

## Impairment of neuromotor and cognitive development in iodine-deficient schoolchildren with normal physical growth

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In order to detect somatic and psychomotor disturbances in children and adolescents residing in areas of iodine deficiency, schoolchildren from three areas with different degrees of iodine deficiency were studied. In Randan, the prevalence of severe endemic goiter was accompanied by alteration in thyroid function, increased thyrotropin levels and retardation of both bone and psychomotor age and decreased intellectual quotient. In Tehran, where iodine deficiency is mild, visible goiter was present in 15% of schoolchildren but no alterations in thyroid function, serum thyrotropin, somatic or psychomotor development could be detected. In Zagoon, where the prevalence and severity of goiter was less than Randan but more than Tehran, thyroid function was normal but slightly decreased as compared to Tehran; somatic development was unaltered, but retardation in psychomotor development was evident and the mean intellectual quotient was less than that of Tehranian schoolchildren. These findings indicate the occurrence of physical and psychomotor disturbances in apparently normal schoolchildren from areas of iodine deficiency. Alteration in psychomotor development may occur in children with normal physical growth, due to iodine deficiency.

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In recent years, much attention has been focused towards the occurrence of neuropsychometric alterations in children residing in areas of iodine deficiency. It has been shown that apparently normal schoolchildren in these areas suffer from varying degrees of physical, auditory, neurological and psychomotor defects (1-4). However, it is not known which of the two, somatic or neuropsychomotor development, is affected first in children residing in areas of mild to moderate iodine deficiency. In order to shed more light on this matter, we studied schoolchildren and adolescents from three schools in Tehran and its suburbs with varying degrees of iodine deficiency disorders (IDD). All children attended daily activity of schools and no apparent case of cretinism could be detected in the area.

### Subjects and methods

Fifty-four schoolchildren from Randan, 20 from Zagoon and 31 from Razi school in Tehran, aged 6-15 years, were studied. In Randan, all students of the only school in the village entered the study, while in Zagoon and Tehran, a simple random sampling was applied. The degree of schooling in the three locations was similar. Age of entering school was between 6 and 7 years, and hours of school per week were 20 to 24 hours in all

locations. The age distribution of the three samples was comparable (Table 1).

Randan and Zagoon are two villages situated in a mountainous region north of Tehran known to have hyperendemic goiter (5). The capital city of Tehran is an endemic region with a high prevalence of goiter but normal thyroid function (6).

Unpublished results of urinary iodine determination obtained during a goiter survey in Tehran and its suburbs have established low excretion of urinary iodine in three locations:  $12.3 \pm 5.4$ ,  $18.0 \pm 9.6$  and  $35.8 \pm 19.1$   $\mu\text{g}/\text{mg}$  creatinine in schoolchildren of Randan (N=25), Zagoon (N=22) and Tehran (N=18), respectively. The difference between the three groups was statistically significant (Randan vs Zagoon,  $p < 0.01$ ; Randan vs Tehran,  $p < 0.001$ ; Zagoon vs Tehran,  $p < 0.001$ ). Urinary iodine excretion rates in iodine-sufficient areas were  $176 \pm 40$   $\mu\text{g}/\text{mg}$  creatinine.

Subjects were brought to Taleghani Medical Center for evaluation. They were examined by an endocrinologist, the status of thyroid function was assessed and goiter was graded according to WHO criteria (7). Psychomotor tests, audiometry and radiological evaluation were performed and assessed by specialists who were unaware of the results of the thyroid status and biochemical evaluation.

After an ear, nose and throat examination, audio-

Table 1. Age and sex distribution and the prevalence of goiter in three groups of schoolchildren residing in areas of iodine deficiency in Tehran and suburbs.

Location	Age (years)		Sex (F/M)	Grades of goiter				
	6-10	11-15		0	1A	1B	2	3
Randan (N=54)	21	33	22/32	0	0	18	54	28
Zagoon (N=20)	7	13	8/12	0	5	40	54	1
Tehran (N=31)	14	17	12/19	34	19	32	15	0

Table 2. Biochemical parameters in schoolchildren with iodine deficiency of varying degrees.<sup>a</sup>

Location	T <sub>4</sub> (nmol/l)	FT <sub>4</sub> I	T <sub>3</sub> (nmol/l)	FT <sub>3</sub> I	TSH (mIU/l)
Randan (N=54)					
Mean ± SD	87 ± 23 <sup>b,d</sup>	19 ± 6.4 <sup>b,c</sup>	2.9 ± 0.6 <sup>b,e</sup>	0.74 ± 0.14	9.4 ± 11.6 <sup>b,c</sup>
Median	85	18	2.9	0.74	5.3
Range	(30-131)	(7-29)	(1.1-4.4)	(0.28-1.12)	(1.2-64)
Zagoon (N=20)					
Mean ± SD	96 ± 21 <sup>b</sup>	26 ± 6.4	2.6 ± 0.5	0.71 ± 0.09	3.5 ± 0.9 <sup>b</sup>
Median	99	27	2.5	0.71	3.6
Range	(58-142)	(16-38)	(2.1-4.2)	(0.57-1.13)	(2.0-5.4)
Tehran (N=31)					
Mean ± SD	116 ± 18	33 ± 6.4	2.4 ± 0.3	0.71 ± 0.11	2.4 ± 1.1
Median	116	33	2.4	0.71	2.5
Range	(80-154)	(23-44)	(1.8-3.5)	(0.53-1.03)	(1.1-5.2)

<sup>a</sup> T<sub>4</sub>: thyroxine; FT<sub>4</sub>I: free thyroxine index; T<sub>3</sub>: triiodothyronine; FT<sub>3</sub>I: free triiodothyronine index; TSH: thyrotropin.

<sup>b</sup> p < 0.001 compared to Tehran.

<sup>c,d,e</sup> p < 0.001, p < 0.01 and p < 0.05, respectively, compared to Zagoon.

metry was carried out by measuring air conduction thresholds with a clinical pure-tone audiometer. The mean hearing level (dB) was obtained as the average of the hearing thresholds at the speech frequencies, i.e. 500, 1000 and 2000 Hz (8).

The Bender-Gestalt test was performed by having each student copy a number of geometrical figures. The number of errors was then detected and psychomotor age was estimated (9). This test explores visual perception and neuromotor activity. The Raven test was performed to evaluate the general intellectual aptitude. This test gives a fair estimation of the intellectual quotient (IQ). Radiographs of hip, knee and hand were taken for assessment of skeletal maturity and estimation of bone age.

A serum sample was obtained and serum concentrations of T<sub>4</sub>, T<sub>3</sub>, TSH (by IRMA) and resin T<sub>3</sub> uptake were assessed by commercial kits. The free T<sub>4</sub> index (FT<sub>4</sub>I) and the free T<sub>3</sub> index (FT<sub>3</sub>I) were then calculated (10). In all assays performed, the intra-assay and interassay coefficients of variation were less than 10% and 12%, respectively.

Statistical analysis were performed by Student's *t*-test, chi-squared analysis and simple linear regression analysis. The results are expressed as means ± SD.

## Results

The height and weight of schoolchildren in Tehran and Zagoon were normal and correlated with those of the National Center for Health Statistics (NCHS) percentile (11). There was marked growth retardation in schoolchildren of Randan, Sixty-one per cent of their heights and 40% of their weights were below the third percentile of the NCHS.

Table 1 shows the prevalence of goiter in the subjects studied. A high prevalence of goiter was found in all three groups. However, in Tehran most goiters were of grade 1. In Zagoon, 54% of the goiters were visible by sight. The prevalence and severity of thyroid enlargement were highest in Randan, where all schoolchildren had goiters of grade 1b or larger. Signs of hypothyroidism were present in only five schoolchildren from Randan. Clinical evaluation of thyroid function was not helpful in predicting biochemical thyroid status. As seen in Table 2, the mean serum T<sub>4</sub> and FT<sub>4</sub>I were decreased and TSH was increased in schoolchildren from Randan as compared to Zagoon and Tehran. The mean serum T<sub>3</sub> was higher in Randan; however, the FT<sub>3</sub>I was not significantly different from the other two groups. In Randan, 16 subjects (30%) had serum T<sub>4</sub> below 64

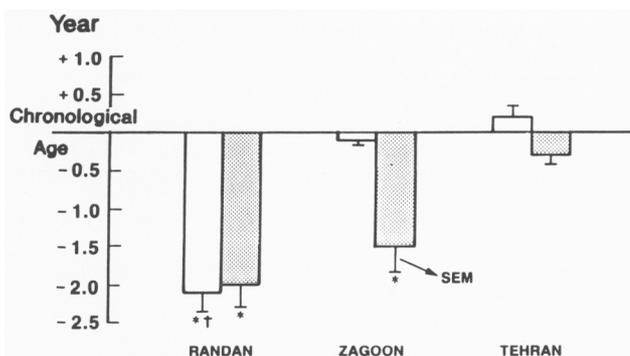


Fig. 1. Difference between chronological age and psychomotor (■) and bone (□) ages in three groups of schoolchildren in Tehran and its suburbs. \* $p < 0.001$ , as compared to values in Tehranian schoolchildren; † $p < 0.001$ , as compared to Zagoonian results. Note retarded psychomotor and bone ages in Randan and delay in only the psychomotor ages in Zagoon.

nmol/l, 24% had serum TSH above 10 mU/l and 22% had TSH levels between 5 and 10 mU/l. Thyroid function tests and serum TSH were normal in Zagoon, although  $T_4$  and  $FT_4I$  were decreased and TSH was increased, as compared to values in schoolchildren from Tehran.

The results of estimation of bone and psychometric ages are seen in Fig. 1. There was marked retardation of both bone and psychometric ages of approximately 2 years in schoolchildren of Randan. Zagoonian children who had no retardation in bone age showed a marked decrease in psychometric age of about 1.5 years. The IQ was also decreased in Randan as compared to Tehran ( $89 \pm 16$  vs  $117 \pm 12$ ,  $p < 0.001$ ). The IQ of schoolchildren from Zagoon were in-between those of the other two groups ( $102 \pm 12$ ). In Randan, 83% of subjects had an IQ below 100, of which 9% showed an IQ below 70 (Table 3) and fulfilled the criteria for mild mental retardation (8). In Zagoon 55% of the IQs were below 100, while in Tehran 92% of schoolchildren had an IQ above 100. The mean hearing thresholds were  $13.0 \pm 2.3$ ,  $13.9 \pm 1.7$  and  $12.4 \pm 2.3$  dB in Randan, Zagoon and Tehran, respectively. The difference was not statistically significant.

The influence of serum TSH concentration on other parameters was assessed in schoolchildren of Randan. There was a negative correlation with the  $FT_4I$

( $r = -0.567$ ,  $p < 0.001$ ). No correlation could be found between serum TSH and age, height, weight, grades of goiter, the  $FT_3I$ , IQ, psychomotor or bone age.

### Discussion

We have reported here the thyroid status and somatic and psychomotor alterations in schoolchildren with varying degrees of IDD. The major finding of this study is that in mild forms of iodine deficiency, thyroid function tests and somatic growth may remain normal while a deficit in psychomotor development and IQ exists.

Alterations in psychomotor development in apparently normal schoolchildren residing in areas of iodine deficiency have been reported from Spain (1), India (2), China (3) and Italy (4). As these deficits occur in both euthyroid and hypothyroid individuals living in iodine-deficient regions, and in concordance with studies in sheep (12) and rats (13), it has been suggested that iodine deficiency and decreased thyroid function in both mother and fetus during 14–18 weeks of gestation, when the development of neurons of cerebral cortex and basal ganglia takes place, may cause irreversible neuropsychological abnormalities (12, 14).

Our findings in schoolchildren from Randan, where iodine deficiency is moderately severe and is accompanied by decreased  $T_4$  and a rise in TSH in many subjects, is in accordance with previous findings (3, 4). Retarded bone and psychomotor age, and decreased IQ, unrelated to serum TSH concentration, suggest the occurrence of permanent damage probably during intrauterine life. Of interest is the findings in Zagoon, where thyroid function tests, although somewhat lower than Tehran, are within normal limits and no alteration in somatic growth could be seen. However, schoolchildren have lower IQs than in Tehran and demonstrate some degree of psychometric retardation. In Tehran, where iodine deficiency is slight (6), the only presentation of IDD is the appearance of goiter. These findings suggest that there might be a crucial level of iodine intake below which damage to the central nervous system may occur, causing alteration in psychomotor function in the absence of somatic deficits.

The degree of somatic and psychomotor retardation, although related to iodine deficiency, also may be caused by malnutrition or other causes and cultural and educational influences. This possibility cannot be excluded completely; however, a careful nutritional study failed to disclose any obvious calorific, protein or mineral malnutrition or use of goitrogens (5). In addition, Bender–Gestalt and Raven tests have been regarded to be culture free and unaffected by the level of education of individuals.

The public health implication of the present investigation is important in terms of the intellectual and learning problems that might occur in apparently normal children and adolescents residing in areas with mild to moderate iodine deficiency. Because approximately 800 million people are at risk of some retardation in somatic

Table 3. Intellectual quotient (IQ) in three groups of schoolchildren with varying degrees of iodine deficiency disorder.

IQ	Randan (N = 54)	Zagoon (N = 20)	Tehran (N = 31)
Mean $\pm$ SD	$89 \pm 15$	$102 \pm 12$	$117 \pm 12$
	$p < 0.005$		
Median	90	100	116
Range	62–112	81–124	90–137
> 100 (%)	17	45	92
70–90 (%)	74	55	8
< 70 (%)	9	0	0

development, it seems reasonable to suggest that many children with psychomotor disturbance of varying degrees are unattended throughout the world, which is good reason for vigorous applications of prevention and better control of IDD.

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