

Autism: Transient *in utero* hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents

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Abstract

The incidence and prevalence of autism have increased during the past two decades. Despite comprehensive genetic studies the cause of autism remains unknown. This review emphasizes the potential importance of environmental factors in its causation. Alterations of cortical neuronal migration and cerebellar Purkinje cells have been observed in autism. Neuronal migration, *via* reelin regulation, requires triiodothyronine (T3) produced by deiodination of thyroxine (T4) by fetal brain deiodinases. Experimental animal models have shown that transient intrauterine deficits of thyroid hormones (as brief as 3 days) result in permanent alterations of cerebral cortical architecture reminiscent of those observed in brains of patients with autism. I postulate that early maternal hypothyroxinemia resulting in low T3 in the fetal brain during the period of neuronal cell migration (weeks 8–12 of pregnancy) may produce morphological brain changes leading to autism.

Insufficient dietary iodine intake and a number of environmental antithyroid and goitrogenic agents can affect maternal thyroid function during pregnancy. The most common causes could include inhibition of deiodinases D2 or D3 from maternal ingestion of dietary flavonoids or from antithyroid environmental contaminants. Some plant isoflavonoids have profound effects on thyroid hormones and on the hypothalamus–pituitary axis. Genistein and daidzein from soy (*Glycine max*) inhibit thyroperoxidase that catalyzes iodination and thyroid hormone biosynthesis. Other plants with hypothyroid effects include pearl millet (*Pennisetum glaucum*) and fonio millet (*Digitaria exilis*); thiocyanate is found in Brassicaceae plants including cabbage, cauliflower, kale, rutabaga, and kohlrabi, as well as in tropical plants such as cassava, lima beans, linseed, bamboo shoots, and sweet potatoes. Tobacco smoke is also a source of thiocyanate.

Environmental contaminants interfere with thyroid function including 60% of all herbicides, in particular 2,4-dichlorophenoxyacetic acid (2,4-D), acetochlor, aminotriazole, amitrole, bromoxynil, pendamethalin, mancozeb, and thioureas. Other antithyroid agents include polychlorinated biphenyls (PCBs), perchlorates, mercury, and coal derivatives such as resorcinol, phthalates, and anthracenes. A leading ecological study in Texas has correlated higher rates of autism in school districts affected by large environmental releases of mercury from industrial sources. Mercury is a well known antithyroid substance causing inhibition of deiodinases and thyroid peroxidase. The current surge of autism could be related to transient maternal hypothyroxinemia resulting from dietary and/or environmental exposure to antithyroid agents. Additional multidisciplinary epidemiological studies will be required to confirm this environmental hypothesis of autism.

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1. Introduction

The Centers for Disease Control and Prevention (CDC) estimate at half million the number of individuals with autism and autism spectrum disorders in the United States [1]. From a prevalence of 0.4 to 1/1000 children aged 8 years in the 1980s,

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