DEVELOPMENT OF FLUORIDE TOXICITY INCLUDING COGNITIVE IMPAIRMENT WITH REDUCED IQ: PATHOPHYSIOLOGY, INTERACTIONS WITH OTHER ELEMENTS, AND PREDISPOSING AND PROTECTIVE FACTORS

ABSTRACT: The development of toxicity to the fluoride ion (F) may be complex and multifactorial with a number of pathophysiological pathways being possible, with the potential for interactions between toxins involving additivity, synergism, and antagonism, and with a number of other factors having predisposing and protective effects. In addition to cognitive impairment with a reduced intelligence quotient (IQ) in children developing through other mechanisms such as disturbed thyroid hormone metabolism and sonic hedgehog signalling, other pathophysiological factors such as reduced brain glucose uptake following a fluoride-induced reduction in insulin secretion may contribute. Environmental contamination with cadmium in a coal combustion fluorosis-affected rural area within China's Three Gorges region may contribute to the dental and skeletal health problems in the population and the possibility of interactions between Cd and F affecting cognitive functioning requires further investigation. The propensity for the development of toxicity to F may involve interactions with a number of other factors as well as the levels of F exposure.

Two notable papers in this issue of Fluoride by Lombarte et al.,1 with the first report of the measurement of insulin secretion in vivo in rats following the administration of the fluoride ion (F), and by Olszowski et al.,2 with the first review on the combined toxicity of F and cadmium, have both drawn attention to the lowered intelligence quotient (IQ) in children living in endemic fluorosis areas. Lombarte et al.1 noted that in endemic fluorosis areas children had a lower IQ than children of areas with low F in drinking water.3,4 This decrease in IQ has also been observed in rats,1,5 and is associated with decreases in brain weight, succinate dehydrogenase activity,1,6 concentration of neurotransmitters (norepinephrine, epinephrine, and serotonin) in the spinal cord,1,7 and nicotinic acetylcholine receptor expression level.1,8

Olszowski et al.2 observed that Choi et al. conducted a systematic review and meta-analysis of published studies to assess the effect of exposure to F on children’s neurodevelopment.9 The authors included 27 eligible epidemiological studies in their meta-analysis.2,9 They found the standardized weighted mean difference in IQ scores between the exposed and the reference populations of children, across studies that gave the average difference in standard deviations (SDs), was −0.45 SDs (95% CI: −0.56, −0.35) using a random-effects model, which means that children living in areas with a high F exposure had significantly lower IQ scores as compared to children living in low-F areas.2,9,10 For commonly used IQ scores with a mean of 100 and a SD of 15, 0.45 SDs is equivalent to 6.75 points (rounded to 7 points).2,10 The results therefore showed an average IQ decrement of about 7 points in children with increased F exposure2,10 and point to the possibility of adverse effects of F exposure on children’s neurodevelopment.2,9 Olszowski et al. commented that such result also raises questions about the legitimacy and safety of drinking water fluoridation in some areas of the world.2
Lombarte et al. measured the glucose uptake rate of insulin-independent tissues, insulin secretion, and insulin clearances in vivo in rats that received a dose of F. A lower secretion and clearance of insulin were found in the animals that received F. In addition, a decrease in glucose uptake rate from insulin-independent tissues was observed. This glucose uptake is mainly the glucose consumed by the nervous system. As a consequence, this decrease could be associated with the effect of fluoride on IQ. They hypothesized that F decreases oxygen consumption because of a deficit in the respiratory chain. This could lead to a decrease in the formation of ATP and an increase in reduced NADH, which determines a cytosolic decrease in oxidized NAD and therefore an inhibition of glyceraldehyde-3-P dehydrogenase by lack of oxidized NAD. This decrease in the availability of oxidized NAD would cause a decrease in glycolysis, generating an increase in glucose-6-phosphate that inhibits hexokinase-I. As the entry of glucose into brain is performed by the GLUT-3 glucose transporter which has a low K_m value (1–2 mM), the uptake of glucose by the brain would be limited by the activity of the hexokinase-I enzyme. This metabolic disturbance leads to decreased brain glucose consumption, which could be the cause of the decline of the IQ. In animals treated with F a decrease in the parameter k_3 (which represents the consumption of glucose independent of insulin, mainly in the nervous system) was observed and this supports this metabolic hypothesis.

In their review, Olszowski et al., found that various types of combined toxicity of Cd and F might occur in the liver, kidney function, bone, teeth including dental caries, and the brain: additive, synergistic, or antagonistic, with the latter two being true interactions. However, the type of combined action occurring seems to depend on many factors, such as which toxic effect is considered, the dose levels of Cd and F and their dose ratio, exposure duration, and the presence of other elements, etc. Moreover, when analyzing the combined toxic effects of F and Cd, the possible interactions of these toxicants with other elements (e.g., F with aluminum and arsenic, Cd with lead, arsenic, zinc, selenium, and calcium) should also be taken into consideration. In addition, they could not exclude the independent action of F and Cd on some selected functions/health outcomes. Due to the huge gaps in knowledge available at present, they considered that additional studies are required to address the important public health issue of the combined effects of exposure to these common environmental toxicants, especially among people with a high exposure to them.

Cognitive impairment with reduced IQ due to fluoride exposure in children can be considered to be one of the fluoride-induced developmental disorders (FIDD). Whether or not one of the FIDD or another form of fluoride toxicity occurs in a particular situation depends not only on the level and duration of the fluoride exposure but also on the presence of predisposing and protective factors including: (i) species differences: e.g., the two species of tadpoles studied by Chen et al. differed in their susceptibility to developing flexural tail deformity and increased bone mineralization which appeared to be related to the longer time required for the R. chensinesis tadpoles to metamorphose into frogs (up to 100 days after fertilization) compared to the R. nigromaculata tadpoles (7–8 weeks.
after fertilization); (ii) genetic differences: e.g., catechol-O-methyltransferase (COMT) polymorphism affects the vulnerability to F-induced cognitive impairment; higher fluoride exposure was associated with a steeper cognitive decline among children with the reference allele Val compared with those homozygous or heterozygous for the variant allele Met; (iii) water hardness, water calcium and magnesium levels, and dietary intake of cations: e.g., in spite of identical concentrations of fluoride in water, variations in the incidence of skeletal fluorosis occurred due to the protective effect of higher water levels of magnesium, calcium, and total hardness; natural calcium fluoride with low solubility and toxicity from ingestion is distinct from fully soluble toxic industrial fluorides; the toxicity of fluoride is determined by environmental conditions and the positive cations present; dietary cations, such as calcium and iron, retard the absorption of fluoride from the gastrointestinal tract by forming complexes which are poorly absorbed; (iv) dietary intake of vitamins, antioxidants, and selenium: e.g., vitamin C, vitamin E, and other antioxidants, from fruits and vegetables, are seen to be able to protect against fluoride poisoning and fluorosis; selenium can improve mitochondrial membrane stability and protect against fluoride toxicity in skeletal muscles although at higher levels selenium is synergistic with fluoride and arsenic in causing toxicity; (v) dietary intake of iodine and dietary goitrogens: e.g., both high fluoride and low iodine levels may adversely affect the IQ but the combination may have a greater negative effect than either alone, particularly at an early stage of embryo and infant development when differentiation of brain cells is occurring and development is most rapid; dietary goitrogens such as cyanogenic glucosides, which are metabolised to thiocyanates, glucosinolates, whose metabolites compete with iodine for thyroidal uptake, and flavonoids, which impair thyroid peroxidase activity, may adversely affect the ability of the thyroid to synthesize thyroxine and thus increase the sensitivity to fluoride toxicity; (vi) exposure to other toxic chemicals and drugs: e.g., interactions may occur between fluoride and other chemicals, such as lead and arsenic, resulting in greater toxicity; two hundred and six chemicals other than fluoride have been identified as causing developmental neurotoxicity in humans and a further 1000 have been reported to be neurotoxic in animals in laboratory studies; and (vii) altitude: e.g., a significant relationship has been found between altitude and dental fluorosis; a prevalence of dental fluorosis of 93% was found in secondary school students in Koohbanan, situated at 2000 m above sea level.

Thus, the development of toxicity to fluoride may be complex and multifactorial with a number of pathophysiological pathways being possible, with the potential for interactions between toxins involving additivity, synergism, and antagonism, and with a number of other factors having protective or predisposing effects. In addition to cognitive impairment with reduced IQ in children developing through other mechanisms such as disturbed thyroid hormone metabolism and sonic hedgehog signalling, other pathophysiological factors such as reduced brain glucose uptake following a fluoride-induced reduction in insulin secretion may also contribute. Environmental contamination with cadmium in a coal combustion
fluorosis-affected rural area within China’s Three Gorges region may contribute to the dental and skeletal health problems in the population and the possibility of interactions between Cd and F affecting cognitive functioning requires further investigation. The propensity for the development of toxicity to F may involve interactions with a number of other factors as well as the levels of F exposure.

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