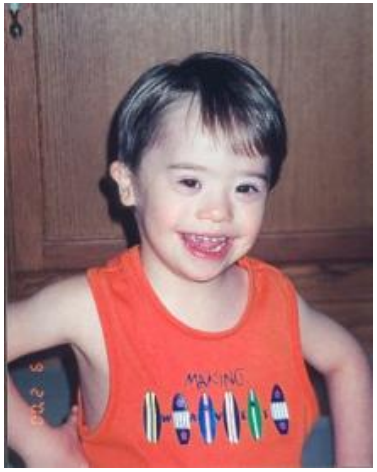
Joan Jory RD MSc PhD



# Micronutrient needs for growth, development and disease management in Down Syndrome - an evidence base.©

Hamilton-November 2015

# Objectives

To provide an evidence base for a trisomy effect on biochemical micronutrient needs for growth, development and disease management in Down Syndrome.

To provide an evidence base for biochemical micronutrient intervention to optimize growth and development, and to mitigate and manage related diseases of the thyroid, leukemia and Alzheimer's-like neurological decline, in Down Syndrome.

# Down Syndrome: the Implications

Down Syndrome results from a (third arm) on chromosome 21.

This trisomy is associated with changes in:

Neurological development

Physical growth

Muscle to fat ratio

Immunity and resistance to infection

Risk of leukemia

Risk of thyroid dysfunction

Risk of diabetes and blood sugar abnormalities

Precocious aging

Alzheimer-like lesions

# Down Syndrome: an Analogy

1. A 2-arm chromosome (normal) is like a recipe:

Arms x 2 → Ingredients x 2 → Product x 2

2. A 3-arm chromosome (trisomy) increases production by 50%:

Arms x 3 → Ingredients x 3 → Product x 3

<u>Where do the extra ingredients come from?</u>

# Down Syndrome: the Functional Paradigm

3. 50% more ingredients required causes:

a) faster depletion of ingredient stores

b) 'stealing' ingredients from other functions in the body

4. Decreased availability of ingredients leads to:

a) → decreased ingredients for growth + development

b) → decreased ingredients for disease prevention

c) → decreased ingredients for healthy aging

# Down Syndrome: Enzyme Overexpression

There are three well-documented enzymes coded on Chromosome 21 which increase requirements for zinc, selenium and vitamin B12 :

1) Cu-Zn SuperOxide Dismutase (SOD): a zinc dependent enzyme.

2) Glutathione Peroxidase: a selenium dependent enzyme

3) Cystathione Beta Synthase: a folate and B12 dependent enzyme

# Down Syndrome: What Evidence of Excess SOD?

Superoxide Dismutase (SOD) levels are increased (47%) in Down Syndrome children and teenagers.

Garlet TR et al. Life Sci 2013 Oct 11;93(16):558-63.

Overproduction of Superoxide Dismutase (SOD) increases oxidative stress and increases oxidative damage to proteins in children with Down Syndrome .

Zitnanova I. Clin Chem Lab Med 2006; 44(3):306-10.

CuZn-SOD is increased by 50% in Down Syndrome as a result of gene dosing. Excess CuZnSOD might result in peroxidative brain damage and possibly contribute to accelerated aging and age-related neuropathology.

Ceballos-Picot I et al. EXS 1992;62:89-98.

# Down Syndrome: Implications of Low Zinc

Low zinc status in Down Syndrome is associated with:
(Mazurek D. Rocz Panstw Zakl Hig 2015;66(3):189-94)

1) decreased immune status

2) decreased growth and body composition

3) thyroid dysfunction

4) altered taste perception

# Down Syndrome: Zinc and Immunity

18 children with Down Syndrome

History of recurrent respiratory, ear and skin infections

2 cycles of zinc supplementation 10 months apart

1 mg elemental zinc/kg/day x 2 months each

Decreased infections, increased school attendance, increased T-lymphocytes

Even among children with **normal plasma zinc** before supplementation

No effect on copper status.

Franceschi C et al**. J Ment Defic Res 1988**;32(Pt3):169-81..

# Down Syndrome: Zinc and Immunity

30 children with Down Syndrome

63.2% with low plasma zinc

Supplementation with zinc 5mg/kg Zn x 2 months

Normalized immunity (lymphocyte response).

0 zinc supplements x 22 months

Decreasing immunity (lymphocyte response) by 24 months.

Stabile A et al. **Clin Imunol Immunopathol 1991**; 58(2): 207-16.

# Zinc and Growth

Meta-analysis of 33 zinc supplementation studies and childhood growth.

Highly significant improvements in height

Greatest improvements among children with lowest height-for-age scores.

Highly significant improvements in weight

Brown KH et al. **Am J Clin Nutr 2002**; 75(6): 1062-71.

# Down Syndrome: Zinc and Growth

35 children with Down Syndrome

No difference in protein intake, carbohydrate or fat intake

No significant difference in dietary zinc.

Low plasma zinc in Down Syndrome (83%) and controls (61%).

Shorter height in 60% Down Syndrome and 3% of controls.

Lima AS et al. **Biol Trace Elem Res 2010;** 133(1): 20-8.

# Down Syndrome: Zinc and Growth

22 children with Down Syndrome

Supplemented with zinc (1 mg/kg) for 6-9 months.

Increased growth percentile and increased growth hormone levels

Increased growth velocity (23.84 --> 40.80 mm over 6 months).

Napolitano G et al. **Am J Med Genet 1990**;37(S7):63-65.

# Zinc and Body Composition

9 Elite female athletes

Plasma zinc is negatively associated with % fat mass.

Lower plasma zinc --> higher fat mass and lower muscle mass

Koury JC et al. Biol Trace Elem Res 2007; 115(1): 23-30.

# Down Syndrome: Zinc and Body Composition

30 adolescents with Down Syndrome

No difference in protein, fat, carbohydrate or zinc intake

No difference in plasma zinc, though low

**Greater zinc losses in urine** in Down Syndrome.

More overweight (26.7%) in Down Syndrome.

More obesity (6.6%) in Down Syndrome.

Marques RC et al. **Biol Trace Elem Res 2007**; 120(1-3): 11-8.

# Down Syndrome: Zinc and Thyroid

25 children with Down Syndrome

Plasma zinc low

Higher TSH;  no difference in T3 or T4

4 months zinc sulphate supplementation

Plasma zinc normal

TSH on par with control children

Licastro F et al. **Int J Neurosci 1992**; 65(1-4): 259-68 .

# Down Syndrome: Zinc and Thyroid

51 children with Down Syndrome

4 months of zinc sulphate supplementation:

Normalized plasma zinc and TSH

1 year after zinc supplementation stopped:

Plasma zinc decreasing

TSH increasing

Licastro F et al. **J Trace Elem Electrolytes Health Dis 1993**; 7(4): 237-9.

# Zinc and Taste Disorders

22 patients with altered taste acuity (hypogeusia)

Zinc acetate supplementation x 50 mg zinc/day.

Improvement in plasma zinc.

Normalization of taste perception for sweet, salt and bitter.

Mahaian SK et al. Am J Clin Nutr 1980'; 33(7): 1517-21.

# Down Syndrome: Zinc Safety

Meta-analysis of preventive zinc supplementation studies among infants, preschoolers and older prepubertal children.

Decreased diarrhea x 20%

Decreased acute respiratory infections x 15%

Decreased mortality in children > 1 yr x 18%

Increased growth in height

**No adverse effect on iron or copper status**.

Brown KH et al. **Food Nutr Bull 2009**; 30(1 Supp): S12-40.

# Zinc Assessment

1) Serum/plasma zinc

-> recent intake only

-> many confounding variables

2) Alkaline phosphatase (zinc enzyme)

-> functional zinc status

-> unreliable if recent growth as alk phos is mobilized into blood during growth

3) Best approach

-> combination of serum/plasma zinc AND alkaline phosphatase

# Zinc Sources in Diet

Absorption blocked by calcium, iron, fibre, phytate.

Richest food sources:

Seafood

Fish

Liver

Beef, Pork, Chicken

Beans

Cashews

Cheese

US National Institutes of Health, 2013

# Glutathione Peroxidase (GPx) in Down Syndrome

# Down Syndrome: What Evidence of Excess GPx?

18 children with Down Syndrome

RBC GPx was significantly increased.

Serum selenium was significantly decreased.

Meguid NA et al. Biol Trace Elem Res 2001; 81(1): 21-8.

29 children with Down Syndrome

RBC GPx in red cells was significantly increased

Plasma selenium was significantly decreased

Neve J et al. Clin Chim Acta 1983; 133; 209-214.

RBC GPx levels were significantly greater in the DS group

RBC GPx was significantly correlated with memory function.

Brugge K et al. Biol Psychiatry 1999; 46(12): 1682-9

# Down Syndrome: Implications of Low Selenium

Low selenium levels in Down Syndrome are associated with:

1) impaired thyroid status

2) decreased immune status

# Selenium and Thyroid

109 healthy individuals:

Decreased serum selenium

Decreased T3/T4 ratio

Decreased conversion of T4 to T3 because of low selenium status

Olivieri O et al**. Biol Trace Elem Res 1996**; 51(1): 31-41.

# Down Syndrome: Selenium and Thyroid

18 adults with Down Syndrome:

Decreased serum selenium

Decreased T4

Increased TSH

Kanavin OJ et al. **Biol Trace Elem Res 2000;** 78(1-3):35-42.

# Down Syndrome: Selenium and Immunity

**1) Natural Killer cells:**

a) Natural Killer (NK) activity is low in Down Syndrome.
Ugazio et al. Am J Med Genet Suppl 1990

b) Selenium supplementation increased natural killer cell activity in the mouse.
Kiremidjian-Schumacker & Roy. Z Ernarhrungswis 1998

**2) T-lymphocyte response:**

a) The T-lymphocyte activation response is patients with dysmorphic disorders.
Cruz et al. Ann Allergy Asthma Immunol 2009

b) Selenoprotein deficiency suppresses T-lymphocyte response.
Shrimali et al. J Biol Chemi 2008.

# Selenium Assessment

1) Serum/plasma selenium -> reflects only recent selenium intake

2) RBC selenium -> longer term selenium status

3) But, there are no established 'normal ranges' for either test

Thomson CD. Eur J Clin Nutr 2004; 58: 391-402.

# Selenium Sources in the Diet

Richest food sources:

Brazil Nuts
Mixed Nuts and Seeds
Oysters
Fish
Liver
Beef, Pork, Lamb, Chicken
Eggs
Beans

Canadian Nutrient File 2012

# Cystathione Beta Synthase (CBS) in Down Syndrome

# Down Syndrome: What Evidence of Excess CBS?

Cystathione beta synthase (CBS) levels are increased by approximately three times in the Down Syndrome brain.

High CBS causes homocysteinuria (homocysteine losses) characterized by Impaired neurological development and vascular disease.

The high CBS may explain the cognitive abnormalities in Down Syndrome, and the vulnerability to Alzheimer's Disease

Ichinohe A et al. **Biochem Biophys Res Commun 2005**; 338(3): 1547-50.

# Down Syndrome: What Evidence of Excess CBS?

42 children with Down Syndrome and 36 siblings

CBS overexpression (157%) altered homocysteine metabolism causing

a) decreased homocysteine

b) decreased glutathione.

c) folate trap due to inadequate methylation.

Improvements with addition of :

a) methyl-folate (MTHF)

b) methyl-B12 or

c) di-methyl-glycine (DMG)

Progribna M et al. **Am J Hum Genet 2001**; 69(1): 88-95

# Folate in Down Syndrome

# Down Syndrome: Folate Status

Canadian Health Measures Survey:

5248 people 6-79 years and 1162 women 15-45 years

'Folate deficiency is **virtually nonexistent** in the Canadian population'
**Very high folate among 40%** of the Canadian population

New reference range for 'normal' RBC folate: **305-1360 nmol/L**

Colapinto CK et al. **CMAJ 2011**; 183(13): 1519.

# Down Syndrome: Folate Status

Following folate fortification of flour in US :

Significant increase in maternal folate status.
''Normal'' serum and RBC folate in infants with Down Syndrome.

Significant decrease in neural tube defects and cleft palate
7% increase in Down Syndrome births (where no prenatal DS testing)

Canfield MA et al. **Birth Defects Res A Clin Mol Teratol 2005;** 73(10): 679-89.

# Down Syndrome: Folate Status

10 children with Down Syndrome

No difference in serum and RBC folate between Down Syndrome and controls

Roizen NJ and AP Amarose. Am J Med Genet 1993; 46(5): 510-2.

50 children with Down Syndrome

No difference in serum or RBC folate between Down Syndrome and controls

Onorata D et al. Pediatr Hematol-Oncol 1996; 13(3): 271-275.

113 patients with Down Syndrome

No difference in serum of RBC folate between Down Syndrome and controls

Howell A et al. Scand J Haematol 1973; 11: 140-147.

# Folate Assessment

1) Serum/plasma folate -> indicator of recent folate intake

2) RBC folate -> longer term folate status

   Reference range for Canadians: 305-1360 nmol/L

   Caution if RBC folate > 1360 nmol/L

Colapinto CK et al. CMAJ 2011; 183(13): 1519.

# Folate Sources in the Diet

All flour and flour products in Canada are fortified with synthetic folate.

All multi-B, multivitamin and prenatal vitamins contain synthetic folate.

Many protein powders and alternate non-dairy milks are synthetic folate-fortified.

Richest non-synthetic dietary sources:

Liver

Beans and lentils

Dark green vegetables

Sunflower seeds

Potatoes

Fruit

Canadian Nutrient File 2010

# B12 in Down Syndrome

# Down Syndrome: B12 Status

50 children with Down Syndrome

Increased hemoglobin
Increased mean cell volume (MCV)

No difference in serum or RBC folate
No difference in serum iron or ferritin
No difference in serum B12 **(but no test for functional B12 status)**

'Macrocytosis (is) an expression of an altered folate remethylation pathway, secondary to enhance CBS activity, the gene for which is present on chromosome 21'

Onorata D et al. **Pediatr Hematol-Oncol 1996;** 13(3): 271-275.

# Down Syndrome: B12 Status

113 patients with Down Syndrome

Increased mean cell volume (MCV)

Decreased serum B12

No difference in serum of RBC folate

Howell A et al**. Scand J Haematol 1973**; 11: 140-147.

10 children with Down Syndrome

Increased hematocrit

Increased mean cell volume (MCV)

Decreased white blood cells (WBC)

No B12 testing

No difference in serum and RBC folate

Roizen NJ & AP Amarose. **Am J Med Genet 1993;**46(5):510-2.

# Down Syndrome: B12 Status

28 adults with Down Syndrome

Increased mean cell volume (MCV)

Increased mean platelet volume (MPV)

De Alarcon PA et al**. Ped Res 1984**; 18: 235A

61 adults with Down Syndrome

Increased mean cell volume (MCV)

Decrease red cell survival

Wachtel TJ & SM Pueschel. **AJMR 1991**; 95(4):417-420.

147 adults with Down Syndrome

Increased mean cell volume (MCV) in 48%

Decreased white blood cells (WBC) and neutrophils in 20%

Prasher VP. **Down Syndrome Research and Practice 1994**; 2(2): 59-66.

# Down Syndrome and Leukemia

Myelodysplastic syndrome (MDS) associated with Down syndrome is now considered a unique biologic entity synonymous with Down syndrome-related myeloid leukemia and is **biologically distinct from other cases of childhood MDS.**

Chatterjee T & VP Choudhry. Indian J Pediatr 2013; 80(9): 764-71.

Many haematopoietic developmental defects are observed in neonates with Down Syndrome, even in the absence of transient abnormal myelopoiesis (TAM).

Studies in mouse models have **suggested a pathogenic role of deregulated expression of several chromosome 21-encoded genes** but their role remains Unclear.

Roberts I et al. Br J Haem 2014; 176(5): 587-599.

# B12 and Leukemia

Vitamin B12 deficiency can cause profound alterations in the bone marrow.

These alterations can mimic the more serious diagnosis of acute leukemia.

Two patients were suspected of having acute leukemia or myelodysplasia on the basis of bone marrow smear.

They were both found to have vitamin B12 deficiency

Parenteral vitamin B12 resulted in normalization of the bone marrow.

Aitelli C et al. **South Med J 2004**; 97(3): 295-7.

# B12 and Leukemia

205 children with pancytopenia (decreased red cells, white cells and/or platelets)

Hematological malignancies = 24%

Megaloblastic (B12/folate deficiency) anemia = 20 %

‘Leukemia and bone marrow failure are the most common causes’ of cytopenia.

But ‘megaloblastic anemias are treatable and reversible causes of pancytopenia

Zeb Jan A et al**. Pak J Med Sci 2013**; 29(5): 1153-7.

# B12 and Leukemia

Plasma concentration of methylcobalamin was significantly lower in CML patients than the reference population.

Low methylcobalamin was associated with a poor prognosis.

Gimsing P**. Br J Haematol 1995**; 89(4): 812-9.

In the mouse model of L1210 leukemia, vitamin B12 + vitamin C inhibited cell abnormal growth and increased survival.

Pydock ME. **Am J Clin Nutr 1991**; 54 (6 Suppl): 1261S-1265S.

# Down Syndrome and Myelination

Down syndrome is characterized by reduced number of neurons and delayed myelination. Kanaumi T et al. Int J Dev Neurosci 2013; 31 (8) : 796-803

The brain of a child with DS develops differently, attaining a form reduced in size and altered in configuration. Becker L et al. **Prog Clin Biol Res 1991;** 373:133-52

Dysfunction in DS is reflected in delayed myelination in pathways of the frontal and temporal lobes. Becker L et al. **Prog Clin Biol Res 1991;** 373:133-52.

# Down Syndrome and Myelination

120 children with Down Syndrome - Delayed myelination in 22.5%.

Wisniewski KE & B Schmidt-Sidor. **Clin Neuropath 1989;** 8(2):55-62.

18 month old infant with DS - Brain myelination equivalent to an 11-month infant.

Koo BK et al**. J Child Neurol 1992;** 7(4):417-21.

# B12 Deficiency and Myelination

Vitamin B(12) deficiency produces a cluster of neurological symptoms.
The underlying mechanisms = delayed myelination or demyelination.

Drok DL & LH Allen. Nutr Rev 2008; 66(5): 250-5.

14 cases of early-onset cobalamin (B12) deficiency.
Delayed neurodevelopment was identified in most cases.

Variable degree of white matter atrophy (altered myelination) was detected.

Selective white matter involvement was the most consistent finding of B12 deficiency.

Biancheri R et al. **Neuropediatr 2001;**32(1):14-22.

# B12 Deficiency and Myelination

14.5-month-old child of vegetarian parents, with severe psychomotor retardation.

MRI of the brain revealed severe brain atrophy with retarded myelination.

T**he frontal and temporal lobes** were the most severely affected

This myelination retardation was due to insufficient intake of vitamin B12.

The patient responded well to B12 therapy with improvement of clinical and imaging abnormalities.

Lovblad K et al Pediatr Radiol 1997; 27(2): 155-8.

# B12 and Major Depressive Episode/Psychosis

The cerebral symptoms may be classified as mental and ophthalmological. The mental symptoms are extremely variable and include mild disorders of mood, mental slowness, memory defect which may be gross, confusion, severe agitation and depression, delusions and paranoid behaviour, visual and auditory hallucinations, urinary and faecal incontinence in the absence of overt spinal lesions, dysphasia, violent maniacal behaviour, and epilepsy.

I**n the absence of anaemia** or of spinal signs **the diagnosis of vitamin-B12 deficiency may never be considered** until the psychosis is far too advanced to respond to treatment.

J MacDonald Holmes. Br Med J 1956; Dec 15: 1394-1397

# B12 Assessment

1) No gold standard for the diagnosis of cobalamin deficiency.

2)Therapeutic trials with pharmacologic doses of cobalamin are suggested when findings consistent with cobalamin deficiency are present regardless of the results of diagnostic tests.

Solomon LR. **Blood Rev 2007**;21(3):113-30

**Serum B12** can be repeatedly **normal in the presence of haematological and neurological symptoms of B12 deficiency**.

Mar N et al. Open J of Hematol 2012; 3: DOI-10.13055/ojhmt_3_1_2.120920.

High intakes of folic acid from fortified food and dietary supplements might mask the macrocytic anemia of vitamin B12 deficiency, eliminating an important diagnostic sign.

Johnson MA. **Nutr Rev 2007**;65(10):451-8.

Occult cobalamin deficiency could become a common disorder.

Ray JG et al. **Clin Biochem 2000**;33(5):337-43

# B12 Assessment

1) Serum B12
   Recent intake only -> will show high if supplementation
   Caution if < 400 (Japanese cutoff for serum B12)

2) MCV and MCH
   If high, may indicate folate or B12 deficiency.
   Test for RBC folate to differentiate.

3) White cell count (WBC) and subsets, red cell count (RBC) and platelets
   If low, may indicate B12 deficiency.
   Test response to sublingual B12 before considering leukemia

4) Homocysteine
   Will be low in Down Syndrome because of CBS overexpression on chromosome 21

# B12 Sources in the Diet

Only 1% of dietary B12 is passively absorbed.
99% requires Intrinsic Factor, produced in the gut

Best dietary sources:
Clams
Liver
Seafood
Trout and Salmon
Beef and wild game

Canadian Nutrient File 2010
US National Institutes of Health 2011

# Iron in Down Syndrome

# Down Syndrome: Importance of Iron

Human infants with iron deficiency anemia test lower in cognitive, motor, social-emotional, and neurophysiologic development than comparison group infants.

Lozoff B & MK Georgieff. **Sem in Pediatr Neurol 2006**; 13(3): 158-165.

Increased likelihood of mild/moderate mental retardation associated with anemia … independent of birth weight, maternal education, sex, race-ethnicity, the mother's age, or the child's age at entry into the US WIC (Women, Infants and Children Supplementation program.

Hurtado EK et al. **Am J Clin Nutr 1999**; 69(1): 115-119

# Down Syndrome: Iron Deficiency

114 children with Down Syndrome

Iron deficiency in 10%

Iron deficiency anemia in 3%

”Screening should include CBC, transferrin saturation and ferritin”

Dixon NE et al**. J Pediatr 2010**; 157(6): 967-971.

149 children with Down Syndrome

Anemia in 8.1%

**Iron deficiency in 50% of children tested for iron. (19/38)**

Tenenbaum A et al. **Int J Pediatrics 2011**; ID 813541. doi: 10.1155/2011/813541.

# Iron Assessment

1) Serum Ferritin

An acute phase reactant -> can be falsely high if infection or inflammation

Can be high if insufficient B12 for attachment of iron to red cells

Caution if ferritin < 30

2) Mean Cell Volume (MCV) and Mean Cell Hemoglobin

Low MCV and MCH in uncomplicated iron deficiency

May be normal or high if co-existing B12 or folate deficiency

Caution if <75-80 or >90-95

# Iron Assessment

3) Iron Saturation

May be low if iron deficiency

May be low if B12 deficiency

4) Serum iron

Recent iron intake; not functional iron status

5) Hemoglobin/Hematocrit

Not specific to iron deficiency

If low – can  be iron, B12 or folate deficiency

Need to test ferritin and RBC folate to determine which deficiency

# Iron Sources in the Diet

Heme iron has a higher absorption, and comes from animal products

Non-heme iron absorption is decreased by the fiber and phytate.

Iron absorption is enhanced by vitamin C, and blocked by calcium

Richest dietary sources of heme iron:

Liver and kidney

Red meat

Seafood

Fish

Richest dietary sources of non-heme iron:

Beans and Soybeans

Spinach and dark greens

Fortified cereals

Canadian Nutrient File 2010

# Vitamin A in Down Syndrome

# Down Syndrome: Vitamin A Deficiency

38 children with Down Syndrome

Serum retinol deficiency (<20mg/dL) in 18.4%

Chavez CJ et al**. An Pediatr (Barc) 2010**; 72 (3): 185-90.

12 patients with Down Syndrome

Lower plasma and red cell retinol.

Shah SN & RD Johnson. **Nutr Res 1989**; 9(7): 709-715.

33 patients with Down Syndrome

No difference in vitamin A intake, serum vitamin A or Vitamin A absorption

But skin symptoms of hypovitaminosis A

Pueschel SM et al**. J Met Defic Res 1990**; 34(Pt 3) : 269-75.

# Vitamin A Assessment and Dietary Sources

Vitamin A assessment

Serum Vitamin A (retinol): recent intake only

Richest dietary sources

Liver

Cod Liver Oil

Eggs

Goat cheese

Cow cheese

Orange vegetables (sweet potato, pumpkin, carrots)

Green vegetables (spinach, kale, swiss chard)

Canadian Nutrient File 2010

# Clinical Pearls

# Clinical Pearls

SOD is high in Down Syndrome
Zinc is often low in Down Syndrome
Zinc supplementation can increase growth in Down Syndrome
Zinc supplementation can improve immune function in Down Syndrome
Zinc supplementation can improve thyroid function in Down Syndrome

CBS is high in Down Syndrome
Macrocytosis is often present in Down Syndrome, with normal folate status
B12 deficiency can alter red cell, white cell and platelet production
B12 therapy can improve red cell, white cell and platelet production
B12 deficiency can decrease myelination and brain growth in infancy/childhood.
B12 therapy can improve symptoms of childhood myelination disorders.
B12 deficiency can cause demyelination in adults.
B12 therapy can improve symptoms of demyelination in adults.

# Clinical Pearls

Iron deficiency is common in Down Syndrome.

Iron deficiency and anemia can lead to significant changes in neurodevelopment

Low iron or low B12 can decrease transferrin saturation.

Low transferrin saturation can contribute to episodic low oxygen, esp. when heart rate is low (during sleep).

Best dietary sources for zinc, iron, selenium, vitamin A and B12:

Liver

Red meat

Game

Eggs

Fish

…. With copious addition of vegetables, especially dark green vegetables, for folate.

# Case Studies

# Case Study 1:

21 year old female with Down Syndrome

History of leukemia at age 6 -> Tmt x 3 years
Ongoing white cell suppression

History of Graves Disease at age 20
Radioactive I tmt -> permanent hypothyroidism

Excellent comprehension (receptive language)
Non- verbal

Poor physical stamina
No independent toiletting, hx of constipation
Anxious with many hand-eye stims and hand-flapping
Significant chewing of non-food items and clothing
Significant need for deep pressure
Significant sleep issues

# Case Study 1:

Blood Profile (November 2008):

| | | |
|---|---|---|
| Hemoglobin | 155 | 120-160 |
| Hematocrit | 0.45* | 0.35-0.45 |
| White Blood Cell | 3.7* | 4-11 |
| Red Blood Cell | 4.52 | 4-6 |
| MCV | 99.1* | 80-97 |
| MCH | 34.3* | 27.5-33 |
| Platelets | 179 | 150-400 |
| Neutrophils | 2.0* | 2.0-7.5 |
| | | |
| RBC Folate | 947 | >362 |
| Ferritin | 82 | 80-300 |
| | | |
| TSH | 2.95 | 0.5-4.5 |

# Case Study 1:

Interventions:

1) Give thyroxine medication upon waking; not at night

2) B12: Nasal spray (625 mcg methyl) x 1/day (AM)
Methyl 5 mg lozenge (PM)

3) Zinc: 30 mg zinc citrate capsule x 1/bedtime
In applesauce away from dairy

4) Vitamin C: 500 mg time-release
With zinc, at bedtime, in applesauce

5) Diet: increase animal protein
eliminate bananas
limit dairy to 2-3 servings/day

# Case Study 1:

Outcomes (Subjective) – Dec 2008 and Feb 2009

Much better mood and many more smiles

Much calmer, brighter and more engaged

Able to have quiet time alone without monitoring

Better eye contact

Decreased anxiety

No more compulsive need to play with feces

Is independently going to the toilet but needs help with wiping

Bowel movements daily, regular and pain-free

Walking much more instead of just sitting on floor

More stamina

Is using sign language a lot

Communicating meaningfully and frequently with parents

Sleeping well

# Case Study 1:

Blood Profile – October 2009

| | | | |
|---|---|---|---|
| Hemoglobin | 148 | (150) | 120-160 |
| Hematocrit | 0.43 | (0.45) | 0.35-0.45 |
| White Blood Cell | 4.2 | (3.7) | 4-11 |
| Red Blood Cell | 4.2 | (4.52) | 4-6 |
| MCV | 97 | (99.1) | 80-97 |
| MCH | 33.7 | (34.3) | 27.5-33 |
| Platelets | 179 | (175) | 150-400 |
| Neutrophils | 2.2 | (2.0) | 2.0-7.5 |
| | | | |
| RBC Folate | 947 | | >362 |
| Ferritin | 106 | (82) | 80-300 |
| | | | |
| TSH | 1.14 | (2.95) | 0.5-4.5 |

# Case Study 2:

4.75 year old boy with Down Syndrome
Duodenal repair at 4 months
Heart repair at 5 months

Progressing appropriately for Down Syndrome until 2.5 years
Diagnosed with acquired/regressive autism at age 3

Loss of language and happiness
Loss of eye contact
Temper meltdowns
Head banging
Decreased socialization and interactiveness
Need for deep pressure
Failure to thrive (no wt gain over 1 year)
Significant decrease in immune competence
Constipation
Does not like feet to touch ground; does not want to walk

# Case Study 2:

Blood Profile – May 2009

| | | |
|---|---|---|
| Hemoglobin | 136 | 120-160 |
| Hematocrit | 0.402 | 0.35-0.45 |
| White Blood Cell | 3.9 * | 4-11 |
| Red Blood Cell | 4.43 | 4-6 |
| MCV | 90.7 * | 75-90 |
| MCH | 30.7 | 27.5-33 |
| Platelets | 340 * | 150-400 |
| Lymphocytes | 0.95 * | 1.5-6.5 |
| | | |
| RBC Folate | 2449 * | >364 |
| Ferritin | 50 | 80-300 |
| | | |
| TSH | not available | |

# Case Study 2:

Interventions

1) Eliminate folate-containing multivitamins

2) 20 mg Iron with 500 mg Vit C x 1/2nd night

3) 60 mg Zinc Citrate x 1/2nd night

4) B12: 1000 mcg hydroxy + 5000 mcg methyl at breakfast
5000 mcg methyl at lunch and supper

5) Probiotic: daily, on empty stomach

6) Diet: Increase protein
Fruit at beginning of meals; stop bananas
Use non-dairy milks
Add nuts for fibre and oils

# Case Study 2:

Outcomes (Subjective) – July through Nov 2009

Increased eye contact
Increased signing and use of PEC symbols
Lots of smiling, laughing and social engagement
Lots of spontaneous hugging of family members
Calm, focused and able to relax
No more head banging; minimal tempers
Increased appetite and range of foods
Sudden increase in length and weight (2 inches in 3 months)
Legs are more solid; willing to walk more
Increased ability to chew and swallow
Increased mimicking (burping friend's doll, playing piano)
More musical – has started drumming again
Very interested in world around him
Constipation resolved with addition of probiotic and 125 mg magnesium
Good immunity

# Case Study 2:

Blood Profile – November 2009

| | | | |
|---|---|---|---|
| Hemoglobin | 134 | (136) | 120-160 |
| Hematocrit | 0.38 | (0.402) | 0.35-0.45 |
| White Blood Cell | 4.8 | (3.9) | 4-11 |
| Red Blood Cell | 4.31 | (4.43) | 4-6 |
| MCV | 88.2 | (90.7) | 75-90 |
| MCH | 31.1 | (30.7) | 27.5-33 |
| Platelets | 265 | (340) | 150-400 |
| Lymphocytes | 1.17 | (0.95) | 1.5-6.5 |
| | | | |
| RBC Folate | 1959 | (2449) | >364 |
| Ferritin | 111 | (50) | 80-300 |
| | | | |
| TSH | 4.36 | | |