Neurolathyrism- an Updated Review

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Summary

Neurolathyrism is spastic paraparesis disease, which affects mostly the legs. It cripples the youngest in the population. It is endemic in Ethiopia, India and Bangladesh. It is caused by a neurotoxic amino acid β-N-oxalyl-L- α,β-diaminopropionic acid (β-ODAP) found in *Lathyrus sativus*(grass pea). Until now there is no critical drug treatment for it but there are some prevention methods. Now a day there are many activities, which are done by different organization around the world to reduce the incidence of disease. This paper strives to review the impact of neurolathrysm, and having a good insight to the pathophysiology of the disease. The interventions taken by the different stakeholders will be recapitulated.

Keywords: Neurolathyrism, *Lathyrus sativus*, β-ODAP

1. Introduction

Neurolathyrism is a form of human spastic paraparesis related to the over consumption of the legume *Lathyrus sativus* or grass pea (1). Grass pea is drought tolerant legume crop and it is resistant to moderate salinity. In drought prone areas the plant is considered as insurance crop. Historically, grass pea has been a daily food for millions in Asia and Africa, and is now reintroduced into popular use in different parts of the world as a manure, forage and food (2).

A study in Northwestern Ethiopia revealed an estimated mean disease prevalence of 0.6%-2.9%. Most patients developed the disease in the epidemic of 1976/77, although new cases appear to have occurred with an estimated mean annual incidence of 1.7:10,000 (3). Study in Debre-Sina district of Ethiopia, the area afflicted by the neurolathyrism epidemic, showed that males aged 10-14 years were most affected by neurolathyrism. Increased household risk was associated with illiteracy of the head of the household and exclusive cooking of grass pea foods (4). Lathyrism was once prevalent throughout Europe, North Africa, Middle East and parts of the Far East; the disease is presently restricted to India, Bangladesh and Ethiopia (5). This paper will review toxicologic aspects of lathyrism- from the etiological factors to its management and prevention.

2. *Lathyrus sativus*: Taxonomy And Morphology

Lathyrus sativus has the following common name: grass pea, chickling pea, Indian vetch (UK and N. America), Almorta(Spain), Khesari or Batura (India), Alverjas (Venezula), Gilban (Sudan), Guaya (Ethiopia), Matri (Pakistan), Gesette (France), Pisello bretonne(Italy)(6). It has a scientific name of Species: *Lathyrus sativus* L and Family: Leguminosae (5).

There are about 150 species in the genus lathyrus that comprises sections among which grass pea is one. Grass pea is a much-branched soberest, straggling or climbing herbaceous; stems are 0.6-9.0m fall and the leaves are pinnately compound with usually two leaflets. The upper leaflets often have modified tendrils (6). The Ethiopia grass pea belongs to the proles abyssinicum of subsepecies asiaticus (7).

Figure 1. *Lathyrus sativus*

3. Uses of *Lathyrus sativus*

Grass pea, which contains significant amount of protein, is usually cheaper than other pulses; but it is known to cause lathyrism among rural populations. The disease affects the poor sections of a community, especially under conditions of acute food shortage when grass pea, it forms a major part of the diet (8). The seeds are boiled and consumed as a pulse; it can also be used in bread making. Grass pea seeds are used in India, Ethiopia and other developing countries as part of the diet of the poor in times of famine (6). In Ethiopia seeds are consumed roasted and are used in the preparation of 'wot'. The crop is not highly esteemed but is used as fodder crop (7).

Seeds contain 18.2 – 34.6% protein, 0.6% fat, 58.2% carbohydrate (about 35% starch). The seeds also contain 1.5% sucrose, 6.8% pentose, 3.6% phytin, 1.5% lignin, 6.69% albumin, 1.5% prolamine, 13.3% globulin, and 3.8% glutelin (7). Oil from the seeds of grass pea has cathartic effect. The seeds are used locally in homeopathic medicine (6).

4. Neurotoxin from *Lathyrus sativus*

As reviewed by Lambein and his group, the most direct confirmation that *Lathyrus sativus* was responsible for human lathyrism came from the unfortunate experience of Romania Jews interned in German forced labor camp in the Ukraine. They developed the disease after being maintained on a daily diet of 400gm of grass pea cooked in salt water with bread made of barley and straw in a 4:1 proportion. Prisoners who consumed less of grass pea (200 gm /day) did not develop the disease (9).

Murti *et.al* (1964) and Rao *et al* (1964) independently isolated the neurotoxic amino acid, β-N-oxalyl-L- α,β-diaminopropionic acid (ODAP) or β-N-Oxalylaino-L- alanin (BOAA), which is suspected culprit of neurolathyrism (10, 11).

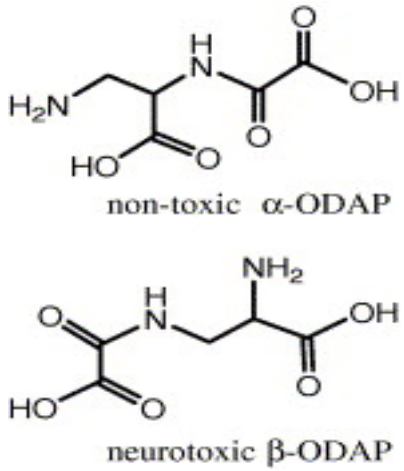

Figure 2. Chemical structure of the neurotoxin Beta- ODAP (12)

β-ODAP has been characterized as the causative agent of human neurolathyrism; an upper motor neuron disease producing corticospinal dysfunction from excessive consumption of the lathyrus pea. Behavioral, tissue culture, and *in vitro* receptor binding investigations revealed β-ODAP might mediate acute neurotoxicity through quisqualate (QA)-preferring glutamate receptors. The cortex QA receptor might be sensitive to β-ODAP attack and represent the initial molecular recognition site responsible for the pathogenesis of this upper motor neuron disease (13).

5. Efforts on Detoxification

For the safe use of pea, effort on crop improvement had been addressed, including direct seed treatment. It was found that water soaking of the seed could lower β-ODAP content but not sufficiently for continuous safe human consumption (2).

Physical and chemical treatments have also been used in the detoxification to induce some mutants. The mutants were not widely used as their characters were unstable or β-ODAP content was not sufficiently low. Further efforts would be a necessary for further improvements (2). Agronomists have also paid much attention to the breeding selection of low toxicity verities (14).

6. Risk Factors of Neurolathryism

The risk factors for neurolathyism are heavy physical activity, male gender, young age (15-25 years), and micronutrient deficiency like Zn, Cu, Vitamin C and A (15). It has been suggested that Zinc deficiency in the soil leads to a greater expression of the neurotoxin in the seeds, thus increasing the toxic hazards from consuming this food (9). Other study indicated that blood group O is associated with lathyrism (4).

Getahun and his group looked at the way the seed is taken as a risk factor for lathyrism. In this study consumption of boiled grass pea and raw unripe green grass peas was associated with neurolathyrism (16). But the study did not rule out whether the process of preparation or the intact boiled pulse was the risk factor.

7. Pathogenesis and Pathology of Neurolathyrism

Knowledge of the neuropathogy of lathyrism is rather limited. Very few postmortem examinations have been performed on case of lathyrism because most patients are poor and die at home in remote regions and in endemic countries there are religious and cultural prohibitions on postmortems. Ross et al. (1987) demonstrated in cerebral cortical slices of the mouse that micromolar concentrations of β-ODAP modify normal cell bodies morphology (postsynaptic vacuolisation and widespread neuronal degeneration) (17).

In vitro studies revealed that β-L-ODAP binds to the non-NMDA glutamate receptors, which are α-amino-3-hydroxy-5- methylisoxazole-4-propionate (AMPA) or quinsqualate (QA) type and inhibit the low and high glutamate uptake systems in synaptosomes (18, 19). Studies also showed that nonconvulsant doses of β-L-ODAP to rats increased the cerebellar cyclic guanosine monophosphate (cGMP) level and induce down-regulation of non-NMDA glutamate receptors in the frontal cortex (20, 21).

Nerve conduction and electromygraphic study revealed that patients with neurolathyrism have electrophysiological signs of lower motor neuron disease in their lower limbs (22). However, there have been many failed attempts to induce irreversible spastic paraparesis in animals fed with *lathyrism sativus* seeds or its components.

8. Prevalence of Neurolathyrism

The mean prevalence of neurolathyrism reaches 6 per 1000 in Ethiopia, 5.3 per 1000 in India and 1.4 per 1000 Bangladesh (7). Studies showed that there were epidemic of neurolathyrism in 1970s and 1990s in Africa and Asia. There were epidemic of neurolarthyrism particularly in China (1973), Bangladesh (1976), Nepal (1998), Afganistan (1998) and Ethiopia (1976 and 1997-99) (23). Ethiopia was affected twice in this period.

9. Stages of the Disease

The onset is sudden and early symptoms include walking difficulties, unbearable cramps, and leg weakness. It produces spastic paralysis, which becomes irreversible. The pyramidal tracts are involved causing motor weakness combined with greatly increased tone in the thigh extensors and adductors (6).

The stages of the neurolathyrism reach five and demonstrated as follows (23, 24):

1. ***Latent stage***: Individual is apparently healthy, but when subjected to physical stress exhibits an ungainly gait. Complete remission occurs by withdrawing pulses from diet.
2. ***No stick stage***: The patient walks with short jerky with out the aid of a stick.
3. ***One stick stage:*** The patient walks with a crossed gait with a tendency to walk on the toes, muscle stiffness is present.
4. ***Two-stick stage:*** The symptoms are more severe due to excessive bending of knees and crossed legs; the patient needs two crutches for a support. The gait is slow and clumsy and the patient tires easily after walking a short distance only.
5. ***Crowing stages***: the erect posture becomes impossible as the knee joint cannot support the weight of the body. The patient is reduced to crawling by throwing his weight on his hand.

The majority (90%) of cases fall in to stage 2 and 3. About 10% are classified as stage 4 and 5. Females tend to have milder involvement than males (25).

10. Movements against Neurolathyrism

Since the discovery of the structure and the neuro-excitatory activity of B-ODAP in grass pea seeds, research has focused on the reduction/removal of this secondary metabolite from the plant. But still no prevention has reached the victims of neurlothyrim (14). In spite of the fact that no prevention has reached the victims of neurolathyrism, there were activities by various organizations in search for interventions.

a. Ethiopian Institute for Agricultural Research organization and Ghent University

A project funded by the flemsih Interuniversity council has explored the alterative road to improve grass pea and prevent neurolathyrism. The Project "Improving nutritional quality of grass pea (*L. sativus*)" was a collaborative effort between Institute for Agricultural Research organization and Ghent University in Belgium (14). Although the output of the project does not reach to the public yet, focal points of the project were:

- Training Ethiopian researchers in plant biotechnology
- Dissemination of information to the populations at risk, concerning the prevention of neurolathyrism.
- Selection of both mutants and some clones for low B-ODAP and improved amino acid composition.
- Study stability of the low B-ODAP trait
- Examining the potential for applying genetic transformation of grass pea.
- Studies on the effect of essential amino acid as food/feed supplements on the nutritional quality of grass pea.

b. Internal Center for Agricultural Research in the Dry Areas

Since 1989-90 grass pea breading program at Internal Center for Agricultural Research in the Dry Areas (ICARDA) has aimed to reduce the neurotoxin concentration by four approaches: germ-plasm evaluation, genetic detoxification, soil micronutrients, Zn^{++} and Fe^{++} (26).

ICARDA scientist trained researchers from Ethiopia and other affected areas to develop locally adapted selection and to begin seed production of the improved varieties. New, low neurotoxin grass pea lines developed by ICARDA are now being shared with Ethiopian researchers for testing and release. These lines might both prevent the occurrence of lathyrism and help in fighting drought (26).

c. Third World Medical Research Foundation (TWMRF) Roles

The TWMRF took the lead in an ambitious research program to promote the need for a toxin-free, wholly nutritious strain of the legume. The program included laboratory based study in Ethiopia; and fieldwork was planned in India and Bangladesh (27).

11. Management of Neurolathyrism

The disease is usually non-progressive but irreversible. Further consumption of these peas should not be allowed. Tolperisone, a centrally acting muscle relaxant has been shown to produce significant reduction in the spasticity of neurolathyrism patients (7). The hypertonicity can to a certain extent be controlled by baclofen (28).

12. Prevention of Neurolathyrism

Lathyrism is a public health problem because it cripples the young and productive age group. The following measures are appropriate and feasible in the countries where the disease is endemic. Public education about the dangers of lathyrism is obviously important but the harsh reality is that people may face a stark choice between lathyrism and starvation (23).

Boiling in water or repeated steeping in hot water and discarding the extracts can detoxify the seeds. Roasting of seeds, at 140^{o}c for 15 to 20 minutes, result in 80 to 90 % destruction of the neurotoxins. Some people soak the seeds overnight and decant the water before cooking. This eliminates about 90% of the toxin (15). Recent research suggests that sulfur amino acids have a protective effect against the toxicity of ODAP (23).

Toxic amino acids are readily soluble in water and can be leached. Fermentation is useful to reduce ODAP content. Moist heat (boiling, steaming) denatures protein inhibitors, which other wise add to the toxic effect of raw grass pea through depletion of protective sulfur amino acid (15).

13. Conclusion and Recommendation

Lathyrism is a spastic paraplegia caused by a toxin amino acid ODAP, which is found mainly in *L. sativus* and its species. It is endemic in India, Ethiopia and Bangladesh. The main feature of this disease is unsteady gait. Risk factors of lathyrism include micronutrient deficiency in soil and in man itself like Zn, Cu, vitamin C and vitamin A, young age (15-25 years), male gender and heavy physical activity. As of now, there is no specific drug treatment but little benefit is

found by using centrally acting spasmolytic drug like tolperisone. Prevention strategies need to be launched in efficient way.

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