Clinical Experiences with a Vitamin B_3 Dependent Family

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Abstract

A vitamin dependency occurs when there is a defect in the binding of the vitamin-related coenzyme to its apoenzyme. The only way to correct a vitamin dependency is to obtain daily amounts much greater than recommended dietary allowances. I believe that the most common vitamin dependency among patients with mental illnesses is vitamin B_3. These three cases involve members of the same family. Each case improved clinically upon taking megadoses (500-1500mg/day) of the vitamin. A fourth member of this family has schizophrenia. This is significant since recent postmortem biopsies of brain tissues have shown defects in the ability of schizophrenic patients to generate adequate amounts of vitamin B_3 coenzymes from tryptophan. Families share similar genetics and environmental factors, and thus this family likely shares varying degrees of the ability to synthesize adequate amounts of vitamin B_3 coenzymes. If schizophrenic genes are common among the entire human population, then the majority of people will suffer from slight-to-severe defects in this biosynthetic pathway.

Introduction

The 16th edition of *The Merck Manual of Diagnosis and Therapy* defines a vitamin dependency as that which relates to "coenzyme function and results from an apoenzyme abnormality that can be overcome by administration of doses of the appropriate vitamin that are many times the recommended dietary allowance (RDA)."[1] In the 17th edition of this prestigious medical text, the definition of a vitamin dependency was slightly modified as resulting "from a genetic defect in the metabolism of the vitamin or in the binding of the vitamin-related coenzyme to its apoenzyme."[2] The authors note that to correct the altered metabolic pathway, vitamin doses of 1000 times the RDA are sometimes necessary.

Thus, a vitamin dependency is only correctable by increasing the intake of a particular vitamin to levels greater than could be achieved from dietary sources alone. This is not unreasonable since many enzyme systems within the body require optimal doses of vitamins to remedy defects in the synthesis of vital metabolic products to sustain adequate health. In Pauling's famous 1968 publication, he reasoned that: "…mental disease is for the most part caused by abnormal reaction rates, as determined by genetic constitution and diet, and by abnormal molecular concentrations of essential substances."[3] He described how megavitamin therapy would be necessary for the optimal treatment of mental disease since the saturating capacity would be much greater for defective enzymes that have diminished combining capacity for their respective substrates. In other words, an enzyme-catalyzed reaction could be corrected by increasing the concentration of its substrate through the use of optimal doses of vital micronutrients.

Other reports have since corroborated Pauling's original ideas that vitamin doses in excess of those obtained from diet are valuable therapeutic interventions for the treatment of mental illnesses. Some of these reports are cited. The illnesses include anxiety,[4-7] bipolar disorder,[8] depression,[9] and schizophrenia.[10] A 2002 report validated the concept of vitamin dependencies for the treatment of 50 common genetic diseases. In this report, the

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need for doses of vitamins far in excess of RDA amounts (i.e., optimal doses) were deemed necessary as a means of increasing coenzyme concentrations and correcting defective enzymatic activity.[11] The authors stated that the "examples discussed here are likely to represent only a small fraction of the total number of defective enzymes that would be responsive to therapeutic vitamins."

In light of the evidence, it is common for the "orthomolecularly-inclined" clinician to consider vitamin dependencies when proposing various differential diagnoses in the evaluation of patients. Hoffer and Osmond devised a simple classification to determine the potential causes of schizophrenia.[12] Their classification easily covers all the mental illnesses that plague us today. I have added "omega-3 essential fatty acid deficiency" to their classification based on the initial work of Rudin involving substrate pellagra,[13] and on more recent published works by Horrobin[14] and Stoll.[15] Thus, in the work-up of the mentally ill it is best to consider the following potential causes:

Vitamin Dependencies
- Vitamin B_3 (niacin or niacinamide)
- Vitamin B_6 (pyridoxine)
- Others such as vitamin C (ascorbic acid), vitamin B_{12} (cobalamin), and the rest of the B-complex vitamins

Mineral Disturbances
- Deficiencies (e.g., chromium, manganese, selenium, zinc)
- Excesses (e.g., copper, lead, mercury)

Cerebral Allergies
- Food
- Inhalant
- Food additives

Omega-3 Essential Fatty Acid Deficiency

Vitamin dependencies were listed first in Hoffer and Osmond's classification scheme. Even though vitamin B_3 was given priority consideration as the most common cause of the schizophrenic syndrome, I believe that the vast majority of all psychiatric patients suffer from a vitamin B_3 dependency. Here, I present 3 cases of non-schizophrenic individuals from the same family who all suffered varying degrees of mental disturbances, and who all responded well to optimal doses of vitamin B_3.

Case #1

This 18-year-old Caucasian female presented to my office on July 6, 2005. She described a history of social anxiety disorder (a.k.a., social phobia) since primary school where she found it very difficult to talk with her peers and to attend school functions. She would often hide in the washrooms to avoid uncomfortable situations. At one time she was told that she might have learning problems. She completed high school and received grades in the high 90s. She was a talented opera singer and loved artistic endeavors such as reading poems and creating drawings. Although she felt that her social anxiety was much improved, she complained of stuttering when reading aloud.

After incorporating a whole-foods diet, her moods improved despite the occasional mood swings prior to menses. Physical examination was unremarkable. Although she was on a very good orthomolecular plan when I saw her, I had her change the 500 mg of inositol hexaniacinate that she was taking once daily to 500 mg of niacinamide twice daily. A follow-up on August 31st, 2005 revealed significant improvements in her abilities to relate to peers and to enjoy the Arts Camp she attended. She had one "meltdown" at the camp which led to crying and the need to be alone. Despite this, she reported that she was doing really well most of the time. Prior to this visit, she had seen a psychiatrist who told the patient that her social phobia required prescription medication for the next two

years. She declined the prescription, and instead agreed to have her niacinamide increased to 1500 mg daily.

One of my final visits with her took place on October 29, 2005. She informed me that she was relatively stable considering the recent circumstances at home. Her schizophrenic brother had become verbally abusive and sometimes physically violent. He would not seek proper treatment. I still keep in touch with her and e-mail her mother on occasion to follow-up. She remained stable since commencing with the niacinamide treatment and she has not required the use of prescription medication.

Case#2

The mother of case#1 came to my office on August 6, 2005. This 46-year-old female described a history of anxiety since age 7. She reported repeated bouts of anxiety and panic that became worse during the past 7-8 years. The recent difficulties at home due to her son's mental illness made her anxiety much worse. Daily meditation that used to be beneficial seemed to have lost its effectiveness. Physical examination revealed stage 1 hypertension, but was otherwise unremarkable. I had her complete the Beck Anxiety Inventory (BAI). Her score was 39, indicating that it was persistently high and in need of treatment. Like her daughter, she was already on a good orthomolecular plan.

I recommended that she start with 500mg of niacinamide. On September 14, 2005 she returned for a follow-up. She had yet to start the niacinamide and was using diet to manage. She felt that even with the enormous amount of stress she was under, the anxiety was not preventing her from functioning adequately in her business as an interior designer. During her third visit on October 29th, 2005 she reported a worsening of her anxiety since the situation with her son was not good. She began taking 500mg of niacinamide during the last month. She came for another follow-up on May 24, 2006. Her stress level was still extremely high. Her son began medication sometime in December 2005, but has not shown any signs of progress. He was arrested several times and was verbally and physically abusive to her, as well as to her husband and daughter. She found that 1500 mg of niacinamide at bedtime helped her relax and sleep better. She would only take 1500 mg on "bad" days, and then reduce the dose to 500 mg on "good" days. A BAI was repeated in October 23, 2006. Her score had decreased from a 39 to a 26. She believed that the niacinamide was responsible for her improvements.

Case#3

The husband of case#2 came to see me on February 27, 2006. He wanted me to review his orthomolecular plan and consider possible adjustments to it. His onset of stress occurred when his son was diagnosed with schizophrenia a couple of years ago. He described several bouts of heart palpitations and sleep problems following his son's diagnosis. He decided to put himself on niacinamide (1000 mg at bedtime) and immediately he felt much better.

Niacinamide significantly improved his quality of life, his ability to sleep, and even helped with his creativity. He meditated regularly and felt that this helped his stress levels. Physical examination was unremarkable. I increased his niacinamide to 1000 mg twice daily. I had a follow-up appointment with him on May 1, 2006. He reduced his dose of niacinamide to 1000 mg at bedtime since he felt too sedated at work with the additional 1000 mg. He felt much better since his stress reactions had resolved. We decided that there was no further need for follow-up visits unless he felt the need.

Discussion

Hoffer has reported that a significant amount of modern mood disorders (i.e., anxiety and depression) and schizophrenia are the result of a vitamin B_3 dependency.[16] Both the daughter and mother suffered from chronic anxiety, and the father suffered from anxiety reactions that were precipitated by his son's mental illness.

Although each patient was taking other nutrients prior to consulting me, niacinamide added further benefit when daily dosages much greater than RDA amounts (500-1500 mg) were prescribed. Their positive clinical responses to niacinamide supplementation confirmed my initial diagnosis of a vitamin B_3 dependency for each treated member of the family. Notwithstanding the clinical use of sophisticated laboratory tests (e.g., testing for individual coenzyme enzymopathies), all vitamin dependencies are confirmed in this manner.

When contrasting the clinical features of pellagra to that of a vitamin B_3 dependency, the main difference is that the former is characterized by more extreme manifestations. Pellagra is commonly referred to as a disease of the four Ds (diarrhea, dermatitis, dementia and death), but more insidious symptoms develop long before the four Ds. Such symptoms include achlorhydria, anorexia, anxiety psychosis, cheilosis, constipation, delirium, dermatitis occurring on sun-exposed areas, diminished strength, glossitis, intermittent stupor, melancholia, nausea, paralysis of extremities, peripheral neuritis, stomatitis, weight loss and vomiting.[17-21] Thus, pellagra is characterized by diverse clinical manifestations mainly involving the dermatological, gastrointestinal and neuropsychiatric systems. This deficiency condition is prevented and cured by obtaining the minimal daily amounts (i.e., approximately 13-20 mg) of vitamin B_3.

A vitamin B_3 dependency, on the other hand, would present as a subclinical (i.e., lesser) form of the deficiency or pellagrous condition. Treatment would require optimal dose quantities for its control and possible eradication. The differences between deficiency and dependency are quantitative since both conditions are manifestations of not obtaining adequate amounts of vitamin B_3. Hoffer eloquently pointed out that: "...the borderline between vitamin deficiency and vitamin-dependency conditions is merely a quantitative one when one considers prevention and cure"[22] At present, we are more apt to see patients suffering from the clinical manifestations of a vitamin B_3 dependency since profound malnutrition and starvation are rare occurrences.

In this family, all the treated members had a vitamin B_3 dependency. Even though I did not formally evaluate and treat the son, he had schizophrenia–another vitamin B_3 dependent condition.[16] Hoffer hypothesized that vitamin B_3 dependency is inherited. He formulated this hypothesis from the clinical experiences he had with more than 100 families during a 10-year period.[23] If one parent is vitamin B_3 dependent, Hoffer noted that one quarter of the children will be similarly affected. If two parents are vitamin B_3 dependent then more three quarters of the children will have the same dependency. Even with a good diet, Hoffer discovered that patients require 3-12 grams daily to effectively treat their vitamin B_3 dependency. In my report, the three family members were able to benefit from smaller daily dosages (500-1500 mg) of vitamin B_3 than those advocated by Hoffer; they might have had more clinical benefits if they tolerated higher daily gram doses.

Why did the three members of the same family develop the same susceptibility? It is difficult to know, except that

all these family members would share the same genes and environmental factors. They all experienced varying amounts of chronic severe psychosocial stress. When that combined with a history of not meeting their unique nutritional needs, a vitamin B_3 dependency developed. It appears that the "key" reason for this familial tendency resides with their schizophrenic son. It is known that patients with this disease do not manufacture adequate amounts of vitamin B_3 coenzymes (i.e., nicotinamide adenine dinucleotide; NAD) to meet their physiological requirements. In 1973, Hoffer hypothesized that schizophrenic patients likely have defects in their metabolism of tryptophan and that such defects or deficiencies in the ensuing reactions would cause a back-up of indole metabolites in the precursor chain.[22] He further hypothesized that such defects would lead to an underproduction of NAD, possibly leading to an increased production of adrenochrome and its derivatives.

A recent postmortem report assessing the brain tissues of schizophrenic patients supports the notion that schizophrenic patients do not manufacture enough NAD.[24] In this report, an upregulation of the enzyme tryptophan 2,3 dioxygenase (TDO2) was found among schizophrenic patients but not among the controls. The brain tissues of the schizophrenic patients showed significant elevations of kynurenine (1.9 fold, p=0.02), TDO2 mRNA (1.7 fold, p=0.049), and the density of TDO2-positive white matter glial cells (p=0.01). In schizophrenia, the TDO2 enzyme was found to be upregulated, causing an over-production of pathway intermediates (e.g., kynurenine). This upregulation might be responsible for the evolution of some schizophrenic symptoms. Instead of linking this upregulation to some defective factor in the TDO2 gene, the authors suggested that it might be due to a diminished niacin effect; possibly, the result of depressed production or reduced signal transduction via the niacin receptor. They recommended that niacin or its congeners are necessary regulators of this biochemical pathway and should be capable of restoring homeostasis. Since schizophrenia is a disease with a genetic basis,[25] I believe that all the family members described in this report have the same genetic fault, but with varying degrees of phenotypic expression: two had a history of chronic anxiety, one had episodes of anxiety, and one had a diagnosis of schizophrenia. All of them are vitamin B_3 dependent, and they all require optimal daily amounts of the vitamin to live a reasonable quality of life.

When looking beyond this genetically susceptible family, vitamin B_3 dependency might actually be a common problem among the entire human population. Horrobin hypothesized that schizophrenic genes have shaped humanity, provided us with important evolutionary advantages, and spread into the population.[26] Although schizophrenia affects one to two percent of the population, he feels that the genes for it are common among the entire population. The one to two percent would carry all four or more of the genes responsible for the full expression of the disease, while most other people would carry one, two, or three of these genes. Thus, the majority of the population could potentially have slight-to-severe defects in the capacity to synthesize adequate amounts of vitamin B_3 coenzymes from tryptophan.

This is similar to what Hoffer recently reported.[27] He believes that we now rely more on preformed vitamin B_3 from our foods since our genetic ability to synthesize niacin has declined as a conservation measure (i.e., to use more of our metabolic machinery for other purposes). Hoffer hypothesizes that this

genetic loss/defect was exaggerated on or around 1800 when pure white flour was manufactured and introduced into our population. Thus, the syndrome of vitamin B_3 dependency arose–a prevalent syndrome of modern society provoked by a combination of genetic conservation, chronic psychosocial stress, and inadequate nutrition.

Conclusion

The family that I reported on all responded well to optimal doses of vitamin B_3. They likely suffer from a biochemical defect in the ability to synthesize vitamin B_3 coenzymes from tryptophan. When this defect occurs in the presence of chronic psychosocial stress and inadequate nutrition, a vitamin B_3 dependency will result. Schizophrenia, a vitamin B_3 dependent condition, has been identified as a disease where the production of NAD is reduced. All humans likely suffer from slight-to-severe defects in this biosynthetic pathway due to the permeation of schizophrenic genes into the population. In my humble opinion, vitamin B_3 dependency is likely to be the main cause of the majority of psychiatric problems that are encountered clinically.

Acknowledgements

Written consent was obtained from these patients for publication of this report. The author would like to thank Mr. Robert Sealey for his editing suggestions.

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