ORIGINAL ARTICLE

Timing of the Effect of Iodine Supplementation on Intelligence Quotients of Schoolchildren

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Iodine deficiency is the most important preventable cause of mental deficiency. The aim of this study was to specify the phase during fetal and postnatal development when iodine supplementation would have optimum effect on the prevention of brain damage.

Materials and Methods: Forty schoolchildren aged 7-13 years, from the previously iodine deficient villages of Kiga and Randan, were divided into 3 subgroups: in subgroup I the mother had received iodized oil 1-4 years prior to conception and infant consumed iodized salt from the age 1-4 years onwards; in subgroup II mothers received iodized oil during pregnancy and the child received iodized salt from the age 2-4 years and in subgroup III the child received iodized oil injection from age 1-3 and iodized salt from 3-6 years of age onwards. Serum T_4, T_3, TSH and T_3 uptake and urine iodide concentrations were measured. Bender-Guestalt and Raven tests were employed for psychomotor evaluation. A group of 40 age and sex matched schoolchildren from Tehran served as controls.

Results: Mean age of subgroups I, II and III were 8.9±1.7, 9.4±1.4 and 11.9±1.2 years, respectively. Serum T_4, T_3, TSH and urinary iodine concentrations were normal in all children. Urinary iodine and serum T_4, T_3 and TSH concentration did not differ between the 3 subgroups. Mean IQ was higher in subgroup I (102±7), as compared to subgroup II (93±10, $p<0.002$) and subgroup III (95±10, $p<0.05$). Mean IQ of subgroup I was not significantly different from age-matched controls, but a significant decrease in IQ was evident in subgroups II (93±10 vs 109±8, $p<0.002$) and III (96±10 vs 114±11, $p<0.001$), as compared to the control children.

Conclusion: It is concluded that children whose mothers received iodide supplementation before conception had normal IQs of significantly higher values than those whose mothers received iodine during pregnancy and the children who received iodine after birth.

Key Words: Iodine supplementation, Intelligence quotient, Iodine deficiency, Urinary iodine

Introduction

The developing human fetal brain is virtually inaccessible to investigation, although it is vulnerable to many exogenous influences. Iodine deficiency is the most widespread nutritional cause of impairment of brain development.[1] Infants born in iodine deficient areas are at risk of mental retardation and neurological disorders.[2] In iodine deficient regions, a mild degree of mental impairment occurs five times as frequently as cretinism[3-5] and the intelligence quotient (IQ) curve of the population shifts approximately 10 points to the left.[6] Yet iodine deficiency remains the world's most common preventable cause of mental retardation and neurologic impairment.

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It is well known that iodine treatment during pregnancy protects the fetal brain from the deleterious effects of iodine deficiency.[7-9] Iodine supplementation after birth may improve brain growth and development slightly but neither does it prevent endemic cretinism, non does it improve neurologic status.[10] We have previously reported, growth retardation, neurological, auditory and psychomotor impairment in the apparently normal schoolchildren of Kiga and Randan villages.[5,11] We designed this study following iodine supplementation to pregnant women and young children in these villages to specify the precise phase during fetal and postnatal development when iodine supplementation would have optimum effect in prevention of brain damage.

Materials and Methods

Kiga and Randan villages, 30-35 km northwest of Tehran, the capital city of Islamic Republic of Iran, were areas of severe iodine deficiency disorders, where impairment of physical, neuromotor and cognitive development and hypothyroidism had been reported previously.[5,11] Both villages are situated in the mountainous region, at an altitude of approximately 2480 meters above sea level. The population of Kiga and Randan, 800 and 600 respectively, live in poor socioeconomic and educational conditions.

Prior to 1989, the concentration of iodine in the water was nearly zero; mean urinary iodine concentrations in Kiga and Randan were 19.8±11.4 and 12.3±5.4 μg/gr of creatinine[5,11] with median of 19 and 12.3 μg/L, respectively. In 1989 and 1991 iodized oil (Lipiodol) was administered to inhibtants of Kiga and Randan aged 6 months to 40 years, respectively. Infants under one year of age received 240 mg and subjects aged one year and older received 480 mg of iodized oil intramuscularly. In 1993, iodized salt was distributed and all villagers have consumed iodized salt since that time.

This study was carried out in the year 2000, nine and eleven years after iodide supplementation was started in Kiga and Randan, respectively and 6 years after the beginning of iodized salt consumption.

Study design

The aim of this study was to find out in which age groups there is the best improvement of indicators of iodine deficiency and whether early supplementation prior to and/or during pregnancy makes a major impact on the developmental status of these children. Therefore, schoolchildren were divided in three subgroups depending on the time of iodide supplementation in mothers and infants (Fig. 1):

Subgroup I: The mother had received iodized oil 1-4 years prior to conception and the infant consumed iodized salt from age 1-4 years onwards.

Subgroup II: The mother had received iodized oil during pregnancy and child received iodized salt from age 2-4 years onwards.

Subgroup III: The child had received iodized oil injection between 1-4 years of age and iodized salt from 3-6 years onwards.

The study subjects were 40 schoolchildren from Kiga and Randan, age 7 to 13 years, whose mothers or the children themselves had received iodine supplementation as iodized oil injection prior to consumption of iodized salt. All children had clear information regarding the dates of iodine supplementation and the dates of birth. Goiter was graded according to WHO classification.[12] Each child underwent psychomotor testing and samples for measurement of serum concentration of thyroid hormones and urinary iodine excretion were obtained.

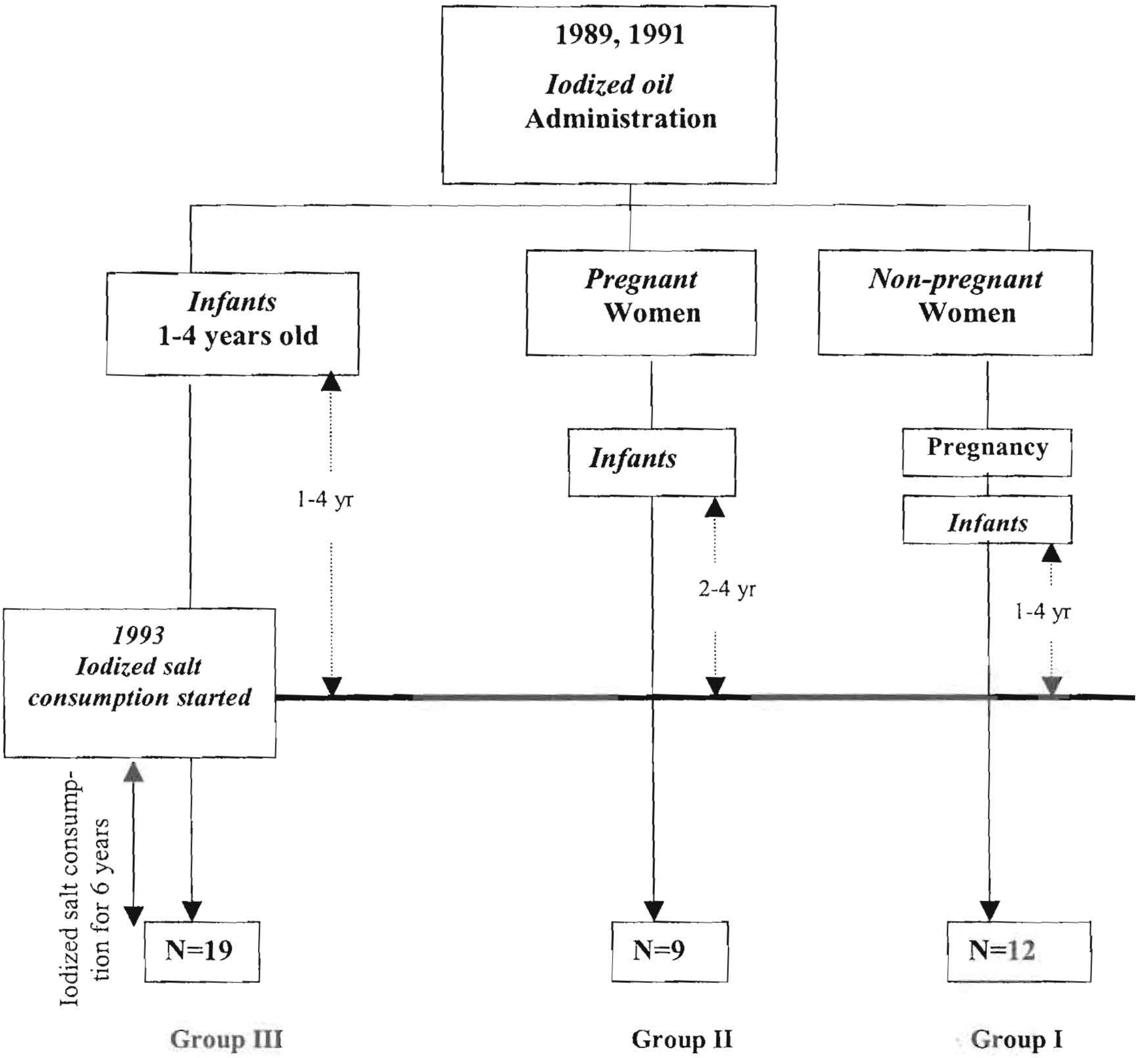

Fig. 1. Scheme of study design

Control group

Since the mean age of the 3 study groups showed some difference and IQ differences between groups may be due to age differences between the subgroups, 40 age- and sex-matched schoolchildren were selected from Tehran for IQ testing. Schoolchildren of Tehran had shown mild iodine Tehran had shown mild iodine deficiency and normal IQ in 1989.[11]

Psychomotor evaluation

The Bender Gestalt (BG) test consists of copying a number of geometrical figures and can be applied to both children and adults, whether literate or illiterate, as well as to subjects with language problems. The BG test explores visual perception and neuromotor ability and is affected by specific portions of intellectual function, i.e. memory, spatial concepts, and the ability to organize and make representations. Individual scores from the BG test were evaluated and the number of errors in copying figures was determined. The psychomotor age was then estimated and the difference between chronological and psychomotor ages was ascertained.[13] The Raven test was employed to assess the intelligence quotient (IQ) of the students. This test tries to evaluate the common denominator in all intelligence operations.

Biochemical evaluation

Serum concentrations of T_4, T_3, TSH and T_3 uptake test were preformed using commercial kits from Fenzia, Finland. In all assays performed, the interassay and intraassay coefficients of variations were 11 and 9%, respectively. Reference ranges for euthyroid subjects were: T_4: 4.5-12.5 μg/dL, T_3: 80-210 ng/dL and TSH: <0.1-4.5 mU/L. Urinary iodine was measured by acids digestion method.[14]

Data analysis

The results of this study were compared to those obtained in studies conducted prior to iodine supplementation in Kiga and Randan villages.[5,11] A comparison of findings between 3 subgroups was also made. Differences between mean values for quantitative variables were evaluated with the Student's t test. Chi-square and Fisher exact tests were employed for nominal and ordinal variables. In the text the arithmetic means are expressed as the mean±1 SD and in tables as mean (SD). All P values were obtained from two-tailed tests, and only values below 0.05 were considered significant. The conversion ratios for T_4 and T_3 from μg/dL and ng/dL to mmol/L are 12.87 and 0.01536, respectively.

Table 1. Urinary iodine, serum T_4, T_3 and TSH concentrations and intelligent quotients in schoolchildren before (1989) and 10 years after iodine supplementation (1999) in Kiga and Randan villages

Variable	1989 (n=246)	1999 (n=40)
Total goiter rate (%)	100	63
Median urinary iodine (μg/L)	15.7	187
Serum T_4 (μg/dL)	5.5 (2.0)	8.2 (1.6)
Serum T_3 (ng/dL)	176 (38)	141 (23)
Serum TSH (mU/L)	14.7 (20.1)	1.8 (0.8)
TSH above 5 mU/L (%)	40	0
Intelligent quotient (IQ)	89 (13)	97 (10)
IQ below 70(%)	12	0

Numbers represent mean (SD).

Results

Table 1 shows findings of biochemical evaluation and IQ in 40 and 246 schoolchildren of Kiga and Randan in 1999 and 1989, respectively. In 1989, 40% had serum TSH above 5 mU/L and 12% had IQ below 70.

In 1999, there were 12, 9 and 19 schoolchildren with mean±SD of 8.9±1.7, 9.4±1.4 and 11.9±1.2 years of age in groups I, II and III, respectively. Individual values for urinary iodine and serum T_4, T_3 and TSH concentrations in each child were within the normal range. Median urinary iodine concentration was 187 μg/L. Serum concentrations of T_4, T_3 and TSH were 8.2±16 μg/dL, 141±23 ng/dL and 1.8±0.8 mU/L, respectively; none had TSH above 5 mU/L. There was no significant difference in urinary iodine, T_4, T_3

and TSH concentrations between the 3 subgroups.

Mean IQ in 40 children was 97.2±10.0 and all children had IQ values above 70. Mean IQ was 102±7, 93±10 and 95±10 in subgroups I, II and III, respectively. As shown in Figure 2, children in subgroup I, whose mothers received iodide supplementation 1 to 4 years prior to conception had significantly higher IQ values than the other two subgroups ($p<0.002$ and <0.005, compared to groups I and II, respectively). Sixty-seven percent of children in subgroup I had IQ values above 100, while only 33% and 37% of children in subgroups II and III had IQ values exceeding 100.

Mean IQ in control group was 111±10. There was significant fall in IQ in subgroups II and III, as compared to the age matched control children (93±10 vs. 109±8 $p<0.002$ and 95±10 vs 114±11, $p<0.001$, respectively. There was no significant difference in IQ between children in subgroup I and the age-matched control children (102±7 vs 108±9, NS). Children in this subgroup had IQ between 92 to 109.

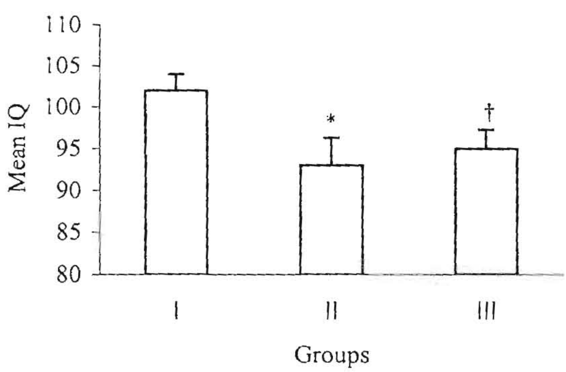

Fig. 2. Mean± standard error (SEM) of intelligence quotient (IQ) in schoolchildren following iodine supplementation

*** p< 0.002; † p<0.05 compared to group I**

The number of errors in the BG test was almost similar in the 3 groups of children. Mean differences between chronological and psychomotor ages were 1.5±1.4, 2.1±1.0 and 1.8±1.2 years in groups I, II and III, respectively (not statistically significant).

Discussion

The results of this study show that iodine supplementation in an area of severe iodine deficiency restored normal thyroid function and caused a rise in urinary iodine, a fall in goiter rate and an increase in IQ. These changes occured in all children, irrespective of the time of iodine supplementation, except for IQ, which showed greater improvement in the group in which iodine supplementation to their mothers had been started 1 to 3 years before conception.

Between 1962-65, two groups of investigators drew attention to the high incidence of endemic cretinism in regions of severe iodine deficiency.[15,16] Since then, numerous clinical observations have established an association between severe iodine deficiency and endemic cretinism.[3-6] The presumed mechanism is a combination of maternal and fetal hypothyroidism at a critical stage in the maturation of the central nervous system[17-19] It has been shown that areas of iodine deficiency are not limited to the two discrete populations of "cretins" and "normals", but instead contain a continuum from frank cretinism through varying degrees of neurologic, auditory, physical and mental impairment and other stigmata of cretinism to apparent normality.[5,20-22]

Iodized salt is an almost ideal medium for correction of iodine deficiency. Iodized vegetable oil offers a temporary alternative to salt iodization. Numerous studies have established that a single intramuscular injection of iodized oil, provides sufficient iodine for up to three years. Iodized oil may have several disadvantages when compared to iodized salt, particularly the supraphysiologic bolus dose which may cause a sudden increase in serum thyroid hormone concentration[23] and occasional induction of hypo- or hyperthyroidism.[24] On the other hand, iodized oil supplementation can be implemented promptly without the complexities and delays involved in altering the salt trade. The major application for iodized oil is in areas of severe iodine deficiency where iodized salt is unavailable.

The present study demonstrates a unique situation in which iodide supplementation is begun with iodized oil injection and continues with iodized salt consumption. We have reported that in schoolchildren of Kiga, who had varying degrees of physical and mental impairment and hypothyroidism,[5] iodized oil administration restored euthyroidism within 3 months following injection of 480 mg Lipiodol.[23,25] Euthyroidism remained 3 years after intervention[26] and was sustained by following iodized salt consumption.[27]

In the past, two methods were employed to investigate the effect of iodide supplementation on human development. Few studies selected a group of persons from an iodine-deficient area before and after treatment with iodine.[28-30] Others compared two groups, both from the same iodine-deficient population, one of which was treated with iodine, and the other given a placebo.[31,32] Although the latter study design is superior, it was unethical to employ this method in the present study, due to proven effectiveness of iodine supplementation in prevention of developmental disorders.

A number of studies have demonstrated the effectiveness of iodine supplementation programs on the prevention and treatment of IDD.[1] Treatment of sporadic congenital hypothyroidism with thyroid hormone beginning in the neonatal period permits normal mental and neurologic development;[33] however, iodine or thyroxine treatment at birth does not prevent endemic cretinism.[10] Both animal and human studies have shown that up to the end of the second trimester, iodine treatment of the mother protects the fetal brain from the effects of iodine deficiency.[7,17-19] Treatment after the beginning of the third trimester showed some improvement in development quotients; it could not however, improve the neurologic status.[7]

In the present study, the effects of iodine supplementation in preventing developmental injury were compared in 3 groups of schoolchildren, with differing timings of iodine supplementation, viz, to the mother before conception, during pregnancy and to the child after birth. The results showed that children whose mothers received iodide supplementation before conception had normal IQ, ranging from 92 to 109. The range of IQ of this group is almost comparable to the range of 91-130, obtained in normal Tehran schoolchildren employing Raven test conducted by the same psychologist.[5,11] The outcome of IQs in the other two groups was not optimal; however, both groups showed some improvement of IQ, as compared to schoolchildren of the same villages before intervention. In children who received supplementation after birth, partial improvement in IQ may have resulted from various additional factors that affect IQ measurement, such as improved eating habits, socio-economic changes in the area surveyed and a rise in educational level. However, it has been shown that improvement in IQ score in similar conditions has a significant association with goiter reduction after iodized oil administration to schoolchildren of an endemic region.[34] Improvement in development quotient has also been reported in children whose mothers were treated with iodine in the third trimester of pregnancy.[7]

In conclusion, the results of this study confirm that iodine supplementation, given before conception, effectively prevents impairment of IQ development. Lesser beneficial effects in IQ scoring along with complete restoration of normal thyroid function in children who receive iodine supplementation after birth, suggest that in areas of severe iodine deficiency, iodine supplementation should be mandatory even for children who have suffered from iodine deficiency during intrauterine life.

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