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Review Article

Chronic Agrochemical Substance-Induced Axonal Neuropathy (CASIAN): A Focused Review of the Literature

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Abstract:

Chronic Agrochemical Substance-Induced Axonal Neuropathy (CASIAN) has emerged as a significant concern in India due to the substantial number of individuals involved in agricultural activities. This article aims to provide a comprehensive review of the association between long-term exposure to pesticides and peripheral neuropathy in pesticide applicators and farmers which was established in several clinical and preclinical studies so far. While the exact molecular mechanisms underlying chronic toxic peripheral neuropathy caused by these substances remain unclear, there is a consensus that it primarily involves axonopathy. Toxic Peripheral neuropathy is characterized by a range of challenging clinical features that can significantly affect an individual's quality of life, especially in the Indian geriatric rural population. These features include but are not limited to, chronic pain, numbness, tingling, burning sensations, muscle weakness, muscle cramps, and difficulty with balance and coordination. Moreover, it is imperative to develop quality biomarkers for chronic exposure to agrochemical substances and validate them for routine use. Genetic factors responsible for chronic toxicity should also be given due consideration by researchers. Ultimately, a national-wide multicentric cohort study is required to comprehensively investigate peripheral neuropathy caused by agrochemical substances and provide valuable insights into effective prevention and treatment strategies.

Keywords:Toxic Neuropathy, Agrochemicals, Neurotoxicology, Pesticides, Organophosphate compounds

Background:

Toxicology-related deaths in India remain a significant public health concern, with multiple factors contributing to the country's high burden of such fatalities. Although acute poisonings receive significant attention from clinicians and researchers in India, the lack of focus on chronic and subacute exposure is contributing to a disregard for the potential long-term health impacts associated with poisonings. While acute poisonings may result in immediate deaths, chronic and subacute exposure can lead to higher morbidity rates and long-term health issues such as cancer, neurological disorders, and infertility. It is crucial to address both acute and chronic poisonings to reduce the overall mortality and morbidity rates associated with poisoning in India.

In India, most of theclinical and forensic toxicology caseloadis attributed to agrochemical substances. Given India's rich biodiversity and significant variability in agricultural practices, there is a wide range and high quantum of agrochemical substances utilized throughout the country on regular basis. However,

organophosphates are the most common agricultural poisonsclosely seconded by herbicides.[1]This paper aims to conduct a comprehensive review of the existing literature regarding the potential link between agrochemical substances and peripheral neuropathy,among those who may be at risk for such exposure, including but not limited toagrochemical industry workers, pesticide sprayers, and farmers.

Discussion:

The recognition of peripheral neuropathy as an illness caused by toxic substances dates to ancient times, with reports of conditions such as 'lead dropsy' in ancient Rome and 'ergot shaking palsy' in Europe during the Middle Ages. While the exact causes of these conditions were not always clear, they suggest that the effects of toxic substances on the nervous system have been recognized for centuries.

With the advent of industrialization, several neurotoxicants surfaced during the last two centuries viz, hexane, carbon disulfide, triethyltin and newer chlorofluorocarbon replacing agents like 1-bromopropane, etc. As of now, the causative agents for toxic peripheral neuropathy vary considerably between developed and developing countries. Occupational and environmental exposures to neurotoxicants are the most common cause in our part of the world and the adverse effects of cancer chemotherapy drugs lead the list in the Western world. The common aetiologies and mechanisms of action of toxicity of several neurotoxicants have been dealt with in detail elsewhere.[2,3]

Organophosphate-Induced Delayed Polyneuropathy (OPIDN) is a neurological syndrome typically occurring within 1-2 weeks of exposure and no later than 4 weeks of exposure to Organophosphorus (OP) compounds. The phosphorylation and ageing of neuropathic target esterasein axonsand the activation of the neuregulin 1/ErbB signalling pathway areimplicatedindisease pathology. The clinical presentation and prognosis of OPIDN have been well documented in literature heretofore.[4] However, some novel emerging insights into the pathophysiology of this disease and therapeutic options suggested by the researchers are worth discussing under the current premise. For instance, animal studiesestablished that the Transient Receptor Potential Ankyrin 1 (TRPA1) channel plays a major role in mediating OPIDN. Inhibiting TRPA1with drugs like duloxetine and ketotifen can have neuroprotective effects against OPIDN, suggesting that targeting TRPA1 is an effective treatment strategy.[5]The same pathway-based interventions, i.e., modulating TRPA1 channels by sigma 1 receptor antagonists have been suggested in the management of oxaliplatin-induced peripheral neuropathy based on results in animal studies.[6]Alongside, Sterile Alpha and toll/interleukin Receptor Motif-containing protein 1 (SARM1) activation following inhibition of neuropathic target esterase was hypothesized as one potential pathway for demyelination in OPIDN.[7] Mutations in human NTE have also been linked to some specific motor neuron disease phenotypes.[8] These examples reinforce the fact that understanding the mechanisms of toxicity on peripheral nerves and the pathophysiology of the diseasewith more alacrity will help us find some common endpoints for intervention. Whatsoever, this classical, delayed, central, and peripheral distal sensorimotor polyneuropathy following acute exposure to OP compounds were selectively excluded from the current review because the focus is on chronic subacute accidental and occupational exposures to agrochemical compounds. The toxicopathology basis of OPIDN and current clinical practices in diagnosis and management requires a separate review.

The curiosity in finding novel therapeutics for war gases has led to a huge volume of papers[9] on the OP group of compounds with different animal models, which have question abletranslational potential, and some of them were even retracted.[10]

The association between long-term exposure to organophosphate (OP) pesticides and peripheral nervous system (PNS) pesticide applicators was studied by various researchers. In one study, the participants were clinically examined and subjected to electrophysiological tests and tests of hand strength, sway speed, and

vibrotactile threshold. Results showed that every use of 10 of the 16 OP pesticides was significantly associated with one or more of six neurological outcomes, particularly abnormal toe proprioception. However, mostly null associations were observed for electrophysiological tests, hand strength, sway speed, and vibrotactile threshold. The study provides some evidence that long-term exposure to OP pesticides is associated with impaired PNS function among pesticide applicators.[4]

In studies conducted among farmers in China, the associations between exposure to various pesticides and peripheral nerve function were investigated. The study found that short- and medium-term exposure to organophosphates (OPs) was associated with peripheral nerve impairment, while exposure to organonitrogens (ONs) showed potential neurotoxicity. Pyrethroids (PYRs) were found to be the least neurotoxic among the pesticides analysed.[11] OP compounds caused demyelinationresulting in reduced velocity of conduction whereas ON compounds also caused axonal damage leading to the reduced amplitude of nerve impulse conduction.[12]

The adverse effects of chronic low-level exposure to organophosphorus compounds among stakeholders in agriculture and animal husbandry (agriculture workers, sheep dippers, and pesticide sprayers) cannot be overlooked.It causes marked electroencephalographic changes to increase the variability of action potential latencies in skeletal muscles. The practical difficulties in investigating this matter scientifically are the lack of proper data about historical exposures, the absence of any specific biomarkers, difficulty in objectively recording sensory neuropathy findings, a wide range of genetic susceptibility to agrochemical substances, lack of environmental epidemiology of ecotoxicological exposures in population, etc to label a few.[13] These challenges underscore a strong responsibility for the researchers to provide a clear molecular mechanistic basis for the toxicity of agrochemical substances on the peripheral nervous system by finding a perfect disease model to ease clinical-level research.

Another cross-sectional analytical study aimed to investigate the effects of organophosphorus (OP) compound exposure on motor nerve conduction velocity (MNCV) and compare MNCV in the median nerve of affected individuals with that of a normal population. The study recruited 60 individuals, including 30 control and 30 exposed participants, matched for height, weight, occupation, and age group. The MNCVs were evaluated using a multichannel pyrite machine, and the results indicated that the exposed population had significantly slower MNCVs than the control group, suggesting the presence of peripheral neuropathy due to OP pesticide exposure through skin absorption, inhalation, or ingestion.[14]

A multimodality assessment of peripheral nerve function in pesticide applicators exposed to organophosphates demonstrated increased vibratory sensory thresholds.[15]In contrast to the findings in the above study, another study reported no association between either past poisoning or current spray activity and vibration sense or tremor outcome.[16] This is just another example of the huge contradicting data in the literature on this subject. A systematic review on this subject would exclude almost most studies into consideration because of flawed design and extremely low sample size.

In a study on farmers in Chile, it was found that workers exposed to OP compounds had a 3.6 times higher risk of developing peripheral polyneuropathy compared to non-exposed workers. This suggests that there is a positive association between chronic occupational exposure to OP and the presence of peripheral polyneuropathy.[17]

The clinical phenotype of peripheral neuropathy due to agrochemical substances, mainly OP compounds can be described as, “slowly progressive, distal symmetric, predominantly sensory”.[18] However, the role of agrochemical substances should be borne in mind before labelling a case as “Chronic Idiopathic Axonal Neuropathy”. The procedure and pitfalls of diagnosing peripheral neuropathy are well presented here.[19]

Large fibre neuropathy affects the joint position and vibration sense, while small fibre neuropathy impairs pain, temperature, and

autonomic functions. Electrodiagnostic tests help to determine the extent of sensory-motor deficits and categorize the neuropathy as demyelinating or axonal. Electrodiagnostic (EDx) tests include sensory, motor nerve conduction, F response, H reflex, and needle electromyography (EMG). EDx helps in documenting the extent of sensory-motor deficits, categorizing demyelinating (prolonged terminal latency, slowing of nerve conduction velocity, dispersion, and conduction block) and axonal (marginal slowing of nerve conduction and small compound muscle or sensory action potential and denervation on EMG).Uniform demyelinating features suggest hereditary demyelination, while differences between nerves and segments of the same nerve favour acquired demyelination. Neuropathy is classified as mononeuropathy (due to entrapment or trauma), mononeuropathy multiplex (due to leprosy and vasculitis), or polyneuropathy (due to systemic, metabolic, or toxic aetiology).[20, 21]

Clinical symptomatology of toxic peripheral neuropathies includes both motor and sensory components.Long-term pesticide exposure was found to be associated with increased abnormality of nerve conductions, especially in sensory nerves among the farmers.[22] Chronic low-dose pesticide exposure also could lead to systemic (skin, eyes, and lungs) complications.[23] The delayed toxic sensory-motor neuropathies among farmers often present with worrisome symptoms like intractable pain, burning sensations, pins and needles, and other neuralgia, etc during old age and the sad part of them is that they are very difficult to manage once the peripheral nerve damage has already set in.

The neuropathy is predominantly sensory and is characteristic of distal, chronic neuropathy with no acute features. Small nerve fibres are more affected than large fibre populations. These medically difficult-to-manage symptoms will also influence the mental health of the geriatric farmer population a lot as several of them were noticed to have suffered from increased anxiety and depression because of incurable delayed toxic neuropathies.[24]

The traditional management protocols for CASIAN include screening and management of nutritional deficiencies, use of opioid and nonsteroidal anti-inflammatory drugs, gabapentinoids, anti-depressants, and topical counter irritants apart from a thorough general and systemic examination for associated disease and their management.

The pathophysiology of all peripheral neuropathies is usually discussed under three broad headings, segmental demyelination, Wallerian demyelination, and axonal demyelination although the exact etiology determines the course of damage.[25] The exact molecular mechanistic basis for CASIAN remains unclear to date.While the inhibition of the carboxylic esterase group of enzymes clearly explains the acute cholinergic crisis in OP poisoning and inhibition of NTE explains OPIDN, the pathophysiology of chronic toxic peripheral neuropathy due to OP compounds and other agrochemical substances remains an enigma. However, there is some consensus that the onslaught on PNS due to agrochemical substances is primarily axonopathy. Although the derangement of calcium homeostasis at the axonal conduction level is one of the primary causative factors, we still need clarity on the accumulation of metabolites, and the formation of any stable and sequestering metabolites which can perturb cardinal housekeeping and conduction pathways of peripheral nerve physiology. The flow diagram suggested by the authors of this paper to carry out PNS mechanistic studies is worth a mention.[26]

The cumulative toxicity due to these substances among at-risk populations can be due to several reasons including constant occupational exposure through dermal, inhalational, and ingestion routes. It is a matter of concern that most agrochemical substances can remain as persistent organic pollutants (POPs) in the environment and cause repetitive exposure. The likelihood of contamination of ground and surface water sources with remnants of agrochemical substances in India adds a huge ecotoxicological angle to the issue at the helm.

Here to fore, rat models with the administration of acrylamide and mouse model with the administration of vincristine are being used for research on PNS toxicity in general.

Commonly, the RT4-D6P2T Schwann cell line has been used in studies to assess the effects of agrochemicals on the myelination and differentiation of Schwann cells. The in-vitroand animal studies in this area are inadequate and failed to address the question of chronic toxicity due to agrochemical substances and find therapeutic interventions for the same. Further research is recommended in this area. I feel more standardized in-vivo studies in mammalian animal studies are the need of the hour.[27]

It is time to work on some quality biomarkers for chronic exposure to agrochemical substances and validate them for routine use. Some of the biomarkers in use are,the presence of metabolites of pesticides in urine,decreased acetylcholinesterase levels in blood or erythrocytes, formation of DNA adducts, nerve conduction studies, etc. However, we should try to work on both surrogate and specific biomarker research with due emphasis on confounding variables and standardizing the existing ones.

Researchers haven't so far given due weightage to the genetic factors responsible for chronic toxicity due to agrochemical substances. Genetic polymorphisms can affect the response to exposure to agrochemical substances. Polymorphisms in genes encoding cytochrome P450 enzymes (CYPs) and genetic variations in glutathione S-transferases (GSTs) can influence xenobiotic metabolism.Aryl hydrocarbon receptor (AHR) polymorphisms can lead to variable responses to exposure to dioxins. Polymorphisms in the paraoxonase 1 (PON1) gene can affect the detoxification of organophosphate pesticides. Genetic variations in multidrug resistance protein 1 (MDR1), a membrane transporter involved in the efflux of many agrochemicals from cells, can affect the efflux and retention of these substances.[28,29]

Several systematic reviews and meta-analysis studies applied Hill's criteria of causation to CASIAN and partially succeeded in proving their point in the positive.[30,31]The employees in manufacturing units of agrochemical substances form a homogenous unit to study the phenomenon which has not been utilized properly so far. The problem of studying peripheral neuropathy-related nociception lucidly remains an unmet research question as well.

To comprehensively investigate peripheral neuropathy caused by agrochemical substances, a national-wide multicentric cohort study is required to collect exposure data. A database of agriculture workers involved in the pesticide spraying process should be maintained to accurately estimate the duration and frequency of exposure. A multimodality assessment that includes clinical neurological examinations and tests for sensory and motor components of toxic neuropathy should be conducted on a timed basis, with swift follow-up. In addition, the current safety practices and preventive strategies of stakeholders should be reviewed to identify any gaps in safety measures and encourage the use of appropriate Personal Protective Equipment (PPE) among workers. Overall, this thorough clinical study will provide valuable insights into the causes and effects of peripheral neuropathy caused by agrochemical substances, paving the way for effective prevention and treatment strategies

Conclusion:

Chronic Agrochemical Substance-Induced Axonal Neuropathy (CASIAN) can be considered a diagnosis worth further investigation by preclinical and clinical researchers. We have a responsibility to spread the message and work on the preventive aspects of this condition with immediate effect. Further, understanding the molecular mechanistic basis can help us fight the condition by using nutraceuticals or drugs. All the stakeholders in the Indian agriculture sector should be educated about this hitherto unquantified morbidity due to long-term exposure to agrochemical substances. It is incumbent upon the scientific community to accurately measure and evaluate potential hazards, assess, and characterize associated risks, conduct thorough exposure assessments, and develop innovative strategies to prevent and treat CASIAN.

Limitations:

This paper selectively reviewed some published data on toxic sensorimotor peripheral

neuropathies due to agrochemical substances. There is a need for a systematic review of all published literature on this subject by future researchers before framing proper PICOT (Population, Intervention, Comparison, Outcome, Timeframe) questions to save valuable time and resources.

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