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RESEARCH ARTICLE

MARKED IMPROVEMENT OF TREATMENT-RESISTANT TARDIVE DYSKINESIA WITH COMBINED NAD AND GLUTATHIONE INFUSIONS: CASE REPORT

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Abstract

Background:-Tardive dyskinesia (TD) is a persistent hyperkinetic movement disorder most commonly associated with prolonged exposure to dopamine rece ptor antagonists. Although vesicular monoamine transporter 2 (VMAT 2) inhibi tors such as valbenazine and deutetrabenazine are first line pharmacologic optio ns,a subset of patients exhibits inadequate response,necessitating alternative therapeutic approaches.

Case presentation:-We describe a 21-year-old male with bipolar II disorder who developed progressive perioral and lower limb dyskinesia after four years of risperidone and lithium therapy. Symptoms worsened following abrupt risperidone discontinuation and showed no improvement with valbenazine. He was switched to deutetrabenazine XR 48 mg daily and treated with baclofen, trihexyphenidyl, and weekly infusions of nicotinamide adenine dinucleotide (NAD) and glutathione. While mild lower limb dyskinesia persisted, marked improvement in perioral dyskinetic movements and swallowing allowed him to resume an unrestricted diet.

Conclusion:-To the best of our knowledge, this is the first reported case of refractory tardive dyskinesia showing marked improvement with combined NAD and glutathione infusions alongside adjunctive pharmacologic agents. These findings suggest a potential therapeutic role for redox targeted interventi ons in treatment-resistant TD and warrant further investigation.

Introduction:-

Tardive dyskinesia (TD) is a hyperkinetic movement disorder characterized by involuntary, repetitive, and polymorphic movements, most frequently involving the perioral region, neck, trunk, and extremities [1]. TD is

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predominantly associated with chronic exposure to dopamine receptor antagonists, such as antipsychotics, certain antiemetics, antidepressants, and calcium channel blockers. The reported prevalence among patients receiving antipsychotic therapy ranges from 21% to 30%, with substantially higher rates documented in geriatric populations [2]. Although second-generation antipsychotics generally confer a reduced risk relative to first-generation agents, the risk remains clinically relevant. Notably, the overall population at risk may be increasing due to the broadening therapeutic indications and frequent off-label prescribing of antipsychotics [3].

The onset of TD is typically insidious, and the condition often remains irreversible even after discontinuation of the offending drug. TD imposes a substantial economic burden, diminishes quality of life, and increases mortality rates [4]. Therefore, appropriate prevention and timely intervention are essential. In cases where involuntary movements persist following withdrawal of the causative agent, the subsequent step involves the introduction of pharmacologic agents aimed at mitigating dopaminergic overactivity.

The most widely used therapeutic approach is the administration of vesicular monoamine transporter 2 (VMAT-2) inhibitors, such as valbenazine and deutetrabenazine. VMAT-2 is a critical presynaptic transporter responsible for the storage and release of monoamines, including dopamine, serotonin, and norepinephrine. By inhibiting VMAT-2, these agents attenuate dopamine signaling dysregulation, thereby alleviating excessive D2 receptor blockade [6]. However, due to the inherently irreversible nature of TD, alternative therapeutic strategies have been actively explored. There are some papers on next-step strategies, including baclofen, anticholinergic agents, benzodiazepines, and botulinum toxin injections. Some cases are reported using electroconvulsive therapy (ECT) and deep brain stimulation (DBS) for managing treatment-resistant TD [7,8].

We report a patient who exhibited a suboptimal response to initial treatment with a VMAT-2 inhibitor, necessitating consideration of alternative therapeutic strategies. The patient subsequently received nicotinamide adenine dinucleotide (NAD) and glutathione infusions in combination with other adjunctive pharmacologic agents, resulting in substantial clinical improvement. This case may contribute to expanding the therapeutic options available for the management of treatment-resistant tardive dyskinesia.

Case Presentation:-

A 21-year-old male presented with involuntary movements involving the jaw, perioral region, and legs. He had been receiving risperidone 2 mg and lithium 900 mg daily for five years following a diagnosis of bipolar II disorder at the age of 16.

Four years after initiating treatment, he developed progressive perioral dyskinesia, initially described as protrusion of the mouth, which worsened to cause difficulty in eating, breathing, and articulation. These symptoms precluded the intake of solid food, necessitating a liquid-only diet. He subsequently noted heaviness of the left foot, resulting in a dragging gait. Following the abrupt discontinuation of risperidone, his tongue movements worsened. Valbenazine 60 mg daily was initiated, and risperidone was reintroduced at 1 mg daily with a gradual tapering plan, but no symptomatic improvement was observed.

Upon presentation to another clinic, his Abnormal Involuntary Movement Scale (AIMS) score was 15. Valbenazine 60 mg daily was prescribed with a planned increase to 80 mg after one week, but no clinical benefit was noted. The regimen was subsequently switched to deutetrabenazine XR 48 mg daily, with the addition of trihexyphenidyl 2 mg twice daily and baclofen 20 mg twice daily, along with weekly infusions of nicotinamide adenine dinucleotide (NAD) 500 mg and glutathione 2000 mg. Concurrent medications included lithium 900 mg daily and a clonidine 0.1 mg transdermal patch applied weekly. This combination resulted in substantial improvement in tongue movements, although mild dysarthria and intermittent involuntary tongue protrusion persisted.

He was later referred to a neurologist for evaluation and pharmacologic therapy. His AIMS score improved to 6. The current regimen consists of deutetrabenazine XR 48 mg daily, baclofen 20 mg twice daily, diazepam 2 mg twice daily, trihexyphenidyl 2 mg twice daily, clonidine 0.1 mg patch weekly, lithium 450 mg daily, quetiapine 100 mg daily, and weekly NAD, glutathione infusions. Although mild lower limb dyskinesia persists, marked improvement in perioral movements and swallowing has enabled the patient to resume an unrestricted diet.

Discussion:-

The general concepts on the pathophysiology of TD involve dopamine receptor hypersensitivity, damage to GABAergic and cholinergic neurons, and oxidative stress. Increasing attention has been directed toward oxidative mechanisms in neuronal injury, partly due to evidence supporting the potential therapeutic benefit of vitamin E in TD. In normal cellular circumstances, oxidative reactions are crucial in energy generation and neural protection. Nitric oxide (NO) plays a key role in the redox system, and excessive production of NO may exert neurotoxic effects, leading to structural and functional impairment of neurons [9]. Elevated NO levels facilitate the formation of reactive nitrogen species (RNS), including peroxynitrite and nitrogen dioxide radicals, which induce oxidative stress and inflammatory injury within the central nervous system (CNS). The oxidative stress hypothesis of TD is not mutually exclusive with the dopamine hypothesis. It is suggested that upregulation of dopamine synthesis leads to increased activity of MAO, which leads to the generation of free radicals like hydrogen peroxide and autooxidation of dopamine and thus formation of free radicals and quinines [20].

NO is synthesized by neuronal nitric oxide synthase (NOS1) and endothelial nitric oxide synthase (NOS3), and genetic polymorphisms in NOS3 have been implicated in increased susceptibility to TD [10]. Several other genes involved in oxidative stress defense have also been implicated in TD, with the most consistent association observed for the manganese superoxide dismutase (MnSOD) gene. Additional antioxidant-related genes studied in this context include glutathione S-transferases, NAD(P)H quinone oxidoreductase 1 (NQO1), glutathione peroxidase 1 (GPX1), and nitric oxide synthases (NOS1, NOS3) [11]. Furthermore, redox stress in TD has been demonstrated in studies reporting decreased levels of antioxidant enzymes, such as GPX1 and catalase (CAT1), along with elevated levels of oxidative damage markers, including malondialdehyde and thiobarbituric acid [12,13].

Glutathione, a tripeptide composed of glutamic acid, glycine, and cysteine, plays a central role in cellular antioxidant defense. Under oxidative conditions, glutathione exerts protective effects by undergoing conversion to its oxidized dimeric form. This process is catalyzed by glutathione peroxidase, which reduces hydrogen peroxide using glutathione as a substrate [14]. In pathological mechanisms underlying TD, characterized by oxidative stress and genetic polymorphisms affecting antioxidant pathways, glutathione may represent a potential therapeutic target. Preclinical studies in hyperkinetic disorders, such as Huntington's disease, have shown that dysregulated glutathione metabolism within the indirect pathway leads to excessive dopaminergic activity in the striatum. Given the shared features of striatal dysfunction and oxidative stress between Huntington's disease and TD, glutathione supplementation could be of therapeutic relevance [15,16]. This is further supported by clinical evidence indicating that other antioxidants, such as vitamin E, confer modest benefits in TD [17].

NAD is a critical redox coenzyme that interconverts between its oxidized (NAD^+) and reduced (NADH) forms. The NAD^+/NADH ratio plays a pivotal role in regulating energy production, metabolic homeostasis, mitochondrial function, and DNA repair, necessitating tight regulation of its synthesis and utilization to preserve cellular integrity [18]. Studies measuring CSF levels of substrates of mitochondrial energy metabolism have found that aspartate levels are significantly elevated in patients with tardive dyskinesia and correlate with the total AIMS score. This finding, consistent with inhibition of complex I of the electron transport chain in the mitochondria, could be associated with increased free radical formation. [19].

This is consistent with findings that antipsychotics, including the second generation, target the mitochondria, alter oxidative phosphorylation & mRNA expression, and lead to significantly decreased ATP production & increased oxidative stress [21]. Supplementation of NAD in neurodegenerative diseases has been shown to reduce free radical stress, and reduce the accumulation of damaged mitochondria [22]. Given the above, NAD must be strongly considered as a potential pharmacotherapy for treatment-resistant Tardive Dyskinesia. This case report is the first to demonstrate the therapeutic utility of this drug to manage this condition.

To the best of our knowledge, this case report represents the first documented instance of treating refractory tardive dyskinesia with combined NAD and glutathione infusions alongside adjunctive pharmacologic agents, potentially contributing to the expansion of therapeutic strategies for managing treatment-resistant cases.

Conclusion:-

TD remains a challenging condition to manage, particularly in patients who exhibit inadequate responses to standard therapies such as VMAT-2 inhibitors. Oxidative stress is increasingly recognized as a key contributor to its pathophysiology, highlighting the therapeutic potential of antioxidant-based interventions. In this report, we

describe, to the best of our knowledge, the first documented case of refractory TD successfully managed with combined NAD and glutathione infusions in conjunction with adjunctive pharmacologic agents. The marked clinical improvement observed in this patient supports further exploration of redox-targeted therapies in treatment-resistant TD. Future studies are warranted to validate these findings and to clarify the underlying mechanisms of benefit.

Declarations:

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