

EDITORIAL

FACTORS ADVERSELY INFLUENCING NEURODEVELOPMENT

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Neurodevelopment has been studied extensively, especially in respect to abuse, anoxia, nutritional status and prematurity/low birth weight. However, less attention has been paid to innate and environmental factors, as well as to inflammatory conditions that may adversely affect neurodevelopment and learning in children. These include heavy metals, herbicides and polyvinyl chlorides (PVCs), mycotoxins, viral infections and Lyme disease-associated pathogens, as well as number of conditions such as chronic inflammatory response syndrome (CIRS) and Mast cell activation syndrome (MCAS). Early recognition of factors/conditions that could interfere with neurodevelopment is critical. Corrective actions, including the use of some unique natural flavonoids, could have lasting beneficial results.

There has been an unexplained increase in children with neurodevelopmental and learning problems (1, 2). Neurodevelopment has been studied extensively. More recently, atopic diseases (3) such as allergies (4, 5), asthma (6), and atopic eczema (7) have been significantly associated with behavioral and learning difficulties, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). Emotional stress (8, 9) both prenatally (10, 11), as well as in children (12, 13) has also been associated with increased risk of a child developing ADHD or ASD.

Less attention has been paid to innate and environmental factors, as well as inflammatory

conditions that may adversely affect neurodevelopment and learning in children (14, 15). These include heavy metals, herbicides and polyvinyl chlorides (PVCs) (Table I), as well as a variety of inflammatory conditions (Table II) such as mold, Lyme disease, viral infections and especially chronic inflammatory response syndrome (CIRS) and mast cell activation syndrome (MCAS).

Recent evidence indicates that inflammation of the brain (8, 16), due to activation of microglia (17, 18) may be involved in neurodevelopment and in the pathogenesis of neuropsychiatric disorders (19, 20) but the reasons are still unknown. We reported that the peptides corticotropin-releasing hormone (CRH)

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Table I. *Factors adversely influencing neurodevelopment.*

•	Electromagnetic waves
•	Heavy metals
✓	Aluminum
✓	Arsenate
✓	Lead
✓	Mercury
•	Herbicides
✓	Atrazine
✓	Glyphosate
•	Inflammatory cytokines
✓	IL-6, IL-31, IL-33, TNF
•	Mitochondrial DNA
•	Mycotoxins
✓	Ochratoxin A
•	Neuroendocrine disruptors
✓	Polyphenols
✓	Xenoestrogens
✓	Bisphenol A
✓	Polyvinyl chloride
•	Neuropeptides
✓	Neurotensin
✓	Substance P
•	Neurotransmitters
✓	Aspartate
✓	Glutamate
✓	Histamine
•	Pathogens
✓	Babesia
✓	Bartonella
✓	Borrelia
✓	CMV
✓	EBV
✓	Fungi
•	Reactive Oxygen Species
•	Toxins
•	Venoms
•	Xenobiotics

and neurotensin (NT) are increased in the serum of patients with ASD (21, 22), and can activate human microglia to secrete the pro-inflammatory cytokine IL-1 β and chemokine CXCL8 IL-8 (22). These molecules may be produced inside the brain or enter

Table II. *Conditions adversely affecting neurodevelopment.*

•	Abuse
•	Allergies
•	Anoxia
•	Anxiety disorder
•	Asthma
•	Attention deficit hyperactivity disorder
•	Atopic dermatitis (eczema)
•	Avitaminosis
•	Chronic inflammatory response syndrome
•	Cyclic vomiting syndrome
•	Food intolerance
•	Hyperthermia
•	Hypothyroidism
•	Idiopathic urticaria
•	Maternal deprivation
•	Mastocytosis
•	Mast cell activation syndrome
•	Multiple chemical sensitivity syndrome
•	Neglect
•	Non-IgE food allergy
•	Nutrition (poor)
•	Pediatric acute neuropsychiatric syndrome
•	Rhinosinusitis

the brain through a disrupted blood-brain barrier (BBB), documented in psychiatric disorders (23) and in ASD (24), due to molecules such as histamine released from brain mast cells (25). Mast cells can stimulate microglia (26) via histamine (27), leading to secretion of pro-inflammatory mediators.

Histamine is secreted from activated mast cells in atopic diseases and mastocytosis (28), but is also found in many foods such as cheese, fermented milk and alcoholic products, nectarines, ripe fruits, sardines, sauerkraut, spinach, spices and tuna. Levels of histamine can build up in patients who have reduced activity of the histamine degrading enzyme diamine oxidase (DAO). Both the activity and the gene expression of DAO can be tested, and DAO can be administered as a dietary supplement that would reduce histamine levels in the intestine. This

approach is complimentary to giving antihistamines, preferably rupatadine (not available in the US, but can be compounded) because it can also inhibit mast cell and eosinophil activation (29) since these cell types are stimulated especially in children exposed to mold (30). However, it should be noted that high doses of antihistamines could interfere with learning and motivation (31).

Natural flavonoids are increasingly discussed as therapeutic agents for neurodegenerative disorders (32, 33). Especially, luteolin (5,7,3',4'-tetrahydroxyflavone) has potent anti-oxidant, anti-inflammatory (34, 35), anti-allergic (36), and neuroprotective (34) actions including significant improvement of children with ASD (37, 38). The purest (>87%) luteolin, with the greatest oral absorption due to its liposomal formulation in olive kernel extract, is found in the dietary supplements BrainGain®, NeuroProtek®, and Purelut®; a new product will combine luteolin with Ashwagandha, which has anti-anxiety properties (39). We recently showed that the structurally-related methoxyluteolin (5,7,3',4'-tetramethoxyflavone) is more potent than luteolin (22, 40) and has even better oral absorption (41) but to date has been formulated only in the anti-inflammatory skin lotion GentleDerm® (42).

Addressing offending conditions and/or minimizing the detrimental effects of suspect molecules as early as possible is of great importance in improving neurodevelopment, cognition and learning in children.

DISCLOSURE: TCT is the inventor of US patents No. 7,906,153; No. 8,268,365 and No. 9,050,275 for the treatment of neuroinflammatory conditions.

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