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CASE REPORT

G6PD deficiency and parkinsonism - an emerging correlation

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ABSTRACT

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency, recognized as the most prevalent enzymopathy globally, limits pentose phosphate pathway, causing oxidative damage to dopaminergic nigrostriatal neurons, has been implicated as a potential risk factor for early-onset Parkinson's disease (EOPD).

Case Presentation: This study details the case of a 45-year-old male presenting with EOPD. The patient presented with unsteady walk, tremors in the left hand and leg, alongside gait disturbances. While biochemical assessments and magnetic resonance imaging investigations yielded unremarkable results, Tc-99m TRODAT brain SPECT/CT imaging indicated presynaptic dopaminergic dysfunction within the bilateral basal ganglia. Treatment with Syndopa and Propranolol proved effective.

Conclusion: The combination of genetic, clinical, and imaging findings suggests a potential link between G6PD deficiency and Parkinsonism, supporting the possibility of G6PD playing a role in the development of Parkinson's disease (PD) in this case. This report underscores the necessity for further epidemiological studies to confirm the association between G6PD deficiency and PD in adults. Further research is essential to elucidate the mechanistic pathways connecting G6PD deficiency to dopaminergic dysfunction and to explore its implications for the pathogenesis, early diagnosis, and therapeutic strategies for PD.

Keywords: Case report, G6PD, Parkinson's disease, oxidative stress.

Background

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive genetic disorder impairing the body's ability to manage oxidative stress from excessive reactive oxygen species, by impairing pentose phosphate pathway (PPP) to reduced production of Nicotinamide Adenine Dinucleotide Phosphate Hydrogen, a critical cofactor for maintaining cellular redox balance (Figure 1A). High oxidative stress harms cells by causing lipid peroxidation, DNA damage, protein oxidation, and the early breakdown of red blood cells (hemolysis), leading to hemolytic anemia. Oxidative stress plays a critical role in the pathogenesis of various diseases, including neurodegenerative disorders such as Parkinson's disease (PD), and affects various tissues, especially the brain where it significantly impacts dopaminergic neurons (1). PD is characterized by the degeneration of dopaminergic neurons, and oxidative stress is believed to play a major role in this degeneration. The metabolic disruptions observed in PD's patients affect several key processes, including glucose uptake, glycolysis, the tricarboxylic acid cycle, oxidative phosphorylation, and the PPP (2). G6PD disrupts PPP which is crucial for maintaining reduced glutathione (GSH) levels that protect against oxidative stress (3).The intricate relationship between G6PD deficiency and oxidative stress-related diseases underscores the complexity of early-onset Parkinson's disease (EOPD). The exact mechanism of G6PD (c.949G>A) role in PD progression is unclear, and no studies have shown an association between G6PD and PD in adults or animal models.

This case describes a 45-year-old male with a likely pathogenic (c.949G>A) missense mutation in exon 9 of the G6PD gene, linking G6PD deficiency to EOPD. In addition, Tc-99m TRODAT brain SPECT/CT imaging in our patient revealed presynaptic dopaminergic dysfunction,

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supporting a PD diagnosis and strengthening the relevance of G6PD deficiency in this context. Importantly, Whole Exome Sequencing (WES) did not identify mutations in other known PD-associated genes, suggesting that G6PD deficiency might play a role in this case.

Case Presentation

A 45-year-old male with young-onset PD on Levodopa was referred to the genetic clinic. Born to non-consanguineous parents, birth and family history were unremarkable. At the age of 43, he developed tremors in his left hand and leg, and later gait abnormalities with dragging his feet and slow walk. He had no dystonia, speech issues, bladder-bowel disturbances, social anxiety, jaundice, or history of transfusions. Neurological examination showed coarse tremors, decreased power, and absent deep tendon reflexes in the left hand. The rest of the examination was normal. He responded well to Syndopa 125 mg q8 hourly and Tab Propranolol 10 mg once a day.

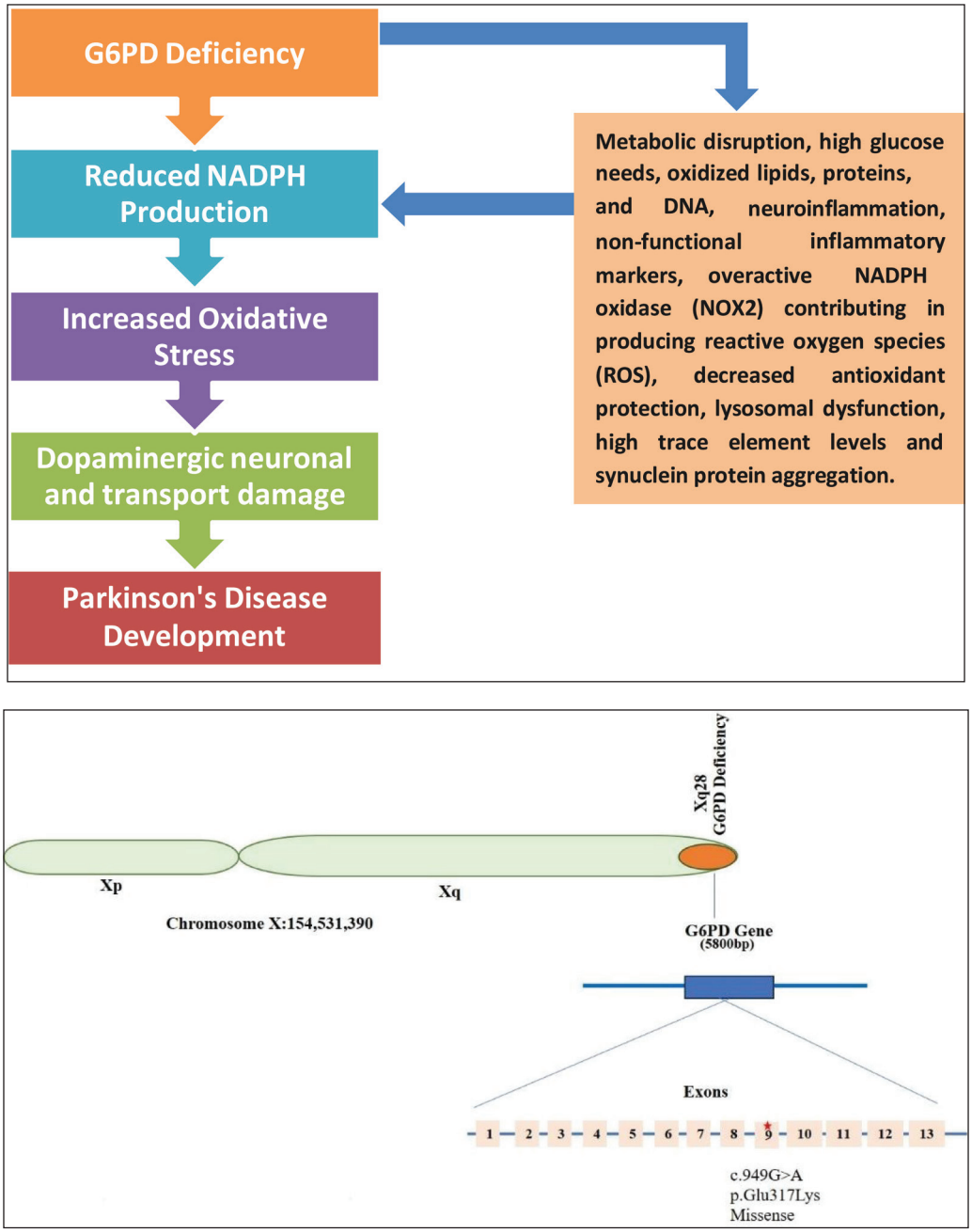

Figure 1. *(A) Schematic representation of G6PD variant leading to the progression from G6PDdeficiency to PD, emphasizing the link between oxidative stress and dopaminergic neuron degeneration. Key stages of this pathway include increased oxidative stress, neuronal apoptosis, and the clinical manifestation of PD. (B) A schematic illustrating the G6PD gene located on the telomeric end of the q arm of the X chromosome (Xq28) highlights its position and associated reported mutations. Mutations in the cDNA linked to severe G6PD deficiency and distribution of reported mutations across the protein are shown with exons represented as thick numbered blocks and introns as thin lines. The mutation c.949G>C (marked by a red star) from our study is prominently indicated.*

Investigations including Tandem Mass Spectrometry - Gas Chromatography Mass Spectrometry and brain Magnetic Resonance Imaging were normal, but Tc-99m TRODAT brain SPECT/CT showed presynaptic dopaminergic dysfunction.

Genetic diagnosis

WES employed IDT's xGen™ DNA Library Prep on NovaSeq platform with parental consent. FASTQ reads were aligned to hg38 via proprietary algorithm SMART-One™/GeneUIS® (www.computegenomics.com). Identified variants were filtered and ranked using SMART-One™ facilitating variant annotation and prioritization that considers known gene-phenotype associations, molecular characteristics, zygosity, and population frequency, in the context of reported clinical presentation.

WES identified a likely pathogenic hemizygous missense variant (c.949G>A) in the G6PD gene (Figure 1B). The biochemical test further showing G6PD deficiency (3.75 U/g of Hb at 37°C, compared to the normal range of 6.40-18.70 U/g of Hb). The diagnosis of G6PD deficiency is supported by both genetic and clinical evidence, suggesting the likely involvement of identified variation in the G6PD gene in PD. His family was counseled on the association between G6PD and PD, and advised to get tested for the same variant. He was instructed to avoid drugs causing oxidative stress and continued on the same medication.

Discussion

G6PD deficiency is a common X-linked genetic disorder that predominantly affects males due to its mode of inheritance, impacting approximately 400 million people worldwide (4). The relationship between G6PD deficiency and PD is an emerging area of research that highlights the importance of genetic factors in neurodegenerative disorders. The presented case highlights the intricate connection between G6PD deficiency and neurodegenerative conditions, particularly PD. More than 200 unique mutations have been discovered in the human G6PD gene which can lead to diverse clinical spectrum and variations in enzyme activity. Identified variant (c.949G>A), causes a substitution of glutamic acid with lysine at position 317, accounts for 1.1% to 24.5% of disease-causing alleles in India, and has been classified as a class III variant according to the World Health Organization. This mutation can significantly impact the catalytic activity and structural stability of the G6PD enzyme, leading to reduced enzyme function and impaired antioxidant mechanisms, particularly those involving GSH. This deficiency increases vulnerability to oxidative stress, disrupts mitochondrial function, and promotes metabolic dysfunction and cellular death pathways, key features of PD (5). Such disturbances not only worsen disease progression but also underscore the intricate relationships between oxidative stress, mitochondrial dysfunction, and neuroinflammation in the pathogenesis of PD (2,6).

Limited literature shows a link between G6PD deficiency and PD in humans or animals. Some studies have highlighted the complex relationship between G6PD activity and neurodegenerative diseases, particularly PD. Mejías et al. (7) demonstrated that aged transgenic mice with moderately increased G6PD activity exhibited greater resistance to the neurotoxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a compound commonly used to model PD. This finding suggests a potential neuroprotective role of G6PD in mitigating oxidative stress, which is a significant factor in PD pathogenesis. Conversely, a postmortem study by Dunn et al. (8) revealed reduced G6PD levels in the cerebellum and putamen of a PD patient, indicating that lower G6PD activity may correlate with disease severity. Studies have shown that G6PD deficiency may contribute to the neurodegenerative processes observed in ALS and PD by increasing susceptibility to oxidative damage and inflammation (9). Murine studies reveal that G6PD-deficient mice exhibit significant oxidative stress, DNA damage, and behavioral deficits, indicating compromised neuronal integrity. In contrast, G6PD-overexpressing mice show improved motor performance, highlighting the enzyme's protective role in mitigating oxidative damage (10).

Conclusion

Exploring G6PD's role at the molecular level is crucial for developing targeted therapies that mitigate oxidative stress in conditions like PD. Future research should further investigate the potential link between G6PD deficiency and Parkinson's through epidemiological studies, paving the way for improved treatments and outcomes for patients.

List of Abbreviations

DNA	Deoxyribonucleic Acid
EOPD	Elevates Risk of Early-Onset Parkinson's Disease
G6PD	Glucose-6-Phosphate Dehydrogenase Deficiency
GSH	Glutathione
NADPH	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen
PD	Parkinson's Disease
PPP	Pentose Phosphate Pathway
ROS	Reactive Oxygen Species
SPECT/CT	Single-Photon Emission Computed Tomography-Computed Tomography
TRODAT	Technetium-99m Labeled Tropane Derivative
WES	Whole Exome Sequencing

Declaration of conflicting interests
The authors declare that they have no conflict of interest regarding the publication of this case report.

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Consent for publication
The authors certify that they have obtained all appropriate patient consent forms. In the form, the parents have given their consent for patient's clinical information to be reported in the journal. The parents understand that patient's name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Ethical approval

Given the observational design of the study, formal ethics approval was not sought.

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