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THE THYROID-AUTISM CONNECTION: THE ROLE OF ENDOCRINE DISRUPTORS

BY RAPHAEL KELLMAN, MD

We are experiencing a wide range of environmentally induced diseases. Autism and hypothyroidism are two such diseases becoming epidemic in scope. A growing body of research indicates that autism and hypothyroidism are indeed connected. Yet routine blood tests frequently miss this connection.

Hypothyroidism and autism are today strongly associated with the increasing burden of environmental toxicity. Both the brain and the thyroid are very susceptible to environmental toxins. Is there a connection between

hypothyroidism and autism? The latest studies point to endocrine-disrupting chemicals (EDCs) as likely major causative or contributory factors in any such connection. This article lays out the details.

HAVE ASDS BECOME EPIDEMIC IN THE US?

An article in *Environmental Health Perspectives* in 2006 noted that since the early 1990s alone, reported cases of autism spectrum disorders (ASDs) have increased tenfold. The Centers for Disease Control and Prevention (CDC) now estimates that 1 in 110

US eight-year-olds has an autism spectrum disorder, with an increase of 57% between 2002 and 2006. This affects an estimated 3-8% of the 4 million babies born in the US each year. A 2009 study in the *Journal of Pediatrics* revealed similar numbers. Autism is the fastest growing developmental disability in the US, affecting more children than cancer, diabetes, and AIDs combined.

HAS THYROID DISEASE BECOME EPIDEMIC IN THE US?

Thyroid disease is the most common endocrine disorder (defined as a problem affecting the hormone glands) in the US. An estimate based on statistics gathered by the American Association of Clinical Endocrinologists (AACE) indicates that approximately 27 million Americans—as much as seven to eight percent of the population—have some form of thyroid disorder. (According to this estimate, roughly half of these cases remain undiagnosed.)

Approximately eight out of ten thyroid disease cases (80%) are hypothyroid conditions (low or underactive thyroid), with the other two out of ten (20%) being hyperthyroid conditions (high or overactive thyroid). Women constitute about 80% of Americans with thyroid disease, and women are five times more likely than men to develop hypothyroidism.

Thyroid *autoimmune* disease (as distinct from thyroid disease) is the most common autoimmune disease in the US.¹ Because only one-third of those with thyroid autoimmune disease are diagnosed, the actual number may be 72 million Americans.²

HOW THE THYROID WORKS

The function of the thyroid is very important to overall health. Thyroid hormone is responsible for the energy production and metabolism of every cell in the body, including the brain. It is a critical hormone for brain development. Thyroid-

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stimulating hormone (TSH) is produced in the brain by the pituitary, which stimulates the thyroid to produce hormones such as T4 (thyroxine) and T3 (triiodothyronine). When a sufficient amount of hormone is produced by the thyroid, then the T4 and T3, in a feedback loop, tell the pituitary to stop producing TSH (or to slow it down). When there is a low amount of thyroid hormone (TH) in the blood, T4 and T3 tell the pituitary to start producing more TSH. The thyroid is very vulnerable to environmental toxins.

EVIDENCE SUPPORTING A THYROID-AUTISM CONNECTION

A number of strands of evidence support a link between hypothyroidism and autism, including research on brain development, gluten sensitivity, methylation defects, and mitochondrial dysfunction.

THE CRUCIAL ROLE OF THYROID HORMONE IN BRAIN DEVELOPMENT

Thyroid hormone is essential for brain development during a period beginning *in utero* and extending through the first 2 to 3 years of life. Deficiencies in thyroid hormone during this crucial period can have significant behavioral and cognitive effects; many of the same symptoms are also associated with ASD.

Normally, thyroid hormone regulates neuronal proliferation, migration, and differentiation in discrete regions of the brain during definitive time periods. Thyroid hormone also normally regulates development of cholinergic and dopaminergic neurons in the brain.

GLUTEN SENSITIVITY

Celiac disease and gluten sensitivity are factors known to contribute to autism. Gluten antigen, similar to an antigen in the thyroid, also can provoke autoimmune thyroid disease.³ Numerous studies confirm the strong link between gluten intolerance and autoimmune hypothyroidism.^{4,5} In a 2000 study,⁴ for example, researchers observed an association between untreated celiac disease, gluten intake, and autoimmune disorders. They reported, "We believe that undiagnosed celiac disease can cause other disorders by switching on some as yet unknown immunological mechanism. Untreated celiac patients produce organ-specific autoantibodies."

One of the most effective therapies for ASDs and PDD is a gluten-free (GF) diet. A gluten-free diet also can help heal an underlying thyroid disorder, as noted by the authors of the 2000 study just



mentioned,⁴ who observed that the organ-specific antibodies "disappeared after 3 to 6 months on a gluten-free diet." This may be one of the reasons why the GF diet is so effective in children with autism.

METHYLATION DEFECTS

Hypothyroidism can contribute to methylation defects. T4 and T3 are tyrosine-based hormones that are primarily responsible for regulation of metabolism. T4 regulates the conversion of riboflavin to FAD (flavin adenine dinucleotide). Composed of riboflavin 5'-phosphate and adenosine 5'-phosphate, FAD serves as an electron carrier by being alternately oxidized (FAD) and reduced (FAeH2). It is important in electron transport in the mitochondria.⁶

With hypothyroidism, conversion of riboflavin to FAD and MTHFR (methylenetetrahydrofolate reductase) is impaired.⁶ MTHFR is the name of a gene that produces an enzyme, also called methylenetetrahydrofolate reductase. In an individual with a genetic mutation that inhibits production of this enzyme, the mutation can lead to hyperhomocysteinemia, a condition in which elevated levels of an enzyme called homocysteine are found in blood plasma. When the body is deficient in MTHFR, its ability to absorb folate (vitamin B9 and folic acid, for instance) is inhibited. Folic acid and B9 are both essential to the development and health of the fetus. Genetic variation in the MTHFR gene also increases susceptibility to acute leukemia, colon cancer, neural tube defects, and occlusive vascular disease. Mutations in this gene are associated with MTHFR deficiency.

MITOCHONDRIAL DYSFUNCTION

Hypothyroidism can cause mitochondrial dysfunction, and mitochondrial dysfunction, in turn, has been found to be associated with autism. A 2010 study by researchers at the University of California found that cumulative damage and oxidative stress in the mitochondria could influence the onset and severity of autism.⁷ This

study observed that mitochondrial dysfunction in autistic children appeared to decrease NADH (nicotinamide adenine dinucleotide) and increase oxidative stress. NADH, which is an activated form of the B vitamin niacin, behaves as a coenzyme that helps in energy extraction. It also enhances the immune system, fights disease, and repairs damage caused by the disease.⁷ The researchers also observed over-replication or deletion of mitochondrial DNA in these children: "Whether the mitochondrial dysfunction in children with autism is primary or secondary to an as yet unknown event," remarked the researchers, "remains the subject of future work; however mitochondrial dysfunction could greatly amplify and propagate brain dysfunction, such as that found in autism."⁷

An earlier paper, published in 2003, found that hypothyroidism alters mitochondrial morphology and induces release of apoptogenic proteins.⁸ We know that TH deficiency can lead to extensive apoptosis (programmed cell death) and that adequate levels of TH maintain mitochondrial architecture and inhibit release of apoptogenic molecules to prevent excess apoptosis during cerebellar development. A review article published in the *Journal of Molecular Endocrinology* in 2001 on TH action in mitochondria discussed, among other things, TH regulation of mitochondrial activity as a link between metabolism and development.⁹



BRAIN DEVELOPMENT: FURTHER CONSIDERATIONS

Before and after birth, thyroid hormone development is characterized by three distinct phases.

PHASE I. The fetus is dependent on maternal TH during the first trimester of pregnancy. Fetal

synthesis of TH takes place after the first trimester. Also during the first trimester, neurons which will develop into the forebrain proliferate, migrate, and differentiate – TH orchestrates all this activity.

PHASE II. During the second phase, the fetus produces its own TH, which then chiefly orchestrates development. Maternal TH still plays a role. Neurons which develop into the cerebellum proliferate, migrate, and differentiate. The forebrain matures. Synapses are formed.

PHASE III. After birth, the infant's TH, acting figuratively as a time clock, stimulates and subsequently terminates brain cell proliferation, migration, and differentiation. Thyroid hormones orchestrate these events at the precise time with the precise dose and in the correct sequence.^{10,11}

Maternal thyroxine (T4) plays a pivotal role in fetal brain development. Iodine is necessary for TH production,¹² and iodine deficiency is related to low levels of T4, a condition known as hypothyroxinemia. Where maternal T4 levels are low normal (0-10th percentile) and maternal iodine is deficient from early gestation to birth, there is an increased risk of neurodevelopmental delay in the offspring.¹³ The main developmental delays resulting from mild hypothyroxinemia are lower performance in gross and fine motor coordination and poorer performance in socialization. An increase in the incidence of autism is also associated with increased iodine deficiency.

According to Grandjean and Landrigan,¹⁴ “The blood-brain barrier, which protects the adult brain from many toxic chemicals, is not completely formed until about 6 months after birth.” These same authors further point out that “The human brain continues to develop postnatally, and the period of heightened vulnerability therefore extends

over many months, through infancy and into early childhood. Although most neurons have been formed by the time of birth, growth of glial cells and myelination of axons continues for several years.”¹⁴

The symptoms of low thyroid function in the fetus and newborn are similar to the symptoms associated with ASD and ADHD.¹⁵ These include:

- general developmental delays
- cognitive dysfunction
- hyperactivity
- attention disorders
- speech delays
- hypotonia/fine motor dysfunction
- repetitive behavior
- social and communication dysfunction

ENDOCRINE-DISRUPTING CHEMICALS (EDCS), AUTISM AND THE THYROID

According to the Environmental Protection Agency (EPA), an EDC is an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and responsible for homeostasis, reproduction and developmental processes. These chemicals disrupt the body's communication network in three main ways:

1. They block or mimic hormone messages.
2. They scramble the signals in these messages.
3. By “sowing misinformation,” they fool the endocrine system into accepting new (but incorrect) instructions.

In cancer, one can say “the dose makes the poison,” meaning that the duration or concentration of

exposure to a toxic substance is mainly responsible for development of the illness. EDCs play by different rules. Here, one can say, “the timing makes the poison.” Thyroid hormones secreted at the right time and in the right dose orchestrate the process of neurological development. In other words, neurological development is like a chemical ballet, dependent on the right hormone message being sent and received at precisely the right time and in the right amount. This ballet opens windows of vulnerability. If exposure to an EDC occurs at one of these vulnerable moments, abnormalities can result. During this critical period, even low doses of EDCs, which may have little effect on adults, can have devastating effects on the unborn, neonate, and child.

Many of the endocrine-disrupting chemicals that are associated with autism also cause thyroid disease. Further, many of the chemicals that contribute to autism mediate their effects through adverse action on the thyroid. Toxins with endocrine-disrupting effects include PCBs, dioxins, perchlorate, phthalates, PBDEs, lead, mercury, cadmium, insecticides, and bisphenol-A.¹⁶ The neurodevelopmental effects of thyroid disruption by EDCs may include learning disabilities, behavioral problems, fine motor dysfunction, poor response to stress, attention problems and hyperactivity, language and speech deficits, and social development deficits.^{10,11} Other effects on neurodevelopment in infants and children include visual-spatial deficits, visual and motor delays, decreased social and perceptual abilities, and decreased auditory discriminating abilities.¹⁷

Thyroid-disrupting chemicals operate through multiple mechanisms. Moreover, the different effects of endocrine disruptors on the thyroid can create cumulative and/or synergistic effects,¹⁸ and different toxins can cause multiple “hits” at different points in the thyroid hormone signaling system (see Table 1).

Table 1. Effects of EDCs on the thyroid

Endocrine-disrupting chemicals	Effects on thyroid hormone signaling system
Chlorinated pesticides, mercury, PBDEs, PCBs, dioxins/TCDD	Direct toxic effect on thyroid gland
Amitrole, benzophenone, Mancozeb	Blocked production of thyroid hormone
Bisphenol A (BPA), dioxins, flame retardants, PCBs, phthalates	Binding to thyroid receptor
Flame retardants, PCBs, pentachlorophenol, phthalates	Competitive binding to thyroid transport protein (TTR)
DDT, PCBs	Effects on TSH receptor
Bromates, perchlorates, phthalates, thiocyanates	Blocked iodide uptake
Cadmium, C red dye #3, HCB, lead, mercury, octylmethoxycinnamate, PBDEs, PCBs	Inhibiting of deiodinases
Acetochlor, PBDEs, PCBs	Enhanced hepatic metabolism

As shown in Table 1, there are a large number of EDCs exerting a wide variety of effects on the thyroid. Several EDCs warrant a more detailed look.

BISPHENOL A (BPA)

BPA is a monomer of polycarbonate plastics, which inhibits thyroid hormone receptor-mediated transcription by acting as an antagonist. In transient gene expression experiments, BPA suppressed transcriptional activity stimulated by thyroid hormone (T3) in a dose-dependent manner.¹⁹

DIOXINS

Widespread, persistent, and highly toxic, dioxins are produced through industrial burning processes and production of herbicides. TCDD is the dioxin prototype and the most toxic. A single dose of TCDD in rats dose-dependently decreased T4 and free T4 and increased TSH.²⁰ In offspring of rats, a single dose of TCDD to the dam during gestation correlated to decreased T4, caused a twofold increase in TSH, and caused hyperplasia of the thyroid gland.²¹ In humans, a large study of Vietnam veterans detected a significant increase in TSH in the group with the highest TCDD levels.²²

In a 1993 study,²³ both PCBs and dioxins were found in high levels in breast milk and were associated with hypothyroidism in both mothers and newborns. This study also found inhibition of enzyme 5-deiodinase, decreased conversion of T4 to T3, and decreased nuclear T-3 receptor occupancy. In the pituitary gland, decreased nuclear T-3 occupancy stimulated TSH secretion.

PBDES

Polybrominated diphenyl ether is used as a flame retardant in plastics, paints, electrical equipment

and synthetic textiles. A report published in *Toxicological Sciences* in 2001 found that in rats that were weaning, a commercial PBDE mixture (DE-7) decreased levels of TH and induced activity of hepatic enzymes UDPGT. High doses of DE-7 caused histopathological changes.

PCBS

Polychlorinated biphenyls (PCBs) are synthetic environmental toxins with a striking structural resemblance to active thyroid hormones. Boas and colleagues describe the effects of PCBs as follows:²⁴

There is substantial evidence that polychlorinated biphenyls, dioxins and furans cause hypothyroidism in exposed animals, and that environmentally occurring doses affect human thyroid homeostasis. Thyroid disruption may be caused by a variety of mechanisms as different chemicals interfere with the hypothalamic-pituitary-thyroid axis at different levels. Growth and development in fetal life and childhood is highly dependent on normal levels of TH (thyroid hormone). Normal levels of THs are crucial for the development of the central nervous system. This critical phase may be vulnerable to even subtle effects of synthetic chemicals. Such developmental deficiencies may not be identifiable until late in life.

There is a negative correlation between maternal total T3 and PCBs, as well as with three pesticides (p'-DDE, cis-nonachlor, hexachlorobenzene) and inorganic mercury at low levels of exposure. PCBs have a positive correlation to fetal TSH²⁵ and TSH levels in children.²⁶ As noted above, PCBs also interfere with the hypothalamic-pituitary-thyroid (HPT) axis by producing a subnormal response of the pituitary to TRH stimulation.²⁷ In adults, adolescents and children from areas highly exposed to PCBs, PCB levels correlate negatively to TH levels.²⁸

In studies of breast milk, there is a positive association between PCB levels in breast milk and TSH levels in infants.²⁹ In Taiwan, a 1988 study of women (N=1,971) who consumed cooking oil contaminated with PCBs and furans during pregnancy found that all of the children studied (n=128) with *in utero* exposure exhibited subsequent impairments in mental and motor abilities, behavioral problems, and hyperactivity-attention deficits.³⁰

PERCHLORATES

A report issued by the CDC in 2006 stated that American women, particularly those with low iodine intake, may have reduced thyroid function due to perchlorate exposure. According to the

Environmental Working Group: "[An] analysis of the CDC data found that for more than 2 million iodine-deficient women nationwide, exposure to perchlorate in drinking water and the food supply, at levels equal to or lower than proposed national and state standards, could lower thyroid hormone levels to the extent that they would require medical treatment to avoid developmental damage to their babies."³¹

PHTHALATES

A 1998-2002 study conducted with children born at Mt. Sinai Hospital evaluated the relationship between phthalate and BPA exposure in mothers whose urine was collected during the third trimester of pregnancy and neurodevelopmental disorders in their children when they reached ages 7-9. Increased exposure to phthalates was associated with greater social deficits, including poorer social cognition, social communication, and social awareness. The investigators postulated that the mechanism of action related to phthalates' thyroid-disrupting effects.³²

Prenatal phthalate exposure is associated with childhood behavior and executive function. In children evaluated at ages 4-9 for behavioral issues and executive function, phthalate levels correlated with poor executive function and decreased ability to control impulses, make a transition between situations, modulate emotional responses, initiate tasks, retain information for task completion, and set goals.³³

THE INSECTICIDE-ASD-THYROID CONNECTION

Just as EDCs have myriad effects on the thyroid, so do they have numerous effects on development and developmental disorders such as autism.

In a study by Roberts and colleagues,³⁴ maternal residence near agricultural pesticide applications during key periods of gestation was shown to be associated with the development of ASD in children. In this study, ASD risk increased with the poundage of organochlorine pesticides applied and decreased with distance from the field sites. According to the researchers, the two pesticides (dicofol and endosulfan) that pregnant women were exposed to during key periods of gestation do not primarily target the brain. Rather, they are endocrine disruptors that target thyroid and estrogen hormone signaling, which secondarily affect the brain. As the researchers put it, "Generally speaking the brain has not been highlighted as the primary target organ for the toxicity of either dicofol or endosulfan. The latter compound has been noted to have estrogen effects as well as effects on the thyroid gland which may be relevant to concerns about the role of the fetal hormonal milieu in ASD pathogenesis."



ORGANOCHLORINE PESTICIDES

Organochlorine pesticides have a number of neurodevelopmental effects, including decreased psychomotor function and decreased mental function (such as depressed memory, attention, and verbal skills). Again, thyroid disruption is thought to be the mechanism of action.³⁵⁻³⁷

SIMILARITY OF CEREBRAL CORTICAL ARCHITECTURE IN AUTISM AND HYPOTHYROIDISM

Many of the studies just cited provide substantial evidence that thyroid disease and autism are intricately connected. An article by Roman published in 2007³⁸ discusses the cerebral cortical architecture in the two types of disorders:

Experimental animal models have shown that transient intrauterine deficits of T hormones result in permanent alteration of cerebral cortical architecture reminiscent of those observed in brains of patients with autism... Both in autism and hypothyroidism, there is faulty differentiation of neurons, particularly Purkinje cells...

Roman also notes that “Transient and limited T hormone deficiency *in utero* may cause the morphological brain lesions of autism.” Discussing hypothyroxinemia, Roman observes that “hypothyroxinemia may have begun in a percentage of children with autism as early as the first trimester *in utero*. This may be caused by subbiochemical maternal hypothyroidism that either preceded pregnancy or developed subsequently due to the excessive need of TH and/or to a decrease in available iodine.” To quote Roman one final time, “The current surge of autism could be related to transient maternal hypothyroxinemia resulting from dietary and/or environmental exposure to anti-thyroid agents.”

As indicated by Roman,³⁸ decreased TH *in utero* causes alterations of cerebral cortical architecture by affecting neuronal migration reminiscent of the alterations observed in the brains of patients with autism. Although the etiology of autism is multifactorial, hypothyroidism *at any point during neurodevelopment* clearly can be a central cause of autism (emphasis added). Therefore, treating hypothyroidism should play a vital role in the treatment of autism.

MISSING THE THYROID DIAGNOSIS IN ASD?

Given that thyroid disease is likely a significant contributing cause of autism, why do routine blood tests then frequently miss the diagnosis? Why are so many children with autism not diagnosed with hypothyroidism? The answer to these questions has to do with the fact that the thyroid signaling system is controlled on two levels: the central HPT axis and control on a local and peripheral cellular level.

THE HPT AXIS: The first level is the central HPT axis (the second level will be discussed hereafter). Routine blood tests frequently fail to detect abnormalities in the HPT axis for a variety of reasons, including that the general population range for TSH is significantly broader than the individual range. Because everyone has a unique set point for TSH, for many individuals even a slight deviation can have profound effects.

The main reason why hypothyroidism is missed in ASD is that the routine tests for TSH, T3, and T4 frequently miss the diagnosis. Only with the TRH (thyrotropin-releasing hormone) stimulation test can we pick up this problem in a large percentage of these children. Everyone has their own set point of TSH, and with routine tests we can't know if one is out of their set point. The TRH stimulation test will frequently detect an underactive thyroid and whether someone is past their set point (which is missed by routine tests).

A landmark study published in 2007 confirmed that routine TSH thyroid tests frequently fail to detect hypothyroidism. Some investigators have noticed, however, that depressed patients with normal TSH can have an exaggerated response to TRH.³⁹ When patients with normal TSH and TH but suggestive clinical symptoms of hypothyroidism were evaluated with a more sensitive TRH test, the researchers concluded: “An exaggerated TRH response indeed occurs in many subjects with normal biochemistry... Even though the TRH test is seldom used in clinical practice at present, a larger prospective study is in order. Until then, physicians may once again need access to TRH for diagnostic use.”⁴⁰

Another noteworthy 2007 study was conducted with 87 female patients with infertility but no other symptoms of hypothyroidism. One subgroup included 39 women with ovulation disorders and polycystic ovary syndrome (PCOS), while a second group (n=48) consisted of women with normal ovulation. The study found that although TH was normal and TSH was in the normal range of 1.72 to 1.87, the TRH test produced abnormal results in 13.8% of all women, and in 20% of women with ovulation disorders or PCOS. These abnormalities were only detected by the TRH test. The researchers concluded with the recommendation that TRH stimulation testing be performed in women suffering from ovulation disorders, even in the presence of normal basal TSH levels.⁴¹

LOCAL CONTROL: In addition to the HPT axis that controls thyroid hormone production, there is also control on a local and peripheral cellular level. This is mediated in part by the deiodinase enzymes (see next section). These enzymes are essential control points of cellular thyroid activity which determine intracellular activation and deactivation of thyroid hormones. Even when the more sensitive TRH test is normal, the thyroid hormone signaling system can

be underactive due to changes in the local control of thyroid hormones. These changes can elude accurate evaluation of thyroid testing, including the TRH test, because the blood test can come out apparently normal or with subtle inexplicable abnormalities.

Remember that even at subclinical and subbiochemical levels, hypothyroidism can adversely affect critical target organs and systems, including the developing brain, the adult brain (observed in depression studies), and the cardiovascular system. (Among angina patients who underwent cardiac catheterization, those with TSH levels above 2.1 were more likely to have multiple vessel disease.)⁴² Thus, it is vital to receive an accurate diagnosis of hypothyroidism.

LOCAL CONTROL: ROLE OF THE DEIODINASE ENZYMES

The deiodinase enzymes include Type 1 deiodinase (D1) and type 2 deiodinase (D2), which increase cellular thyroid activity by converting inactive T4 to the active T3. Type 3 deiodinase (D3) reduces cellular thyroid activity by converting T4 to the anti-thyroid reverse T3.⁴³ The activity of each deiodinase enzyme type changes in response to differing physiologic conditions. Moreover, local control of intracellular T4 and T3 levels results in different tissue levels of T4 and T3 under different conditions. Because the deiodinases determine *cellular* thyroid levels and not *serum* thyroid levels, serum thyroid levels may not necessarily predict thyroid tissue levels under a variety of physiologic conditions.

Although D1 converts T4 to T3, D1 is not a significant determinant of pituitary T4 to T3 conversion, which is controlled by D2. D1 (but not D2) is suppressed and downregulated in response to physiologic and emotional stress, inflammation, autoimmune disease, exposure to toxins, and chronic illness. This state is known as “sick euthyroid syndrome.”⁴⁴ (Interestingly, tumor necrosis factor or TNF, a potent inflammatory mediator known to play an important role in inflammation associated with autism, is also a mediator in sick euthyroid syndrome.) Under these conditions, TSH levels are usually normal because D2 bound in the pituitary is not downregulated and therefore is a poor indicator of tissue thyroid levels.

As should by now be apparent, a complete definition of thyroid status requires more than the measurement of serum concentrations of thyroid hormones. For some tissues, the intracellular T3 concentration may only partly reflect concentration in the serum. Recognition that intracellular T3 concentrations in each tissue may be subject to local regulation, and an understanding of the importance of this process in the regulation of TSH production, should permit a better appreciation of the limitations of the measurements of serum thyroid hormones and TSH levels.

Because children with autism are stressed emotionally and physiologically and are in an inflammatory state, they are likely to have low cellular thyroid hormone levels (that is, an underactive thyroid). However, because their blood tests may be normal, their low cellular TH levels frequently are overlooked.

In children with autism, stress and inflammation may cause reverse T3 (RT3) to be high. RT3 blocks D1 and T4 to T3 conversion, blocks T3 from binding to receptors, and blocks the T3 effect. As the pituitary does not contain D3, and D3 is responsible for RT3 production, the pituitary will have normal levels of T3, and the TSH can be normal. Nonetheless, because children with autism are stressed emotionally and physiologically and are in an inflammatory state, they are likely to have low cellular thyroid hormone levels (that is, an underactive thyroid). However, because their blood tests may be normal, their low cellular TH levels frequently are overlooked. Only with a comprehensive understanding of how various environmental toxins can affect local control, and how physiological conditions such as stress and inflammation can alter thyroid control, can one correctly “read” thyroid blood tests.

OTHER BIOMARKERS OF HYPOTHYROIDISM

Several other biomarkers can signal the presence of hypothyroidism even with normal TSH and serum T4 and T3. In children with autism, one cannot rely on routine thyroid blood tests to determine if they have low T3 in peripheral cells, including the brain.

The first set of markers includes TNF, IL-1, IL-6, CRP, and other inflammatory markers; because these decrease D1 activity and reduce tissue T3 levels, if they are high, one should consider hypothyroidism.

Secondly, autoimmune disorders (including autism, which is associated with autoimmune antibodies) should raise a red flag for tissue hypothyroidism, even with normal serum TSH, T4, and T3.⁴⁵ In autoimmune conditions, there is a decrease in T4 to T3 conversion in the tissues, but in the pituitary the inflammatory cytokines will increase the activity of D2, suppressing TSH production.

Thirdly, high cortisol levels also downregulate D1 and increase D3 activity in peripheral tissues, while stimulating D2 in the pituitary. This will lead to a decrease in TSH yet low levels of T3 in peripheral cells.

EDCS, THYROID RECEPTOR RESISTANCE, AND ATYPICAL THYROID BLOOD RESULTS

EDCs may interfere with thyroid hormone signaling in a variety of ways. Some environmental chemicals alter TH signaling by selectively interfering with subsets of TH receptors. The consequences for brain development, then, may be a mosaic of effects on the nervous system. This is because different thyroid receptors mediate different actions of TH during development.⁴⁶ To make matters more confusing, many toxins cause thyroid signaling dysfunction by binding to receptors, leaving thyroid hormone levels and TSH normal in the serum. Toxins can also affect the thyroid hormone signaling system at multiple sites. Both yield blood test results that are difficult to interpret.

A number of endocrine-disrupting chemicals cause a decrease in serum and total and free T4 without a concomitant increase in TSH. One example is Aroclor 1254, which causes a significant decrease in serum T4 (total and free) but does not affect serum TSH or T3 levels.⁴⁷ BPA can also render thyroid blood tests difficult to interpret. BPA can selectively bind to thyroid receptors in the pituitary, leading to elevated serum T4 and either normal or slightly elevated TSH.⁴⁷ In this scenario, all other thyroid parameters will be normal. BPA selectively antagonizes the TR beta receptor in the pituitary, which blocks T4 uptake by the pituitary. Low levels of T3 will result, causing the pituitary to produce and release higher levels of TSH and high T4 in the thyroid.

Certain dioxins can also produce high TSH levels and high levels of total T4. Because there are structural similarities between some dioxins and T4, the dioxins might interfere with transport of T4 into the cell, the conversion of T4 into T3, or binding of T3 to its nuclear receptor. In the pituitary, decreased nuclear T3 receptor occupancy will stimulate TSH secretion. This causes the thyroid to produce high levels of T4.

In a 2010 paper in *Hormones*,⁴⁷ Zoeller advises: “Because of the complex nature of the regulation of thyroid function and TH action, the consequences of

EDC exposure are also likely to be complex and our ability to understand these effects as well as to screen for potential EDCs must consider this complexity.” Importantly, Zoeller adds:

Animal studies are revealing both the complexity of the thyroid system and the complexity of the ways in which EDCs may interfere with TH signaling.. The current clinical strategy of evaluating thyroid disease (i.e., measure blood levels of hormones, antibodies and proteins) is not sufficient to identify EDC actions on thyroid hormone signaling that may well be associated with disease in the human population.

MY FINDINGS

Nearly three-quarters of children with autism have an underactive thyroid. Many children who are being treated for hypothyroidism are either on the wrong dose or not on the appropriate balance of T3 and T4. Treatment with thyroid hormones helps children with autism achieve improvements in:

- language
- cognition
- hyperactivity
- motor function
- sociability
- gastrointestinal function

SUMMARY

Research indicates that thyroid dysfunction due to endocrine-disrupting toxins likely plays a role, perhaps a significant one, in autism. Through the use of the more sensitive thyroid test (the TRH stimulation test), and with an understanding of local control of thyroid signaling, I have found that approximately seven out of every ten children with ASD have an underactive thyroid. Yet many children with autism remain undiagnosed and untreated for their hypothyroidism. Treatment with properly balanced thyroid hormones and a dose guided by the TRH test can help many of these children experience significant improvement. Some make a complete recovery.

Many toxins cause thyroid signaling dysfunction by binding to receptors, leaving thyroid hormone levels and TSH normal in the serum. Toxins can also affect the thyroid hormone signaling system at multiple sites. Both yield blood test results that are difficult to interpret.

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