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Case Report

Exploring the role of glutathione therapy in schizophrenia: a case report

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ABSTRACT

Schizophrenia is a psychiatric disorder consisting of debilitating symptoms. Accumulating evidence suggests that oxidative stress is one of the main mechanisms of pathogenesis, and patients with schizophrenia have lower levels of glutathione, a crucial antioxidant. In this case, we present a 23-year-old male with severe schizophrenia who was undergoing treatment with multiple antipsychotics but showed minimal improvement in general psychopathology on the Positive and Negative Syndrome Scale (PANSS). Given that the patient was on numerous medications, we introduced glutathione as a novel approach. We hypothesize that glutathione is an antioxidant that reduces oxidative stress and enhances the overall functioning of schizophrenia patients. We administered weekly glutathione treatment for 10 weeks. Our findings suggest that glutathione as an adjunct therapy significantly improves symptoms in patients with schizophrenia. No important adverse effects occurred during follow-up.

Keywords: Schizophrenia, Glutathione, Oxidative stress

INTRODUCTION

Schizophrenia is one of the most severe and complex psychiatric disorders, affecting 1% of the population, and is characterized by a range of symptoms. These include positive symptoms, such as delusions, hallucinations, disorganized thinking, and catatonia. It also presents with negative symptoms, including social withdrawal, diminished emotional expression, and amotivation. Cognitive and functional impairments such as memory deficits and slowed processing speed are also common in individuals with schizophrenia. The disorder is associated with a reduced life expectancy of approximately 15 years shorter than that of the general population, along with a 5-10% lifetime risk of death by suicide.[1,2]

Although schizophrenia typically manifests in early adulthood, its pathogenesis begins during neurodevelopment.[2] The pathogenesis of schizophrenia involves several mechanisms, including synaptic dysfunction, dopaminergic dysregulation, neuroinflammation, and disruptions in neurodevelopment. Genetic and environmental factors play significant roles in these processes.[3-6]

Oxidative stress (OS), results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defenses. As the brain is especially susceptible to oxidative stress, it plays a role in the development of psychiatric disorders. Its relatively high oxygen demand, limited antioxidant defenses, and lipid-rich structure make it more vulnerable to oxidation. Many factors contribute to an individual's susceptibility to oxidative stress. One key factor is glutathione deficiency. Glutathione (GSH) is an antioxidant that protects against oxidative stress-induced damage by neutralizing reactive oxygen species (ROS). Evidence suggests that GSH levels are reduced in individuals with schizophrenia.[7]

The rationale for exploring glutathione's effectiveness in schizophrenia originates from the role of oxidative stress in the development of the disorder. OS leads to neuronal toxicity through lipid peroxidation, activates various inflammatory pathways, and further promotes neuroinflammation by triggering microglial activation. Additionally, high concentrations of ROS diminish synaptic signaling and impair mechanisms of brain plasticity.[7-9]

Previous studies have shown that antioxidants such as Vitamin C, Vitamin E, and N-acetylcysteine (NAC) can improve symptoms in patients with schizophrenia. NAC, in particular, serves as a precursor to glutathione, supports its synthesis, and may contribute to restoring antioxidant balance. Therefore, directly supplementing with GSH may offer a promising approach to alleviating schizophrenia symptoms.[10]

The present case report describes a severe schizophrenia patient who underwent glutathione therapy and showed improved functioning after treatment. We will explore the theoretical basis for this intervention.

CASE REPORT

Background history

A 23-year-old white male, with diagnosis of schizophrenia since 14 years old, single, currently unemployed, lives with his parents in New York. The patient has a family history of bipolar disorder in his paternal uncle. Early developmental progression was without any delay. The patient has a history of severe agitation and disorganized behaviors, leading to his first hospitalization. In total, he has had four inpatient psychiatric hospitalizations and multiple psychiatric visits. He does not attend college but is involved in a local church. He denies using any substances and having any symptoms of mania. He has no history of self-harm or suicidal thoughts.

Interventions and outcomes

He was diagnosed with schizophrenia disorder, according to DSM-5. He was prescribed haloperidol 5 mg BID and clozapine 300 mg daily, but there was minimal improvement in the patient's clinical symptoms.

The patient exhibits severe anxiety, with intense fears and obsessive thoughts leading to insomnia. He also demonstrates irritability and impulsivity, as evidenced by screaming episodes. He reports restlessness, feelings of isolation, and social withdrawal. The patient appears disheveled and exhibits psychomotor agitation and frequent pacing. His speech is disorganized. He exhibits a distressed mood with a restricted affect. His thought process is racing and disorganized. Moderate auditory hallucinations are reported. He presents with confusion, poor attention, and poor concentration. His insight is limited, and his judgment is impaired. The Positive and Negative Syndrome Scale (PANSS) is used to evaluate his symptoms. The initial PANSS score while on haloperidol 5 mg and clozapine 300 mg totals 112. This includes a positive symptoms score of 26, a negative symptoms score of 28, and a general psychopathology score of 58.

We administered glutathione as an adjunct therapy alongside antipsychotic treatment, given once a week for 10 weeks. Each infusion contained 200 mg/10 ml of glutathione diluted in 250 ml of 0.9% saline solution. The infusion was delivered using an infusion pump through peripheral venous access, with each session lasting 20 minutes. The only adverse effect was mild nausea during infusion.

After 10 weeks of treatment, the patient and his parents reported considerable improvements. The patient's speech is noticeably more organized. Although he is still anxious, his fears and obsessive thoughts no longer cause insomnia. His mood has improved, and he is less irritable than before, impulsive behaviors have significantly decreased. Hallucinations exhibited mild improvement. Current symptoms are assessed using the PANSS scale. The scores are as follows: positive symptoms score is 16, negative symptoms score is 23, general psychopathology score is 43, and the overall score is 82. Furthermore, the improvement based on the PANSS scale is reported at 27%. The PANSS scores prior to treatment with glutathione and after 10-weeks of therapy are presented in Figure 1.

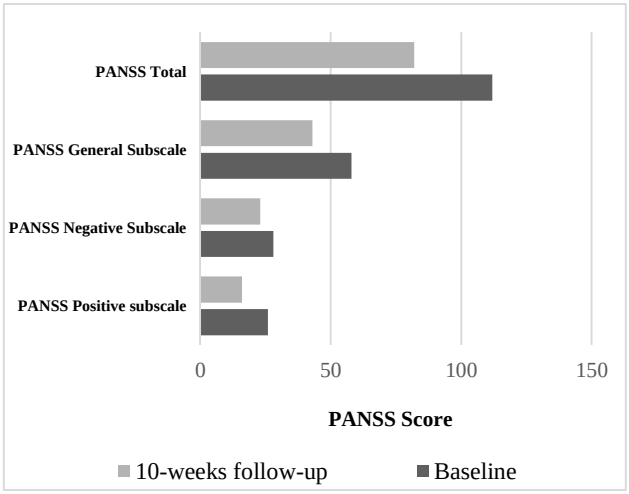

Figure 1. Changes in PANSS scores before and after treatment with glutathione.

DISCUSSION

Reactive oxygen species (ROS), including superoxide (•O2-), hydrogen peroxide (H2O2), and hydroxyl radicals (•OH), are highly reactive molecules generated from electron transfer processes. ROS production in the body primarily occurs in the mitochondria, peroxisomes, and membrane-bound NADPH oxidases (NOXs), while

exogenous sources include anticancer therapy, radiation, smoking, alcohol, and certain drugs.[11]

ROS play significant roles in cellular processes such as proliferation, differentiation, migration, apoptosis, and necrosis. A low to intermediate level of ROS is essential for physiological functions. However, oxidative stress occurs if an imbalance shifts towards excessive ROS production rather than efficient elimination, potentially leading to cellular damage.[11]

Oxidative stress (OS) is one of the key mechanisms driving the pathogenesis of schizophrenia. The brain is highly sensitive to oxidative damage due to its high oxygen consumption, which is used in synaptic connections, maintaining membrane potential, synthesizing neurotransmitters, and neuronal plasticity. Additionally, neurons have relatively low levels of antioxidant systems. Compared to other cells, the neuronal content of catalase is 50 times less, and reduced glutathione levels are 50% lower, which are antioxidants.[7]

Several factors can make an individual prone to oxidative stress. The main factor is genetic predisposition; polymorphisms in GSH (glutathione) related genes are associated with this disorder with a polygenic nature. Other factors contributing to oxidative stress include altered gene expression, mitochondrial dysfunction -a major site for electron transfer-, pro-inflammatory cytokines, and sources of ROS like in-utero infections, gestational diabetes, obesity in pregnancy, and psychosocial stress.[7]

ROS inhibit calcium (Ca) channels in the endoplasmic reticulum and neurolemma, leading to an increase in intracellular calcium concentrations. Since intracellular Ca regulates neurotransmitter release, it plays a role in modulating synaptic activity and neuroplasticity. Elevated Ca levels activate phospholipase A, an enzyme that hydrolyzes phospholipids—the main compounds of cell membranes—by oxidizing polyunsaturated fatty acids. This cascade ultimately results in neuronal damage.[7,12]

Oligodendrocytes are responsible for producing myelin, which consists of membrane domains rich in polyunsaturated fatty acids. The maintenance of these lipid-dense membranes requires significant energy, making oligodendrocytes particularly susceptible to oxidative stress. Metals with mixed valence (especially iron and copper) further contribute to the development of OS in neurons. Myelin's high iron content exacerbates OS when damaged, releasing iron into the extracellular space. Some brain regions are more susceptible than others: the amygdala, hippocampus, and cerebellar cortex.[7]

Oxidative stress (OS) activates microglia, increasing their phagocytic activity. This activation leads to the release of reactive oxygen species (ROS) and other molecules that degrade perineuronal nets, which are extracellular matrix structures essential for synaptic stabilization and neural protection.[13] Increased levels of ROS further contribute to synaptic dysfunction by causing NMDA and GABA receptor hypofunction, thereby disrupting glutamate and GABA neurotransmission, respectively.[14,15] Given that schizophrenia is widely recognized to impair dopamine, glutamate, and GABA neurotransmitter systems, OS-induced synaptic dysfunction may play a crucial role in its pathophysiology.[16]

The most prevalent antioxidant in the brain is glutathione. Recent studies have shown a decrease in glutathione levels in the prefrontal cortex, as well as in erythrocytes, blood, and cerebrospinal fluid (CSF), in patients with schizophrenia.[17] Glutathione, in its reduced form (GSH), can reduce hydrogen peroxide (H2O2) to water (H2O) by oxidizing itself to its oxidized form (GSSG). This reaction effectively neutralizes hydrogen peroxide, which is a free radical. During periods of oxidative stress, the ratio of GSH/GSSG decreases, leading to an increase in the number of free radicals.[12] As previously discussed, oxidative stress from free radicals leads to neurodegeneration, ultimately resulting in a significant reduction in gray matter volume and functional dysconnectivity.[13]

N-acetyl cysteine (NAC) is a glutathione precursor that has been studied in clinical trials for the treatment of schizophrenia. In one trial, NAC was administered as an add-on therapy for 24 weeks to schizophrenia patients. The Positive and Negative Symptoms Scale (PANSS) assesses the results. The findings indicated improvements, particularly in negative symptoms of schizophrenia, rather than in positive symptoms.[18]

Finally, by administering glutathione therapy to schizophrenia patients, we aim to shift the imbalance toward antioxidant defense mechanisms, thereby reducing oxidative stress. As discussed earlier, lowering oxidative stress may help mitigate neuronal and overall brain damage associated with schizophrenia.

CONCLUSION

In conclusion, we observed clinical improvement in various aspects of schizophrenia, with the most significant symptom reduction in positive symptoms and the least in negative symptoms, as indicated by changes in PANSS score. Since treatment responses can vary among individuals, further research is necessary better to understand the role of glutathione in schizophrenia treatment. This case suggests that glutathione therapy, when used alongside antipsychotic medications, may be a promising adjunctive option for patients with severe schizophrenia. However, larger-scale studies and controlled clinical trials are essential to confirm its efficacy and generalizability.

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