

Niacin-respondent subset of schizophrenia – a therapeutic review

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Abstract. – It is well known that niacin deficiency manifests with several psychiatric manifestations. Also historically evidence has accumulated that niacin augmentation can be used for treatment of schizophrenia. However, the etiopathological associations between niacin deficiency and schizophrenia as well as the mechanism of action of niacin in its treatment. More importantly, the subgroups of schizophrenia which will respond to niacin augmentation has never been highlighted in the literature. In this article, we review three of the mechanisms in which niacin deficiency could lead to schizophrenic symptoms: (1) Niacin deficiency neurodegeneration (2) Membrane phospholipid deficiency hypothesis and (3) Adrenochrome hypothesis. We will further move towards the clinical as well as treatment related associations as reviewed from the literature. Here, we propose a model that a subset of schizophrenia can respond to niacin augmentation therapy better than other subsets because these patients have contributions in their psychotic manifestations from the neural degeneration resulting from niacin deficiency. We present a short description of our case report which showed rapid improvement in schizophrenic psychotic symptoms subsequent to administration of niacin as an augmentation therapy. We, thus, propose that niacin deficiency is a contributory factor in schizophrenia development in some patients and symptom alleviation in these patients will benefit from niacin augmentation, especially in some particular psychotic features.

Key Words:

Niacin, Schizophrenia, Psychiatric manifestations, Neurodegeneration.

Introduction

Niacin, also known as nicotinic acid, is a water-soluble B complex vitamin. It has an important role in several metabolic pathways. Most importantly, it is the precursor of nicotinamide ade-

nine nucleotides NADH, NAD, NAD+) and nicotinamide adenine dinucleotide phosphate (NADP). Niacin derivatives are vital for several detoxication processes, DNA repair, and synthesis of steroid hormones in the body. *In vivo* synthesis of niacin occurs from the precursor tryptophan. 1 mg of niacin is synthesized from 60 mg of the essential amino acid tryptophan in the human¹. The biochemical action of niacin is mediated by binding to appropriate receptors in skin macrophages and epidermal Langerhans cells^{2,3}. That is followed by the synthesis and release of prostaglandins D2 and E2 (PGD2 and PGE2). Studies have demonstrated that serum concentration of prostaglandins can be increased up to several hundred times following niacin priming⁴.

The precursor molecule, pivotal for prostaglandin synthesis, is arachidonic acid (AA)⁵. Arachidonic acid is created from diacylglycerol via phospholipase-A2, then subjected to either the cyclooxygenase pathway or the lipoxygenase pathway to form either prostaglandin and thromboxane or leukotriene respectively. Prostaglandins stimulate the production of cyclic AMP, which causes relaxation of smooth muscles in skin capillary walls, and consequent vasodilatation^{6,7}, flushing and edema. Therefore, abnormalities within the PLA2/COX2 cascade pathway have been implicated in the flush response to niacin. Niacin non-responsiveness may, among other possibilities, indicate the disturbance of the membrane phospholipid metabolism that results in a decreased concentration of AA, which is an indispensable precursor of prostaglandins^{3,8}.

While this basic understanding of biochemistry of niacin is important for its implications in schizophrenia, it is also well known that niacin deficiency manifests with several psychiatric manifestations. Also historically evidence has accumulated that niacin augmentation can be used for treatment of schizophrenia. However, the etiopathological associations between niacin de-

iciency and schizophrenia as well as the mechanism of action of niacin in its treatment. More importantly, the subgroups of schizophrenia which will respond to niacin augmentation has never been highlighted in the literature. In this proposal, we review three of the mechanisms in which niacin deficiency could lead to schizophrenic symptoms: (1) Niacin deficiency neurodegeneration (2) Membrane phospholipid deficiency hypothesis and (3) Adrenochrome hypothesis. We will further address the clinical as well as treatment related associations as reviewed from the literature. Here, we propose a model that a subset of schizophrenia can respond to niacin augmentation therapy better than other subsets because these patients have contributions in their psychotic manifestations from the neural degeneration resulting from niacin deficiency. In this model we will cite examples from our case report which deals with treatment of comorbid schizophrenia with clinical pellagra. We, thus, propose that niacin deficiency is a contributory factor in schizophrenia development in some patients and symptom alleviation in these patients will benefit from niacin augmentation, especially in some particular psychotic features.

Niacin Deficiency Basis of Schizophrenia: a Review of Mechanisms of Degeneration

The idea that schizophrenia is a progressive disorder was introduced by Kraepelin E (1856-1926), a concept which he named as “*Dementia praecox*,” implying a progressive deterioration from which recovery was not possible. It was earlier believed that the course of schizophrenia was always progressive and improvement was not possible. On examining the clinical course of the disorder, we see that some patients have a deteriorating rather than a static course; a subgroup of patients has a chronic course with multiple exacerbations. The likelihood of deterioration correlates with the number of periods and the duration of positive symptoms⁹.

A longer duration of untreated psychosis (DUP) predicts a poorer outcome, which raises the possibility of neurotoxic effects of untreated psychosis consequently leading to neurodegeneration. It has, thus, also been proposed that early treatment with antipsychotic medications may arrest this progression. Long DUP predicted worse response to medications, higher relapse risk, and mixed association with other outcome measures^{10,11}. This indicates that a pathological process is occurring in the brain, against which

drugs played a protective role. It is also seen that patients appear to take longer to recover and show less complete recovery over successive episodes of this illness¹².

Longitudinal neuroimaging studies using techniques like MRI have been done. Longitudinal studies show changes that occur in the brain after the illness has begun, thereby, representing the effect of the illness on the brain¹³. MRI studies, in which tissue classification was used, noted abnormal volume loss for the whole brain, total cortical, frontal, and temporal grey matter (GM) and progressive expansion of the lateral ventricles, as compared with findings in healthy control subjects¹⁴⁻²¹. Prospective brain MRI studies in patients with COS reveal a more striking progressive loss of total cerebral volume and total and regional cortical GM volumes during childhood and adolescence, as compared with findings in healthy control subjects^{22,23}.

In spite of these findings of progressive cortical GM loss and a subgroup of patients showing progressive deterioration the molecular/biochemical understanding of this neurodegenerative process remains unknown. Although it will be premature to conclude that niacin deficiency is the etiology of this progressive degeneration but it seems that this could contribute to the neurodegenerative process because of its ability to cause neurodegeneration in first place. Niacinamide has been long implicated in neuro-degenerative processes by various biochemical pathways. As elaborated by Fu et al²⁴, there are at least five biochemical pathways through which niacin can affect the neural degeneration:

1. The Tryptophan-Kyurenic acid pathway;
2. The mitochondrial ATP generation related pathways;
3. The poly (ADP- ribose) polymerase (PARP) pathway;
4. The BDNF-TRKB Axis abnormalities;
5. The genetic influences of niacin deficiency.

These biochemical pathways are implicated in the neurodegenerative processes found in pellagra. Post mortem examination has revealed chromatolysis in such patients. Indirect evidence suggests that niacin antagonism is associated with evident neuroglial (especially astrocytic) degeneration and subsequent disturbances in signal transmission across neurons. On the other hand, the ultrastructural changes in the neurodegeneration in schizophrenia has been poorly characterized. In neuropathological reports of childhood schizo-

phrenia central chromatolysis and gliosis in a restricted distribution of the brainstem and thalamus has been observed. Other neurodegenerative ultrastructural changes in schizophrenia patients have been observed, like loss of volume and cell number in the thalamus²⁵⁻³⁰, especially in the mediodorsal nucleus^{27,28}. Synaptic degeneration in the thalamus²⁹, reduced parvalbumin-immunoreactive thalamocortical projection neurons³⁰.

Evidence has also steadily accumulated that cellular NAD, the concentrations of which can be modified by niacin or niacinamide administration, plays critical roles in metabolic regulation and repair¹⁴. In pharmacologic doses niacinamide is neuroprotective¹⁵. Such effects are potentially relevant to the pathogenesis or mitigation of schizophrenia.

Niacin Deficiency Basis of Schizophrenia – the Membrane Phospholipid Dysfunction Theory

Above mentioned neurodegeneration has been implicated in schizophrenic etiopathogenesis but the most appreciated theory of, the pathogenesis of schizophrenia has been that involving subtler forms of neural impulse transmission resulting from the disturbances of polyunsaturated fatty acids. Neuronal membranes are rich in docosahexaenoic acid (DHA) (~50%), particularly in the cytosolic portion of the phospholipid double layer (Singh M. Indian J Pediatr 2005; 72: 239-242), indicating an important role of this fatty acid in the structure and function of neurons. Long chain polyunsaturated fatty acids (LC-PUFAs) are essential for normal development, structure and function of the brain

The DHA/AA (n-3/n-6) ratio is an important indicator for the maintenance of an appropriate level of biological membrane fluidity. This membrane fluidity in turn is essential for ion channels function, membrane receptor activity, release of neurohormones. All these in turn are needed in the signalling processes of every cell. The EFAs are a substrate for fatty acid desaturases and elongases that can metabolize them into forms with more unsaturated bonds and longer chains. These forms may be incorporated into membrane phospholipids.

The release of AA, 20:4n-6), docosahexaenoic acid (DHA, 22:6n-3) and other fatty acids from the membrane phospholipid molecules (which are structural components of biological membranes) constitutes a part of neuronal impulse transmission. The released fatty acids, particularly AA, and their derivatives (prostaglandins,

leukotrienes, thromboxanes) are important signalling molecules, but these substances are also recognized as important mediators of inflammation. Fatty acids in the membranes are bound to the trivalent alcohol glycerol within the phospholipid molecules; during neuronal transmission they are released by the phospholipase (PLA) group of enzymes. AA and DHA are incorporated in the phospholipid molecules mostly at the position sn-2; in their release from the membrane the phospholipase A2 family (PLA2) is engaged. Cytosolic, calcium – dependent phospholipase A2 (cPLA2, product of PLA2G4A gene, 1q25) catalyzes mostly the release of AA, while calcium – independent phospholipase A2 (iPLA2, product of PLA2G6A gene, 22q13.1) participates in the release of DHA³¹. After releasing the fatty acid from the sn-2 position, the remaining lysophospholipid may act as an important signalling molecule as well as a mediator for phagocyte infiltration in the inflammatory response. Enzymes of the PLA2 family work in the areas of neuronal membranes that contain monoamine receptors and are directly linked to neurotransmission.

Numerous studies have indicated that a deficit of AA and n-3 group fatty acids in the membranes of peripheral and central cells of schizophrenic patients may be casually related to an increased activity of PLA2 enzymes³²⁻³⁴ although dietary factors^{23,35}, effect of medications³⁶, oxidative stress and desaturase abnormalities have also been suggested as causative factors of FA deficiencies. As a consequence of an increased PLA2 activity there would follow an increased release of LC-PUFAs from membrane phospholipids, increased synthesis of pro-inflammatory mediators (AA derivatives), augmented peroxidation of lipids and free radicals formation; finally, resulting in an imbalance of membrane phospholipid fatty acids turnover.

Disruption of multiple neurotransmitters in schizophrenia (dopamine, serotonin, norepinephrine, epinephrine, glutamate, GABA-ergic) further supports the phospholipid hypothesis that places neuronal membranes and membrane – related processes in the center of the pathophysiology of this disease³⁷.

In addition to these theoretical perspectives, there has been an accumulation of evidence in past few years regarding altered phospholipid metabolism in schizophrenia. These include:

1. Increased activity of pPLA2 E, a vital enzyme for deacylation of phospholipid molecules and the release of fatty acids as mentioned

above, has been observed in the serum, plasma, blood cells and brain tissue of schizophrenic patients³²⁻³⁴.

- Peripheral cell membranes of patients with schizophrenia have reduced level of PUFAs (particularly AA and DHA that are abundant in the central nervous system)³⁸.

An increase in the nervous cell's membrane phospholipid disintegration has been observed in various nuclear magnetic resonance images of untreated patients^{38,39}. The role of DHA has also been recognized during pre-natal development. In the rat brain, the accumulation of DHA followed the period of active neurogenesis and synaptogenesis.

Niacin Deficiency Basis of Schizophrenia: the Adrenochrome Theory

The adrenochrome theory of schizophrenia has been conceptualized, propounded and much worked up on by Hoffer, often known as the father of orthomolecular medicine. Hoffer et al proposed this theory after studying and researching the effects of substances such as mescaline, lysergic acid diethylamide (LSD), and amphetamines – substances which cause a clinical syndrome clinically indistinguishable from schizophrenia. Osmond and Hoffer⁴⁰ noted that mescaline had a similar chemical structure to that of adrenaline. Osmond and Hoffer⁴¹ concluded that since both can be converted to indoles in the body, the potential schizophrenic toxin might be an indole derivative of adrenaline with similar neurochemical properties to that of mescaline or LSD. They eventually deduced that the schizophrenic toxin was an oxidized derivative of adrenaline known as adrenochrome. Since the early 1950s, the adrenochrome theory has been one of the most established and discussed theories in this field.

Following evidences are often cited as evidences of this theory:

- Adrenochrome and its close relatives – dopaminochrome (from dopamine) and noradrenochrome (from noradrenaline) – are present in the human brain⁴²⁻⁴².
- These compounds probably induce a combination of neurotoxic and mind- mood-altering effects⁴²⁻⁴².
- Reducing adrenochrome, dopaminochrome, and noradrenochrome is therapeutic for the treatment of schizophrenia⁴⁵.

To reduce the production of adrenochrome, Hoffer and his team decided on the methyl acceptor vitamin B 3. This vitamin, previously used to treat pellagra (a disease clinically indistinguishable from schizophrenia) had relevant biochemical properties.

Hoffer and his team researched the metabolism of adrenaline^{46,47}. They knew that the reaction involving noradrenaline to adrenaline required the addition of one methyl group. Because vitamin B 3 was known to function as a methyl acceptor, Hoffer's team theorized that an optimum dose of niacin might decrease the amount of noradrenaline that would be converted to adrenaline. Since adrenochrome was thought to be an oxidized derivative of adrenaline, vitamin B 3 could help reduce the quantity of adrenochrome by simply limiting the production of adrenaline.

Hoffer and his team also discovered an additional biochemical property of vitamin B 3 that would help to explain its therapeutic efficacy^{39,45,47}. Vitamin B 3 is a precursor to nicotinamide adenine dinucleotide, which is present in both oxidized (NAD) and reduced (NADH) forms in the body. In the brain, adrenaline loses one electron to become oxidized adrenaline. If enough NAD and NADH are available then the oxidized adrenaline is reconverted to adrenaline. These back and forth processes continue to occur in the presence of sufficient vitamin B3 coenzymes. However, in the absence of sufficient NAD and NADH, the oxidized adrenaline loses an additional electron and becomes adrenochrome. This last reaction is irreversible, and presumably occurs in much greater concentrations in the schizophrenic brain.

Niacin Deficiency Basis of Schizophrenia: the Clinical Correlation

Although pellagra is a rare condition in present day scenario, previous scientific literature has shown that this condition may present with several psychiatric features. Psychotic features although not very common can present in this condition. Rudin et al⁴⁸ has classified the psychiatric manifestations of niacin deficiency into three main types, which are (a) Schizophreniform, (b) Manic depressive types, and (c) Anxiety and depressive disorders. Schizophreniform manifestations include auditory hallucinations and persecutory delusions.

Presence of delusory parasitosis is a rare phenomenon in this deficiency state. This usually develops secondary to the patients' complaints of

pruritus and paraesthesias due to pellagra skin lesions. This is the reason why patients with such complaints are referred to a dermatologist rather than to a psychiatrist). However, from our case report, it seems that such patients are also prone to develop delusory parasitic ideas independent of the skin lesions⁴⁹. However, delusional parasitosis is known for its resistance to antipsychotic treatment. An autosomal dominant genetic disease characterized by psychiatric symptoms, and specifically cured by niacinamide, has been described⁵⁰.

Present scientific literature reporting the effect of niacin on improvement of psychotic conditions is limited to only few case reports. Although the exact relation between nicotinic acid deficiency and pathogenesis of delusions or hallucinations is not clear, it is likely to involve subtle neuronal insult which can be explained by either of the above mentioned theories reduced niacin sensitivity is associated with greater functional impairment among patients with schizophrenia. These findings raise the possibility that a subset of schizophrenia patients possesses a biochemical abnormality that reduces niacin sensitivity in the skin and contributes to functional impairment from the disease.

Recently Messamore⁷ conducted a study in which following psychiatric assessment, a Global Assessment of Functioning (GAF) score was assigned to each of 40 volunteers with schizophrenia. For each subject, the blood flow responses to several concentrations of topical methylnicotinate were recorded. Blood flow was measured objectively, using laser Doppler flowmetry. From the dose-response data, EC(50) values were derived. GAF scores were assigned without knowledge of the participants' niacin response data. The author found that there was a significant negative correlation between GAF scores and EC(50) values for methylnicotinate.

Niacin-Respondent Schizophrenia: the Treatment Based Model

In the most cited study by Hoffer and Osmond, the authors had treated schizophrenic patients treated with nicotinic acid in 1952 and found that 10 years later, 12 (75%) did not require any further treatment in hospital, 4 had required a total of six admissions, but none were in hospital 10 years later. Based on this data, they concluded that 75% of the treated group had achieved a 10-year-cure rate as compared to 37% of a comparison group.

Early studies^{51,52} have attempted to use niacin as an augmenting agent for the treatment of schizophrenia with positive results. In recent past, there have been several study reports like this showing that nicotinic acid based treatment is effective in schizophrenia patients^{30,31,40,41}. The first report on the therapeutic use of vitamin B 3 for schizophrenia⁵³ was presented in 1952 at the Saskatchewan Committee on schizophrenia. At this meeting, eight cases were presented, each demonstrating favorable effects from giving 1-10 g vitamin B 3, and, in the majority of cases, equal amounts of vitamin C.

After a more involved pilot study demonstrated excellent therapeutic responses to vitamin B 3⁵², the first North American double-blind, placebo-controlled experiment was undertaken to assess whether or not this vitamin was effective for schizophrenia. The study, which began in 1952 but was not published until 1957, involving 31 acute schizophrenic patients who were each randomized to placebo, niacinamide, or niacin⁵³. They were given 1 g three times daily for 30 days, and then were followed for one year. After one year, the patients given vitamin B 3 with the standard treatments at that time had more than double the recovery rate (80%) compared to patients in the placebo group (33%). In their second double-blind, placebo-controlled experiment, Hoffer and his team used only niacin and placebo⁵³. The study lasted 33 days and involved 82 patients (43 in the placebo group and 39 in the niacin group). Vitamin B 3 once again contributed significantly to the recovery of acute schizophrenic patients. In the niacin group, 79.5 percent improved compared to 41.9 percent in the placebo group.

Other parameters evaluated by the team included the number of patients readmitted, the number of readmissions, the number of well or much improved patients, and the number of patients who were considered cured. This data involved the following groups of patients: (1) those who only took vitamin B 3 in the hospital and not in the community; (2) patients who did not take vitamin B 3 in the hospital but did take the vitamin when in the community; (3) patients who took vitamin B 3 in the hospital and community; and (4) patients who never took vitamin B 3. The results demonstrated that patients in the community who were taking niacin (groups 2 and 3) had more community years that were free of readmissions compared to patients not taking vitamin B 3 (groups 1 and 4) – 91 percent versus 62 percent of the community years free of readmissions.

Table I. Niacin respondent schizophrenia-the therapeutic model.

Schizophrenia subset	Etiopathological association with Niacin	Clinical and treatment related association with Niacin	Recommendations for augmentation Niacin
1) Schizophrenia patients with clinical/subclinical	Highly prone to developing Pellagra related neuropathology and psychopathology	Early intervention helps in both schizophrenia and Pellagra treatment	• Recommended in clinical doses
2) Patients with delusional parasitosis	Literature suggests that delusional parasitosis can be both secondary to Pellagra skin lesions as well as primary psychopathology of schizophrenic with Pellagra	Niacin augmentation can lead to both improvement in skin lesions and schizophrenic delusional parasitosis	• High dose Niacin recommended
3) Schizophrenia patients with alcoholism	<ul style="list-style-type: none"> • Delirium tremens as well as alcoholic encephalopathy present with psychotic features which can precede development of schizophrenia • Alcoholism presents with multiple vitamin deficiencies 	–	• Clinical doses of Niacin
4) Patients with impaired Niacin flushing test	<ul style="list-style-type: none"> • Impaired Niacin flushing shows poor phospholipid functioning due to Niacin deficiency 	Repetition of the Niacin flushing test after treating with Niacin augmentation shows improvement	• High dose Niacin
5) Childhood onset schizophrenia	<ul style="list-style-type: none"> • Neurodegenerative pathology and progressive nature of clinical picture show its close association with Pellagrous neurodegeneration 	–	<ul style="list-style-type: none"> • Clinical dose of Niacin • Long time therapy with niacin augmentation to prevent chronic degeneration

The entire niacin group (group 3) was readmitted 38 times for 67 readmissions (average 64 days per patient); whereas, the placebo/non-niacin group (group 4) was readmitted 36 times for 81 readmissions (average 147 days per patient). Once all the data was combined, the results revealed that the most five-year cures and best treatment responses were among the patients who took vitamin B 3 in the hospital and in the community.

The biggest follow-up study in this direction was performed by Hoffer⁵³, who followed patients from 1953 to 1960, publishing a total of six double-blind, randomized controlled clinical trials. All trials confirmed the positive effects that vitamin B 3 had on the recovery of acute schizophrenic patients, and that the use of this vitamin substantially reduced patients' reliance on the health care system. In terms of treating chronic schizophrenic patients, Hoffer's early studies did not show a favorable response among chronic schizophrenic patients who were ill longer than one year. When Hoffer reviewed this problem

more thoroughly, however, he discovered that the treatment duration was not long enough to have produced adequate results. Chronic patients required vitamin B 3 treatment for five or more years in order to derive observable benefits^{47,53}.

In one study involving 32 chronic patients⁵³, no patient responded to vitamin B 3 after two years of use. Nineteen patients discontinued the vitamin, while the remaining 13 patients continued with the vitamin treatment. Data was obtained for the years, 1956-1964. Of the patients not on niacin, the mean number of days spent in hospital was 691 compared to 79 in the niacin group. The proportion of time spent in the hospital was substantially less for the chronic patients who remained on the vitamin.

In a more recent analysis of 27 chronic schizophrenic patients who had been under treatment for at least 10 years, consistent treatment with vitamin B 3 produced the following results: 11 patients were able to work; two patients were able to marry and look after their families and homes; two patients were single mothers able to care for

their children; and three patients were able to manage their own businesses⁴⁷. These results are remarkable when one considers the state of these patients prior to receiving optimal doses of vitamin B 3. The average age of these patients was 40, the majority of them were ill for seven years before they sought treatment from Hoffer, and all had been unresponsive to previous treatments.

Niacin-Respondent Schizophrenia Subset – When Niacin Augmentation Will Help?

The discussion till now has covered to topics of neuropathological, clinical and treatment based correlations of niacin and schizophrenia. In this section we will synthesize the whole concept of niacin-respondent subset of schizophrenia based on the previous sections. Recently there has been an appraisal of the importance of taking all the possible factors which influence the response to antipsychotics in Schizophrenia⁵⁴. In this context, the role of niacin as an augmentation therapy requires a proper addressing. From the literature as well as from our own experiences, we can easily conclude that niacin is effective as an augmentation therapy in schizophrenia patients for multiple reasons. However, not all patients of schizophrenia respond to niacin augmentation therapy uniformly. It is, thus, important to identify the patient subgroup of schizophrenia who are more likely to responding to niacin augmentation. We can suggest here that negative symptoms in Schizophrenia result from cingulate cortex abnormalities and Niacin has been found to especially affect the kynurenic pathway in Cingulate cortex of Schizophrenia patients⁵⁵. Therefore, such patients can be especially benefitted from niacin augmentation. Literature review as well as our own experiences, suggest that there are some important features which suggest that such patients would respond to niacin augmentation. Here we try to point out some of these variables based on the etiopathological and treatment related associations that we discussed on previous sections.

Schizophrenia Patients With Clinical/ Subclinical Pellagra/Chronic Malnutrition

Schizophrenia patients often present with vitamin deficiencies. Such patients, may present with clinical/subclinical pellagra⁴⁹. Such patients often present with schizophrenic symptoms. Such patients may especially be benefitted by niacin augmentation not only for the treatment of pellagra but also for the treatment of schizophrenic symptoms. Patients with chronic malnutrition present-

ing with schizophrenia are especially important subgroup for niacin augmentation for the same reason.

Patients With Delusional Parasitosis

Delusional parasitosis is a rare finding in schizophrenia. It has been often seen in association with skin lesions and thus such patients are more likely to visit a dermatologist rather than psychiatrist. A case reported by present authors⁴⁹ was a significant addition to the scientific literature in this field. We found that the patient with overt clinical pellagra had delusional parasitosis and this delusion responded to the addition of niacin in the treatment. This could have been both because of the skin lesions as well as due to the pschopathology. In either of the situation, our patient responded to the niacin augmentation showing that delusional parasitosis especially in association with clinically evident pellagra should be treated with niacin augmentation in addition to antipsychotics. We, thus, propose that delusional parasitosis is an important component of schizophrenia patients for which niacin augmentation should be tried.

In a placebo-controlled comparative study by Ramsay et al⁵⁶, it was found that, while no significant differences were seen in total Brief Psychiatric Rating Scale (BPRS) scores prior to commencement of the clinical trial, statistically significant improvement in 'emotional withdrawal' was seen only with nicotinamide and not with placebo.

Schizophrenia Patients with Alcoholism

Alcoholism is a common comorbidity of schizophrenia. In alcoholism, it may be difficult to differentiate between delirium tremens and psychosis but as Ishii and Nishihara⁵⁷ point out, alcoholic pellagra presenting with psychosis may be actually indicator of future development of schizophrenia. Neurodegeneration is a common feature in chronic alcoholism¹⁸. However, more important association between alcoholism and schizophrenia is because of the multivitamin deficiency commonly associated with alcoholism⁵³.

Patients with Impaired Niacin Flushing Test

Several studies^{2,56} have demonstrated an impaired and even absent niacin flushing response in schizophrenia patients which has not been replicated in other psychiatric group of patients. Hoffer observed that treatment with high doses

of the non-flush NAD precursor, nicotinamide, resulted in recovery from acute schizophrenia similar to recovery from pellagra dementia. Restoration of the nicotinic acid-mediated flush response correlates with niacin-mediated recovery from schizophrenia⁵⁸ (in fact, the first reports of impaired niacin response was observed while being treated with niacin by Hoffer. It was a double-blind, placebo-controlled experiment, in which Hoffer and his team used only niacin and placebo. The study lasted 33 days and involved 82 patients (43 in the placebo group and 39 in the niacin group). Vitamin B3 once again contributed significantly to the recovery of acute schizophrenic patients. In the niacin group, 79.5 percent improved compared to 41.9 percent in the placebo group.

Childhood-onset Schizophrenia

Childhood-onset schizophrenia is an important subgroup which needs to be addressed not only because of the possible effects of niacin augmentation but also because of its poor prognostic course. Especially, the neurodegenerative changes similar to pellagra has been reported in Childhood-onset schizophrenia.

Conclusions

Niacin deficiency seems to be an important contributor in the development of the clinical picture of schizophrenia. Studies and sparse case reports indicate that niacin augmentation could help a subset of patients suffering from schizophrenia. These patients could benefit from an early intervention of addition of therapeutic doses of schizophrenia in addition to ongoing treatment.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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