Chapter 18

Toxic disorders of the upper motor neuron system

D. DESIRE TSHALA-KATUMBAY* AND PETER S. SPENCER

Center for Research on Occupational and Environmental Toxicology and Department of Neurology, School of Medicine, Oregon Health and Science University, Portland, Oregon, USA

18.1. Introduction

Dysfunction of the motor system has been associated with dietary dependence on food plants with neurotoxic potential, notably the grass pea (chickling pea) and cassava (manioc), in various and geographically distinct regions of the world. Reliance on grass pea (*Lathyrus sativus* or related neurotoxic species) or on insufficiently processed bitter cassava (*Manihot esculenta* Crantz) as staples, the latter in association with malnutrition, has resulted in epidemics of (neuro)lathyrism and konzo (neurocassavism), respectively; these are clinically similar self-limiting neurodegenerative disorders confined to the upper motor neuron system. Studies of outbreaks of lathyrism and konzo have suggested individual susceptibility to the toxic effects of these plants varies with subject age, gender, nutritional status and motor activity, as well as the toxin content of grass pea (lathyrism) or cassava (konzo), methods of food preparation and duration of consumption. The common clinical picture is a spastic paraparesis or, in the potentially more severe cassava-associated disorder, a tetraparesis. Electrophysiological studies reveal prominent pyramidal dysfunction in both lathyrism and konzo; neuropathological data are sparse or lacking, respectively. Molecular mechanisms of these remarkably similar neurotoxic disorders have yet to be understood. Though there is no effective treatment for these persistently disabling conditions, lathyrism and konzo can both be prevented by modifying food preparation or changing diet.

18.2. Epidemiology

18.2.1. Historical background

Lathyrism has affected humans and animal populations since antiquity. The disease was known to ancient Hindus, to Hippocrates (460–377 BC), Pliny the Elder (23–79 AD), Pedanius Dioskurides (50 AD) and Galen (130–210 AD) (Desparanches, 1829; Hippocrates, 1846; Proust, 1883; Hubert, 1886; Schuchardt, 1887; Spirtoff, 1903). Lathyrism affects populations reliant on food products derived from neurotoxic species of the *Lathyrus* genus, member of the Fabaceae family, most commonly *L. sativus* (Stockman, 1917; Selye, 1957; Dwivedi and Prasad, 1964; Rao et al., 1969; Kislev, 1985). Sale of flour prepared from *L. sativus* was banned by George, Duke of Württemberg (1671) because of its ‘paralysing effects on the legs’ (Schuchardt, 1887). Years later (1873), the disease was referred to as *latirismo* (‘lathyrismus’) (Cantani, 1873). Since the 17th century, outbreaks of lathyrism have been reported on the Indian sub-continent (Bangladesh, India, Pakistan), in Europe (France, Italy, Germany, Romania, Spain, Ukraine), Afghanistan, China and North Africa (Algeria, Ethiopia and Eritrea) (Desparanches, 1829; Proust, 1883; Grandjean, 1885; Stockman, 1917, 1929; Selye, 1957; Dwivedi and Prasad, 1964; Rao et al., 1969; Kislev, 1985). Sale of flour prepared from *L. sativus* was banned by George, Duke of Württemberg (1671) because of its ‘paralysing effects on the legs’ (Schuchardt, 1887). Later years (1873), the disease was referred to as *latirismo* (‘lathyrismus’) (Cantani, 1873).

Konzo (Fig. 18.2(B)), a lathyrism-like handicapping disorder, was first documented by Tessitore (1936) in the south-western region (Bandundu province) of Zaire, the former ‘Belgian Congo’, presently the Democratic Republic of Congo (DRC) (Trolli, 1938). Despite the existence of striking clinical similarities between lathyrism and konzo, outbreaks of these two diseases occur in two distinct, non-overlapping geographical areas of the globe (Fig. 18.1). Whereas lathyrism has occurred among populations that cultivate the grass pea, outbreaks...
of konzo have been reported mainly in sub-Saharan Africa among those who subsist on cassava as staple food (Rosling and Tylleskär, 2000). Cassava is a member of the Euphorbiaceae family (DeBower, 1975). The plant was cultivated in tropical America for approximately 5000 years before it was exported into Africa around the 1600s by Portuguese traders to feed slaves (Jones, 1959; DeBower, 1975; Allem, 1994; Olsen and Schaal, 1999). Today, it is used worldwide and constitutes the prime source of dietary calories for over 500 million people in the tropics and subtropics (Cock, 1982). It is not known whether konzo has also occurred during ancient times and/or among the Indians from the Amazonian forests who cultivate cassava (Lathrap, 1970).

Available literature indicates the disease was known to the local populations (Yaka) of the Bandundu province in the DRC in the late 1800s. The Yaka named the disease ‘konzo’, which means ‘tied legs’ in kiyaka, the local spoken language (Trolli, 1938; van den Abeele and Vandenput, 1956; van der Beken, 1993). This designation was a good description of the ‘cross-legged gait’ of affected subjects. Since the 19th century, outbreaks of

---

**Fig. 18.1.** World map depicting zones where lathyrism has been reported (dark gray) and those affected by konzo (light gray).

**Fig. 18.2.** (A) Young Bangladeshi male affected by lathyrism (courtesy of Third World Medical Research Foundation). (B) Young Congolese male affected by konzo (photograph by Thorkild Tylleskär, by permission).
konzo have occurred in many other countries of the sub-Saharan Africa including Mozambique (where it is called mantakassa), Tanzania, Central African Republic, Cameroon, Angola and Uganda (Fig. 18.1) (Ministry of Health Mozambique, 1984a,b; Cliff et al., 1985; Rosling, 1989; Tylleskär et al., 1991, 1994; Howlett et al., 1992; Banea et al., 1993; Davis and Howarth, 1993; Mlingi et al., 1993; Lantum, 1998; Bonmarin, 2002; Rosling and Tylleskär, 2000; Tshala-Katumbay et al., 2001a).

18.2.2. Role of environmental and contextual factors

Epidemics of lathyrism and konzo usually appear when adverse environmental conditions result in heavy dietary reliance on the grass pea (Figs. 18.3(A, B)) or on cassava (Figs. 18.3(C, D)), respectively (Spencer, 1999). Both the grass pea and cassava are annual high-yielding crops with relative resistance to harsh environmental conditions such as drought, insect attacks and/or pests. Grass pea has a high protein content (with most of the essential amino acids well represented) while cassava is a rich source of carbohydrate (Gopalan and Balasubramanian, 1963; Roy and Roa, 1978; Cock, 1982). Food products derived from these two plants usually make a major component of the diet among populations in areas endemic for either lathyrism (grass pea) or konzo (cassava). However, adverse environmental conditions, such as extreme weather leading to flood or drought, pestilence or war, have forced populations to rely almost exclusively on food products made from these two drought-resistant crops; this situation has often led to outbreaks of characteristic neurologic disease (Spencer, 1994; Rosling and Tylleskär, 2000).

During World War II, outbreaks of lathyrism occurred among a group of Rumanian Jews interned in a German hard-labor camp in the Ukraine and among Germans held in a French prisoner-of-war camp. The causative chain of lathyrism is best illustrated in the outbreak that occurred in the Ukrainian town of Wapiarka (Kessler, 1947; Cohn and Streifler, 1981a,b). On September 16, 1942, 1200 Rumanian Jewish males were put on a diet of 400 g grass pea daily cooked in salt water and 200 g of bread. Three months later, there was a monophasic outbreak of lathyrism involving 800 inmates. Ukrainian and Russian inmates who had survived prior to the arrival of the Rumanians on a diet of 200 g per day grass pea remained free of disease for 3–6 months, but developed lathyrism when their intake was doubled with the arrival of the latter. Those previously incarcerated were affected earlier and in a greater proportion than prisoners brought (in relatively good health) from their homes. The outbreak of lathyrism among Wapiarka inmates was documented by Kessler, a physician and prisoner who himself developed mild lathyrism. He identified the disease and its cause, and persuaded the guards to change the diet. Consumption of the grass pea was subsequently stopped at the end of 1942 and no new cases were thereafter reported (Kessler, 1947).

Other illustrative examples include outbreaks of lathyrism on the Indian sub-continent and in Ethiopia. In India, the disease historically has been mainly confined to Uttar Pradesh, Madhya Pradesh (where Acton identified the presence of 60,000 cases) and Bihar.
(Acton, 1922; Dwivedi, 1989). In these settings, lathyrism has occurred mostly among small land-holders and farmers who cultivate grass pea. In Bangladesh, a large producer and consumer of the grass pea, especially in the northwest of the country, the prevalence rates of lathyrism have fluctuated in proportion to the production and consumption of the grass pea. Low prevalence rates (0.48%) of lathyrism during the period 1945–1950 rose dramatically to reach the level of 66.45% during the famine period of 1971–1975 (Haque, 1989). A more recent outbreak of lathyrism has been reported in northeastern Ethiopia where drought has led to famine and excessive consumption of the grass pea (Getahun et al., 1999).

Clinical similarities between konzo and lathyrism have played an important role in identifying dietary factors in the causation of konzo. Literature from the 1930s indicates that konzo was thought to be caused by either infection or food toxins (Trolli, 1938). Decades later, epidemiological studies showed a consistent and reliable pattern of disease occurrence. Konzo occurs among populations that rely on cassava as a major crop for their subsistence. However, the disease affects mainly those whose diet is almost exclusively made of food products that derive from insufficiently processed (toxic) bitter cassava. Shortcuts in processing have often occurred in time of drought, war and/or disruption of social conditions that have forced populations to rely on insufficiently processed (toxic) bitter cassava as a staple (Rosling and Tylleskär, 2000).

For example, because of favorable weather and road conditions in the province of Bandundu during the dry season, there is increased cassava trading which in turn creates opportunities for local vendors to reduce the processing (detoxification) time for the cash crop in order to sell it quickly and massively. As a consequence, the diet of the local population becomes increasingly dominated by insufficiently processed bitter cassava. By the end of the dry season and early in the rainy season (July–November) outbreaks of konzo are reported. Similar trends in cassava trading and subsequent outbreaks of konzo have been reported months after an epidemic of Ebola had affected the same province in 1995. Increase in cassava trading and shortcuts in cassava processing were noticed months after the military roadblock that was made to quarantine populations affected by Ebola (Tylleskär et al., 1995; Banea et al., 1997a,b; Tshala-Katumbay et al., 2001a). In Mozambique, particularly in the northern regions, outbreaks of konzo (mantakassa) have been associated with famine and severe drought (1981) and war (1992–1993) and consumption of insufficiently detoxified bitter cassava (Ministry of Health Mozambique, 1984a,b; Cliff, 1994; Cliff et al., 1997).

Because poverty and war appear to be linked to the occurrence of konzo, it is not surprising the disease persists in the DRC and neighboring countries, including Angola, Uganda and Central African Republic, all theaters of armed conflict.

18.2.3. Prevalence, age and gender distribution

While isolated cases of lathyrism and konzo may occur, they usually appear in epidemic form. In recent times, prevalence rates of lathyrism have been as high as 66.45%, particularly during the famine period (1971–1975) in northwest Bangladesh (Haque, 1989). While outbreaks are now rare, living cases of lathyrism are found in Bangladesh, China, Ethiopia, Eritrea, India and Spain, the latter occurring during the Spanish Civil War when food was scarce (Spencer, 1994).

As of 2004, the total number of cases of konzo has been estimated to be as high as 100,000, with most of the cases occurring in regions of sub-Saharan Africa (Cassava Cyanide Diseases Network, 2004). Accurate regional prevalence rates (perhaps as high as 5%) are difficult to obtain because of fluctuating and unreliable demographic data (Rosling and Tylleskär, 2000).

Both lathyrism and konzo affect individuals across the span of postnatal life except that neither disease has been reported in children under 2 years of age. These two diseases show differential patterns of gender and age susceptibility that are difficult to explain. In the case of lathyrism, young males are commonly and more severely affected than young females, and this differential gender sensitivity appears to be related to factors other than grass pea intake (Spencer et al., 1984). Women tend to develop lathyrism before puberty, during pregnancy or after menopause (Dwivedi, 1989). However, in the case of konzo, young males and females seem to be similarly affected, while women of childbearing age are more susceptible to the disease than men of the same age (Tylleskär et al., 1995). As a result, women tend to be more affected in konzo-affected areas, whereas male cases predominate in lathyrism areas. Whether this impression reflects the true population distribution of these diseases is unknown since the two conditions occur in distinctly separate regions that have not been subjected to a comparative epidemiology survey. Population and individual genetic susceptibilities have not been looked for and cannot be ruled out.

18.3. Clinical picture

The most prominent signs of both lathyrism (Fig. 18.2(A)) and konzo (Fig. 18.2(B)) are symmetrical postural abnormalities and spastic (cross-legged or
lathyrism or konzo: independently developed epidemiological criteria for clinically indistinguishable as evidenced by the following diseases is so uniform that the two entities may be clinically indistinguishable as evidenced by the following independently developed epidemiological criteria for lathyrism or konzo:

(a) Lathyrism: (1) a history of heavy ingestion of Lathyrus sativus or other neurotoxic Lathyrus sp for at least 2 weeks prior to and at the time of acute or subacute onset of walking difficulty, (2) a largely symmetrical and pyramidal distribution of leg weakness, with exaggerated thigh adductor, patellar and ankle reflexes, in the presence or absence of ankle clonus and extensor plantar reflexes bilaterally, (3) an essentially normal sensory examination, and (4) intact mentation, cerebellar and cranial nerve function (Gopalan, 1950).

(b) Konzo: (1) a heavy reliance on cassava as staple food, (2) abrupt onset (<1 week) of leg weakness and a non-progressive course of the disease in a formerly healthy person, (3) a symmetric spastic abnormality when walking and/or running, and (4) bilaterally exaggerated knee and/or ankle jerks without signs of disease of the spine (WHO, 1996).

The main criteria for differential diagnosis of lathyrism and konzo are geographic and nutritional. Whereas konzo has been reported only in sub-Saharan Africa in association with dietary dependence on cassava, lathyrism has occurred on many continents with use of grass pea as a staple. In Africa, lathyrism seems to be restricted to the Horn, notably Ethiopia and Eritrea. The clinical manifestations of lathyrism and konzo are almost identical, although there is a tendency for konzo to be a more severe upper motor neuron disorder with clinical evidence of pyramidal deficits in both upper and lower extremities (Ludolph et al., 1987; Spencer, 1994; Tshala-Katumbay et al., 2001a,b). Both diseases affect the poorest of the poor because of their dependency on single inexpensive staples, and minimal nutrition or malnutrition is common and possibly necessary for florid disease to emerge. Excessive physical activity is often reported at onset and may be a predisposing factor that stresses the motor pathway and promotes cortical motor neuron susceptibility to the plant-derived toxins in cassava and grass pea.

18.3.1. Prodromal phase

During the prodromal phase, subjects affected by lathyrism or konzo experience mainly motor symptoms such as a sensation of leg weakness, heaviness or stiffness; muscle cramping usually confined to calf musculature and tremulousness. Acutely reversible sensory symptoms are often reported and may include paresthesia, numbness, muscle aching and a sensation of electrical discharge (Lhermitte’s sign) in the back and legs. Urological involvement is not common. Blurred vision and difficulties in swallowing have been occasionally reported in konzo. Clinical deficits are usually greater at the onset of the disease and the subject may be bedridden. Once the course of the disease has stabilized, deficits are mainly confined to the motor system. The most noticeable feature is the cross-legged (scissoring) gait of affected subjects who are able to walk and/or run.

18.3.2. Neurological examination

On physical examination, the main clinical picture consists of an isolated symmetric spastic paraparesis. Deep tendon reflexes of the lower limbs are exaggerated and extensor plantar responses can be elicited in most cases when patients are tested in the recumbent position. Ankle clonus is frequently found. Upper extremities also show pathological reflexes in severely affected subjects, with palmo-momental and superficial abdominal reflexes often present in konzo and the former rarely in lathyrism (Ludolph et al., 1987; Spencer, 1994; Tshala-Katumbay et al., 2001a,b). Severely affected subjects may show a spastic tetraparesis associated with weakness of the trunk. In some cases, exaggerated tendon reflexes can occur as an isolated feature in the absence of functional deficit such as muscle weakness. Disuse muscle atrophy may be seen. Cognition, hearing, coordination and sensory function, as well as urinary, bowel and sexual functions, remain normal (Ludolph et al., 1987; Tshala-Katumbay et al., 2001a,b).

Subjects affected by konzo may also present with pseudobulbar signs – not reported in lathyrism – that mainly consist of speech and/or swallowing problems. These signs are often encountered in severe cases. The longest motor tracts are consistently involved before and to a greater extent than shorter ones. Thus, subjects with speech and/or swallowing problems always show pathological reflexes in severely affected legs and arms. A subject with signs in the arms (weakness, increased deep tendon reflexes or Hoffman’s sign) will always have pronounced...
spasticity of the lower extremities (Tylleskär et al., 1995; Tshala-Katumbay et al., 2001a,b).

Degrees of severity of the disability, often inappropriately referred to as stages, vary from mild to severely affected subjects. Based on the ability to walk, the following classification has been proposed:

- Lathyrisn: mild form (Acton’ no stick-stage or stage I) represents subject with mild spastic gait with no need for a walking stick, complaints of increased leg stiffness, brisk deep tendon reflexes at knee or ankle and Babinski’s sign equivocal or present. The moderate form (Acton’ 1-stick stage or stage II) represents subject with spastic gait that requires the use of a stick for support during ambulation, mild rigidity and increased deep tendon reflexes and ankle clonus and Babinski sign present. The moderately severe form (Acton’ 2-stick stage or stage III) presents with severe spastic gait that requires the use of two sticks for support during ambulation, crossed adductor gait, markedly increased deep-tendon reflexes with clonus at ankle and knee and Babinski’s sign present. The severe form (Acton’ crawler stage or stage IV) represents crawling, wheelchair-bound or bedridden state. Subject shows extreme muscle rigidity and has completely lost use of his legs (Acton, 1922; Spencer, 1994).
- Konzo: mild form represents subject able to walk without support, in the moderate form the subject has to use one or two sticks, and in the severe form the subject is unable to walk (WHO, 1996).

With cessation of exposure to cassava, spasticity remains largely stable across the lifespan, with painful calf muscle spasms representing an ongoing major symptom. Very few subjects with konzo may suffer a sudden second aggravating episode, which is in fact an episode identical to that experienced at the initial onset of the disease.

The spastic para/tetraparesis that characterizes konzo may be associated with other signs. Ophthalmologic studies have shown konzo patients with bilateral optic neuropathy in addition to their para/tetraparesis. This condition encompasses visual impairment, temporal pallor of the optic discs and defect of visual fields. A pendular nystagmus has also been reported in few cases. The presence of visual symptoms at disease onset and/or optic neuropathy on subsequent examination seems to not be correlated with the severity of konzo (Mwanza et al., 2003a,b).

There is evidence of another cassava-associated neurological disorder that develops in older subjects who have a heavy intake of incompletely detoxified cassava. The typical pattern is a slowly evolving ataxic neuropathy with or without evident pyramidal deficits, as well as occasional visual and sensorineural auditory deficits. The disorder was first reported in Nigeria (Osuntokun, 1973) and more recently in Kottayam District, Kerala, India, where patients are reported to improve with a nutritious diet (Madhusudan, personal communication, World Congress of Neurology, Sydney 2005). Other neuromuscular syndromes that have been reported in association with cassava dependency include a ‘motor neuron–cerebellar–Parkinson–dementia’ syndrome among Nigerians (Osuntokun, 1981), proximal myopathy and a movement disorder resembling ballism among Indians (Madhusudan, personal communication, World Congress of Neurology, Sydney 2005). Extrapyramidal disorders of this type are seen in subjects with mildewed sugarcane poisoning, which raises the question of fungal contamination of food in cassava-associated cases with ballistic movement disorders (Ludolph et al., 1991). Other conditions that have been associated with cassava dependency include thyroid dysfunction and growth stunting, and a Type 3 (tropical) diabetes mellitus (Ihedioha and Chineme, 1999; Rosling and Tylleskär, 2000; Mbanya et al., 2003). Indian cases with cassava-associated ataxic neuropathy reportedly do not present with diabetes.

18.4. Ancillary investigations

18.4.1. Clinical chemistry

The clinical chemistry profile of lathyrisn has not been reported. Studies on konzo have focused on understanding underlying nutritional and metabolic factors and levels of exposure to the culpable cyanogenic compounds in cassava. Serum levels of albumin and pre-albumin (indicators of protein nutritional status), and urinary sulfate – reflecting the dietary intake of sulfur-containing amino acids needed to convert cyanide (CN) to thiocyanate (SCN) – are usually below normal reference values in most of the subjects affected by konzo. Serum and urinary levels of SCN may reach values as high as 1000–1500 µmol L⁻¹. However, these biochemical values remain non-specific to konzo subjects and may also be found in apparently normal subjects living under the same conditions in zones endemic for the disease. SCN has been the most useful chemical biomarker for cassava cyanogenic exposure because (a) cheap, specific and sensitive determination methods are available, (b) it is a very stable metabolite and urinary samples do not need to be frozen and (c) it has a slow urinary excretion with a half-life in serum of 1 of 3 days; thus, urinary levels of SCN reflects almost the mean daily SCN load during preceding days. Other analytical methods exist to measure levels of the
minor cyanide metabolite aminothiazoline-carboxylic acid in urine and/or cyanate (OCN) in plasma (Lundquist et al., 1979, 1983, 1993, 1995; Rosling, 1994; Spencer, 1999). These methods could potentially be used to study the relationship between cassava cyanogenic exposure and occurrence of neurological disease. There is no biological marker for lathyrism.

**18.4.2. Electrophysiology**

Comprehensive electrophysiological testing (Table 18.1) has been performed on subjects with lathyrism or konzo mainly to assess the functional integrity of motor pathways. Magnetic or electric stimulation of the motor cortex has been used to assess the motor pathways subserving the upper and lower extremities. Additional investigations have included peripheral nerve conduction studies (NCS) and conventional needle electromyography (EMG), evaluation of somatosensory evoked potentials (SEP) and visual evoked potentials (VEP) and electroencephalography (EEG). Because of the paucity of data using morphologic (neuropathologic) and imaging techniques, electrophysiological testing has provided a major contribution to the understanding of the lesion in lathyrism and konzo.

**18.4.2.1. Studies of peripheral nerve conduction and electromyography**

Most subjects with lathyrism or konzo have normal motor and/or sensory peripheral nerve conduction.

<table>
<thead>
<tr>
<th>Table 18.1</th>
<th>Comparative clinical electrophysiology in lathyrism vs. konzo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lathyrism</strong></td>
<td><strong>Konzo</strong></td>
</tr>
<tr>
<td><strong>Causal factors</strong></td>
<td>Heavy dietary reliance on Grass pea (<em>Lathyrus sativus</em> sp.). Minimal nutrition possibly necessary for florid disease to emerge. Toxic candidate: (β,N-oxalylamino-L-alanine (see pathogenesis).</td>
</tr>
<tr>
<td><strong>Main clinical picture</strong></td>
<td>Spastic para/tetraparesis.</td>
</tr>
<tr>
<td><strong>MEP studies</strong></td>
<td>Increased stimulation strength needed to trigger a volley.* Frequent inability to elicit MEP. When present, central motor conduction time is increased.**</td>
</tr>
<tr>
<td><strong>Peripheral nerve conduction studies</strong></td>
<td>Normal motor and sensory nerve conduction. Evidence of deficits has been found in a minority of subjects with long-standing disease (probably unrelated disorders such as poliomyelitis, diabetes mellitus).</td>
</tr>
<tr>
<td><strong>SEP studies</strong></td>
<td>Cortical responses following tibial stimulation frequently absent. If present, the latency is prolonged. Median SEP normal.</td>
</tr>
<tr>
<td><strong>VEP studies</strong></td>
<td>Not available.</td>
</tr>
<tr>
<td><strong>EEG studies</strong></td>
<td>Not available.</td>
</tr>
</tbody>
</table>

* Consistent with reduction of the upper motor neuron pool. ** Consistent with loss of pyramidal conductivity from spinal tract (axonal) damage.
Electrophysiological deficits have been noticed in only a few subjects with lathyrism, and these are likely to be related to supervening factors such as malnutrition or diabetes. Approximately 7% of a large cohort of Rumanian Jews with lathyrism showed evidence of sensorimotor neuropathy and signs of muscle denervation almost 30 years after the onset of the disease (Cohn et al., 1977; Cohn and Streifler, 1981a,b; Drory et al., 1992). Similar abnormalities were reported in six of 14 Bangladeshi subjects with 9–13 years of lathyrism. Two of 10 subjects who developed lathyrism 45 years earlier had peripheral neuropathy (Hugon et al., 1990, 1993; Gimenez Roldan et al., 1994). Etiologies unrelated to lathyrism (diabetes, malnutrition) often account for the presence of peripheral neuropathy.

In konzo, F-waves in legs often display high amplitude, presumably reflecting disinhibition at the level of the anterior horn cell. Only limited needle EMG has been done in konzo. Spontaneous activity has not been recorded in the examined muscles. In several muscles the motor unit potentials were small in amplitude and/or duration without an increase of polyphasic potentials. These minor changes may be explained by disuse atrophy seen in the patients (Karin Edebol Eeg-Olofsson, personal communication).

**18.4.2.2. Motor evoked potential (MEP) studies**

The integrity of motor pathways was investigated in 14 Spanish subjects with long-standing lathyrism (> 40 years) using techniques of transcranial magnetic stimulation with separate spinal cathodic stimulation at the cervical level (C6) for upper limbs and thoracic level (T12) for lower limbs (Hugon et al., 1993). Transcranial electrical stimulation was used to study the motor pathway of 14 Bangladeshi subjects with stable lathyrism (duration of disease: 9–13 years) (Hugon et al., 1990).

For konzo, investigations were performed on Congolese subjects using either electrical unifocal scalp stimulation in 21 subjects (duration of konzo: 2–11 years) or transcranial magnetic stimulation in 15 subjects (duration of disease: 1–18 years) and two Tanzanian subjects (duration of konzo: 6 years) (Tylleskär et al., 1993; Tshala-Katumbay et al., 2002b).

Magnetic and electrical stimulation methods show that most subjects with konzo or lathyrism have abnormal motor evoked potentials (MEP). Common abnormalities include either the absence of responses in lower limbs or a prolonged central conduction time (delayed responses). Another major electrophysiological finding consisted of MEP abnormalities in upper limbs of subjects with konzo. Although more clinically affected in lower limbs, MEP studies revealed an absence of responses, even in apparently clinically preserved upper limbs. A similar abnormality (delayed MEP) has been found in a subject with lathyrism during the aforementioned study, although other subjects showed brisk tendon reflexes and the Hoffman sign.

MEP deficits were markedly increased in Spanish patients with severe form (grade III or IV) of lathyrism whereas such a correlation has not been found among subjects with konzo.

The significance of MEP abnormalities, together with normal peripheral nerve conduction, demonstrates (a) a selective dysfunction of the upper motor neuron system both in konzo and lathyrism, and (b) the possibility of a presynaptic cortical failure especially because magnetic stimulation revealed abnormalities in apparently preserved upper limbs. These findings also raise the possibility of a common pathogenetic mechanisms for lathyrism and konzo.

**18.4.2.3. Somatosensory evoked potential (SEP) studies**

Objective sensory deficit is not observed in either lathyrism or konzo. However, sensory symptoms such as paresthesia, pain and a sensation of electrical discharge in the legs may be present at the onset of the disease; these symptoms usually dissipate within weeks of onset (Spencer, 1994; Tshala-Katumbay et al., 2001a,b). Electrophysiological testing has revealed frequent abnormalities of tibial SEP (in lathyrism and konzo) and much less frequent abnormalities of the median SEP (and only in konzo). The main abnormality consists of absence of cortical responses after stimulation of posterior tibial nerve. Most patients have normal absolute latencies to both cervical and lumbar levels. Increased central sensory conduction time through the spinal cord is common in patients with prolonged latencies of cortical evoked potentials (Hugon et al., 1990; Tshala-Katumbay et al., 2002a).

The frequent tibial SEP abnormalities and associated history of sensory symptoms in the legs at disease onset suggests that somatosensory pathways are subclinically involved in lathyrism and konzo. Mechanisms underlying these SEP abnormalities, also commonly found in other motor neuron diseases, are unknown. They may indicate a more widely distributed lesion in the nervous system, with the motor system being predominately affected; reflect the impact of motor system dysfunction on the input and output pathways of the somatosensory system without any structural or functional alterations of these pathways; or they may be attributed to other causes such as nutritional deficiencies.

**18.4.2.4. Visual evoked potential (VEP) studies**

Visual deficits are peculiar to cassava-associated disease and are not reported in lathyrism. A study of VEP
in 23 Congolese konzo subjects (duration of disease: 2–25 years) was conducted to investigate the nature of ophthalmologic manifestations often reported in konzo. Latencies of the P100 VEP-component and peak-to-peak amplitude of N75-P100, for each eye, were compared with values recorded in 38 apparently healthy subjects who served as a reference group. About half (11) of 23 konzo subjects showed symmetrical abnormalities of VEP consisting of both prolonged latency and decreased amplitude. There was no correlation between VEP abnormalities and the severity of the disease. These abnormalities, together with the spastic paraparesis in konzo, may well result from intoxication by cassava cyanogens and/or their neurotoxic metabolites, including free cyanide (Tylleskär et al., 1993; Mwanza et al., 2003a,b).

18.4.2.5. Electroencephalography
Standard EEG recordings have been performed on 21 konzo patients aged 10–49 years (disease duration: 2–11 years). These cases had no history of seizures, skull trauma, loss of consciousness or cognitive problems. However, they showed significant EEG abnormalities of which the main abnormality was a generalized slowing (θ rhythm) of background activity. In severely affected subjects, non-specific paroxysmal activity and decreased frequency of the post-central background rhythm occurred in addition to generalized slowing. Some patients had focal slowing of the background activity with a dominant distribution in the frontal areas. Generalized EEG abnormalities were more frequent in severe cases. Whether these abnormalities are intrinsic to the disease process of konzo is unknown. Plausibly, malnutrition and exposure to cyanogenic compounds in konzo-affected areas may interfere with thyroid function and thus brain development and/or function with consequences seen at EEG (Tshala Katumbay et al., 2000). There are no reports on EEG recordings in subjects affected by lathrysim.

18.5. Imaging
A study using magnetic resonance imaging (MRI) on two Tanzanian konzo subjects has revealed no abnormalities (Tylleskär et al., 1993). MRI has not been performed on subjects with lathrysim.

18.6. Pathology
Neuropathological data on lathrysim and/or konzo are rare and incomplete. A study of the brain of a subject who developed lathrysim 31 years prior to his death showed loss and shrinkage of pyramidal neurons in the upper part of the precentral gyrus (Filiminoff, 1926). Most neuropathological studies, which have focused on the spinal cord, show predominantly distal symmetrical degeneration of lateral and ventral corticospinal tracts, sometimes with distal degeneration of spinocerebellar and gracile tracts (Buzzard and Greenfield, 1921; Filiminoff, 1926; Puis and Devinals, 1943; Sachdev et al., 1969; Hirano et al., 1976; Striefler et al., 1977). An autopsy report on a man who developed the disease 32 years prior to death showed anterior horn cells with Hirano bodies but no reduction of the lower motor neuron pool (Hirano et al., 1976).

The two reported autopsies of konzo cases are of little value: one limited to the brain revealed punctate hemorrhages and cerebral edema 3 hours post-mortem; the other showed no abnormalities in the spinal cord (Trolli, 1938).

It is difficult with these sparse reports to determine the primary site of the lesion in either lathrysim or konzo, but evidence from clinical and electrophysiological studies indicates these are diseases mainly confined to the upper motor neuron and thus comparable to primary lateral sclerosis (PLS). There is no evidence to support the suggestion that lathrysim progresses to involve the lower motor neuron, the final picture resembling amyotrophic lateral sclerosis (ALS). Muscle biopsies in five konzo subjects with small motor unit potentials on EMG revealed minor non-specific fiber atrophy, presumably due to muscle disuse (Karin Edebol-Eeg Oloffson, personal communication).

18.7. Pathogenesis
Clinical and neurophysiological studies of human lathrysim and konzo show these two diseases to be remarkably similar. One of the striking similarities, apart from the clinical picture and the abnormalities of motor evoked potentials, is that physical exertion appears to be an important triggering factor for the disease. Many subjects affected by lathrysim or konzo report intense physical activity (e.g. prolonged walking or bicycling) prior to a sudden onset of walking difficulties that eventually progressed into stable disease states. Whether these similarities underlie a common pathogenetic mechanism for lathrysim and konzo remains enigmatic.

18.7.1. Lathrysim
The link between lathrysim and excessive consumption of the grass pea by humans or domestic animals (e.g. ducks, geese, hens, peacocks, pigs, oxen, sheep, cows, bullocks, elephants and horse) has been known for centuries (Sleeman, 1844; Stockman, 1917; Sugg et al., 1944; Selye, 1957; Gardner and Sakiewicz, 1963). Several experimental studies have attempted to reproduce
the disease in animals. A study in the horse, allegedly the most susceptible species, indicated that a diet made exclusively of *L. sativus* precipitated signs after 10 days. Horses fed only 1–2 quarts per day succumbed after 2–3 months, and neurological manifestations appeared a month or more after the diet is withdrawn (Stockman, 1929). There have been several attempts to model human lathyrism in primates. Stockman (1917) claimed success, but details of his methods and results are not available. Rao et al. (1967) reported the induction of either flaccid or spastic paraplegia in macaques after intrathecal administration of synthetic β-N-oxalyl-

lamino-L-alanine (BOAA), the major neurotoxic compound extracted from the grass pea.

Other studies have shown that monkeys fed grass pea, plus an extract thereof, for up to 15 months, developed a spastic paraparesis (Srinavassa Rao and Roy, 1981). Signs of pyramidal dysfunction resembling the early phase of human lathyrism were demonstrated in well-nourished cynomolgus monkeys fed a fortified diet of pure *L. sativus* plus daily oral gavage with an alcoholic extract of grass pea, for a total daily intake of 1.1–1.4 g of BOAA/kg body weight (Spencer et al., 1986, 1988). Additional animals on a control diet of chickpea (*Cicer arietinum*) that was matched for protein, carbohydrate, fat, mineral and vitamin content, were given either pure BOAA (300 mg kg⁻¹ per day, increasing by 300 mg kg⁻¹ every 15 days) or an alcoholic extract of BOAA plus pure synthetic BOAA. The animals developed comparable neurological signs after 2–4 weeks (300 mg kg⁻¹ per day, increasing by 300 mg kg⁻¹ every 15 days), 2–6 weeks (alcoholic extract of BOAA plus pure synthetic BOAA) and 3–10 months (alcoholic extract of BOAA plus grass pea diet). Affected monkeys showed a variable combination of neurological signs including fine tremor, periodic myoclonic-like jerks, mild-to-moderate increase in muscle tone of leg muscles, hind limb extensor posturing and a skater-like gait. The most severely affected monkey showed exaggerated patellar reflexes, crossed thigh adductor reflexes, bilateral extensor plantar reflexes and hind limb withdrawal after downward stroking of the tibia. Arm functions and skilled finger movements appeared to be intact. There was no sign of sensory dysfunction, cerebellar, cranial nerve or urological involvement. Neurological improvement occurred after cessation of grass pea administration. Both groups of BOAA-treated animals showed increase in central motor conduction time following transcranial (motor cortex) electrical stimulation. However, neuropathological studies showed no evidence of neuronal degeneration in motor cortex or spinal cord. These studies suggest (a) prolonged exposure to BOAA induces a pattern of motor neuron disease reminiscent of human lathyrism, (b) clinical signs consistent with neuroexcitation (myoclonus) occur early in primate lathyrism, as in the human disease, (c) early functional improvement is seen in both species and, by extrapolation, (d) BOAA is likely the key etiological agent in human lathyrism. Pharmacological effects of this potent excitatory amino acid may precede the onset of neuronal degeneration and account for reversible components of the disease. Studies with BOAA-doses animals subject to malnourishment or excessive physical exercise have not been performed. It is possible that BOAA is a potent neurotoxin that may be largely excluded from the central nervous system in well-nourished subjects. Perhaps leakage of the blood–brain regulatory interface in association with poor nutrition or harsh exercise accounts for the sudden onset of disease in some cases.

The mechanism of action of BOAA appears to involve excessive neuronal stimulation (Watkins et al., 1966; Olney et al., 1976; Pearson and Nunn, 1981; MacDonald and Morris, 1984; Ross et al., 1987; Bridges et al., 1989; Riepe et al., 1995). Experimental studies show that BOAA (Fig. 18.4(A, B)) is both a potent glutamate agonist at alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors and an inhibitor of glutamate uptake in synaptosomal preparations (Spencer, 1999). Recent study indicates that BOAA neurotoxicity in vitro may also be partially mediated by activation of group I metabotropic glutamate receptors by an indirect mechanism (Kusama-Eguchi et al., 2004). Taken together, these observations suggest that BOAA induces neuronal degeneration as a