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Neuro-ophthalmologic findings in konzo, an upper motor neuron disorder in Africa

J.-C.K. MWANZA[1,5], D. TSHALA-KATUMBAY[2,3], D.L. KAYEMBE[1], K.E. EEG-OLOFSSON[4], T. TYLLESKÄR[5]

[1] Department of Ophthalmology, Kinshasa University Hospital, Kinshasa
[2] Department of Neurology, Kinshasa University Hospital, Kinshasa - Democratic Republic of Congo
[3] Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland, Oregon - USA
[4] Department of Neurosciences, Section for Clinical Neurophysiology, Uppsala University Hospital, Uppsala - Sweden
[5] Center for International Health, University of Bergen, Bergen - Norway

PURPOSE. *To investigate the neuro-ophthalmological manifestations in konzo, a non-progressive symmetric spastic para/tetraparesis of acute onset associated with consumption of insufficiently processed bitter cassava roots combined with a low protein intake.*
METHODS. *Twenty-one Congolese konzo patients underwent neuro-ophthalmological investigations including visual acuity testing, assessment of light pupillary reflexes, evaluation of ocular motility and deviation, direct ophthalmoscopy, and visual field perimetry. Objective refraction including retinoscopy and keratometry, and slit-lamp biomicroscopy were also done.*
RESULTS. *Five patients had visual impairment, and 14 had temporal pallor of the optic disc. Fourteen presented visual field defects, the most frequent being concentric constriction and peripheral defects. Overall, 11 subjects had symptoms qualifying for the diagnosis of optic neuropathy. Two had spontaneous pendular nystagmus in primary position of gaze. Visual field defects and pallor of the optic discs were found in mild, moderate and severe forms of konzo. No correlation was found between the severity of the motor disability of konzo and the extent of visual field loss.*
CONCLUSIONS. *Konzo was associated with optic neuropathy and a few patients had nystagmus. Although the etiopathogenesis of this optic neuropathy remains to be elucidated, the symmetry of the involvement suggests a toxic origin. We suggest that cyanide causes the neuro-ophthalmological damage in konzo. However, the optic neuropathy in konzo patients does not resemble the features of the epidemic optic neuropathy in Tanzania, Cuba or Nigeria, Leber's hereditary optic neuropathy, tobacco amblyopia or vitamin B deficiency. (Eur J Ophthalmol 2003; 13: 383-9)*

KEY WORDS. *Konzo, Motor neuron disorder, Cassava, Cyanide, Optic neuropathy*

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INTRODUCTION

Konzo is an upper motor neuron disorder reported in rural areas of the Central African Republic (1), the Democratic Republic of Congo (DR Congo) (2), Mozambique (3) and Tanzania (4). The disease was first described in the Bandundu region in the DR Congo (5), and named after a local designation which means "tied legs". Konzo causes the abrupt onset of a permanent spastic paraparesis or tetraparesis in severely

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affected subjects (4, 6). It mainly affects children aged 3-13 years and women of childbearing age.

Epidemiological studies have suggested konzo is associated with a high level of exposure to cyanogenic compounds from the consumption of insufficiently processed bitter cassava roots, combined with a low intake of sulphur amino acids from animal proteins (2, 7). Recent electrophysiological studies to locate the precise site of the neurodamage in konzo point mainly to a neuronal dysfunction in intracerebral motor pathways (8-11). Many patients complain of visual disturbances at the onset of the disease (3-5, 12). An earlier epidemiological and clinical field study on 20 patients in present-day DR Congo concluded that permanent ocular lesions are very rare in konzo (13), even though patients complained of blurred vision and diplopia. In contrast, a study on two severely affected Tanzanian konzo subjects found temporal atrophy of the optic discs, atrophy of the papillomacular nerve fiber layer and a corresponding visual field defect in one of them, with eye movement disorders in both (8).

Although several authors (1, 4) have mentioned ophthalmological disturbances in some konzo patients, systematic information on the ophthalmologic manifestations of the disease is scarce. In 1998, as part of a larger neuro-physiological study (9-12), neuro-ophthalmological examinations were done on 21 Congolese konzo subjects. This paper describes the findings in these patients and relates them to the clinical picture.

PATIENTS AND METHODS

In July 1998, twenty-one Congolese konzo patients were invited to Kinshasa for neurophysiological and neuro-ophthalmological investigations during a two-week period. Fifteen were females and six males. The mean age was 22 years (range 10-49, median 17) and the mean duration of the disease (from onset to the study) was 8 years (range 2-20). The diagnosis of konzo had been made two years earlier in a survey close to Popokabaka (350 km from Kinshasa), one of the most konzo-affected health districts in the Bandundu province (12, 14). Ten of the 21 patients were mildly, 6 moderately and 5 severely affected, according to the WHO criteria (6).

All underwent neuro-ophthalmological examination which included: visual acuity testing using a Snellen E-chart, evaluation of direct and consensual light pupillary reflexes, assessment of ocular motility in the nine directions of gaze, ocular deviation using the cover test method, and direct ophthalmoscopy before and after dilating pupils. Color vision was tested with the unsaturated version of the Fansworth D15 test. Visual field was tested using a Goldmann perimeter. In addition, objective refraction (retinoscopy and keratometry) and examination of the anterior segment with a Haag Streit 900 slit-lamp were done, and intraocular pressure (IOP) was measured by applanation. Optic neuropathy was considered when at least two of the following findings were present in at least one eye of the same subject: 1) impaired visual acuity, 2) optic disc changes, 3) a visual field defect. The ophthalmologic examinations were done at the Department of Ophthalmology, Kinshasa University Hospital. The studies were approved by the National Medical Council in the DR Congo and the Ethical Committee at Uppsala University in Sweden.

RESULTS

Nine (43%) of the 21 konzo patients could recall a history of transient visual difficulties at onset of the disease. Visual acuity was impaired in five (24%), one of whom had unilateral and four bilateral visual impairment (Tab. I). In these five patients, no apparent cause could be found for the visual impairment. Examination of the ocular fundus showed temporal pallor of the optic discs in 14 patients (67%), 13 with bilateral and one unilateral changes. This pallor was symmetric in most subjects.

Visual field examination revealed defects in 14 of 20 patients examined (70%). Eight had bilateral and six unilateral defects (Tab. I). The visual field defects were seen in eyes with pale or apparently normal optic discs. Different varieties of visual field defects were found (Fig. 1), either isolated or in association, i.e. concentric constriction, centrocecal scotoma and tubular visual fields, central scotoma, and temporal constriction. Concentric constriction, found in 13 subjects, was the most frequent visual field defect. In cases with bilateral defects, there was a strong tendency to symmetry in both visual fields. In addition,

visual field defects were found in all forms of konzo, and the extent of the defects was not related to the severity of the disease. Eleven patients had visual field defects despite normal visual acuity.

Neither oculomotor palsy nor abnormalities of the pupillary reflexes were found. However, two patients presented with spontaneous pendular nystagmus in primary position, bilateral in one and unilateral in the other. Relatives who accompanied them asserted that the nystagmus and the paraparesis had started simultaneously. None of the patients had abnormal colour vision.

DISCUSSION

This is the first systematic collection of neuro-ophthalmologic data in a series of konzo patients. This study revealed two types of neuro-ophthalmological abnormalities: optic neuropathy in more than half of the patients and oculomotor symptoms in some. Optic neuropathy was found in 11/21 patients based on the presence of visual impairment together with temporal pallor of the optic disc (1 patient), visual impairment together with visual field defects (2), temporal pallor of the optic disc together with visual field defects (6) and all the above symptoms and signs (2). Out of the 14 patients with visual field defects, 11 had normal visual acuity. This may explain why previous studies (13) without visual field quantification have failed to show such a degree of neuro-ophthalmological involvement in konzo.

The present study also shows that optic neuropathy may occur at any level of severity of konzo, though particularly in severely ill patients. Overall, the findings indicate that an optic nerve lesion seems to be concomitant with the damage to upper motor neurons.

Oculomotor symptoms in konzo are less frequent than optic neuropathy. Other investigators (1, 5) have also reported nystagmus, noted in two patients in the present series. In motor neuron diseases (amy-

TABLE I - CLINICAL STAGING, DEMOGRAPHIC CHARACTERISTICS AND THE MAIN OPHTHALMOLOGICAL FINDINGS IN 21 PATIENTS WITH KONZO

Pats no.	Severity of konzo	Age	Sex	Visual acuity		Ocular fundus		Ocular motility		Visual field	
				right	left	right	left	right	left	right	left
1	mild	10	F	1.0	1.0	N	N	N	N	N	CC
2	mild	10	F	1.0	1.0	N	N	N	N	N	CC
3	mild	10	F	CF	CF	pallor	pallor	N	N	CC+CCS	CC+CCS
4	mild	18	M	1.0	1.0	pallor	pallor	N	N	N	N
5	mild	18	F	1.0	1.0	N	N	N	N	N	N
6	mild	18	M	1.0	1.0	pallor	pallor	N	N	N	N
7	mild	21	F	1.0	1.0	N	pallor	N	N	N	CC
8	mild	23	F	1.0	1.0	pallor	pallor	N	N	N	CC
9	mild	25	F	1.0	1.0	pallor	pallor	N	N	N	N
10	mild	40	F	0.4	0.4	pallor	pallor	N	N	N	CC
11	moderate	12	M	1.0	1.0	N	N	nyst	nyst	not done	not done
12	moderate	22	F	1.0	1.0	pallor	pallor	N	N	N	N
13	moderate	30	F	1.0	1.0	N	N	N	N	CC	CC
14	moderate	34	F	1.0	1.0	pallor	pallor	N	N	TC	CS
15	moderate	39	F	1.0	0.6	pallor	pallor	N	N	N	N
16	moderate	49	F	0.8	0.5	pallor	pallor	N	N	CC+CCS	CC+CCS
17	severe	11	F	1.0	1.0	N	N	N	N	CC	N
18	severe	11	M	1.0	1.0	pallor	pallor	N	N	TVF	TVF
19	severe	14	F	0.1	0.8	N	N	nyst	N	not done	CC
20	severe	17	M	1.0	1.0	pallor	pallor	N	N	CCS	CC
21	severe	20	M	1.0	1.0	pallor	pallor	N	N	TC	CC

CF= Counting fingers; N= Normal; nyst= Nystagmus: CC= Concentric constriction; CCS= Centrocecal scotoma; TC= Temporal constriction; CS= Central scotoma; TVF= Tubular visual field

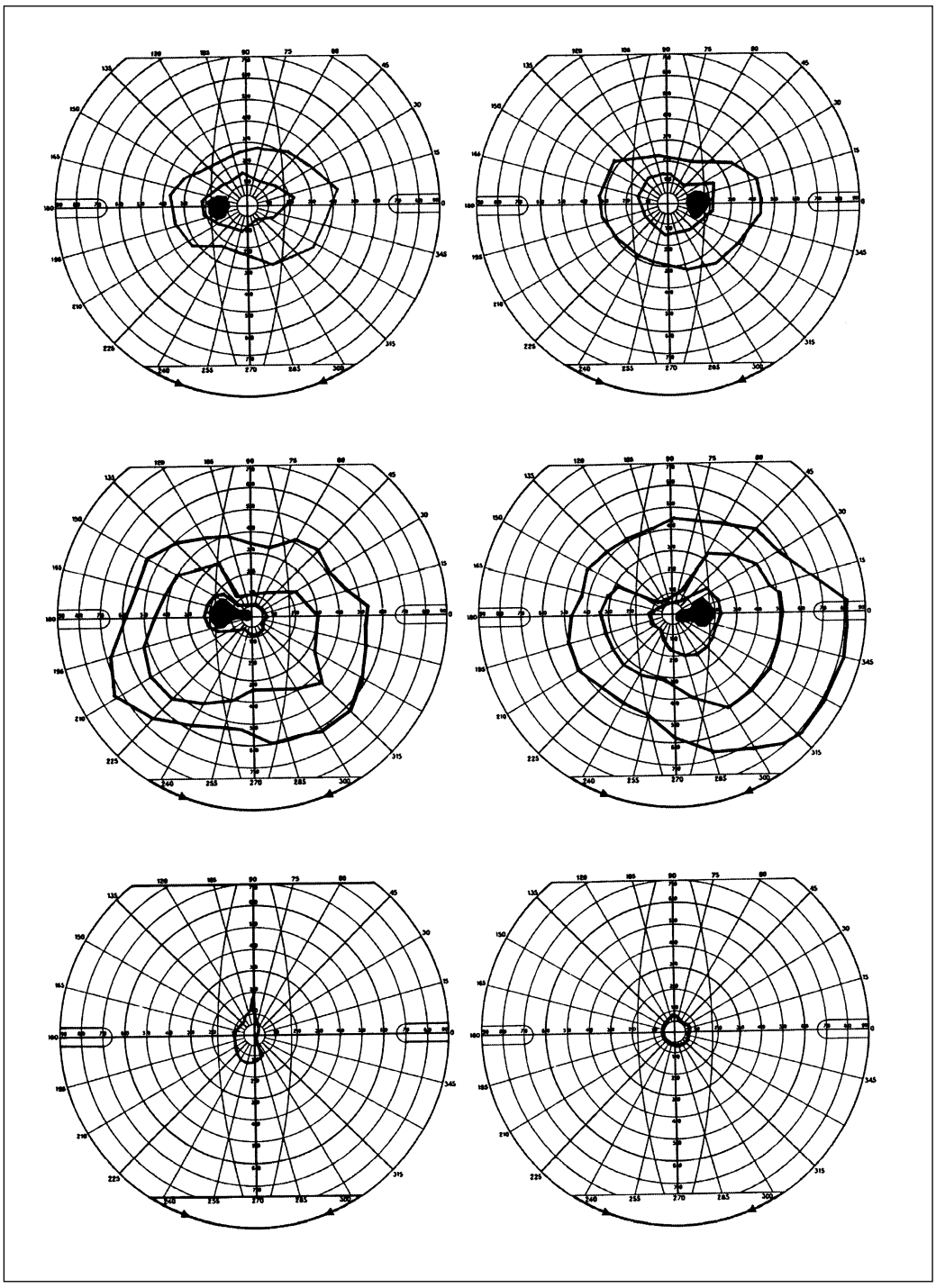

Fig. 1 - *Visual fields of three konzo patients with different kinds of visual field defects. Patient no. 13 (top) had a symmetric concentric constriction. Patient no. 16 (middle) had symmetric centrocecal scotoma. Patient no. 18 (bottom) had symmetric tubular visual fields.*

otrophic lateral sclerosis and to some extent hereditary spastic paraplegia) the presence of ocular movement disorders has been debated in recent years, but they are widely held to exist (15, 16). The oculomotor disorders reported include abnormal smooth pursuit and saccadic movements, ophthalmoplegia, and defective convergence. In addition, nystagmus has been reported (17, 18) though it is said to be rare in motor neuron disease (15). In hereditary spastic paraplegia, oculomotor disorders (nystagmus included) ap-

pear early in the course of the disease (18). Even when not clinically apparent, they may be present on electro-oculography and electro-nystagmography. This is in accordance with previous findings in two konzo patients (8). Our impression is therefore that a small proportion of patients with different disorders affecting the upper motor neuron commonly presents with oculo-motor symptoms. It is conceivable that these symptoms have a common pathogenesis in all these diseases.

We will briefly review these findings in the light of epidemic optic neuropathies, Leber's hereditary optic neuropathy, tobacco amblyopia and vitamin B12 deficiency. Epidemics of different optic neuropathies have been reported in Tanzania (19), Cuba (20), and Nigeria (21). These have been associated with neurological disorders, mostly peripheral neuropathies which are absent in konzo. The clinical pictures of the Tanzanian and Cuban optic neuropathies are very similar: most patients were respectively 10-40 and 25-45 years old in the two countries, and subacute and bilateral progressive vision loss over weeks was combined with bilateral and symmetric centrocecal scotoma and loss of the papillomacular fiber layer. The optic nerve was normal in most of the Cuban cases whereas symmetrical temporal optic atrophy was characteristic in Tanzania. In konzo, however, the main complaint was transient blurred vision at onset of the disease, and there was no history of progressive loss of vision. Most konzo patients had good vision despite visual field defects. Despite the fact that both Tanzanian and Cuban patients were potentially exposed to cyanide, the etiology of the Tanzanian epidemic has not been clarified while the Cuban one is generally thought to be due to micronutrient deficiencies, particularly thiamine, as treatment with thiamine and folic acid gave satisfactory results in most cases.

Another neuropathy syndrome, tropical ataxic neuropathy (TAN), has been reported from Nigeria. The following optical features of TAN differentiate it from konzo: amblyopia is the main presenting symptom, antedating the other manifestations of the disease by months to years, and some patients have an abnormal pupil reflex to light. In addition, TAN mostly affects adults mainly in the fourth and fifth decade, has a gradual onset and is associated with peripheral neuropathy and sensorineural deafness.

Leber's hereditary optic neuropathy is a maternally inherited disease preferentially affecting young- adult men between 15 and 35 years, and associated with mitochondrial DNA mutations (22). These mutations alone are not usually enough to induce an optic neuropathy, but they are predisposing factors. In these subjects, cyanide from smoking is known to be an additional stress factor that could precipitate the development of optic neuropathy (23), after reduction of mitochondrial complex I activity (24). The clinical picture involves severe and permanent bilateral visual loss in the acute stage, hyperemia, papilledema, telangiectatic angiopathy, atrophy of the papillomacular nerve fiber bundle, and ultimately whole optic disc atrophy as well as a typical central scotoma.

In contrast, konzo mainly affects children between 3-13 years and women of childbearing age. In addition, its general clinical picture differs very much from Leber's neuropathy, and most of the fundus lesions seen in the latter, such as retinal vessel abnormalities and papilledema, were absent in our patients. Is papilledema an early manifestation of optic neuropathy in konzo? There is little support for this idea. If the optic atrophy was a consequence of papilledema, one would expect the whole disc to be affected rather than only the temporal part. The patients in our study were examined late after onset of the disease and they presented with temporal pallor only, which does not support the idea of initial papilledema. Reports on ophthalmoscopic changes in the early stages of konzo are very rare because of the remoteness of the affected areas. However, in Mozambique at the time of the first outbreak, ophthalmoscopic examinations one day to 4 months after onset showed normal optic discs (3).

Tobacco amblyopia is most common in middle-aged and elderly men. The inability to distinguish between red and green is an early feature. The characteristic visual field deficit is a strict centrocecal scotoma while konzo patients present different types of visual field deficits. Vision loss is bilateral and progressive over a long period of time, and usually improves, together with the visual field defects, if the patient stops smoking and starts taking vitamin B12 in the form of hydroxocobalamin (25).

Deficiency of the vitamins from group B, especially thiamine and cobalamin, can also induce optic neuropathy with bilateral visual loss and centrocecal scotoma. This, however, is frequently associated with pe-

ripheral neuropathies in the upper and lower limbs, diminution or loss of tendon reflexes and other specific non-neurologic manifestations of each of the deficient vitamins. The clinical picture of konzo, on the other hand, is consistent with involvement of the brain only rather than the spinal cord and/or peripheral nerve (8-12).

Konzo patients and populations where the disease is common are often exposed to potential toxins: linamarin (7), cyanohydrin (2) and cyanide (2). The symmetry of the involvement in the present series of patients suggests an underlying toxic mechanism. Which of these toxins actually precipitates the neurodamage of the sub-population of upper motor neurons - if any - has not been established. Possibly two different toxins are responsible for the two sub-populations (the upper motor neurons and the optic neurons) and this might explain why not all konzo patients present with optic neuropathy. Since cyanide can cause optic neuropathy in genetically predisposed persons, we suggest that cyanide exposure in konzo, in combination with a genetic predisposition, is the cause of the neuro-ophthalmological damage. Whether it is the same agent that precipitates the neurodamage of the neuronal sub-populations of the upper motor neurons remains to be elucidated.

In conclusion, the present study shows that optic neuropathy is common in konzo. In addition, a few patients have nystagmus starting at the onset of the disease. The optic neuropathy is mainly symmetric, which suggests a toxic origin. We propose that cyanide is at least one cause. However, the optic neuropathy in konzo patients does not resemble the features of the epidemic optic neuropathy in Tanzania, Cuba or Nigeria, or of Leber's neuropathy, tobacco amblyopia or vitamin B deficiency.

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Reprint requests to:
Jean-Claude K. Mwanza, MD
Center for International Health
University of Bergen
Armauer Hansen Building
N-5021 Bergen, Norway
jcmwanza@hotmail.com

REFERENCES

1. Tylleskär T, Légué F, Peterson S, Kpizingui E, Stecker P. Konzo in the Central African Republic. Neurology 1994; 44: 959-61.
2. Tylleskar T, Banea M, Bikangi N, Cooke RD, Poulter NH, Rosling H. Cassava cyanogens and konzo, an upper motoneuron disease found in Africa. Lancet 1992; 339: 208-11.
3. Ministry of Health Mozambique. Mantakassa: An epidemic of spastic paraparesis associated with chronic cyanide intoxication in a cassava staple area in Mozambique. 1. Epidemiology and clinical and laboratory findings in patients. Bull WHO 1984; 62: 477-84.
4. Howlett WP, Brubaker GR, Mlingi N, Rosling H. Konzo, an epidemic upper motor neuron disease studied in Tanzania. Brain 1990; 113: 223-35.
5. Trolli G. Paraplégie spastique épidémique, "Konzo" des indigènes du Kwango. In: G. T, editor. Résumé des observations réunies, au Kwango, au sujet de deux affections d´origine indéterminée. Brussels: Fonds Reine Elisabeth; 1938. pp. 1-36.
6. WHO. Konzo, a distinct type of upper motoneuron disease. Wkly Epidemiol Rec 1996; 71: 225-32.
7. Banea M, Tylleskär T, Nahimana G, Nunga M, Gebre-Medhin M, Rosling H. Geographical and seasonal association between linamarin and cyanide exposure from cassava and the upper motor neuron disease konzo in Zaire. Trop Med Int Health 1997; 2: 1143-51.
8. Tylleskär T, Howlett W, Rwiza H, Aquilonius S-M, Stål-

berg E, Lindén B, et al. Konzo: A distinct disease entity with selective upper motoneuron damage. J Neurol Neurosurg Psychiatry 1993; 56: 638-43.
9. Tshala-Katumbay D, Mutombo-Lukusa V, Edebol Eeg-Olofsson K. EEG findings in konzo: A spastic para/tetraparesis of acute onset. Clin Electroencephalogr 2000; 31: 196-200.
10. Tshala-Katumbay D, Edebol Eeg-Olofsson K, Kazadi-Kayembe T, Tylleskär T, P. F. Analysis of motor pathway involvement in konzo using transcranial electrical and magnetic stimulation. Muscle Nerve 2002; 25: 230-5.
11. Tshala-Katumbay D, Edebol Eeg-Olofsson K, Kazadi-Kayembe T, Fällmar P, Tylleskär T, Kayembe-Kalula T. Abnormalities of somatosensory evoked potentials in konzo - an upper motor neuron disorder. Clin Neurophysiol 2002; 113: 10-5.
12. Tshala-Katumbay D, Banea Mayambu J, Kazadi-Kayembe T, Nunga-Matadi R, Bikangi-Nkiabungu F, Edebol Eeg-Olofsson K, et al. Neuroepidemiology of konzo - a spastic para/tetraparesis of acute onset - in a new area of the Democratic Republic of Congo. Afr J Neurol Sci 2001; 20: 8-13.
13. Carton H, Kazadi K, Kabeya, Odio, Billiau A, Maertens K. Epidemic spastic paraparesis in Bandundu (Zaire). J Neurol Neurosurg Psychiatry 1986; 49: 620-7.
14. Banea M, Tylleskar T, Rosling H. Konzo and Ebola in Bandundu region of Zaire. Lancet 1997; 349: 621.
15. Kushner MJ, Parrish M, Burke A, Behrens M, Hays AP, Frame B, et al. Nystagmus in motor neuron disease: Clinicopathological study of two cases. Ann Neurol 1984; 16: 71-7.
16. Ohki M, Kanayama R, Nakamura T, Okuyama T, Kimura Y, Koike Y. Ocular abnormalities in amyotrophic lateral sclerosis. Acta Otolaryngol Suppl 1994; 511: 138-42.
17. Gascon GG, Chavis P, Yaghmour A, Stigsby B, Shums A, Ozand P, et al. Familial childhood primary lateral sclerosis with associated gaze paresis. Neuropediatrics 1995; 26: 313-9.
18. Landau WM, Schmidt RE, McGlennen RC, Reich SG. Hereditary spastic paraplegia and hereditary ataxia, Part 2: A family demonstrating various phenotypic manifestations with the SCA3 genotype. Arch Neurol 2000; 57: 733-9.
19. Plant G, Mtanda A, Arden G, Johnson G. An epidemic of optic neuropathy in Tanzania: Characterization of the visual disorder and associated peripheral neuropathy. J Neurol Sci 1997; 145: 127-40.
20. Roman GC. An epidemic in Cuba of optic neuropathy, sensorineural deafness, peripheral sensory neuropathy and dorsolateral myeloneuropathy. J Neurol Sci 1994; 127: 11-28.
21. Osuntokun B, Osuntokun O. Tropical amblyopia in Nigerians. Am J Ophthalmol 1971; 71: 708-16.
22. Riordan-Eva P, Sanders MD, Govan GG, Sweeney MG, Da Costa J, Harding AE. The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. Brain 1995; 118: 319-37.
23. Tsao K, Aitken PA, Johns DR. Smoking as an aetiological factor in a pedigree with Leber's hereditary optic neuropathy. Br J Ophthalmol 1999; 83: 577-81.
24. Smith PR, Cooper JM, Govan GG, Harding AE, Schapira AH. Smoking and mitochondrial function: A model for environmental toxins. Q J Med 1993; 86: 657-60.
25. Rizzo JF 3rd, Lessel S. Tobacco amblyopia. Am J Ophthalmol 1993; 116: 84-7.