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EXPLORING THE POSSIBLE LINK BETWEEN G6PD DEFICIENCY INDUCE MIGRAINE: A REVIEW

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ABSTRACT
Migraine is a prevalent neurological disorder characterized by recurrent headaches, often accompanied by nausea, photophobia, and phonophobia. Although its exact pathophysiology remains unclear, growing evidence suggests that oxidative stress plays a crucial role in its development. An imbalance between reactive oxygen species (ROS) and antioxidant defenses may contribute to the frequency and severity of migraine attacks. This review explores the potential association between Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency and migraine, highlighting oxidative stress as a common pathological mechanism. G6PD deficiency disrupts the pentose phosphate pathway, leading to reduced glutathione production and increased oxidative susceptibility. While primarily affecting erythrocytes, this heightened oxidative stress may extend to the brain, exacerbating neuroinflammation and migraine pathogenesis. Additionally, individuals with G6PD deficiency often exhibit elevated Red Cell Distribution Width (RDW), a marker of systemic inflammation, which has been implicated in migraine development. Persistent oxidative stress in migraine sufferers, even between attacks, promotes neuroinflammation and central pain sensitization. Given these overlapping mechanisms, it is hypothesized that G6PD deficiency could intensify migraine symptoms. Targeting oxidative stress through antioxidant-based interventions and personalized migraine management strategies may offer therapeutic benefits, particularly for individuals with G6PD deficiency. Further research is needed to elucidate this relationship and develop optimized treatment approaches.

KEYWORDS: Migraine, G6PD deficiency, oxidative stress, neuroinflammation, pentose phosphate pathway, antioxidant therapy

INTRODUCTION
Migraine is a highly prevalent and disabling neurological condition, characterized by recurring, often one-sided headaches accompanied by symptoms such as nausea and, in some cases, sensory disturbances like aura. Despite its widespread impact on quality of life, the precise mechanisms that initiate migraine episodes remain incompletely understood. Current evidence points to a multifactorial pathophysiology involving genetic predisposition, environmental triggers, and neurovascular dysregulation.[1] A substantial body of research highlights oxidative stress as a key contributor to the development and persistence of migraine. This imbalance between the generation of reactive oxygen species (ROS) and the efficiency of the body's antioxidant defense mechanisms can lead to cellular dysfunction.[2] In migraine patients, elevated ROS levels have been linked to neuroinflammatory processes, which sensitize nociceptive pathways and intensify headache symptoms.[3] Interestingly, oxidative stress appears to influence migraine pathology not only during acute attacks but also in the interictal phase, suggesting a chronic underlying dysfunction in redox homeostasis.[4] Among metabolic conditions known to amplify oxidative stress, Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is particularly notable. G6PD plays a vital role in the pentose phosphate pathway, generating NADPH, which supports the regeneration of reduced glutathione, a key intracellular antioxidant.[5] A deficiency in G6PD compromises the antioxidant defense, thereby increasing vulnerability to oxidative damage and potentially heightening susceptibility to migraine and related neuroinflammatory conditions. This review article aims to explore the potential link between G6PD deficiency and migraine, focusing specifically on oxidative stress as a shared pathophysiological mechanism and discussing its relevance for novel treatment strategies.

Oxidative Stress in Migraine: Patients with migraine frequently exhibit signs of elevated oxidative stress,

resulting from an imbalance between ROS production and the body's ability to neutralize their harmful effects. The brain's high oxygen consumption and lipid-rich composition make it especially susceptible to oxidative damage. This, in turn, promotes neuroinflammation, neuronal injury, and sensitization of pain processing pathways. Evidence also indicates that oxidative stress persists even between migraine episodes, reinforcing the hypothesis that it contributes to both the initiation and chronicity of migraine symptoms.[6,7]

Role of Glucose-6-Phosphate Dehydrogenase Deficiency: G6PD is a critical enzyme in the pentose phosphate pathway (PPP), which produces NADPH, a key molecule required for maintaining the body's antioxidant defenses, including the regeneration of glutathione (GSH). GSH neutralizes ROS, protecting cells from oxidative damage. In individuals with G6PD deficiency, the reduced activity of the enzyme leads to decreased NADPH production, impairing the antioxidant system and making erythrocytes and other tissues more vulnerable to oxidative stress. In particular, erythrocytes are more prone to hemolysis due to oxidative damage to cell membranes and hemoglobin.[8] This oxidative vulnerability extends beyond erythrocytes and may affect other tissues, including the brain, which is highly susceptible to oxidative damage. Studies suggest that G6PD deficiency may exacerbate neuroinflammation, contributing to the neurological manifestations of migraine. Furthermore, the presence of elevated Red Cell Distribution Width (RDW), commonly observed in G6PD-deficient individuals, has been linked to systemic inflammation, which may further influence migraine pathophysiology.

Shared Pathophysiological Mechanisms: Given the role of oxidative stress in both G6PD deficiency and migraine, it is plausible that the increased oxidative burden in G6PD-deficient individuals may exacerbate the neuroinflammatory processes that trigger or amplify migraine attacks. The pentose phosphate pathway, which is impaired in G6PD deficiency, is essential for maintaining NADPH levels, which in turn support the antioxidant defense systems that protect against oxidative damage. The disruption of this pathway in G6PD-deficient individuals may lead to an imbalance in ROS production and clearance, further exacerbating oxidative stress in tissues, including the brain.

Potential Therapeutic Implications: Considering the shared mechanisms of oxidative stress in G6PD deficiency and migraine, targeting antioxidant pathways may offer therapeutic benefits for individuals affected by both conditions. Antioxidant therapies aimed at restoring glutathione levels or enhancing NADPH production through alternative pathways could be beneficial in mitigating oxidative damage and reducing the frequency and severity of migraine attacks. Furthermore, careful management of oxidative stress triggers, such as specific medications, infections, and lifestyle factors, may reduce the risk of exacerbating migraines in G6PD-deficient individuals.

One enzyme that plays a critical role in cellular antioxidant defense is glucose-6-phosphate dehydrogenase (G6PD), the rate-limiting enzyme of the pentose phosphate pathway (PPP). G6PD regulates NADPH production, which is essential for maintaining adequate levels of reduced glutathione (GSH) in cells. GSH serves as a major antioxidant, protecting cells from oxidative damage by neutralizing ROS. In red blood cells (RBCs), G6PD activity is particularly important, as RBCs are highly susceptible to oxidative damage due to their role in oxygen transport and the exposure to oxidative stress from the lungs and other tissues.[8]

G6PD, NADPH, and Glutathione in Red Blood Cells: The G6PD enzyme is especially important in red blood cells (RBCs), where it ensures the adequate supply of NADPH, a critical molecule for maintaining the reduced form of glutathione (GSH). GSH functions as a potent antioxidant, scavenging free radicals and protecting cells from oxidative damage. In G6PD-deficient individuals, this enzymatic deficiency impairs NADPH production, leading to decreased GSH levels and a reduced capacity to neutralize ROS. This results in increased oxidative damage in RBCs, contributing to hemolysis and other complications (Tuncel et al., 2008). The G6PD-NADPH-GSH axis plays a vital role in safeguarding RBC integrity, and its disruption can compromise cellular defenses against oxidative stress.[5]

G6PD Deficiency and Mitochondrial Dysfunction in Migraine: In the context of migraine, emerging evidence suggests that mitochondrial dysfunction and altered oxidative metabolism may play a key role in disease initiation and progression. Mitochondria, the energy-producing organelles in cells, are highly sensitive to oxidative stress, and impaired mitochondrial function has been implicated in the pathophysiology of migraine. Mitochondrial dysfunction may lead to excessive ROS production, triggering neuroinflammation and sensitizing pain pathways in the brain. Given the role of G6PD in maintaining cellular energy metabolism and antioxidant defenses, it is plausible that deficiencies in this enzyme may contribute to mitochondrial dysfunction and oxidative stress in migraineurs. Deficits in G6PD could lead to a decreased capacity to neutralize ROS, thereby exacerbating oxidative damage and promoting the development of migraine attacks. The association between G6PD deficiency and migraine may provide insights into the molecular mechanisms underlying both conditions, highlighting the importance of maintaining antioxidant defenses in the brain.[7]

Potential Molecular Connections between G6PD Deficiency and Migraine: Several studies have suggested that oxidative stress plays a key role in both the development and exacerbation of migraines. Fyn, a tyrosine kinase involved in oxidative radical sensing, has

been implicated in regulating G6PD activity through tyrosine phosphorylation. The activation of G6PD via Fyn may enhance the enzyme's ability to combat oxidative stress. However, the inability of this pathway to activate G6PD may be a significant factor limiting the capacity of G6PD-deficient RBCs to tolerate oxidative stress, potentially contributing to the neuroinflammatory processes seen in migraine.[5]

Moreover, mitochondrial dysfunction resulting from altered cellular metabolism could further amplify oxidative stress in the brain, contributing to the sensitization of pain pathways and the increased frequency and severity of migraine attacks. By understanding the molecular connections between G6PD deficiency, mitochondrial dysfunction, and oxidative stress, we may uncover new therapeutic approaches to managing migraine in individuals with this enzymatic deficiency approached with explain in figure-1.

Deciphering the Linkage: G6PD Deficiency as a Precursor to Migraine

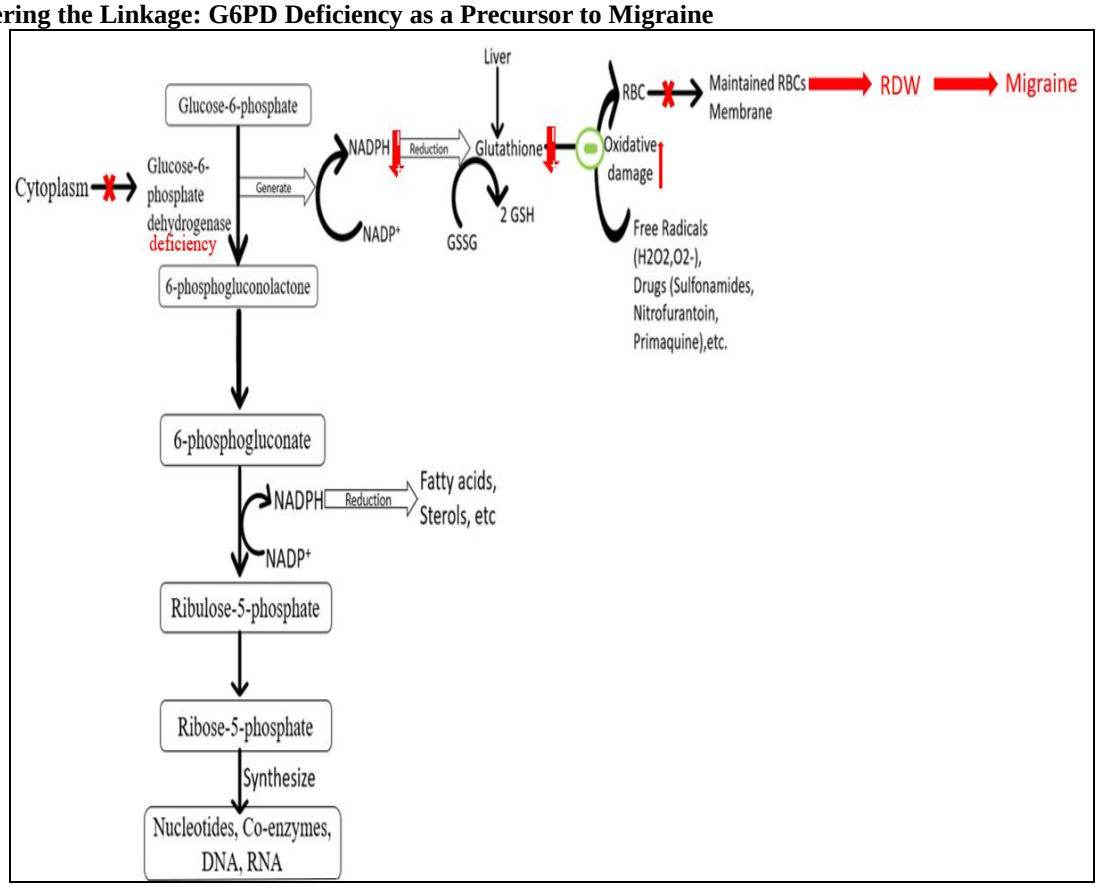

Figure 1: Mechanism of relation between G6PD and Migraine.

G6PD Deficiency and Mitochondrial Dysfunction in Migraine

In the context of migraine, emerging evidence suggests that mitochondrial dysfunction and altered oxidative metabolism may play a key role in disease initiation and progression. Mitochondria, the energy-producing organelles in cells, are highly sensitive to oxidative stress, and impaired mitochondrial function has been implicated in the pathogenesis of migraine.[8, 10] Mitochondrial dysfunction may lead to excessive reactive oxygen species (ROS) production, triggering neuroinflammation and sensitizing pain pathways in the brain.[10] Given the role of glucose-6-phosphate dehydrogenase (G6PD) in maintaining cellular energy metabolism and antioxidant defenses, it is plausible that deficiencies in this enzyme may contribute to mitochondrial dysfunction and oxidative stress in migraineurs. Deficits in G6PD could lead to a decreased capacity to neutralize ROS, thereby exacerbating oxidative damage and promoting the development of migraine attacks. Studies indicate that G6PD translocates to mitochondria and interacts with VDAC1, influencing mitochondrial membrane potential and energy metabolism.[11] Additionally, G6PD supports mitophagy by stabilizing PINK1, a process critical for mitochondrial quality control.[12] The association between G6PD deficiency and migraine may provide insights into the molecular mechanisms underlying both conditions, highlighting the importance of maintaining antioxidant defenses in the brain. Migraine-associated vomiting may provide symptom relief through activation of brainstem emetic centers via vagal afferents. This response is mediated by serotonin and substance P released from enterochromaffin cells in the GI tract.[13-14]

In summary, G6PD is the rate-limiting enzyme in the pentose phosphate pathway (PPP). A deficiency here initiates a chain reaction leading to oxidative vulnerability. NADPH is also used in detoxification processes and in neutralizing ROS. Its deficiency allows ROS accumulation, which is often seen in the interictal period of migraine patients. GSH is a frontline antioxidant, especially in the brain and RBCs where oxidative stress can be damaging. Low GSH = Higher oxidative stress, which contributes to central sensitization and neuroinflammation seen in migraine pathogenesis. Studies show that migraineurs have elevated ROS even between attacks, suggesting persistent oxidative stress that triggers or maintains headache pathways. Oxidative stress is a potent trigger of neuroinflammatory cascades involving IL-6, TNF-α, and NF-κB activation. Neuroinflammation sensitizes trigeminal nociceptors and amplifies migraine symptoms, contributing to chronicity and pain severity. In G6PD-deficient individuals, the inability to counter oxidative stress exacerbates neuroinflammation**,** increasing migraine frequency and severity. G6PD Deficiency → Low NADPH → Low GSH → High ROS → Neuroinflammation → Increased Migraine Susceptibility.

CONCLUSION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency significantly contributes to increased oxidative stress, a factor increasingly implicated in the development of migraines. In individuals lacking adequate G6PD activity, diminished antioxidant defenses result in excessive reactive oxygen species (ROS) production, elevated neuroinflammatory responses, and increased pain sensitivity—factors that may heighten both the risk and severity of migraine episodes. The observed association between raised red cell distribution width (RDW) and migraine further underscores this oxidative imbalance. Implementing antioxidant-based therapies and individualized treatment regimens could offer a valuable strategy for managing migraines in G6PD-deficient patients. Future studies should aim to clarify the molecular pathways involved and design targeted therapeutic approaches to enhance clinical outcomes.

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Conflict of Interest: None.

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