The Biochemistry of Autism

Gregory Russell-Jones, B12 Oils Pty Ltd, Sydney, Australia.
russelljonesg@gmail.com

Abstract

Metabolic analysis of the biochemistry of children with autism has revealed a complex nutritional deficiency in these children that ultimately results in functional vitamin B12 deficiency. As such the children closely resemble those with developmental delay resulting from a deficiency in vitamin B12 in the womb. Deficiency of Iodine, Selenium and/or Molybdenum is seen in all the children, which then results in functional vitamin B2 deficiency, which in turn results in functional deficiency in vitamin B12. The resulting deficiency leads to lower production of melatonin, resulting in delayed myelination of neurons, particularly in the area of the brain involved in speech, and in poor motor skill development. Lack of melatonin also leads to the many sleep issues common in the children as well as poor gut health. The situation is compounded by deficiencies in iron and vitamin D. A potential protocol for resolution of the condition is discussed, as well as methods for prevention of the condition.

Keywords: Vitamin B2, vitamin B12, Iodine, Selenium, Molybdenum, Iron, Vitamin D, Autism, Developmental Delay, Organic acids test.

1. Introduction

Autism is a **complex neurodevelopmental disorder, that often presents as developmental delay in language (sometimes with complete lack of speech), impairments** in social interaction and communication skills, rigid, repetitive behaviors, and delayed physical development of fine motor skills, and even delayed continence. This may be accompanied by challenges with sensory processing and executive functioning The frequency of autism has been steadily increasing from the mid-1960s, when the incidence was less than 1 in 1000, to a current rate of nearly 1 in 30 as is found in the US. The economic cost of autism is enormous, with over one third of the National Disability Insurance Scheme in Australia going to the care and treatment of those with the condition. There are numerous charities that have been set up with the charter to support the individuals with autism and their families. The majority of these organizations are working on the premise that the cause of autism is not known and that therefore there is no cure for autism. Despite this assumption, it is already known that several nutritional deficiencies are associated with delayed mental development of young children, including Iodine deficiency (one of the single

most important preventable cause of developmental delay in the world) [1, 2, 3], iron deficiency (the second most preventable cause of developmental delay in the world [4, 5, 6], as well as vitamin B12 deficiency [7, 8, 9]. As such it was highly likely that one or more of these deficiencies was the causative agent for the increase in the rate of autism spectrum disorder. To glean further insight into this condition Urinary Organic Acid analysis was carried out on over 600 children with diagnosed autism spectrum disorder and data was compared to 50 neurotypical individuals.

2. Metabolic Testing

Examination of Urinary Organic Acids has proven to be a reliable indicator of functional vitamin B2, vitamin B12, biotin, vitamin B1, iron and functional vitamin D [4-6]. Vitamin B2 (riboflavin), obtained from diet or supplement, must first be modified (activated) within the cell. Such activation is indirectly controlled by the function of the thyroid, and requires sufficiency of three minerals, Iodine, Selenium and Molybdenum. Iodine is essential for the formation of Tetraiodothyronine (T4), whilst Selenium is required by the deiodinase, which then removes one Iodine from T4 to produce the active form of thyroid hormone, triiodothyronine (T3). T3 then stimulates the cell to produce riboflavin kinase, which then phosphorylates riboflavin to produce one of the active forms of riboflavin, flavin-mononucleotide. Finally, Molybdenum is required to form the active form of FAD synthase, which then converts FMN to FAD (Fig 1.). Each of FMN and FAD have different roles within the cell and are required by around 100 different enzymes, one of which is responsible for the activation of vitamin B6. In a deficiency of Iodine and/or Selenium there is reduced production of FMN and reduced activation of vitamin B6. Another essential role of active B2 (as FMN and FAD) within the cell is the maintenance of functional vitamin B12 activity (Figs 2,3). Hence, in what can be thought of as a cascade, a single nutrient deficiency in any one of Iodine, Selenium, Molybdenum, vitamin B2, vitamin B6 or vitamin B12 will result in the eventual inactivation of what vitaminB12 is circulating.

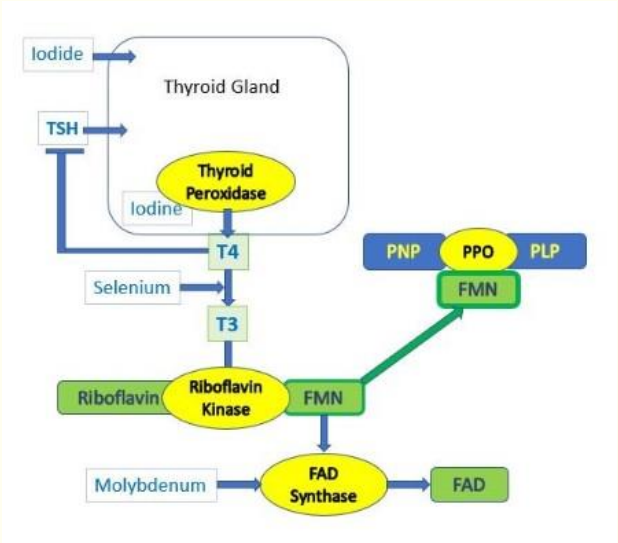


Figure 1. Involvement of Iodine, Selenium and Molybdenum in the Activation of vitamin B2

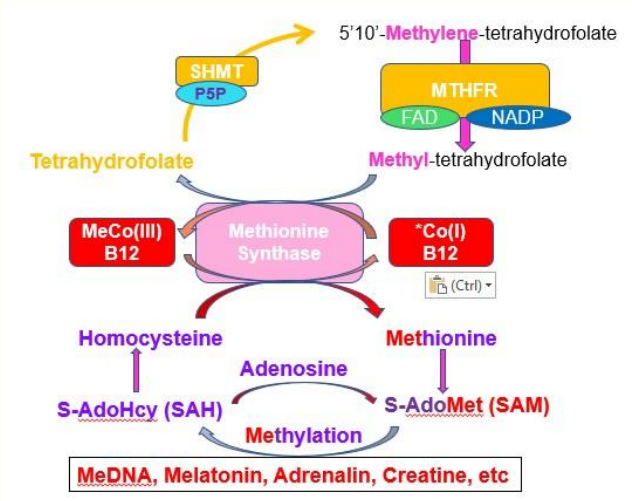


Figure 2. Role of vitamin B6 (P5P) and vitamin B2 (FAD), in the cycling of methylcobalamin (methylB12) and in regeneration of Methionine from Homocysteine, via methyl donation from methyltetrahydrofolate (5MTHF).

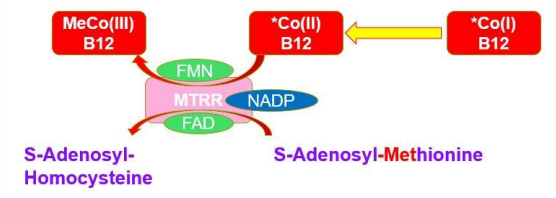


Figure 3. Regeneration of MethylCo(III)B12 from inactive Co(II)B12 by the FMN/FAD dependent enzyme methionine synthase reductase (MTRR)

Functional vitamin B12 deficiency, due to any of I/Se/Mo/B2/B6, is somewhat different to overt vitamin B12 deficiency, in that it can be accompanied by other symptoms which are associated with deficiency in

vitamin B2 or B6 alone. Further, in functional vitamin B12 deficiency serum levels of vitamin B12 can be normal or elevated but metabolically it can be shown that the individual is functionally deficient in vitamin B12 (also known as Paradoxical B12 deficiency). Hence, one might expect that depending upon the cause of the functional vitamin B12 deficiency, there may be a range of symptoms and this may explain the current breadth of Autism Spectrum Disorders.

Infants born with cobalamin (vitamin B12) deficiency are at significant risk of lasting brain damage. Further, the deficiency can cause developmental and intellectual delay, hypotonia, tremor, seizure, and failure to thrive. Without therapy, there can be irreversible intellectual impairment, as well as cognitive and developmental delay (15). Thus, the concurrence of hypotonia with developmental and intellectual delay, especially with premature birth, low birth weight, difficulties feeding, and problems sleeping are all "Red Flags" for Vitamin B12 deficiency. Lower levels of vitamin B12 have been found in the brains of children with autism [7]. Absolute vitamin B12 deficiency can readily be ascertained by serum levels of vitamin B12 as well as elevations in the two metabolites, homocysteine (see Fig. 2) and methylmalonic acid (MMA). The deficiency in the children is normally associated with a vegan or vegetarian diet in the mothers, and hence lower serum vitamin B12 and low transfer to the developing embryo. There has been a dramatic increase in the incidence of vegan and vegetarian diets, such that in a study in Canada in 2008 revealing that 1 in 20 pregnant women in Canada were deficient in vitamin B12 [8,9]. Treatment of overt B12 deficiency in these children involves daily injection of vitamin B12 for one to two weeks followed up by monthly injections, with almost all symptoms resolving [8-14]

Children born with functional vitamin B12 deficiency differ from those with overt vitamin B12 deficiency in that they may have some of the symptoms of overt deficiency, however since serum levels may be normal or elevated, the deficiency is missed, thus, the children have paradoxical B12 deficiency [6]. In these individuals, there may still be developmental and intellectual delay plus difficulty feeding, poor sleep habits, hypotonia and seizures. Additionally, the children may have speech, linguistics and social impairments, as well as behavioural disorders, and problems with fine and gross motor movement. Many also have multiple food intolerances, particularly to foods with sulphites, nitrites or histamine in them. Treatment of these children by injection with vitamin B12 does little to resolve the condition.

2.1. Mineral Deficiency in Paradoxical B12 deficiency

Iodine deficiency has been recognized by the WHO as the single most preventable cause of mental retardation in the world and has mandated Iodine supplementation in all countries. It has been known for many years that Iodine deficiency in pregnancy impairs the neurological development of the foetus, and

as such Iodine deficiency in the mother can cause irreversible brain damage to the foetus resulting in severe mental retardation [15-23]. Thus, Iodine deficiency in the neonate is associated with mental retardation, increased perinatal mortality, retarded physical development, and reduced verbal IQ [24].

Despite this, insufficient iodine intake in mothers is common in many countries including the USA [25], Canada, UK (73% deficient) [26], Spain [27], Australia, and New Zealand [28]. Iodine deficiency is more common in families that do not use Iodized salt, who have low dairy intake, or consume "gluten-free" products. Plant-based diets are low in Iodine, and as such vegans may be at risk of Iodine deficiency [29, 30]. The incidence of "gluten-free" consumption now is very common with as much as 25% of persons in the US, UK, and Australia adopting a nutrient poor, gluten-free diet.

Iodine deficiency and its effects have been known for over 100 years, and Iodine supplementation was introduced into the USA in 1924, however, Iodine levels have been dropping in the US since 1971, and levels of Iodine intake halved in the period 1971 to 1994. The situation has steadily become worse, and over 50% of women admitted into Boston Maternity wards in 2008 were found to have insufficient Iodine intake [25], with 23% being deficient in Iodine in Michigan, USA [31, 32]. Similarly, in a recent study in Australia, over 40% of women of child-bearing age were found to have insufficient Iodine intake [33]. Iodine intake tended to be lower in women on vegan diets.

Selenium is an essential cofactor in 25 selenoproteins in the body, including glutathione peroxidase, thiodoxin reductase and three different selenium-dependent iodothyronine deiodinases (types I, II, and III) that can both activate and inactivate thyroid hormones, making selenium an essential micronutrient for normal development, growth, and metabolism. Selenium levels in many soils in many countries has recently been identified as a nutrient deficiency of concern in the UK, Europe, New Zealand, many states in the USA, and in Canada. Selenium deficiency is more common in those on a low dairy diet, or those who have adopted the nutrient poor gluten-free diet.

Selenium deficiency can exacerbate the effects of iodine deficiency [28, 34-37], and has independently been associated with poor cognitive performance in children [36,37] and poor neurological development, developmental delay, particularly if combined with Iodine deficiency [39]. In countries such as New Zealand, and Malawi, which are known to have low Selenium levels in the soils, many women receive less than the recommended daily allowance of Selenium [28, 39].

Molybdenum levels in many countries have been steadily declining and molybdenum deficiency is common. Molybdenum deficiency is common in children with sulphite sensitivity, a common preservative in many foods. Molybdenum cofactor deficiency has previously been associated with

developmental delay [42], hypersensitivity to sulphite [43], and seizures [44] and neonatal convulsions [45] and encephalopathy [46].

Each of Iodine, Selenium and Molybdenum are essential metals involved in the activation of vitamin B2 to the two biologically active forms, flavin mononucleotide (FMN) and Flavin-Adenine-dinucleotide (FAD). Hence a deficiency in one or all of Iodine, Selenium and/or Molybdenum would lead to functional vitamin B2 deficiency, which would in itself lead to functional B12 deficiency.

Analysis of HMTA data from 250 children diagnosed with ASD revealed that a deficiency of one of Iodine, Selenium and/or Molybdenum was very common with every child having a deficiency in Iodine, Selenium and/or Molybdenum, as defined by the bottom quartile of the standard range. Many children were below and outside the standard range as measured by DData laboratories. Hence for Iodine 17% were below the standard range, with 46.6% low for Selenium and 46.7% low for Molybdenum (Table 1).

Iodine			
Normal range	0.25 – 1.8 ppm		
Autism %			
<0.25 ppm	17%	<0.5 ppm	31%
Selenium			
Normal range	0.7-1.5 ppm		
Autism %			
<0.7 ppm	46.6%	<0.9 ppm	82%
Molybdenum			
Normal Range	0.05-1.3 ppm		
Autism %			
<0.05 ppm	46.7%	<0.07 ppm	72%

Table 1.

Ranges of Iodine, Selenium, Molybdenum, Calcium and Magnesium from HMTA of children with autism.

Note Data is represented for children with autism as the percentage of individuals with Iodine levels <0.25 ppm, and <0.5 ppm; Selenium levels <0.7 ppm, and <0.9 ppm; Molybdenum levels <0.05 ppm, and <0.07 ppm.

The data is strongly suggestive that the cause of the developmental delay seen in autism is a nutrient deficiency of Iodine, Selenium, and/or Molybdenum in the mother, which would then result in functional vitamin B2 deficiency and subsequent functional B12 deficiency, which would result in developmental delay in the child.

In summary, a deficiency of one of Iodine, Selenium and/or Molybdenum was found in the HMTA of every child diagnosed with Autism Spectrum Disorder who was examined in this study. Given the known association between deficiencies in Iodine and Selenium and developmental delay, there would be a strong reason to believe that these deficiencies were directly linked to the condition in these children.

2.2. Functional vitamin B2 deficiency in Autism Spectrum Disorder

The observation that all children with ASD were deficient in one or more of Iodine, Selenium and Molybdenum, should in turn result in metabolic deficiency of vitamin B2 as FMN – for a deficiency in Iodine, and/or Selenium and in FAD for a deficiency in any of Iodine, Selenium and/or Molybdenum (See figure 1). Metabolically such deficiencies can be seen by **elevations** in various markers, such as succinate (FMN deficiency), the QA:KA ratio (deficiency in FMN leading to deficiency in vitamin B6), lactic acid, oxalic acid, adipic acid, suberic acid, sebacic acid, and glutaric acid (FAD – deficiency) (See Table 2).

Marker	**NT**	**Autism Spectrum Disorder**
Succinate	4.34 +/- 3.41	26.35 +/- 4.7
QA:KA	3.4 +/- 3.0	6.77 +/- 27.68
Oxalic acid	70.3 +/- 46.3	263 +/- 218
Lactic acid	14 +/- 15.6	33 +/- 74
Adipic acid	1.2 +/- 1.16	7.25 +/- 16.4
Suberic acid	1.6 +/- 2.1	6.8 +/- 14
Sebacic acid	0.12 +/- 0.27	3.7 +/- 37.5
Glutaric acid	0.25 +/- 0.22	1.25 +- 1.6

Table 2. Elevations in functional vitamin B2 deficiency markers in the urine of children with Autism Spectrum Disorder.

2.3. Functional vitamin B12 deficiency in Autism Spectrum Disorder

Given the essential role of vitamin B2 in the maintenance of activity of vitamin B12 (as outlined in Figures 2 and 3), an OAT analysis was carried out to look for metabolic markers of vitamin B12 deficiency. The major markers used were the classical marker of AdenosylB12 deficiency, Methyl Malonic Acid (MMA), and "inferred markers" of methyl B12 deficiency which become elevated in deficiency of methyl B12 in the synthesis of Adrenalin and of Melatonin.

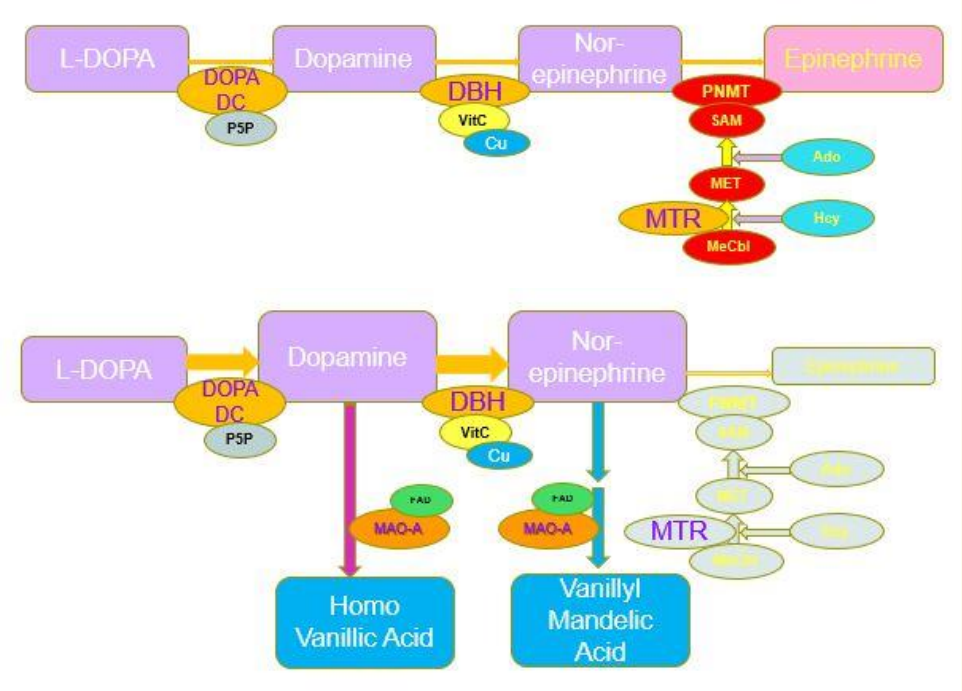
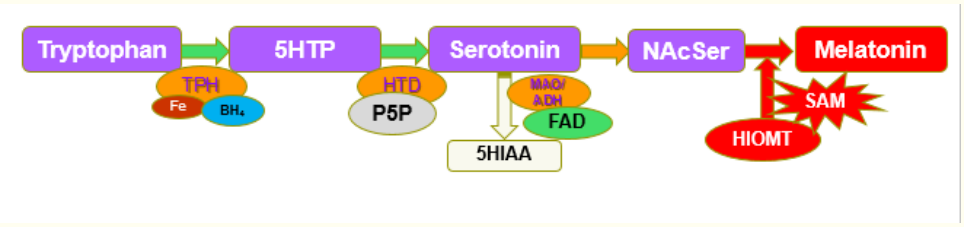


Figure 4. Role of methylation in the formation of epinephrine (top) and alteration in the metabolic breakdown products of dopamine and nor-epinephrine in functional methyl B12 deficiency (bottom)



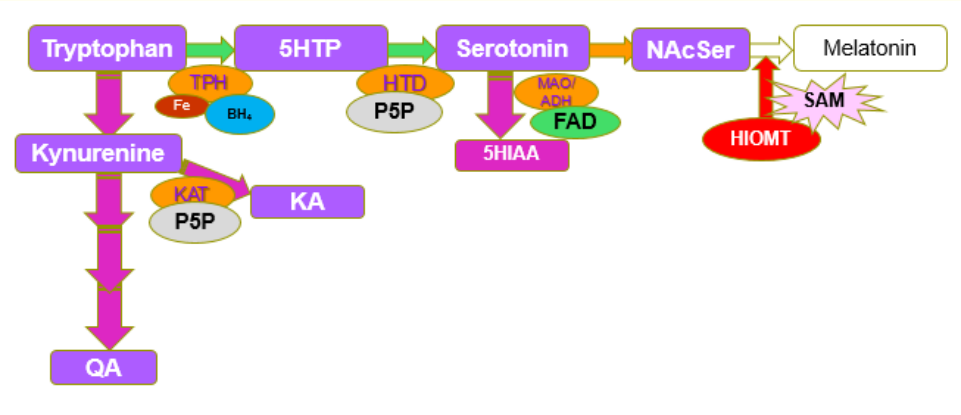


Figure 5. Role of methylation in the formation of melatonin (top) via the action of Hydroxy-Indole-Methyl Transferase (HIMT) and alteration in the metabolic breakdown products of serotonin (5HIAA) and tryptophan (QA, KA) in Methyl B12 deficiency (bottom)

Marker	NT	Autism Spectrum Disorder
MMA	0.65 +/- 0.3	2.29 +/- 2.95
HVA	1.68 +/- 1.3	6.08 +/- 5.2
VMA	1.05 +/- 0.5	2.86 +/- 1.55
5HIAA	0.65 +/- 0.7	6.44 +/- 14.7
QA	1.21 +/- 0.69	5.1 +/- 3.2
KA	0.5 +/- 0.35	2.39 +/- 3,25

Table 3. Elevations in Adenosyl B12 deficiency marker (MMA) and methyl B12 deficiency markers (HVA, VMA, 5HIAA, QA, KA) in the urine of children with Autism Spectrum Disorder.

All children examined were found to be deficient in both Adenosyl and Methyl B12, and so would “fit” the classical cause of developmental delay seen in overt B12 deficiency in the mothers, and the child. The difference being that the majority of the children had paradoxical B12 deficiency in which serum B12 was normal or elevated, but the child was functionally deficient in vitamin B12.

2.4. Sleep issues in children with Autism Spectrum Disorder

As can be seen in Figure 5 (upper panel), vitamin B12 – methyl B12 (methylcobalamin), has a role in the synthesis of melatonin, and so levels of melatonin would be reduced in these children. The deficiency of melatonin then would explain the known association of sleep disorders with developmental delay [47-55]. The data is similar to that described previously in which elevated serum serotonin, and reduced melatonin was found in patients with autism spectrum disorder [56, 57].

2.5. Reduced melatonin and myelination in Autism Spectrum Disorder

Vitamin B12 has a critical role in the production of melatonin, and Vitamin B12 deficiency, with retarded myelination has been associated with severe brain atrophy and delayed myelination particularly of the frontal and temporal regions of the brain [57]. Melatonin works in combination with vitamin D in the activation and differentiation of neuronal stem cells into oligodendrocytes. Lack of melatonin results in delayed myelination in the brain [58]. Melatonin has also been shown to have a role in peripheral neuroregeneration [59, 60]. Lack of myelination has been associated with poor myelination in the brain, and developmental and mental delay in conditions such as ASD and in mental deterioration such as in dementia. Delayed myelination of Broca's area in the brain is associated with lack of development of articulated speech, a common feature of the Autism Spectrum Disorders (ASD).

2.6. Vitamin B12 deficiency, creatine deficiency and developmental delay in Autism Spectrum Disorder

Over 40% of all methylation in the body goes to the production of creatine. The penultimate step in energy production within the cell is the transfer of ATP across the mitochondrial membrane via the enzyme creatine-kinase, to an awaiting creatine molecule in the cytoplasm of the cell to make the high energy phosphate donor Creatine-Phosphate. Without this step, the generation of ATP within the mitochondria is futile. Lack of activity of the enzyme GAMT has been shown to give rise to many of the symptoms of autism. In children GAMT deficiency can cause severe developmental and mental retardation, speech delay, recurrent seizures (and TICS), behavioral changes, and movement disorders, including Muscular hypotonia, mild spasticity, and coordination disturbances [61 – 64]. In many ways, autism could be regarded as a Guanidinoacetate-N-Methyl-transferase deficiency syndrome (GNMTDS). Lack of creatine production is also associated with hypotonia, or floppy baby syndrome.

Figure 6 Role of methylation in the formation of creatine by the action of Guanidinoacetate-Methyl Transferase (GAMT) on Guanidinoacetate and S-Adenosylmethionine (SAM).

2.7. CoQ10 deficiency developmental delay in Autism Spectrum Disorder

Production of the electron shuttle vector, CoQ10 requires 3 methylation steps, and in Methyl B12 deficiency, there is reduced production of CoQ10, resulting in elevation of 3-hydroxymethylglutarate (HMG) in ASD. Greatly increased levels of HMG are seen in the urine of those with Autism Spectrum Disorder, which would in turn suggest reduced production of CoQ10 and greatly reduced activity of the electron transport chain.

	NT	Autism Spectrum Disorder
3-hydroxymethylglutarate	8.23 +/- 8.18	34.27 +/- 26.00

Table 4. Elevations in the CoQ10 deficiency marker (3-hydroxymethylglutarate) in children with Autism Spectrum Disorder.

2.7. Vitamin B12 deficiency in Autism Spectrum Disorder – Interim Summary

Our studies have shown that all children with Autism Spectrum Disorder have functional vitamin B12 deficiency.

Functional vitamin B12deficiency results in

- **Reduced production of melatonin, thereby causing**
  - **Delayed myelination of nerves**
  - **Developmental delays**
  - **Poor sleep production**
  - **Poor gut health**
- **Reduced production of Creatine, thereby causing**
  - **severe developmental and mental retardation,**
  - **speech delay,**
  - **recurrent seizures (and TICS),**
  - **behavioral changes, and**
  - **movement disorders, including Muscular hypotonia, mild spasticity, and coordination disturbances**
- **Reduced production of CoQ10, with resultant drop in energy transfer on the Electron transport chain.**

2.8. Vitamin B2 deficiency in Autism Spectrum Disorder – Other Sequelae

In contrast to overt vitamin B12 deficiency, functional vitamin B12 deficiency due to functional vitamin B2 deficiency can cause other sequelae, thereby accounting for the broad Spectrum of the Autism Spectrum Disorder.

2.8.1 Metabolism of fat

Vitamin B2 as FAD is required for effective lipolysis. Vitamin B2 deficiency results in less efficiency of fat metabolism resulting in elevations in short and medium chain fatty acids in urine.

	NT	Autism Spectrum Disorder
Adipic Acid	1.25 +/- 1.1	7.25 +/- 16.4
Suberic Acid	1.64 +/- 2.06	6.76 +/- 14.03
Sebacic Acid	0.12 +/- 2.06	3.68 +/- 37.45

Table 5. Elevations in the fatty acids in urine of children with Autism Spectrum Disorder.

The inability to burn fat may explain the unhealthy weight gain and obesity in many children with autism [65].

2.8.2 Metabolism of Glucose

Metabolism of glucose is quite complex. Glucose that is taken up from the intestine is rapidly taken up by cells in tissues such as the liver, muscle or brain, and is either acted upon directly via the glycolysis pathway, or in glucose excess, glucose is converted to glycogen. In the process of glycolysis, the 6-carbon glucose molecule is converted to 2 copies of the three carbon molecule, pyruvate. Vitamin B2 as FAD is required by the enzyme pyruvate dehydrogenase in order to convert pyruvate, the final product of glycolysis, to acetyl-CoA (Figure 7). In functional B2 deficiency, the activity of the enzyme is reduced and there is a build-up of lactic acid. The lactic acid then suppresses uptake of further glucose into the cell (Figure 8, 9).

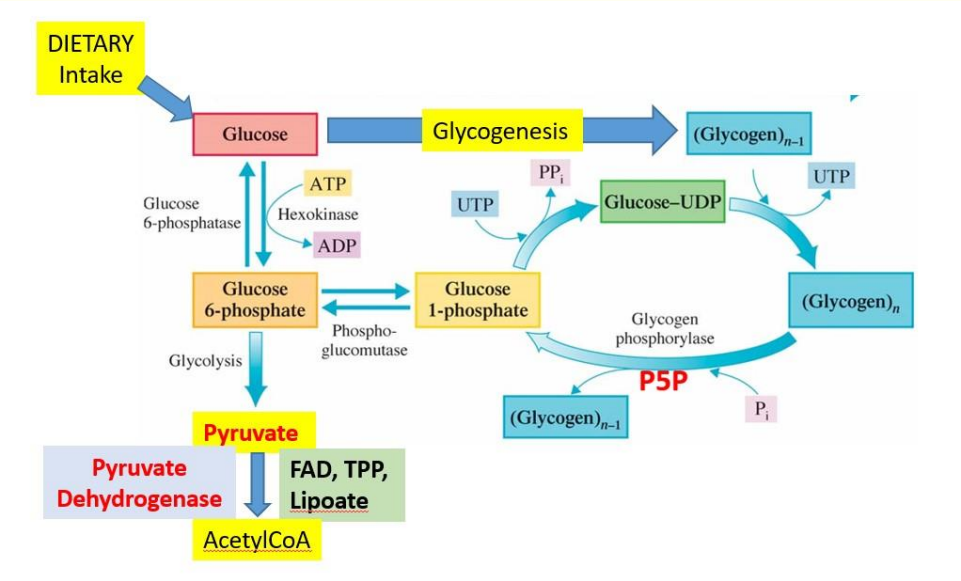


Figure 7 Metabolism of ingested glucose. In glucose deficiency, dietary intake of glucose is taken up by cells, which then use glycolysis to convert the C6 compound to pyruvate (C3). Pyruvate is subsequently converted to AcetylCoA via Pyruvate dehydrogenase in the presence of FAD, TPP, and Lipoate. In glucose excess glucose is converted to glycogen.

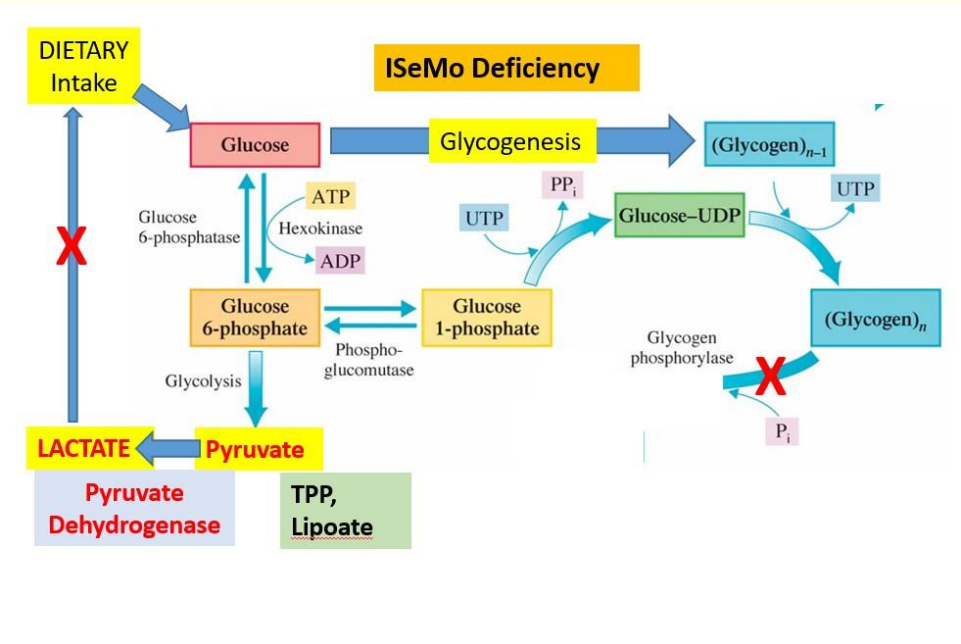


Figure 8 Metabolism of ingested glucose in functional B2 deficiency. Dietary glucose is converted to pyruvate, but due to the deficiency of FAD, the pyruvate is converted to lactate. Glycogenolysis is blocked due to lack of P5P, and so as there is reduced blood glucose, hypoglycemia results

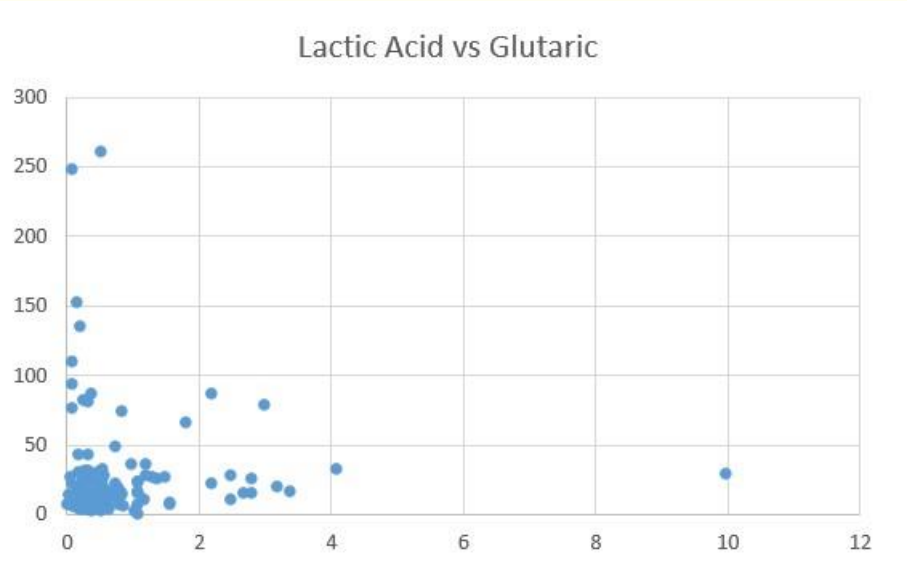


Figure 9 Metabolism of ingested glucose in functional B2 deficiency. In slight deficiency of active B2, as FAD, there is an increase in glutaric acid, which is accompanied by a rapid increase in lactic acid. As functional B2 increases lactic acid generation is greatly reduced.

Potentially children with autism could present as having diabetes, if functional B2 deficiency was low, or having hypoglycemia if functional B2 deficiency was high. This would explain the heterogeneity of data in studies on diabetes and autism spectrum disorder [66, 67]. Deficiency of Iodine, Selenium and/or Molybdenum in the mothers of children who give birth to children with autism spectrum disorder, would result in gestational diabetes, a known associative factor for having a child with autism [68].

2.8.5 Iron deficiency in Autism Spectrum Disorder

Iron deficiency is the second most preventable cause of developmental delay [10 – 12]. Deficiency of iron leads to lower levels of oxygen carriage due to lower haemoglobin in serum, but more importantly, as the serum iron-carrying protein, ferritin decreases below 70 ug/L there is an uncoupling of the citric acid cycle due to the denaturation of the enzyme aconitase. This, in turn, leads to reduced energy transfer into the citric acid cycle, and excretion of citric acid into urine. This lack of energy, can be associated with hypotonia, which is common in Autism Spectrum Disorder.

	NT	Autism Spectrum Disorder
Citric Acid	144 +/- 123	312 +/- 245

Table 6. Elevations in citric acid in the urine of children with Autism Spectrum Disorder.

2.8.6 GABA deficiency in Autism Spectrum Disorder

Production of GABA requires the P5P-dependent enzyme, Glutamate decarboxylase. In Iodine and/or selenium deficiency, levels of P5P will be reduced and so synthesis of GABA will be reduced resulting in the observed elevations of glutamate – an excitatory neurotransmitter, in the brains of children with Autism Spectrum Disorder [70], and will presumably explain some of the behavioural issues observed in these individuals.

2.8.7 Vitamin D deficiency in Autism Spectrum Disorder

Vitamin D deficiency has previously been associated with developmental delay. Lack of vitamin D leads to poor uptake of calcium from the intestine as well as bone demineralization and an increased fracture rate has been noted in children with autism spectrum disorder. Elevations in urinary phosphoric acid and decreased calcium was found in the hair of children with autism, suggesting a co-deficiency with vitamin B2 and vitamin B12.

	NT	Autism Spectrum Disorder
Phosphoric Acid	1420 +/- 470	3253 +/- 1357
Calcium HMTA	546 +/- 609	380 +/- 255

Table 7. Elevations in Phosphoric acid in the urine of children with Autism Spectrum Disorder and reduced calcium in hair.

3 Treatment of Functional vitamin B12 deficiency in Autism Spectrum Disorder

Resolution of functional vitamin B12 deficiency is a relatively simple process (the RnB protocol), which is designed to fix functional riboflavin (vitamin B2) deficiency, and then addressing the functional B12 deficiency. First one must identify the mineral deficiency that has caused the functional vitamin B2 deficiency, which is normally Iodine, Selenium and/or Molybdenum. This can be done via a simple Hair Metals Analysis test, and can be supported by thyroid data. Hence in HMTA, Iodine should be > 1.0, Selenium >1,0 and Molybdenum > 0.1 ppm. TSH levels indicating Iodine sufficiency should be as close to 1.0 as possible, with biochemical deficiency of functional B2 seen at values >1.5. These findings can be backed up by Organic Acid testing for functional B2 sufficiency (see Section 2.2. for representative markers). Supplementation

should be Iodide >150 ug/day, Selenite >55 ug/day and Molybdate >100 ug/day. Once sufficiency is established children should be supplemented with at least 5 mg per day riboflavin. Finally, vitamin B12, preferably a mix of Adenosyl/Methyl B12 should be administered by injection or topical administration of the B12Oils Adenosyl/Methyl B12 oils product. Oral administration has not been found to be effective. The biochemical status of the children should be monitored to ensure that the treatment has been effective and adjustments made accordingly.

4 Prevention of Autism Spectrum Disorder

Evidence to date strongly supports the notion that it is the deficiencies in the womb that ultimately cause autism, hence the potential mother needs to be nutritionally sufficient before pregnancy. Suggested ranges are

Iron: Ferritin >70 ug/L, Haemoglobin >14, Haematocrit >0.4
Vitamin B12 > 400 pg/ml (300 pmol/L).
Supplementation
Iodide 225 ug/day,
Selenite 100 ug/day
Molybdate 200 ug/day
Folate > 400 ug/day

At the start of the second and third trimester nutritional status should be checked by TSH/T4/T3 and preferably by Organic Acids Testing, and supplementation adjusted accordingly.

Conclusion

Dietary deficiency in Iodine, Selenium and/or Molybdenum, when combined with the increased rate of vitamin D deficiency has resulted in a rapid increase in the rate of autism, worldwide. The developmental delay, which results is very similar to that seen in children with overt vitamin B12 deficiency. The major difference being that serum vitamin B12 is normal or elevated, which is paradoxical and so the association with vitamin B12 deficiency is almost always missed. Close examination of the urinary organic acids quickly reveals functional vitamin B2 deficiency, which is accompanied by Vitamin B12 deficiency associated markers. The corollary to these findings is that the cause of the disorder is relatively easy to understand and as such enables a treatment regime to be established and also provides a strategy to prevent the development of the condition in the first place. This in turn should provide considerable relief in the emotional pain and suffering of parents and carers of these individuals. In addition, the findings have the potential to dramatically reduce the costs to society of a condition that is entirely preventable by ensuring adequate nutrition in the womb of pregnant mothers.

Conflict of Interest

The authors declare no conflict of interest.

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