Review

Eurasian Journal of Toxicology

"Paraquat Brain": Have We Researched Enough?

Ananth Rupesh KATTAMREDDY[1], Mohit Kumar Moses THATHAPUDI[1], Victor GHOSH[1], Jacinth Karunya MIDDE[1], Pravin KALYANKAR[2]

[1]Department of Forensic Medicine and Toxicology, Andhra Medical College, Visakhapatnam, India.
[2]Department of Internal Medicine, Fortis Escorts Hospital, Faridabad, Haryana, India.

Abstract

Paraquat (PQ), a widely used herbicide, has gained ill repute due to its highly toxic nature and involvement in suicidal poisoning incidents, particularly in Asian countries. PQ-induced cellular toxicity is characterized by the generation of reactive oxygen species (ROS) and oxidative stress, leading to death. While research has primarily focused on the mortality associated with PQ poisoning, its morbidity implications, notably a potential link with Parkinson's disease (PD), remain underexplored by the scientific community.

Parkinson's disease, a neurodegenerative disorder, has been associated with the exposure to neurotoxicants resembling PQ, such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Animal studies suggest that PQ may serve as a valuable tool for modelling PD. However, limited human autopsy data on PQ-related brain effects raise critical questions.

This paper discusses the need for comprehensive toxicopathological studies on PQ-exposed brains, focusing on the potential correlation between PQ exposure and PD. The results of such studies could offer valuable insights into this intricate relationship, impacting both public health policy and potential legal implications. Despite the absence of conclusive evidence linking PQ and PD, the scientific community must remain open to the possibility and commit to further dedicated research in this area.

Keywords: Parkinson's disease, neurotoxicants

Introduction

Paraquat (PQ, 1,1′-dimethyl-4-4′-bipyridinium dichloride) is a highly toxic quaternary ammonium nonselective herbicide commonly used in agricultural practices the world over[1]. The escalating incidences of poisoning related to paraquat (PQ) are a primary global concern, notably in India, where cases of suicidal ingestion are prevalent in rural areas owing to lax regulation by the state and the inexpensive nature of PQ[2]. Looking at it from a clinician's standpoint, two pivotal factors compound this issue. Primarily, there is an absence of a viable antidote, coupled with the potential for fatal consequences even with the ingestion of small quantities of PQ.

PQ induces cellular toxicity by generating reactive oxygen species (ROS) and impairing NADPH-linked cellular defense mechanisms against oxidative stress[3]. PQ has the propensity to accumulate more in the lung even as the concentration in body fluids tend to decrease. The polyamine transporters on the type I, type II, and Clara cells are responsible for this phenomenon and further toxicity stems from redox cycling and intracellular oxidative stress due to the generation of ROS[4]. The common causes of death associated with PQ poisoning as reported in the literature are oesophageal perforation or corrosive effects of the gastrointestinal tract (often associated with high concentration PQ 20%), multiorgan failure (hepatorenal failure), progressive proliferative lung damage, or paraquat lung[5].

Paraquat is rapidly absorbed through the gastrointestinal system, and it gets eliminated unchanged within 24 hours via urine. However, the observed clinical features are due to formation of intracellular Reactive Oxygen Species (ROS) which damages tissues by cellular lipid peroxidation, mitochondrial damage and kickstarting apoptotic changes leading to multi organ failure.

The clinical features of Paraquat poisoning are nausea, vomiting, epigastric pain, lesions over the mucosal lining of oral cavity, lethargy, and loss of consciousness. Upon endoscopy, lesions over the mucosal linings of pharynx and

Corresponding Author: Ananth Rupesh KATTAMREDDY **e-mail:** ananth.kattam@gmail.com
Received: 17.08.2023 • **Revision**: 26.09.2023 • **Accepted:** 29.09.2023
Cite this article as: Karahalil B, Kordbacheh H, Thathapudi MKM, Ghosh V, Midde JK, Kalyankar P. "Paraquat Brain": Have We Researched Enough? Eurasian J Tox. 2023;5(3): 25-28

oesophagus, ulcerations, and inflammatory changes over the gastro intestinal tracts are observed. The simple diagnostic test at the bed side is dithionate test. Clinical chemistry shows leucocytosis, anaemia thrombocytopenia, elevated liver enzymes, raised serum creatinine and metabolic acidosis. Serum paraquat nomograms and Severeity Index of Paraquat Poisoning (SIPP) score are of practical interest for clinical toxicologists.

Due to the unavailability of specific antidote only supportive treatment can be done which includes gastric lavage, activated charcoal or sorbitol as adsorbent, and drugs such as metoclopramide, ranitidine, pantoprazole, soda bicarbonate and glucocorticoids (hydrocortisone, dexamethasone, cyclophosphamide, methyl prednisolone) for immune suppression. Haemodialysis is used as a last resort with less success[6].

While researchers are actively investigating PQ poisoning mortality and searching for anitdotes[7], there has been insufficient attention to its morbidity implications, notably its potential connection with Parkinson's disease (PD), which remains a matter of contention[8]. There are some systematic reviews indicating an association between PQ and PD, yet warranting further studies in this area[9]. Paraquat's toxicity closely resembles that of a neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), making it a valuable tool for inducing Parkinson's disease models in animal studies (safety evaluation studies in drug development)[10,11]. With the growing recognition of environmental pesticide exposure as a contributing factor to PD, researchers began to rigorously explore the potential connection between PQ and PD. The research in this domain encompasses exploring the structural, ultrastructural, and functional basis of PD upon exposure to PQ in animals[12].

Parkinson's disease is characterized by reduced dopaminergic neuron levels in the striatum, resulting in immobility and rigidity. It involves the degeneration of dopaminergic neurons in the substantia nigra and a decline in striatal dopamine content. The neurotoxicant MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and PQ induce acute Parkinsonian syndrome by damaging neurons in the substantia nigra of mammals. Acting as a substrate for MAO-B(Monoamine oxidase B), MPTP crosses the Blood Brain Barrier (BBB) and transforms into the damaging MPP+(1-Methyl-4-phenylpyridinium). The acute and chronic toxicity exerted by MPP+ in causing acute Parkinson-like syndrome and a slow neurodegenerative disease is well documented in the literature. Notably, the latent manifestation of early PD symptoms following low-concentration MPTP exposure over time underscores the complexity of the disease progression, marked by the gradual loss of dopaminergic neurons in the substantia nigra. The striking parallelism between the neurotoxic effects of MPTP and certain pesticides, particularly paraquat, has raised a compelling flag of concern regarding the potential link between pesticide exposure and the development of Parkinson's disease (PD).

On gross examination of the brain in PD induced by MPTP and other toxicants, there was depigmentation in the substantia nigra and locus ceruleus, while the cortex, hippocampus, and amygdala showed relative preservation. On histopathology, alpha-synuclein-containing aggregates were observed in the medulla, contiguous brain regions, brainstem, limbic structures, and neocortex. Additionally, there's pallor in the substantia nigra and locus ceruleus, with Lewy bodies present in the locus ceruleus, dorsal motor nuclei of the vagus, cortex, and brainstem. Neuronal loss areas are accompanied by gliosis, and cortical Lewy bodies contain alpha-synuclein[13].

Human autopsy data of the PQ brain is extremely limited except for a few case reports published by toxicopathologists across the globe. In one study it was shown that the brain was edematous with or without focal minimal hemorrhages[14]. In another remarkable study, hemorrhagic leukoencephalopathy/ 'purpura cerebri' was noticed throughout the white matter of the brain. Further, it was associated with focal hemorrhages of various stages accompanied by demyelinating processes of different extents. Globular and/or amorphous proteinaceous materials were also seen in the vascular lumina throughout the brain[15].

During an autopsy in a case of paraquat poisoning, the brain revealed anoxic neuronal depletion and damage to the central white matter around the lateral and third ventricles. Electron microscopy showed edema and destruction of myelin with abundant myelin breakdown products, and astrocytic fibrous gliosis[16] .

In a fatal case of diquat poisoning (which shares a structural similarity with PQ), brain stem infarction, generalized hyperemia of the brain, and purpuric brain findings were reported histologically[17]. In another autopsy study following exposure to PQ, the brain showed intense congestion, and no changes attributable to anoxia were found[18].

According to a paper that published early histopathological changes in paraquat which compared human findings with animal studies, there was a proportionate increase in Virchow Robin spaces, indicating edema of the brain. Further, it was stated that the brain also showed substantial edema and hypoxic purpuric staining/mottling of the basal ganglia[19].

The plethora of brain findings presented herein offers a compelling impetus to earnestly pursue further research within this domain, with the prospect of yielding significant insights to turn some grey areas into black and white. Curiously, recent times have witnessed a dearth of autopsy studies on paraquat, raising questions about the motivations of the research community. Could it be that corporate interests are influencing researchers, or has the decline in

reported poisonings, potentially due to bans in the Western world, played a role?

In the context of India, a unique opportunity emerges to continue "*paraquat brain*" autopsy studies, providing a vantage point to explore and comprehend the intricate intersections of science, policy, and public health. The outcome of this research might have a lot of legal implications in the form of revision of PQ regulation and compensation lawsuits as well.

While autopsy results from fatal poisonings may not accurately reflect situations of prolonged unintentional exposure to neurotoxic substances in work or environmental settings, they still provide valuable insights for modeling. This assumes that data from animal experiments can effectively guide risk assessment in such a world. In a scenario where animal experimental data is considered dependable for human risk assessment, it is logical to also model data from human autopsies for similar purposes.

The field of toxicological research often fails to recognize the untapped arena of toxicopathological data garnered from human autopsy studies, despite its potential to serve as a pivotal link connecting the outcomes of animal studies to their applicability in human contexts. An illustrative example lies in a thorough toxicopathological examination of the brain in fatal human poisonings involving paraquat, which can offer invaluable insights for investigating the intriguing correlation between paraquat exposure and Parkinson's disease. This avenue offers a unique opportunity to transcend the confines of animal study data and delve into a deeper understanding that is both scientifically sound and ethically aligned, sidestepping the infeasibility of creating randomized controlled trial evidence in this particular domain. Similarly, neuro morbidity assessment in paraquat poisoning survivors is also a useful tool to know the link between PQ and PD by carefully studying the clinical phenotype (if any) that exists.

While current laboratory investigations employing the C57BL/6J mouse model[20] and epidemiological studies have not definitively established a direct connection between PQ exposure and PD, it is vital to emphasize that the absence of conclusive evidence should not discourage the continuation of research efforts. It is essential to acknowledge that the present lack of correlation does not necessarily preclude the potential association between PQ exposure and PD. Despite not fully meeting Hill's criteria for causation in accordance with existing literature, it is essential to remain open to the possibility that a causal link might exist, justifying further dedicated exploration. In epidemiology, the criteria are carefully designed for attribution rather than exclusion, and the pursuit of understanding demands a balanced recognition of these nuances before ruling out things. *Simply said, "Paraquat Brain" is yet another unexplored black box at autopsy.*

References

1. Gao L, Yuan H, Xu E, Liu J. Toxicology of paraquat and pharmacology of the protective effect of 5-hydroxy-1-methylhydantoin on lung injury caused by paraquat based on metabolomics. Sci Rep 2020;10. https://doi.org/10.1038/s41598-020-58599-y
2. Shanbhag V, Sukumar CA, Shastry AB. Paraquat: The poison potion. Indian J Crit Care Med 2019;23:0–0. https://doi.org/10.5005/jp-journals-10071-23306.
3. Suntres Z. Role of antioxidants in paraquat toxicity. Toxicology 2002;180:65–77. https://doi.org/10.1016/s0300-483x(02)00382-7.
4. Dinis-Oliveira RJ, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F. Paraquat poisonings: Mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol 2008;38:13–71. https://doi.org/10.1080/10408440701669959.
5. Delirrad M, Majidi M, Boushehri B. Clinical features, and prognosis of paraquat poisoning: a review of 41 cases. Int J Clin Exp Med 2015;8:8122–8.
6. Delirrad M, Majidi M, Boushehri B. Clinical features and prognosis of paraquat poisoning: a review of 41 cases. Int J Clin Exp Med. 2015;8(5):8122–8.
7. Wang X, Wang X, Zhu Y, Chen X. ADME/T-based strategies for paraquat detoxification: Transporters and enzymes. Environ Pollut 2021;291:118137. https://doi.org/10.1016/j.envpol.2021.118137.
8. Vaccari C, El Dib R, Gomaa H, Lopes LC, de Camargo JL. Paraquat and Parkinson's disease: a systematic review and meta-analysis of observational studies. J Toxicol Environ Health B Crit Rev 2019;22:172–202. https://doi.org/10.1080/10937404.2019.1659197.
9. Tangamornsuksan W, Lohitnavy O, Sruamsiri R, Chaiyakunapruk N, Norman Scholfield C, Reisfeld B, et al. Paraquat exposure and Parkinson's disease: A systematic review and meta-analysis. Arch Environ Occup Health 2019;74:225–38. https://doi.org/10.1080/19338244.2018.1492894.
10. Briñez-Gallego P, da Costa Silva DG, Cordeiro MF, Horn AP, Hort MA. Experimental models of chemically induced Parkinson's disease in zebrafish at the embryonic larval stage: a systematic review. J Toxicol Environ Health B Crit Rev 2023;26:201–37. https://doi.org/10.1080/10937404.2023.2182390.
11. Lama J, Buhidma Y, Fletcher EJR, Duty S. Animal models of Parkinson's disease: a guide to selecting the optimal model for your research. Neuronal Signal 2021;5. https://doi.org/10.1042/ns20210026.
12. Uversky VN. Neurotoxicant-induced animal models of Parkinson's disease: understanding the role of rotenone, maneb and paraquat in neurodegeneration. Cell Tissue Res 2004;318:225–41. https://doi.org/10.1007/s00441-004-0937-z.
13. Cicchetti F, Lapointe N, Roberge-Tremblay A, Saint-Pierre M, Jimenez L, Ficke BW, et al. Systemic exposure to paraquat and maneb models early Parkinson's disease in young adult rats. Neurobiol Dis 2005;20:360–71.
14. Soontornniyomkij V, Bunyaratvej S. Fatal paraquat poisoning: a light microscopic study in eight autopsy cases. J Med Assoc Thai 1992;75 Suppl 1:98–105.

15. Mukada T, Sasano N, Sato K. Autopsy findings in a case of acute paraquat poisoning with extensive cerebral purpura. Tohoku J Exp Med 1978;125:253–63. https://doi.org/10.1620/tjem.125.253.

16. Hughes JT. Brain damage due to Paraquat poisoning: a fatal case with neuropathological examination of the brain. Neurotoxicology Park For South. 1988;9(2):243–8.

17. Jovic-Stosic J, Babic G, Todorovic V. Fatal diquat intoxication. Vojnosanit Pregl 2009;66:477–81. https://doi.org/10.2298/vsp0906477j.

18. Demonstrated at the Division of Medicine (Clinical) Royal Infirmary, Edinburgh., Matthew H. Paraquat poisoning: clinicopathological conference. Scott Med J 1971;16:407–21. https://doi.org/10.1177/003693307101600905.

19. von der Hardt, H., Cardesa, A. Early histopathological changes after paraquat intoxication. Klin Wochenschr 49, 544–550 (1971). https://doi.org/10.1007/BF01487992

20. Paraquat. Safety - Humans: Paraquat and Parkinson's Disease [Internet]. Paraquat; [cited 2023 Aug 15]. Available from: https://www.paraquat.com/en/safety/safety-humans/paraquat-and-parkinsons-disease