Impairment of Mental Development by Iodine Deficiency and Its Correction. A Retrospective View of Studies in Peru

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During the last three decades an increased awareness of iodine deficiency disorders has stimulated a growing concern because of its impact on the quality of life in terms of handicapped mental and neuromotor development, poor school and work performance, and reproductive failure. Such impairment depends on the severity of the deficiency and on the period of fetal or postnatal life in which it occurs. A large number of studies in human beings and experimental animals have demonstrated that iodine deficiency affects maternal and fetal thyroid function with a consequent insufficient thyroid hormone supplementation to the brain during fetal and early postnatal life (1).

Many observations in humans have pointed out the negative effect of the lack of iodine on mental and neuromotor development as well as its prevention by the early correction of that deficiency. The majority of these observations were carried out after the administration of iodinated oil for correcting the deficiency. Some studies had a lack of statistical significance or were otherwise inconclusive. This stemmed in part from inappropriate experimental design, inappropriate definition of the tested subjects, or difficulties in the use of test tools. Among these studies was one carried out in Andean Peru on children born to iodine deficient and iodinated oil treated mothers, originally designed to measure the effects of iodine deficiency and its correction during early life (2).

The objective of this presentation is to reassess the results of that study in the light of more recent understanding of the effects of iodine deficiency on brain development and function and of the pathogenesis of the neurological insult. The whole subject was extensively reviewed at a conference on iodine and the brain held in 1988 (3).

DESCRIPTION OF THE ENDEMIC AND THE CORRECTIVE APPROACH

Our studies were conducted in three Andean villages with similar severe iodine deficiency. The prevalence of goiter was 83% in the general population, and 50% among children under 5. Cretinism occurred in from 1 to 3.6% of the population. The severe deficiency of iodine was demonstrated by a UEI of 17 μg/24 h. The mean serum T_4 was 6.4 μg/100 mL (2.7–10).

The pilot study was begun in October 1966, and followed up for 7 years. Of a total of 3,183 subjects included in the study, 1,992 were injected with iodinated oil (the I-T group). The dose of iodinated oil in adults ranged from 0.2 mL (96 mg iodine) to 2.0 mL (960 mg iodine). Effectiveness proved to be about 1 year for the smaller dose and 3 years for the larger (4).

Table 1. Iodine Content of Human Milk in Iodine-Deficient and Iodine-Treated Mothers

	μg I/dL	Median
I-Deficient (15)	0.6 ± 0.7[a]	0.2
I-Treated		
0.2 mL IM iodized oil (12)	1.3 ± 1.7	0.5
2.0 mL IM iodized oil (15)	8.1 ± 4.2	7.0

Number of subjects in parentheses.
[a]$\bar{x}$ ± SD of values 18–36 months after iodized oil.

Table 2. Maternal Urinary Iodine and Serum Thyroxine Levels

Group	Age (years)	UEI (μg/g cr)	T_4 (μg/dL)
I-Deficient			
$\bar{x}$ ± SD	29.1 ± 6.8	32 ± 15	7.4 ± 1.7
Range	17–42	12–71	4.5–9.9
n		33	17
I-Treated			
$\bar{x}$ ± SD	26.9 ± 6.8	230 ± 260	11.4 ± 2.6
Range	17–38	68–1300	7.0–16.3
n		22	13
p		0.000	0.000

DISTINCTIVE FEATURES IN MATERNAL–FETAL THYROID FUNCTION AND GROWTH OF CHILDREN BETWEEN GROUPS

A total of 747 women of childbearing age were in the program; 332 were classified as iodine-deficient and 415 as iodine-treated. A physician who worked full time with the project controlled the progress of these women and followed their pregnancies through delivery and the development of the children. He rotated continuously among the villages. A total of 456 newborn children were registered, with 44% in the iodine-deficient group and the others in the treated group.

Samples of blood and urine were collected during pregnancy, at the time of delivery, and afterward in mothers and children in order to measure serum T_4, T_3, total serum iodine, thyroxine binding proteins, TSH, and UEI. The children born into the program were followed up during the next 5 years after injection of their mothers. The findings have been published previously (5) and are summarized briefly here.

1. Serum thyroxine binding protein and thyroxine binding capacity were normal in both groups. Iodine deficiency in pregnant women was clearly associated with low T_4, F-T_4 and T_3 values. Thus in the I-D pregnant women 67% of T_4s were well below the normal range. On the contrary, the situation was reversed in the I-T group, in which T_4 were normal in 87%.
2. There was a significant correlation between T_4 and UEI values in pregnant I-D women (r = 0.569).
3. Congenital transitory hypothyroidism was found in 22% among the I-D group. It should be noted that extremely low fetal T_4 values corresponded to very low maternal values. Neonatal T_4s in the I-T group were all normal.
4. Iodine content of human milk at 2–3 years after the initial treatment of mothers showed a sixfold higher mean value in those injected with 2.0 mL iodinated oil than the ones injected with 0.2 mL, whose results were already comparable to the I-D group (Table 1).
5. Although mean values were not significant, a consistent tendency for lower birth weight, length, and cephalic circumference, as well as a slower rate of height and cephalic circumference growth was observed in children from the I-D group as compared to those from the I-T group. Nutritional status, as judged by skinfolds and upper arm circumference, was comparable in the two groups.
6. UEI in I-D children was lower than in I-T children at 2 and 5 years-of-age.

REASSESSMENT OF RESULTS ON MENTAL AND NEUROFUNCTION DEVELOPMENT OF CHILDREN IN THE VILLAGE OF HUASAHUASI

Forty-nine children born to I-D mothers and 40 born to I-T mothers from the same village of Huasahuasi were tested by the Stanford–Binet and the Brunet–Lezine intelligence scales. The Stanford–Binet was employed in the 2–4 year-old group only and the Brunet–Lezine in those under two years. The Brunet–Lezine scale was employed in a few children older than 2 years, but with marked mental retardation. Audiometry, voice, buccofacial praxis, articulation praxis, verbal expression, and comprehension were tested by methods adapted to our environment (6). Electroencephalographic studies were made with an eight channel Nikon Kode portable unit on a few subjects in each group between the ages of 2 and 4 years. These studies were cross-sectional. All investigators were unaware of the injection status of the subjects. Grouping of results

Table 3. Mean IQ Scores and Psychological Age Retardation in Children Born to Iodine-Deficient and Iodine-Treated Mothers

	IQ			Psychological Retardation (%)		
	I-Deficient	I-Treated	*p*	I-Deficient	I-Treated	*p*
<2 years	71.3 ± 15.5 (22)	84.4 ± 15.3 (14)	0.018	29.1 ± 14.1	16.5 ± 12.6	0.011
3–5 years	77.1 ± 12.6 (22)	86.9 ± 12.7 (14)	0.029	24.1 ± 13.9	14.4 ± 10.9	0.035
Girls	74.3 ± 14.6 (23)	83.5 ± 14.4 (13)	0.076	26.2 ± 13.4	16.0 ± 13.0	0.051
Boys	74.1 ± 14.2 (21)	87.5 ± 13.6 (15)	0.007	26.9 ± 15.1	14.3 ± 10.5	0.008
Total	74.4 ± 14.8 (44)	85.6 ± 13.9 (28)	0.002	26.6 ± 14.1	15.5 ± 11.6	0.000

Values are mean ± SD. Numbers of subjects in parentheses.

according to protocol injection of the mothers occurred only after the studies were completed.

In the process of reassessing the previously published interpretation of our results (5) for a more critical selection of the children who were tested, the following have been taken into account:

1. that the critical period of insult to brain development is the second trimester of fetal life and that concomitant severe maternal and fetal hypothyroidism is more likely to be associated with neurological cretinism (7); and
2. that iodinated oil given IM at 0.2 or 2 mL to fertile-aged women secures a normal iodine supplementation for both mother and fetus, and in human milk up to 1 and 3 years after administration, respectively.

Accordingly, in a recalculation of results only the children of mothers who had UEI or T_4 levels that were verified and found to be consistent with a definition of iodine deficient or normal were included (Table 2). In five instances from the I-T group these data were not available but gestation took place within a safe time after injection of iodinated oil. On these bases, in the I-D group five subjects were excluded because of high maternal UEI possibly due to contamination or inappropriate identification. In the I-T group three subjects whose mothers were treated within the first trimester were included, but six were excluded because treatment was given by the end of gestation. Additionally, four subjects were also excluded because pregnancies took place a long time after iodinated oil administration without information on UEI, and two be-

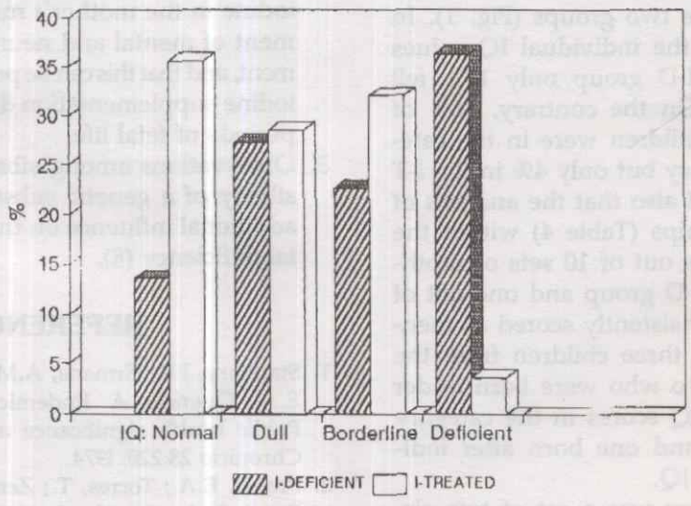

Figure 1. Comparison of the frequency of various intelligence levels between iodine-deficient and iodine-treated children.

Table 4. Intelligence Scores in Sibships

I-Deficient				I-Treated		
Mother				Mother		
J127	71 (f, 4)	97 (m, 18)	86 (m, 30)	J121	90 (f, 1)	78 (m, 32)
J181	100 (f, 7)	82 (f, 26)	83 (f, 53)	J145	111 (m, 8)	90 (m, 30)
J201	80 (f, 10)	65 (f, 53)		J009	87 (m, 18)	100 (m, 42)
J024	79 (f, 12)	82 (m, 58)		J126	81 (m, 33)	100 (f, 57)
J183	70 (f, 26)	76 (m, 53)		J041	71 (m, 15)	86 (m, 38)
J071	88 (f, 28)	84 (f, 53)		H188	60 (f, 20)	71 (f, 52)
GCHE	40 (f, 13)	51 (m, 40)				
NH004	60 (f, 10)	64 (f, 64)				
J192	55 (m, 18)	65 (f, 38)			81 (f, 11)	
J186	80 (f, 11)				82 (m, 37)	

The sex and age appear in parentheses.

cause of inappropriate identification.

Following the above process of selection, the results of IQ scores, as shown in Table 3, clearly demonstrates a significant lower mean value in the I-D children than in the I-T children (74.4 ± 4.8 vs. 85.6 ± 13.9, $p < 0.002$). No significant differences were found in relation to age or sex. Age psychological retardation expressed as percent of chronological age was significantly higher in the former group. The lowest IQ (48) in the I-D group corresponded to a twin daughter of a cretin, and another very low (63) to a twin boy. The twin brother and sister in each instance died.

Moreover, the percent distribution of IQ scores is quite different in the two groups (Fig. 1). In the I-T group 36% of the individual IQ values were normal, in the I-D group only 14% fell within this category. On the contrary, 36% of the IQ values of I-D children were in the category of mental deficiency but only 4% in the I-T group. It may be noted also that the analysis of IQ scores among sibships (Table 4) within the groups shows that four out of 10 sets of brothers and sisters in the I-D group and one out of six in the I-T group consistently scored as mentally deficient. Among three children from the same mother (J192), two who were born under iodine deficiency had IQ scores in the category of mental deficiency, and one born after iodinated oil had a normal IQ.

In the I-T group there was a set of two sisters (H-188) with low IQ scores whose mother's UEI was still very high (1300 μgI/gm creatinine) at 2 years after injection of iodinated oil. It is difficult to know whether this woman had taken iodine from another source and whether this had any relation to the low IQ of her children.

Table 5. Neurological Data on I-Deficient and I-Treated Children

Group	Language Subnormal (%)	Audition Subnormal (%)	EEG Abnormal (%)
I-Deficient	56.8 (44)	9.8 (41)	9.1 (11)
I-Treated	39.3 (28)	0.0 (28)	0.0 (7)

Number of subjects in parentheses.

The results of neurofunctional indicators appear in Table 5. It may be seen that language and auditory deficiencies were more frequent among the iodine deficiency children than in those who were treated. A single abnormal EEG was recorded among the I-D children. This showed disorganized background activity with bursts of theta and delta activity and scattered low waves. The findings suggested mildly diffuse disorganized activity, but the small number of observations does not permit firm conclusions.

SUMMARY

1. Studies from Highland Peru a number of years ago on the effects of iodine repletion of mothers on the neurological development of their children have been reexamined in the light of new information and understanding.
2. The results clearly demonstrate that iodine deficiency during fetal life, and maintained through early postnatal life because of lack of iodine in the mother's milk, results in impairment of mental and neurofunctional development, and that this can be prevented by appropriate iodine supplementation during the critical time periods of fetal life.
3. Observations among sibships favors the possibility of a genetic substrate contributing an additional influence on the occurrence of mental deficiency (8).

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