Moratorium on mayhem lest there be a requiem

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A warm summer evening, June 25, 1965, and resident in medicine, Nick Pinheiro, was seated at his favorite tasca in Porto enjoying Portugal's outstanding seafare and a bottle of chilled vinho verde. This had become Nick's usual haunt on Friday evenings and he now knew most of the staff including Carlos, a waiter whose hoarse voice and slurred speech made deciphering the evening's specials a challenge. Tonight Carlos was quite troubled mumbling that sharp, shooting pains in his feet and deep stabbing pains in his calves made tending tables difficult. Also troublesome was brother Juan, a chef in Lisbon, who earlier in the week was dismissed because too much salt had been added to meals he prepared. Carlos explained this was not because Juan was careless or that he had overindulged in his favorite wine. Instead, this incident was more likely related to Juan's recent unsteadiness and faltering vision. Nick offered assistance, but Carlos politely declined and departed in a rather wide-based, stumbling gait.

Friday next again found Nick dining at the tavern reflecting on several of his patients while gazing out at the River Douro. His reverie was interrupted by the clatter of fallen dishes. Not 10 feet away stood an embarrassed, unsteady Carlos. Nick rushed to his aid. Carlos brushed the incident off as nothing more than a result of summer's heat. Perhaps too he was weakened by diarrhea of several days duration, but this was an intermittent problem to which he had grown accustomed. Nick found Carlos' pulse to be irregular and insisted he call an ambulance. A second episode of near-syncope convinced Carlos that hospitalization was unavoidable. Nick wondered if this episode could be explained solely by fluid loss and subsequent orthostatic. Why arrhythmia? Perhaps there was hypokalemia.

At the hospital Nick found Carlos normotensive and indeed orthostatic and began intravenous fluids. Bedside ECG demonstrated right bundle branch block, left axis deviation and sinus rhythm with premature atrial contractions and runs of atrial fibrillation (AF). Carlos' right pupil was dilated with irregular outline and fringed edges; it did not react to light or accommodation. Thyroid non-palpable; neck veins not distended; lungs clear. Cardiovascular examination did not reveal cardiomegaly, gallop, or murmur. Pain and temperature sensations in both lower extremities were blunted while position and vibration sensations were lost in feet and ankles. Romberg's test would have to wait. Pertinent laboratory tests revealed: hemoglobin 10 g/dl with 3.9 red blood cells/cm³; normal white cell count and differential, serum electrolyte- and creatinine, albumin, and glucose; negative serology for syphilis; urine negative for porphyrins and Bence-Jones protein; cerebrospinal fluid protein 200 mg/dl, otherwise negative.

On rounds the following morning, Nick found Carlos sitting upright in bed with labored breathing and bilateral inspiratory rales on examination. A diuretic was given followed by sequential doses of intravenous digoxin over several hours. Why pulmonary congestion? Heart size and configuration on X-ray were normal. Since admission Carlos had received 3 liters of normal saline. Could he have occult constrictive pericardial disease? Perhaps intravascular volume was normal on admission and yet Carlos remained orthostatic. Ventricular extrasystoles—presenting as parasystole on bedside ECG—were evident later in the day.

Consuelo, Carlos' 33-year-old frail and ill-appearing sister, came to visit him. Nick met with her in hopes of obtaining pertinent historical information and family history. Like Carlos and Juan, Consuelo too had become unsteady and walking was difficult, particularly at nights, when she often fell in attempting to reach the bathroom. And there was incontinence of urine and chronic constipation. She mused: "Doctor, all seems to be failing me." Only this morning, in preparing for her visit, she scalded her right foot unable to gauge the temperature of her bath.
water. She also reported that their father had died suddenly at age 45. Prior to his demise he had complained of progressive weakness of his legs, nausea, vomiting and constipation. Nick had formed his differential diagnosis and was eager to discuss his thoughts on professor rounds.

Before he could commit his thoughts to paper, Nick was summoned by a floor nurse to another patient he had admitted yesterday. Mrs. F., a 51-year-old housewife with known rheumatic mitral stenosis, had been hospitalized because of troublesome palpitations of several days duration associated with breathlessness at rest and on exertion. ECG indicated AF and intravenous digoxin had been given with slowing of the ventricular response. Earlier today she was begun on a 2-hourly schedule of quinidine and after 4 doses sinus rhythm had been restored. A sudden convulsive seizure appeared 2 hours after her last dose. She now was pulseless and without blood pressure; CPR had been initiated. Nick noted polymorphic ventricular tachycardia that gave way to ventricular fibrillation (VF) on bedside ECG and promptly applied electrical cardioversion. Sinus rhythm was restored and recovery was uneventful. QT interval was prolonged to 60 ms. Why had this episode occurred? A coronary embolus? Not likely. Mrs. F. had not experienced a toxic reaction to quinidine, such as fever, rash or cinchonism, and her serum potassium was normal. Still, quinidine seemed the culprit. Nick thought he best revise his use of this ‘antiarrhythmic’ agent lest there be a requiem for other patients less fortunate than Mrs. F.

Answer

In 1952 Corino Andrade reported on 74 patients belonging to 12 different families living in Povoa de Varzim, a fishing town in the Oporto region of Portugal. Patients presented with a puzzling constellation of symptoms and signs not unlike Carlos and his family. The illness had a long history in the region where it was known as ‘mal dos pésinhos’ or ‘foot disease’. Features included: insidious onset in young adults; peripheral neuropathy predominantly of lower extremities with impaired sensory and motor functions; autonomic dysfunction (e.g., Adie’s pupil, sphincteric disturbance, orthostatic hypotension). Vitreous opacities blurred vision. Postmortem studies would demonstrate generalized amyloidosis.

Cardiac infiltration by amyloid leads to abnormalities of atrioventricular and intraventricular conduction and appears after the onset of progressive neuropathy. Amyloid deposition in atria account for atrial arrhythmias while in the ventricles’ interstitial space they account for a restrictive cardiomyopathy with diastolic dysfunction that can simulate constrictive pericarditis. In 1981, it was reported that digitalis selectively binds to amyloid fibrils leading to heterogenous concentrations of this sodium-potassium ATPase inhibitor within the myocardium. This perhaps provides substrate for abnormal automaticity, or spontaneous impulse formation, and parasystole—an ectopic, fixed rate, asynchronously discharging pacemaker tissue.

Today it is recognized that familial amyloidotic polyneuropathy, a rare systemic disorder involving the peripheral nervous system, is based on a genetic variant of normal prealbumin, or transthyretin, that transports thyroxine in the circulation. Its variant causes autosomal dominant inherited forms of amyloidosis when deposited as amyloid fibrils and accounts for peripheral neuropathy, cardiac amyloidosis, amyloid kidney and ocular disturbances. More than 30 amyloidogenic mutations of the transthyretin gene have been described. The mutated transthyretin in which valine has been replaced by methionine at position 30, the Met-30 variant, is most common. Most transthyretin is produced by the liver. In selected patients, liver transplantation has been effective in eliminating the source of variant transthyretin, reducing the circulating concentration of transthyretin and ameliorating the disease.

Selzer and Wray in 1964 described the association between syncope and ventricular fibrillation in patients receiving quinidine—so-called ‘quinidine syncope’—and which is unrelated to hypersensitivity to the drug. A distinctive polymorphic ventricular tachycardia (VT), characterized by QRS complexes of changing positive and negative amplitude with respect to the isoelectric line and often referred to as ‘torsades de pointes’, can accompany quinidine-induced prolonged QT interval and may deteriorate to VF. This VT has been related to inhomogeneous recovery of repolarization and to early afterdepolarizations. Cinchonism is a syndrome caused by toxicity to quinidine and quinine alkaloids found in the bark of the cinchona tree. It includes ringing in the ears, headache, nausea and blurred vision. An early reference to the use of cinchona bark in the management of AF is that of a French physician, de Senac, who in 1749 noted its use in the successful management of a ‘rebellious palpitation’. It would appear that quinidine can create its own mayhem.