

EPIDEMIC OPTIC NEUROPATHY IN CUBA — CLINICAL CHARACTERIZATION AND RISK FACTORS

THE CUBA NEUROPATHY FIELD INVESTIGATION TEAM*

Abstract Background. From 1991 to 1993, epidemic optic and peripheral neuropathy affected more than 50,000 people in Cuba. The number of new cases decreased after the initiation of vitamin supplementation in the population. In September 1993, Cuban and U.S. investigators conducted a study to characterize and identify risk factors for the optic form of the syndrome.

Methods. We conducted ophthalmologic and neurologic examinations, assessed exposure to potential toxins, administered a semiquantitative food-frequency questionnaire, and assessed serum measures of nutritional status in 123 patients with severe optic neuropathy, matched for sex and age to randomly chosen normal subjects.

Results. In the case patients, prominent clinical features were subacute loss of visual acuity with field de-

fects, diminished color vision, optic-nerve pallor, and decreased sensitivity to vibration and temperature in the legs. Tobacco use, particularly cigar smoking, was associated with an increased risk of optic neuropathy. The risk was reduced among subjects with higher dietary intakes of methionine, vitamin B₁₂, riboflavin, and niacin and higher serum concentrations of antioxidant carotenoids. The risk was also reduced among subjects who raised chickens at home or had relatives living overseas — factors that may be indirect measures of increased food availability.

Conclusions. The epidemic of optic and peripheral neuropathy in Cuba between 1991 and 1993 appears to be linked to reduced nutrient intake caused by the country's deteriorating economic situation and the high prevalence of tobacco use. (N Engl J Med 1995;333:1176-82.)

FROM late 1991 through 1993, epidemic neuropathy affected more than 50,000 people in Cuba,¹ peaking in March 1993, when there were 3000 to 4000 cases per week. Two forms of neuropathy were reported: an optic form, characterized by decreased visual acuity and color vision, central scotomas, pallor of the optic disks, and loss of papillomacular-bundle fibers; and a peripheral form, with painful dysesthesias, diminished ankle reflexes, and decreased sensitivity to vibration, pinprick, and light touch.^{1,2} Studies by the Cuban Ministry of Public Health suggested an association with tobacco use and low intake of protein and micronutrients.^{2,3} No patients died, and the condition of most patients improved after treatment with vitamins, including parenteral vitamin B₁₂. From April to May 1993, the Ministry of Public Health initiated oral supplementation with multiple vitamins in the general population; the incidence of disease decreased substantially after June 1993 (unpublished data).

In response to the epidemic, the Pan American Health Organization coordinated a program of emergency humanitarian support, including the initiation of a collaborative study with scientists from multiple institutions (see the Appendix). Our objectives were to describe and identify risk factors for epidemic optic neuropathy. Because the diagnosis was thought to be more specific for the optic than the peripheral form, only patients with optic neuropathy meeting the case definition devised by the Ministry of Public Health² were study candidates.

We hypothesized that etiologic agents included cya-

nide or other toxins from tobacco use or occupational exposure, cyanogenic glycosides from the consumption of cassava, and medicinal toxins or contaminants. Because the epidemic coincided with recent economic difficulties in Cuba, we considered that an increasingly limited diet — in particular, inadequate intake of vitamin B₁₂, folate, or methionine, which are involved in cyanide detoxification — might be important. We investigated these factors and attempted to cast a broad net for other unanticipated risk factors.

METHODS

Case Selection

All components of the field investigation were conducted during September 1993 in Pinar del Rio, the province with the earliest occurrence and highest incidence of cases. From the registry of all patients with epidemic optic neuropathy in the five study municipalities, we selected 150 potential case patients who had severe or very severe disease.² All potential case patients were completely reexamined but were included in the analysis only if at least two neuro-ophthalmologists concurred that pallor of the optic-nerve head or loss of the papillomacular-nerve fiber layer was present on fundoscopic examination of dilated eyes in September 1993. Our case patients were therefore chosen from a more severely affected subgroup, and their illnesses probably represent the most severe cases in the province.

The control subjects were randomly selected from voter-registration lists and matched to the case patients for sex, municipality, and age (within five years). During recruitment, most potential control subjects were prescreened by family physicians, and those who had abnormal visual acuity, lower-extremity reflexes, or sensitivity to vibration were excluded. All control subjects were also examined by neuro-ophthalmologists and were required to have no ophthalmoscopic evidence of optic neuropathy. If either member of a pair of case patients and control subjects did not meet the criteria, the pair was excluded, yielding a total of 123 case-control pairs for the analysis. The protocol was approved by the Internal Review Board for Studies on Human Subjects of the Centers for Disease Control and Prevention, and all subjects gave written informed consent. The examining clinicians and field interviewers were unaware of the participants' case-patient or control status.

Ophthalmologic Examination

A certified ophthalmic technician determined best corrected visual acuity. Color vision was tested with Ishihara pseudo-isochromatic color plates, and contrast sensitivity with a near-card Vision Con-

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trast Test System (Vistech Consultants, Dayton, Ohio). Threshold Amsler-grid testing was performed.⁴ Visual fields were charted on a 1-m tangent screen with use of 1-to-10-mm white and red test objects. Slitlamp examination and tonometry were performed to exclude other causes of abnormal visual function. At least two neuro-ophthalmologists performed the funduscopic examinations. Fundus photographs were used to confirm the results of the funduscopic examination.

Clinical and Quantitative Neurologic Examination

Two neurologists obtained neurologic histories and used bedside clinical methods to assess cranial nerves III to XII; motor strength; sensitivity to light touch, pinprick, vibration, and position; cerebellar function and gait; and deep-tendon reflexes.

Cutaneous vibrotactile thresholds were measured with an electro-mechanical vibrometer.⁵ Stability while standing was measured with a digitized head-position monitor.⁶ The thermal-discrimination threshold was measured with a two-surface controlled-temperature device.⁷ Gross grip strength was measured with a Jamar type of dynamometer.⁸ Values were considered abnormal if they were above the 95th percentile of normative data for sway (Letz R, Gerr F, Emory University: unpublished data) and vibrotactile⁵ and thermal⁷ thresholds, and below the 5th percentile of normative data for pinch and grip.⁸

Toxic Exposure and Socioeconomic Data

Family physicians trained in interviewing techniques administered a questionnaire regarding exposures during the two-month period before the onset of symptoms for the case patients and for the same calendar period for the respective control subjects. Information was obtained about occupation; exposures to pesticides, heavy metals, and medications; tobacco use; meal patterns; factors affecting access to supplemental food; patterns of cassava consumption; and intake of home-brewed and commercial liquor.

Dietary Assessment

Trained nutritional interviewers administered a semiquantitative food-frequency questionnaire modified from one previously used in Cuba.³ Participants were asked to report their average consumption of 93 foods in the two-month period before the onset of symptoms for the case patients and the corresponding period for the respective control subjects. Food models were used to estimate portion size.

Dietary data were linked to a Cuban food-composition data base to yield the average daily intake of each food, energy (in kilocalories), and 17 individual nutrients.⁹ Intakes of additional micronutrients (vitamin B₁₂, methionine, cysteine, and cystine) were estimated by linking the food-intake data to information from two standard food-composition data sets.^{10,11}

Laboratory Methods

Serum concentrations of vitamin A (retinol) and four carotenoids (α - and β -carotene, cryptoxanthin, and lycopene) were measured by high-performance liquid chromatography.¹² Serum selenium was measured by atomic-absorption spectrometry.¹³ Serum retinol-binding protein was measured by an enzyme-linked immunosorbent assay modified from a published method.¹⁴ Urinary cotinine concentrations were measured with an enzyme-linked immunoassay kit (STC Diagnostics, Bethlehem, Pa.). Serum albumin and total protein were measured with a Cobas FARA II analyzer (Roche Diagnostic Systems, Montclair, N.J.).

Statistical Analysis

Data were tabulated by teams in both Havana and Atlanta, and any discrepancies were resolved. Although simple cross-tabulations are shown between disease status and the exposure variables, the matched-pair design guided the statistical analyses. Associations with disease were assessed with two-tailed matched-pair t-tests, Wilcoxon's tests, and conditional logistic-regression analysis.¹⁵

Several analytic approaches were used to examine the relation of dietary data to disease. The results presented were derived by dividing the intake of the specific food or nutrient by the total caloric intake; these nutrient densities, along with the total caloric intake, were then included as predictors of disease in conditional logistic-regres-

sion models.¹⁶ The estimated odds ratios indicate the effect of increasing the percentage of each dietary component while keeping total energy intake constant. Similar results were obtained in analyses that included energy intake as a covariate along with either the intake of the specific food or nutrient or the residual values from a linear regression of the intake of food or nutrient on the total caloric intake.¹⁷

Many of the exposure distributions were skewed, but most associations with disease were fairly linear on the logit scale. The results presented are based on the use of a single exposure variable with multiple (typically four) levels, and the estimated odds ratios contrasting the extreme categories are shown. Forward stepwise-regression procedures were used to help develop multivariable models; possible interactions, multicollinearity, and influential observations were examined.¹⁸

RESULTS

Clinical Characteristics

Among the case patients, the dates of onset of illness ranged from July 1991 to June 1993; the mean period between the onset of symptoms and the investigation was 10 months (range, 3 to 26). Approximately two thirds of the case-control pairs were men (Table 1). The distribution of occupations differed significantly between the case patients and control subjects, and the case patients had a lower median monthly income and less formal education. Serum total protein and albumin values were within the normal range in all subjects.

Symmetric bilateral loss of vision occurred within the year before examination among 90 of the 123 case

Table 1. Characteristics of the 123 Pairs of Case Patients and Control Subjects.

CHARACTERISTIC	CONTROL SUBJECTS (N = 123)	CASE PATIENTS (N = 123)	P VALUE
Age — yr			0.99*
Mean	44	45	
Range	18–69	20–69	
Female — %	39	39	
Occupation — %			<0.001†
Agriculture	9	31	
Service	66	35	
No work outside home	8	22	
Median monthly income — pesos	183	141	<0.001‡
Mean years of education	11	7	<0.001§
Ophthalmologic findings — no. of subjects (%)¶			
Visual acuity			
20/40 or better¶¶	123 (100)	41 (33)	<0.001
20/200 or worse**	0	25 (20)	<0.001
Normal threshold Amsler-grid test††‡‡	119 (100)	94 (79)	<0.001
Normal visual fields††	119 (100)	30 (25)	<0.001
Normal contrast sensitivity††	114 (96)	16 (13)	<0.001
Color-vision testing			
≥23 plates identified correctly	120 (98)	20 (16)	<0.001
≤16 plates identified correctly	2 (2)	64 (52)	<0.001

*Paired t-test for H₀ (absolute difference ≤5 years) versus H₁ (absolute difference >5 years).

†Matched-pairs logistic regression on occupational categories.

‡Matched-pairs signed-rank test.

§Paired t-test.

¶All P values were derived with McNemar's test of matched-pair results.

¶¶Worse eye, 20/40 or better.

**Better eye, 20/200 or worse.

††Data were available for 119 pairs.

‡‡Testing was performed as described by Wall and Sadun.⁴

patients. The visual difficulties usually stabilized within 30 days (range, 3 to 90). Of the case patients, 95 percent reported photophobia, 90 percent flashes of light or glare, and 54 percent eye pain. The control subjects reported virtually no symptoms.

Among the case patients, the best corrected visual acuities ranged from 20/20 to 20/400 (Table 1). More than two thirds of the case patients had bilateral central or cecentral scotomas, three fourths had an abnormal visual field in at least one eye, and most had impaired color vision. No subject had anterior-segment abnormalities that prohibited adequate dilated ophthalmoscopic examination.

Cranial-nerve abnormalities were rare, except for decreased auditory acuity among the case patients (Table 2). More of the case patients than control subjects had decreased sensation, decreased motor strength, or absent deep-tendon reflexes in the legs. On all quantitative neurologic measures, more of the case patients had abnormal results; the most frequent abnormalities were increased thermal and vibrotactile thresholds in the great toe.

Analysis of Risk Factors

All measures of tobacco use were strongly associated with optic neuropathy (Table 3). For cigar smoking, we found a dose-response relation, with the odds ratio increasing to 23 for subjects who smoked four or more cigars per day as compared with those who did not smoke cigars. Cigarette smoking was less strongly re-

Table 2. Clinical and Quantitative Neurologic Findings in the 123 Pairs of Case Patients and Control Subjects.

TEST RESULT	CONTROL SUBJECTS	CASE PATIENTS	P VALUE*
	<i>no. of subjects (%)</i>		
Decreased auditory acuity†	5 (4)	15 (12)	0.012
Diminished proprioception and pinprick or light-touch perception†			
Arm	18 (15)	37 (30)	0.004
Leg	33 (27)	66 (54)	<0.001
Decreased strength‡			
Arm	1 (1)	22 (18)	<0.001
Leg	0	13 (11)	<0.001
Deep-tendon areflexia‡			
Leg	1 (1)	16 (13)	<0.001
Abnormal vibrotactile threshold§			
Nondominant great toe	38 (31)	70 (58)	<0.001
Abnormal thermal threshold‡			
Nondominant great toe	29 (24)	88 (72)	<0.001
Abnormal postural-stability sway speed (eyes closed)			
Men¶	2 (3)	11 (15)	0.007
Women	4 (9)	9 (19)	0.166
Diminished gross grip strength			
Men**	10 (13)	29 (39)	0.001
Women††	4 (8)	19 (40)	0.001

*By McNemar's test. For bilateral tests, abnormal was defined as either the right or left side abnormal.

†Data were available for 122 pairs.

‡Data were available for 123 pairs.

§Data were available for 121 pairs.

¶Data were available for 72 pairs.

||Data were available for 47 pairs.

**Data were available for 75 pairs.

††Data were available for 48 pairs.

Table 3. Relation of Smoking Behavior to the Risk of Optic Neuropathy.

VARIABLE	CONTROL SUBJECTS	CASE PATIENTS	ODDS RATIO	95% CONFIDENCE INTERVAL
Tobacco use				
No	66	21		
Yes	57	102	6.6	3.2-13.9
Cigars per day*				
0	101	71	1	
<1	12	13	1.8	0.6-5.3
1-3	8	22	8.7	2.5-30.7
≥4	2	17	22.8	4.0-131
Cigarettes per day*				
0	75	44	1	
1-9	21	30	2.5	1.2-5.2
10-20	19	41	3.6	1.8-7.1
≥20	8	8	2.1	0.6-6.5

*The reference group is the lowest quartile.

lated to optic neuropathy, and there was no dose-response relation. Subjects in the highest quartile for urinary cotinine, a measure of exposure to tobacco, were nearly 12 times as likely to have disease as those in the lowest quartile.

The risk of optic neuropathy was significantly lower among the subjects who reported higher consumption of two groups of nutrients: those related to animal products, including animal protein, animal fat, and methionine, and the group of B-complex vitamins, notably vitamin B₁₂, riboflavin, niacin, and pyridoxine (Table 4). However, the intakes of many of these nutrients were interrelated, with the strongest correlations between intakes of animal protein and vitamin B₁₂ ($r=0.89$) and animal protein and methionine ($r=0.85$) and among intakes of the B-complex vitamins ($r=0.53$ to 0.78).

After adjusting for energy intake, we found that subjects with high (upper quartile) cassava consumption were three times as likely to have optic neuropathy than those reporting intakes in the lowest quartile (Table 4). However, the median daily consumption of cassava was identical among the case patients and control subjects, and greater consumption was associated with an increased risk of disease only when we adjusted for energy intake.

Of the serum measures of nutritional status, lycopene, a carotenoid with marked antioxidant activity but no provitamin A function, was most strongly associated with a reduced risk of disease (Table 5). Subjects with serum lycopene concentrations in the highest quartile were 1/20 as likely to have optic neuropathy as those in the lowest quartile. Other serum measures associated with protection included higher levels of α - and β -carotene and selenium, but the magnitudes of these associations were weaker.

Several other characteristics were associated with an altered risk of optic neuropathy (Table 6). Less-regular consumption of meals was associated with greater risk of disease, whereas indirect measures of increased food availability, such as raising chickens, were associated with protection. There was no association between consumption of home-brewed alcoholic beverages and

disease status (odds ratio for disease among those who consumed such beverages, 0.8; 95 percent confidence interval, 0.4 to 1.5).

A multivariable model, developed with use of stepwise regression procedures, identified several factors as independent predictors of disease: cigar smoking, cigarette smoking, cassava consumption, low serum lycopene concentration, low dietary intake of energy and of methionine, and not raising chickens in the household. The association with cigar smoking was very strong: the risk of disease among subjects smoking four or more cigars per day was estimated to be 34 times that of people who did not smoke cigars. Subjects in the highest quartile of cassava consumption had a fourfold increased risk as compared with those in the lowest quartile. A high serum lycopene concentration and high dietary intakes of energy and of methionine were each associated with a substantial reduction in risk (odds ratios for highest vs. lowest quartile, 0.03 for lycopene; 0.10 for energy intake; 0.20 for methionine intake). However, because many of the characteristics examined were intercorrelated, several other multivariable models were nearly as predictive of disease. For example, urinary cotinine concentrations could be substituted for self-reported smoking status, and dietary intake of vitamin B₁₂, riboflavin, or niacin showed strong inverse associations with disease.

DISCUSSION

This study provides a clinical description and an analysis of risk factors for epidemic optic neuropathy in Cuba. Our design, using fundoscopic abnormalities to define case-patient status and excluding control subjects with evidence of optic neuropathy, gave a rigorous assignment of case patients and control subjects. The prominent clinical features were loss of visual acuity with scotomas, diminished color vision, and increased vibratory and thermal thresholds in the legs, findings consistent with previous reports.¹⁹ However, we found a higher prevalence of signs of peripheral neurop-

Table 4. Relation of Dietary Intake of Various Nutrients and Cassava to the Risk of Optic Neuropathy.

VARIABLE*	GROUP	QUARTILE				ODDS RATIO†	95% CONFIDENCE INTERVAL
		LOWEST	2	3	HIGHEST		
<i>no. of subjects</i>							
Energy intake	Controls	19	29	39	36	0.2	0.1–0.5
	Patients	42	33	23	25		
Animal-protein intake	Controls	20	28	33	42	0.3	0.1–0.6
	Patients	41	34	29	19		
Animal-fat intake	Controls	16	29	39	39	0.2	0.1–0.5
	Patients	45	33	23	22		
Methionine intake	Controls	21	36	26	40	0.3	0.1–0.6
	Patients	43	26	36	21		
Cassava intake	Controls	37	32	30	24	3.0	1.3–6.6
	Patients	24	30	32	37		
Thiamine intake	Controls	24	31	31	37	0.5	0.2–1.1
	Patients	37	31	31	24		
Riboflavin intake	Controls	20	28	38	37	0.3	0.2–0.7
	Patients	41	34	24	24		
Niacin intake	Controls	23	30	34	36	0.5	0.2–1.0
	Patients	38	32	28	25		
Pyridoxine intake	Controls	22	29	35	37	0.4	0.2–0.9
	Patients	39	33	27	24		
Folic acid intake	Controls	28	24	34	37	0.5	0.2–1.1
	Patients	33	38	28	24		
Vitamin B ₁₂ intake	Controls	17	25	40	41	0.2	0.1–0.4
	Patients	44	37	22	20		

*With the exception of energy, all intakes were expressed as a proportion of total energy.

†The odds ratio is for the highest as compared with the lowest quartile; a linear relation across quartiles is assumed. All analyses are based on conditional logistic-regression models that include energy intake as a four-level ordinal variable based on quartile rankings.

Table 5. Relation of Serum Measures of Nutritional Status to the Risk of Optic Neuropathy.

SERUM CONSTITUENT*	GROUP	MEAN LEVEL†	RANGE	QUARTILE				ODDS RATIO‡	95% CONFIDENCE INTERVAL
				LOWEST	2	3	HIGHEST		
<i>µg/dl</i>									
Lycopene	Controls	11±8	1–43	10	33	30	48	0.05	0.02–0.2
	Patients	5±3	0–21	43	45	22	11		
Cryptoxanthin	Controls	12±7	1–41	25	27	34	35	0.5	0.3–1.0
	Patients	11±8	2–48	34	36	23	28		
α-Carotene	Controls	6±4	1–26	16	32	36	37	0.2	0.1–0.5
	Patients	4±3	1–17	35	39	26	21		
β-Carotene	Controls	15±10	1–65	18	29	31	43	0.2	0.1–0.4
	Patients	10±6	1–34	35	45	22	19		
Retinol	Controls	53±13	27–100	27	27	33	34	0.6	0.3–1.2
	Patients	50±13	25–110	36	27	29	29		
<i>mg/liter</i>									
Retinol-binding protein	Controls	37±12	13–71	27	28	29	37	0.5	0.2–1.0
	Patients	33±12	0–67	33	33	32	23		
<i>ng/ml</i>									
Selenium	Controls	95±14	69–144	18	30	34	38	0.3	0.1–0.6
	Patients	89±14	52–139	41	30	26	23		

*To convert values for lycopene to micromoles per liter, multiply by 0.019; to convert values for cryptoxanthin to micromoles per liter, multiply by 0.018; to convert values for α-carotene to micromoles per liter, multiply by 0.019; to convert values for β-carotene to micromoles per liter, multiply by 0.019; to convert values for selenium to micromoles per liter, multiply by 0.00013; and to convert values for retinol to micromoles per liter, multiply by 0.035.

†Values are means ±SD.

‡The odds ratio is for the highest as compared with the lowest quartile; a linear relation across quartiles is assumed. All analyses are based on conditional logistic-regression models.

Table 6. Relation of Various Types of Behavior and Circumstances to the Risk of Optic Neuropathy.

VARIABLE	CONTROL SUBJECTS	CASE PATIENTS	ODDS RATIO	95% CONFIDENCE INTERVAL
Having relatives overseas				
No	63	92		
Yes	60	31	0.4	0.2–0.6
Raising chickens at home				
No	65	89		
Yes	57	33	0.4	0.2–0.7
Eating lunch <5 times per week				
No	117	100		
Yes	6	23	4.4	1.7–11.6
Eating breakfast less than once a week				
No	70	48		
Yes	53	75	2.2	1.3–3.7
Going whole days without food				
No	116	101		
Yes	4	22	5.9	1.8–15
Eating any frozen cassava				
No	74	104		
Yes	49	19	0.3	0.1–0.5

athy among case patients with optic neuropathy than in earlier studies.² Furthermore, the disturbance in thermal thresholds suggests the involvement of small nerve fibers in addition to the large myelinated fibers most often involved in toxic or metabolic neuropathies.²⁰

Ophthalmologically, this disorder resembles nutritional amblyopia, tobacco amblyopia, and toxic optic neuropathy,^{21,22} as well as Leber's hereditary optic neuropathy.²³ However, an analysis of specimens from the case patients did not reveal any pathogenetic role for mitochondrial DNA mutations or for any specific mitochondrial genetic background.^{24,25}

We found that tobacco use, particularly cigar smoking, and high cassava consumption relative to total energy intake were both associated with an increased risk of optic neuropathy. In contrast, the risk was reduced among the subjects with higher serum concentrations of carotenoids and higher dietary intakes of nutrients from animal products and some B complex vitamins.

Epidemics of neuropathy have been reported primarily during wartime, especially among prisoners of war in Asia during World War II.²⁶ Remarkably, an epidemic in which the clinical abnormalities were identical to those in the 1991–1993 Cuban epidemic was reported in Havana during the Spanish–American War.²⁷ Although the cause of these earlier epidemics was never established, contemporary neurologists linked them to dietary deprivation and lack of B-complex vitamins,²⁶ and tobacco use was implicated in optic neuropathy among prisoners of war.²⁸

In our study, the stronger association with cigar than cigarette smoking is consistent with previous reports of tobacco amblyopia.²² However, in Pinar del Rio, the center of cigar-tobacco cultivation, cigar smoking is more prevalent than elsewhere in Cuba, and studies in other provinces demonstrated a similar

risk for cigarette smoking (Zacca E, Ministry of Public Health: unpublished data). Improved diet and supplementation with B-complex vitamins, especially vitamin B₁₂, are important in the treatment of tobacco amblyopia; patients who continue to smoke may recover their vision with nutritional therapy.²² Cyanide in tobacco smoke may be toxic to the optic nerve, especially when inadequate intake of B vitamins, methionine, cysteine, and cystine impair detoxification,²⁹ but studies in animals have failed to demonstrate a role for cyanide in the development of isolated optic-nerve toxicity.³⁰

In Africa, exposure to cyanide from cassava consumption has been implicated in epidemics of neurologic disease. However, unlike those in the Cuban epidemic, affected subjects in Africa have usually had spastic paraparesis.³¹ The cyanide content of cassava varies, depending on the variety and method of preparation. Biochemical studies conducted in Cuba in 1993 indicate that even consumption of large amounts of cassava was unlikely to result in exposure to large amounts of cyanide.³² High cassava consumption with lower energy intake may identify a dietary pattern associated with a greater risk of disease, rather than reflecting a direct toxic effect.

The strong association of higher serum lycopene concentrations with protection suggests that inadequate intake of carotenoids may have contributed to the development of neuropathy through impairment of protective antioxidant pathways.³³ Exposure to tobacco is thought to cause injury through oxidative damage.³⁴ The antioxidant activity of lycopene, which is found in tomatoes, watermelon, and other red fruits, exceeds that of other carotenoids,³⁵ and in our study lycopene was the carotenoid most strongly associated with protection. The association of riboflavin intake with protection is also consistent with an antioxidant mechanism. Riboflavin is a cofactor in the regeneration of reduced glutathione,³⁶ a primary intracellular antioxidant associated with protection from tobacco amblyopia.³⁷

The deteriorating economic situation in Cuba may have set the stage for this epidemic. Between 1991 and 1993, a combination of events, including the loss of Cuba's major trading partners and a severe storm, abruptly decreased the availability of many foods, especially animal products. Factors such as having relatives overseas, raising chickens at home, or eating frozen cassava may be surrogates for increased access to food.

This study has several limitations. Because of the selection procedure, our case patients represented the most severely affected subgroup of patients with epidemic optic neuropathy, and we are unable to draw any conclusions about the purely peripheral form. Because the epidemic subsided without documented change in food availability or smoking prevalence, an exposure not assessed may have had a role. In addition, because we asked the subjects to recall their diets from a time before the onset of illness, whereas serum measurements were taken months after onset of illness and

treatment, our results might reflect changes due to illness. However, because of the continued monotony of the Cuban diet, retrospective dietary assessment is probably valid, and laboratory values that reflect a relatively constant diet, such as serum lycopene concentrations, should be stable over time.

Although we cannot assign a definitive cause to this epidemic, our findings suggest that its occurrence was linked to a deterioration in diet affecting nutrients such as methionine, vitamin B₁₂, riboflavin, and carotenoids, in conjunction with a high prevalence of tobacco use and possibly cassava consumption. The balance of these factors, and the degree of individual susceptibility, may have determined who became ill and who remained well. The Cuban Ministry of Public Health had already implemented vitamin supplementation and an antismoking campaign at the height of the epidemic. Although it cannot be proved that these interventions led to the decline in the number of cases, this study supports the continuation of these measures until increased dietary quality and diversity can be achieved in Cuba.

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APPENDIX

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REFERENCES

1. Epidemic neuropathy — Cuba, 1991–1994. *MMWR Morb Mortal Wkly Rep* 1994;43:183-92.
2. National Operative Group. Epidemic neuropathy in Cuba. Havana, Cuba: Ministry of Public Health, 1993.
3. Gay J, Porrata C, Hernández M, et al. Factores dietéticos de la neuropatía epidémica en la Isla de la Juventud, Cuba. *Bol Oficina Sanit Panam* 1994; 117:389-99.
4. Wall M, Sadun AA. Threshold Amsler grid testing: cross-polarizing lenses enhance yield. *Arch Ophthalmol* 1986;104:520-3.
5. Gerr F, Hershman D, Letz R. Vibrotactile threshold measurement for detecting neurotoxicity: reliability and determination of age- and height-standardized normative values. *Arch Environ Health* 1990;45:148-54.
6. Letz R, Gerr F, Harris-Abbott D. Heterogeneity of effects of ethanol ingestion on postural stability as measured by two devices. *Neurotoxicology* 1994;15:603-7.
7. Bove FJ, Letz R, Baker EL Jr. Sensory thresholds among construction trade painters: a cross-sectional study using new methods for measuring temperature and vibration sensitivity. *J Occup Med* 1989;31:320-5.
8. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers A. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985; 66:69-74.
9. Rodríguez A, Gay J, Prieto Y, Suarez A, Martin I, Siberio I. NUTRISIS version 4.02 (subsistema de VAD: sistema para la vigilancia automatizada de dietas). Havana, Cuba: Institute of Nutrition and Food Hygiene, Ministry of Public Health, 1992.
10. Pennington JAT. BOWES and Church's food values of portions commonly consumed. 16th ed. Philadelphia: J.B. Lippincott, 1994.
11. Department of Agriculture. Composition of foods: raw, processed, prepared. Agricultural handbook series. No. 8. Washington, D.C.: Government Printing Office, 1986.
12. Sowell AL, Huff DL, Yeager PR, Caudill SP, Gunter EW. Retinol, alpha-tocopherol, lutein/zeaxanthin, beta-cryptoxanthin, lycopene, alpha-carotene, trans-beta-carotene, and four retinyl esters in serum determined simultaneously by reversed-phase HPLC with multiwavelength detection. *Clin Chem* 1994;40:411-6.
13. Paschal DC, Kimberly MM. Automated direct determination of selenium by electrothermal atomic absorption spectroscopy. *Atomic Spectroscopy* 1986;7:75-8.
14. Topping MD, Forster HW, Dolman C, Luczynska CM, Bernard AM. Measurement of urinary retinol-binding protein by enzyme-linked immunosorbent assay, and its application to detection of tubular proteinuria. *Clin Chem* 1986;32:1863-6.
15. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 1. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980:165, 248-79. (IARC scientific publications no. 32.)
16. Brown CC, Kipnis V, Freedman LS, Hartman AM, Schatzkin A, Wacholder S. Energy adjustment methods for nutritional epidemiology: the effect of categorization. *Am J Epidemiol* 1994;139:323-38.
17. Willett WC. Implications of total energy intake for epidemiologic analyses. In: Willett WC, ed. Nutritional epidemiology. Vol. 15 of Monographs in epidemiology and biostatistics. New York: Oxford University Press, 1990:245-71.
18. Hosmer DW Jr, Lemeshow S. Applied logistic regression. New York: John Wiley, 1989.
19. Lincoff NS, Odel JG, Hirano M. 'Outbreak' of optic and peripheral neuropathy in Cuba? *JAMA* 1993;270:511-8. [Erratum, *JAMA* 1994;271:664.]
20. Schaumburg HH, Berger AR, Thomas PK. Disorders of peripheral nerves. Philadelphia: F.A. Davis, 1992.
21. Retrobulbar toxic and deficiency optic neuropathies. In: Miller NR. Walsh and Hoyt's clinical neuro-ophthalmology. 4th ed. Baltimore: Williams & Wilkins, 1982:289-307.
22. Rizzo JF III, Lessell S. Tobacco amblyopia. *Am J Ophthalmol* 1993;116:84-7.
23. Newman NJ. Leber's hereditary optic neuropathy: new genetic considerations. *Arch Neurol* 1993;50:540-8.
24. Newman NJ, Torroni A, Brown MD, Lott MT, Fernandez MM, Wallace DC. Epidemic neuropathy in Cuba not associated with mitochondrial DNA mutations found in Leber's hereditary optic neuropathy patients. *Am J Ophthalmol* 1994;118:158-68.
25. Torroni A, Brown MD, Lott MT, Newman NJ, Wallace DC. Cuba Neuropathy Field Investigation Team. African, Native American, and European mitochondrial DNA in Cubans from Pinar del Rio province and implications for the recent epidemic neuropathy in Cuba. *Hum Mutat* 1995;5:310-7.

26. Spillane JD. Nutritional disorders of the nervous system. Edinburgh, Scotland: E&S Livingstone, 1947.
27. Madan D. Nota sobre una forma sensitiva de neuritis periferica, ambliopia por neuritis optica retrobulbar. *Cronica Med Quirurgica Habana* 1898;24: 81-6.
28. Knox DL, Chen MF, Guilarte TR, Dang CV, Burnette J. Nutritional amblyopia: folic acid, vitamin B-12, and other vitamins. *Retina* 1982;2:288-93.
29. Dang CV. Tobacco-alcohol amblyopia: a proposed biochemical basis for pathogenesis. *Med Hypotheses* 1981;7:1317-28.
30. Lessell S. Experimental cyanide optic neuropathy. *Arch Ophthalmol* 1971; 86:194-204.
31. Mozambique Ministry of Health. Mantakassa: an epidemic of spastic paraparesis associated with chronic cyanide intoxication in a cassava staple area of Mozambique. 1. Epidemiology and clinical and laboratory findings in patients. *Bull World Health Organ* 1984;62:477-84.
32. Hernandez T, Lundquist P, Oliveira L, Perez Cristia R, Rodriguez E, Rosling H. The fate in humans of dietary intake of cyanogenic glucosides from roots of sweet cassava consumed in Cuba. *Nat Toxins* 1995;3:114-7.
33. Dixon ZR, Burri B, Clifford A, et al. Effects of a carotene-deficient diet on measures of oxidative susceptibility and superoxide dismutase activity in adult women. *Free Radic Biol Med* 1994;17:537-44.
34. Lannan S, Donaldson K, Brown D, MacNee W. Effect of cigarette smoke and its condensates on alveolar epithelial cell injury in vitro. *Am J Physiol* 1994;266:L92-L100.
35. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys* 1989;274:532-8.
36. McCormick DB. Riboflavin. In: Shils ME, Olson JA, Shike M, eds. *Modern nutrition in health and disease*. Philadelphia: Lea & Febiger, 1994:366-75.
37. Costagliola C, Cotticelli L, Menzione M, Rinaldi M, Russo S, Rinaldi E. Red cell reduced glutathione and tobacco smoke-induced optic neuropathy. *Metab Pediatr Syst Ophthalmol* 1990;13:96-8.

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