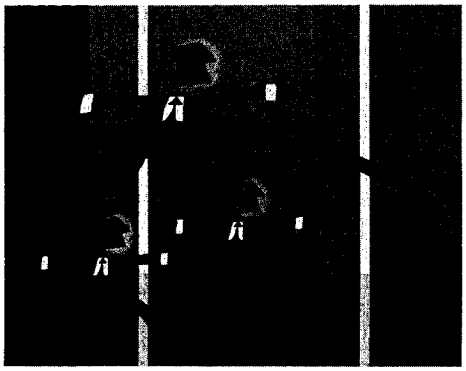

Links between ADHD and Environmental Pollutants:

Implications for Preventative Naturopathic Clinical Practice

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Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a chronic neurobehavioral mental-health disorder with functional impairments as a result of concentration/attention or impulsivity/hyperactivity.[1] The disorder affects one in every 20 Canadian children, and is thought to be multifactorial, resulting from interactions of early childhood learning, genetic expression, dietary intake, and neurotoxic pollutant exposure during development. Diagnosis per the *Diagnostic and Statistical Manual of Mental Disorders* 4th ed. (DSM-IV) criteria requires the presence of six of nine characteristic behaviors that significantly affect at least two areas of the patient's life for a period greater than six months.[2] DSM-IV criteria identify three subtypes of ADHD: Primarily inattentive (ADHD/I), primarily hyperactive-impulsive (ADHD/HI), and combined (ADHD/C). New developments in the understanding of ADHD show the need not only to diagnose but also to treat it based on the identification of these distinct subtypes.[3,4] While the etiology of ADHD is not clearly understood, it is believed that environmental pollutants may be contributing to a potentially increasing incidence of this debilitating disorder.[5]

Naturopathic treatment seeks to identify the root cause of disease, and ADHD is no exception. Food sensitivities are addressed through the elimination of common allergenic foods and additives ubiquitous in processed foods. Genetic methylation deficits can be addressed by administration of methylcobalamin and folic acid. Identification and treatment of increased heavy-metal burden is clinically more challenging, due in part to the lack of standardized diagnostic testing and well-defined reference ranges. However, given that an increasing volume of evidence implicates heavy metals and environmental pollutants as a contributing factor in ADHD, it is important that NDs consider this in their assessment and treatment plans.

Diagnosis of ADHD is often first made in school-aged children (age six through nine years), with prevalence rates ranging from 4% to 12% of all school-aged children in North America.[6] In the US, 4.2% of children of ages four to fifteen (equivalent to 1.8 million children) have ADHD and are treated with stimulant medications.[7] Among schoolchildren, males show predominance, with a diagnostic prevalence ratio of between 2:1 and 4:1 over females.[8]

Studies on the etiology of ADHD reveal an inheritable component related to neurobiological deficits in the prefrontal cortex and related subcortical regions, resulting in the dysregulation of dopaminergic, serotonergic, and noradrenaline neurotransmitter systems.[9-11] There are a number of pharmacological treatment options based on the effects of the release/inhibition ➤

of neurotransmitters, including stimulants (methylphenidate, amphetamine, modafinil, pemoline), selective norepinephrine/serotonin reuptake inhibitors (atomoxetine), antidepressants (bupropion, desipramine), nicotinic agents (nicotine analogs), and antihypertensives (clonidine, guanfacine).[3] An estimated 30% to 50% of children with ADHD either do not respond to or do not tolerate treatment with these stimulants.[12] In addition, recent pharmacoepidemiologic studies demonstrate that compliance with stimulants is poor, with less than 10% of patients still taking prescribed medications after one year.[13-15] Both the medical community and the public have expressed concern about the severalfold increase in prescriptions of stimulant medications for children over the past decade[16,17] and the potentially serious physical and social side effects of these medications.[18-21] Unquestionably, ADHD is a common disorder in Canada; and its negative burden on individuals, their families, and society as a whole is profound. There is a great need for exploration of the elements that contribute to ADHD and into related strategies to prevent and mitigate this disorder.

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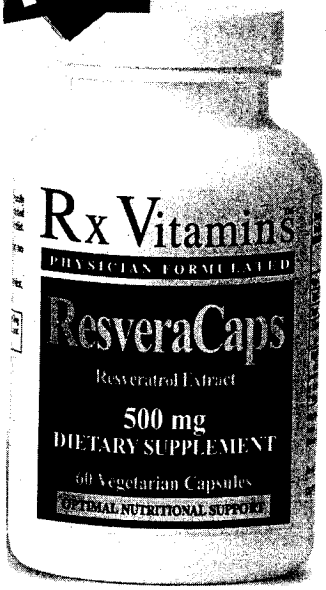

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OPTIMAL NUTRITIONAL SUPPORT

Associations between Environmental Pollutants and ADHD

An expert committee from the US National Research Council found that 3% of developmental disabilities are a direct result from exposures to environmental pollutants, and a further 25% extend from genetic susceptibilities to environmental factors.[22] Currently, there is no comprehensive analysis on the role of environmental pollutants and ADHD. There is a wide base of evidence linking environmental toxins with ADHD, and we believe that there are associations between certain pollutants and the development, prognosis, and treatment of ADHD. The following discussion on two heavy metals and exposure to tobacco smoke serves to provide preliminary evidence signifying the importance of these associations and to highlight specific exposures to consider in the assessment and treatment of ADHD.

Heavy Metals and ADHD

In chemistry, the term *heavy metal* is currently used to describe metals (and by extension, metalloids) commonly associated with contamination and potential toxicity or ecotoxicity. Lead, mercury, arsenic, cadmium, and manganese are examples of highly toxic heavy metals.[23] Two neurotoxic metals, lead and manganese, are associated with ADHD and are discussed below to elucidate some of the evidence regarding the risk that heavy metals pose to children and their neurological development.

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Lead: Evidence is building that links exposure to lead with the development of ADHD. In a recent cross-sectional study of 150 children from Michigan aged 8 to 17, blood lead levels were found to be significantly higher in ADHD/C than in non-ADHD control children.[24] Of note is that this was demonstrated amongst a subject population with lead levels still defined as "low" by the Centers for Disease Control (<5 μg/dL). This is the first study to correlate ADHD with "low" blood lead levels (<5 μg/dL) comparable to levels found in the general population (1-2μg/dL). The study also supports previous findings that have confirmed a linear association between higher blood lead levels >10 μg/dL and symptoms of ADHD.[24] While higher lead levels have been shown to correlate with lower IQ, the apparent link to ADHD and lead appeared independent of this effect on IQ. This study also found that there was no correlation of maternal blood lead levels and child ADHD diagnosis or symptoms, indicating that critical exposure was likely to have occurred postnatally.[24] Potential sources of lead include paint from toys, enameled or ceramic pots, dishware that may be improperly glazed, drinking water from pipes of old houses, as well as paint from old houses, fertilizers, fungicides, and herbicides (in the form of lead arsenate). Renovation work, especially where floors, walls, and ceilings are torn up, may provide a source of lead exposure in older homes.

Konofal and Cortese have hypothesized that iron supplementation may be beneficial in cases of lead toxicity due to a neuroprotective role of iron.[25] When researchers gave 80 mg/d ferrous sulfate to 23 nonanemic children (ferritin levels >30 ng/mL) who met DSM-IV criteria for ADHD, there was a progressive and significant decrease in symptoms of ADHD as measured by the ADHD Rating Scale.[26] The iron hypothesis is supported by the fact that lead in the central nervous system contributes to a dopaminergic dysfunction, which may also disrupt the structure of the blood-brain barrier. However, as iron supplementation may protect the integrity of the blood-brain barrier against lead insult, it is suggested that iron deficiency could potentiate the toxic effects of lead.[27] Alternately, it is hypothesized that lead may also contribute to iron deficiency by reducing iron's bioavailability. Lead also affects neurotransmitter pathways via decreased heme synthesis and consequent increased levels of the precursor, δ-aminolevulinic acid (ALA), which in turn suppresses GABA-mediated neurotransmission.[28] Regardless of the mechanism, given the potential impact of iron status on ADHD, these children ought to be screened for iron deficiency.

Manganese: In trace amounts, manganese is an element required for proper physiological function via its role as an enzymatic cofactor. At higher doses, however, manganese can become highly toxic. Although the evidence for lead is much stronger, it is important to consider the potential for this lower-profile element to be a contributing factor in a child's diagnosis of ADHD. Current knowledge of manganese neurotoxicity is based on occupational inhalation exposure, resulting in an extrapyramidal syndrome, characterized by symptoms of gait dysfunction with a propensity to fall backward, postural instability, bradykinesia, rigidity, micrographia, masked facies, speech disturbances, and muscle tremors. Clinical and subclinical effects of intoxication have also been implicated and involve the striatal dopaminergic system through GABA and serotonin imbalances. In a Quebec community, a pilot study of 46 children ranging from 6 to 15 years old found that higher exposure to manganese in well-water, reflected by higher manganese levels in hair, was positively correlated with hyperactive behaviors.[29] It is interesting to note that girls had significantly higher levels than boys (mean 6.3 ± 4.4 μg/g vs. 4.0 ± 4.0 μg/g).

Manganese also exerts a strong inhibitory effect on iron absorption. As iron deficiency is correlated with ADHD symptoms, the possible confounding effect by iron also deserves examination for investigating the impact of manganese in children with ADHD. As with lead, toxic-metal induced decreases in iron absorption may also represent an indirect mechanism by which manganese exerts its deleterious effects.

Assessment of Heavy Metal Status

In addition to direct blood testing of lead levels, lead may be assessed through provocative urine testing with DMSA and EDTA, and potentially hair mineral analysis.[30] Reference ranges for hair lead in adults is 0-7.2 nmol/g; however, no ranges are given for children, since no lead level is considered safe in children.[31] There are currently no established reference ranges for provocative urine testing; ranges depend on the laboratory used and appear based on normal (that is, unchallenged urine levels). Blood tests are recommended for lead in children, with alert levels being >0.12 μmol/L for whole blood samples in children under 16 years. Alert level for erythrocyte lead concentration is >0.27 μmol/L. Urine is not recommended for manganese testing; however, there are no current reference ranges for manganese blood or hair measures.[31]

Tobacco Smoke and ADHD

In a cross-sectional analysis, the National Health and Nutrition Examination Survey found that exposure to prenatal tobacco, as well as environmental lead, was a clear risk factor for ADHD.[7] In this study, a representative sample, 4.2% of 4704 children (ages 4 through 15) were reported to have ADHD. While the highest levels of lead were shown to be linked to ADHD incidence, prenatal exposure to tobacco smoke was also significantly associated with ADHD.

The heritability of genetic factors contributing to the ADHD phenotype is considered to be 65 to 90%, and interactions between the genotype and the environment can be decisive.[32] In a prospective longitudinal study of 305 subjects from birth to age 15, it was confirmed that children homozygous for the 10-repeat allele of the common dopamine transporter (DAT1) polymorphism, who were also exposed to prenatal tobacco smoke, had much higher hyperactivity-impulsivity than children without this combination of environmental and genetic risk factors.[32] Maternal prenatal smoking was assessed during a standardized interview when infants were three months old, and postnatal smoking was assessed periodically during child development via interview. At 15 years of age, subjects were genotyped for the DAT1 40bp polymorphism variable, and assessed for inattention, hyperactivity-impulsivity, and oppositional defiant/conduct disorder symptoms. There was a significant interaction between the DAT1 genotype and prenatal smoke exposure as well as an association in males with prenatal smoke exposure who were homozygous for the DAT1 10r allele and with higher hyperactivity-impulsivity levels ($p = 0.012$).[32] This supports the hypothesis of environmentally moderated risk for ADHD, and that effects can depend on genetic susceptibility operating through gene-environment interactions.

Pediatric Vulnerability to Environmental Pollutants

Children at all stages of growth, and especially during fetal development, are uniquely vulnerable to toxins in the environment.[5] Not only are they more physiologically susceptible to the effects of pollutants, but the rate of uptake of these agents can be greatly increased as well. More important than increased exposure levels, however, is the developmental heterogeneity that exists in children, and their potential vulnerability at critical junctures in neurological development.[26,27] Rapid and profound physiological changes are experienced by the growing child, and this is greatly magnified *in utero*. The potential for environmental pollutants or other xenobiotics to cause irreversible damage upstream in a child's neurological development is a risk much greater than that for a fully grown adult. The effects of exposure to toxins on early embryological development from well-established examples like alcohol and thalidomide are well known and acknowledged. However, our understanding of the health impacts from the myriad chemicals synthetically produced and in the environment is still grossly inadequate.

Clinical Directions

Although the role of the environment on health has recently been receiving more attention, awareness and continued efforts need to be directed towards prevention and decreased exposure to environmental pollutants. While screening and assessment of exposure to these harmful chemicals is a basic first step towards better patient care, little formal research has been conducted on successful means of decreasing the levels or effects of these toxins in children.

One small noncontrolled study demonstrated a decrease in serum (162%) and urine (132%) levels of lead in non-ADHD children with the use of 15g of modified citrus pectin (MCP) split into three 5-mg doses/day over 28 days.[28] No adverse effects were reported in participants in this study, although allergy to MCP, changes to electrolyte levels, and potential for constipation or fluid loss have been identified as possible side effects.[29]

As mentioned above, treatment of children with ADHD using 80 mg/day of ferrous sulphate may also help decrease the impact of lead or other heavy metals on the severity of symptoms in ADHD.[30]

Representing a somewhat more "naturopathic" approach, a small uncontrolled prepilot study of ten children previously diagnosed with both ADHD and autistic spectrum disorder investigated the effect of a comprehensive treatment protocol, consisting of nutritional, environmental, and chelation interventions, on decreasing symptoms associated with these conditions.[31] Specifically, the protocol used in the study included a mix of therapeutic interventions. First of all, environmental control was advised, by which avoidance of mold, tobacco smoke, pesticides, cosmetics, and cleaners was to be maintained during the study. Other suggestions included an organic rotation diet free from food additives and salicylates, and low in refined sugar; a gluten-free, casein-free diet in patients with sensitivity to these proteins (8/10 tested positive to food allergens on IgG testing); gastrointestinal support including probiotics and digestive enzymes; injections 1 to 3 times per week with methylcobalamin and glutathione; and chelation therapy with IV EDTA, DMPS, and glutathione, administered 1 to 2 times per week for a total of 10 to 20 treatments. Antigen injection therapy and nutritional supplementation were also part of the program. This comprehensive protocol was followed for 3 to 6 months. Provocative urinary metal testing was performed at baseline and upon completion of the study. None of the children took psychotropic medications during the study, but other behavioral and special education interventions were continued. The results of the trial indicate that the treatment protocol was associated with significant reductions in urinary lead levels (high at baseline for all participants) and significant clinical improvements in all ten of the children. In addition to reduction in urinary lead levels, patients had a large though not statistically significant drop in urinary levels of mercury, cadmium, and aluminum. Comparison of motor, behavioral, and education capacity by parents,

teachers, and the treating physician(s) from baseline to completion of the study found improvement in all ten children. Four were able to return to regular classroom education, and eight showed dramatic improvements in verbal skills by study end.[31]

Although small and uncontrolled, this study is important in that it represents the combined effect of an integrated intervention protocol, rather than a single-agent intervention. While not standard practice, the interventions utilized in the study are reflective in many ways of the eclectic treatment approach commonly employed by naturopathic doctors and integrative medical practitioners who treat ADHD. Certainly, larger controlled studies are needed to further investigate these interventions; however, this study begins to provide compelling evidence on a holistic approach to treating children with ADHD.

With respect to heavy metal reduction, chelation as a treatment approach for ADHD is still very much unestablished. Chelating agents have a proven use for treating heavy-metal toxicities, yet their immediate impact on cognition or behavior in ADHD children is limited,[32] with no statistically significant improvements being observed more than 4 years posttreatment.[33]

A number of studies have noted relative deficiencies in detoxification enzymes (superoxide dismutase, paronaxase[34], glutathione peroxidase[35], and sulphation enzymes[36]) and nutrients pertaining to liver detoxification pathways[37] (methionine, s-adenosyl methionine, cysteine, glutathione) in children with autistic or autistic-spectrum disorders; these studies may not be applicable to children who have ADHD with heavy metal toxicities. It does seem reasonable that an increased ability to process or remove environmental toxins may benefit children with ADHD who have demonstrated an elevated burden, although there is a paucity of research on this topic.

Other treatments with historical or theoretical uses that may address toxic exposure to heavy metals include adrenal extract, algin, arrowroot (*Maranta arundinacea*), blue flag (*Iris versicolor*), calamus (*Acorus calamus*), colloidal silver, copper, Essiac, ground ivy (*Glechoma hederacea*), liver extract, hydrotherapy, kudzu (*Pueraria lobata*), marshmallow (*Althaea officinalis*), melatonin, organic food, ozone therapy, reflexology, SAMe, spirulina, urine therapy, and vitamin C.[38] As yet, these interventions are not well supported by the evidence, and they should be undertaken with caution, or avoided in lieu of treatments with greater evidence to support their use.

Faced with a child with ADHD, if an etiology of heavy metal toxicity is suspected, it is essential to balance potential benefit with risk before engaging a process of therapeutic elimination. Chelation with synthetic chemicals, nutritional supplements, or herbal agents is not without risk, especially in the pediatric population. Issues to consider include the fact that a child's organs of elimination (most relevantly the kidneys and liver) are still developing and may be adversely affected. In addition, the possibility of mobilizing heavy metals resulting in redistribution to more sensitive tissues (such as the brain) without adequate clearance is also a real concern. Finally, the toxicity of the chelating agents, herbal or synthetic, must also be carefully considered and weighed against possible benefits.

In general, the increased understanding of epigenetics and ontogeny is clarifying the ways in which our chemical environment might influence early development through gene-environment interactions. The role of such factors as heavy metals and environmental tobacco smoke in this interaction and subsequent disease evolution deserves much further consideration, particularly with respect to ADHD. The role of NDs is to identify and address the root cause of disease. Whether root cause is dietary, genetic, environmental, or a combination thereof, naturopathic doctors' ability to assess and influence contributing factors will translate into more effective preventative and holistic care.

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