Haymaker and Kernohan's Landry-Guillain-Barré syndrome paper: an essential contribution for accurate understanding of its early pathophysiology

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ABSTRACT

Introduction. Autopsy studies in early (≤ 10 days after onset) or very early (≤ 4 days), classic Guillain-Barré syndrome (GBS) are scarce. In 1949, Webb Haymaker and James Kernohan reported 50 clinical pathology studies of fatal GBS cases, with 32 patients having died between days 2 and 10 after onset.

Objective. To analyze Haymaker and Kernohan's GBS paper and its implications for establishing the boundaries of the syndrome, and their contributions in setting out a reliable interpretation of its early pathophysiology.

Development. The article is divided into two sections. The first includes brief biographies of Haymaker and Kernohan; their pioneering description of the inaugural endoneurial edema in spinal nerves; corroboration of these findings by Krücke, which were later questioned by Asbury and colleagues; and support of the pathogenic role of edema in experimental autoimmune neuritis. The second comprises six sections in which we review the nosological overturning of GBS through the work by Haymaker and Kernohan, and the enormous impact that their study has had on the current pathophysiology of the syndrome.

Conclusions. The contribution of Haymaker and Kernohan was pivotal in establishing the nosological boundaries of GBS, and in identifying the characteristics and topography of the inaugural histopathological changes. To a large extent, the current pathophysiology of the syndrome, in its very early stage, is based upon these changes.

KEYWORDS

Acute febrile polyneuritis; AIDP; AMAN; AMSAN; axonal degeneration; blood-nerve barrier; CSF; demyelination; electric root stimulation; endoneurial fluid pressure; experimental autoimmune neuritis; Guillain-Barré syndrome; Haymaker Webb; Kernohan James; Landry paralysis; MRI; nerve conduction study; NfL; nerve inexcitability; nerve inflammatory edema; nerve ischemia; peripherin; spinal nerve; spinal roots; triple stimulation technique; ultrasonography

Introduction

In 1949, Haymaker and Kernohan reported a clinical pathology study of 50 fatal cases of Guillain-Barré syndrome (GBS), with 32 patients having died between two and 10 days after symptom onset, namely during the period currently accepted as very early (≤ 4 days after onset) or early GBS (≤ 10 days).[1-3] Haymaker and Kernohan's contributions continue to be an essential step for accurate understanding of early GBS pathophysiology. But before diving into this matter, it is worth commenting briefly on the syndrome's current nosological framework, with a view to clarifying certain semantic issues raised later.

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GBS is an acute, post-infectious, immune-mediated polyneuropathy, encompassing three basic patterns[4,5]: *i)* acute inflammatory demyelinating polyneuropathy (AIDP); *ii)* axonal GBS, including acute motor axonal neuropathy and acute motor-sensory axonal neuropathy (AMAN and AMSAN, respectively); and *iii)* Miller Fisher syndrome, which presents with the triad of ophthalmoplegia, ataxia, and areflexia. Clinically, GBS is subdivided into classical forms (with a variable degree of flaccid tetraparesis; AIDP and axonal GBS) and localized forms (eg, pharyngeal-cervical-brachial variant of GBS), whereas Miller Fisher syndrome may present with complete (ie, with the classical triad) and incomplete forms (eg, acute ataxic neuropathy).[6] Half of patients with AMAN/AMSAN are seropositive for anti-GM1 or anti-GD1a antibodies; in Miller Fisher syndrome, nearly all patients present anti-GQ1b antibodies. In AMAN/AMSAN, antiganglioside antibodies bind complement to the axolemma, attracting macrophages and generating a membrane attack complex, leading in turn to Wallerian degeneration.[5] No specific antibodies have been detected in AIDP, and the mechanism of inflammatory demyelination is yet to be identified. Classification of disease into either demyelinating or axonal forms has been based on electrophysiological criteria, though in very early GBS only a minority of patients can be subtyped; serial nerve conduction studies (NCS) are needed for this purpose.[7-10] Experimental autoimmune neuritis (EAN) is a widely accepted model of GBS.[4,5]

Seventy-five years after the publication of the seminal paper by Haymaker and Kernohan,[1] the reported characteristics and topography of histopathological lesions in early stages of GBS, essentially consisting of endoneurial edema predominantly affecting spinal nerves, remain essential issues for a reliable understanding of the pathophysiology of the initial stages of the syndrome. Among such issues, the following seem to us to be the most relevant: *i)* which could be the pathological hallmark and the mechanism of ascending paralysis in patients with very early classic GBS showing normal or non-contributory NCS findings?[7-11]; *ii)* is there any correlation between selective spinal nerve pathology and axonal degeneration in early AMAN/AMSAN?[1,12]; *iii)* is there any correlation between Haymaker and Kernohan's histopathological findings and modern imaging studies in the early stages of the syndrome?[13]; *iv)* what might be the histopathological basis of nerve inexcitability in very early GBS?[9,10,14]; *v)* what might be the mechanism of elevated serum neurofilament light chain (NfL) or peripherin levels in very early GBS?[15-20]; and *vi)* was the autopsy material available to Haymaker and Kernohan sufficient to reach reliable conclusions on early GBS?

The aim of this paper is twofold: *i)* to present a brief historical review of Haymaker's and Kernohan's biography and their GBS paper; and *ii)* to answer the six questions set out above.

Material and Methods

For this paper, we used biographic data on Webb E. Haymaker and James W. Kernohan from both peer-reviewed papers[21-25] and online documents.[26,27] In the 1940s, the syndrome of acute ascending paralysis was a subject of deep nosological confusion, this question having been addressed by Haymaker and Kernohan[1]; to assess the enormous significance of their contribution, we felt compelled to review the original papers on acute ascending paralysis,[28] acute febrile polyneuritis,[29,30] and the Guillain-Barré-Strohl report.[31] When it was deemed appropriate, Haymaker and Kernohan's contributions will be compared against posterior studies, including our own.

Results

Haymaker's biography in brief

This biography has been taken almost literally from references by Earle[22] and Schiller.[23] Webb Edward Haymaker (Figure 1A[27]) was born in Washington, DC, on 5 June, 1902, and died in Berkeley, California, on 5 August, 1984.

He attended the Medical College of South Carolina 1922-23. In the summer of 1923, he interrupted his medical education for a tour of Europe, spending two years studying at the University of Würzburg and University of Vienna. He was awarded his medical degree at the University of South Carolina in 1928.

His postgraduate education took him to the Pennsylvania Hospital, where he completed a residency in pathology (1928-29) and a rotating internship (1929-31). In 1931-32, he studied part-time at the Henry Phipps Institute in Philadelphia, working on clinical and experimental tuberculosis with Dr Opie and Dr Freund, and part-time at the Pennsylvania Hospital, under Dr Alpers.

His insatiable appetite for travel and his thirst for new ideas and knowledge took him to the American Hospital in Paris 1932-33 where he was an intern, and as

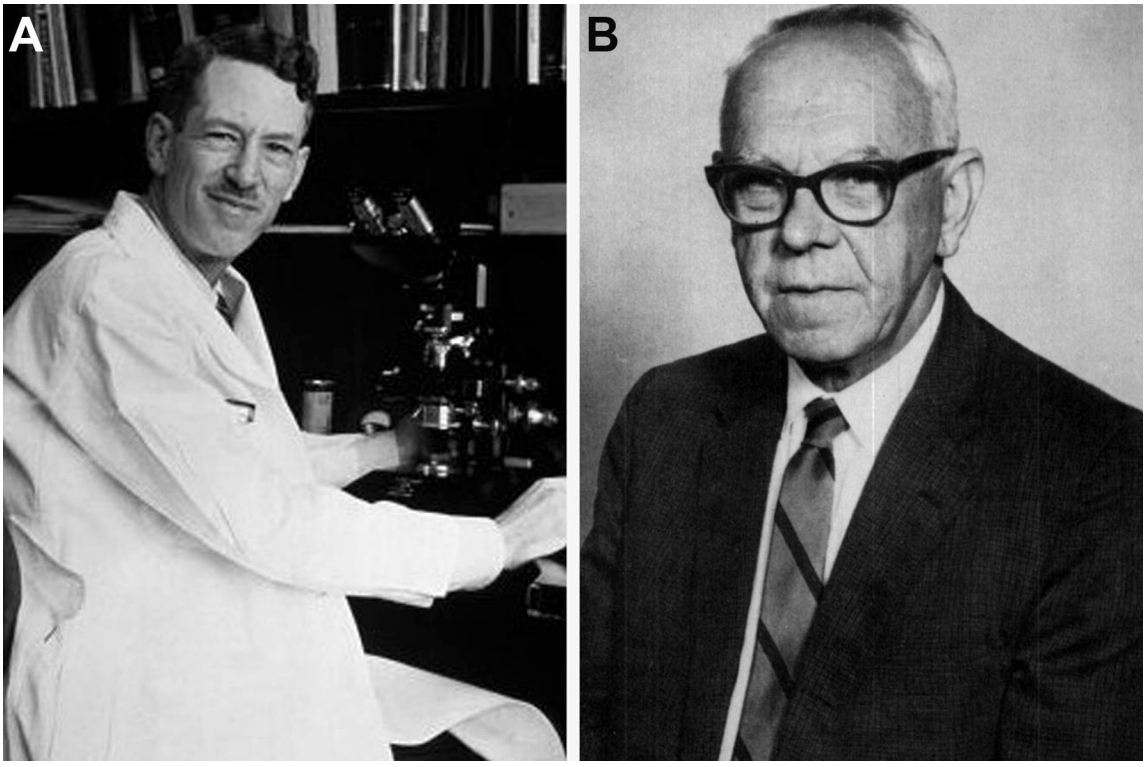

Figure 1. Webb Edward Haymaker (1902-1984)[27] (A) and James Watson Kernohan (1896-1981)[26] (B). Both photographs are in the public domain and can be used without further permission.

part-time research visitor, at the Institut du Cancer of the University of Paris with Dr Roussy and Dr Verne, where he observed tissue culture of the CNS.

He returned to the United States and spent a year (1933-34) as director of the State Laboratories at the State Sanatorium (Rhode Island). Attracted by the reputation of the newly opened Montreal Neurological Institute, he served as a Fellow under Dr Wilder Penfield in 1934-1935, receiving an MSc degree from McGill University. Returning to Europe (1934-1936), he served as a clerk at the National Hospital in London with Dr Carmichael, and at the Instituto del Cancer in Madrid, with Dr Pío Del Río-Hortega; this stay was soon interrupted by the Spanish Civil War. It is worth noting that Haymaker himself wrote the biographical annotation on Del Río-Hortega for the book *The founders of neurology.*[32] Upon his return to the US, he became Assistant Clinical Professor of Neurology and Lecturer in Neuroanatomy at the University of California School of Medicine, in San Francisco and Berkeley.

With the US' entry into the Second World War, he was commissioned in the Army and assigned to the Army Institute of Pathology (AIP) in Washington, DC, where he rose to the rank of Lieutenant Colonel (AUS 1942-7). When released from active duty, he was employed as civilian Chief of the Neuropathology Branch of the AIP, at 7th Street and Independence Avenue, Washington, DC; the branch was later renamed the Armed Forces Institute of Pathology (AFIP) and moved to new quarters on the grounds of the Walter Reed Army Medical Center, at 16th Street and Alaska Avenue NW. He served as Chief of Neuropathology until 1961, when he resigned to accept a research position with the National Aeronautics and Space Administration (NASA), where he remained until his death.

Haymaker was a prolific writer, traveler, and lecturer of all visitors to the AFIP. He was President of the American Association of Neuropathologists in 1955-56. Of his many publications, the best known are probably the following: *The Founders of neurology*,[32] *Bing's local diagnosis in neurological diseases,*[33] and *Histology and histopathology of the nervous system.*[34] One of his major research interests was the effects of ionizing radiation on the nervous system.

Kernohan's biography in brief

This biography has also been taken almost literally from references by Sayre,[20] Haines et al.,[24] and Etienne et al.[25] James Watson Kernohan (Figure 1B[26]) was born in Moyasset, County Antrim (Northern Ireland), on 1 October, 1896, and died in Rochester, Olmsted (Minnesota), on 5 May, 1981.

Kernohan attended Queen's University, Belfast, where he received a degree in medicine in 1920, and a bachelor of science with first class honors in 1921. Four years later, he joined the staff of the Mayo Clinic, Minnesota, headed by Dr HE Robertson, a dynamic and forceful personality with whom he worked until he succeeded him as head of the section in 1945. Robertson, like most general pathologists, was uninterested in neuropathology, and gladly turned over that subject to his young colleague. Kernohan worked for the entirety of his fruitful neuropathological career at the Mayo Clinic, mainly focusing on brain neoplasms. His immense contributions on grading gliomas appeared in two AFIP fascicles (35 and 37) on tumors of the central nervous system in 1952.[24]

Dr Kernohan was always interested in teaching, both in lecturing and personal contacts, and supervised many theses in pathology. During a sabbatical leave at the AIP, he came into contact with Dr Haymaker[35]; together, they reviewed the clinical and pathological features of 50 fatal cases of GBS and both, as great masters of neuropathology, gave a very detailed histological description,[1] which probably represents a *magnum opus* in the history of this syndrome. Kernohan was president of the American Association of Neuropathologists in 1938-39, and vice-president of the American Neurological Association in 1955.

Both Haymaker and Kernohan were recognized with laudatory obituaries, but none mentioned the immense contribution of the authors to GBS. This is a shame because, as will be seen below, their pathological findings play an irreplaceable role to understanding the pathophysiology of early GBS.[2]

Acute ascending paralysis

In 1859, Octave Landry described 10 cases of acute ascending paralysis and sensory tingling with sparing of bowel and bladder function.[28] Two patients died, their autopsies failing to demonstrate the cause of illness after examination of brain and spinal cord and muscles; apparently, the peripheral nervous system (PNS) was not examined. The remaining patients recovered.

Acute febrile polyneuritis

Acute febrile polyneuritis (AFP) was described by Osler in 1892,[29] and is characterized by high fever (up to 40°C) followed by limb and back pain, paresthesia, and ascending or descending paralysis with respiratory insufficiency. Some patients died, while others remained stable for several weeks, subsequently presenting a slow recovery. Osler pertinently indicated that the clinical picture is indistinguishable from that of Landry paralysis (for a review, see Berciano[3]).

In 1917, during the First World War, Gordon Holmes presented a masterful new definition of AFP.[30] His series included 12 soldiers attended in the winter of 1916-17, whose initial symptoms included general discomfort and fever up to 40°C, in the absence of a localized septic focus ("pyrexia of unknown origin"). One patient had a history of recurrent trench fever, and another had a recent history of diarrhea and vomiting. Patients subsequently developed pain in the legs and lumbosacral region. This was followed by weakness of the legs, with difficulty walking short distances; weakness progressed, rapidly ascending to the arms. At the same time, patients presented facial weakness, dysarthria, and dysphagia. Holmes stressed that tetraparesis was symmetrical, affecting both distal and proximal muscles, though it was more pronounced in the lower than in upper limbs. Patients experienced difficulty starting micturition, although none needed a urinary catheter. Two patients died due to bronchopulmonary complications; in the remaining 10 patients, symptoms peaked during the first week after onset, with improvement in the following weeks. No cerebrospinal fluid (CSF) alterations were detected in the three patients who underwent lumbar puncture. Autopsy in the two deceased patients revealed peripheral nerve changes

consisting of incipient degeneration of myelin sheaths and central chromatolysis of spinal motor neurons. Holmes cautiously concluded that "unavoidable circumstances [in reference to the war] made more complete examination of the nervous system impossible, but these changes are sufficient to confirm the diagnosis of peripheral neuritis."

Original description of Guillain-Barré syndrome and subsequent questioning of diagnostic criteria by Guillain himself

At the 13 October 1916 session of the Medical Society of Hospitals of Paris, Guillain and colleagues described the cases of two soldiers with acute paresis, who had been admitted to the neurological center of the French Sixth Army in Amiens during the Battle of the Somme in the First World War.[31] The clinical features of these patients, including tendon areflexia and early regressive evolution, have already been reviewed in this journal.[3] The characteristic finding in both cases was the presence of albumin-cytological dissociation in CSF, which according to the authors had only previously been described in spinal cord compression syndromes and in Pott disease. Without any bibliographic reference, the paper was entitled "Sur un syndrome de radiculo névrite avec hyperalbuminose du liquide céphalo-rachidien sans reaction cellulaire" (On a syndrome of radiculoneuritis with cerebrospinal fluid hyperalbuminosis with no cellular reaction).

Over the next two decades, the syndrome was largely overlooked in the North American literature. This probably prompted Georges Guillain himself to publish a review article in the *Archives of Neurology and Psychiatry* setting out the fundamental diagnostic criteria for his "syndrome."[36] It is worth noting that the author considered marked CSF *hyperalbuminosis* a constant finding, with typical values ranging between 1 and 2 g/100 mL, and mild *hyperalbuminosis* (0.3-0.4 g/100 mL) indicating atypical or "abortive" forms of the syndrome; this interpretation was subsequently corrected by Wiederholt and colleagues,[37] who noted that, in all likelihood, the values reported by Guillain as grams per 100 mL were in fact grams per liter. According to Guillain, other obligatory diagnostic criteria were abolition of tendon reflexes and a favorable clinical course; in fact, he considered the two fatal cases reported previously "not to belong to this syndrome group." Finally, and without mentioning the paper by Landry, Guillain considered that AFP was distinct from GBS. His proposal had an undeniable impact on the literature, and particularly in the French-language literature.[38]

The seminal paper by Haymaker and Kernohan: opening up a new nosological stage of Guillain-Barré syndrome

In an 82-page article including 17 figures, nine tables, and 225 references, Haymaker and Kernohan comprehensively reviewed the literature on GBS, Landry paralysis and AFP, describing the clinical-pathology study of 50 fatal cases of GBS, including 32 patients who died between days 2 and 10 after symptom onset.[1] Anatomical specimens from these cases, fixed in formaldehyde, were sent to the AIP during the Second World War. Largely in contradiction to Guillain's criteria (see above),[36] Haymaker and Kernohan raised the following concepts:

— For the first time in the literature, GBS, Landry palsy, and AFP were considered as one and the same disease.

— The increase in CSF protein content may vary depending on the stage of the disease. The authors asserted that "were Guillain's criteria strictly adhered to, one would be obliged to remove from consideration many cases in the literature designated by the term GBS […]. Thus, the protein value may be low initially, only to rise subsequently to abnormally high levels" (see their figure 1). It is worth noting that in their series, protein levels were elevated in 27 (79%) of the 38 cases, the amount varying from 50.5 to 375 mg/dL, and exceeding 150 mg/dL in only six. Furthermore, they underlined that a single sampling of total protein did not necessarily reflect the level of protein during the entire course, as in four patients from their series, protein rose from normal to excessive levels during the course of the disorder. These notions are entirely valid today.[3]

— Paraphrasing Haymaker and Kernohan, another criterion on which Guillain was adamant was the absence of increased CSF cell count. In fact, Guillain declared that "I refuse to recognize radiculoneuritis with hyperlymphocytosis or hypernucleosis as belonging to this syndrome."[36] Following an exhaustive literature review (see their table 1), the authors argued that "the paucity of cells has been overstressed as a criterion of the disorder, and that, although the cells are usually within the limits of normal, their number may be considerably increased and may fluctuate during the illness […]. Pleocytosis in cases falling clinically in the realm of the disorder under discussion has frequently been reported."

— With respect to mortality, the authors quoted the words of Guillain himself (from a symposium on GBS held in Brussels 1938), according to which, and contrary to what he had expressed two years earlier (see above), the syndrome may be fatal: "a concession which seems to have escaped the notice of most subsequent workers on the subject […]. [Guillain himself] likened the GBS to chickenpox, which has a favorable prognosis but occasionally is fatal […]. Thus, another barrier which has been said to separate Landry's paralysis from the GBS was removed."[1]

Undoubtedly the most important contribution of Haymaker and Kernohan was their detailed description, for the first time, of the histopathological background of GBS, which always involved the PNS.[1] Starting from their 32 early GBS cases, they gave a masterful analysis of the topography and progression of the observed lesions, which were summarized as follows[1-3]:

> As a whole, the observed pathological changes were more prominent in the region where motor and sensory roots join to form the spinal nerve. Edema of the more proximal part of the peripheral nervous system constituted the only significant alteration the first three days of illness. By the fourth day, slight swelling and irregularity of myelin sheaths were detected, and by the fifth, clear-cut disintegration of myelin and swelling of axis cylinders. On the ninth day a few lymphocytes sometimes began to appear, on the eleventh, phagocytes, and on the thirteenth, a proliferation of Schwann cells […]. The most severe changes were noted in the cases of longest duration, namely 46 days […]. In all the cases in which appropriate material was available, the degenerative changes, decidedly focal in early stages of the disorder, were concentrated in the region of the spinal nerves and extended both proximally and distally for a short distance […]. Where motor symptoms were most prominent the lesions tended to predominate in the anterior roots, and where widespread hypoesthesia accompanied the paralysis the lesions were found in anterior and posterior roots.

As lymphocyte populations tend to increase over the course of the disease, the presence of these cells was interpreted as being part of a repair process; in fact, the syndrome was characterized as a "polyradiculoneuropathy," in which both elevated CSF protein level and mild CSF pleocytosis were considered incidental findings.[1] Spinal cord motor neurons and spinal ganglion sensory neurons presented central chromatolysis; Figure 2 shows examples of these findings in one of our pathological studies.[39]

In short, the contribution of Haymaker and Kernohan may be considered a masterpiece in the field of GBS, for several reasons[2]: *i)* it delimited the nosology of the syndrome, strongly rebutting some of Guillain's proposals; *ii)* it situated the pathological process in the PNS and defined the chronology of lesions; *iii)* it established that the initial pathological finding is endoneurial edema, predominantly involving the spinal nerves, a key notion in understanding the pathophysiological mechanisms involved in the early stage of the syndrome; *iv)* it demonstrated the presence of demyelination for the first time; and *v)* the late detection of inflammatory infiltrates explains how these were misinterpreted as a reparative phenomenon; however, it should be noted that the detection of inflammatory cells frequently requires immunostaining or plastic sections, techniques that were not available for routine anatomical pathology in 1949.[12,39-41]

Krücke corroborates the pathological relevance of spinal nerve pathology in early Guillain-Barré syndrome

In 1955, Krücke performed a detailed histopathological study of seven autopsy samples from patients who died with GBS.[42] Extensive histological sampling of the PNS is illustrated in Figure 3A.[42] A patient who died 24 hours after onset presented more pronounced endoneurial inflammatory infiltrates than another patient who died on day 3. Endoneurial edema was systematically accompanied by cellular infiltrates; due to the absence of pure serous exudation, as described by Haymaker and Kernohan (see above), Krücke interpreted the edema as being an integral part of the inflammatory process (Figure 4).[42] Florid demyelination of nerves occurred as of day 14. In early stages of the syndrome, lesions were focal and predominantly affected proximal nerve trunks, particularly in spinal nerves, where edema was sufficiently severe that it could be detected with the naked eye (Figure 3B and C).[42]

Asbury and colleagues deny the existence of an endoneurial inflammatory edema stage in early Guillain-Barré syndrome

In a clinical pathology paper including 19 cases of fatal GBS, including five patients who had died within nine

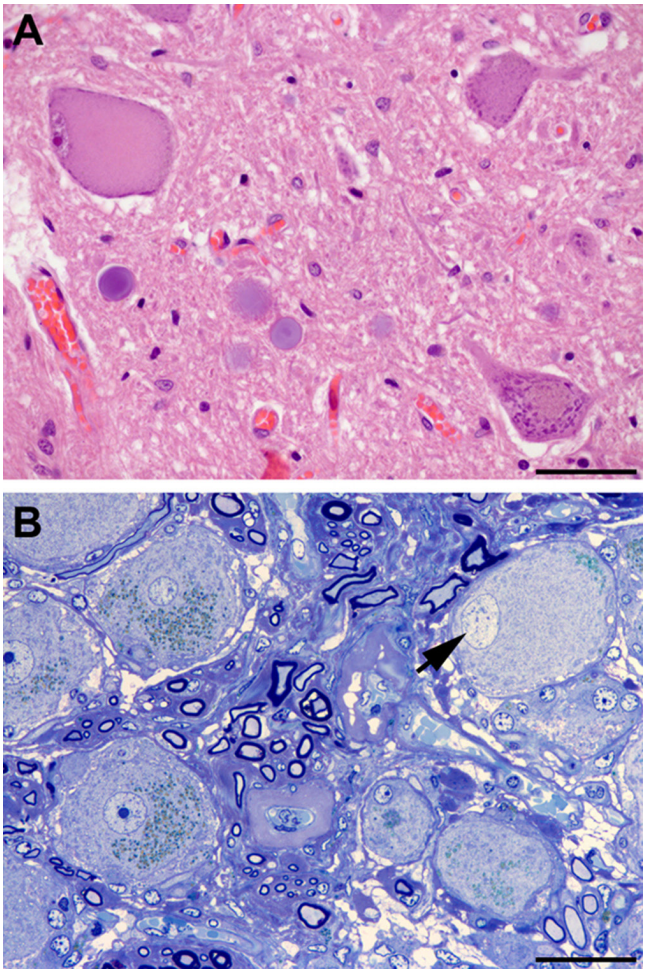

Figure 2. Images from a patient with fatal AIDP who died 30 days after onset. A) This detail of the anterior horn of the lumbar spinal cord displays central chromatolysis in two of the three motor neurons shown (hematoxylin and eosin stain). B) Semithin section from the L5 spinal root ganglion, showing several preserved neurons and two with central chromatolysis, displaying the characteristic eccentric nuclei (arrow) (toluidine blue stain). Scale bars: A: 90 µm; B: 65 µm. Taken from Berciano et al.[39]

days after onset (cases 1-5), Asbury and colleagues reported that the "common pathological denominator […] was an inflammatory demyelinative neuritis marked by focal, perivascular lymphocyte infiltrate, affecting any level of the PNS."[43] Although this is the case in advanced stages of the disease,[44] it is worth noting that in both of their early cases (cases 2 and 3) with pure motor signs, lesions predominantly affected the ventral roots, with more distal nerve trunks presenting minimal involvement. The authors suggested that, on the basis of pathological features, GBS and EAN are a cell-mediated immunologic disorder, in which the PNS, and particularly myelin, is attacked by specifically sensitized lymphocytes, but noted that the fact "that no edema was observed in our series strengthens rather than weakens the homology between EAN and idiopathic polyneuritis […]. It may be that our histologic criteria for accepting the presence of edema differ from those of others."[43] After this influential paper, the pathogenic role of inflammatory edema in early GBS was overlooked for decades. With the benefit of hindsight, this was a glaring mistake.

Endoneurial edema is also a pathological feature at the onset of P2-induced experimental autoimmune neuritis

As reviewed elsewhere,[12,39-41] the chronology of lesions in early EAN was masterfully reported by Izumo and colleagues in Lewis rats inoculated with autoreactive T cells sensitized to residue of bovine P2 myelin protein.[45] Almost literally, lesion evolution is reported as follows:

> Flaccid tail and weakness of the hind-limbs, started between 3.5 and 4 days post-inoculation, which rapidly progressed to peak between days 7 and 9. On day 4 post-inoculation, the first pathological change was marked edema with or without cellular infiltrates in the sciatic nerve and lumbosacral nerve roots. Between days 7 and 9, while inflammatory edema declined, there appeared florid demyelination; independently of this, there were some nerve fibers showing distinct axonal degeneration.

In a similar P_2-EAN model, at peak disease (day 6), there were minimal fiber changes: the mean number of demyelinated axons was 79/mm^2 (0.7% of the total number), with degenerating axons amounting to 121/mm^2 (1.0% of the total)[46] Certainly, such low percentages of abnormal fibers do not account for the semiology at peak disease.

In short, both P_2-EAN models demonstrate that inflammatory edema is pathogenic by itself at the onset of neurologic deficit, probably compromising the transperineurial microcirculation and causing endoneurial ischemia.[47]

Blood-nerve barrier efficiency dictates lesion topography at onset of Guillain-Barré syndrome

The PNS possesses a blood-nerve barrier that restricts the passage of soluble mediators and cells from the bloodstream into the endoneurium.[48] To that end, endoneurial capillaries are continuous, presenting endothelial cells

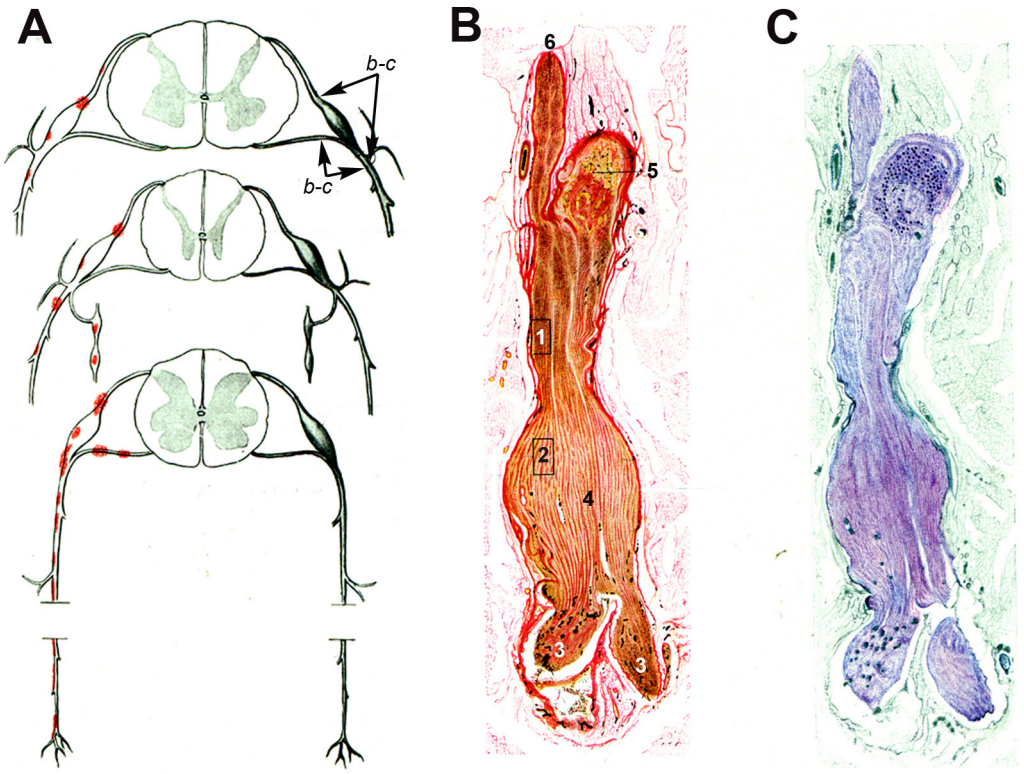

Figure 3. Minimally altered reproduction of figures 65 to 67 from Krücke's article.[42] A) Diagram of lesion topography in GBS (from top to bottom: cervical, thoracic, and lumbar regions). Lesions (red dots) are observed in the proximal nerve trunks, including the ventral and dorsal spinal roots, spinal ganglia, sympathetic ganglia, and the ventral rami of the spinal nerves. The labels b and c are used by the author to signal the localization of other of his figures (see Figure 4). B) Longitudinal section of a nerve segment between the ventral spinal root and the spinal nerve, taken from a patient with GBS who died on the 18th day of progression. The original numbering is maintained: 1 and 2: areas illustrated by Krücke in other figures (see Figure 4), demonstrating extensive "mucoid [inflammatory] endoneurial oedema"; 3: spinal nerve rami (the ventral and the dorsal rami); 4: fusiform dilation of the spinal nerve; 5: spinal ganglion; and 6: ventral spinal root (Van Gieson stain, magnification not specified). C) Another longitudinal section from the same location, showing the purple coloration of the fusiform dilation of the spinal nerve (cresyl violet stain). The figure is from an out-of-print book, so permission to reproduce it was not sought.

sealed with tight junctions (*zonula occludens*), which are fully surrounded by basement membrane and pericytes with their own basement membrane. Only the spinal ganglia present fenestrated capillaries, with pores of 80-100 nm diameter. In his classic experimental studies on vascular permeability in the PNS, using albumin labelled with fluorescein isothiocyanate or Evans blue, Olsson observed several topographical differences[49]: *i)* the ventral and dorsal spinal roots presented positive fluorescence, both within the blood vessels and in the interstitium of the fibers; this phenomenon extended to the junction with the peripheral nerves (spinal nerves); *ii)* extravascular fluorescence was very intense in the spinal ganglia; *iii)* in the peripheral nerve trunks, fluorescence was only visible in the vascular lumen; and *iv)* intense fluorescence was observed both in the vessels and in the interstitium of the epi-perineurium. This demonstrates that vascular permeability in the PNS is greatest in the spinal roots, spinal nerves, and spinal ganglia. Nerve terminals, surrounded by presynaptic glia, lack the characteristic blood-nerve interface of the intermediate nerve trunks, which also implies greater permeability[50]; this probably extends to pre-terminal nerve segments.[51]

At this point, it is very important to remember the microscopical anatomy of the PNS (Figure 5).[12] Intrathecal spinal roots are surrounded by a lax, elastic arachnoid envelope that may accommodate early edema by increasing their cross-sectional areas but conceivably without

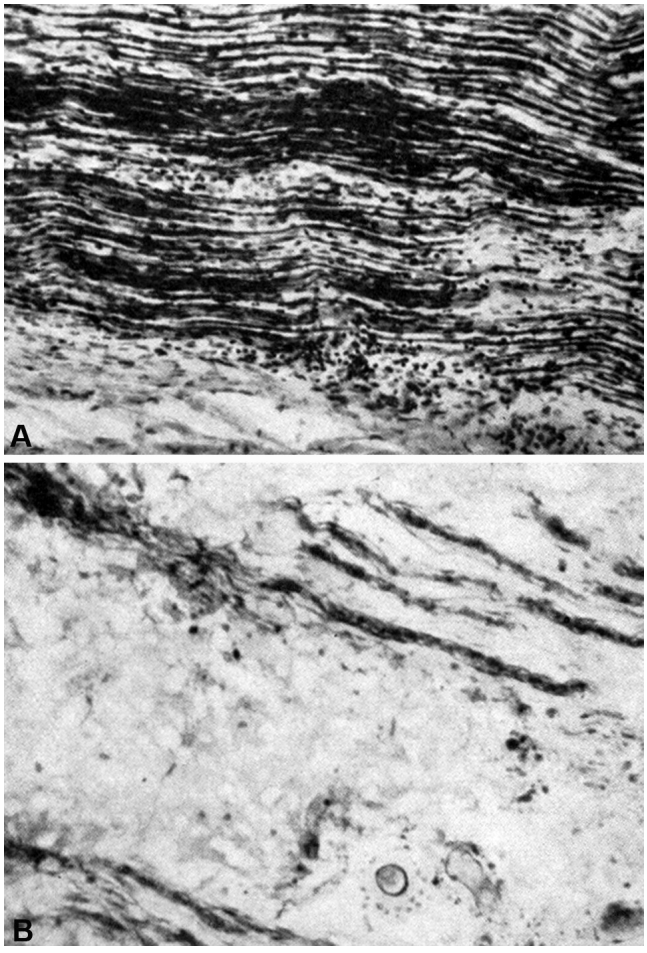

Figure 4. Reproduction of figure 68 from Krücke's article.[42] This figure includes two sections of spinal nerve (label c in Figure 3A). A) Focal inflammatory infiltrates with preservation of myelinated fibers (Heidenhain-Wolcke stain, magnification not specified). B) Extensive "mucoid" exudate separating myelinated fibers, which appear largely disrupted (Hotchkiss reaction, magnification not specified). The figure is from an out-of-print book, so permission to reproduce it was not sought.

significant changes in endoneurial fluid pressure (EFP). From the subarachnoid angle, proximal nerve trunks possess epi-perineurium that is relatively inelastic; here, inflammatory edema may increase EFP, which is believed to "stretch the perineurium and constrict the transperineurial microcirculation, compromising nerve blood flow and producing the potential for ischemic nerve injury."[47] The morphological consequence of this perineurial stretching is the appearance of wedge-shaped or centrofascicular areas of endoneurial ischemia, especially in the proximal nerve trunks and above all in the spinal nerves (Figure 6).[39,40,52]

Discussion

When Haymaker and Kernohan published their paper, the nosological position of GBS was very unclear.[1] Therefore, we consider it appropriate to begin by paraphrasing certain parts of the introduction of this pioneering paper:

> In reviewing case after case of this group it became apparent that the pathologic changes in the nervous system were relatively constant, being confined, as a rule, to the more proximal part of the peripheral nervous system, whereas the clinical picture varied considerably. The diagnoses made by the medical officers who saw these patients also differed, but, in general, the diagnosis of *Landry's paralysis* was made when the illness was brief and was characterized by rapidly spreading paralysis with minimal sensory symptoms and little or no increase of protein in the spinal fluid, and the diagnosis of *Guillain-Barré syndrome* when the course was slower, the symptoms included pain and facial paralysis, and the spinal fluid protein was considerably increased and the cell count minimal […]. In a preliminary analysis of the clinical history in this series, we were confronted with a number of cases which defied inclusion in one or the other of these categories […]. In addition to reviewing the pertinent literature on the subject, the purpose of this paper is to describe the clinical and pathologic features of the 50 cases of our series, and to analyze the data in an effort to determine whether or not the many appellations refer to one and the same basic disorder.

Certainly, this purpose was entirely achieved. Moreover, their well-argued criticisms of the rigid diagnostic criteria, set out by Guillain himself two decades after the original description of GBS,[36] remain fully valid.

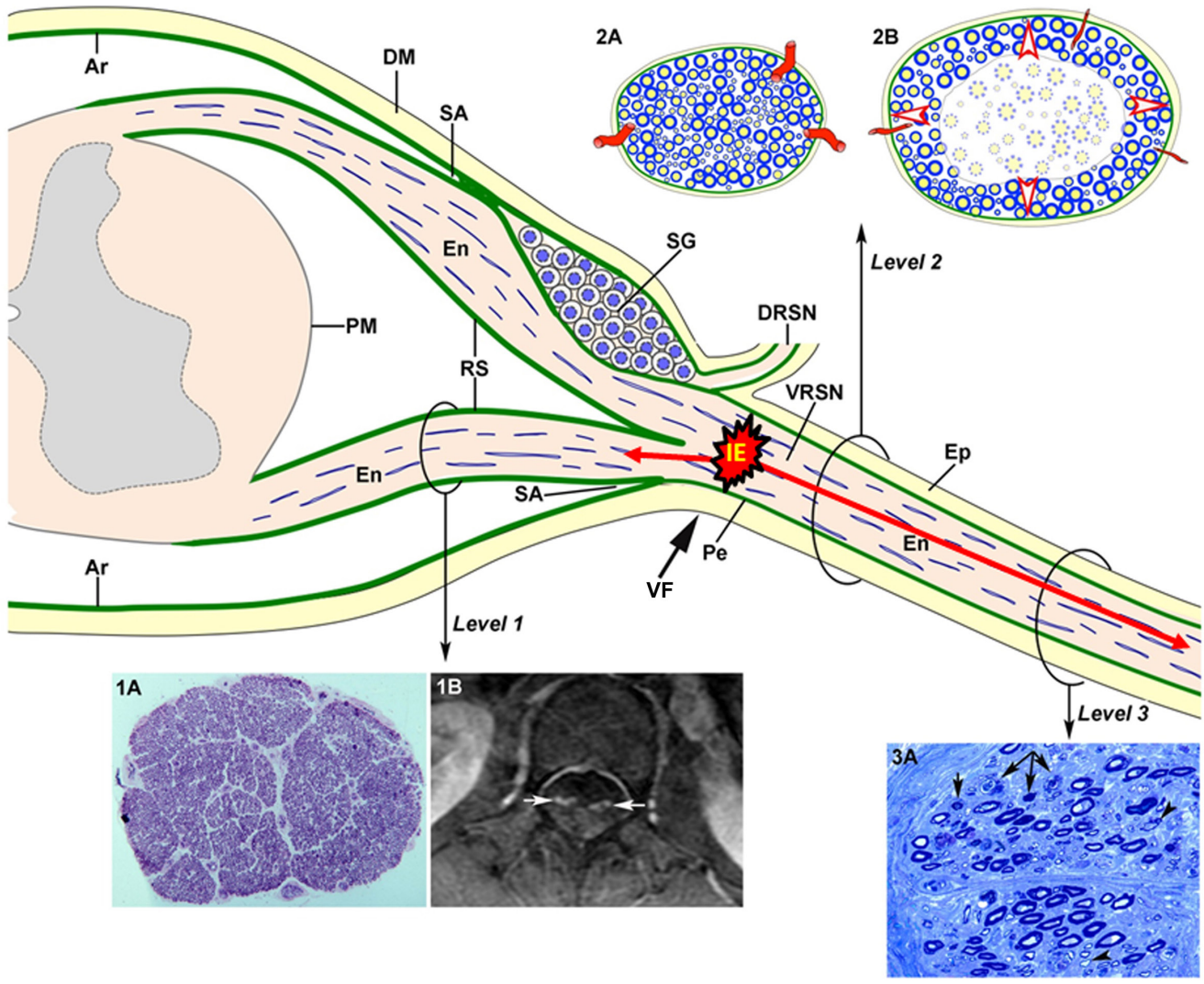

Figure 5. Diagram of the microscopic anatomy of the spinal root and spinal nerve, illustrating the topography of early GBS lesions and their consequences. As of the subarachnoid angle (SA), the epineurium (Ep) is in continuity with the dura mater (DM). The endoneurium (En) persists from the peripheral nerves through the spinal roots to their junction with the spinal cord. At the SA, the majority of the perineurium (Pe) passes between the dura and the arachnoid (Ar), but a few layers appear to continue over the roots as the inner layer of the root sheath (RS). The arachnoid is reflected over the roots at the SA and becomes continuous with the external layers of the RS. At the junction with the spinal cord, the outer layers become continuous with the pia mater (PM). Immediately beyond the spinal ganglion (SG), at the SA, the ventral and dorsal nerve roots merge to form the spinal nerve, which emerges through the intervertebral foramen (VF; large black arrow) and divides into a dorsal ramus (DRSN) and a ventral ramus (VRSN). Therefore, intrathecal nerve roots are covered by an elastic root sheath derived from the arachnoid, whereas spinal nerves possess epi-perineurium which is relatively inelastic. Proximal-to-distal early GBS inflammatory lesions are illustrated as follows: ventral lumbar root (*level 1*), spinal nerve (*level 2*), and sciatic nerve (*level 3*). At *level 1*, this semithin complete cross-section of the L5 ventral root shows preservation of the density of myelinated fibers (1A), though inflammatory lesions, observable at higher magnification (not shown), may account for the increased surface area and thickening and contrast enhancement of ventral roots on spinal MRI (1B, white arrows). The diagrams at *level 2* illustrate the following features: *i)* normal anatomy of the spinal nerve, usually monofascicular with epi-perineurial covering (2A), which account for its sonographic appearance usually consisting of a hypoechoic oval structure surrounded by a hyperechoic perineurial rim; and *ii)* endoneurial inflammatory edema may cause a critical elevation in endoneurial fluid pressure that constricts transperineurial vessels by stretching the perineurium beyond the limits of its compliance (2B, arrowheads), which may result in areas of endoneurial ischemia, here centrofascicular (see Figure 6). As illustrated herein (2A vs 2B), despite low spinal nerve compliance, early inflammatory events in GBS may cause an increase in cross-sectional area (see Figure 8). Inflammatory edema (IE) may cause anterograde (centrifugal) axonal degeneration (longer red arrow) and retrograde axonal degeneration (short red arrow), which at earliest stages of the disease predominates in the distal segment of the anterior spinal root, as originally reported in AMAN and AMSAN (see text). At *level 3*, this semithin cross section from the sciatic nerve from a fatal case of AIDP shows several myelinated fibers exhibiting Wallerian-like degeneration (myelin collapse, small black arrows) secondary to more proximal inflammatory lesions; note the presence of remyelinated fibers (arrowheads) and lipid-laden macrophages. Without knowledge of proximal nerve pathology, such distal florid Wallerian-like lesions would make it very difficult to reach an accurate diagnosis. Taken from Berciano.[12]

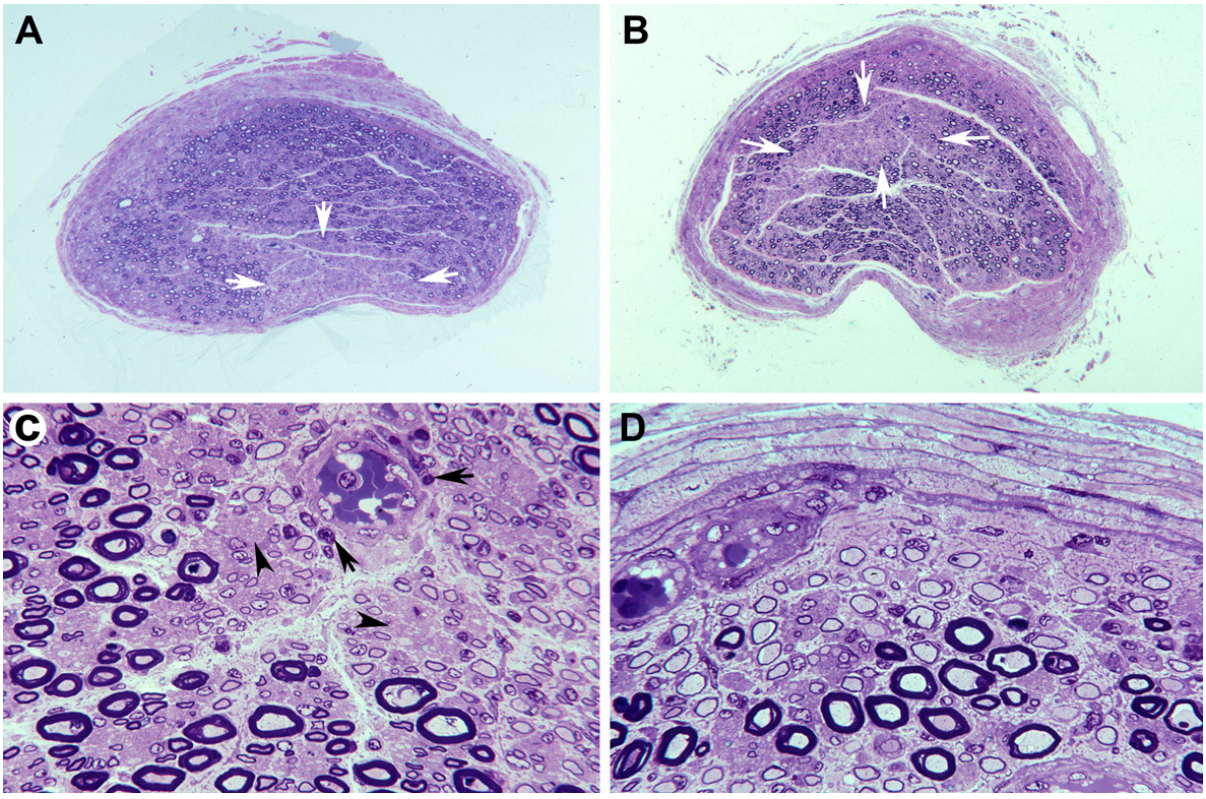

Figure 6. Proximal nerve ischemic lesions in a patient with AIDP, who died 60 days after onset. A) Semithin cross-section of the third lumbar nerve showing a wedge-shaped area (arrows) with marked loss of myelinated fibers (Toluidine blue; ×62 before reduction). B) Semithin cross-section of the lumbosacral trunk with a centrofascicular area (arrows) also exhibiting marked loss of myelinated fibers (Toluidine blue; ×62 before reduction). Both in A and B, note the apparent widespread reduction in myelinated fibers. C) This high-power view of the central region of the lumbosacral trunk illustrates severe reduction of large myelinated fibers, thinly myelinated small axons, preserved unmyelinated axons (arrowheads), and widespread edema and endoneurial mononuclear inflammatory cells, some of them with perivascular distribution (arrows) (Toluidine blue; ×375 before reduction). D) This high-power view of the subperineurial region of the lumbosacral trunk shows numerous de-remyelinated fibers and mononuclear cells and inflammatory edema; both features account, to some degree, for the apparent widespread loss of myelinated fibers observed in A) and B) (Toluidine blue; ×475 before reduction). Adapted from Berciano et al.[52]

Based upon the early pathological features reported by Haymaker and Kernohan,[1] we will now proceed to answer the six questions set out in the Introduction.

Which could be the pathological hallmark and the mechanism of ascending paralysis in patients with very early classic Guillain-Barré syndrome showing normal or non-contributory nerve conduction study findings?

By definition, all patients with classic GBS exhibit a variable degree of flaccid tetraparesis.[6] As GBS is a PNS disease, one would expect conventional NCS to show specific alterations from the very beginning. However, this is hardly ever the case; let us examine this subject.

Using Uncini's optimized electrodiagnostic criteria,[8] only 20% of cases of very early GBS may be categorized within the demyelinating or axonal subtypes, with the remainder exhibiting a mixed or equivocal pattern, or even normal findings.[11,12] At such an early clinical stage, the most frequent electrophysiological features were abnormal late responses (F and H) and attenuated distal CMAPs, pointing to predominant pathological involvement of proximal nerve trunks and pre-terminal nerve trunks, respectively.[7,10-12,52-54] Two special electrophysiological studies deserve separate consideration.

Kurt Incesu and colleagues investigated the diagnostic value of electrical root stimulation (RS) at the laminar

level in the early stage of 15 classic GBS patients.[55] In all patients, the amplitudes elicited by RS were significantly attenuated, while conventional electrophysiological findings were normal or not diagnostic in 40% of cases. Motor latencies by the RS were not significantly prolonged in comparison with controls. The authors concluded that M-responses elicited by lumbar RS appeared to be helpful in disclosing proximal conduction abnormalities of GBS early in the clinical course.

Sevy and colleagues evaluated the diagnostic efficiency of the triple stimulation technique in highlighting proximal conduction blocks in six patients with early AMAN, which did not meet the electrophysiological criteria for GBS.[56] All six patients had conduction blocks situated between the root emergence and the Erb point, namely in spinal nerves.

In short, NCS and special electrophysiological techniques strongly suggest that inaugural paralysis in any classic GBS subtype is accounted for by nerve conduction dysfunction in proximal nerve trunks, thus confirming Haymaker and Kernohan's seminal findings that spinal nerve edema is a hallmark of the syndrome.[1]

Is there any correlation between selective spinal nerve pathology and axonal degeneration in early AMAN/AMSAN?

AMAN/AMSAN, originally recognized under the term Chinese paralytic syndrome, was addressed in an article by McKhann and colleagues,[57] reporting:

> 36 patients from rural areas of northern China, aged from 15 months to 37 years (median, 7 years) admitted to hospital during a 2-week period in August 1990 with acute paralytic disease, whose electrophysiology showed distal CMAP amplitude reduction and normal motor conduction velocity […]. The disorder was considered a type of reversible distal motor terminal or anterior horn lesion.[57]

Two years later, McKhann and colleagues reported the results of 10 autopsy studies, showing non-inflammatory Wallerian-like degeneration of motor fibers in five, demyelination in three and absence of lesions in two.[58] The acronym AMAN was applied to cases showing selective degeneration of motor fibers; in this regard, the authors wrote that "the major pathological finding was Wallerian-like degeneration of the ventral roots and motor fibers within the peripheral nerves […]; the proportion of degenerating radicular fibers increased distally toward the ventral root exit from the dura [where] 80% of motor fibers were degenerating"[58]; namely, the greatest pathology affected spinal nerves. One might wonder why the main changes are located within spinal nerves in a primary motor axonopathy. Let us now address this question.

Afterwards, the histopathological features of the Chinese paralytic syndrome were reassessed by Griffin and colleagues in two series encompassing 16 patients, with autopsies performed between three and nine days after onset in 11 cases.[59,60] Focusing on their early cases, two were classified as AMAN, three as AMSAN, three as AIDP, and the remaining three as minimal pathology. As described by the authors:

> the pathological picture suggested that most of the initial lesions were in the spinal roots, rather than in the peripheral nerves […]. Some degenerating fibers could be identified within 200 μm of the ventral root exit zone […]. The process of Wallerian-like degeneration was more advanced in the ventral roots than in the peripheral nerves […]. Because Wallerian degeneration proceeds centrifugally from the site of axonal interruption down affected fibers, the picture is consistent with interruption of most of the degenerating fibers at the level of spinal roots, rather than the peripheral nerves.[59]

AMSAN histopathological features were considered similar to those reported by Feasby and colleagues,[61] but with the insightful addition that "Strictly speaking, these cases are neither *nondemyelinating* nor *noninflammatory*, but rather predominantly axonal and minimally inflammatory."

In short, the original pathological studies of early AMAN and AMSAN demonstrated that the brunt of changes, as in early AIDP, involved the ventral root exit from the dura, that is, where the anterior and posterior roots merge to form the spinal nerve, and where the dura mater is in continuity with the epineurium. Although endoneurial edema is not specifically mentioned, this could have gone unnoticed. Based upon previous autopsy studies (see above) and further pathological and imaging studies (see below), there is a rational basis to propose that initial inflammatory edema of proximal nerve trunks possessing epi-perineurium, when critical enough, could have the following effects (see Figure 5)[12]: *i)* an increase in EFP; *ii)* ischemic conduction block,

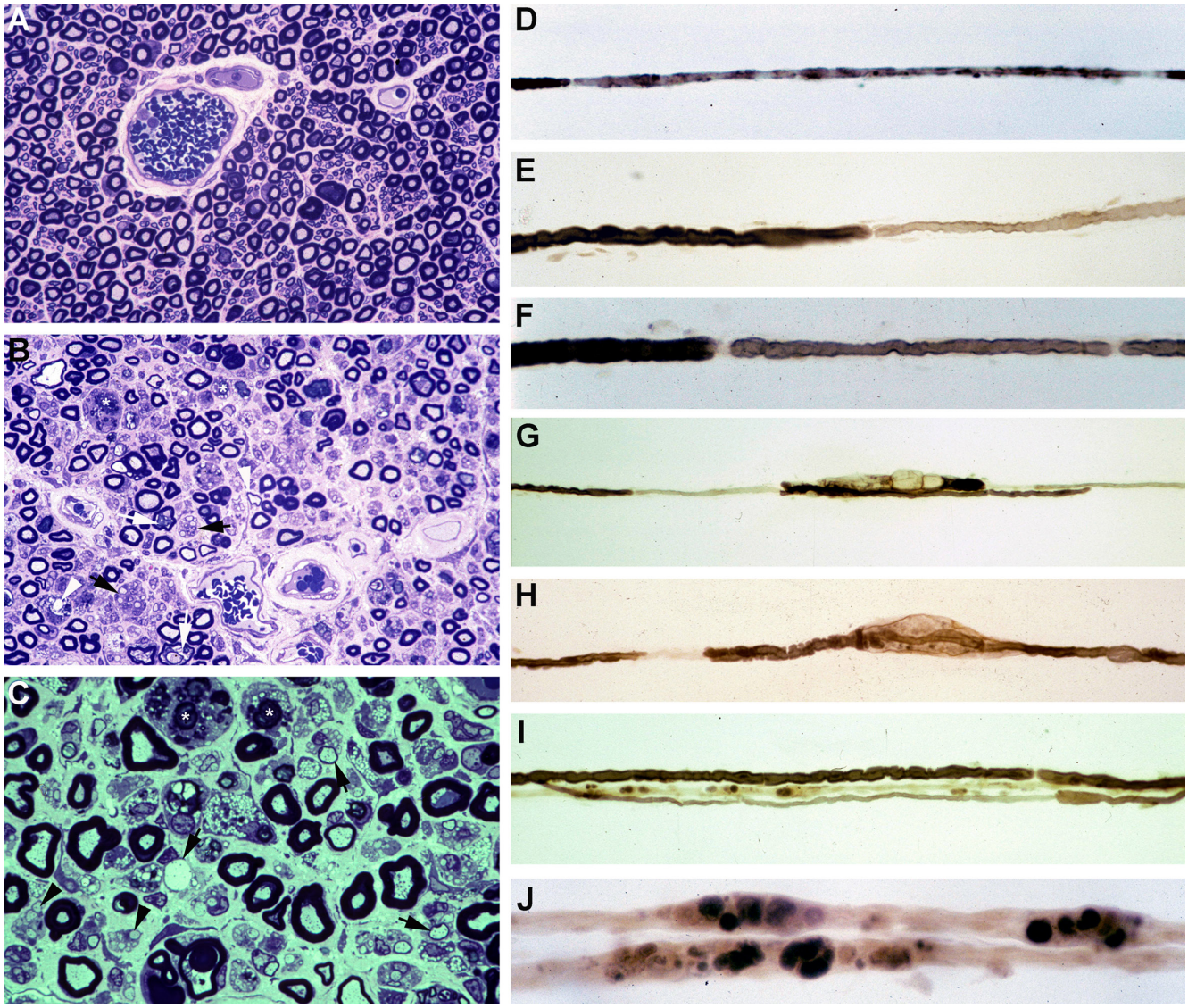

Figure 7. Pathology of pure motor GBS in a patient who died 29 days after onset. A) Semithin section from the L5 dorsal root showing preservation of myelinated fibers (toluidine blue stain; original magnification: ×400). B) On the contrary, this semithin section from the L5 ventral root displays a clear reduction in the density of myelinated fibers, presence of lipid-laden macrophages, endoneurial edema, fibers showing vacuolar myelin dissolution (white arrows), de-remyelinated fibers (white arrowheads), fibers presenting myelin breakdown, indicating active axonal degeneration (asterisks), and clusters of regeneration (black arrows) (toluidine blue stain; original magnification: ×400). C) At greater magnification, this semithin section from the L5 ventral root displays numerous lipid-laden macrophages, endoneurial edema, de-remyelinated fibers (black arrows), fibers presenting myelin breakdown (white asterisks), and clusters of regeneration (black arrows). Based on these images, it is difficult to establish whether the pathology is primarily axonal or demyelinating. To answer this question, we conducted a teased-fiber study of the L5 ventral root (D-J), observing the following findings: complete internodal demyelination (D); complete internodal remyelination (E, F); paranodal demyelination with vesiculovacuolar myelin dissolution (G, H); some groups of fibers of variable morphology (I), including a normal fiber (top), one presenting axonal degeneration (middle), and one presenting de-remyelination (bottom); and fibers with linear rows of osmiophilic droplets, characteristic of active axonal degeneration (J). Taken from Berciano et al.[64]

detected by exploring late electrophysiological responses (see above); and *iii)* axonal damage manifesting as Wallerian-like degeneration, both centrifugally in more distal nerve trunks, and centripetally, predominating in distal parts of intrathecal spinal roots, as masterfully described by Griffin's group.[58-60]

Be that as it may, there is again a striking similarity between the topography of early histopathological changes described by Haymaker and Kernohan in GBS and those of the Griffin's group in AMAN/AMSAN.

Is there any correlation between Haymaker and Kernohan's histopathological findings and modern imaging studies in early stages of the syndrome?

Post-contrast T1-weighted magnetic resonance imaging (MRI) studies of the spinal cord and (intrathecal) spinal roots display radicular contrast enhancement in the vast majority of cases of GBS.[12,40,41] This enhancement may be circumscribed to the ventral roots in cases of pure motor GBS[62,63]; this correlates well with histopathological findings, which show selective involvement of these roots (Figure 7).[64] Spinal nerve hyperintensity has been well illustrated with coronal short-tau inversion recovery (STIR) sequences.[65,66] One limitation of MRI is its poor applicability in patients whose clinical and neurophysiological data already suggest acute polyradiculoneuropathy, and particularly in those needing ventilatory support and in pediatric patients requiring sedation. Whatever the case, MRI has demonstrated the great importance of proximal nerve trunk pathology, which is applicable to all classical GBS subtypes.

Ultrasonography is a highly valuable diagnostic technique for studying PNS pathology.[67] Our study group conducted an ultrasonography study in consecutive patients with early GBS over a one-year period (1 February 2013 to 31 January 2014).[13] The series included six patients with severe classical GBS (five required mechanical ventilation): two cases of AMSAN and four cases of AIDP. The main alterations detected in the ultrasound study affected the ventral rami of the C5-C7 spinal nerves (in four of the six patients). These alterations were characterized by a significantly increased cross-sectional area, blurring of the epineurial hyperechoic rim, or both findings (Figure 8).[13] One fatal AIDP case presented an excellent correlation between sonographic and histopathological alterations (Figure 9).[13] Intriguingly, dissection from the L5 root to the fifth lumbar ganglion and lumbar nerve showed histological findings that mimicked those described by Krücke[42] (Figures 10 and 11; cf. Figure 3).[13] These findings confirm that inflammatory edema of the spinal nerves is the outstanding pathological hallmark in early stages of GBS.[1,42] In this early stage of progression, ultrasonography of the distal trunks only demonstrated alterations in 8.8% of the studied nerves, mainly detecting changes in the proximal segment of the median nerve. Our ultrasound findings in the C5-C7 nerves were confirmed by other authors,[68-71] despite discrepancies regarding the frequency of alterations in more distal nerve trunks. If we also consider the fact that sonography results depend on the skill of the clinician performing the study, there is a great need for new prospective studies with an international consensus.[72]

Thus, there is a strong concordance between modern imaging studies and Haymaker and Kernohan's classical findings in early GBS: changes are mainly localized in the intrathecal spinal roots and spinal nerves.

What might be the histopathological basis of nerve inexcitability in very early Guillain-Barré syndrome?

A pattern of motor nerve inexcitability is universally recognized within the acute stage of GBS (usually at first electrophysiological exam), which is defined as follows: "dCMAP absent in all nerves (or present in only one nerve with dCMAP amplitude < 10% of the lower limit of normal)."[8] In very early GBS, unexcitable nerves occurred in 11% of cases.[54] In this respect, two limitations should be taken into account: *i)* there is no unanimity on the number of motor nerves to be examined; it has been tentatively established that at least four motor nerves should be tested; and *ii)* concerning early GBS, the timing for the first examination varies between different studies, with delays of ≤ 4 days, ≤ 7 days, or even ≤ 10 days,[7,9,10,53,54] thus complicating the interpretation of the mechanism of reduced nerve excitability. Motor nerve inexcitability or severe dCMAP attenuation in early GBS can be caused by a number of mechanisms[73]: *i)* demyelinating conduction block in distal nerve terminals; *ii)* axonal conduction block in distal nerve segments; *iii)* primary axonal degeneration in distal nerve segments; *iv)* Wallerian degeneration secondary to demyelination in proximal nerve segments; and *v)* primary axonal degeneration in proximal nerves resulting in Wallerian degeneration. In very early GBS, we should remember that such mechanisms ought to be operational when, from a histopathological perspective, neither demyelination nor

axonal degeneration has begun to appear, which usually occurs from day 5 onwards.[1,46]

As mentioned above, over the first four days of illness, both in GBS and EAN, the only pathogenic factor is inflammatory edema predominating in proximal nerve trunks and probably in pre-terminal nerve segments, the potential cause of ischemic conduction block, which might be regressive, adding a novel cause of reversible conduction failure (Figure 12).[10] At this point, let us recall two basic notions to avoid misunderstanding of the mechanisms operating in very early nerve inexcitability in GBS. Firstly, when nerve supply vessels are clamped, nerve excitability is lost within 10 to 26 minutes, as shown by the failure of muscle contractions in response to nerve stimulation.[74] Secondly, when considering the possibility of axonal degeneration as the cause of nerve inexcitability, it should be taken into account that motor-evoked amplitudes are reduced by 50% at three to five days after nerve injury.[75] Therefore, edema in selective nerve trunks leading to endoneurial ischemia most probably accounts for nerve inexcitability in the first few days of any classic GBS subtype.

Once again, Haymaker and Kernohan's seminal paper helped to elucidate the pathophysiology of inaugural inexcitability in GBS[1]: endoneurial edema is most probably the key pathogenic factor!

What might be the mechanism of elevated serum neurofilament light chain or peripherin in very early Guillain-Barré syndrome?

NfL is a neuronal cytoplasmic protein that is highly expressed in large-caliber myelinated axons. Its levels in the CSF and blood increase proportionally to the degree of axonal damage in a variety of neurological disorders. New immunoassays capable of detecting biomarkers at ultralow levels have allowed for the measurement of NfL in blood, thus making it possible to easily and repeatedly measure NfL for monitoring the course of different diseases.[76]

There have been four reported series of very early classic GBS, either demyelinating or axonal, that describe serum levels of NfL or peripherin.[15-17,20] Intriguingly, levels of both biomarkers were increased in most patients, with no significant differences between demyelinating and axonal subtypes, though higher levels were correlated with poor outcomes. To explain the mechanism of axonal damage in AIDP it has been argued that "recent ideas of GBS being a spectrum of nodo-paranodopathy with varying degrees of paranodal and axonal damage determining the electrophysiological phenotype may be supported by these data. Although almost all GBS cases in the UK are 'demyelinating,' the data here suggest peripherin consistently rises, indicating axonal damage in most cases."[17] The author of the present study argued that as AIDP is not a form of nodo-paranodopathy, there must be other mechanisms explaining such axonal damage.[18]

The above-mentioned biomarker studies demonstrating axonal damage in all early GBS subtypes are an exciting area of study, which merits special reflection.

In classical P_2-induced EAN model, using conventional immunogen doses (25 μg SP_{26}), inflammatory edema and demyelination were the predominant histological features in lumbosacral roots and sciatic nerves.[77] When immunogen doses were quadrupled, spinal roots continued exhibiting inflammatory demyelination, whereas axonal degeneration and accentuated inflammatory edema were the outstanding lesions in sciatic nerves. The authors interpreted the findings as indicating that axonal degeneration is caused by more florid inflammation of distal nerves in comparison with spinal roots, with macrophages appearing to be the major effectors in axonal destruction. This proposal was not confirmed in our detailed clinicopathological study of a patient with fulminant GBS showing universal nerve inexcitability on days 3, 10, and 17 after onset.[14] Post mortem examination (day 18) showed pure demyelination in the nerve roots and mainly axonal degeneration in more distal nerve trunks. This discordant lesion topography had been associated with a bystander effect, with more intense inflammatory reactions at higher immunogen doses and in extradural nerve trunks. We then argued that this mechanism did not seem to apply in our material, as macrophage infiltration in the roots and more distal nerve trunks was comparable. Having in mind the seminal papers reporting the relevance of early spinal nerve pathology,[1] we wondered whether the appearance of epi-perineurium at the subarachnoid angle might play a pathogenic role in early stages of GBS (see Figure 5).[12] The affirmative answer to this question was given in three clinicopathological studies (see Figures 9-11).[13,39,52] Furthermore, as in EAN,[78] we reported areas of endoneurial ischemia in nerve trunks possessing epi-perineurium (see Figure 6).[39,52]

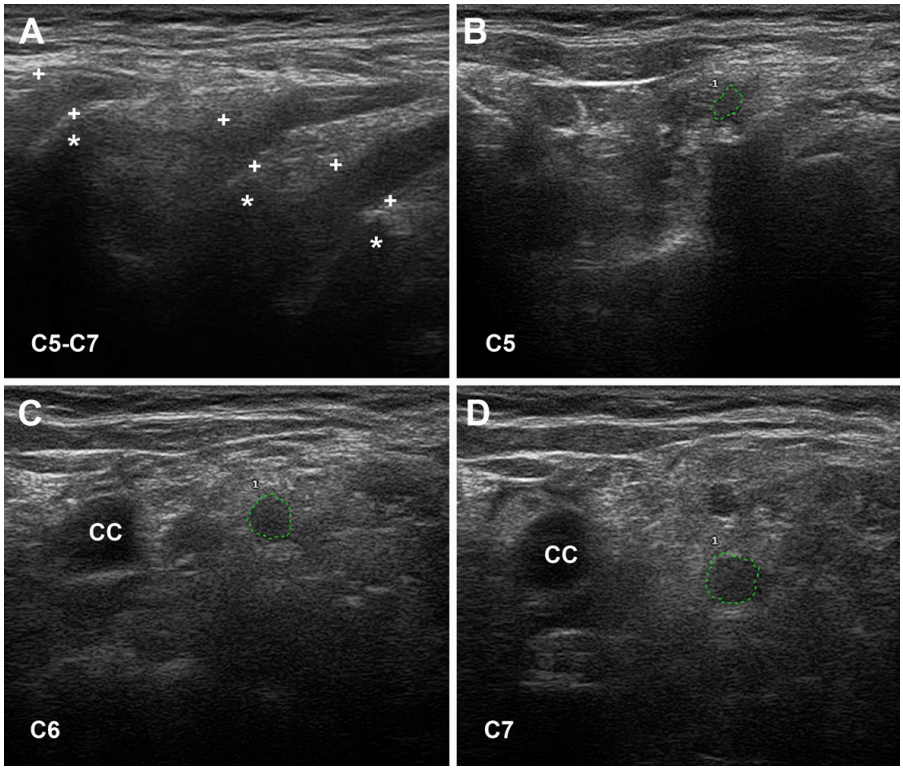

Figure 8. Ultrasound study of the ventral rami of nerves C5-C7, obtained on the fifth day of progression in a patient with fulminant AIDP. A) Sagittal images showing disappearance of the epineurial hyperechoic rims (crosses indicate calipers; asterisks indicate the transverse processes). B-D) Short-axis ultrasound of the three cervical nerves, whose perimeters are marked with green dotted lines; their cross-sectional areas are abnormally large. Note the disappearance of the epineurial rims. CC: common carotid artery. Taken from Gallardo et al.[13] See next Figure 9 for sonographic-pathological correlation.

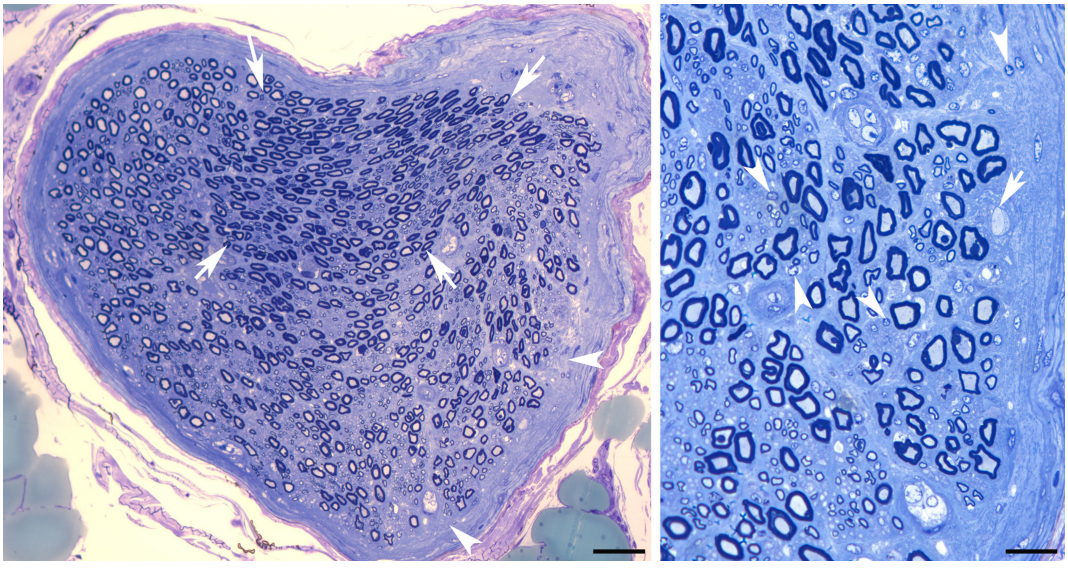

Figure 9. A) Semithin cross-section of a fascicle of the ventral ramus of the sixth cervical nerve (same patient as in the previous picture, who died on day 9 after onset). There is a blunt, wedge-shaped zone with preserved density of myelinated fibers (arrows), whereas the remaining endoneurial areas exhibit widespread edema, which is particularly conspicuous at the subperineurial level (arrowheads) (Bar, 50 µm). B) Higher-power view of the subperineurial area indicated with arrowheads in A). Note the presence of patchy subperineurial edema, mononuclear inflammatory cells (arrowheads) and occasional denuded axons (arrow); note the absence of active axonal degeneration (Bar, 20 µm). Taken from Gallardo et al.[13]

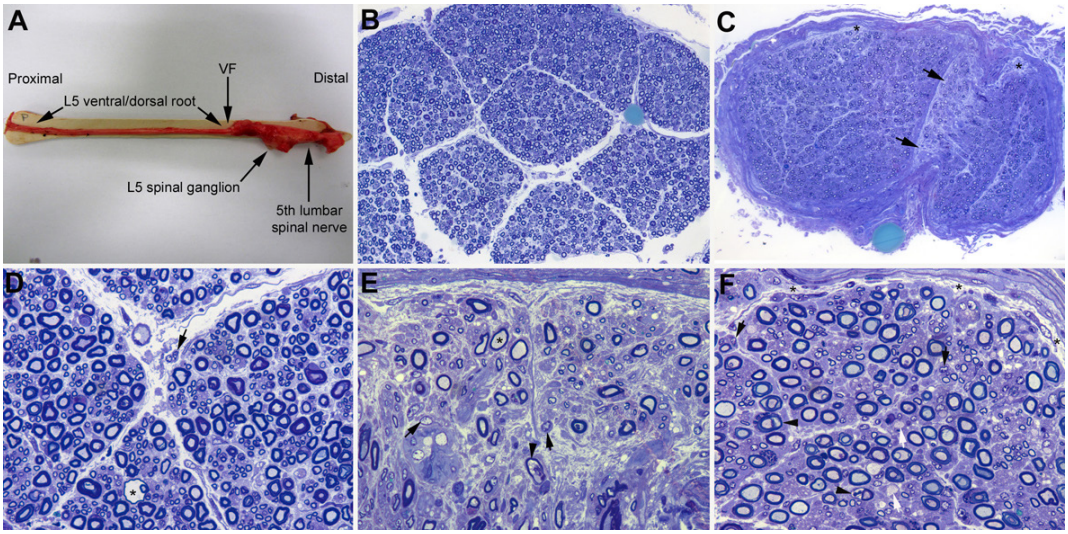

Figure 10. Pathological features in early AIDP (same the patient illustrated in the two previous figures). A) After being dissected down, macroscopic appearance of the right L5 spinal root, L5 spinal ganglion and fifth lumbar spinal nerve. Whereas the pre-foraminal root shows normal morphology, note visible nerve enlargement as of the vertebral foramen (VF). B) Semithin cross-section of L5 ventral root, taken 1 cm above its entrance to the VF, showing that the density of myelinated fibers is preserved (Toluidine blue; original magnification ×100 before reduction). C) Semithin cross-section of the ventral ramus of the fifth lumbar nerve, taken at its emergence through the intervertebral foramen, showing widespread endoneurial edema, which is more conspicuous in septum-adjacent areas (arrows) and sub-perineurial areas (asterisks); such edema results in a spacing-out phenomenon, giving the observer the false impression of reduced density of myelinated fibers (Toluidine blue; original magnification ×65 before reduction). D) High-power view of the L5 ventral root showing preserved density of myelinated fibers with occasional presence of mononuclear cells (arrow) and a fiber exhibiting myelin vacuolization (asterisk). E) High-power view of the sub-septum area arrowed in C). Note the presence of florid inflammatory edema with numerous mononuclear cells (arrows), fibers with inappropriately thin myelin sheaths (asterisk), and fibers exhibiting myelin vacuolation (arrowhead). Having in mind the spacing-out phenomenon, note the false impression of reduced density of myelin fibers in comparison with the L5 ventral root and sciatic nerve (Toluidine blue; original magnification ×630 before reduction). F) Semithin section of sciatic nerve showing some demyelinated axons (arrows), fibers with vacuolar degeneration (arrowheads), and widespread but discreet endoneurial edema, which is more marked in sub-perineurial areas (asterisks) with presence of mononuclear cells (arrows) (Toluidine blue; original magnification ×630 before reduction). Taken from Gallardo et al.[13]

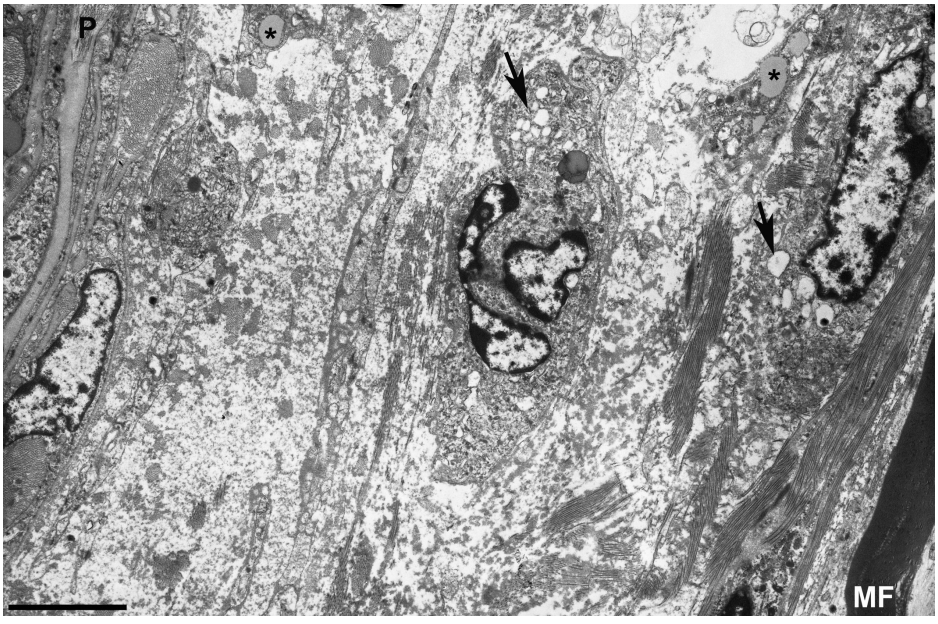

Figure 11. Electron micrograph of a subperineurial area of the fifth lumbar nerve (the same patient as illustrated in the three previous figures) showing extensive edema on a ground substance of amorphous material, most likely proteoglycans, with sparse bundles of collagen fibrils. Note the presence of lipid-laden macrophages (asterisks) and numerous electron-lucent endocytic vesicles (arrows) and lysosomes. The edematous area is empty of myelinated fibers, the only one observed (MF) being separated about 20 μm from the inner perineurial layer; P indicates perineurium (Bar, 3 μm). Taken from Gallardo et al.[13]

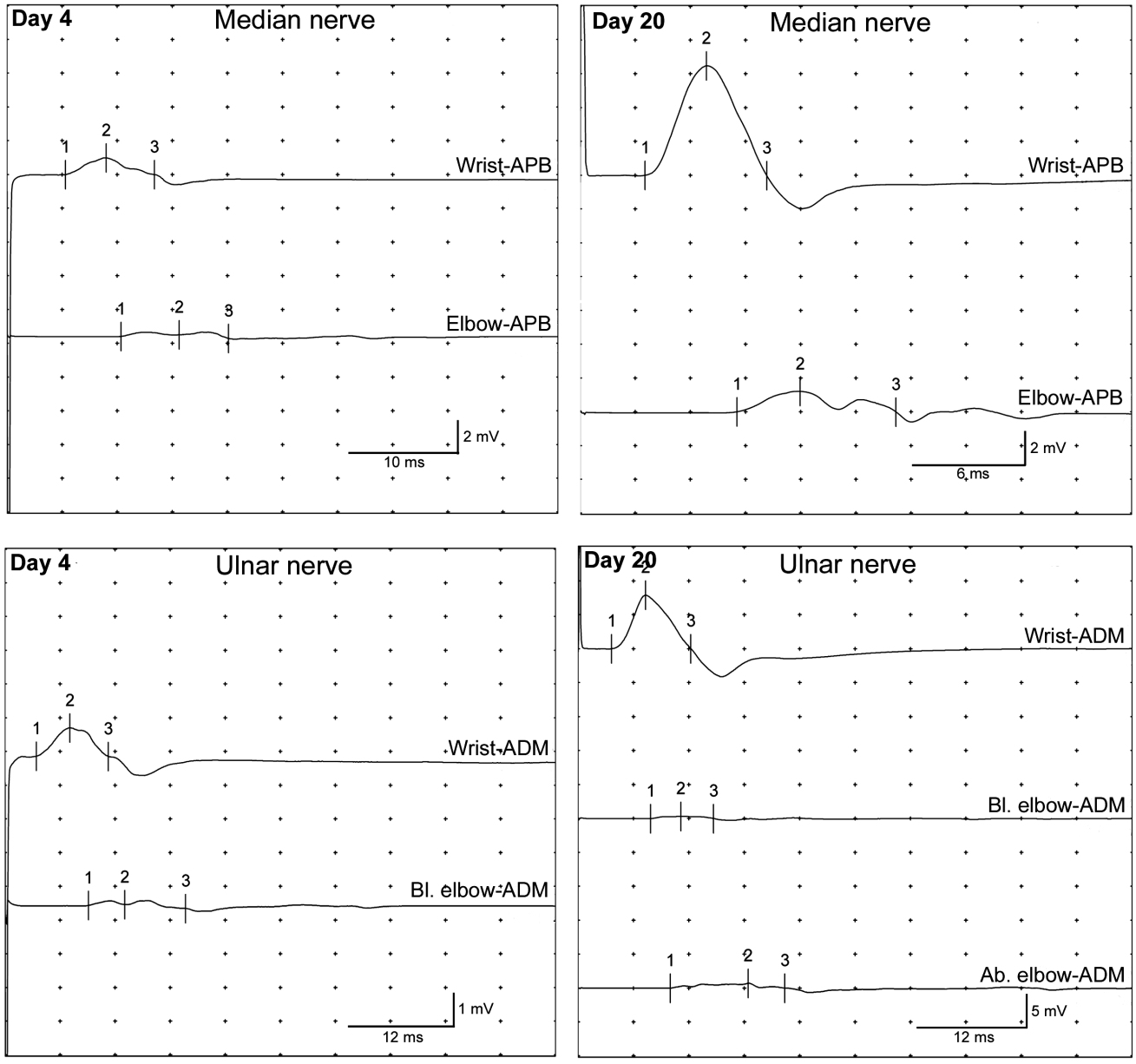

Figure 12. Serial motor conduction studies of median and ulnar nerves in a patient with AIDP. On day 4, note severe CMAP amplitude reduction in both nerves, which is more marked on elbow stimulation; DML and CMAP duration are slightly abnormal the median nerve, but preserved in the ulnar nerve; MCVs are normal in both nerves (see values in reference 10). On day 20, distal CMAP amplitudes are normalized (amplitude increase of 650% for the median nerve and 987% for the ulnar nerve) with preserved or mild prolongation of their duration, a fact suggestive of reversible conduction failure; however, there is marked CMAP attenuation on elbow stimulation, pointing to persistent conduction block in intermediate segments of both nerves. There is a clear slowing of MCV, which is in the demyelinating range for the ulnar nerve only (see values in Nedkova et al.[10]). CMAP duration is further increased in both nerves; conversely, DMLs are normal. Mixed conduction pattern is now categorized as being indicative of AIDP. Ab.: above; ADM: abductor digiti minimi; APB: abductor pollicis brevis; Bl.: below. Taken from Nedkova et al.[10]

Therefore, abnormal levels of NfL or peripherin in any very early GBS subtype, pointing to axonal damage, are most probably accounted for by endoneurial ischemia associated with inflammatory edema of proximal nerve trunks possessing epi-perineurium. As noted by Powell and Myers,[79] "whereas brain edema is universally understood as medical emergency, the destructive impact of endoneurial edema is less well appreciated; measures to inhibit edema and to ameliorate its effects have potential importance in protecting nerve fibers from ischemic injury." In other words, there may be a therapeutic window for the use of intravenous glucocorticoids in early, severe GBS; furthermore, on the basis of the clinical and experimental data previously analyzed, we think that it would be worth testing to inhibit endoneurial edema as soon as possible, probably through a combination of corticosteroids and plasma exchange or intravenous immunoglobulin regimen.[12,80] In any case, this therapeutic question calls for future controlled trials.

As mentioned above, the major pathological finding in AMAN is extensive Wallerian-like degeneration of the ventral roots and, usually to a lesser degree, of motor fibers within the peripheral nerves. AMAN is considered a prototypic example of acute nodo-paranodopathy, whose immunopathological cascade begins with anti-ganglioside antibody (IgG1 and IgG3 subclasses) deposition at the node of Ranvier, complement activation, and formation of membrane attack complexes (MAC) that induce Nav loss, paranodal myelin detachment, and finally nodal lengthening. With advance of the immune attack, Ca^{2+} penetrates into the axon through the pores formed by MAC, activating proteases such as calpain, which causes damage to neurofilaments and ultimately axonal degeneration.[5,18,81,82] Therefore, axonal damage in early AMAN may be associated with ischemic damage to proximal nerve trunks and perhaps pre-terminal nerve segments, nodo-paranodopathy, or both mechanisms.

Was the autopsy material available to Haymaker and Kernohan sufficient to reach reliable conclusions on early Guillain-Barré syndrome?

The only reference to the autopsy material on which Haymaker and Kernohan[1] worked is as follows: "In the past years, especially since Pearl Harbor, the Army Institute of Pathology received 50 fatal cases of the disorder [Guillain-Barré syndrome]. Thirty-two of these occurred in the United States, 13 in the European and Mediterranean Theaters of Operation, and 5 in the Pacific Area." This information was supplemented by Asbury,[35] who commented that

> the clinical information they received was whatever the military sick bays and hospitals sent to the AIP, along with bits of fixed pathologic tissues and microscopic slides made in the field. The wet specimens of fixed nervous system were mainly short segments of spinal cord with shorter bits of attached spinal root, either ventral or dorsal or both, or some of the specimen. The paucity of the pathologic specimen and clinical information was brought to my attention approximately 25 years later in discussions with Dr Haymaker, who was a longtime professional colleague and friend of both my mother and my aunt […]. When I had the chance to converse at length with Dr Haymaker in the mid-1970s, he was fully aware of our clinicopathologic study [Asbury[43]] published 20 years after his effort with Dr Kernohan. He expressed envy and amazement when I described the details of the clinical information available to us for the 19 autopsy cases of GBS we reported, and the extent to which peripheral nerve, plexuses, and spinal roots and spinal cord were dissected […] [see above].[35]

Asbury made no comment on his denial of endoneurial edema of the spinal nerves as the inaugural lesion in GBS, which had been one of the key histopathological findings of Haymaker and Kernohan.[1]

Concerning the technique for removal of the spinal cord at autopsy, American Army pathologists probably performed it from the ventral side.[83] In short, after routine autopsy is completed, a strong saw is used to cut through the bodies of the vertebrae on the sagittal plane, after which a broad chisel is used to cut through each intervertebral disc in the horizontal plane, leaving the spinal cord completely exposed, enabling its extraction together with spinal roots, spinal ganglia and prolonged nerves surrounded by the dura, as elegantly illustrated by Haymaker and Kernohan in their figures 3 and 13.[1] Thus, these authors had in their hands a restricted material, but which today we know is the setting for the inaugural histopathology in GBS. As both were excellent pathologists, in our humble opinion their histopathological description remains an invaluable document for understanding the pathophysiology of very early GBS.

Conclusions

The contribution of Haymaker and Kernohan has been pivotal in establishing the nosological boundaries of GBS, and in identifying the characteristics and topography of the inaugural histopathological changes. To a large extent, the current pathophysiology of the syndrome, in its very early stage, is based upon such changes.

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Conflicts of interest

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