A geographical cluster of konzo in Tanzania

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Summary

Konzo, an upper motor neuron disease, was diagnosed in 116 subjects in a community-based survey of 28,500 inhabitants in the Tarime District in Tanzania. All cases had a uniform clinical picture with isolated non-progressive paraparesis of abrupt onset identical to the findings in earlier studies of konzo. The fishing population along Lake Victoria was not affected but farming villages only 5 km from the shore had a maximum prevalence of 14 per 1000 inhabitants. New cases of konzo have occurred annually since 1979 but 62% were affected during an epidemic at the end of a drought in 1985. The geographical and temporal distribution is compatible with the proposed dietary aetiology of cyanide exposure from insufficiently processed cassava roots as the main factor. Other toxic-nutritional factors may also be involved. An aetiological role of HTLV-I has earlier been excluded and the exclusion of the fishing population makes an involvement of another type of infectious agent unlikely.

Résumé

Konzo, une affection du neurone moteur supérieur, a été diagnostiqué chez 116 malades parmi les 28,500 habitants du district de Tarime en Tanzanie. Tous les cas étaient présentés une symptomatologie unifiée caractérisée par la survenue brutale d’une paralysie spasmodique isolée et non-progressive, identique à celle rapportée dans des études antérieures du konzo. La population de pêcheurs au bord du lac Victoria n’était pas touchée par le konzo mais dans les villages agricoles, à une distance de 5 km sur une prévalence maximale de 14 sur 1000 habitants. Des nouveaux cas de konzo sont survenus annuellement depuis 1979 mais 62% des cas ont été affectés pendant une flambée épidémique à la fin d’une sécheresse en 1985. La distribution géographique et temporelle est compatible avec une étiologie alimentaire propo­sée ayant comme facteur principal l’exposition au cyanure. Cette ingestion de cyanure provient des racines amères de manioc insuffisamment préparées. D’autres facteurs d’ordre toxico-nutritionnel peuvent être impliqués mais l’épargnement de la population de pêcheurs parle contre une étiologie infectieuse, comme par le HTLV-I.

Resumen

Konzo es una enfermedad de la motoneurona superior descrita en África. En el presente estudio se diagnosticaron 116 pacientes con konzo en un estudio de prevalencia en una comunidad de 28,500 habitantes en el Distrito Tarime de Tanzania. Todos los pacientes presentaban un cuadro clínico similar caracterizado por la presencia de una paraparesia no progresiva de comienzo abrupto, sin otro compromiso neurológico, similar a la descrita en estudios previos del konzo. Se encontraron casos en las poblaciones de pescadores de las orillas del Lago Victoria. Sin embargo, en las comunidades agrícolas situadas tan sólo a 5 km del lado las cifras de prevalencia alcanzaron valores hasta de 14 por 1000 habitantes. Nuevos casos de konzo continuán presentándose anualmente desde 1979, pero el 62% de los casos ocurrieron en forma epidémica hacia el final de la sequía de 1985. La distribución geográfica y temporal de los casos es compatible con la hipótesis de que el konzo se debe a una posible causa dietética cuyo factor etiológico más importante es la exposición al cianuro por la dieta exclusiva de tubérculos de la yuca (mandioca o casava) procesada en forma inadecuada. Otros factores tóxicos nutricionales pueden también intervenir. Anteriormente se demostró que el retrovirus HTLV-I no juega un papel etiológico en casos de konzo. Por otra parte, la ausencia de la enfermedad
en las poblacioness pesqueras estaría en contra de una etiología infecciosa.

Introduction

Recent reports from three African countries strongly indicate that konzo is a distinct form of upper motor neuron disease\(^1\)\(^-\)\(^3\). Konzo is named after the local designation in the first reported epidemic\(^4\). The disease is characterized by an abrupt onset of isolated and permanent but not progressive spastic paraparesis. The paralysis is always symmetrical, but may vary in severity from mild gait difficulties to a severe paralysis of the legs, the trunk, and occasionally the arms. The most severely affected subjects may in addition have dysarthria and visual disturbances\(^5\).

Lathyrism is the disease most similar to konzo, but there is no evidence for the consumption of *lathyrus sativus* in any of the konzo-affected populations\(^6\). Konzo has been attributed to several weeks of almost exclusive consumption of cassava roots that because of short cuts in processing have high remaining amounts of cyanogen substances. It has been postulated that the resulting dietary cyanide exposure in combination with low intake of sulphur needed for detoxification selectively damages the upper motor neurons through some mechanism\(^7\).

A clinical study of konzo during an outbreak in the Tarime District of Tanzania in 1985 suggested that the epidemic was related to prolonged drought. This study in combination with dietary and laboratory results supported a causative role of cyanide in konzo\(^8\). An infectious cause has also been proposed\(^9\), but konzo differs clinically from the progressive form of spastic paraparesis induced by HTLV-I infection. The 39 konzo cases studied earlier in Tarime District were all seronegative to HTLV-I\(^1\) as were all konzo cases earlier studied in other areas\(^2,3,9\).

We have surveyed the population in the northern part of Tarime District for locomotor disabilities four years after the konzo epidemic to determine if the geographical and temporal distribution of konzo fitted the proposed toxico-nutritional aetiology or if the occurrence of the disease suggested the involvement of an infectious agent.

Methods

Tarime district is situated in northern Tanzania and borders Kenya. The study area in the dry northern part is on the shore of Lake Victoria. It is inhabited by the Luo tribe and has, compared to other parts of rural Tanzania, a fairly dense population with about 70 inhabitants per km\(^2\). The study area has relatively homogeneous agro-ecological characteristics with a landscape varying between 1100–1200 m above sea level in the fishing villages along the shore of Lake Victoria. Some hills reach 200 m higher in the inland villages where the population depends on farming in spite of a relatively low soil fertility. The inhabitants live in large villages created during the villagization programme in the mid-70s, and during the last decades cassava has become both their main staple and their cash crop. They mainly grow bitter cassava varieties that were introduced in 1979–1980 because of high yields and drought tolerance. Before consumption the cyanogen substances are normally removed from these roots by processing, as described elsewhere\(^9\).

We surveyed the 15 northern villages in the district (Figure 1) in April 1989. The number of inhabitants in each village was obtained from local census records and rounded to the nearest hundred. With informed consent and assistance from village leaders and village health workers, all subjects with gait difficulties were identified in each village and examined in their homes by a physician (WPH, HR). Subjects with non-neurological locomotor disorders such as arthritis, skeletal deformities, and rickets were excluded. With a pretested questionnaire each subject was asked in Lou through an interpreter about type of onset, place of residence at onset, the course of the disease, and possible occurrence of subsequent attacks. The year and month of onset of paralysis was determined by the use of a local event calendar. Women in a fertile age were also asked about how the onset related to pregnancies and breast feeding. Abnormalities of gait and running, number of walking sticks in regular use, and speech abnormalities were observed. The clinical and neurological examination was mostly carried out in the sitting position.

The criteria for a diagnosis of konzo\(^1\) were as follows: (1) the presence of a visible symmetrical spastic abnormality of gait and/or running; (2) a history of distinct onset in time in a previously healthy person; (3) non-progression; and (4) the presence of bilaterally exaggerated tendon reflexes in the legs. A clinical diagnosis was also made for persons suffering from other neurological diseases causing gait difficulties, and when necessary they were referred to Shirati Hospital for treatment.

Monthly rainfall data from 1960 to 1990 was obtained from Shirati Hospital.

Results

In the 15 villages surveyed we identified 208 subjects with neurological locomotor disabilities, of whom 116 fulfilled the criteria for konzo (Table 1).
Five subjects with konzo who lived just outside the study area at the time of the survey were included as they had lived in the study area at the onset. Two konzo patients who were temporarily staying with relatives in shore villages, but who had lived in villages east of the study area at the time of onset, were excluded. Excluded also were two earlier verified patients with konzo in inland villages who had died before the survey and seven persons suspected of having konzo in inland villages who had either moved from the study area or who were unavailable for examination for other reasons. A further six subjects in inland villages presented a history of abrupt onset of mild spastic gait problems typical for konzo; they had bilaterally exaggerated leg reflexes but were excluded because they had no visible disturbance of gait or running at the time of examination. The semi-urban community surrounding Shirati hospital was not surveyed since it was well known that none were affected by konzo in this population that consisted of mainly hospital staff.

A total of 91 subjects with gait difficulties were found to have other neurological disorders that are listed in Table 1. The sequelae of poliomyelitis was diagnosed in 59, of whom 24 had right and 21 had left lower limb paralysis; the others had combined

Table 1. Number of persons with neurological locomotor disabilities in the shore and inland villages

<table>
<thead>
<tr>
<th></th>
<th>Shore villages</th>
<th>Inland villages</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of villages</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Population</td>
<td>9400</td>
<td>19,100</td>
</tr>
<tr>
<td>Konzo</td>
<td>11</td>
<td>105</td>
</tr>
<tr>
<td>Polio sequelae</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Paraparesis</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Quadriplegia</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Polyneuritis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>157</td>
</tr>
</tbody>
</table>
forms of paralysis. No case of polio had an onset after 1983, when vaccination was started. Of those with hemiparesis three had an infantile onset. The differential diagnosis between konzo and other disorders was clear in all subjects seen in the shore villages. Two of the three patients with paraparesis in the shore villages were diagnosed as having tuberculosis with a typical history, gibbus and corresponding sensory level on the trunk. The third had spastic diplegia present since birth. Two of the cases with quadriplegia in the shore villages were congenital and diagnosed as cerebral palsy, and the cases with quadriplegia in the shore villages were diagnosed as having tuberculous with a typical history, gibbus and corresponding sensory level on the trunk. The third had spastic diplegia present since birth. Two of the cases with quadriplegia in the shore villages were congenital and diagnosed as cerebral palsy, and the third had resulted from a severe acute cerebral infection in infancy. A case of sensory neuropathy of five month's duration was seen in a shore village in a 65-year-old woman, and a relapsing post-inflammatory polyneuritis was diagnosed in a 12-year-old girl.

In inland villages the differential diagnosis of konzo was difficult only in four cases. A 28-year-old man with spastic paraparesis, weakness in the arms, and dysarthria since 1986 was not diagnosed as having konzo due to slow onset and steady progression. A 10-year-old boy had permanent isolated spastic paraparesis but did not fulfil the criteria for konzo because of a very slow onset during which he lived in Dar-es-Salaam. A 47-year-old woman was unable to stand because she had severe spastic paraparesis. She had an abrupt onset in February 1989 but was not diagnosed as having konzo as she gave a clear history of successive progression during the last months. A 4-year-old boy with isolated spastic paraparesis did not fulfil konzo criteria since he was born with the disorder in May 1985. Interestingly, his mother had a first attack of konzo in 1983 and had an exacerbation one month before his birth.

Of the 116 konzo patients 67% stated that the onset occurred abruptly within one day, mostly without any other symptoms. The remaining 33% gave a history of subacute onset extending over several days. Five patients stated that they had improved slightly some months after the onset and the other 96% stated that the paralysis had remained unchanged since the onset several years earlier. Twelve patients gave a clear description of a subsequent attack that left them with an increased disability. One woman had suffered two such attacks. Konzo in one first or second degree relative was reported by 29% of the patients; an additional 12% had two or more relatives affected; and in one family four of five children had been disabled by konzo. In 11 of 13 adult women information was obtained on the relation between the onset and delivery of a baby. Only two had the onset during pregnancy; five during the first four months of breast feeding, three later during the first year of breast feeding, and one had the onset two years after delivery.

In 14% of the 116 konzo cases we observed only a spastic abnormality on running. Fifty-three per cent had a spastic gait but did not require sticks; 19% used one stick to walk, 9% used two sticks; and a further 5% were unable to stand. All had bilaterally exaggerated knee reflexes. Bilaterally exaggerated ankle reflexes were found in 92%, one had a unilaterally exaggerated ankle reflex; and the remaining 7% had normal ankle reflexes. Bilateral non-sustainable ankle clonus was noted in 17%, sustainable clonus in 67%, unilateral non-sustainable in two and non-sustainable on one side and sustainable clonus on the other side was found in three patients. Ankle clonus was absent in 9% and could not be adequate tested in three cases. Plantar reflexes were bilaterally extensor in 72%, unilaterally in one patient, and flexor in 24% and were not tested in two patients. With only one exception all of the 32% of the patients who used one or two sticks or were unable to stand had bilaterally exaggerated ankle reflexes and sustained ankle clonus, and bilateral extensor plantar reflexes were observed in all but three.

Minor difficulties in vision were reported by six patients and eight patients had spastic speech abnormalities and of these four and six, respectively, were unable to walk without support. Kyphoscoliosis was seen as a sign of trunk paralysis in severely affected cases, but no other spine abnormalities were found. Minor leg ulcers were noted in seven cases but none had abnormal sensory functions. None had oedema and only one had a small nodular goitre.

The geographical distribution given in Figure 1 shows that all inland villages were affected by konzo with a prevalence of 14 per 1000 inhabitants in the most affected village. No case of konzo was found in the population living within three km of Lake Victoria. The families of all the 11 patients with konzo who belonged to the shore villages (Table 1) were farming households and stayed more than three km from the shore in hilly parts adjacent to inland villages, as marked in Figure 1.

The age at onset versus sex distribution given in Figure 2 reveals that none had been crippled by konzo during the first two years of life. Below the age of 20 years konzo was more common in men but at higher ages slightly more women than men had been affected.

Figure 3 shows that the first incidence of konzo occurred in 1979 and was followed by a slowly increased annual incidence until the epidemic outbreak in 1985, during which 62% of the recorded cases occurred. The start of the epidemic in February 1985 followed a drought in 1984 that
continued into 1985. Figure 4 shows that the epidemic occurred in the last dry month and the first three months of the rainy season. During the other years the incidence of konzo was also slightly higher during the same season.

Discussion

The use of paramedical staff for identification of neurological diseases in epidemiological surveys is customary in developing countries. However, as diseases like konzo result in an easily observed gait abnormality of long duration, we successfully utilized village leaders in our identification process. In inland villages some subjects with other neurological locomotor diseases may have been missed as village leaders perceived the study as a search for konzo, a disease they could distinguish from other locomotor disabilities. The higher prevalence of non-konzo disabilities found in shore villages may also partly be explained by an additional intensive house-to-house search that was made along the shore to verify the complete absence of konzo in this area.

The clinical pattern of konzo was very similar to that reported from other affected areas. To distinguish konzo clinically from other causes of paralysis was easy. The proportion of the various degrees of disability was almost identical to that found in Zaire, as was the occurrence of problems of speech and vision in some of the most severe cases. The uniform clinical picture of abrupt onsets, isolated and symmetrical spastic paraparesis without any progressions but occasional occurrence of subsequent aggravating attacks, supports the view that konzo is a distinct disease entity almost exclusively affecting the function of the upper motor neurons. The clinical picture of konzo clearly differs from that of HTLV-I associated myelopathy, a disease with slow onset and progressive course. However, subclinical forms of konzo that lack a clear spastic abnormality of running are obviously arbitrarily distinguished from mild forms of the disease. If the entire population could have been examined we might also have identified more mild cases of konzo, but we believe that we did not miss any subjects with moderate or severe konzo, especially not along the shore.

The main finding of this study is the absence of konzo among the fishing population along the shore of Lake Victoria and the sharp increase of prevalence from 0 to 14 per 1000 over a distance of 5 km inland. Even four years after a major epidemic in villages five km away not one single case of konzo has been 'transmitted' to the shore.
population. This is in spite of the occurrence of frequent daily contacts in both directions between populations that belong to the same tribe. Konzo cases from inland villages have even lived for periods of time with relatives at the shore. The observed geographical distribution with restriction of konzo to farming households thus runs counter to a contagious mechanism in the disease.

This geographical distribution is identical to that of the konzo epidemic in Mozambique in 1981. The epidemic spared fishing villages along the Indian Ocean, whereas villages 10 km inland that depended exclusively on agriculture were severely affected during the drought that triggered the epidemic. The peculiar geographical distributions of these epidemics are compatible with a causative chain that starts with food shortage in a peasant population that becomes entirely dependent on toxic cassava varieties. As a consequence of the food shortage the cassava processing was shortened and the roots were consumed with high remaining amounts of cyanogen substances. The fishing populations were not severely affected by the drought as they had a supply of fish. They were not forced to consume as much insufficiently processed cassava and they also had a higher intake of sulphur aminoacid containing proteins supplying the sulphur needed for cyanide detoxification.

No case occurred in the area before 1979, when the bitter cassava variety was introduced. New cases have occurred annually since then but rainfall data clearly shows that the 1985 epidemic started at the end of a year with very low rainfall. The outbreak peaked during the first month of the rains when the dietary situation is the most difficult following a drought. The temporal and geographical distributions thus support the proposed toxico-nutritional causation with cyanide exposure from cassava as the major factor.

The absence of konzo in breast-fed children under two years of age fits with the proposed dietary aetiology, but as in earlier studies we have no explanation for the higher frequency of konzo among boys compared to girls. The finding of secondary attacks in more than 10% of the patients shows that no immunity is acquired. On the contrary, the risk for a second attack seems to be much higher in those already affected by konzo compared to the risk for a first attack in healthy subjects. This has also been found in konzo cases in Zaire as well as in other neurological diseases induced by poverty and monotonous diet. HTLV-I has already been excluded as a causative agent in konzo and we are not aware of any infectious agent that may cause the type of temporal and geographical distribution and clinical picture that is typical for konzo. The observation of one child born with spastic paraparesis by a mother who suffered an attack of konzo during the end of pregnancy suggests for the first time that a fetus may acquire konzo.

Contrary to the evidence of an early study, it was recently shown that an association between konzo and high cyanide and low sulphur intake due to almost exclusive consumption of insufficiently processed cassava also exists in Zaire. A case-control study in Zaire has also verified that blood cyanide is very high at the onset of konzo. Konzo epidemics were induced in the Bandundu region of Zaire by construction of a new road that made cassava the main cash crop. This made poor populations change the efficient traditional cassava-processing method to a dangerous short-cut method. The use of shortcuts in processing resulted in high remaining amounts of cyanogens in cassava flour. However, following only a few days' storage, these cyanogens disappear, which can explain why only the cassava-producing families were exposed. Several traditional cassava-processing methods reduce the amount of cyanogen substances to negligible levels even in roots from the most toxic cassava varieties. This explains why cassava has been used as the main staple food for many centuries.

A similar commercial mechanism, as observed in Zaire, may also have operated in the konzo epidemic in Tarime. When the drought in 1984–5 resulted in high prices of staple foods the old border trade with cassava from Tanzania to Kenya was probably intensified and may have induced shortcuts in processing. Elucidation of such practices is difficult but crucial for preventive action. Interviewed families, in this as well as earlier studies, were very hesitant to answer questions about shortcuts in cassava processing as they are regarded as shameful.

The five rural areas in Africa where konzo has been reported all have severe agro-economical problems and a rapid population growth that has resulted in an almost exclusive dependence on high-yielding bitter cassava varieties as both staple food and cash crop. Future epidemics of konzo can be expected in other areas with similar characteristics. We think the evidence for a cyanide aetiology is strong enough to urge preventive efforts. To advise populations at risk to cultivate less cassava runs counter to common sense since it is the only crop that can produce sufficient food in these areas. Prevention should focus on promotion of efficient processing, which can provide a safe food even from very bitter cassava varieties. However, further elucidation and confirmation of causal mechanisms are important, since a cyanide aetiology can be questioned for two reasons. First, because the same neurological lesion has not been described
from exposure to cyanide in other sources and second because a different neurological lesion with ataxic neuropathy also has been associated with cyanide exposure from cassava.

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