ORIGINAL ARTICLE

Thyroxine Levels in the Nephrotic Syndrome

by

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Abstract

Thirteen children, seven boys and six girls aged between 3 to 12 years with the diagnosis of Nephrotic Syndrome were assessed for clinical and laboratory signs with special attention on T_4 levels.

In the first examination, done during the full blown illness, T_4 levels ranged between 1 ug % to 10 ug % (mean : 5.4 ± 3.14 ug %).

In remission the levels were significantly elevated, ranges between 3.6 ug % to 18.6 ug % (mean : 11.6 ± 5.34 ug %).

Meanwhile, the observation of serum albumine and globuline concentrations showed a significantly rise ($p<0.005$).

Comparison with the results of other investigators have also been discussed.

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Introduction

It has many years been accepted that one of the best ways of studying the functional state of the Thyroid is the measurement of the concentration in the circulation of the Thyroid hormon. Both Thyroxine (T_4) and triiodothyronins (T_3) are almost entirely protein bound in the circulation (Robins et al., 1957; Williams, 1980).

The usual first assay in a routine study is the total circulating T_4 levels (Williams, 1980).

This figure is often combined with the result of an indirect assessment of the binding capacity of thyroxine binding globuline to provide a so called Free T_4 index. Although the details of action of the Thyroid hormones on the cells of the body are incompletely understood, their metabolic activity appears to be more closely related to the amount of hormone which is free than to the total concentration in the circulation (Williams, 1980).

Thus it is increasingly common to assay directly the circulating free T_4 and less commonly T_3 (Burger et al., 1976; Geola et al., 1980).

T_4 and T_3 loss in the urine is associated with proteinuria (Murray et al., 1971). It had been proven that T_3 and T_4 in many instances were found to be reduced, although the pathophysiology is yet not known. Reduced serum levels of T_3 was reported in many clinical situations : myocardial infarction, severe chronic diseases, starvation, malnutrition, after surgery (Burger et al., 1976; Geola et al., 1980), and renal failure (Kalk et al., 1980). Burger et al. (1976) reported the reduce of T_3 and T_4 in acute illness.

The problem or question arises is : How does the level of T_4 alter in the Nephrotic Syndrome where massive proteinuria exists. This investigation is aimed to describe the T_4 levels in Nephrotic Syndrome and its correlation with the remission of the disease.

Materials and methods

All patients admitted to dr. Soetomo Hospital, with the diagnosis of Nephrotic Syndrome, during the periods of April — December 1980, were subjected into this investigation.

Criteria for the diagnosis of Nephrotic Syndrome :

1. The presence of oedema anasarca.
2. The presence of massive albuminuria in the urine.
3. Protein losses more than 0,05 mg/kg BW/24 hours.
4. Hypercholesterolemia : cholesterol level more than 240 mg%.
5. Hypoalbuminemia : Serum albumine level less than 2,5 g/dl.

The presence of granular cast and oval fat in the examination of sediment urine support the diagnosis.

Other examinations, which is necessary for the management of Nephrotic Syndrome, such as blood urea nitrogen, serum creatinine, serum electrolyte, urine culture, kidney biopsy (when indicated), ASTO titer, L.E. cells, C-Reactive protein and radiologic study were also done.

Criteria of remission : No oedema, and urine free of protein by qualitative testing for 5 consecutive days.

T_4 levels were examined : 1. on admittance. 2. on the day when remission was achieved.

The normal of T_4 is determined using the criteria the Dept. of Clinical Pathology, dr. Soetomo Hospital : 4,55 - 11,87 microgram %.

Result

20 children aged between 3 - 13 years with the diagnosis of Nephrotic Syndrome were admitted to dr. Soetomo Hospital during the periods of April — December 1980. Thirteen patients fulfilled the criteria of this investigation.

Seven patients mere excluded due to several reasons, i.e :

— two patients were discharged on request before remission.
— remission was not achieved in one patient.
— incomplete examination of T_4 in four patients.

We were unable to obtain the quantitative proteinuria in 4 patients due to the difficulty in collecting 24 hours urine. However, qualitative protein examination of the urine showed a massive proteinuria.

T_4 levels in the first examination ranged between 1 ug% to 10 ug% with the mean of 5.4 ug% ($\pm$ 3.14). Unfortunately a control study could not be carried out due to difficulty to obtain blood sample from healthy children. In remission the levels were significantly elevated, with the range between 3.6 to 18.6 ug% (mean: 11:6 $\pm$ 5.4 ug%). ($p < 0.005$). (Fig.1).

Low serum albumine concentrations were found in the first examination, ranged between 0.7 g% to 2.4 g% with the mean of 1.36 g% ($\pm$ 0.44).

Serum globuline concentrations were found in range between 1,6 g% to 3,0 g% (mean : 2.3 $\pm$ 0.4 g%).

In remission serum albumine and globuline concentrations were significantly elevated, ranged between 1.4 g% to 3.8 g% (mean : 2.1 $\pm$ 0.69 g%) and 2.0 g% to 3.8 g% (mean: 2.7 $\pm$ 0.59 g%) respectively ($p<0.005$) (Table 1).

Discussion

Despite lack of control study in this investigation, it appeared that T_4 levels in our patients decreased during full blown illness.

In five out of 13 patients, the serum T_4 levels were below the normal levels. The mean value although remain in the normal zone, was only a little bit higher than the lower normal level. The remaining 8 patients showed normal levels of serum T_4 concentrations during this period.

Striking elevation of serum T_4 levels were observed during the period of remission, however, only 1 patient had T_4 level lower than the normal zone.

The other 8 patients had T_4 levels in the normal zone, and the remaining 4 patients had T_4 levels higher than the normal levels. A statistical analysis showed that T_4 was significantly elevated during the remission period when compared with the T_4 levels during the full blown illness ($p<0.005$).

Thyroxine (T_4) is almost entirely protein bound in the circulation (Di George, 1975; Robins et al., 1957). The most important substance is Thyroxine-Binding Globuline (TBG); of lesser significance are Thyroxine-Binding Pre Albumine (TEPA) and Albumine (Di George, 1975).

Since the concentration or binding capacity of TBG and concentration of albumine are altered, it is concluded that the alteration of T_4 levels is due to this condition.

Some authors suggested that the low level of T_4 in Nephrotic syndrome was due to metabolic disturbances allied to hypothyroidism (Kalant et al., 1959; Rasmussens and Rapp, 1956).

This suggestion was supported by the evidence of hypercholesterolemia and lowered basal metabolic rates in some patients.

This hypothesis was also supported by the finding of diminishing serum protein bound iodine concentration in Nephrotic patients (Kalant et al., 1959).

However it was also suggested that the low basal metabolic rates and high concentration of serum cholesterol in this disease were due to some other cause than hypothyroidism (Rasmussens and Rapp, 1956).

Although recent studies have indicated that thyroidal uptake of iodine is in fact normal or increased in this condition. There are still conflicting reports about the state of thyroxine metabolism, since some of the latter discrepancies may have been due to variability among the subjects with regard to the degree of proteinuria, oedema and iodine intake and the problem of thyroid-nephrosis interrelationships (Rasmussens and Rapp, 1956; Recant, 1956).

Recant (1956) investigated 15 Nephrotic patients has found that a distinctly abnormal binding pattern was noted. In 70 to 100% the thyroxine was bound in the alpha-2 globuline area. The abnormal binding in the Nephrotic does not appear to be due to hypoalbuminemia since normal pattern are observed in the hypoalbuminemias of liver disease and sprue.

On the other hand, Robbins et al. (1957) concluded that in Nephrotic state, the serum protein which interact with thyroxine are normal from a physical stand point.

Kalant et al. (1959) in their experiment concluded that in Nephrotic Syndrome thyroid function and thyroid hormon metabolism differed from normal subject in three ways :

1. Thyroxine was lost in the urine in conjunction with protein.
2. The respons to pharmacological doses of thyroxine as determined by increase in oxygen consumption rates was decreased by about 30%.
3. The rates of iodine uptake and thyroxine secretion by the thyroid were increased.

Subnormal concentration of serum PBI found by Recant (1956), together with normal to high uptakes of I^{131} by the thyroid gland, low basal metabolic rates and high serum cholesterol in their Nephrotic subjects a decrease in the thyroidal uptake of I^{131} following thyroid therapy and the ability of the thyroid gland to respond to thyrotropic hormone, led to the conclusion that in Nephrotic Syndrome the thyroid gland functions normally, that a deficiency of the plasma is reduced but that a normal supply of thyroid hormon is delivered to the peripheral tissue and presumably a normal amount degraded each day. Whereas Rasmussens and Rapp (1956) found a lower than normal amount of thyroxine degraded each day.

Some other authors found that the low levels of T_4 in Nephrotic syndrome is a results of subsequent progression of urinary loss of PBI. Rance et al. (1976) stated that the occurrence of increase glomerular permeability led to excessive loss of PBI. The result of this condition is low concentration of PBI and subsequently concentration of T_4.

Rasmussens and Rapp (1956) in their investigation arrived to the conclusion that the low PBI in the serum of some patients with Nephrotic Syndrome is a result of at least four factors :

1. a significant loss of iodine in urine.
2. a proportionately greater loss of iodine in the feces.
3. dilution of the organic iodine present because of an expanded extracellular fluid volume.
4. inability of the pituitary-thyroid axis to augment the output of thyroxine in the face of apparent thyroxine deficiency.

On the basis of the results of the present investigation, combined with the reviews of other investigations reported by several authors, it is concluded that an excessive protein loss and concomittantly loss of T_4 itself may be one of several factors that play an important role in the cause of the decrease of serum T_4 levels in Nephrotic Syndrome.

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TABLE 1 : *Data of patients*

Pat. No.	Sex	Age (years)	B.W. (Kg)	Main Symptom	Albumine g%		Globuline g%		Cholesterol mg%		Esbach g/24 h		Oval Fat body		Gran. Cast		T4 ug%	
					I	II	I	II	I	II	I	II	I	II	I	II	I	II
1.	♂	6	10	Oedema Anasarca + Ascites + Pleural Effusion	1,0	2,1	2,4	3,6	480	400	6	—	+	—	+	—	2,4	8,3
2.	♂	5	12	Oedema Anasarca + Ascites	1,2	2,3	3,0	3,8	500	380	12	—	—	—	+	—	2,6	11,0
3.	♂	6	17,5	Oedema Anasarca + Ascites	1,3	1,6	3,0	3,0	310	250	2	—	+	+	+	—	6,5	8,5
4.	♂	3	12	Oedema Anasarca + Ascites	2,4	3,8	2,2	3,3	400	252	1	—	+	—	—	—	1,0	25,0
5.	♂	3	13,5	Oedema Anasarca	2,0	2,1	3,0	3,0	410	240	—	—	—	—	+	—	1,1	7 8
6.	♂	8	17	Oedema Anasarca	1,8	3,3	1,8	3,0	437	380	1	—	—	—	+	—	5,7	8,7
7.	♂	8	21	Oedema Anasarca	1,3	2,1	1,7	2,4	252	460	2	—	+	—	+	—	6,4	8,8
8.	♀	8	21	Oedema Anasarca	0,7	1,7	2,0	2,0	585	342	1	—	+	—	+	—	1,8	14,4
9.	♀	8	20	Oedema Anasarca	1,2	2,4	1,6	1,9	490	390	—	—	+	—	+	—	10,3	14,2
10.	♀	12	21	Oedema Anasarca	1,0	1,6	1,8	2,0	350	200	2	—	—	—	+	—	8,5	8,5
11.	♀	5	14	Oedema Anasarca	1,6	1,6	2,5	2,7	340	222	—	—	—	—	—	—	9,6	18,6
12.	♀	9	19	Oedema Anasarca	1,0	1,4	2,3	2,4	300	200	0,5	—	+	—	+	—	6,5	9,5
13.	♀	9	20	Oedema Anasarca	1,3	1,4	2,3	2,4	400	400	—	—	+	—	+	—	7,9	3,6
				Mean :	1,36	2,1	2,3	2,7	404	316							5,4	11,6
				S.D. :	0.44	0.69	0.47	0.59	90	87							3,14	5,34
				P. :	0,0007		0,0007		0,0007								0,0036	

FIGURE 1 : *Comparison of T4 levels before (I) and after (II) remission.*