

# Cuban Epidemic Neuropathy: Insights into the Toxic–Nutritional Hypothesis through International Collaboration

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## ABSTRACT

From 1991 to 1993, an epidemic of optic and peripheral neuropathy—the largest of the century—broke out in Cuba, affecting more than 50,000 people. Initially the main clinical features were decreased visual acuity, central and cecentral scotomas, impaired color vision and absence of the papillomacular bundle. Later, peripheral and mixed optic–peripheral forms began to appear. Due to the magnitude of the epidemic, the Cuban government requested help from the international community at the 46th World Health Assembly in 1993. PAHO and WHO immediately responded by sending a mission of international experts. Several hypotheses regarding the pathogenesis of Cuban epidemic neuropathy were put forward including: toxic, nutritional, genetic and infectious. The authors refer to extensive studies by researchers sponsored by the Cuban government and PAHO/WHO, joined by scientists from several other countries, including the USA. This paper describes their multidisciplinary work, particularly devoted

to investigating the hypothesis of a primary toxic–nutritional cause of the epidemic. Clinical aspects, such as case definition and clinical description, were vital issues from the start. Cuban physicians who first examined patients received a clear impression of its toxic–nutritional origin, later confirmed by international experts. Research then focused on the mechanisms contributing to damage under the toxic–nutritional hypothesis. These included injuries to the mitochondrial oxidative phosphorylation pathway, nutritional deficiencies, excitotoxicity, formate toxicity and dysfunction of the blood–brain barrier. It was expected that the results of such international collaboration into this major health problem would also shed more light on mechanisms underlying other nutritional or tropical myeloneuropathies.

**KEYWORDS** Optic neuritis, optic neuropathy, peripheral neuropathy, neurotoxicity syndromes, disease outbreaks, international cooperation, Cuba

## INTRODUCTION

The outbreak of optic and peripheral neuropathy in Cuba at the beginning of the 1990s affected more than 50,000 persons throughout the country.[1] The epidemic followed an abrupt economic crisis due to the collapse of the socialist bloc (1989–1991) and the tightening of the US embargo, which led to severe food shortages and greater physical demands on the population (motor-driven transportation was at a near standstill). These deprivations were the underlying factors in what became the largest epidemic of neurological disease in the 20th century.[2]

The first cases were reported in Cuba's westernmost province, Pinar del Río, towards the end of 1991: patients presented bilateral vision loss, suggesting a diagnosis of retrobulbar neuritis. As case numbers continued to climb, in April–June 1992, Cuba's Ministry of Public Health (MINSAP) sent a multidisciplinary commission to examine the patients in the field. Visual deficits described included decreased visual acuity and color perception, and/or central or cecentral scotomas, with a normal fundus or slight temporal pallor of the optic nerve. In some cases, neurological impairments such as a predominantly sensory peripheral neuropathy and hearing loss were observed. Cuban scientists began investigating the possible etiology and hypothesized that the cause was probably multifactorial, with emphasis on nutritional and toxic factors.[3] without ruling out

a possible viral contribution, based on virologists' findings from cerebrospinal fluid (CSF) studies.[4]

After months of research, two types of neuropathy were defined: an optic form (characterized by subacute onset of the symptoms and signs previously described) and a peripheral form, a predominantly sensory neuropathy, with posterior spinal cord involvement in some cases, with or without concurrent optic neuropathy. The optic form was more prevalent in men, the peripheral form in women. Both forms were often accompanied by weight loss and fatigability. Incidence rates were 926.7 per 100,000 population for persons aged 45–65 years and 290.9 per 100,000 for persons aged >65 years, lowest in children aged <15 years, 4.2/100,000.[3] The epidemic spread from west to east with the highest incidence rates in Pinar del Río Province (1332.8/100,000) and lowest in Guantánamo, Cuba's easternmost province (65/100,000). Risk was associated with smoking; lower body mass index; and lower intake of animal protein, fat, and foods containing B vitamins. Beginning 1993, Dr Hector Terry Molinert (then MINSAP's Vice Minister for Epidemiology) and his team proposed distribution of vitamin supplements (including B vitamins) to the entire population. After this was implemented, the epidemic began to decline as of May 1993.[3] At first, the disease was named Cuban epidemic optic neuropathy, but as peripheral nervous system involvement became apparent, a more general term was applied: Cuban epidemic neuropathy (CEN).[5]

**IMPORTANCE** Cuban epidemic neuropathy research exemplifies how intensive and widespread international collaboration can help solve important health problems, in this case, shedding light on other metabolic or mitochondrial optic neuropathies.

Due to CEN's scale as a public health problem, the Cuban government requested help from the international community at the 46th World Health Assembly in 1993. Among the first to arrive in Cuba to investigate the outbreak through the US-based International Peace for Cuba Appeal were Norah Lincoff and Michio Hirano, who examined patients between May 4 and 11,

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1993, and soon published their impressions of the epidemic.[6] Almost simultaneously, PAHO and WHO responded by sending missions May 16–26 and June 16–24, 1993, briefed on arrival by Cuban experts in nutrition, toxicology, ophthalmology, neurology and epidemiology. The missions' objectives were mainly to review and analyze available information regarding CEN's clinical and epidemiological features and possible causes, and to recommend and collaborate in research areas that could be useful to determine etiology and eventual control. US scientists from various clinical and scientific backgrounds who participated in the PAHO/WHO missions published a detailed account in 1997.[7]

The information gathered by Cuban and international experts who visited the country from May 1993, was presented at the International Workshop on Cuban Epidemic Neuropathy, held in Havana in July 1994. At that time, the main conclusion was that inflammatory or infectious origins were unlikely. Morphologic changes were consistent with an axonal neuropathy, similar to that observed in toxic-metabolic, or nutrition deficiency conditions. The Workshop emphasized the need to continue investigating and to design further studies with a multidisciplinary and multicenter approach.[8]

**The Role of International Collaboration** A vast program was established between MINSAP, PAHO/WHO, Orbis International, CDC, US NIH and other international organizations to investigate CEN's causes. Experts from Cuba, the USA and Venezuela collaborated in studying CEN's clinical, toxicologic and neurochemical characteristics in order to understand its underlying mechanisms. The authors' experience reported in this paper are related to joint work carried out in patients in Pinar del Río during the epidemic period and later in development of models of low-dose chronic methanol administration in experimental animals.

### OBJECTIVES

1. Describe the clinical ophthalmological and neurological characteristics of the CEN epidemic in patients residing in Pinar del Río Province.
2. Propose a pathophysiological hypothesis for CEN etiology.

**Justification** The CEN investigation was started early in 1992 by Cuban scientists and continued from May 1993 in collaboration with scientists mainly from the USA, but also from the United Kingdom, Venezuela, Russia and elsewhere. The need to identify the possible causes or contributing factors generating this unique disease outbreak led to an extensive research network that would eventually investigate various hypotheses about the epidemic's origins.

**Participating institutions** Researchers from Cuba's Neurology and Neurosurgery Institute (INN) studied CEN in Pinar del Río Province during the first quarter of 1992. Rosaralis Santiesteban Freixas (RSF), head of the Neuro-Ophthalmology Department, and Santiago Luis (SL), neurologist and Director of the Institute, carried out extensive clinical examinations of CEN patients, while Alina González-Quevedo (AGQ) and Ileana Alfaro, of the Neurochemistry and Neuroimmunology Laboratory, conducted serum and CSF studies.

Alfredo Sadun (AS) was a member of the PAHO/WHO delegation (at the time, professor of ophthalmology and neurosurgery at the Doheny Eye Institute, University of Southern California, Los Angeles, USA). He travelled to Cuba in May and September 1993 to perform clinical assessments on a small number of CEN patients. In 1994, he visited Cuba twice again, the second time accompanied by Janis Eells (JE), professor of pharmacology and an international expert in methanol toxicity at the Department of Pharmacology and Toxicology, University of Wisconsin–Milwaukee, USA.

Two years later, after the epidemic had subsided, Dr Lucimey Lima (LL), an expert in basic retinal and optic nerve neurochemistry, participated in a scientific meeting in Cuba and subsequently joined the research group.

**Mechanisms** Collaboration with US colleagues began in 1993–1994 under the aegis of a larger cooperation effort between MINSAP and PAHO/WHO. Financial support came from PAHO, Orbis International, and US NIH. Collaboration with Venezuelan colleagues in 1997–2002 was supported by grants and fellowships from Venezuela's National Foundation for Science, Technology and Innovation (Grant S1-2001-903) and the Scientific and Technological Research Council (Grant S1-723, fellowship from Project PI-3277, scholarship PI-98-3277).

### Activities

- **April–June 1992:** clinical and physical ophthalmological examinations in Pinar del Río Province, neurological examinations of patients, serum and CSF sample collection
- **May and September 1993:** clinical and physical ophthalmological examination of 20 patients in Pinar del Río, reassessment of patients in September, analysis of methanol content in sample of home-brewed rum from Pinar del Río
- **1994:** formate and folate analysis of serum and CSF samples stored at INN, histological analysis of four sural nerve and one optic nerve biopsy from CEN patient
- **1995:** development of a rat model of chronic methanol intoxication by AS (in USA) and rat/human comparative histological studies
- **1998–2000:** development of a rat model of chronic methanol intoxication by AGQ (in Venezuela) and neurochemical studies

**Ethics** Studies conducted in human subjects and animal experimentation were approved by the ethics committees of Cuba's INN and the Venezuelan Institute of Scientific Research and were conducted according to the Declaration of Helsinki for experimentation in human subjects and animals. [9] Participants gave written informed consent.

### ANALYSIS

In response to Cuba's request and PAHO/WHO's call, several cooperative initiatives were planned and carried out jointly by US, Latin American and Cuban researchers.

**Clinical findings** Researchers from Cuban institutions started investigating the neuropathy outbreak from its onset in Pinar del Río Province. RSF carried out ophthalmological examinations, for which a protocol was established in April–May 1992. As a result, visual impairment was described as follows:[10,11]

- Bilateral decreased near and far visual acuity, not corrected with lenses
- Impaired red–green color vision on the Ishihara test[12]
- Bilateral and symmetrical central and cecocentral scotomas, especially for red and green, in tangent field testing
- Normal fundus examination or slight temporal optic disc pallor

The first cases were mainly men aged 25–64 years, heavy smokers and/or alcohol consumers, who complained of blurred vision, light sensitivity and weight loss. This, together with the ophthalmological findings, pointed to an initial diagnosis of tobacco–alcohol amblyopia.[13]

In May–June 1992, more Cuban experts visited Pinar del Río (biostatisticians, epidemiologists, neurologists and nutritionists, among others). By then, the morphology of visual evoked potentials was also found to be altered, displaying a bifid p100 wave. Neurological signs and symptoms were also detected in some patients with optic neuropathy, consistent with a predominantly sensory peripheral neuropathy: hearing loss, deep tendon hyperreflexia indicating corticospinal tract involvement, and increased urinary frequency, urgency in urinating and in some cases urinary incontinence.

Three forms of neuropathy were identified: optic, peripheral and optic–peripheral. Later, cases were also reported in other provinces with an apparent pattern spreading from west to east. House-to-house surveys and case–control studies in Pinar del Río reported vision improvement in most cases when patients were treated with B-complex vitamins. The multidisciplinary commission's hypothesis was that the epidemic stemmed from toxic–nutritional causes. Although a viral contribution was not ruled out at the time, the epidemiological pattern was inconsistent with that of a communicable disease.[13]

Venezuelan neuro-ophthalmologist, Rafael Muci, a PAHO/WHO expert who participated in the mission to Cuba in May 1993, had shown Cuban researchers the use of red-free light for fundus examination, permitting visualization of loss of nerve fiber layers in the retina. In December 1992, his expertise had been requested by Cuban neuro-ophthalmologists cognizant of the need to demonstrate anatomical correlates of functional damage to the papillomacular bundle observed in visual field studies.

Alfredo Sadun and his colleagues conducted extensive neuro-ophthalmological and psychophysical examinations and interviews on 20 patients upon his arrival to Cuba with the PAHO/WHO delegation in May 1993. Several common features and patterns were subsequently determined, recommended and accepted by the Cuban epidemic task force for a new case definition.

Diagnosis required evidence of nerve fiber layer loss in the papillomacular bundle and any three of the following five symptoms and signs: subacute bilateral vision loss, dyschromatopsia, saccadic smooth pursuit, central or cecocentral visual field defect and impaired contrast sensitivity. Cuban ophthalmologists were trained by Muci in the new recommended case definition and in use of neuro-ophthalmological (red-free funduscopy) and psychophysical tests (threshold Amsler grid testing)[14] required to diagnose epidemic optic neuropathy. This considerably reduced the number of false positives.[5]

**Neurochemical studies and experimental models** Among the first laboratory studies conducted early in the outbreak were serum and CSF analyses to assess the possibility of immune-mediated inflammatory optic neuropathy. The results did not support this hypothesis, since only a minority of patients exhibited intrathecal IgG synthesis. These findings and CEN's epidemiological and clinical features made an infectious process unlikely.[15] Increased blood–CSF barrier permeability was observed in approximately 30% of cases, blood–CSF damage being more frequent within 16 to 60 days of disease onset and disappearing after 120 days. Blood–CSF barrier dysfunction was more prevalent in patients with severe neurological impairment but was not found to be related to severity of ophthalmological damage. These results were later confirmed in a larger sample of patients. Considering that the most favored hypothesis for CEN origin was toxic–nutritional, it was suggested that blood–brain barrier dysfunction could be associated with metabolic derangements and/or neurotoxicity.[16]

Although previous epidemiological studies indicated that intake of essential amino acids in CEN patients was below 70% of recommended values,[17] we found levels of essential amino acids were generally preserved, except for a selective reduction of taurine and threonine.[18] Serum albumin levels were also preserved.[15] Taurine, a sulfur containing neutral  $\beta$  amino acid, was of particular interest because of its important CNS trophic function, especially in the retina and optic nerve, as well as its antioxidant properties.[19] Taurine was lower in patients with more severe ophthalmological impairment, but was not associated with severity of polyneuropathic manifestations, indicating that taurine deficiency could play a role in the optic form's pathophysiologic mechanisms.[18] Although endogenous taurine synthesis occurs in the liver and brain (pyridoxine required as a cofactor), the human body has limited capacity to synthesize it. Thus, vitamin B6 would be considered an essential amino acid in situations of widespread vitamin deficiency. Furthermore, animal products are the main sources of taurine in humans, and these were very scarce in the Cuban diet in the early 1990s.

CEN patients' CSF displayed accumulation of glutamate and aspartate (excitatory amino acids), suggesting that excitotoxicity could also be involved in the disease's pathophysiology.[18]

In the search for toxins that may have triggered CEN, noncommercial (home-brewed) rum samples acquired in Cuba by AS were tested in the USA, revealing methanol levels from 0.87% to 1%.[5] Although this amount would not lead to acute methanol intoxication, prolonged exposure, especially in the presence of folate deficiency, could lead to formate accumulation and subacute impairment of visual function. Furthermore, it should be noted that physiological levels of methanol are present in the blood, from environmental exposure and derived from diet through normal metabolic processes. Methanol and/or formate can be found in some foods, including fruits, vegetables, juices (mainly orange, grapefruit and tomato), fermented beverages, aspartame sweetened foods, beans, honey and roasted coffee.[20]

In order to investigate folate and formate levels in CEN patients, JE traveled to Cuba in 1994 with AS and contacted the INN's Neurochemistry Laboratory, which had stored serum, and CSF samples from CEN-confirmed patients in Pinar del Río. Formate analysis was conducted at INN and samples were transported to the USA for folate analysis. Marked folate deficiency was detected in more than 50% of samples analyzed, and serum formate



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accumulation in 25%. Folate concentration was inversely correlated with severity of optic neuropathy, while formate concentration was directly correlated.[21] Although it is unlikely that classic methanol poisoning (which produces an acute formate acidosis) could have significantly contributed to the entire epidemic, consumption of ethylic alcohol containing small amounts of methanol was a risk factor for developing the disease.[5] It should be emphasized that this study included patients from the same region where the home-brewed rum samples had been taken, and 55% were alcohol drinkers; thus chronic formate toxicity may have contributed to triggering the disease in some patients.[22] Gay's Isle of Youth study concluded that smoking and alcohol consumption did not by themselves account for disease occurrence but reinforced the effects of dietary deficiencies.[23]

At this point in the investigation of CEN, the need emerged to develop animal models matching some characteristics of the Cuban patients, especially the possibility of chronic low-level methanol exposure in the presence of folate deficiency. The rationale was to combine folate deficiency with chronic methanol toxicity so as to increase formate production to match serum levels observed in CEN patients. Two models were developed independently by Cuban researchers. One was an experimental model of chronic methanol administration in rats with dietary folate deficiency.[22] Analysis of optic discs disclosed prelaminar axonal swelling anterior to the lamina cribrosa, indicating axoplasmic blockage at this level. Ultrastructural examination revealed early axonal degeneration and a relative abundance of mitochondria, many of which were swollen and with disrupted cristae. These histopathologic features matched very closely those observed in the optic disc of a CEN patient who died of unrelated causes. Due to the selective action of formic acid as an inhibitor of mitochondrial function,[24] these results supported the hypothesis that impaired mitochondrial oxidative phosphorylation produced axoplasmic blockage.


The second model was developed in rats with chronic low-level methanol administration and folate deficiency induced by methotrexate, where accumulation of aspartate (an excitotoxic amino

acid) was detected in the optic nerve,[25] results which paralleled the increased levels of aspartate and glutamate in CEN patients' CSF,[18] suggesting participation of excitotoxic mechanisms.

**Pathophysiological mechanisms underlying CEN** Very early in the investigation, striking clinical similarities with Leber hereditary optic neuropathy (LHON) were recognized and later discussed with international experts, leading to the search for mutations in patients.[26,27] However, later it was definitively demonstrated that CEN was not associated with LHON.[28] As the main pathogenic mutations of LHON affect subunits of the mitochondrial complex in the respiratory chain, it was suspected that CEN was possibly affecting mitochondria on an acquired basis.[29]

Clinical, epidemiological, neurochemical and experimental studies revealed possible mechanisms underlying CEN, most likely resulting from insults to the mitochondrial oxidative phosphorylation pathway from severe nutritional deficiencies (folic acid and other B-complex vitamins), leading to impaired detoxification mechanisms and thus to chronic accumulation of exogenous and endogenous toxins (formate from methanol metabolism, and/or exposure to cyanide from dietary products and cigarette smoke).[22] Furthermore, in CEN's pathophysiological mechanism, where oxidative stress was definitely the "conductor of the orchestra," three interrelated processes may have been present: excitotoxicity, blood-brain barrier dysfunction and formate toxicity. Additionally, a selective taurine deficiency may have complicated the picture due to its abundance in the retina and well-known antioxidant and neuroprotective properties.[30]

## CONCLUSION

Cuban epidemic neuropathy research exemplifies how intensive and widespread international collaboration can work to solve important health problems, in this case, further shedding light on other metabolic or mitochondrial optic neuropathies. US-Cuba cooperation, under the PAHO/WHO umbrella, was key to developing, pursuing and generating evidence to support the nutritional-toxic hypothesis of CEN etiology. 

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*Submitted: October 30, 2017*

*Approved for publication: March 13, 2018*

*Disclosures: None*



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