

Ecological studies in Pinar del Rio Province support a toxico-nutritional etiology of epidemic neuropathy in Cuba

Hans Rosling, Alberto Perez Sierra, Guillermo Mesa Ridel,
Mariluz Rodriguez, Evelio Velis Barroso, Carmen Serrano,
Rafael Perez Cristiá

Hans Rosling, MD, International Child Health Unit, Uppsala University, Sweden.
Alberto Perez Sierra, MD, Finlay Institute, Havana, Cuba. Guillermo Mesa Ridel, MD,
Ministry of Public Health, Havana, Cuba. M. Rodriguez, MD, Ministry of Public Health,
Havana, Cuba. Evelio Velis Barroso, MD, Provincial Health Bureau, Pinar del Rio, Cuba.
Carmen Serrano, MD, Provincial Health Bureau, Pinar del Rio, Cuba.
Rafael Perez Cristiá, National Center for Toxicology, Havana, Cuba.

To study risk factors of epidemic neuropathy with ecological study design, we used surveillance data to calculate cumulative incidence in 59 small areas in the most affected part of Pinar del Rio Province, Cuba. The rates ranged from 2 to 55 per 1000 inhabitants and focus group discussions consistently revealed that rural high rate areas had a monotonous carbohydrate diet because of decreased state food rations and poor access to unofficial food production due to dense populations and state tobacco production. Adjacent low rate areas had a more diverse diet due to lower population densities and private agriculture with surpluses sold on the unofficial market. Analyses of digitalized land tenure maps confirmed higher ($p < 0.05$) neuropathy rates in state tobacco areas as compared to private agriculture areas.

The epidemic peak was preceded by the lowest ever distributed rations of meat and egg. Vitamin supplementation in March was followed by incidence decline in May. Access to the unofficial food market for urban families was estimated by family doctors using an economy index. Only one (3%) of 32 families with an index +2 SD above the mean had neuropathy compared to 186 (22%) of 859 families with average economy. The neuropathy rate among the 7 700 pregnant women in the province who received extra meat and milk rations, was 0.5/1000, whereas the rate in fertile-age non-pregnant women was 33/1000. The consistent association of monotonous carbohydrate diet and the resulting unbalanced nutritional status, aggravated by tobacco smoking is the most probable causes of the neuropathy affecting about 50 000 Cubans in 1992-93.

Övervakningsdata och en ekologisk studiedesign användes för att studera riskfaktorer för epidemisk neuropati på Kuba. Kumulativ förekomst beräknades för 59 små områden i den mest drabbade delen av provinsen Pinar del Rio. Mellan områdena varierade förekomsten från 2 till 55 fall per 1000 invånare. Landsbyggsområden med hög förekomsten karakteriserades av hög befolkningstäthet och statliga tobaksfarmer. Fokusgruppsdialo-

ger visade konsekvent att befolkningen i dessa områden hade en monoton kolhydratdiet på grund av minskade statliga matransoner och dålig tillgång till inofficiell matproduktion. I intilliggande områden med låg förekomst hade befolkningen en mer varierad diet då befolkningstäthet var lägre och områdena hade en större andel privat jordbruk som genererade ett överskott som såldes på den inofficiella marknaden. Analyser av digitaliserade ekonomiska kartor bekräftade högre ($p < 0,05$) neuropati i statliga tobaksområden jämfört med områden med privat odlingsmark.

Epidemins topp följde på de genom tiderna lägsta ransonerna av kött och ägg. I mars kompletterades den statliga matransonen med ett vitamintillskott varpå antalet nya fall av neuropati gick ner. För stadsfamiljer uppskattades tillgång till den inofficiella livsmedelsmarknaden med hjälp av ett ekonomiindex utvecklat med lokala familjedoktorer. Endast en (3%) av 32 familjer med ett index +2 SD över medelvärdet hade neuropati jämfört med 186 (22%) av 859 familjer med genomsnittlig ekonomi. Bland provinsens 7 700 gravida kvinnor som fick extra kött- och mjölkrationer var neuropati förekomsten 0,5/1000, medan förekomsten hos icke gravida kvinnor i fertil ålder var 33/1000. Monoton kolhydratdiet och resulterande obalanserade näringsstatusen, förvärrad av tobaksrökning, är den mest sannolika orsakerna till att cirka 50 000 kubaner drabbades av neuropati under 1992-93.

Introduction

An outbreak of epidemic neuropathy of unprecedented magnitude occurred in Cuba in 1993. It started with increased incidence of optic neuropathy in male smokers in the westernmost province of Pinar del Rio in 1992. By the end of the year, the clinical pattern changed and included additional or isolated peripheral neuropathy of the distal axonopathy type (Borrajero et al. 1994). An exponential increase of incidence and spread to all provinces in the beginning of 1993 created an emergency situation. The epidemiological surveillance registered 50.963 cases up to the end of June 1993, but with a rapidly declining incidence in May and June. Decreased food rations following the abrupt decline in Cuban foreign trade in 1990 had resulted in monotonous diet in Cuba. The clinical findings resembled those attributed to

nutritional deficiencies (Lincoff et al. 1993) and patients responded well to B-vitamin treatment. Therefore, vitamin prophylaxis was given to the entire population from mid-March. However, the extensive changes of food sources, processing practices and storage methods induced by the same factors also suggested that a specific toxin could be the main etiology and the epidemic character merited search for infectious factors.

We report epidemiological investigations of the etiology of the epidemic neuropathy that were done with ecological study design in the most affected part of Cuba. The epidemiological surveillance data was used to analyse geographical, temporal and social distribution of the disease. Secondary data sources, qualitative interviews and unconventional methods were used to explore and correlate varia-

tions in food rations, access to the unofficial food market and new dietary practices with variations in disease rate.

Material and methods

Study area:

Pinar del Rio is an agricultural province with 710 000 inhabitants on the western tip of Cuba with the highest rates of epidemic neuropathy (Figure 1a) in the country. The 1992 infant mortality rate of 12/1000 reflects the advanced health situation. Following the loss of trade with former socialist countries the centrally planned Cuban economy has decreased rapidly since 1990 resulting in severe reduction of

meat and dairy products in the general state food rations, but young children, pregnant women and sick persons continued to receive additional rations. The official sales of non-rationed food ceased and the unofficial food market grew in importance. Severe reduction in transport facilities, cuts in electrical power supplies and reduced access to consumer goods were other effects of the economic crisis.

Temporal distribution and changes in food rations

Diagnostic criteria, surveillance organization and public awareness were stepwise changed during the epidemic (Table 1) and therefore it is not meaningful to analyse temporal distribu-

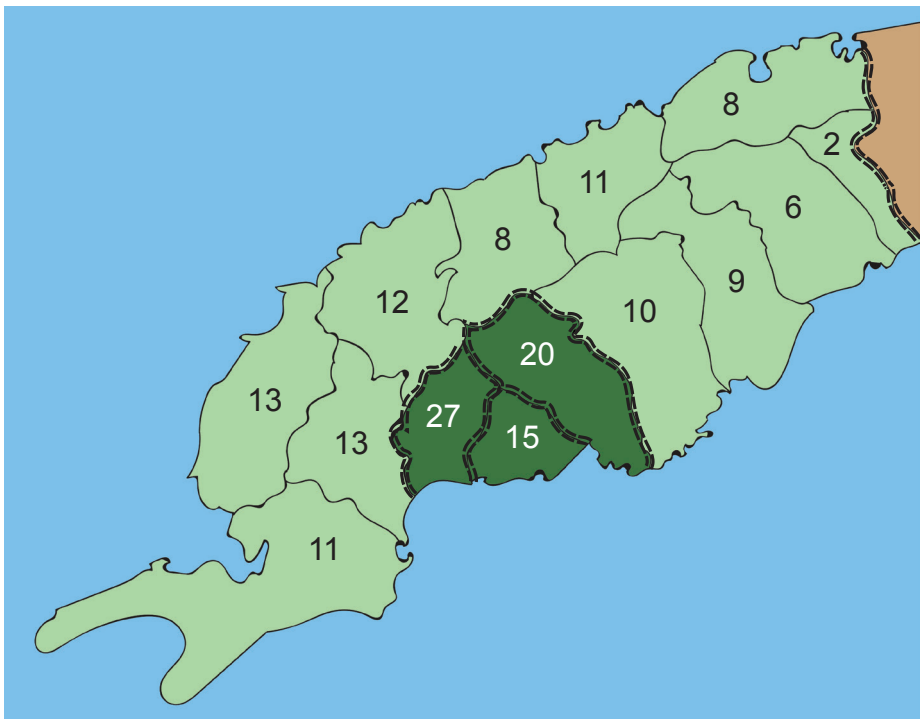


Figure 1a. Geographical distribution of neuropathy as cumulative incidence/1000 inhabitants in the municipios of the Province Pinar del Rio.

Table 1. Changes in surveillance organisation and public awareness.

	Year/Month/Day
Clinical diagnosis of optic neuropathy (ON)	92/01
Diagnosis of ON with perimetri and Ichihara test	92/05
Clinical diagnosis of polyneuropathy (PN)	93/06
Active case finding of ON in primary health care	92/06
Diagnosis of ON without perimetri due to case accumulation	93/01/15
Distribution of vitamin B1 to risk groups	93/01/18
National registration of isolated PN	93/02/18
Decentralized diagnosis in Municipio de Pinar del Rio	93/03/02
Decentralized diagnosis in Municipios San Luis and San Juan	93/03/15
Distribution of vitamins to the whole population	93/03/17-28
Civil defense support to epidemiological surveillance	93/03/27
First media communication of the epidemic	93/04/12
Active community based case finding	93/04/12
Diagnosis with perimetri reestablished for ON	93/04/20
New national criteria for severity grading	93/06/10

tions in units shorter than a month. Diagnosis required gradual progression of optic and/or peripheral neuropathy in formally healthy subjects where other neurological disease could be excluded. Optic neuropathy was diagnosed as Mild when visual acuity (VA) was 0.9-0.8 and defect color vision was indicated by 2-6 Ichihara errors (IE) per 21 plates, as Moderate when VA was 0.2-0.7, IE 7-14 and paracentral scotoma was found and as Severe when VA was < 0.2 and IE ≥ 15 and cecocentral or central scotomas were found. When different, the result from the most affected eye was used for grading and when subjects had both optic and peripheral neuropathy they were registered as optic. Peripheral neuropathy was diagnosed as Mild when only subjective symptoms were present, as Moderate when clinical signs of sensory deficiency and re-

duced tendon reflexes were found and as Severe when in addition absent tendon reflexes, reduced muscle strength and abnormal gait was observed.

Until March 1993 all diagnosis was made after examination in the provincial hospital and thereafter by one specialist team in each municipio to which all suspect cases were referred. For this study, we used the epidemiological data registered on a special form for each patient on the day of diagnosis and thereafter compiled and stored in surveillance headquarters at provincial and municipality level, respectively. To validate the epidemiological surveillance all 355 eligible adults aged 20-64 in a local community with both urban and rural characteristics in the Municipio of San Luis were screened for color vision defects by the Sahlgrens Saturation Test (SST) (Frisén & Kalm, 1981).

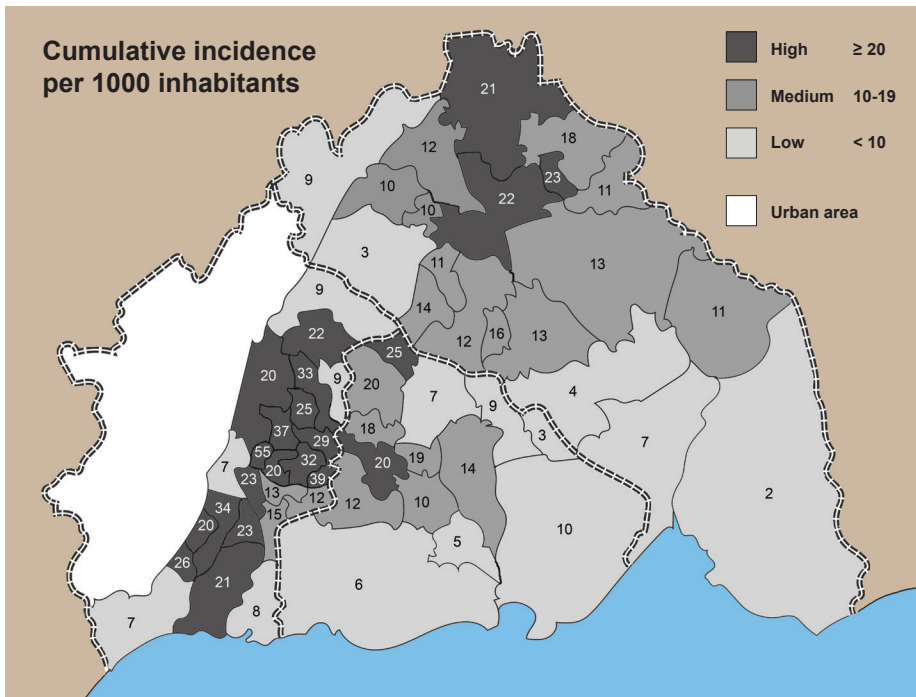


Figure 1b. Small area geographical distribution of neuropathy as cumulative incidence/1000 inhabitants in the three most affected municipalities.

Data on amounts of monthly delivery of general food rations of 33 food items for the whole Province was obtained from the 6 distributing companies situated in the provincial capital.

Monthly mean prices in the unofficial market for 23 food items was obtained from the provincial branch of the Institute for Internal demand and the number of purchases per month by the 50 informants was also registered since July 1992.

Geographical distribution and variations in dietary practices

”Circumscription” is the smallest administrative division in Cuba. It has some hundred inhabitants and borders were available on maps in 1:25 000

and population from a local census in March 1993. Circumscriptions were joined 2-10 into 59 areas that correspond to rural communities and 4 urban areas for which registered addresses of cases could be identified without errors by local informants and hence the cumulative incidence for each form of neuropathy be calculated (Figure 1b).

Differences in socioeconomic, agro-ecological and dietary situation in 8 pairs of adjacent high and low incidence areas were explored by a total of 30 focus group discussions, observations and interviews with various informants by two investigators and six family doctors.

The proportion of land ownership and use was calculated for each of the

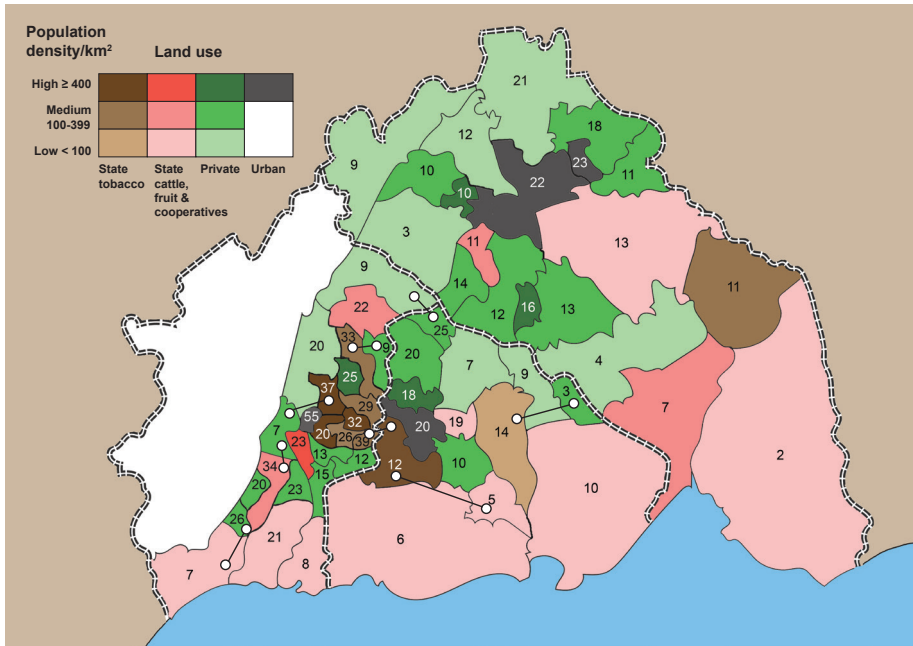


Figure 1c. Small area geographical distribution of neuropathy as cumulative incidence/1000 inhabitants in the most affected municipios. Areas are categorized according to main land (color) use and population density (hue). The 8 pairs of neighboring high and low incidence communities selected for focus group discussions are also marked.

59 areas by superimposing them on 1:25 000 maps with this information for 1992 done by provincial agricultural authorities. After digitalizing the maps in Roots and Arcinfo programs the areas of a total multiple polygons were measured and the total areas of each of the 6 land use types as well as of lakes and forests were calculated for each of the 59 areas. Categorization of areas into main type of land use yielded 7 by cattle, 3 by fruit and 4 by agricultural cooperatives and these are presented jointly. A further 10 were dominated by state tobacco, 31 by private farmers and 4 were urban areas, including 3 capitals of the municipios (Figure 1c).

Social distribution, food access and housing quality

Family economy was studied in a suburb with new flats found to have the highest incidence of epidemic neuropathy in Pinar del Rio town. Interviews with family doctors and other key-informants indicated that access to complementary food for these urban families depended on a number of factors, some of whom families may be reluctant to communicate. The personal knowledge of each families' situation by 6 family doctors enabled them to make an anonymous grading of the economy of the 892 families in their catchment areas. This was done by a semi-quantitative index developed jointly with the doctors. Positive

and negative grade options corresponded to the estimated magnitude of each of the eight factors as follows: support from relatives in rural areas (0,1,3), support from relatives abroad (0,1,3), extra labor activity (0,1,3,5), access to food and/or other products from workplace (0,1,3,5), family food production (0,1), smokers in the family (0,-1), low per capita salary, (0,-1) and one or more children in the family (0,-1,-2). After, and separate from the grading, the families with registered cases of neuropathy were noted from the surveillance registration.

All pregnant women in Cuba have access to high quality ante-natal care, including ultrasonic examinations, and service coverage is close to 100%. From week 14 food rations for all pregnant women are increased with 0.5 kg meat and 12 l milk per month. This offered a possibility to study the relation between diet and neuropathy. Information on simultaneous pregnancy and epidemic neuropathy was available both through epidemiological surveillance and reporting from ante-natal service. Clinical information was obtained on the 6 reported cases in the province of Pinar del Rio for determination of onset in relation to week of pregnancy.

Quality of the 1449 houses and apartments in the small town of San Luis had recently been mapped in 1:1000 by the municipality into good flats and houses with optimal water and sanitation, intermediate and bad houses with deficient sanitation. The 78 households affected by neuropathy were marked on this map during a

house-to-house survey by local authorities to all households marked.

Results

Temporal distribution and changes in food rations

The number of optic and peripheral neuropathy diagnosed per month in the province peaked in March and April 1993 as shown in Figure 2 house-to-house screening of 355 adults for color vision deficiency using SST method identified 3 subjects with defect, all of whom were already diagnosed as optic neuropathy.

The major food groups in the monthly general rations distributed in the province is also shown in Figure 2. These data exclude additional rations for young children, pregnant women and sick persons as well as lunch meals at workplaces, schools and other institutions. Staple foods include a mean of 1,617 ton of rice with small variations and wheat bread (including some pasta products) that decreased slightly in 1992 from 1,400 to below 1,300 ton. Included are also starchy staples seasonally varying from 147 to 552 ton given as cereal equivalents (30% of fresh weight) with a slight increase in 1992 compensating for decreased energy supply from wheat. The increase in starchy staples was due to increased amounts of cassava in its main season between September 1992 to January 1993, with a maximum of 301 ton dry weight in October. A mean of 373 ton of legume, include beans, chick-peas and 60-120 ton of processed soya protein pro-

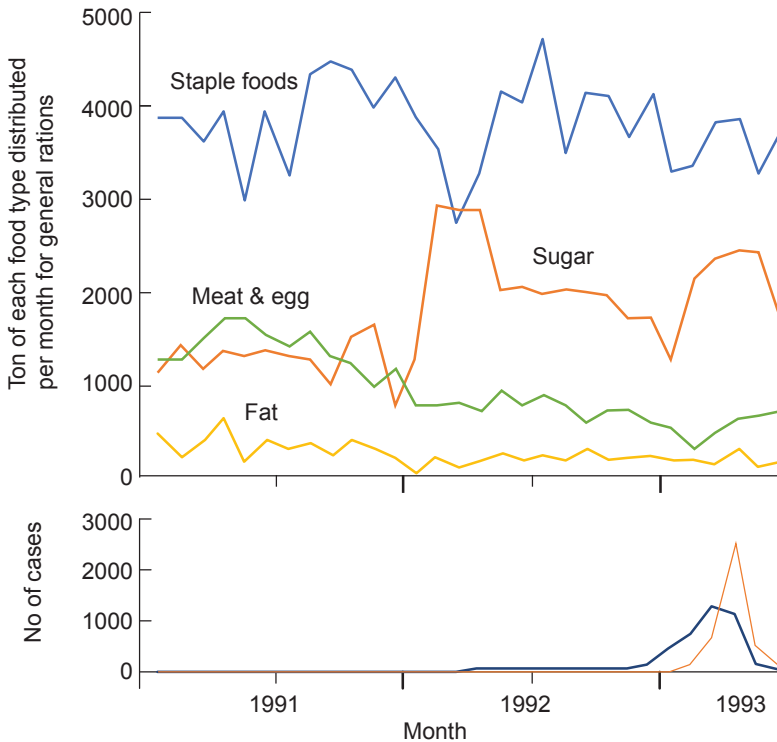


Figure 2. Monthly number of cases of optic (O) and peripheral (X) neuropathy in the Province Pinar del Rio (lower panel) and monthly distribution in tons of main food items in general food rations (upper panel).

ducts from April 1992 and onwards, was distributed with wide variations but with the same average over time. The initial monthly mean of 1,258 ton of sugar was almost doubled from February 1992 to a mean of 2,086 ton per month up to June 1993. The mean oil and butter ration decreased from 388 to 124 ton per month in the first and last six-month period, respectively. Meat products, including fresh and canned meat, poultry and fish products, fell from a mean of 1,497 in the first six months studied to 487 ton in the last six-month period with a lowest monthly amount of 487 ton in February 1993. A mean of 2036 ton of milk with 1,1 % fat and 1,4 %

protein was distributed with small variations but is not shown in Figure 2. Neither are the amounts of vegetables and fruits that vary from 120 to 1,680 ton with a maximum in the period of January to March, a quarter of which was cabbage.

The general food rations were the basic food security for all 710 000 inhabitants, but especially so for the groups with limited access to other food sources. The start of the epidemic coincided with the lowest monthly amounts of animal proteins and fat whereas the amount of calories in general rations were not lower than in preceding and following months. Data on prize per item purchased

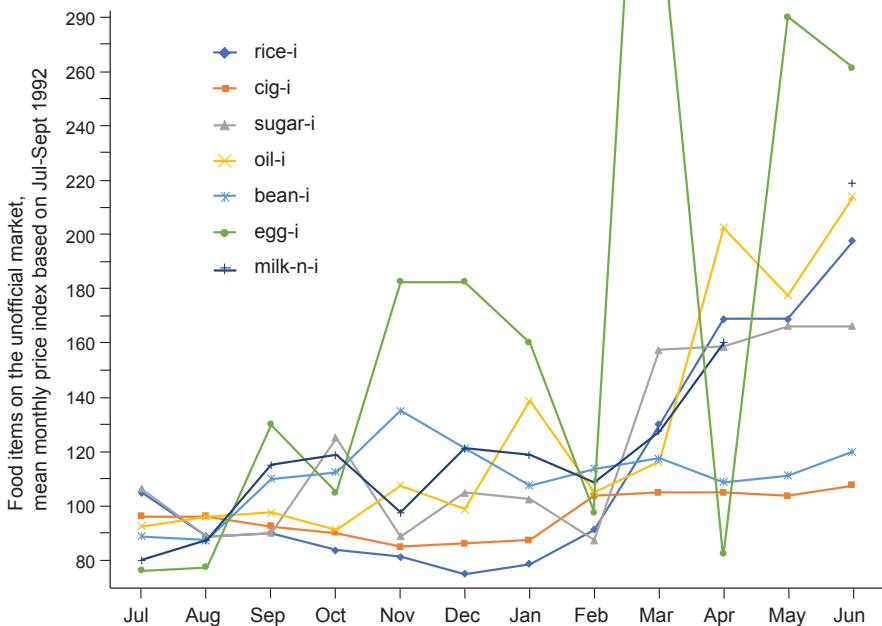


Figure 3a. Mean monthly price index for the unofficial market based on July to September 1993 prices for cigarettes and 6 major food items as noted by 50 families selected by the institute for internal demand. *Sic* The green graph is depicted as in the original manuscript.

and number of purchases per month by 50 representative families selected from the whole province was available from a survey done by the Provincial branch of the institute for internal demand. The prices index calculated for rice, sugar, oil, beans, egg and milk increase with 58% during the year (Figure 3a). A particular feature of the data was that the number of purchases per month was stable between 180 to 200 until January and February 1993 when it dropped to less than half (Figure 3b).

Geographical distribution and variations in food accessibility

The geographical distribution in Figure 1a is given as total incidence of

optic and peripheral neuropathy per 1000 inhabitants. This reveals a wide variation of cumulative incidence between municipios and Figure 1b still wider variations in rates between the 59 small areas studied in the three most affected municipios. Figure 1c shows the main land use in each of the 50 areas as well as the population density. It also shows the 8 pairs of high and low incidence areas selected for focus group interviews because they constituted the maximum incidence disparity in adjacent areas. The 30 focus group discussions had as main objective to search for toxic etiological factors induced by dietary changes related to processing, storage and use of new foods and surrogates

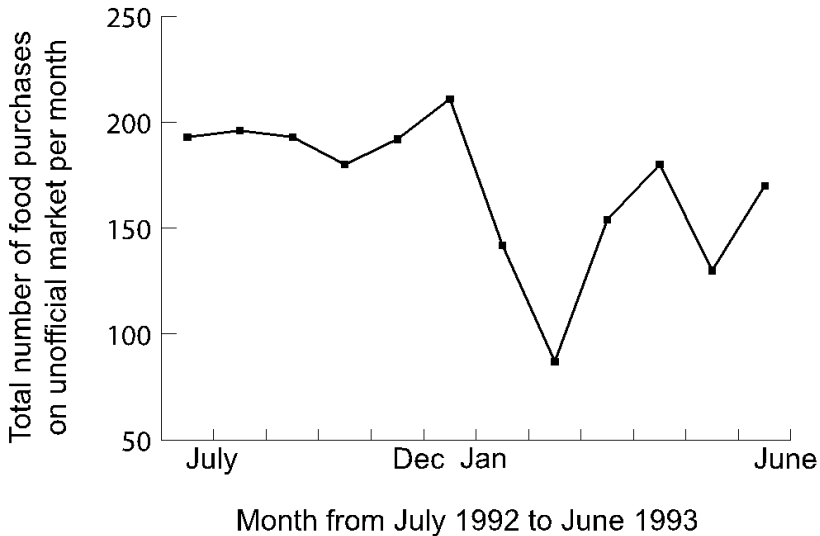


Figure 3b. Mean monthly number of purchases of 23 food items in the unofficial market by 50 families interviewed by the institute for internal demand.

but no such factors were identified and the main finding from the group discussions was that sharp incidence disparity corresponded to the marked agroecological and socio-economic differences as summarized in Table 2. Consistently, the groups in high incidence communities described diet in their communities as dominated by mainly rice, sugar, beans, cassava and cabbage with low fat and protein content. They considered diet to be better in neighboring low incidence communities and reciprocal statements were made by groups from these communities. In low incidence communities, the groups stated that dietary changes had been moderate as they had access to land for a varied local production but a steep increase of thefts of food products from the fields and farm constituted a major problem.

Table 3 summarizes the findings of the small area study. It shows that rates were associated to both population density and type of main land use. The rates in areas dominated by state tobacco production were significantly higher than in areas with mainly private agriculture when stratified for population density.

*Social distribution,
food access and housing quality*

Family economy index in the 892 families had a mean (\pm SD) of 0.19 (\pm 2.0) and the range was -4 to +10, with a tail of families with higher values (Table 4). The mean \pm 2 SD was used as cut-off between ordinary (-4 to +4) and good ($>$ +4) family economy. A total of 187 families were affected by neuropathy, 37 had cases of

Table 2. Main differences identified in pairs of adjacent high and low incidence areas based on a total of 30 focus group discussions and observations.

	Low incidence areas	High incidence areas
Main land use	Private agriculture	State tobacco
Population density	Low	High
Complementary food production	High and varied	Low or absent
Local food trade	Selling	Buying
Local alcohol trade	Buying	Selling
Diet	Moderate changes	Severe changes to monotonous carbohydrate diet low in fat and protein

Table 3. Mean cumulative incidence per 1000 inhabitants of epidemic neuropathy in groups of areas with similar main land use and population density (number of areas in parentheses).

Population/ km ²	State tobacco	State cattle & fruit & cooperatives	Private varied agriculture	Urban	Total
High	31.9±4.2	23.0	17.0±3.1 *	30.1	26.1
(≥ 400)	(4)	(1)	(4)	(4)	(13)
Medium	22.2±4.6	18.4±6.1	14.5±1.5*		16.5
(100-399)	(5)	(4)	(18)		(27)
Low	13.9	10.2	10.6		10.6
(<100)	(1)	(9)	(9)		(19)
TOTAL	25.3	13.5	13.7	30.1	16.7
	(10)	(14)	(31)	(4)	(59)

Table 4. Family economy index in affected and non-affected families.

	Affected n:187	Un-affected n:705	Total N:892
Ordinary economy	186	673	859
(-4 to +4)	(22%)	(78%)	(100%)
Good economy	1	32	33
(>+4)	(3%)	(97%)	(100%)

optic neuropathy and the remaining 150 only peripheral forms. A total of 21 families had two cases and 2 had three cases. The frequency of neuropathy was significantly lower among

family with good economy, chi-square with continuity correction yielded a p-value of 0.02. The only neuropathy registered among the 33 families with an index above 4 was one case of mild

Table 5. Pregnant and non-pregnant women aged 15-44 years with and without neuropathy in January to June 1993 in Piniar del Rio Province.

	Cases	Not affected	Rate per 1000
Pregnant < 14 weeks	3	2575	1.2
Pregnant ≥ 14 weeks	1	5150	0.19
Non pregnant 20-24 years	473	36648	12.9

Table 6. House standard in affected and non-affected families in urban San Luis.

	Affected n:78	Un-affected n:1391	Total N:1449
Good standard	53 (5.4%)	922 (94.6%)	975 (100%)
Bad standard	25 (5.2%)	449 (94.8%)	474 (100%)

peripheral neuropathy. Half of the 6 families with an index of -4 were affected by neuropathy.

Pregnancy and peripheral neuropathy were simultaneously reported in 6 women aged 22-33 years but 2 were found to have had onset of symptoms before pregnancy and three before week 14 of pregnancy. This leaves only one woman with later onset (week 37) of neuropathy. In July 1992 to June 1993 the mean monthly number of newly registered pregnancies in the province were 917 (range 737-1153) and the mean monthly number of women in first 3 and last 6 months of pregnancy during the first half year of 1993 is estimated to 2,570 and 5,150, respectively. The cumulative incidence of optic and peripheral neuropathy during the same period among women aged 15-19, 20-24 and 25-44 years were 2.4 and 5.5, 4.3 and 8.6, and 12.7 and 27.0 per 1000, respectively. The number of women in these age groups were 30,455, 36,648 and 113,602, respectively. Table 5

shows the rates of neuropathy in non-pregnant women aged 20-24 years is considerably higher than rates in those pregnant, especially after week 14.

Housing quality was not associated to occurrence of neuropathy in the small town of San Luis as shown by Table 6. In the capital town of Pinar de Rio the registered cumulative incidence was in fact highest in the suburb with newly built flats with good sanitary situation.

Discussion

The tropical myeloneuropathies (TMN) constitute a group of vaguely defined conditions from which HTL V-1 induced tropical spastic paraparesis and the epidemic upper motoneuron disease konzo, attributed to cyanide exposure from cassava, was separated in the last decade. The main clinical signs of remaining TMN's are peripheral and optic neuropathy, sometimes combined with signs of myelopathy. Most of these conditions are attributed to toxico-nutritional

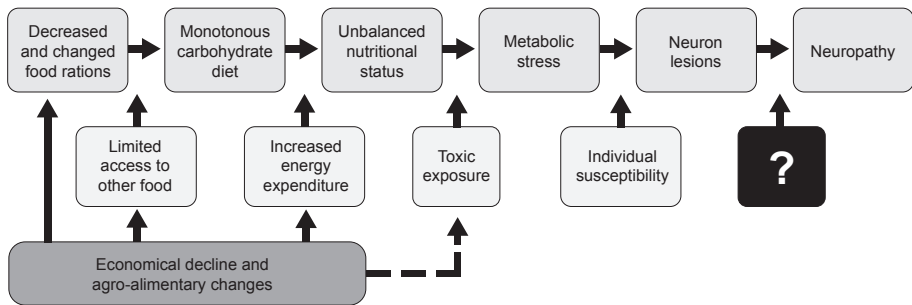


Figure 4. A conceptual framework for the main, contributing and basic factors of the toxico-nutritional hypothesis regarding the etiology of epidemic neuropathy in Cuba in 1993.

factors and they are difficult to differentiate from beri-beri and alcohol-tobacco neuropathies.

The main outcome of these ecological studies was that no specific dietary practice or other environmental factor could be linked to the disease. On the contrary the temporal, geographical and social distributions studied were all association to monotonous carbohydrate rich diet. Higher disease rates were associated to more severe form of the same type of dietary change that occurred throughout the country during the economic decline following the changes in international trade. Together with other studies they support a web of causation as presented in the conceptual framework in Figure 4.

The combination of ecological study design and use of unconventional qualitative and semi quantitative methods for exposure measurements was purposely chosen for three reasons. First because one aim was to try to identify possible etiological factors which had not formerly been considered. Second because these methods are advantageous for elucidation of interlinkages

between underlying, indirect and direct factors involved in the causative changes of events behind epidemics in marginal life conditions. Third because these methods can provide valid data on delicate and unofficial practices in local communities that are not easily quantifiable at individual or family level through interviews with structured questionnaires.

All studies are based on the surveillance data, the quality of which may be questioned. The data on temporal distribution that do not seem relevant to analyse in shorter time units than months. The reason is that the disease had a gradual onset and that awareness, criteria and surveillance organisation changed gradual over time as shown in Table 1. This means that the time of diagnosis in relation to time of onset will have changed gradually over time. The degree of misclassification of cases as non-cases and vice versa will also have change over time. Especially peripheral neuropathy may have been diagnosed late in the beginning and later on been over-diagnosed. Several actions taken during the epidemic surveillance (Table 1) makes

it reasonable to assume that this effect did not influence the analysis of geographical and social distribution. The short survey on color vision deficiency, the great awareness created and the intensive case findings in all areas makes it not probable that a significant number of cases have been missed.

The lowest levels of distributed amounts of meat and egg coincide with the start of the epidemic (Figure 2). The decline in number of purchases (Figure 3b) and more rapid increase of prices (Figure 3a) on the unofficial market in the same period may represent a very difficult period for supply of complementary food. The change to high amount of sugar occurred almost a year before the main epidemic and continued thereafter.

The geographical data also shows an association between the disease and more severely monotonous diet. The consistency between the qualitative findings in the focus group interviews and the quantitative analysis of land use maps should be noted. Table 2 shows that disease rate was linked to both population density and state production of tobacco and the explanation given by focus groups that this give very limited possibility for complementary food production seems plausible. The finding from the urban areas that families with better purchasing power have less disease is a further indirect support for an etiological role of monotonous diet.

The differences in rates between pregnant and non-pregnant women is a stronger argument for a dietary etiology linked to low protein intake since it is very unlikely that many pregnant

women with the disease should not have been noted through either disease surveillance or anti-natal statistics.

The findings cannot exclude that a single toxin is the major cause, but in this case it must be a toxin only taken in proportion to the monotony of the diet. This means a cheap and not tasty toxin that is generally available. It seems more probable to assume that the unbalanced nutritional situation has a direct etiological role without which the disease does not occur. Toxic contributing factors like tobacco smoking and unknown metabolic factors may operate only on individual level. It has not been possible to find any plausible mechanism by which an infectious factor could have been the main cause of the epidemic.

Epilogue

This paper was presented at the international workshop on epidemic neuropathy arranged by WHO and the Ministry of Health of Cuba in Havana July 12-15, 1994, but remained unpublished after that. Until his death Hans Rosling kept the print out of the manuscript and accompanying data, figures and references in a file cabinet. His wife Agneta Rosling and daughter Anna Rosling decided that the special issue of SMT in memory of Hans Rosling was an excellent opportunity to finally get this paper published. They proof read and prepared the manuscript for publication together with the senior author Rafael Perez Cristiá, formatting of text and figures was performed by Cajsa Lithell.

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Hans vid datorn, på plats på Kuba.

Foto: Privat

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Upphovsmännens tack

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