The Importance of Micronutrients in Autism

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Essential Nutrients in Autism

- Iron
- Zinc
- Iodine
- B12/Folate/B6/Selenium
- Essential Fatty Acids
- Protein/Sugar

Where’s the Research?

Iron

Beard & Connor. Annu Rev Nutr 2003; 23: 41-58

Iron deficiency in early life is associated with delayed development…. which persists…… after iron therapy has corrected iron status.

Iron is required for as a cofactor for many reactions in the body.

Iron (heme) is the carrier molecule for oxygen in the blood. Without adequate iron, there is inadequate transport of oxygen to the brain, the lungs, the heart and the muscles.

Iron deficiency is therefore synonymous with hypoxia, and is associated with decreased neurological development, decreased physical energy, laboured breathing, decreased immunity, and behavioural changes.

Iron

Latif et al. Autism. 2002; 6(1): 103-4

Iron Deficiency in Autism and Asperger Syndrome

52 children with Autism

- 12% anemia
- 52% low ferritin

44 children with Asperger Syndrome

- 5% anemia
- 14% low ferritin

Iron

Dosman et al. Pediatr Neurol 2007; 36(3): 152-8.

Children with Autism: Effect of Iron Supplementation on Sleep and Ferritin

33 children

8 week open trial of oral iron suplementation

77% had restless sleep at baseline
69% of preschoolers and 35% school age children = low iron intake

Significant increase in serum ferritin (16 to 29 mcg/L)
Significant improvements in Sleep Disturbance Scale.

Iron

- *Konofal et al. Arch Pediatr Adolesc Med 2004; 158(12): 1113-5*
- **Iron deficiency causes abnormal dopaminergic neurotransmission and may contribute to the physiopathology of ADHD.**
- 53 Children w ADHD; 27 Controls; 4-14 years
- Children with ADHD - ferritin < 30 ng/ml in 84%
  - mean 23 +/- 13 ng/ml
- Control Children - ferritin < 30 ng/ml in 18%
  - mean 44 +/- 22 ng/ml
- Low serum ferritin significantly correlated with severity of Connor ADHD rating scale ($p<0.02$) and cognitive deficits ($p<0.01$).

Iron

- *Sever Y et al. Neuropsychobiology 1997; 35(4): 178-80.*
- 14 non-anemic Israeli boys with ADHD (7-11 years)
- Ferrocal @ 5mg/kg/day x 30 days.
- Ferritin increase 25.9 +/- 9.2 to 44.6 +/- 18 ng/ml
- Connor Rating Score decrease 17.6 +/- 4.5 to 12.7 +/-5.4.

- *Konofal E et al. Pediatrics 2005; 116(5): 732-4.*
- 3 year old French child with hyperactivity, AD, impulsivity and sleep problems
- Connor Teacher and Parent Rating Scale 30 and 32 resp.
- Ferrous sulfate 80 mg/d x 8 months
- Serum ferritin increase from 12 to 102 ng/ml
- Connor Ratings decrease to 19 and 13 resp.

Iron Content of Food

- Select Summary of Changes in the Mineral Content of Vegetables, Fruit and Meat Between 1940 and 1991

Year of Analysis	Mineral	Vegetables	Fruit	Meat
1991	(Na)	Less 49%	Less 29%	Less 30%
1991	(K)	Less 16%	Less 19%	Less 16%
1991	(P)	Plus 9%	Plus 2%	Less 28%
1991	(Mg)	Less 24%	Less 16%	Less 10%
1991	(Ca)	**Less 46%**	Less 16%	Less 41%
1991	**(Fe)**	Less 27%	Less 24%	**Less 54%**
1991	(Cu)	Less 76%	Less 20%	Less 24%

Zinc

- *Shay & Mangian. J Nutr 2000; 130 (5S): 1493S-9S*
- Zinc is essential to more than 100 reactions in the body.
- Zinc is necessary for the immune system, growth, lean tissue development, bone and tooth integrity, neurological development, behaviour, appetite and taste bud integrity, digestive enzyme production and release
- Children with low zinc status may present with lowered immunity, poor muscle development, altered height development, decreased appetite, decreased range of foods, predisposition for carbohydrate-rich foods, digestive disorders esp diarrhea.

Zinc

- *Jing et al. Biol Tace Elem Res 2007; 115(2): 187-94*
- It has been known for more than 50 years, that zinc deficiency regularly and consistently causes anorexia (loss of appetite)
- Deficiency of zinc produces several pathological disorders and abnormalities in its metabolism, such as poor efficiency of growth and growth retardation
- *Rains & Shay. J Nutr 1995; 125(11): 2874-9*
- Zinc depletion decreased food intake but increased carbohydrate intake among rats.
- Zinc repletion increased food intake, and increased protein intake by 50%.

Zinc

- Zinc is an essential component of the enzymes necessary for protein digestion. (Prasad & Oberleas, 1971)
- The secretion of the enzymes by the pancreas is also a zinc-dependent process (Mills et al, 1969)
- The byproducts of casein and gluten maldigestion are opioid peptides know as casomorphine and gliadomorphine
- Elevated levels of these opioids have been documented in the urine of children with autism (Reichelt et al, 1993, Shattock et al, 1991), and can cross the blood-brain barrier (Gao et al, 2000)
- The enzyme necessary for degrading these opioids, dipeptidyl peptidase (DPP IV), is zinc dependent.

Zinc

- *Jory & McGinnis*
- 20 children with autism
- RBC zinc = 134.95 +/- 23.94

- 15 control children
- RBC zinc = 148.27 +/- 17.09 $p<0.03$

- *Yorbik O et al. Turk Psikiyatri Derg 2004; 15(4): 276-81.*
- 21 boys with oppositional defiance disorder (ODD) (mean age 8.6)
- 24 controls (mean age 8.3).
- 61% of ODD had comorbid ADHD
- plasma zinc was significantly lower in ODD children ($p<0.05$)

Zinc

- *Arnold, LE et al. J Child Adolesc Psychopharmacol 2005; 15(4): 628-36.*

- 48 children with ADHD, aged 5-10 years.
- Serum zinc levels highly correlated with parent-teacher ratings of inattention ($p<0.004$).

- *Bilici M et al. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28(1): 181-90.*

- N = 72 f, 328 m, mean age 9.6 years; ADHD
- randomized to 150 mg zn sulfate/d or placebo.
- Zinc group was statistically superior in reducing hyperactive, impulsive and impaired socialization symptoms but not reducing attention deficits.

Iodine

- *Adams et al. Biol Tace Elem Res 2006; 110 (3): 193-209.*
- Iodine is an essential component of the thyroid hormones T3 (tyrosine + 3 iodine) and T4 (tyrosine + 4 iodine)
- Iodine levels were 45% lower (p=0.005) among children with autism. The low iodine levels are consistent with previous reports of abnormal thyroid function, which likely affect development of speech and cognitive skills.

Methylation Hypothesis of Autism

- *Deth et al. Neurotoxicology 2008; 29(1): 190-201.*
- Autistic children exhibit evidence of oxidative stress and impaired methylation.
- Genetic polymorphisms adversely affecting sulfur metabolism, methylation, detoxification, dopamine signaling and the formation of neuronal networks occur more frequently in autistic individuals.
- Redox/methylation hypothesis of autism: oxidative stress, initiated by environmental factors in genetically vulnerable individuals, leads to impaired methylation and neurological deficits secondary to reductions in the capacity of synchronizing neural networks.

B12 and Methylation

- *James et al. J Autism Dev Disord 2008; Epub.*
- Parents share similar metabolic deficits in methylation capacity and glutathione-dependent antioxidant/detoxification capacity observed in many autistic children.

- *Jones et al. J Nutr 2007; 137(5): 1307-13.*
- In linear regression, infant plasma B-12 concentration was strongly and positively associated with maternal plasma vitamin B-12 and B-12 intake from complementary foods (Guatemala)

B12 and Myelination

- *Lovblad et al. Pediatr Radiol 1997; 27(2): 155-8.*
- Lack of vitamin B-12 in the maternal diet during pregnancy has been shown to cause severe retardation of myelination in the nervous system.
- 14.5 month old child of vegetarian parents had severe hypotonia and psychomotor retardation.
- MRI indicated severe brain atrophy with signs of retarded myelination, esxpecially of the frontal and temporal lobes.
- B12 treatment improved clinical and imaging abnormalities.

B12 and Myelination

- *Casella et al. Brain Devb. 2005; 27(8): 592-4.*
- 6 month child with insidious developmental regression and brain atrophy on CT scan
- Vitamin B12 therapy normalized clinical symptoms and brain CT.
- *Smolka et al. Cas Lek Cesk 2001; 140(23): 732-5.*
- 8 mo child with megaloblastic anemia, high methymalonic acid (MMA) and high homocysteine
- Vitamin B12 treatment normalized biochemical and metabolic markers, but there continued a generalized hypotonia, microcephaly and language delay.

Etiology of Low B12 Status

- *Volkov et al. Ann Nutr Metab 2007; 51(5): 468-70.*
- As a result of media information associating meat, cholesterol and cardiovascular disease, consumption of meat, particularly beef, has decreased.
- In addition to changes in lifestyle among those of high socioeconomic status, the existence of poverty is a second main factor in the decreasing consumption of animal products
- Together, these factors have contributed to a decrease in the level of vitamin B12 in the general population, and an increase in pathology due to vitamin B12 deficiency.

Etiology of Low B12 Status

- *Johnston. Nutr Rev 2007; 65(10): 451-458.*
- There is concern that high intakes of folic acid from fortified food and dietary supplements might mask the macrocytic anemia of vitamin B12 deficiency, thereby eliminating an important diagnostic sign.
- *Ray et al. Clin Biochem 2003; 36(5): 387-91.*
- Using combined provincial data from Ontario, the mean serum folate concentration increased by 64% after fortification between 1996 and 2000.
- The prevalence of combined B12 insufficiency with supraphysiological concentrations (extra-high) of serum folate increased from 0.09% to 0.61% after folate fortification.

Etiology of Low B12 Status

- *Selhub et al. Proc Natl Acad Sci USA 2007; 104(50): 19995-20000.*
- A recent study of older participants in the 1999-2002 NHANES survey demonstrated a combination of high serum folate and low vitamin B12 status which was associated with a high prevalence of cognitive impairment and anemia than other combinations of vitamin B12 and folate status.
- In subjects with lower serum vitamin B12, concentrations of homocysteine and methylmaloninc acid (associated with B12 deficiency) increased as serum folate levels increased, suggesting a worsening of B12 status with increasing folate intake.

B12 Deficiency in Autism

- *Pasca SP et al. Life Sci 2005; Nov 16.*

- 12 children with autism and 9 controls (mean age 8.3)

- Homocysteine levels ($p<0.01$)
  - autism 9.83 +/- 2.75 mumol/L
  - controls 7.51 +/- 0.93 mumol/L
  -

- Among children with autism, there was a strong negative correlation between homocysteine, glutathione activity and suboptimal B12 levels.

- Glutathione is a B12 and selenium-dependent molecule.

B12 Deficiency in Autism

- *Wakefield et al. Lancet 1998; 351(9103): 637-641.*
- 12 children with regressive pervasive developmental disorder and chronic enterocolitis. 9/12 with autism, 1/23 with disintegrative psychosis, 2/12 with postviral encephalitis.
- Low haemoglobin in 4/12 (33%)
- High urinary methylmalonic acid (MMA) compared to controls ($p<0.003$).
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- MMA is an early diagnostic indicator of cobalamin deficiency - superior to serum B12.

B12 Deficiency in Infancy

- *Biancheri et al. Neuropediatrics 2001; 32 (1): 14-22.*
- Early onset subtype of cobalamin deficiency is characterised by feeding difficulties, failure to thrive, hypotonia, seizures, microcephaly and developmental delay.
- In 11/14 patients (79%), there was selective white matter atrophy shown by both neuroradiologic and neurophysiological studies.
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- Mental retardation present in most patients
- Possibly mediated through a reduced supply of methyl groups

Methylation Intervention in Autism

- *SJ James et al. Am J Clin Nutr 2004;80:1611-7*

- Intervention 1:
  - 8 autistic children
  - 800 mcg folinic acid + 1000 mg DMG (betaine) x 3 months

  Significant increases in methionine, SAM, homocysteine, cystathionine, cysteine, total glutathione, SAM:SAH and tGSH:oGSH.

  Normalization of methionine, SAM, SAH, adenosine and homocysteine to Control children's levels.

  Improvement but NOT normalisation of tGSH, oGSH, tGSH:oGSH ratio.

Methylation Intervention in Autism

- *SJ James et al. Am J Clin Nutr 2004;80:1611-7*
- Intervention 2:
  - 800 mcg folinic acid, 1000 mcg DMG AND 75 ug/kg injectible methylcobalamin (methylB12) x 1 month.
- Further decreases in adenosine and oGSH
- Further increases in methionine, cysteine, tGSH, SAM:SAH and tGSH:oGSH to Control children's levels
- **Clinical improvements in speech and cognition noted by attending physician but not measured in a quantifiable manner.**

Protein Intake

- *Morgan J et al. J Pediatr Gastroenterol Nutr 2004; 39(5) 493-8.*
- 144 full-term 4 month olds monitored to 24 months.
- Meat intake from 4-16 months had a significant positive correlation with psychomotor developmental indices ($p<0.013$)
- *Shannon E et al. J Nutr 2003; 133: 3965S-71S*
- 155 grade 1 Kenyan children.
- Meat, Milk, Energy suppl diet or placebo x 21 months.
- Children receiving supplemental food with meat significantly outperformed all other groups on performance tests ($p<0.001$)
- No diff in performance among milk, energy or placebo .

Protein/Neurotransmitters in Autism

- *Zeisel SH. Adv Pediatr 1986: 33: 23-47.*
- Tryptophan and tyrosine in the diet are used as precursors for neuronal synthesis of serotonin, dopamine and norepinephrine.
- *Naruse et al. No To Hattatsu 1989; 21 (2): 181-189.*
- Among a subgroup of autistic infants, there was a marked disturbance in uptake of tryptophan and phenyalanine from the intestine into the blood.
- Among a further subgroup, there was a decrease in blood turnover of tyrosine.

Neurotransmitters/Zinc Interaction

- *Johnson S. Med Hypotheses 2001; 56(5): 641-645.*
- Serotonin is an essential precursor to melatonin synthesis.
- Serotonin synthesis requires zinc-dependent enzymes.
- Zinc deficiency may therefore limit the production of both serotonin and melatonin.

- *Wallwork et al. J Nutr. 1223(3): 514-519.*
- In the rat model, zinc deficiency is associated with significant increases in brain norepinephrine, an important neurotransmitter.

Essential Fatty Acids

- *Chen JR et al. J Nutr Biochem 2004; 15(8): 467-72.*

- 58 with ADHD (mean age 8.5); 52 controls (mean age 7.9)
- RBC linoleic (n-6) and DHA (n-3) significantly lower in Taiwanese children with ADHD but no significant differences in intake.

- *Ross BM et al. Nutr Neurosci 6(5): 277-81.*

- 10 children with ADHD and 12 controls
- Significantly higher levels of exhaled ethane among children with ADHD.
- High ethane is indicative of excessive oxidative breakdown of n-3 fatty acids.

Essential Fatty Acids

- *Richardso & Puri. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26(2): 233-239.*

- 41 children with ADHD and learning difficulties
- Supplemented with HUFAs or placebo x 12 weeks
- Significant increases in cognitive and behaviour rating scales

- *Vancassel et al. Prostaglandins Leukot Essent Fatty Acids 2001; 65 (1): 1-7.*

- Normal n-6 PUFA levels of autistic children compared with controls with mental retardation
- 23% lower n-3 PUFA for autistic children than controls

Tests

- CBC and smear
- serum ferritin
- serum B12
- RBC folate
- homocysteine/MMA
- alkaline phosphatase
- fasting blood sugar and triglycerides
- AST/ALT
- TSH, T3 and T4