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Neuritis cordis due to the acute polyneuritis of the Guillain-Barré syndrome*

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Summary. Three patients with the Guillain-Barré syndrome which followed the course of Landry's acute ascending paralysis died a sudden cardiac death. Autonomic dysfunction had appeared clinically, consisting of sphincter disturbances in one patient and fluctuating blood pressure and bradycardia in the other. In a twenty-three year old female patient cardiac function had been inconspicuous, apart from tachycardia, but the ECG showed S-T segment depression and flat T waves. Postmortem examination revealed acute inflammatory demyelinating polyradiculoneuritis involving the peripheral autonomic nervous system and especially the nerves of the heart. Immunohistochemically, the inflammatory cell infiltrations of this neuritis cordis consisted of macrophages (MAC 387 positive) and T lymphocytes (UCHL1 positive). No indication of a direct viral infection of the inflamed cardiac nerves was detectable by immunohistochemistry (HSV, CMV, influenza virus) nor by electron microscopy. The neuritis cordis was classified as an inflammatory cardioneuropathy secondary to a patchy acute polyneuritis of the Guillain-Barré syndrome, involving the autonomic nervous system. Myocarditis could be discounted, and the neuritis cordis was thought to be responsible for the sudden cardiac death.

Key words: Guillain-Barré syndrome – Autonomic nervous system – Sudden cardiac death – Neuritis cordis – Immunohistochemistry

Introduction

The pathological changes of the Guillain-Barré syndrome (GBS) (Guillain et al. 1916), the most common generalized paralytic disease of the peripheral nervous system, consist of segmental demyelinating inflammation of nerve roots and peripheral nerves (Pette and Kornyey 1930; Haymaker and Kernohan 1949; Krücke 1955; Asbury et al. 1969; Prineas 1981). Clinical signs of autonomic dysfunction are more common than is generally thought in this mainly motor paralytic disease (Lichtenfeld 1971). Apart from abnormalities in blood pressure, vascular reflexes, sweating, bowel and bladder function there may be disturbances of the heart rate and cardiac rhythm (Lichtenfeld 1971; Schuchardt et al. 1983; Henze et al. 1986). As early as 1892 W. Osler observed that some patients with "acute febrile polyneuritis" succumbed to "paralysis of the heart". Even today, autonomic dysfunction, especially of the cardiovascular system, may lead to sudden death in GBS, and is therefore responsible in part for the fatal outcome of this disease. Now as formerly, the mortality rate is unexpectedly high in severe cases (Schuchardt et al. 1983) despite the advances made in artificial respiration, preventing the frequently occurring respiratory insufficiency resulting from Landry's acute ascending paralysis (Landry 1859). In a recent clinical report (Keenlyside et al. 1980) the immediate cause of sudden death in 15 of 35 fatal GBS cases had either been uncontrolled arrythmia, a sudden change in blood pressure, or circulatory collapse. Pathological investigations of the peripheral autonomic nervous system in GBS are very rare (Stochdorph 1961; Matsuyama and Haymaker 1967), and no special attention has been paid to the cardiac nerves (Lichtenfeld 1971). However, Asbury et al. (1969) have stated in their study of inflammatory lesions in idiopathic polyneuritis that "when sympathetic nerves were sampled, they were involved". Since Haymaker and Kernohan's detailed clinicopathological report of 50 fatal GBS cases (1949), seven of which showed focal perivascular collections of

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lymphomonocytic cells in the myocardium, focal myocarditis has been discussed as a relevant finding (Lichtenfeld 1971; Kunst and Grosser 1974; Henze et al. 1986).

In this study we present the histological changes of the cardiac nerves in three fatal cases of GBS and discuss the phenomenon of neuritis cordis.

Case reports

Case 1: This 35-year old man was admitted to hospital in November 1971 because of numbness in his legs and suspected intervertebral disk prolapse. Seven days before he had abdominal pain. Two days after admission he developed shortness of breath and cyanosis. Body temperature rose to 39.0° C. Paralysis of the legs, weakness of the arms, and sphincter disturbances were found, neurologically. CSF examination revealed mild pleocytosis (40 cells per mm^3) and protein elevation (150 mg%). A single, routinely done electrocardiogram showed no abnormalities. The cyanosis was thought to be due to lung oedema, which was treated with furosemide. Intensive care measures and cardiac monitoring were not undertaken. In the early morning of the third hospital day the patient was found dead in his bed.

The postmortem examination (Dr. H.J. Richter, Institute of Pathology, University of Essen Medical School) revealed a lymphomonocytic polyradiculoneuritis, involving the cranial nerves (Fig. 1a) and peripheral autonomic nerves, such as the coeliac ganglion. The adrenal medulla was also infiltrated by lymphocytes and monocytes. An additional finding was bronchopneumonia. The coronary vessels showed a slight fatty change without stenosis.

Case 2: In January 1979, this 23-year old woman developed tingling and numbness of the extremities after a common cold which had begun two weeks earlier. On admission to hospital her body temperature was 38.6° C. Her lips were strikingly cyanotic. Neurological examination showed signs of polyneuritis and slight meningism. The CSF contained 25 lymphocytic cells per mm^3, and the protein content was elevated. Except for tachycardia her heart function was inconspicuous, but electrocardiography showed abnormalities consisting of S-T depression and flat T waves. Ascending paralysis appeared without necessitating assisted ventilation. However, two days after admission the acute illness terminated suddenly in cardiac failure.

The postmortem examination (Dr. W. Lenz, Institute of Pathology, University of Düsseldorf) revealed severe lymphocytic polyradiculoneuritis, mild meningitis and myelitis (examination of the CNS was done by Prof. Dr. W. Wechsler, Institute of Neuropathology, University of Düsseldorf). Intra-alveolar lung oedema and acute bronchopneumonic infiltrates were also found. An attempt to isolate virus from postmortem samples of lungs, liver, spleen, and brain were made (Prof. Dr. E. Kuwert, Institute of Medical Virology and Immunology, University of Essen Medical School) without result.

Case 3: This 53-year old man was admitted to hospital in January 1986 because of back pain radiating into the legs, distal paresthesias, and numbness and weakness of the lower extremities. The first examination revealed severe paresis of the lower extremities and a mild one of the arms. On admission, the cell content of the CSF was 50, in the control examination 8 per mm^3; total CSF protein content was 140 mg%. During the following days the patient's paresis increased and was associated with paresis of the cranial nerves (ophthalmoplegia). The respiratory muscles were also involved, and assisted ventilation was needed. Moreover, gastrointestinal bleedings due to a chronic gastric ulcer occurred. Because of repeated phases of blood pressure fluctuation and bradycardia, treatment with a cardiac pacemaker and arterenol was necessary. But despite this treatment, the patient died from cardiovascular failure on the 10th hospital day.

The postmortem examination (Dr. V. Reinhardt, Institute of Neuropathology, University of Essen Medical School) revealed a lymphomonocytic polyradiculoneuritis, including vegetative nerves. The ventral horn cells showed central chromatolysis, and the meninges were focally infiltrated by some lymphocytic cells. Further findings were bronchopneumonia and intra-alveolar lung oedema, thromboembolism of small peripheral lung arteries, and hypoxic cell changes of the brain. The heart was normal on gross inspection; the coronary vessels showed mild atherosclerosis without stenosis.

Material and methods

Blocks of heart tissue and other organ tissues routinely taken during the autopsy were embedded in paraffin after fixation in 4% formaldehyde solution. Additionally, the formalin fixed hearts, which were grossly normal, were available from cases 2 and 3; therefore several tissue blocks of the conduction system could be studied.

The deparaffinized sections were stained by conventional methods (haematoxylin and eosin; elastic van Gieson; luxol fast blue and cresyl violet) and immunohistochemically using the PAP method and a system consisting of biotinylated anti-mouse immunoglobulins and peroxidase-conjugated avidin for the detection of primary polyclonal rabbit antisera and hybridoma-derived monoclonal antibodies, respectively (DAKO-PATTS, Glostrup, Denmark). The peroxidase was made visible by the diaminobenzidine reaction, and the sections were counterstained with haematoxylin. In detail, polyclonal rabbit antisera against protein S-100 (Dako), herpes simplex virus (DAKO), cytomegalovirus (Polysciences, Warrington, U.S.A), and influenza virus (Wellcome, Burgwedel, F.R.G) were used. The antisera against cytomegalovirus and influenza virus originated from goat and cow, respectively; therefore, the corresponding detection system consisted in goat-PAP (DAKO) and peroxidase-conjugated anti-cow immunoglobulin (DYNA-TECH, Denkendorf, F.R.G). Biopsy specimens, including structural proteins of the viruses named, served as positive controls in immunohistochemistry (Feiden et al. 1984; Feiden, unpublished data). The monoclonal antibodies employed were DAKO-LC (CD45); DAKO-UCHL1 (CD45R, T lymphocytes; Norton and Isaacson 1986); DAKO-L26 (B lymphocytes; Norton and Isaacson 1987); DAKO-MAC387 (histiocytes/macrophages; Flavell et al. 1987); MB1 and MB2 (B lymphocytes, EURO-DIAGNOSTICS BV, Holland; Poppema et al. 1987).

For electron microscopy (cases 1 and 2), small pieces of the paraffin embedded tissue were taken from defined spots, deparaffinized, and thoroughly washed in cocadylate buffer before postfixation in buffered osmium tetroxide. After embedding in Epon, thin sections were contrasted with uranyl acetate and lead citrate.

Results

Histologically, patchily distributed mononuclear cell infiltrations of the subepicardial and smaller intramyocardial vegetative nerves including those

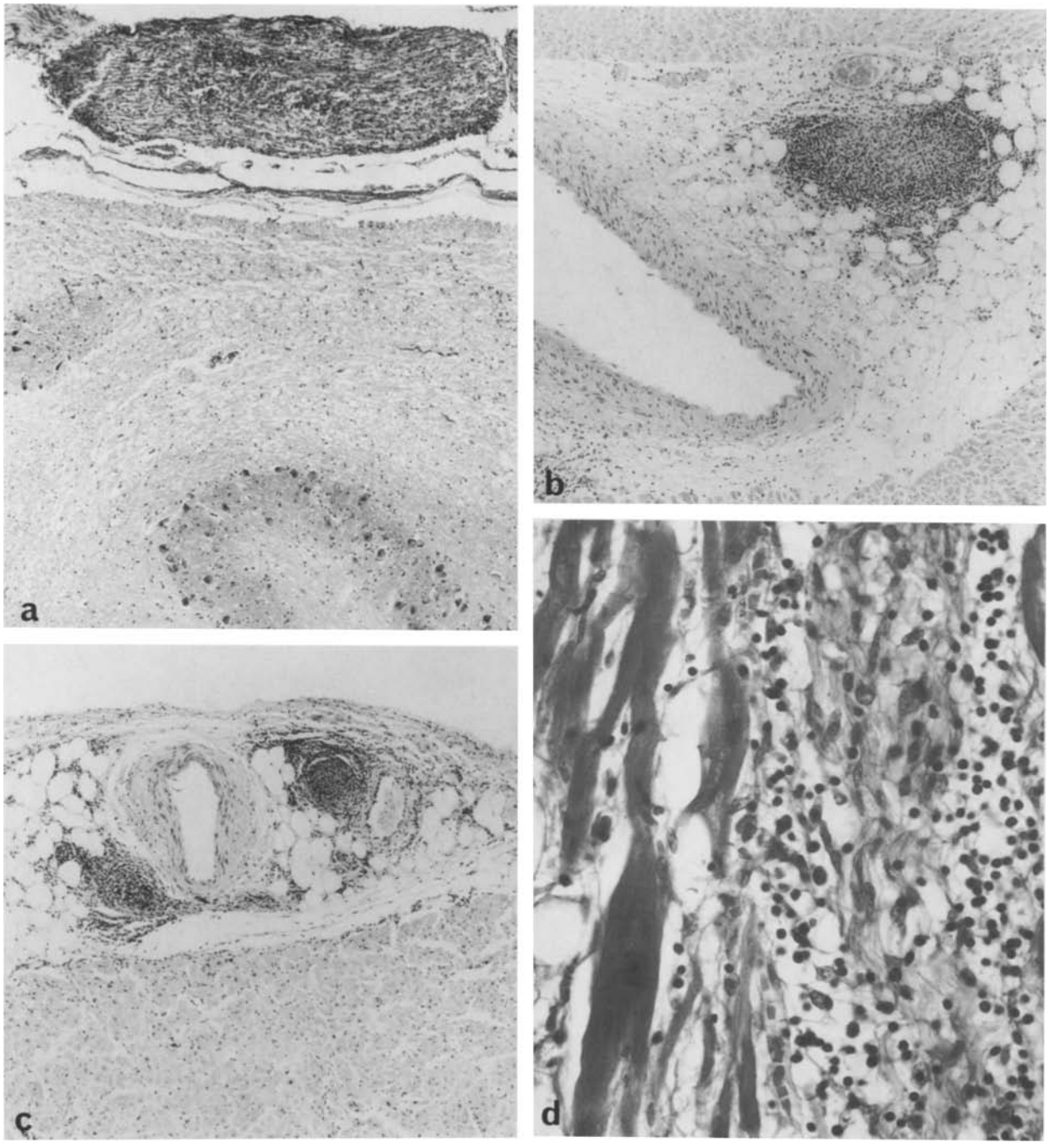

Fig. 1. (**a**) Root of the 12th cranial nerve (*top*) with mononuclear cell infiltration; inferior olive of the medulla oblongata (*bottom*); case 1. (**b**) Large perivascular nerve in the wall of the left cardiac ventricle with mononuclear inflammatory infiltrates; case 1. (**c**) Neuritis cordis in the epicardial plexus; wall of the left cardiac ventricle; case 2. (**d**) Small cardiac nerve (*on the right*) with perineural and intraneural infiltration by mononuclear cells; region of the sinuatrial node; case 3. (**a–c**) Luxol fast blue and cresyl violet, × 55. (**d**) Haematoxylin and eosin, × 340

of the conduction system are conspicuous in all three cases (Fig. 1b–1d) and also in the cardiac ganglia.

Moreover, small foci of interstitial myocardial infiltrations by mononuclear cells are found without any myocardial cell damage or collagen scars (Fig. 2a). Immunohistochemistry reveals that these interstitial infiltrates are arranged with small intramyocardial nerve fibers, including Schwann cells, which show a positive staining reaction to protein

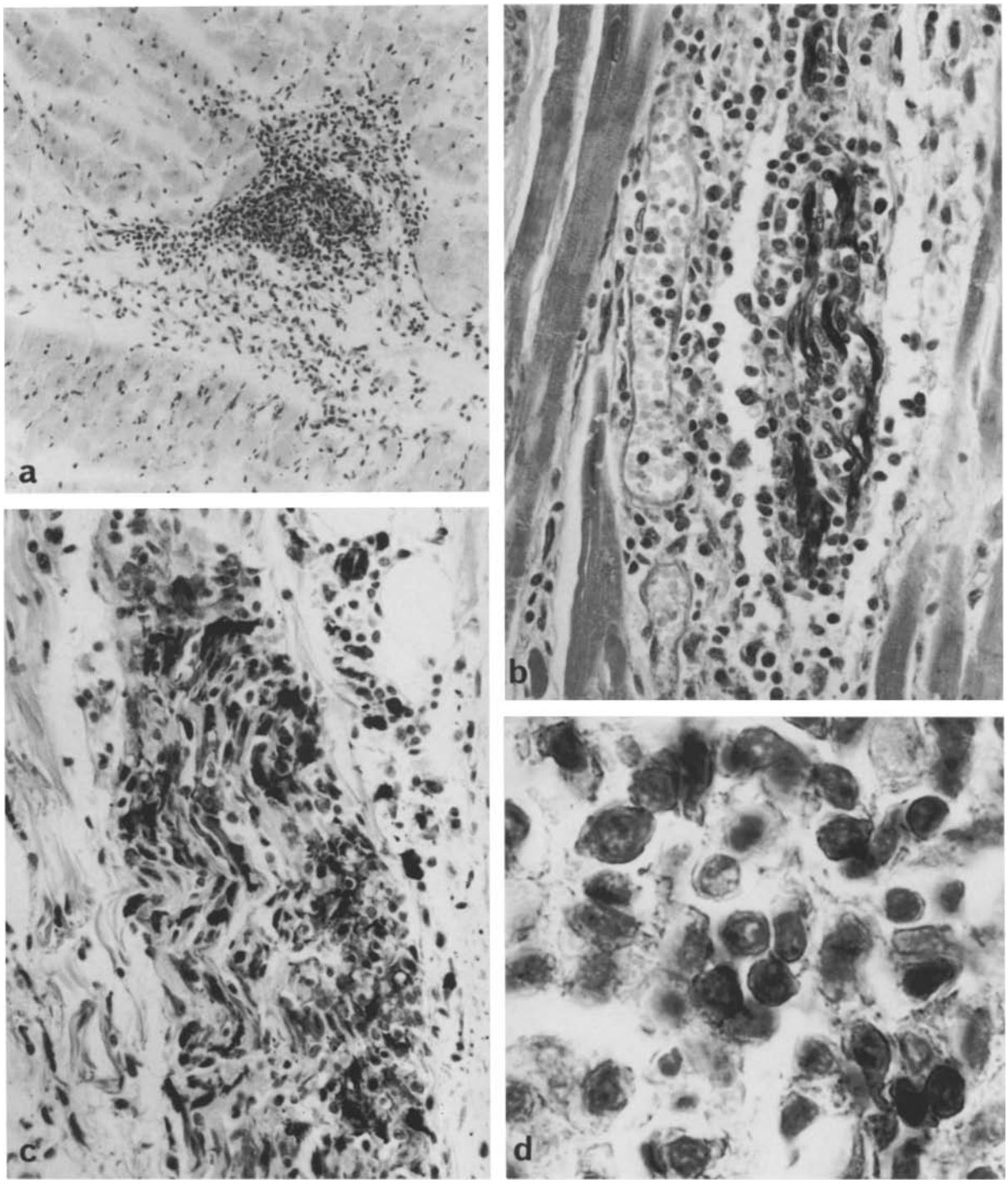

Fig. 2. (**a**) Focal mononuclear cell infiltrates in the myocardial interstitium covering a small nerve branch; case 1; luxol fast blue and cresyl violet, ×140. (**b**) Delicate intramyocardial nerve decorated by immunohistochemical protein S-100 positivity of Schwann cells (*dark cells*); perivenular and intraneural infiltrations by small lymphocytes and macrophages; case 2; PAP and counterstain with haematoxylin; ×340. (**c and d**) Immunohistochemical detection of macrophages (*dark cells* in (**c**) and T lymphocytes (*dark cytoplasmic membranes* in (**d**) of neuritis cordis; case 1; immunohistochemistry with monoclonal antibody MAC 387 (**c**) and UCHL1 (**d**), peroxidase-conjugated avidin-biotin system, counterstain with haematoxylin, (**c**) ×340, (**d**) ×1360

S-100 (Fig. 2b). The mononuclear cell infiltrations are generally more pronounced in the thicker epicardial and intramyocardial nerves of cases 1 and 2 and less pronounced in case 3. Aside from single mononuclear cells, mainly of the histiocytic type (MAC 387 positive), no diffuse or focal cell infiltrations are found in the myocardial interstitium with the exception of small intramyocardial nerve fibers. However, the immunodetection of S-100 positive Schwann cells reveals that very fine intramyocardial and subendocardial nerve fibers exist, which do not show any inflammatory cell infiltrations.

The immunohistochemically LC positive cell infiltrates consist of small lymphocytes, the majority of which are decorated by UCHL1 (Fig. 2d) and of macrophages which are characterized by a different size and shape of the cytoplasm and nuclei and positive labelling with MAC 387 (Fig. 2c). Only a few lymphocytes reactive to L26 and to both MB1 and MB2 are seen.

No positive immunostaining is obtained with the polyclonal antisera against herpes simplex-, cytomegalo- and influenza virus. Electron microscopy reveals no viral particles, neither within the cardiac nerve fibers nor in the inflammatory cell infiltrations. It must be considered, however, that the preservation of ultrastructural morphology is impaired due to autolysis of the autopsy tissue and previous formalin fixation and paraffin embedding.

Discussion

The clinical course and the histological findings in the three cases presented are consistent with the disease group GBS (Arnason 1984; Dowling et al. 1987) and morphologically with acute inflammatory demyelinating polyradiculoneuritis (Krücke 1955; Asbury et al. 1969; Prineas 1981). The peculiarity of the three cases consists clinically of cardiovascular symptoms and sudden cardiac death and, as shown by postmortem investigation, of a lymphomonocytic inflammation of the vegetative nerves of the heart. In the 35-year old male and the 23-year old female patient, death had occurred suddenly and unexpectedly; the clinical symptoms did not seem to be life-endangering, and intensive care had been deemed unnecessary. However, the admission electrocardiogram of the young female patient (case 2) showed abnormalities consisting of S-T depression and flat T waves; such changes have been frequently encountered in GBS patients (Lichtenfeld 1971; Kunst and Grosser 1974) and have been ascribed to the mild focal "myocarditis" seen in seven of the fifty fatal GBS cases of Haymaker and Kernohan (1949). However, Lichtenfeld (1971) has re-evaluated the concept that these changes imply myocarditis.

In the recently observed case of the 53-year old male in whom GBS took the course of Landry's acute ascending paralysis which made intensive care and assisted ventilation necessary, the patient had repeated phases of fluctuating blood pressure and bradycardia and was treated with a cardiac pacemaker. Further clinical signs of an involvement of the autonomic nervous system in the inflammatory nerve disease were the sphincter disturbances observed in case 1. Tuck and McLeod (1981) have pointed out that the severity of the autonomic involvement occurring to some degree in many GBS patients was not related to the degree of sensory-motor impairment. This is also consistent with the patchy distribution of the inflammatory lesions throughout the whole peripheral nervous system, inclusive of the autonomic one. The clinical consequences of autonomic dysfunctions in GBS are usual trivial or without any risk to life, for instance abnormalities of sweating or bowel and bladder function, but in occasional patients, as in our cases, they may be life-threatening and lead to sudden death (Dowling et al. 1987).

We think that the neuritis cordis found in the three GBS patients was responsible for their death. The heart is innervated by sensory and motor fibers derived from the sympathetic and parasympathetic-vagal nervous system (Hirsch and Borghard-Erdle 1962 and 1963; Jansen 1963). Nerves containing these fibers form the epicardial plexus on the surface of the heart, accompanying the branches of the coronary arteries or extending directly into the myocardium, thus forming a rich plexus of large and small vegetative nerves of the cardiac wall (Woollard 1926). Histologically these nerves consist of fine, unmyelinated fibrils and thick myelinated fibers; the latter are considered to be sensory (Woollard 1926). Unmyelinated and myelinated fibers of the cardiac autonomic nervous system are the recognized pathways of effective and sensory impulses in the overall cardiac function. It is obvious that an inflammatory process of rapid onset of these structures, which are partly in close anatomical and functional connections to the heart conduction system, can result in arrhytmias and bradycardia. Any pathological process of the cardiac nerves may alter tonic or reflex neural control of cardiac rhythm, conduction, or repolarisation and thus lead to sudden death (James 1979).

In recent years considerable evidence has been

brought forward to suggest that GBS represents an aberrant immune response pathogenetically, mainly relative to myelin (Arnason 1984). The close connection of unmyelinated effective and myelinated sensory fibers that form the cardiac nerves implies that noxae chiefly directed against the myelin sheath and resulting in an imflammatory cell infiltration of the whole nerve may also disturb the function of the unmyelinated fibers. The composition of the inflammatory cell infiltrates, mainly T lymphocytes (UCHL1 positivity) and macrophages (MAC 387) positivity), observed by immunohistochemistry in our cases, is in agreement with findings in experimental allergic neuritis (Olsson et al. 1984; Lassmann et al. 1986) which in many respects resemble acute inflammatory polyneuritis or GBS, respectively. Although myocarditis is generally characterized by mixed inflammatory infiltrates composed of macrophages and T lymphocytes (Marboe et al. 1984), as was the neuritis cordis of our cases, no acute myocardial cell damage was obvious, and the lymphomonocytic infiltrates were restricted throughout to the cardiac nerves. It seems therefore probable that the "focal myocarditis" described by Haymaker and Kernohan (1949) truly corresponds to an inflammation of the small intramyocardial nerve branches which were obscured by the inflammatory cells. In the case of Hodson et al. (1984) presenting with the clinical picture of GBS with dysautonomia, diffuse mixed inflammatory cell infiltrations were striking in the myocardium together with degeneration of myocardial fibers and foci of necrosis which indicate myocarditis; moreover, the usual histological features of GBS were not found in this case.

Neuritis cordis was first described by Askanazy (1925) in the curious case of a 32-year old man who had suffered from cardiac arrhythmias and suddenly died. The only gross pathological changes consisted of an "idiopathic" hypertrophy and dilatation of the heart and, microscopically, of a neuritis cordis of small nerves which was confined to a circumscribed area of the ventral wall of the ventricles near the apex of the heart. Subsequent observations of similar findings remained rare in the literature, as Askanazy (1925) thought. In 1939, Krücke reported a case of so called hypertrophic neuritis which involved the autonomic nervous system, including cardiac nerves. In a study of some 500 human autopsy cases and 80 animal hearts that focused on pathological changes in the cardiac nerves, Salfelder (1950) found only one case of a tuberculuous cow with inflammatory round cell infiltrations of cardiac nerves and of the myocardial interstitium.

Table 1. Classification of cardioneuropathies

I.	Primary (localized) cardioneuropathies
	a) primary neuritis cordis (Askanazy 1925; James 1979)
	b) due to myocardial hypertrophy (Kyösola et al. 1976; Borchard 1978)
	c) due to ischemic heart disease (Lasowsky 1931; Borchard 1978)
II.	Secondary cardioneuropathies due to generalized neuropathies
	a) hereditary neuromyopathies (Wenger 1978)
	b) metabolic and toxic neuropathies (Lloyd-Mostyn and Watkins 1976; Borchard and Wolters 1978; Duchen et al. 1980; Borchard et al. 1981)
	c) inflammatory neuropathies (Köberle 1968; Feiden et al. 1986)

(James 1979; Borchard 1982)

James (1979; James et al. 1979; James and MacLean 1980) who studied cases of sudden death has recently introduced the term "cardioneuropathy" which embraces a wide variety of inflammatory and non-inflammatory, degenerative and toxic lesions of cardiac nerves. He made a classification of primary cardioneuropathies, including in particular neuritis cordis characterized by the absence of extracardiac nerve disease, and cardioneuropathies secondary to generalized lesions of the peripheral nervous system. In the table we give a systematic classification of cardioneuropathies (Borchard 1982) according to James (1979). It is in part a hypothetical one because the cardiac nerves in human have so far not been studied extensively. In our three cases we found no references to a direct viral infection of the cardiac nerves, as described in "primary" neuritis cordis by James (1979), neither immunohistochemically (HSV, CMV, influenza virus) nor by electron microscopy, and also not by virological methods applied in case 2.

To summarize, the clinical courses, the postmortem findings, and the cell composition of the inflammatory nerve infiltrations are in agreement with the definition of the disease group of GBS/acute inflammatory polyneuritis (Arnason 1984; Dowling et al. 1987). The observed neuritis cordis may be classified with James (1979) as a secondary cardioneuropathy due to a generalized inflammatory process of the peripheral nervous system. It might be a special local variant of this patchily distributed nerve disease. However, the possibility of cardiac nerve involvement in acute polyneuritis should give rise to special attention to cardiovascular function and histomorphology in GBS patients.

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Furthermore, W. Doerr has mentioned a case of sudden unexpected death with inflammatory cell infiltrations in cardiac nerves (Doerr W (1981) Sekundenherztod. Beitr Gerichtl Med 49:1–25)