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New findings and symptomatic treatment for neurolathyrism, a motor neuron disease occurring in North West Bangladesh

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Neurolathyrism is a form of spastic paraparesis caused by the neuroexcitatory amino acid 3-N-oxalyl-L-2,3-diaminopropanoic acid (β-ODAP) present in the seeds and foliage of *Lathyrus sativus*. The disease is irreversible and usually nonprogressive. Tolperisone HCl, a centrally acting muscle relaxant, has been shown to reduce significantly the spasticity in neurolathyrism patients. Sporadic occurrence of HTLV-1 infection (0.9%) and of osteolathyrism was found among the neurolathyrism patients. Osteolathyrism is linked to the consumption of the green shoots of *Lathyrus sativus*.

Keywords: neurolathyrism; *Lathyrus sativus*; HTLV-1; osteolathyrism; tolperisone HCl; motor neuron disease.

Introduction

Neurolathyrism is a motor neuron disease caused by overconsumption of the seeds of *Lathyrus sativus*,[1] a pulse grown and consumed in some Asian and African countries. The most recent epidemics occurred between 1970 and 1974 in Bangladesh, China, Ethiopia and India. The disease affects pyramidal cells and tracts leading to an irreversible condition.[2] The toxin responsible is the neuroexcitatory nonprotein amino acid 3-N-oxalyl-L-2, 3-diaminopropanoic acid (β-ODAP, sometimes referred to as β-oxalylamino-alanine or BOAA) which is structurally and neuropharmacologically a glutamate analog. The green shoots of *L. sativus* contain an additional neurotoxin and an osteotoxin.[3] Most of the patients develop heavy legs, spasms of the muscles of the legs and spasticity. At present there is no treatment available for neurolathyrism.

Methods

We have diagnosed 882 neurolathyrism patients recorded in three districts in Rajshahi Division of North West Bangladesh. Most of these patients were affected during the epidemic of 1970–74. Patients were selected for treatment with tolperisone HCl (Mydocalm, chemical name: 2,4-dimethyl-3-piperidinopropiophenone, Gedeon Richter, Budapest, Hungary) along with controls. A permuted block randomisation chart was followed, taking z value of 8, sample size of 40. The study was conducted for a period of 3 months. The parameters followed for symptoms were flexor spasm, muscle cramp, repeated fall, heavy legs, startle attack, automatic clonus, stiffness of adductor muscles, stiffness of Achilles tendon, speed of walk. The signs that were considered are tone, tendon reflexes, clonus and power.

An ELISA test (Vironostika HTLVI192 T) from Organon Technica (Turnhout, Belgium) was used to detect HTLV-1 antibodies in serum and cerebrospinal fluid.

Results

In about 30% of the patients examined the disease has been progressing for the last 4–6

years after about 15 years of static condition, even after discontinuation of consumption of *L. sativus*. The follow up study after the patients had been on a dose of 150 mg/day of tolperisone HCl in divided dose for a period of 3 months indicated improvement of varying degrees in all the symptoms mentioned. Among the patients treated 60% had normal tone after 3 months. In 70% of the patients who had spontaneous clonus before treatment, this symptom disappeared whilst in the other patients its occurrence was drastically reduced. The time to walk 100 meters decreased for all treated patients but for none of the control group. All treated patients had increased power and improved physical abilities.

Four patients out of 444 patients tested for HTLV-1 infection were seropositive.

In a radiological survey of 60 neurolathyrism patients, who had skeletal deformity and who had developed the disease before the age of 18 years, it was found that two patients had lack of union of ossification centres of vertebrae and pelvis, indicative of osteolathyrism (details to be published separately).

Discussion

Although the disease is supposed to be epidemic in nature, 2% of the cases were affected before the epidemic of 1970–74 and 7% of the cases were affected after the epidemic, suggesting that the disease can also occur sporadically. It should be mentioned that in the afflicted areas most people also consume the green shoots as a vegetable, unaware of the toxicity in the shoot. These patients also have some degree of wasting of the small muscles of legs which is difficult to explain by disuse atrophy only. There has been no radical treatment for neurolathyrism patients reported. To our knowledge the only symptomatic treatment that is available in an experimental stage is a surgical incission in the aductor muscles to release contracture (Dwivedi & Spencer, personal communication). Tolperisone HCl inhibits multisynaptic reflex activity and reduces strychnine induced hyperreflexia. It reduces the convulsive effect of electroshock and has a marked antinicotinic activity. Tolperisone HCl also has an inhibitory effect on muscle contraction.[4]

In some patients affected by tropical spastic paraperesis (TSP), a disease comparable to neurolathyrism, an association with HTLV-1 was observed.[5] In Ethiopia, Haimanot *et al* examined 115 neurolathyrism patients for HTLV-1 association, with negative results.[6] We examined 444 patients for the presence of antibodies against HTLV-1. Four patients were found to be seropositive. Although HTLV related myelopathy has sensory symptoms, no such symptoms were observed in the above patients, who perhaps may be considered as carriers only of the virus. This should not be surprising considering the low rate of HTLV-I-associated myelopathy in relation to the seroprevalence of HTLV-I.[7] Because of this low prevalance of HTLV-1 infection we can state that this virus cannot be responsible for the spastic paraparesis attributed to neurolathyrism in Bangladesh.

It is known that β-aminopropionitrile (BAPN) present in *L. odoratus* can produce the bone-deforming osteolathyrism by inhibiting the cross-linking in collagen and elastin.[8] Cohn & Streifler had also reported the occurrence of minor skeletal lesions in neurolathyrism patients.[9] *L. sativus* does not contain free BAPN but Lambein & coworkers detected an unstable isoxazolinone derivative (2-cyanoethyl-isoxazolin-5-one) in the shoots of *L. sativus* that can be metabolised into BAPN and produce osteolathyrism in experimental animals.[10,11] The concentration of this osteotoxin in the seedlings of different varieties of *L. sativus* seems not to be correlated to the concentration of the neurotoxin in the seeds.[3] As the green shoots of *L. sativus* are a popular vegetable in *L. sativus* growing areas of Bangladesh, we suggest that this habit may be associated with osteolathyrism, which in many cases might remain undiagnosed. The two cases identified as clinical osteolathyrism are the first reports on the occurrence of osteolathyrism in Bangladesh. Further surveys might indicate a different susceptibility to osteolathyrism as compared to that to neurolathyrism.

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