

In our study the mean TSH levels in cases and controls were within normal limits, though it was low normal in cases and high normal in controls. The levels decreases as the severity of malnutrition increases and the difference between the TSH levels among cases with moderate and severe malnutrition was statistically significant (p <0.001). The result were similar to that seen by Shaheen B et al. in their study where the mean TSH value in cases was 1.30±0.41 mIU/L and in controls was 1.69±0.062 mIU/L (one–way ANOVA; p <0.05).[6] In contrary to our study, the study conducted by Kumar S et al found that mean TSH levels showed a positive increase with increase in severity of PEM with maximum increase been observed in grade III PEM (One-way ANOVA; p=0.015).[9] In study conducted by Shahjadi S. et al the mean serum TSH were 2.97±0.21µIU/L, 4.98±0.32µIU/l, 5.02±0.29µIU/l.[6] in group A (control group), B1 (marasmus group), B2 (kwashiorkor group) respectively; the mean ± SD of serum TSH levels in group B1 and B2 were significantly higher (p <0.001) than that of control. Abrol et al. and Turkay S et al. in their study found no significant difference in TSH when PEM children were compared to healthy controls.[10,11]

The normal TSH levels in children with PEM is possibly due to T4 undergoing intracellular monodeiodination to form T3 at pituitary level causing negative feedback inhibition of secretion of TSH , central unresponsiveness to low T3 levels due to low intracellular receptor capacity.[4] In short term and mild forms of PEM, observed changes are limited to the thyroid hormonal transport system and appropriate feedback response allow the mantainence of euthyroid state. But in chronic and more severe forms of PEM, the reserves are depleted causing a fall in thyroidal secretion rate and the thyroid adaptation may fail.[9]

In present study the mean total protein and albumin level were lower in cases when compared with controls and the

decrease was statistically significant (p <0.001). The decrease was seen more in children with severe malnutrition. The result were similar to that seen in the study conducted by Adegbusi et al, Sandeep et al Shaheen B et al, (Table 5).[3-5] The alterations in serum total protein and serum albumin in PEM could be explained on the basis of decreased protein intake and reduced biosynthesis.

In our study the fT3, fT4 and TSH had significant positive correlation with serum total protein and albumin in cases which was similar to the study done by Shaheen B et al.[6]

Table 5: Comparision of serum total protein and albumin in various studies.

Parameters		Present study	Shaheen B et al[5] study	Adegbusi HS et al[3] study	Sandeep M et al[4].study
Total protein (gm/dl) (mean±SD	Case	5.9±0.9***	6.6±0.42***	5.2±0.9*	6.3±0.8***
	Control	6.9±0.6	7.4±0.31	6.3±0.7	7.2±0.6
Serum albumin(gm/dl) (mean±SD)	Case	3.4±0.60***	3.3±0.4***	3.4±0.7*	3.3±0.6***
	Control	4.6±0.41	4.1±0.4	4.6±0.8	4.2±0.4

* p< 0.05, *** p< 0.001

There are various limitations in the study that, the changes in thyroid profile would have been manifested better if sample size was more. Thyroxine - binding globulin (TBG), thyroxine binding prealbumin (TBPA) levels were not estimated in the present study which could have been more informative.

CONCLUSION

Serum thyroid hormone levels (fT3, fT4, TSH) decreased as the severity of malnutrition increases. The altered thyroid hormone status in malnourished children with limited calorie reserve help the child to tide over the unfavourable situation and early death. The present study also highlight that children of malnutrition are in a stage of subclinical hypothyroidism which may contribute to retarded growth and development.

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