Thirty-year follow-up observation of the impact of iodine fortification strategy on intellectual development of children

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Abstract

Objective:

To follow up and observe the intellectual development of school children aged 8-10 in Baicheng County, Xinjiang Uygur Autonomous Region, historically a region with prevalence of severe iodine deficiency disorders, before and after effective control of the disease, to evaluate the impact of iodine supplementation on protection of children's intellectual development and provide a theoretical basis for scientific supplements of iodine.

Methods:

The Combined Raven's Test for Rural China (CRT-RC) was used to observe the intellectual development of 660 Uyghur school children aged 8-10 in Baicheng County in 1989, 2002, 2006, 2012 and 2018, respectively. Children's intelligence quotient (IQ) was calculated using CRT-RC's 1987 normal sample of rural children in the same age group. Data on average iodized salt coverage (C-IS) and childhood total goiter rate (TGR) from multiple local surveys and the median urinary iodine (mUIC) of children were collected, combined with the "Criteria for Elimination of Iodine Deficiency Disorders" (GB 16006-2008) and the United Nations International Children's Fund (UNICEF) recommended standards. The status of iodine deficiency during children's growth (IDG) was divided into complete exposure to iodine deficiency, no exposure, and semi exposure. The Flynn effect (FE) gain was calculated using norm samples of children aged 8-10 in 1987, 1996 and 2006 of CRT-RC, and the differences in children's intellectual development after FE correction before and after IDG reached the standard were compared.

Results:

The IQ of children were (81.67±14.13), (83.26±14.05), (89.68±13.58), (98.50±14.33) and (103.23±15.25) points in Baicheng County in 1989, 2002, 2006, 2012 and 2018, respectively. The difference between different years was statistically significant ($F = 58.357$, $P < 0.01$). The three indicators of C-IS, TGR, and mUIC did not meet the standards during the IDG evaluation period in the 1989, 2002, and 2006 groups, which were during complete exposure to iodine deficiency. In the 2012 group, which was semi-exposed, only mUIC met the standard. In the 2018 group, three indicators all met the standard, which was no exposure. The FE gains from 1987 compared to 1996, and 1996 compared to 2006 were 0.96 points/year and 0.74 points/year, respectively; after FE correction, the actual gains of IQ in 2002 and 2006 compared with 1989, and 2012 and 2018 compared with 2006 were - 9.57, - 6.11, 4.38, and 4.67 points, respectively.

Conclusions:

In iodine deficient areas, intermittent iodine supplementation (1989-2009) for children exposed to iodine deficiency during growth did not effectively protect children's intellectual development. Continuous and effective iodine supplementation (2010-2018) with iodized salt as the core and covering children's growth period has obvious positive effects on protection of children's normal intellectual development. In the future, we will continue to observe the influence of IDG full-cycle suitable iodine nutrition on children's intellectual development.

Keywords:

Iodine; Deficiency diseases; Child; Intellectual development Fund program: National Nature Science Foundation of China (81573103)
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Introduction

The most negative effect of iodine deficiency is harmful impact on brain development, resulting in abnormal neuronal migration patterns and irreversible damage to the cerebral cortex, hippocampus, and cerebellum caused by insufficient synthesis of thyroid hormone (TH). TH has essential effects on brain neurodevelopment during gestation, especially the first two years of life, such as neuronal migration and differentiation, myelin sheath formation, axon growth, transcriptional regulation, synaptic plasticity, and neurotransmitter release.[1] At the same time, myelin sheath formation and axonal growth are important for the development of cognitive functions. These processes occur rapidly in the first 20 years of life, remain in a constant state of development during adulthood, peak around 40 years of age, and begin to degenerate after that.[2] TH plays a protective role in demyelinating diseases as well as in myelin repair.[3] Severe iodine deficiency during pregnancy leads to the development of endemic cretinism. Mild to moderate iodine deficiency during pregnancy also causes varying degrees of neurocognitive developmental delay, manifested as significant mental retardation, with an absolute value of about 12.45 points in lost IQ of children with iodine deficiency.[4-5] Iodized salt is important to prevent iodine-deficiency and protect brain development and is safe, effective, convenient, and economical. Effective iodine supplementation, especially salt iodization, can save 8.7 points of IQ in children.[5] Therefore, effective iodine supplementation **based on salt iodization throughout the life cycle**, especially in the early stages of fetal development, is essential.

Baicheng County was once an endemic area of historical severe iodine deficiency disease. Iodine deficiency disorders were widespread, with prevalence of endemic cretinism reaching 9.77% in some townships. Early interventions to prevent and control iodine deficiency included supplying iodized salt, injection of iodized oil, iodization of drinking and irrigation water, and oral iodized oil capsules.[7-8] During that time, children of different ages intermittently faced varying degrees of iodine deficiency, and experienced delayed development of their intellectual capacity.

In 2006, after the discovery of younger children with endemic cretinism after 11 years of Universal Salt Iodization (USI),[9] the then Ministry of Health pressed the "Emergency Iodine Replacement Measures to be Taken in the Areas at High Risk of IDD" (Trial Implementation Opinions) (File: Health Office of Disease Control and Development [2008] No. 71) to implement a prevention and control strategy, of which USI was the core, with the addition of oral iodized oil capsules for key populations. The local government provided iodized salt free to poorer populations. Since 2010, Coverage of Iodized Salt has continuously met the National Standard for IDD Elimination (95%), and no more children with cretinism are found by local monitoring surveys.[10] The strategy based on adequate iodized salt assists Baicheng to realize sustained elimination of iodine deficiency disorders.[10]

Longitudinal observation of children's intellectual development over time is one of the most important methods to describe the effectiveness of iodine supplementation and prevention. However, this method must consider the effects of educational, economic, and social-environmental changes. The Flynn effect (FE) explains how intelligence is affected over time in an intergenerational population. FE is influenced by the rapid development of formal education, training in reasoning and abstract thinking, and environmental factors[11] and is related to the psychological tests used. The FE for the IQ points of the general IQ test increases by 3.1 points per decade, and the nonverbal test by 7 points.[12] After considering an FE gain of approximately 3 points per decade, one study estimated that salt iodization in the United States raised children's IQ in iodine-deficient areas by approximately 12 points.[13] In the present study, we used the Combined Raven's Test for Rural China (CRT-RC) five times

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during the past 30 years to assess the changes in the IQ development of schoolchildren aged 8-10 years in Baicheng. We analyzed FE gain using the normative data among the same age group in the rural areas in the CRT-RC data in 1987, 1996, and 2006. We also used the normative data of the rural population of the same age group in CRT-RC in 1987, 1996, and 2006 to analyze the FE gain and objectively assess the effect of the iodine supplementation strategy.

1. Objectives and methods

1.1 Subjects:

In 1989, 2002, 2006, 2012, and 2018, in Baicheng, a historical IDD area, Uyghur schoolchildren aged 8-10 years old were selected as survey respondents to observe changes in intellectual development using a clustered randomly sampling method. A total of 660 children were investigated. The male-to-female ratio was 1.17:1.00 (356:304). The study was approved by the Ethics Committee of Tianjin Medical University, and the surveyed group signed an informed consent form.

1.2 Intelligence assessment:

There were five investigation groups: 1989, 2002, 2006, 2012, and 2018. The unified CRT atlas was used, and the group test method was used for the assessment under the guidance of the investigators in the Uyghur language; all raw scores were based on the 1987 norm of CRT-RC to calculate the IQ value. When the IQ value was <54 points, they were all recorded as 54 points.

1.3 Iodine nutrition assessment:

The level of iodine nutrition of children was determined by the status of iodine deficiency during the period of their growth (IDG). IDG years were reviewed from the quiz year forward to 11 years IDG, because the age of the investigation subjects were all 8-10 years old, one year was added to the preparation and pregnancy period. The severity of iodine deficiency was based on three indicators, including household C-IS, average of total goiter rate (TGR) and median urinary iodine in children (mUIC) from multiple local monitoring data during the IDG period. IDG was assessed from these indicators, which described prevention and treatment, condition, and iodine nutrition respectively. According to the National Standard for the Elimination of Iodine Deficiency Diseases (GB 16006-2008), prevention and treatment indicators were judged based on C-IS ≥95%, and condition indicators were judged based on children aged 8-10 years old GR <5%; the iodine nutrition standard for the general population (including children) was adopted as the mUIC of 100~299μg/L recommended by UNICEF in 2018.[14-15] Three indicators of IDG did not meet the standard for complete exposure to iodine deficiency; all of them met the standard for non-exposure, and at least 1 met the standard for semi-exposure.

1.4 Calculation and correction of FE gain:

The raw data for children aged 8-10 from national normative data of CRT-RC version of 1987, 1996, and 2006 were transferred to IQ points according to the 1987 norm. FE gain was calculated according to the chronological difference between twice normative data (1987 and 1996, 1996 and 2006). The formula is: corrected IQ value = IQ points of starting year - IQ points of current year - FE gain.

1.5 Statistics:

SPSS24.0 software was used for statistics and analysis. If found to be normal distribution by the homogeneity of variance test with F value >0.05, quantitative data were described by x ±S. One-way ANOVA were used to analyze the difference of multiple groups, and further two-by-two comparisons were performed by LSD-t test. Quantitative data which did not conform to normal distribution were described by median (quartile). Qualitative data were described by rate (%). The value of p<0.05 was taken as the difference was statistically significant.


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2. Results

2.1 Intelligence assessment:

Comparison of IQ values of children aged 8-10 in the 1989, 2002, 2006, 2012 and 2018 groups showed statistically significant differences (F = 58.357, P<0.01). The IQ values of children in the 2006, 2012 and 2018 groups were significantly higher than those of the 1989 and 2002 groups, and the 2012, 2018 groups were significantly higher than the 2006 group (all P<0.01). (*Table 1*).

2.2 Results of iodine nutrition survey during the growth period of children:

For the groups of 1989, 2002, and 2006, the indicators of C-IS, GR, and mUIC during the assessment period of IDG did not reach the National Standard of IDD control and were judged to be full exposure to iodine deficiency. For the 2012 group, only mUIC reached the Standard and was judged to be semi exposure. For the 2018 group, all indicators reached the Standard and was judged to be control. (*Table 1*).

2.3 Calculation and correction of FE gain:

IQ values of normative samples of children aged 8-10 years from the data of CRT-RC norm of 1987, 1996, and 2006 were 100.00±15.48, 108.65±15.17 and 116.07±15.20 points respectively, with statistically significant differences in the comparison between the groups (F=164.93, p<0.01). The FE gain in IQ values was 0.96 points/year and 0.74 points/year for the 1987 vs. 1996 group and the 1996 vs. 2006 group, respectively.

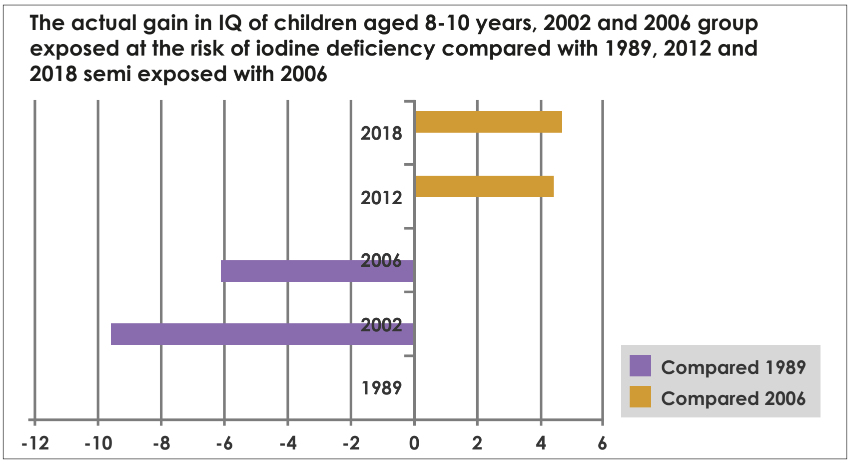
The correction of IQ value before 1996 was calculated with the FE gain of 0.96 points/year; after 1996, it was calculated with 0.74 points/year. The interval from 1989-2009 was the period of intermittent iodine supplementation, and the results of the IQ assessment were all based on the results of 1989 as the starting value. 2010-2018 was the period of sustainable and effective iodine supplementation, and the results of IQ assessment were based on the results of 2006 as the starting point. After correction of FE gain, the actual gain in IQ of children aged 8-10 years in 2002, 2006, 2012, and 2018 were -9.57, -6.11, 4.38, and 4.67 points, respectively.

Table 1: Intelligence and iodine nutritional assessment results of children aged 8-10 years in Baicheng, Xinjiang Uygur Autonomous Region in different years[26-29]

Year	N	IQ (x ± s)	Number of low intelligence (percentage, %)[a]	IDG Evaluation Timeframe	C-IS(%) M(P_{25}~P_{75})	TGR(%) M(P_{25}~P_{75})	UIC[µg/L, M(P_{25}~P_{75})
1989	72	81.67 ± 14.13	16 (22.22)	1978 – 1989	5.00[f]	29.14 (23.67~33.9)	-[g]
2002	94	83.26 ± 14.05	13 (13.83)	1991– 2002	44.8 (36.15~77.2)	32.06 (25.64~50.00)	78.05 (70.48~117.30)
2006	167	89.68 ± 13.58[bc]	3 (7.78)	1995 – 2006	60.00 (57.12~80.73)	26.60 (21.75~32.29)	90.10 (65.65~136.97)
2012	60	98.50 ± 4.33[bcd]	1 (1.67)	2002 – 2013	88.50 (61.00~96.53)	15.40 (2.53~28.08)	142.71 (72.35~211.82)
2018	267	103.23 ± 5.25[bcd]	6 (2.25)	2007 – 2018	97.30 (88.80~98.63)	1.67 (1.59~6.41)	208.59 (176.77~232.05)

Note: IQ: intelligence quotient;
IDG: status of iodine deficiency during children's growth;
C-IS: coverage of iodized salt;
TGR: goiter rate;
M is the median;
P25 and P75 are the 25th and 75th percentiles, respectively;
a: Low intelligence is defined as an IQ value of <69 points;
b: P<0.01 compared with the 1989 group;
c: P<0.01 compared with the 2002 group;
d: P<0.01 compared with the 2006 group;
e: There were emergency iodine supplementation measures in all 5 assessment time periods;
f: Only data were reported at one time during this assessment time period;
-: means no data available.

Figure 1: IQ improved and exposed at the risk of iodine deficiency



3. Discussion

Iodine is essential for the normal development of the brain in children, especially during brain plasticity, which is during gestation and for two years after birth.[4] The development of myelination is very closely related to intelligence, and it is due to myelination that children's performance in all areas improves, as demonstrated by animal experiments.[30] The process of myelination continues into adulthood, and also depends on the action of TH. Therefore, iodine intake is important during pregnancy and continuously during the child's entire growth period.

Baicheng is rich in rock salt (soil salt) resources, which are easily accessible and inexpensive. This, together with a need for greater awareness of the problem of iodine deficiency among its residents, has made it severely challenging to popularize iodized salt. Since the 1960s, Baicheng has been engaged in prevention and control of IDD, and large-scale surveys and iodine supplementation were carried out in 1972, 1978, 1983, 1990, and 1993, respectively, with the main measures including injection or oral iodized oil. Since then, measures have been taken to iodize drinking and irrigation water. By 2000, the local C-IS was 59%. These measures helped to prevent and control iodine deficiency during the period when the C-IS was difficult to increase. However, the effects fluctuated, as reflected in the fact that the IDGs were very unstable, and new cases of cretinism in children with cretinism were found.[9] Our research also showed that the IDG indicators, C-IS, TGR and mUIC of children in the 1989, 2002, and 2006 groups, did not meet the standards defined. However, although the absolute value of the IQ among children aged 8-10 years increased from 81.76 points in 1989 to 89.68 points in 2006, the IQ's value did not increase after correction by FE.

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After gradual implementation of the national policy in 2008, mUIC reached more than 100 µg/L, C-IS was more than 95% since 2010, and TGR was less than 5%. For children surveyed in 2012, the three indicators of IDG gradually improved from 2008 to the standard for IDD control in 2010. However, because the children were exposed to iodine deficiency for half of their growth period, after correction for FE gain, IQ values of children in the 2012 cohort were higher than those of children in the 2006 cohort by 4.38-points. Although children in the 2018 cohort may have received emergency iodine supplementation during pregnancy, they were still exposed to iodine-deficient environments for the first two years of life. Moreover, this period is a critical period for cognitive development, and there was a 4.67-point increase in IQ compared with the 2006 cohort, corrected for FE gain. This finding was lower than that of similar studies in the United States, mainly because the critical period of brain development was still affected by iodine deficiency, suggesting that it is necessary to continue to follow up and observe the study.

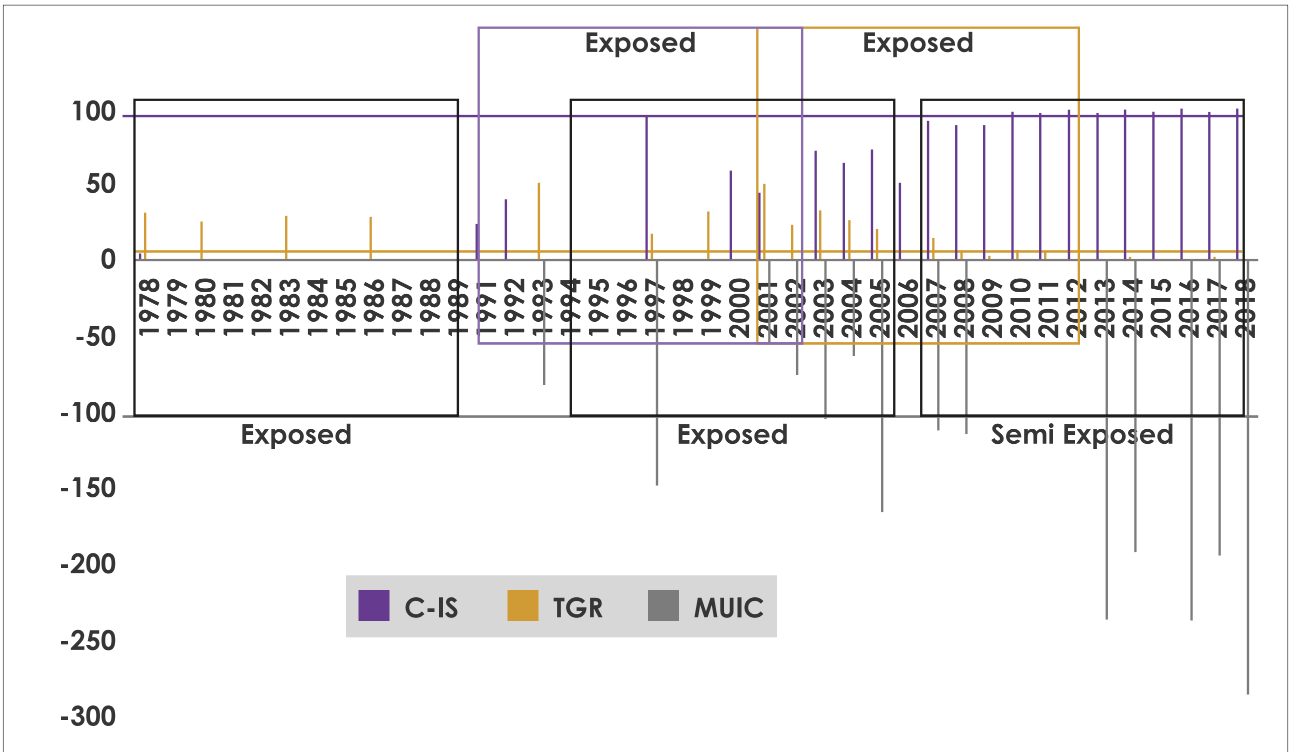
Factors affecting children's intellectual development include education, socioeconomics, and nutritional status. The current view is that FE arises mainly due to environmental factors, including formal education patterns, cultural and scientific enhancement, pre- and postnatal nutrition, childlessness, and increased environmental complexity, which improve people's ability to engage in complex thinking and problem solving. The CRT is a culturally fair (culture-fair test) and nonverbal test that measures fluid intelligence, biased toward testing problem-solving skills.[11] General tests are more dependent on what is learned, and FE gain is lower than that of CRT-type tests, 0.31 points/year.[12] Flynn's[31] analysis of 14 national IQ tests showed an FE gain of 0.588 (0.181 ~ 1.250) when CRT was used. It has been proven that FE does continue to grow, but has a pattern of fast and then slow growth, and when the environment is suitable, will quickly reach the average curve and then will plateau and not grow endlessly.[32]

Therefore, the effectiveness of iodine supplementation still needs to be examined despite the 21.56-point increase in the absolute value of children's IQ in 2018 compared to 1989. Before 2010, children's IDG indicators were not fully met, and prevention and treatment measures were intermittent. In 2006, there was an 8.01-point increase in the absolute value of children's IQ compared with that in 1989, but the actual change was negative after corrected by the FE gain. After realization of sustained and effective iodine supplementation in 2010, IQ values were all positive after corrected by the FE gain, compared with the results in 2006.

This study is still limited by some factors. The samples in the CRT-RC norm are from Han Chinese population, which may have some influence on the magnitude of FE gained due to different cultures and thinking. The collection of IDG ratings was also limited to the status of iodine supplementation during the growth period of the children, which may have relied too much on the results of the data and did not clarify whether emergency iodine supplementation was received during pregnancy or not, and also on the individual's iodine nutritional. Sample sizes in some years were not large enough. At the same time, it was not observed that the brain development of children protected by adequate iodine nutrition during the whole growth period of IDG, and it is still valuable to continue to observe the intellectual development of local children.

In summary, continuous effective iodine supplementation, which can be achieved only through salt iodization may benefit children's intellectual development more positively than intermittent iodine supplementation strategies during their growth.

Figure 2: IDG



Notes

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