ANALYSIS OF CHILDREN'S SERUM FLUORIDE LEVELS IN RELATION TO INTELLIGENCE SCORES IN A HIGH AND LOW FLUORIDE WATER VILLAGE IN CHINA

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SUMMARY: As part of a 2002-2003 investigation on the effects of high fluoride drinking water on IQ scores of children, serum fluoride (F) levels in the children were subjected to further study. Among the new findings, although IQ scores of boys and girls differed in the seven IQ level categories, there were no overall gender differences (boy/girl ratio 1.220 vs. 1.214 in the high and low F villages, respectively). However, the mean IQ was significantly higher and there were fewer children with an IQ less than 80 in the two quartiles with a serum fluoride level of less than 0.05 mg F/L. Analysis of the overall relationship between IQ scores and serum F levels indicates there may be no serum F level below which adverse effects on IQ might not be present.

Keywords: Children in China; Fluoride in serum; Fluoride in water; Intelligence quotient.

INTRODUCTION

Following our 2002–2003 study on children's IQ scores in a high and low fluoride (F) water village in China,[1,2] we presented in 2005, at a conference of the International Society for Fluoride Research, a report on serum F levels of the children in that study.[3] In a recent critical review, urinary and serum F levels associated with neurotoxicity were proposed to be of value in assessing whether or not there is a threshold for this adverse effect.[4] In our 2005 report, we noted that the mean serum F was 0.081±0.019 mg/L in the children living in the high F village of Wamiao in Jiangsu Province (mean water F 2.47±0.79 mg/L, range 0.57–4.50 mg/L) and in the low F village of Xinhuai it was 0.043±0.009 mg/L (mean water F 0.36±0.11 mg/L, range 0.18–0.76 mg/L).[3] The regression coefficient between serum F and children's IQ was –0.163 ($p = 0.015$) in high F Wamiao and 0.054 ($p = 0.362$) in low F Xinhuai. The relationship between serum F and drinking water F had a highly significant Pearson correlation coefficient of 0.860 ($p < 0.001$). The Bench Mark Concentration (BMC) and the lower bound confidence limit of the BMC (BMCL) of serum F concentration were 0.077 mg/L and 0.064 mg/L, respectively.

When the data from all 512 children in the two villages were combined and divided into subgroups according to the level of the serum F, we found that Intelligence Quotient (IQ) scores below 80 were significantly associated with higher serum F concentrations. However, we did not report the serum F levels used for defining the subgroups. This information, together with serum F levels by gender, is given in the present communication.

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MATERIALS AND METHODS

The study design has been published in detail.[1] Here, in brief, among 512 children aged 8–13, who did not differ in their urinary iodine or blood lead levels, the IQ scores and serum F were measured in the high F village of Wamiao (n = 222), and the low F village Xinhuai (n = 290).[1-3] IQ was measured with the Combined Raven's Test for Rural China (CRT-RC). A fasting venous blood sample (2–2.5 mL) was obtained from each child and preserved in a clean plastic centrifuge tube, which was immediately centrifuged at 3,000 r/min for 10 min. The serum was removed to another clean plastic tube and kept in a refrigerator (–40ºC), and was subsequently analyzed within 1 week. F levels in serum were measured with a F ion selective electrode. The 512 subjects were classified into quartiles according to the serum level of F. To compare differences in categorical variables and to analyze differences in continuous variables among groups, we used the chi-square test. For association between serum F levels and the risk of low IQ, we used logistic regression models, adjusting for age and sex. In the logistic regression, first and second quartiles of serum F were combined and used as the reference group. Tests of linear trends across different levels of serum F were computed using ordinal scoring. Values were considered significant when $p<0.05$ (two sided). The analyses were performed using STATA software (version 9; StataCorp, College Station, TX, USA) and SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA).

Before the investigation, written informed consent was obtained from the children's parents. The study was approved by Jiangsu Provincial Center for Disease Control and Prevention, and School of Public Health, Fudan University.

RESULTS AND DISCUSSION

As reported earlier, the IQ scores of the boys and girls in each of the two villages differed in the various IQ level categories, but the overall ratios were essentially identical for the high and low F villages (1.220 and 1.214, respectively).[1] Moreover, no gender differences in serum F were detected (Table 1).

Table 1. Serum fluoride in children in high F Wamiao and low F Xinhuai (Mean±SD)

Village	Male		Female		Total	
	N	Serum F mg/L	N	Serum F mg/L	N	Serum F mg/L
Wamiao	123	0.080±0.016*	99	0.081±0.022*	222	0.081±0.019*
Xinhuai	159	0.043±0.009	131	0.040±0.009	290	0.041±0.009

*p<0.001 compared with Xinhua, Mann-Whitney Test.

However, the mean IQ was significantly higher and there were fewer children with an IQ less than 80 in the two quartiles with a serum fluoride level of less than 0.05 mg F/L (Table 2).

Table 2. Association between serum F and children's IQ[a]

Serum fluoride level quartiles	N	Mean IQ	SD IQ	p[b]	IQ<80 (%)	p[c]	OR (95% CI) for IQ<80
Q1 and Q2 (<0.05 mg/L)	259	100.1	13.4	<0.001	7.0		1
Q3 (0.05–0.08 mg/L)	126	95.9	13.7		15.1	0.004	2.22 (1.42–3.47)
Q4 (>0.08 mg/L)	127	92.1	13.4		17.3		2.48 (1.85–3.32) p trend<0.001[d]

[a]Adjusted for age and gender using Logistic regression analysis. The data from two villages were combined.
[b]NOVA.
[c]Chi-square test.
[d]Tests of linear trend were computed using ordinal scoring.
Abbreviations: CI Confidence Interval, IQ Intelligence Quotient, OR Odds Ratio, SD Standard Deviation.

Serum F concentration has been recognized as a reliable indicator of F exposure and is also used as one of the biomarkers to assess the effect of endemic fluorosis control and prevention.[5-8] The literature, however, contains a wide range (0.4–2.4 µmol/L, 0.0076–0.046 mg/L) of measures defining "normal" plasma serum F concentration. The large differences in these values may in part be attributable to testing fasting individuals in some studies and nonfasting in others.[9] Currently, there appears to be no cut-off point of serum F that is considered acceptable by WHO or various academic organizations.[8,10]

The reference value for serum F concentration (RfC) is given by the equation

$$\text{RfC} = \frac{\text{BMCL}}{\text{UF} \times \text{MF}}$$

where UF is an uncertainty factor and MF a modifying factor. In the abstract of our study published in 2005 we chose the value of 1 for both the uncertainty factor and the modifying factor, thereby giving a reference value concentration (RfC) of serum F, among children aged 8–13 of 0.064 mg/L. However, a recent review considered that in order to allow for the large within- and between-subject variations in F absorption, the differences in water consumption by individuals, and the presence of factors that increase the sensitivity to F toxicity such as low iodine levels, a safety or uncertainty factor of 10 is indicated for determining the appropriate serum F level in a population.[4] Applying this factor to our study gives a RfC of serum F among children aged 8–13 of 0.0064 mg/L. However, it is not possible to determine from our study whether this is a true threshold below which no F neurotoxicity can occur, and an analysis of the study by Ding et al.[11] suggests that the only assuredly safe level of F in drinking water is zero.

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