

Review Article

A REVIEW ON THE IMPACT OF THE ENVIRONMENTAL ADVERSITIES ON VARIOUS DEVELOPMENTAL DISORDERS OF BRAIN IN CHILDREN

SALAHUDDIN MOHAMMED^{*1}, BIRHANU MOTBAYNOR², DEMISSEWBERIHUN HAILE³

College of Health Sciences, Department of Pharmacy, Mizan Tepi University, Mizan Teferi, Ethiopia.
Email: salahuddin_pharma48@yahoo.com, dovehod@gmail.com

Received: 24 Mar 2014 Revised and Accepted: 26 Apr 2014

ABSTRACT

Scientific researches over the last 30 years in defining the role of various toxins and stresses during the utero and postnatal phase, malnutrition, brain injuries and selective food deficiencies have shown enough evidence of their role in neurodevelopmental disorders. The effect of environment on various developmental disorders such as Attention deficit hyperactivity disorder (ADHD), autism spectrum and learning disabilities has paved the way for better understanding of genetic influences. Several types of genetic and environmental adversities indicate that neurodevelopmental disorders suggest a causal role. There is marked variation in the susceptibility of individuals to these adversities. Thus their vulnerability to the disease could influence the extent they are prone to that disease. The aim of this review is to bring together various aspects of environmental factors and genetic susceptibilities and summarize their toxic effects towards neurodevelopment in children.

Keywords: ADHD, Autism, Learning disability, Neurodevelopmental disorders, Methyl mercury, Polychlorinated biphenyls.

INTRODUCTION

Neurodevelopmental disorders are the disabilities associated with the functioning of neurological system and brain. The examples of disorders are Attention deficit hyperactivity disorder (ADHD), Autism, Learning disabilities. The children susceptible to these disorders experience difficulties with the language, motor skills, behaviour, learning and memory.

Based on the parental exposure to the survey on neurodevelopmental disorders, it was found that majority of children suffer from ADHD and autism and the rate is increasing alarmingly over the last four decades[1-6].

Genetics play an important role in many neurodevelopmental disorders but most of the disorders have more than one cause. These disabilities are a combination of genetic, environmental, biological and psycho-social risk factors.

Environmental factors

Studies found that the environmental contaminants damage the child's developing brain and nervous system. There had been evidence regarding the childhood lead exposure added to learning problems and reduced cognitive development[7], ADHD [8] and hyperactivity and distractibility [9]. Furthermore lead exposure have been found detrimental in memory and planning [10, 11] causing impulsiveness in children [12].

Methyl Mercury

Children's neurological development has been negatively impacted by methyl mercury. In Japan and Iraq, prenatal exposure to particularly high levels of mercury was found to cause intellectual disability as well as impaired motor and sensory function [13, 14]. Mercury's more subtle effects were studies on island population of New Zealand and Faroe islands where frequent fish consumption by pregnant woman lead to mercury exposure. Results from such studies suggested that intelligence was impacted due to increased prenatal exposure which was linked to maternal fish consumption [15, 16] and functioning in the areas of language, attention and memory were also impacted[17-20].

Polychlorinated biphenyl's (PCB's)

Prenatal exposure of polychlorinated biphenyls has been linked to the neurodevelopmental effects in children including lowered intelligence and behavioural deficits such as inattention and

impulsive behaviour [21-26]. PCB's exposure has also been linked to problems with learning and memory [21-27]. Chen and Rogan also studied the adverse effects on intelligence and behaviour found in women who were highly exposed to PCB's, chlorinated dibenzofurans and other pollutant mixtures prior to conception [28-30].

Metals

Adverse effects on neurological developments upon exposure to metals such as cadmium, arsenic and magnesium have been reported in few studies [9, 31].

In animal studies adverse effects on behaviour, learning and memory due to polybrominated diphenyl ethers (PBDE's) were found [32-34]. Another risk factor for neurodevelopmental impairment is the disruption of the thyroid hormone levels in pregnant women caused by perchlorate, a naturally occurring man-made chemical used for manufacturing fireworks, explosives and rocket propellant [35-37].

The development process of child's brain begins shortly after conception and continues through adolescence, hence the brain of the child and nervous system are vulnerable to adverse effects from pollutant exposure. Even the slightest or the shortest exposure of the environmental contaminants can hamper the precise coordination of cell growth and movement if they occur at the critical developmental stages. Neurological deficits that arise from such disruption might have an effect on the child's achievements and behaviour even though it might not be a diagnosable disorder.

Attention Deficit Hyperactivity Disorder (ADHD)

Attention Deficit Hyperactivity Disorder (ADHD) is a disruptive behaviour disorder that not only diminishes academic performance but also makes family and peer relationships difficult and also reduces vocational achievements. ADHD is characterised by ongoing inattention or hyperactive-impulsivity occurring frequently in several settings than typical for other individuals in the same setting.

ADHD is diagnosed by observing the multiple symptoms of inattention or hyperactivity. Symptoms of ADHD vary in children where some display hyperactive behaviour traits and others display inattentive traits. Nigg explained that there is possibility of an individual's primary symptoms of ADHD to change as the age advances and inattentive behaviours are more likely to be displayed by adults [38]. Furthermore, Nigg also disclosed that children with ADHD often have other disorders such as learning disabilities and conduct disorders [38, 39].

Research on ADHD is rapidly expanding and many researchers have indicated through their work that ADHD is not only influenced by genetic factors but also by environmental factors. Epidemiological studies mostly published in 2006 have exposed the link of increased levels of lead in hair and blood, mercury in blood, phthalate metabolites in urine and the presence of chlorpyrifos (pesticides) in cord blood with increased likelihood of ADHD [8, 40-48].

Research carried to study the link between environmental contaminants and ADHD revealed that children diagnosed with ADHD have altered levels and activity of the neurotransmitter dopamine [49-54]. Exposure to lead, mercury, PCB's and pesticides have caused such an alteration of chemical activity in children and animals, thus emphasizing a potential cause of ADHD disorder [55-66].

Learning Disability

Learning disability is a neurological disorder that affects the ability of a child's brain to receive process, retain and respond to information. Although learning disability vary from child to child but commonly they may have trouble learning and using certain skills including understanding, inscription, paying attention, speaking, perception and doing mathematics. As per national dissemination centre for children with disabilities, children with learning disabilities are not unintelligent or unmotivated but there are differences in the way their brains process the information. Children with learning disabilities usually have average or above average intelligence [67]. Heredity may play a possible role of learning disability in a child. According to National centre for learning disabilities, problems during pregnancy and birth, low birth weight, use of drugs or alcohol during pregnancy, lack of oxygen or premature or prolonged labour may also be the contributing factor to learning disabilities [68]. There have been ongoing researches by various research bodies which show potential role of metals and other environmental contaminants in the development of learning disabilities.

Diagnoses of learning disabilities in children have been associated with elevated levels of lead in teeth and hair, cadmium in hair, magnesium in hair and dioxins and furans in blood [69-73]. Impaired memory, rule learning, difficulty following directions, planning verbal abilities and speech processing in children have been associated with exposure to lead [10, 74-79]. Mercury has been linked to dysfunctions in children's language abilities and memory [18, 20]. Prenatal exposure of PCB's has been associated with poorer concentration and memory deficits in children with learning disabilities compared to unexposed children [21, 27].

Autism Spectrum disorders (ASD's)

Autism Spectrum disorders (ASD's) are a group of disabilities that cause significant social, communication and behavioural challenges. Spectrum disorders is a term associated with autism which explains the fact that although autistic people share common symptoms, the experience varies from mild to severe symptoms. Social adaptability is one common symptom shared by all children with ASD's. Lack of interest in other people resisting physical contact, trouble showing emotions or talking about feelings are the traits observed in children with ASD's. Children with ASD's have a range of communication problems. Some autistic children speak very well while other forty percent do not speak at all. Another distinguishable characteristic of ASD's is the demonstration of restrictive or repetitive interests or behaviours like repeating words more than once, lining up toys, rocking their bodies flapping hands or spinning in circles.

The combinations of multiple risk factors are likely to have caused ASD's and no single cause has been identified. Environmental contaminants may play an important role in causing ASD's. Hertz-Pannier reported that in younger ages the increase in prevalence cannot be fully explained by diagnosis migration patterns, changes in diagnostic criteria and inclusion of milder cases[80]. Certain environmental chemicals are likely to affect the neurological signalling systems that are impaired in children with ASD's. Pessah reported that several pesticides interfere with Acetylcholine and Gamma amino butyric acid (GABA) neurotransmission, which are chemical messenger systems altered in certain subsets of autistic

individual [81]. As reported by Kinney, several environmental contaminants have been identified that cause mutations in DNA and inhibit the body's normal ability to repair the DNA damage [82].

Mercury may play a possible role in the development of ASD's. High levels of mercury have been found in the blood, baby teeth and urine of children with ASD's when compared with control children in earlier studies [83-85], however recent studies found no such difference in children with ASD's and typically developing children [86]. A study conducted in Texas showed that increased autism prevalence was linked to the proximity of industrial and power plant sources of environmental mercury [87]. Lastly, a study of indoor environments like polyvinyl chloride flooring which contain phthalates have been found to increase the risk of ASD's in children [88].

REFERENCES

1. Visser SN, Bitsko RH, Danielson ML, Perou R, Blumberg SJ. Increasing prevalence of parent-reported attention-deficit/hyperactivity disorder among children United States, 2003 and 2007. *Morbidity and Mortality Weekly Report* 2010;59:1439-43.
2. Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS. Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Archives of Pediatrics & Adolescent Medicine* 2007;161:857-64.
3. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006;368:2167-78.
4. Newschaffer CJ, Falb MD, Gurney JG. National autism prevalence trends from United States special education data. *Pediatrics* 2005; 115:e277-282.
5. Prior M. Is there an increase in the prevalence of autism spectrum disorders? *Journal of Paediatrics and Child Health* 2003; 39:81-82.
6. Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatrica* 2005; 94:2-15.
7. Bellinger D, Sloman J, Leviton A, Rabinowitz M, Needleman HL, Waterman C. Low-level lead exposure and children's cognitive function in the preschool years. *Pediatrics* 1991;87:219-27.
8. Lanphear BP, Dietrich K, Auinger P, Cox C. Cognitive deficits associated with blood lead concentrations <10 micrograms/dL in U.S. children and adolescents. *Public Health Reports* 2000;115:521-29.
9. Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environmental Health Perspectives* 2006;114:1904-1909.
10. Surkan PJ, Zhang A, Trachtenberg F, Daniel DB, McKinlay S, Bellinger DC. Neuropsychological function in children with blood lead levels <10 microg/dL. *Neurotoxicology* 2007;28:1170-77.
11. Calderon J, Navarro ME, Jimenez-Capdeville ME, Santos-Diaz MA, Golden A, Rodriguez-Leyva I, et al. Exposure to arsenic and lead and neuropsychological development in Mexican children. *Environmental Research* 2001;85:69-76.
12. Stewart PW, Sargent DM, Reihman J, Gump BB, Lonky E, Darvill T, et al. Response inhibition during Differential Reinforcement of Low Rates (DRL) schedules may be sensitive to low-level polychlorinated biphenyl, methylmercury, and lead exposure in children. *Environmental Health Perspectives* 2006;114:1923-29.
13. Bakir F, Rustam H, Tikriti S, Al-Damluji SF, Shihristani H. Clinical and epidemiological aspects of methylmercury poisoning. *Postgraduate Medical Journal* 1980;56:1-10.
14. Harada M, Akagi H, Tsuda T, Kizaki T, Ohno H. Methylmercury level in umbilical cords from patients with congenital Minamata disease. *Science of the Total Environment* 1999;234:59-62.
15. Crump KS, Kjellstrom T, Shipp AM, Silvers A, Stewart A. Influence of prenatal mercury exposure upon scholastic and psychological test performance benchmark analysis of a New Zealand cohort. *Risk Analysis* 1998;18:701-13.
16. Kjellstrom TP, Kennedy P, Wallis P, Mantell C. Physical and Mental Development of Children with Prenatal Exposure to Mercury From Fish. Stage 2: Interviews and Psychological Tests at Age 6. Solna, Sweden. *National Swedish Environmental Protection Board* 1989;3642.

17. Budtz-Jorgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. *Environmental Health Perspectives* 2007;115:323-27.
18. Debes F, Budtz-Jorgensen E, Weihe P, White RF, Grandjean P. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicology and Teratology* 2006;28:536-47.
19. Grandjean P, Budtz-Jorgensen E, White RF, Jorgensen PJ, Weihe P, Debes F, et al. Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. *American Journal of Epidemiology* 1999;150:301-05.
20. Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicology and Teratology* 1997;19:417-28.
21. Jacobson JL, Jacobson SW. Prenatal exposure to polychlorinated biphenyls and attention at school age. *Journal of Pediatrics* 2003;143:780-88.
22. Sagiv SK, Nugent JK, Brazelton TB, Choi AL, Tolbert PE, Altshul LM, et al. Prenatal organochlorine exposure and measures of behavior in infancy using the Neonatal Behavioral Assessment Scale (NBAS). *Environmental Health Perspectives* 2008;116:667-73.
23. Stewart P, Fitzgerald S, Reihman J, Gump B, Lonky E DT, Pagano J, et al. Prenatal PCB exposure, the corpus callosum, and response inhibition. *Environmental Health Perspectives* 2003;111:1670-77.
24. Stewart P, Reihman J, Gump B, Lonky E, Darvill T, Pagano J. Response inhibition at 8 and 9 1/2 years of age in children prenatally exposed to PCBs. *Neurotoxicology and Teratology* 2005;27:771-80.
25. Stewart PW, Lonky E, Reihman J, Pagano J, Gump BB, Darvill T. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. *Environmental Health Perspectives* 2008;116:1416-22.
26. Lai TJ, Liu X, Guo YL, Guo NW, Yu ML, Hsu CC, et al. A cohort study of behavioral problems and intelligence in children with high prenatal polychlorinated biphenyl exposure. *Archives of General Psychiatry* 2002;59:1061-66.
27. Vreugdenhil HJ, Mulder PG, Emmen HH, Weisglas-Kuperus N. Effects of perinatal exposure to PCBs on neuropsychological functions in the Rotterdam cohort at 9 years of age. *Neuropsychology* 2004;18:185-93.
28. Chen YC, Guo YL, Hsu CC, Rogan WJ. Cognitive development of Yu-Cheng ("oil disease") children prenatally exposed to heat-degraded PCBs. *Journal of the American Medical Association* 1992;268:3213-18.
29. Chen YC, Yu ML, Rogan WJ, Gladen BC, Hsu CC. A 6-year follow-up of behavior and activity disorders in the Taiwan Yu-cheng children. *American Journal of Public Health* 1994;84:415-21.
30. Rogan WJ, Gladen BC, Hung KL, Koong SL, Shih LY, Taylor JS, et al. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. *Science* 1988;241:334-36.
31. Bouchard M, Laforest F, Vandelaer L, Bellinger D, Mergler D. Hair manganese and hyperactive behaviors:pilot study of school-age children exposed through tap water. *Environmental Health Perspectives* 2007;115:122-27.
32. Eriksson P, Jakobsson E, Fredriksson A. Brominated flame retardants:a novel class of developmental neurotoxicants in our environment? *Environmental Health Perspectives* 2001;109:903-08.
33. Kuriyama SN, Talsness CE, Grote K, Chahoud I. Developmental exposure to low dose PBDE 99:effects on male fertility and neurobehavior in rat offspring. *Environmental Health Perspectives* 2005;113:149-54.
34. Rice DC, Reeve EA, Herlihy A, Zoeller RT, Thompson WD, Markowski VP. Developmental delays and locomotor activity in the C57BL/6J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. *Neurotoxicology and Teratology* 2007;29:511-20.
35. Greer MA, Goodman G, Pleus RC, Greer SE. Health effects assessment for environmental perchlorate contamination:the dose response for inhibition of thyroidal radioiodine uptake in humans. *Environmental Health Perspectives* 2002;110:927-37.
36. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine* 1999;341:549-55.
37. Miller MD, Crofton KM, Rice DC, Zoeller RT. Thyroid-disrupting chemicals:interpreting upstream biomarkers of adverse outcomes. *Environmental Health Perspectives* 2009;117:1033-41.
38. Nigg JT. What Causes ADHD? Understanding What Goes Wrong and Why. *New York, The Guilford Press* 2006.
39. Pastor PN, Reuben CA. Diagnosed attention deficit hyperactivity disorder and learning disability:United States, 2004-2006. *Vital and Health Statistics* 2008;10.
40. Nigg JT, Knottnerus GM, Martel MM, Nikolas M, Cavanagh K, Karmaus W, et al. Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. *Biological Psychiatry* 2008;63:325-31.
41. Tuthill RW. Hair lead levels related to children's classroom attention-deficit behavior. *Archives of Environmental Health* 1996;51:214-20.
42. Wang HL, Chen XT, Yang B, Ma FL, Wang S, Tang ML, et al. Case-control study of blood lead levels and attention-deficit hyperactivity disorder in Chinese children. *Environmental Health Perspectives* 2008;116:1401-06.
43. Sagiv SK, Thurston SW, Bellinger DC, Tolbert PE, Altshul LM, Korrick SA. Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. *American Journal of Epidemiology* 2010;171:593-601.
44. Cheuk DK, Wong V. Attention-deficit hyperactivity disorder and blood mercury level:a case-control study in chinese children. *Neuropediatrics* 2006;37:234-40.
45. Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, et al. Impact of prenatal chlорpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. *Pediatrics* 2006;118:e1845-59.
46. Ribas-Fito N, Torrent M, Carrizo D, Julvez J, Grimalt JO, Sunyer J. Exposure to hexachlorobenzene during pregnancy and children's social behavior at 4 years of age. *Environmental Health Perspectives* 2007;115:447-50.
47. Kim BN, Cho SC, Kim Y, Shin MS, Yoo HJ, Kim JW, et al. Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. *Biological Psychiatry* 2009;66:958-63.
48. Froehlich TE, Lanphear BP, Auinger P, Hornung R, Epstein JN, Braun J, et al. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. *Pediatrics* 2009;124:e1054-63.
49. Thapar A, Holmes J, Poulton K, Harrington R. Genetic basis of attention deficit and hyperactivity. *British Journal of Psychiatry* 1999;174:105-111.
50. DiMaio S, Grizenko N, Joober R. Dopamine genes and attention-deficit hyperactivity disorder:a review. *Journal of Psychiatry and Neuroscience* 2003;28:27-38.
51. Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. *Biological Psychiatry* 1998;44:951-958.
52. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry* 2001;158:1052-57.
53. Jucaite A, Farnell E, Halldin C, Forssberg H, Farde L. Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder:association between striatal dopamine markers and motor hyperactivity. *Biological Psychiatry* 2005;57:229-38.
54. Sagvolden T, Johansen EB, Aase H, Russell VA. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences* 2005;28:397-419.
55. Agrawal AK, Tilson HA, Bondy SC. 3,4,3',4'-Tetrachlorobiphenyl given to mice prenatally produces long-term decreases in striatal dopamine and receptor binding sites in the caudate nucleus. *Toxicology Letters* 1981;7:417-424.
56. Bourdineaud JP, Fujimura M, Laclau M, Sawada M, Yasutake A. Deleterious effects in mice of fish-associated methylmercury

- contained in a diet mimicking the Western populations' average fish consumption. *Environment International* Epub2010.
57. Cory-Slechta DA. Relationships between lead-induced learning impairments and changes in dopaminergic, cholinergic, and glutamatergic neurotransmitter system functions. *Annual Review of Pharmacology and Toxicology* 1995;35:391-415.
 58. Cory-Slechta DA, O'Mara DJ, Brockel BJ. Nucleus accumbens dopaminergic medication of fixed interval schedule-controlled behavior and its modulation by low-level lead exposure. *Journal of Pharmacology and Experimental Therapeutics* 1998;286:794-805.
 59. Cory-Slechta DA, Pokora MJ, Preston RA. The effects of dopamine agonists on fixed interval schedule-controlled behavior are selectively altered by low-level lead exposure. *Neurotoxicology and Teratology* 1996;18:565-75.
 60. Dam K, Garcia SJ, Seidler FJ, Slotkin TA. Neonatal chlorpyrifos exposure alters synaptic development and neuronal activity in cholinergic and catecholaminergic pathways. *Brain Research, Developmental Brain Research* 1999;116:9-20.
 61. Kala SV, Jadhav AL. Low level lead exposure decreases in vivo release of dopamine in the rat nucleus accumbens:a microdialysis study. *Journal of Neurochemistry* 1995;65:1631-35.
 62. Khan MA, Lichtensteiger CA, Farooq O, Mumtaz M, Schaeffer DJ, Hansen LG. The hypothalamo-pituitary-thyroid (HPT) axis:a target of nonpersistentortho-substituted PCB congeners. *Toxicological Sciences* 2002;65:52-61.
 63. Seegal RF, Okoniewski RJ, Brosch KO, Bemis JC. Polychlorinated biphenyls alter extraneuronal but not tissue dopamine concentrations in adult rat striatum:an in vivo microdialysis study. *Environmental Health Perspectives* 2002;110:1113-37.
 64. Seegal RF, Pappas BA, Park GA. Neurochemical effects of consumption of Great Lakes salmon by rats. *Regulatory Toxicology and Pharmacology* 1998;27:S68-75.
 65. Shain W, Bush B, Seegal R. Neurotoxicity of polychlorinated biphenyls:structure-activity relationship of individual congeners. *Toxicology and Applied Pharmacology* 1991;111:33-42.
 66. Zuch CL, O'Mara DJ, Cory-Slechta DA. Low-level lead exposure selectively enhances dopamine overflow in nucleus accumbens:an in vivo electrochemistry time course assessment. *Toxicology and Applied Pharmacology* 1998;150:174-85.
 67. National Dissemination Center for Children with Disabilities. 2010. Disability Fact Sheet-No. 7:Learning Disabilities. Available from:<http://www.nichcy.org/InformationResources/Documents/NICHCY%20PUBS/fs7.pdf>. [Cited April 6, 2010].
 68. National Center for Learning Disabilities. 2010. LD at a Glance. Available from:<http://www.ncld.org/ld-basics/ld-explained/basic-facts/learning-disabilities-at-a-glance>. [Cited April 6, 2010].
 69. Lyngbye T, Hansen ON, Trillingsgaard A, Beese I, Grandjean P. Learning disabilities in children:significance of low-level lead-exposure and confounding factors. *Acta Paediatrica Scandinavica* 1990;79:352-60.
 70. Marlowe M, Cossairt A, Welch K, Errera J. Hair mineral content as a predictor of learning disabilities. *Journal of Learning Disabilities* 1984;17:418-21.
 71. Pihl RO, Parkes M. Hair element content in learning disabled children. *Science* 1977;198:204-06.
 72. Lee DH, Jacobs DR, Porta M. Association of serum concentrations of persistent organic pollutants with the prevalence of learning disability and attention deficit disorder. *Journal of Epidemiology & Community Health* 2007;61:591-596.
 73. Capel ID, Pinnock MH, Dorrell HM, Williams DC, Grant EC. Comparison of concentrations of some trace, bulk, and toxic metals in the hair of normal and dyslexic children. *Clinical Chemistry* 1981;27:879-81.
 74. Counter SA, Buchanan LH, Ortega F. Zinc protoporphyrin levels, blood lead levels and neurocognitive deficits in Andean children with chronic lead exposure. *Vital and Health Statistics* 2008;41:41-47.
 75. Leviton A, Bellinger D, Allred EN, Rabinowitz M, Needleman H, Schoenbaum S. Pre-and postnatal low-level lead exposure and children's dysfunction in school. *Environmental Research* 1993;60:30-43.
 76. McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ. Port Pirie cohort study:environmental exposure to lead and children's abilities at the age of four years. *New England Journal of Medicine* 1988;319:468-75.
 77. Needleman HL, Schell A, Bellinger DC, Leviton A, Allred EN. The long term effects of exposure to low doses of lead in childhood, an 11-year follow-up report. *New England Journal of Medicine* 1990;322:83-88.
 78. Canfield RL, Gendle MH, Cory-Slechta DA. Impaired neuropsychological functioning in lead-exposed children. *Developmental Neuropsychology* 2004;26:513-40.
 79. Froehlich TE, Lanphear BP, Dietrich KN, Cory-Slechta DA, Wang N, Kahn RS. Interactive effects of a DRD4 polymorphism, lead, and sex on executive functions in children. *Biological Psychiatry* 2007;62:243-249.
 80. Hertz-Pannier I, Delwiche L. The rise in autism and the role of age at diagnosis. *Epidemiology* 2009;20:84-90.
 81. Pessah IN, Seegal RF, Lein PJ, LaSalle J, Yee BK, Van De Water J, et al. Immunologic and neurodevelopmental susceptibilities of autism. *Neurotoxicology* 2008;29:532-45.
 82. Kinney DK, Barch DH, Chayka B, Napoleon S, Munir KM. Environmental risk factors for autism:do they help cause de novo genetic mutations that contribute to the disorder? *Medical Hypotheses* 2010;74:102-06.
 83. Adams JB, Romdalvik J, Ramanujam VM, Legator MS. Mercury, lead, and zinc in baby teeth of children with autism versus controls. *Journal of Toxicology and Environmental Health* 2007;70:1046-51.
 84. Bradstreet J, Geier DA, Kartzinel JJ, Adams JB, Feier MR. A case-control study of mercury burden in children with autistic spectrum disorders. *Journal of American Physicians and Surgeons* 2003;8.
 85. Desoto MC, Hitlan RT. Blood levels of mercury are related to diagnosis of autism:a reanalysis of an important data set. *Journal of Child Neurology* 2007; 22:1308-11.
 86. Hertz-Pannier I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. Blood mercury concentrations in CHARGE Study children with and without autism. *Environmental Health Perspectives* 2010;118:161-66.
 87. Palmer RF, Blanchard S, Wood R. Proximity to point sources of environmental mercury release as a predictor of autism prevalence. *Health Place* 2009;15:18-24.
 88. Larsson M, Weiss B, Janson S, Sundell J, Bornehag CG. Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age. *Neurotoxicology* 2009;30:822-31.