Chapter 19
Groundwater Toxicity Link to Epidemiology of Parkinson's Disease

Poonam Yadav, Akchhara Pandey, Anusha Ramdoss, Mounika Aradala, Bishal Pokharel, M. D. Deepthi Nair, Tamanna Tazin, Farzaneh Dadvar, Farima Fakhri, Rukhsana Miraj Uddin, Nermeen Kolta, and Nirupama Nayudu

Abstract *Background* Groundwater is described as an unsaturated liquid that exists out of sight and below land surface. It appears as a layer of water that accumulates at depths between 5 and 500 feet below the land surface and often contains halogens in concentration hazardous to humans. The most common source of halogens, chlorine and bromine, are found in local groundwater at levels which exceed EPA drinking

P. Yadav
Department of Neurology, Apex Hospital, Jaipur, Rajasthan, India

A. Pandey (✉)
Department of Pharmacology, Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh, India
e-mail: akchharaa@gmail.com

A. Ramdoss
PSG Institute of Medical Science and Research, Coimbatore, India

M. Aradala
University of Soochow, New Taipei, China

B. Pokharel
Department of Neurosurgery, Bhaktapur Cancer Hospital, Bhaktapur, Nepal

M. D. Deepthi Nair
Department of Child Neurology, Seattle Children's Research Institute, Seattle, USA

T. Tazin
Department of Internal Medicine, Greenville Community Shelter Clinic, Greenville, NC, USA

F. Dadvar
University of Toronto, Kensington Eye Institute, Toronto, Canada
e-mail: fdadvar@kensingtonhealth.org

F. Fakhri
Department of Neuroscience, Kerman University of Medical Science, Kerman, Iran

R. M. Uddin
Women Medical College, Peshawar, Pakistan

N. Kolta
Department of Internal Medicine, MM Jersey City Breathing Center, Jersey, USA

N. Nayudu
Zhengzhou University, Zhengzhou, China

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water guidelines for lifetime exposure. When present in high concentration over long periods of time, these contaminants can cause multisystem disorders. *Objective* This chapter's purpose is to contextualize the fundamental mechanism of organic molecules found in groundwater over the period of time due to use of pesticides and insecticides. As a result of conditioning, molecules incorporate into physiology of human body and its effects on neurobiology. *Discussion* The covering knowledge on increment of environmental pH and risks of nutrient deficiencies identifies a problematic model of groundwater and its chemistry. Lack of nutrient uptake or loss from digestive system of animal and human body mounts for exploration of metal biology of soil and water. Over the time period, groundwater became an important source for domestic and irrigation purpose. However, rapid increase in population growth led to rapid industrial and economic growth, hence tremendous use of groundwater. The largest natural groundwater calamities in recorded history have been caused by metal poisoning of groundwater in the vast plain built by Ganga and Brahmaputra River in India and also fluvial plains of Padma and Meghna in Bangladesh. According to data from the Parkinson Environment and Gene Study, those who drank pesticide-tainted well water that has been around for a while in California's central valley possess high potential for development of Parkinson's disease than people who did not (Chen in J Parkinsons Dis 8:1–12, 2018). The epidemiological studies on progression of non-familial form of PD emphasize on prodromal period of toxin exposure. Access point of pesticides is via eating, drinking, nose, and skin contact. Various animal studies showed these entry points for pesticides initiate pathogenesis of synucleinopathy via olfactory-gut-brain axis. The objective is to discuss effects of environmental geochemistry on neurological well-being of human health in developing countries. *Conclusion* Analysis of exposure is easy to quantify through advanced experimental methods versus adequately measuring the organic molecule along with its persistence use affecting the neurobiological system. Overall exposure and monitoring over a very long period can align our understanding of gene-environmental etiology causing neurodegenerative diseases.

Abbreviations

PD	Parkinson's disease
SN	Substantia nigra
DDT	Dichlorodiphenyltrichloroethane
EPA	Environmental Protection Agency
WHO	World Health Organization
Na	Sodium
Ca	Calcium
K	Potassium
IMA	Indian Medical Association
ROS	Reactive oxidation species
TCA	Tricarboxylic Acid

DAT Dopamine transporter
BBB Blood-Brain Barrier
NITI National Institute of Technology
HQ Head Quarter
TR Targeted Risk
HI Hazard index
CA Correlation analysis
FA Factorial Analysis

19.1 Introduction

India makes up 15% of the global population, but it only possesses 2.5% of the world's land and just 6% of its water resources. Based on April 2015, the country's potential annual river water availability is 1869 BCM/year; however, its actual useable water availability is 1123 BCM/year. 433 BCM/year is the portion of groundwater that is useable. The yearly contribution of rainfall to groundwater is 68% (Suhag 2016).

According to Flora SJS study, 63 samples were taken during the southwest monsoon from sedimentary formations. The hard rock aquifers were examined for the presence of heavy metals such as lithium, beryllium, aluminum, Rb, strontium, cesium, barium, lead, manganese, iron, chromium, zinc, gallium, copper, arsenic, nickel, and cobalt. While Zn predominated in sedimentary formations, Ba predominated in hard rock aquifers, with concentrations ranging from 441 to 42,638 g/l to 44 to 118,281 g/l. In both formations, the Fe, Ni, Cr, Al, and Ni contents were higher than allowed. To prevent the potential health risks connected with intake, statutory limitations of these concentrations of contact zone and long-term monitoring for the threshold value are necessary. According to WHO, arsenic safe limit is 0.01 mg l^{-1}, but in India due to poor availability of potable drinking water, the acceptable level is 0.05 mg l^{-1} (Flora 2022). Multiple studies have been conducted on the quality of potable water and the effect it has on the population consuming it. These studies have assessed the risk associated with utilization of poor quality of water for drinking and cooking purposes.

Interference and exposure of organic molecules such as mercury, drug molecule, and alcohol prenatally cause metabolic changes in neuronal development and its neurotransmitters. Likewise, these heavy metals and organic molecule inhibit the nerve cells from communicating through electrical signals. With the help of ion channel, these nerve cells generate signals. These ion channels are voltage dependent and get activated through potential difference generated by ion (Na, Ca, K) concentration. These changes across membranes contribute to further alteration in biochemical mechanism and affect processes of cognition, memory circuit and behavior.

Due to the simplicity of use and capacity for large-scale data comparisons, the multivariate method models are used for extremely challenging data to accomplish number tables with information (Bingo 2013). The most commonly used

statistical methods are factor analysis, cluster analysis, and correlation analysis for identifying what is causing the increasing poor quality of groundwater, among multivariate approaches. The correlations between hydro-chemical variables are analyzed using correlation in order to pinpoint their possible causes. Comparison and dissimilarities among the samples are assessed by CA. FA is used to identify probable significant natural and man-made elements (such as hydrogeochemical processes) that affect groundwater quality without prior information on number of sources or the pollutants' source characteristics. There have been numerous studies conducted throughout the world using multivariate statistics to pinpoint the groundwater trace element sources. These investigations demonstrated that hydrogeochemical processes and possible sources of contaminants in water could both be found using multivariate techniques. For instance, use of multivariate statistical analysis helped to evaluate likely source of toxins in few chosen areas of Northwest Iran's groundwater of shabestar region. The results demonstrated that effects of weathering and dissolution of rocks formed into silicates and its evaporites, causing groundwater toxicity. Furthermore, through ion exchange the salinity of water increased and the pH skewed towards alkalinity. 10% of the total variation in groundwater quality was caused by the effects of nitrate and zinc in fertilizers and agrochemicals.

Sodium (Na) channel gates are the primary site for the action of pesticides such as pyrethroid, aldrin, dieldrin, and dichlorodiphenyltrichloroethane (DDT). During rising phase of action potential, these organic molecules keep the gate open for extended period of time causing depolarization and hyperexcitation of cell. This state of sodium channel causes behavioral changes in rodents such as hypersensitivity, tremor, convulsions, choreoathetosis, and excessive salivation. Though human cells are not very sensitive to these kind of changes in sodium channel, some percentage of mammals shows sensitivity to pyrethroids. The pyrethroids cause two kinds of behavior: 1st is aggression, hypersensitivity, tremor, and convulsions, and 2nd is choreoathetosis and hypersalivation.

19.2 Overview of Groundwater and Usage

The groundwater layering on hydrogeological setting has a vulnerable position. The layering starts with land surface, unsaturated zone, and surface water, followed by saturated zone with groundwater. The lowest layer beneath are the fracture rocks and gravel which is sandwiched with soil (Shrikant and Limaye 2013). The groundwater fills spaces between soil and fracture rocks below the unsaturated zone (Suhag 2016). Water travels through the rocks and fills in aquifers. The large spaces between the graveled stones, sand, and sandstone are connected which defines the permeability of surface hence called saturated zone. The hydrogeological setting in India is divided into two categories:

1. Hard rock aquifers of central peninsular India: It contains 65% of overall aquifer area. The hard rock formation is complex, which creates low water storage space.

Due to low water storage, in order to reach the water table, one must dig farther. Once the water table which is a boundary between soil surface and sediments of rocks, fall more than 2–6 meter, then the level of water drops too. This means one has to dig deeper to reach the water table. Moreover, due to poor permeability, there is limitation in recharge from rainfall and hence aquifer dry out with continuous usage.

2. Alluvial aquifers of indigo gangetic plains: It is found in northern India with significant storage in gangetic and Indus plains. Combination of water resource vulnerability along with excessive exploitation significantly reduces the recharge rates and makes the process irreversible (Suhag 2016).

Majority of groundwater, i.e., approx. 89%, is used in irrigation sector, remaining 9% for domestic use and 2% by industrial use. With Green revolution, extensive use of groundwater increased exponentially. Government provided incentives and subsidies with credits for equipment to boost farm production. These low power tariffs worsened the situation of water tables. This also led to overuse of fertilizers and pesticides which contaminated the groundwater with bacteria, heavy metals, and pollutants, leading to chronic multisystem disorder.

19.3 Overview of Groundwater Toxicity

The landowners have substantial power over groundwater. Water requirements by urban population are 50% versus rural domestic usage, which is 85% of groundwater. Usage of private wells is most risk for contamination with pesticides, as pesticide travels through soil. It can easily affect more than 100 m of nearby area. The monitoring of private well is not done unlike municipal water supplies. These exogenous contaminants have shown to be linked with Parkinson's disease; the research is backed up by animal studies. Various epidemiological studies showed relatively consistent relationship between people using private well water for a very long time who have 15–57% likely chances of getting Parkinson's disease than control. Stronger association was found with use of paraquat, trichloroethylene and tetrachlorethylene, rotenone and organochlorines, and much consistent with women (Goldman 2013). Heavy metal exposure (lead, cadmium, mercury, arsenic) in groundwater is characteristic of non-biodegradable products which can contaminate living system and damage the molecular level of living organisms.

Small towns in India, including Sukinda in Orissa and Vapi in Gujarat, are among the top 10 most polluted places in the world, according to Leading US Business magazine. Sukinda water contains high concentrations of chromium affecting more than 2.6 million people. Vapi seen to have high industrial pollution especially high mercury level, which is said to be 96 times higher than standards set by WHO. Also stated, West Bengal has that highest arsenic concentration than acceptable standards, in turn affecting a population of more than 50 million population. According to IMA (Indian Medical Association) report, the major causality of contamination in drinking

water is due to poor disposal of industrial wastes. Based on the Indian toxicology report, there is enough awareness for the matter on groundwater contamination and ground radiation from nuclear testing but India lacks in decisive plans and program to aid with the development of preventive programs (Flora 2022).

Additionally, many organizations came to the conclusion that these heavy metals also contribute to fluorosis, chemical dermatitis, skin, lung, and throat malignancies, high incidence of abortions, infertility, and abnormal fetuses. Additionally, these heavy metals lessen energy at multisystem level. The metalloids cause the molecular damage of muscles and neurons causing imbalance of antioxidant and free radical production. These changes detoxify the protective reactive intermediates. As a result, ROS (reactive oxygen species) increases and causes cell death by apoptosis and other enzymatic reactions at cellular level also affecting release of neurotransmitter such as dopamine and also its regulation simultaneously. Neurological disease like Parkinson, Alzheimer's, metal deposition like disease such as Wilson disease, muscular dystrophy, and multiple sclerosis are all examples of degenerative neurological and muscular diseases caused by chronic oxidative stress.

According to several studies, human health can suffer significantly from exposure to potentially harmful chemicals, such as trace elements in water, and these impacts include a range of malignancies and multiple system involvement such as kidney, cardiac events, and neurological and generalized neurological impairment. Human health can suffer significantly from exposure to potentially harmful chemicals, such as trace elements in water, and these impacts include a range of malignancies, intellectual impairments, neurological, cardiovascular, kidney, and bone problems. An evaluation of the health risks can be used to estimate the likelihood of source, which release risk agents into the environment, how many risk agents will come into contact with human-environment boundaries, and the potential health effects of exposure to a mixture of trace elements. Numerous researchers have written about the risks posed to human health, are caused by these trace elements in groundwater (Esmaeili et al. 2018; Barzegar et al. 2017) used the two factors such as hazard quotient and target risk factor to assess the health risk of as pollution in drinking groundwater in southern Taiwan. Results indicated that TR levels exceeded the threshold value of 10E-6 and that HQ values for the 95th percentile were above the value of 1. They came to the conclusion that 0.01–7.5% of the population had HQ levels higher than 1, and 77.7–93.3% of people had TR values of 10E-6, placing them in the high cancer risk category. The results of the TR exposure estimates, implied that drinking groundwater put people at risk. In a rural part of Thailand's Ubon Ratchathani province, looked into the risks on human health caused by consuming water from shallow groundwater wells. They found that few of the wells with arsenic, copper, zinc, and lead had unsatisfactory non-carcinogenic health risk levels with HQs ranging from 0.004 to 2.901, 0.053 to 54.818, 0.003 to 6.399, and 0.007 to 26.80, respectively. In 58% of the wells, the hazard index (HI) values (range from 0.10 to 88.21) were higher than permitted (Liang et al. 2016).

19.4 Overview of Parkinson's Disease

In general, a syndrome of bradykinesia (slow voluntary movement) with rigidity or tremor is referred to as Parkinsonism in general. Idiopathic Parkinsonism, or Parkinson's disease, is Parkinsonism with a limited neurological manifestation. A disease that gradually destroys the brain's nerve cells which make the neurotransmitter, called Dopamine. Dopamine sends signals to the brain that regulate coordination and movement. Dopamine deficiency causes the following hallmark motor signs of Parkinson's disease: tremor during rest, bradykinesia, rigidity of the limbs (cogwheel rigidity), along with small handwriting, decreased facial expression, difficulty swallowing, and soft speech. With the progression of the disease, patient experiences postural instability and imbalanced shuffling gate, leading to falls causing more injuries.

19.4.1 Overall Disease Burden

In India, with a population of more than one billion, the population of PD is approx. 7 million (Behari et al. 2002), i.e., 70 per 100,000. 70% population is rural resident, of which a large number of populations live under the poverty line with an average income of $250. A total number of trained neurologists in India are about 1200, of which 400 work in major metro cities. Therefore, the burden of disease depicts the misery of the country. Due to lack of social security in India, drugs are expensive for low-income population. On comparison of cheaper living cost, treatment is expensive and increases exponentially as the disease progresses. On the face of odd circumstances, the resilience and ability to remain in balance of mind are praiseworthy.

19.4.2 Identifying Etiology

Identifying triggering factor for Parkinson's disease pathogenesis is multifactorial, and hence, it is complex. The methods for early identification of disease are elusive. Population of Parkinson's disease is growing exponentially with growing age, i.e., between 60 and 65 years. Based on epidemiological data, the experimental database is wide and inconsistent; thus, the plausible biological causes vary too. According to the database, Parkinson's disease has two main causes: environmental factors (which can be reversed) and hereditary factors. However, the experimental data observation demonstrated opposite causality, such as smoking, coffee consumption, intense exercise, ibuprofen use, plasma urate, and pesticide use which have an inverse connection with Parkinson's disease. Consequently, thorough monitoring in the upcoming years will aid in identifying the most prevalent etiological causes producing PD.

A history of using pesticides, herbicides, insecticides showed link to heightened potential for Parkinson's disease with respect to particular age. Pesticides showed high risk for Parkinson's disease between ages of 26 and 35, herbicides between ages 26 and 55, whereas insecticides usage demonstrated between the ages of 46 and 55 (Semchuk et al. 1992).

Tyrosine hydroxylase activity is upregulated in response to effects on the striatal dopaminergic system, which may result in a short-term rise in dopamine turnover or a temporary fall in dopamine levels as a short-term compensatory mechanism. This is crucial to consider in analyzing the mechanistic evidence of pesticide's impact of novel compound on development, of Parkinson's disease. This is important to take into account in epidemiological or experimental investigations.

19.4.3 Understanding Pathogenesis of Organic Molecule

The significant loss of pigmented neurons, particularly in the pars compacta of the substantia nigra (SN), is the primary pathologic characteristic of PD. The loss of pigmented neurons is accompanied by the appearance of Lewy bodies, which are substantial eosinophilic inclusions made of a variety of proteins, including neurofilaments, alpha-synuclein fibrils, ubiquitin, parkin, and proteasomal components. The probable underlying cellular mechanisms of Parkinson's disease (PD) and the presence of external agents are outlined in Fig. 19.4.

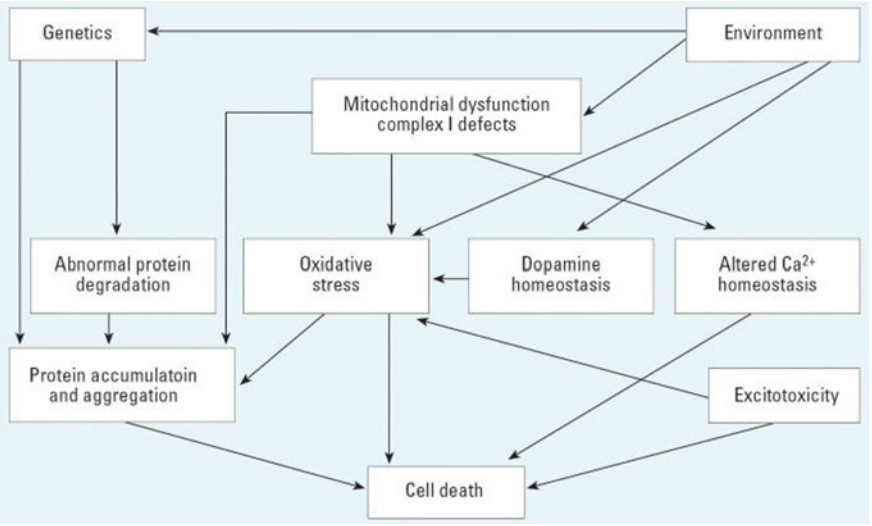

Fig. 19.4 Picture is inspired from (Betarbet et al. 2000)

The wide observational contribution of epidemiologic studies suggests association of pesticides and environmental toxins with PD implies defect in mitochondria complex 1. The prolonged chronic use of pesticides systemically inhibits the complex 1 during prodromal stage. This damage to complex 1 degenerates the selective nigrostriatal dopaminergic pathway located in substantia nigra (an area of the brain associated with voluntary movement) responsible for debilitating motor symptoms such as tremors, bradykinesia, and muscle rigidity. Rotenone is known potent inhibitor of mitochondrial TCA cycle enzymes; furthermore, it causes degenerative effect on nigral neurons damaging axons and accumulation of fibrillar cytoplasmic inclusion containing ubiquitin and alpha-synuclein.

19.4.4 Toxicological Evidence of Pesticides

The monitoring of data over decades at different point in time shows late-onset Parkinson's disease is triggered due to environmental factors, which is modifiable.

Rotenone: Naturally occurring pesticide easily penetrates biological membranes, inhibiting complex 1 systemically without needing dopamine transporter (DAT) to enter cytoplasm (Betarbet et al. 2000). At a low free rotenone concentrations of 20–30 nmol/L in the brain shows that rotenone affects striatal nerve ends more severely than nigral bodies. There were cytoplasmic inclusions containing synuclein that resembled pale bodies, which are progenitors to the Lewy bodies observed in individuals with Parkinson's disease, in the nigral neurons of rats with these lesions. Even when the rotenone therapy is stopped, rotenone-treated rats continued to exhibit anomalies in movement and posture that are typical of PD, whose severity was correlated with the number of pathologic lesions.

Rotenone and the inflammatory substance lipopolysaccharide jointly caused dopaminergic degeneration in mouse and rat neuron-glial cell cultures (Gao et al. 2002). According to Niehaus and Lange 2003, environmental and inflammatory agents such as lipopolysaccharide may influence in causing neurological disease PD. The formation of ROS, the free radical, and inflammatory mediators produced by microglia of the brain have been linked to toxicity caused by rotenone (Naylor 1995).

Paraquat: It is a potential neurotoxin which does not easily cross BBB. It causes severe pulmonary toxicity as per study by (Corsaniti et al. 1998). But majority of molecular structure changes by paraquat are formed outside BBB (Naylor 1995). In contrast to the mechanism of increased activity of four dopaminergic pathways in Parkinson's disease, when a neonatal mice dosed with paraquet on days 10–11 of gestation, it shows slowness and reduction in input model of striatum with release of DA (dopamine) and its metabolite. Although it causes neuronal cell death, it just does not depend upon common dopaminergic pathway of human brain to cause neurotoxicity (Bagetta etal. 1992; Calò et al. 1990; Corsaniti 1998).

Pyrethroid: It is not a dose-dependent insecticides. This insecticide inhibits dopamine and related metabolite in region of the brain causing marked damage to both dopaminergic and cholinergic pathways.

Mixture of pesticide (Paraquat and Maneb): Maneb is also an herbicide like paraquat and contains manganese dithiocarbonate, used widely geographically. Combined exposure causes decreased dopaminergic levels triggering reduced motor activity, also as central nervous depressant, proving relevant pathophysiology. This means mixtures of pesticides enhance the nigrostriatal dopaminergic pathway and cause significant neurotoxicity (Thiruchelvam et al. 2002).

Role of neuronal protein: According to (Uversky et al. 2001) study, he demonstrated Lewy body formation is an integral part of the disease and reactive system conditions for change in α-synuclein (neuronal protein), exaggerating formation of fibrils. Majority of these pesticides have a similar mechanism of action and hence increase risk for development of Parkinson's disease.

19.5 Conclusion

Based on the epidemiological studies, along with aging, exposure of environmental toxins showed significant multifactorial association with Parkinson's disease. However, because of inconsistent finding with the confounding variables like residents of rural area, farmers, and well water consumption, it is yet to be explored more for causal nature of pesticides use in relation to Parkinson's disease. Combined exposure of pesticides developed exaggerative effects and susceptibility in adults. Selective collection of all ages and reporting for extended period of time can provide appropriate sample size for adequate information on exposure and causes.

Identification of physiological mutation in voltage-gated channels also added significant amount of knowledge to pharmacological properties in mammals and insects. The distinct pharmacology exhibited by sodium channels in insects can serve as a source of inspiration for the research and development of novel insecticides. Additionally, research on the effects of new neurotoxins should advance our fundamental knowledge of sodium channel gating and pharmacological traits specific to insects. Numerous neurotoxins, including the present crop of pesticides, target sodium channels. Some peptides only affect sodium channels in insects and do not affect sodium channels in mammals (Bosmans et al. 2005).

The abrupt decrease in rainfall needed to replenish the city's aquifers is what is causing Bengaluru's impending disaster. A city that was formerly known for its thousand lakes has completely changed how much water is available due to population increase, droughts, and inefficient water use. The groundwater supply in New Delhi was also examined by NITI, and it was discovered to be equally severely depleted. Researchers from the National Institute of Technology (NITI) cautioned more than 20 million residents of New Delhi, the capital of the country, on a collision course with rising demand and declining moisture that is so uncompromising that it could

run out of groundwater in two years. Critical groundwater supplies, which supply 40% of India's water, are depleting at unsustainable rates, according to NITI analysts.

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