Thyroidal iodide clearance and radioiodide uptake in protein-calorie malnutrition

Y. Ingenbleek and C. Beckers

ABSTRACT The thyroid function was evaluated in two comparable groups of 12 protein-calorie malnourished children respectively by oral and intravenous test using radioiodine $^{131}$I. Maximal radioiodide uptake (RAIU$_{max}$) peaked within 24 hr in the intravenously investigated children, but only after 48 hr in the orally investigated children. In both protein-calorie malnutrition groups, the mean RAIU$_{max}$ was significantly decreased by comparison with the mean normal RAIU$_{max}$ ($P < 0.01$). In protein-calorie malnutrition children, the RAIU curve reached intermediate values ranging from subnormal to about nearly half the normal. Thyroidal clearance was early depressed and in some cases, dropped to values as low as one tenth of the normal mean ($P < 0.001$), reflecting a severe thyroid involution. There is a high correlation between the RAIU$_{max}$ and thyroid clearance values ($r = 0.95$); the regression line is defined by the equation $Y = 1.12X + 17.08$. Both functional parameters of thyroid activity appear to be mainly lowered in relation to the duration of protein deficiency. Am. J. Clin. Nutr. 31: 408-415, 1978.

Marfan (1) was the first to recognize the consequential effects of infant malnutrition on thyroid function. Different studies from several countries have given some general approach to the characteristics of thyroid activity in human malnutrition (2-6). Collected data remain however conflicting and do not allow the definition of an universally acceptable pattern for thyroid behavior in protein-calorie malnutrition (PCM). The present survey attempts to clarify a peculiar aspect of this endocrine organ function in malnourished children; i.e., the thyroid trapping capacity for iodide, as expressed by the radioiodide uptake (RAIU) curves and the radioiodide clearance (A).

Materials and methods

Twenty-four PCM Senegalese children from 18 to 27 months of age were selected for this investigation. They all presented clinical signs of typical and uncomplicated kwashiorkor with growth failure, height retardation, edema, skin lesions, and diarrhea in varying degrees. Their nutritional status was appraised by the measurement of thyroxine-binding prealbumin (TBPA) plasma level, as elsewhere described (7) and by the estimation of weight and height deficits plotted against the Boston standards (8), as suggested by Waterlow (9). These 24 PCM patients were divided amongst two comparable groups. The former one (subjects 1 to 12) was investigated by gastri radioiodine $^{131}$I administration whereas the latter one (subjects 13 to 24) was investigated by intravenous administration. Doses of Na$^{131}$I averaged 0.25 μCi/kg body weight.

Six healthy Senegalese children with normal weight, height, TBPA, and the same cross-sectional age and two Senegalese children (ages 2 and 4 years) with Graves' disease were studied for comparison. These reference subjects all received an oral tracer dose of $^{131}$I as previously indicated (10). Complete intestinal absorption of $^{131}$I occurs in normal children (10), a finding implying that the comparative study by intravenous $^{131}$I is not dispensable in further studies.

RAIU was measured according to International Atomic Energy Agency recommendations (11). Resulting RAIU was the mean of the 3 count running operations, each of them registered in succession during a preset time of 100 sec at the 1st, 2nd, 3rd, 9th, 24th, 48th, and 72nd hr after $^{131}$I administration. Corrections were made for background, extrathyroidal activity and physical decay. Final RAIU was expressed in percentage of the given dose (%DT).

A was measured by the method of Myant et al. (12) hereafter modified (13) as shown by the following formula:

$$A(\text{ml/min}) = \frac{\text{RAIU at 3rd hr (%DT) - RAIU at 1st hr (%DT)}}{\text{Plasma } ^{131}\text{I at 2nd hr (%DT/ml)} \times 120}$$

1 These studies have been partly supported by a research grant from the Fonds de la Recherche Scientifique Médicale, Brussels, Belgium.

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3 From the Centre de Médecine Nucléaire et Laboratoire de Pathologie Générale, University of Louvain, 1200 Brussels, Belgium.
The plasma stable inorganic iodide (PII) was calculated according to the isotopic method of Stanley (14) which evaluates the ratio between urinary and plasma specific activities:

\[
\text{PII} = \frac{\text{urinary } ^{131}\text{I}}{\text{plasma } ^{131}\text{I}}
\]

Measurement of urinary stable iodide (\(^{131}\)I) was achieved by the method of Benotti et al. (15).

In all PCM children, measurement of A and PII values was performed the morning after admission and prior to any dietetic or therapeutic management. Results are presented as mean ± SD and their statistical significance was assessed by the t test (16).

**Results**

In the six normal orally investigated children, TBPA plasma level was 22.43 ± 1.71 mg/100 ml (range 19.8 to 24.8 mg/100 ml), the mean maximal RAIU was 39.6 ± 3.08% DT (range 35.4 to 44.7% DT), the mean 2 hr plasma radioactivity was 259 ± 26.10-5 % DT/ml (range 232 to 291.10-5 % DT/ml) and the mean A was 21.5 ± 2.14 ml/min (range 19.4 to 25.0 ml/min) (Table 1).

**TABLE 1**

<table>
<thead>
<tr>
<th>Radioiodine studies</th>
<th>Normal children (n = 6)</th>
<th>PCM children (n = 12)</th>
<th>PCM children (n = 12)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Oral dose of radioiodine</td>
<td>Oral dose of radioiodine (1-12)</td>
<td>Intravenous dose of radioiodine (1-12)</td>
</tr>
<tr>
<td>TBPA (mg/100 ml)</td>
<td>22.43 ± 1.71</td>
<td>7.12 ± 1.20</td>
<td>7.15 ± 0.97</td>
</tr>
<tr>
<td>Albumin (g/100 ml)</td>
<td>3.35 ± 0.39</td>
<td>1.67 ± 0.41</td>
<td>1.73 ± 0.39</td>
</tr>
<tr>
<td>TBG (g/100 ml)</td>
<td>36.47 ± 3.84</td>
<td>21.03 ± 3.95</td>
<td>19.62 ± 3.81</td>
</tr>
<tr>
<td>Total T(_3) (mg/100 ml)</td>
<td>8.47 ± 1.17</td>
<td>3.74 ± 0.86</td>
<td>3.51 ± 0.66</td>
</tr>
<tr>
<td>FT(_4) (ng/100 ml)</td>
<td>2.09 ± 0.17</td>
<td>1.97 ± 0.39</td>
<td>1.86 ± 0.30</td>
</tr>
<tr>
<td>Total T(_4) (ng/100 ml)</td>
<td>233 ± 47</td>
<td>48 ± 41</td>
<td>53 ± 39</td>
</tr>
<tr>
<td>TSH (units/ml)</td>
<td>8.9 ± 3.1</td>
<td>9.7 ± 4.2</td>
<td>9.5 ± 4.8</td>
</tr>
<tr>
<td>RAIU 1 hr</td>
<td>21.08 ± 1.44</td>
<td>15.18 ± 3.71</td>
<td>16.23 ± 2.73</td>
</tr>
<tr>
<td>2 hr</td>
<td>24.81 ± 1.44</td>
<td>16.25 ± 3.82</td>
<td>18.58 ± 3.01</td>
</tr>
<tr>
<td>3 hr</td>
<td>27.77 ± 1.36</td>
<td>17.53 ± 3.91</td>
<td>20.83 ± 3.52</td>
</tr>
<tr>
<td>9 hr</td>
<td>33.35 ± 1.91</td>
<td>20.78 ± 5.28</td>
<td>24.46 ± 5.10</td>
</tr>
<tr>
<td>24 hr</td>
<td>39.60 ± 3.08</td>
<td>23.90 ± 6.24</td>
<td>27.29 ± 6.10</td>
</tr>
<tr>
<td>48 hr</td>
<td>36.68 ± 3.05</td>
<td>26.10 ± 7.57</td>
<td>25.37 ± 5.75</td>
</tr>
<tr>
<td>72 hr</td>
<td>34.55 ± 3.08</td>
<td>23.91 ± 6.79</td>
<td>23.39 ± 5.60</td>
</tr>
<tr>
<td>(I(^{-}))^2 hr in plasma</td>
<td>259 ± 26</td>
<td>587 ± 361</td>
<td>613 ± 438</td>
</tr>
<tr>
<td>10-5% DT/ml</td>
<td>0.131 ± 0.024</td>
<td>0.391 ± 0.143</td>
<td>0.352 ± 0.132</td>
</tr>
<tr>
<td>PII (µg/100 ml)</td>
<td>21.46 ± 2.14</td>
<td>7.31 ± 4.08</td>
<td>9.04 ± 5.18</td>
</tr>
</tbody>
</table>

* TBPA (thyrobinding prealbumin); TBG (thyrobinding globulin maximal T\(_4\) binding capacity); T\(_3\) (total thyroxine); FT\(_4\) (free thyroxine); T\(_3\) (total 3,5,3'-triiodothyronine); TSH (thyroid-stimulating hormone); RAIU (\(^{131}\)I radioiodide uptake); (I\(^{-}\))^2 (\(^{131}\)I plasma radioactivity); PII (plasma inorganic iodide); A (\(^{131}\)I thyroidal clearance).

* Mean values ± SD.  
* Significantly lower (P < 0.001).  
* Mean values without any significant difference as compared with the normal group.  
* Significantly lower (0.001 < P < 0.01).  
* Significantly higher (P < 0.001).
both malnourished groups is characterized by a wide dispersion of results (range 251 to 1437 and 267 to 1729.10⁻⁵% DT/ml, respectively) and by a mean value significantly higher (587 ± 361 and 613 ± 438.10⁻⁵% DT/ml respectively, or P < 0.001 and P < 0.001, respectively), than that the one recorded in the normal group. As a consequence, the thyroidal clearance was decreased to 7.31 ± 4.08 and 9.04 ± 5.18 ml/min (P < 0.001 and P < 0.001, respectively). Here too, A is characterized in both PCM groups by a wide dispersion of values ranging from subnormal to very low values (17.21 to 2.15 and 16.05 to 1.86 ml/min, respectively).

Values for RAIU max plotted against those recorded for A in each malnourished group give a highly significant linear correlation (r = 0.87 and r = 0.95, respectively). The corresponding regression line calculated in the parenterally investigated PCM children is determined by the equation Y = 1.12X + 17.08 (Fig. 2).

Discussion

All the children investigated in this survey come from the suburbs of Dakar. The capital of Senegal is situated in the westernmost part of the Cap-Vert peninsula on the Atlantic Ocean. There is no evidence of endemic goiter in this part of the country and urinary iodine normally ranges from 25 to 35 µg/day in healthy children of 2 years old. Before any hospital care, the standard diet of the investigated children was composed of traditional meals whose iodine content presumably remains constant. No argument exists in Senegal, as reported in the United States, in favor of progressive enrichment of iodine in dietary products that might be accountable for RAIU depression (17).

Plasma values recorded in Table 1 for the normal group and for both PCM groups on admission are in good agreement with previously collected data (7, 18, 20). Results obtained for serum-albumin, for TBPA and for thyrobinding globulin are significantly reduced as compared with the normal group (7, 18). The significant depression of total thyroxine concomitantly reflects the

<table>
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<tr>
<th>TABLE 2</th>
<th>Thyroidal and nutritional status in 12 PCM children parenterally investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>RAIU (µIU/ml)</td>
</tr>
<tr>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>A</td>
<td>2.4 ± 1.13</td>
</tr>
<tr>
<td>A (ml/min)</td>
<td>2.4 ± 1.13</td>
</tr>
</tbody>
</table>
FIG. 1. The *midline* ○—○ represents the mean thyroidal RAIU recorded in the euthyroid group. ●—● and ×—× show the thyroidal RAIU curves obtained in two thyrotoxic children. Note the additional uptake of the 6th hr. All euthyroid and thyrotoxic children were orally investigated. ●—● symbolizes the mean RAIU curve in 12 PCM patients orally investigated. ▲—▲ outlines the mean RAIU curve in 12 PCM patients parenterally investigated.

FIG. 2. Individual values recorded for maximal RAIU and for thyroidal clearance of iodine in six normal children (○) and in 12 malnourished children parenterally investigated (●). The latter group is characterized by a progressive decrease of both functional parameters of thyroid activity along the depicted regression slope.
drop of the three specific carrier proteins and the declining thyroidal secretion (19). The fall of total triiodothyronine to less than one fourth of the normal level appears as the converging effect of low plasma thyro-binding proteins and defective liver thyroxine monodeiodination reaction (20). Finally, the persistancy of free thyroxine and of thyroid-stimulating hormone within normal limits suggests that the interaction between these last circulating hormones plays, at least in early malnutrition, the major role in maintaining euthyroid status (19, 20).

Both groups of PCM children orally and parenterally investigated show a similar TBPA level and may be considered as comparable in respect with their nutritional status (7). The maximal RAIU registered in both groups is characterized by a wide dispersion of values ranging from 44.3 to 17.2 percent of the administered dose. All the children parenterally investigated show a maximal RAIU 24 hr after 131I administration. Except in one case, all the children orally investigated reveal a delayed RAIU peak 48 hr after gavage. This retarded peak must presumably be correlated with iodine malabsorption in PCM (10). The mean average value obtained for RAIU_max (26.1% DT) in the orally surveyed group is also slightly lower than the one defining the parenterally surveyed group (27.3% DT), but without any reliable significance (P < 0.1). It is thus apparent that morphological changes of the intestinal mucosa are responsible for the delayed iodine absorption. However, the total amount of 131I transferred through the intestinal wall is clearly determined by the level of thyroidal activity (10). It is likely that some individual patients, characterized by a more decreased thyroidal uptake might be affected by a significantly more severe iodine malabsorption. The delayed intestinal absorption apparently does not aggravate the prevalence of iodine deficiency in conditions where dietary iodine is abundant. On the contrary, with a borderline iodine intake, any intestinal malabsorption of iodine as described in PCM children may represent a contributory factor in endemic goiter epidemiology. This concept is consistent with a study pointing out generalized malnutrition in endemic areas as an underlying background for iodine deficiency goiter (21).

The decreased thyroidal RAIU may be partly explained by mental anorexia and behavioral changes, which are common features in mishandled weaning of breast-fed children. These traumatizing circumstances probably involve some derangement of the hypothalamic-pituitary feedback mechanisms which seems capable of depressing thyroidal RAIU (22). Moreover, recent data have demonstrated that protracted malnutrition is marked by a relative unresponsiveness of TSH secretion to peripheral hypothyroid status (20). This functional abnormality resembles pseudohypopituitarism as described in experimental malnutrition (23) and is concordant with light- (24) and electron-microscopic (25) figures displaying complete failure of thyroid stimulation by thyrotropin.

Our study agrees with previous works showing low 131I uptake proportional to the duration of malnutrition (2, 3). The investigated children present varying PCM stages ranging from acute protein malnutrition to prolonged marasmic kwashiorkor. In this survey, nearly normal values for RAIU (above 32% DT) were recorded in recent protein-depletion with mild height and weight failure and swollen limbs. The lowest values for RAIU (below 20% DT) were obtained in marasmic malnutrition of long-term duration with marked height and weight retardation and moderate edema. Patients suffering from PCM of medium duration exhibit intermediate values for RAIU. A low RAIU appears to be a biological sign of long-standing disease leading to a progressive impairment of thyroid function. None of the surveyed children were in the throes of death and all recovered normally. It is not excluded that moribund PCM children could be affected by RAIU_max values depressed below our lowest results, as an effect of terminal alterations.

Thyroidal iodine clearance faithfully reflects the trapping ability of the thyroid gland (12, 13). The thyroid clearance of iodide may be decreased more than 10 times the normal mean at the very same time when RAIU_max is only reduced by half. This indicates that protein deprivation may evolve within a few weeks, a similar
depression of thyroid functional parameters as that recorded after radioiodine therapy (26) and with advancing age due to natural processes (27, 28).

The thyroid dysfunction appears to be mainly responsible for the high P11 and high plasma $^{131}$I values recorded at the acute stage of malnutrition. Another study, however, reveals that kidney activity is also impaired and contributes, at least in part, to the upstream retention of inorganic and radioactive iodide in the body fluids of PCM children (19). The simultaneous depression of renal and thyroidal iodide clearances and the coexistence of body overhydration at the acute stage of the disease entail thus the accumulation of an increased iodide pool in an expanded iodide space (19). Kidney dysfunction in PCM children may be regarded as a direct result of protein shortage (29) and of associated potassium (30) and magnesium (31) deficiencies. Studies in progress in Senegal show that appropriate refeeding, as well as potassium and magnesium supplementation, produce within ten days a rapid restoration of renal activity and a concomitant decline of P11 levels to normal. By contrast, the very slow return of RAIU to normal requires 6 to 8 weeks of optimal dietary therapy (20). This last recovery pattern is not significantly affected by the faster renal and P11 normalization, implying that P11 elevation has no significant interfering influence on the low RAIU results, which thus more clearly reflects a proper thyroid involutive process. The possible occurrence of such a Wolff-Chaikoff effect at the acute stage of malnutrition was considered in the study, and subsequently discarded.

The existence of an increased iodide pool may lead to the false impression that the absolute iodine uptake (AIU), resulting from the product P11 $\times$ A, is paradoxically normal or increased on admission. The relative rise of P11 in short-term malnutrition may equalize or even exceed the corresponding drop of A, a situation apparently leading to significant intrathyroidal iodine overload.

This concept however is invalidated by the direct measurement of intrathyroidal iodine content performed on deceased children (Y. Ingenbleek, unpublished data) and by kinetic studies (19). These works show a mean thyroidal halide concentration significantly lowered as compared with the mean value in age-matched controls dying of other than nutritional reasons. It is, therefore, believed that an initial higher AIU is not followed by a parallel organification. Some inorganic iodide leaves the normal thyroid gland, especially on high daily iodine intakes (32). Vastly greater nonhormonal iodide leak occurs in diseased organs (33). It is highly probable that the thyroid gland of malnourished patients is similarly characterized by an increasing free iodide escape. In long-term malnutrition, the continuous impoverishment of intrathyroidal iodide pool is occurring, and the elevation of P11 is largely counterbalanced by a more marked depression of A, implying a gradual AIU drop.

Despite an apparently transient AIU increase, the present study obviously demonstrates that the thyroid gland trapping avidity for iodide regresses in process of time as a result of dietary inadequacy. This observation is in close agreement with other data pointing out a global deterioration of varying thyroidal parameters in prolonged malnutrition, such as reduced oxygen consumption (34), diminished basal metabolic rate (35), and deficient response of the endocrine organ to exogenous thyroid-stimulating hormone administration (36). In addition, histological aspects of the PCM thyroid includes, in Senegal as in Central America (37), some atrophy with collapsed follicles, absence of colloid and extensive interstitial fibrosis.

**Summary**

Severe infantile malnutrition involves a progressive depression of radioiodine uptake and thyroidal clearance which in turn, seems proportional to the duration of the protein deficiency. In PCM children, both functional parameters of thyroid activity decline are associated with a highly significant correlation coefficient ($r = 0.95$). The decrease of thyroidal clearance may reach less than one tenth of the normal whereas the corresponding RAIU$_{\text{max}}$ is only reduced by half. These results stress again the importance and sensitivity of thyroid iodine clearance as an index of thyroid involution.
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References
THYROIDAL IODINE CLEARANCE, RADIOIODIDE UPTAKE IN PCM


