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SM Journal of Environmental Toxicology

Case Study

Neurolathyrism – A Case Report and Current Views

Khosa Shaweta[1], Khosa Gurveer S[2] and Mishra Shri K[3]

[1]*Department of Neurology, Olive View-UCLA Medical Center, USA*
[2]*Department of Neurology, Indira Gandhi Medical College, Ridge, India*
[3]*Department of Neurology, University of Southern California, Keck School of Medicine, USA*

Article Information

Received date: Aug 22, 2018
Accepted date: Oct 01, 2018
Published date: Oct 03, 2018

***Corresponding author**

Mishra Shri K, Department of Neurology, University of Southern California, Keck School of Medicine, Health Sciences Campus, 4AE Clinic Tower 1100 North State Street, Los Angeles, CA 90089-9315, USA,
Tel: (322) 409-7381;
Fax: (323) 226-5869;
Email: smishra@usc.edu

Keywords Lathyrism; Animals; Human; Epidemiology; Neurotoxicity

Key Messages Neurolathyrism is caused by excessive consumption of *Lathyrus sativus* and manifests as irreversible spastic paraparesis and quadriparesis, *Lathyrus sativus* if consumed in appropriate quantities may provide valuable source of nutrition for the lower socioeconomic strata and tough environments

Abstract

Neurolathyrism is caused by excessive consumption of *Lathyrus sativus* (grass pea) and seen in India and parts of sub-Saharan Africa. The disease manifests as irreversible spastic paraparesis and quadriparesis leading to permanent disability. We report two unique cases of Lathyrism secondary to consumption of *Lathyrus sativus* and review the literature available. Two brothers from a remote village in India presented with slowly progressive spastic paraparesis of unknown aetiology. On neurological examination, they were found to have motor neuron pattern of weakness. Routine laboratory work-up, CSF studies and imaging of the brain and spine were all found to be unremarkable. Upon further review, it was found that the patients had a prolonged history of consumption of *Lathyrus sativus* legume. There is no known cure for neurolathyrism. As a result, the legume was banned from staple diet. However, the legume continues to be consumed despite the ban and public education.

Introduction

Neurolathyrism is a neurodegenerative disorder caused by chronic consumption of the legume *Lathyrus sativus* (Khesari dal). Excessive consumption of the neurotoxic amino acid β-N oxalyl-L-α, β-diaminopropionic acid (β-ODAP) leads to irreversible damage to motor neuron characterized by symmetrical degeneration of pyramidal tracts in the spinal cord, and loss of pyramidal cells in the motor cortex of the brain [1,2]. Despite the continued consumption of the Khesari dal in India no new cases have been reported over the past three decades [3]. In this article we review 2 cases of neuro lathyrism and data regarding Neurolathyrism.

Case History

Case 1

A 25-year-old male farmer presented with history of bilateral lower limb spasticity. His past medical history was significant for no other medical condition except the lower extremity weakness that developed couple of years ago. The weakness had gradually progressed to the level of requiring assistance in ambulation and daily activities. He denied associated sensory deficit or sphincter disturbances. On neurological examination, he was found to have normal upper extremity strength and reflexes. Lower extremity examination revealed increased spasticity and paraparesis. Hyperreflexia was observed along with positive Babinski bilaterally. Routine laboratory investigations including blood count, liver function test, renal function tests and HIV were found to be normal. Additional work up including imaging of the brain, nerve conduction studies and electromyography were all found to be unremarkable. A lumbar puncture was performed that showed normal cerebrospinal fluid analysis.

Case 2

A 27-year-old male who was the brother of the case 1 presented with similar complaint of bilateral lower extremity spasticity. The symptoms had developed acutely over a period of 2 weeks more than 5 years ago. The patient had no prior medical history, medication or drug use, or any allergies. Family history was significant for similar presentation of lower extremity spasticity in his brother. On neurological examination he was found to have increased tone in his lower extremity with brisk deep tendon reflexes. There were no associated sensory deficit or sphincter disturbances. Routine laboratory investigations were normal like his brother. Imaging of the brain and spinal cord was unremarkable. Cerebrospinal fluid analysis was normal.

Given the symptoms of lower extremity motor symptoms the differential diagnosis included Human T-Lymphotrophic Virus (HTLV)-associated myelopathy, HIV vacuolar myelopathy, other causes of myelopathies including metabolic, toxic, inflammatory, autoimmune, and demyelination. Upon further review, it was found that both patients had a prolonged history of consumption of *Lathyrus sativus* legume given poor socio-economic status. With the toxic exposure, physical

findings and investigational work up likely diagnosis of neuro lathyrism was established. They were started on Baclofen (muscle relaxant) and physical therapy, however, minimal improvement was seen on subsequent visits.

Discussion

Various mechanisms have been proposed regarding the neurotoxicity caused by Lathyrus sativus.ODAP, a glutamate analogue is found in the legume is one of the most excitatory substances in the spinal interneurons and acts as an alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate-type glutamatergic receptor agonist. Glutamate activates AMPA- and NMDA-type glutamate receptors in neurons leading to increase in intracellular Ca^{2+} ($[Ca^{2+}]_i$) via activation of voltage-dependent Ca^{2+} channels . Recently Kusama-Eguchi at al also showed prolonged $[Ca^{2+}]_i$ mobilization through the involvement of transient receptor potential (TRPs) and group I metabotropic glutamate receptors (mGluR) in L-β-ODAP-induced motor neuron toxicity . Glutamate is also believed to increases the ($[Ca^{2+}]_i$)via mGluR and ryanodine receptors [4]. This increase $[Ca^{2+}]_i$ makes the neurons susceptible to Ca^{2+} overload-induced cell death due to low intracellular content of Ca^{2+}-binding proteins such as calbindin $D_{28K,}$ parvalbumin and other Ca^{2+}-buffering proteins in motor neurons [5,6]. Recently Tan et al proposed a relative complete signal pathway to neurolathyrism involving distortion of cell microfilament, inhibition of cytoskeleton polymerization and cytoskeletal collapse ultimately. This is brought on by ODAP induced increased Ca^{2+} in the cellular matrix that leads to over expression of β1 integrin on the membrane followed by overexpression of paxillin which inhibits cytoskeletal polymerization [7]. Another proposed mechanism of ODAP toxicity is via generation of ROS and inhibition of mitochondrial complex I [8,9]. The high levels of arginine and homoarginine found in *Lathyrus sativus* lead to formation of peroxynitrite radicals via Nitric oxide production causing mitochondrial damage. L-ODAP is also shown to inhibit Tyrosine Amino Transferase (TAT) both in vitro and in vivo. This might explain the species difference in ODAP toxicity. However, the exact mechanism for ODAP toxicity in humans is still not understood as Jyothi P et al in their study showed that humans can actually metabolize orally ingested ODAP [10].

As result of the neurotoxicity, *Lathyrus sativus* has been banned in various states of India. However, it still continues to be used for human consumption despite the ban and has become a part of usual diet of people in various states of India including Maharashtra and Uttar Pradesh. Interestingly, recent studies conducted in these states screening for Neurolathyrism have not yielded any new cases of Neurolathyrism despite consumption by 61% of house hold surveyed [11]. Given these findings the Indian Council of Medical Research (ICMR) and Indian Council of Agricultural Research (ICAR) has proposed to lift the nationwide ban on the legume whilst some states like Maharashtra have already lifted the ban [12]. A recent study by Khandare et al., [11] in 2018 in India found lower content of β- ODAP in split grass pea compared to previous reports. This was attributed to genetic improvement of the legume. Not only in India, there have been attempts to re-introduce *Lathyrus sativus* into Balkan countries for diverse purposes including grain and forage production given the harsh weather conditions [13]. Most of the cases of Neurolathyrism were seen after prolonged consumption of Khesari dal in large quantities especially during periods of draughts or famines [2]. If consumed as a normal part of regular diet it would provide a good and cheap source of nutrition to the masses. *Lathyrus sativus* has also generated interest in terms of its therapeutic applications. The L-ODAP is an activator of protein kinase C known to possess neurotropic and neuroprotective properties. Similarly, homoarginine holds promise for its vasodilatory effects and bone metabolism. Current studies are also evaluation the role of ODAP as a wound healing agent as it can stabilize Hypoxia Inducible Factor (HIF) -1α under normoxic condition [14].

Conclusion

Neurolathyrism is apreventable irreversible disease caused by excessive consumption of Lathyrus sativus. We report 2 old cases of neurolathyrism after prolonged consumption of the legume. As the management is mostly supportive, efforts must be taken to educate the masses, however, this legume continues to be consumed in states across India as it not only provides a rich source of protein but also withstands harsh environmental conditions such as drought or flood making it a "life saver crop". Besides this, it also holds therapeutic applications although these prospects need further exploration and we might see this poor mans' crop getting generalized acceptance.

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