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Review Article

Spinal nerve involvement in early Guillain-Barré syndrome: The Haymaker and Kernohan's legacy

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ABSTRACT

Pathological studies of early Guillain-Barré syndrome (GBS), defined as of 10 days of disease onset, are scanty making it difficult to interpret the physiopathology of clinical and electrophysiological features. In 1949, Webb Haymaker and James Kernohan reported 50 clinico-pathological studies of fatal GBS cases, 32 of them having died between days 2 and 10 after onset. They established that the brunt of initial lesions, consisting of endoneurial oedema interpreted as degenerative, relied on spinal nerves. That this oedema was inflammatory was soon thereafter recognized. Two decades later, however, the pathogenic role of endoneurial oedema was disputed. In experimental allergic neuritis, considered an animal model of GBS, the initial lesion appearing on day 4 post-inoculation is marked inflammatory oedema in the sciatic nerve and lumbosacral nerve roots. Additional detailed clinico-pathological studies corroborated that the appearance of epi-perineurium at the subarachnoid angle, where anterior and posterior roots join to form the spinal nerve, is a pathological hotspot in early GBS, there developing inflammatory oedema, incipient demyelination and endoneurial ischemic zones with axonal degeneration. Furthermore, nerve ultrasonography has demonstrated predominant spinal nerve changes in early GBS, either demyelinating or axonal. Other outstanding Haymaker and Kernohan's contributions were to clarify the complex nosology of the syndrome bringing under the same rubric Landry's paralysis, acute febrile polyneuritis and GBS, and critically analyzing GBS exclusion criteria by then prevailing. It is concluded that the authors' legacy remains as relevant as ever.

1. Introduction

Almost seven decades ago, Haymaker and Kernohan reported a clinico-pathological study in 50 cases of fatal Guillain-Barré syndrome (GBS), 32 of them having died between 2 and 10 days after symptomatic onset, namely during the period currently accepted as early GBS [1]. The authors found that the brunt of initial lesions, consisting of endoneurial oedema interpreted as degenerative, relied on spinal nerves. Remarkably, these features have been most important to understanding the physiopathology of the disease. At the time of publication, the paper was also essential to clarify the nosological limits of GBS with Landry's palsy and acute febrile polyneuritis (AFP). The aim of this paper is to carry out a review of Haymaker and Kernohan's contributions to the knowledge of GBS. For this purpose, there will be two introductory paragraphs devoted to overview the disorder with emphasis on its early stage, followed by a historical revision of the original descriptions of GBS, Landry's palsy and AFP, and the landmark paper by Haymaker and Kernohan. Subsequently, the key role of early endoneurial inflammatory oedema will be analysed through reported pathological papers on GBS and experimental allergic neuritis (EAN), and more recently by means of nerve ultrasonography (US). This review provides evidence that spinal nerve involvement is a hotspot for early GBS.

2. Brief overview of the present GBS nosology

GBS is an acute-onset, immune-mediated disorder of the peripheral nervous system, which is currently divided into several subtypes based on electrodiagnostic, pathological and immunological criteria [2–6]. GBS includes at least three disease patterns: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal and motor-sensory axonal neuropathy (AMAN and AMSAN), and Fisher syndrome [7]. AIDP is pathologically characterized by demyelination and inflammatory infiltrates in spinal roots and nerves [8,9]; in a variable proportion of cases, however, demyelination is accompanied or substituted by axonal degeneration [10–14]. AMAN is a pure motor disorder frequently associated with serum antibodies against gangliosides, GM1, GM1b, GD1a or GalNAc-GD1a, and antecedent of *Campylobacter*

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jejuni enteritis [2–6]. Autopsy studies in AMAN have revealed axonal degeneration of motor fibres without demyelination, indicative that there may be an immune response directed primarily against the motor axolemma; it is now established that carbohydrate mimicry between bacterial lipo-oligosaccharide and human gangliosides is an important cause of AMAN. It is worth noting that in the early AMAN pattern, predominant wallerian-like pathology usually occurs within 200 μm of the ventral root exit zone, the stage of this pathology being more advanced in the roots than in the peripheral nerves [7,15–17]. In Europe and North America, GBS is usually caused by AIDP, whereas in East Asia a considerable number of GBS patients have AMAN or AMSAN [5,7,15–18]. The Fisher's syndrome is especially associated with antibodies to GQ1b and characterized by the triad of acute ophthalmoplegia, ataxia and areflexia. The GBS crude average annual incidence rate in our Community (Cantabria, Spain) was 0.95 cases per 100,000 population (95% CI: 0.72–1.17) [19].

3. GBS diagnosis with emphasis on its early stage

Most patients will have an acute neuropathy reaching a peak within 4 weeks of onset, and this progressive weakness is one of the core diagnostic clinical features of GBS [2,3]. At the nadir of the disease, the clinical diagnosis of GBS is not difficult for the trained clinical neurologist and relies on diagnostic criteria having stood the test of time [2,20]. This is not the case in early GBS, arbitrarily defined as the 10 days of disease onset [21], when atypical clinical signs and symptoms may lead to delayed diagnosis [22]. Neurophysiological testing plays a very important role in confirming the diagnosis of peripheral neuropathy and GBS subtype classification, though syndromic subtyping may require serial studies [23–26]. It is a rooted concept that electrical abnormalities in GBS may not be sufficiently widespread for definite diagnosis in the first 2 weeks [10].

Involvement of proximal nerve trunks, including spinal roots, spinal nerves and plexuses, is an important nosological notion in early GBS for the following reasons: i/weakness may initially be proximal in 58% of cases [27], a sign that cannot be accounted for by distal nerve segment pathology; ii/often there is inaugural severe nerve trunk pain that may be accompanied by a Lasègue's sign or neck and back stiffness, these manifestations having been correlated with swollen nerve roots [15,16,27–31]; iii/elevated cerebrospinal fluid (CSF) protein concentration is characteristic of the syndrome, even in the first few days of the clinical course, and explained as the result of breakdown of the radicular blood-CSF barrier [27]; and iv/in a significant proportion of patients, initial electrophysiology shows just abnormal late responses (F waves and H waves) pointing to a dysfunction of proximal nerve segments [32,33].

4. Original description of GBS: from Guillain, Barré and Strohl to Haymaker and Kernohan

In the “Séance de la Société Médicale des Hopitaux de Paris” held on 13 October 1916, Guillain, Barré and Strohl reported the case of two soldiers with acute paralysis admitted, during the Battle of the Somme, to the Neurological Centre of the French Sixth Army (Amiens) [34]. The first patient was a hussar, aged 25 years, hospitalized on 25 August 1916 with a 25-day history of progressive pins and needles and weakness of his limbs. No preceding illness was reported. Examination showed marked tetraparesis, absent tendon reflexes and mild sensory loss. There was rapid recovery, so the patient was discharged on September 30. The second patient was a 35-year-old infantryman with an 8-day history of erratic limb pains and progressive weakness initiated in lower limbs. The authors' eloquent description is as follows: “Le quatrième jour il veut partir vers cinq heures avec ses camarades, s'équipe mais tombe à la renverse avec sa musette et ne peu se relever” (On the forth day, at 5:00 h, he wanted to set off with his comrades, put on his military equipment, but fell over backwards and was unable to stand up). Again no preceding illness was reported. On admission, 5 September 1916, there was severe tetraparesis and bilateral facial palsy, absence of lower-limb reflexes evolving to generalized areflexia, and slight glove and stocking hypoesthesia. The patient improved in the following days, he being transferred to a rearguard area on October 4. In both cases CSF examination revealed albumino-cytological dissociation, a finding that, as underlined by the authors, had been described only in association with compression of the spinal cord and with Pott's disease. The authors carried out graphic records of the knee and ankle reflexes, which showed delayed responses to almost twice the normal latency. Based upon these findings, they concluded that the syndrome seemed to result from a concomitant attack on the spinal roots, nerves and muscles, probably by an infectious or toxic agent. As of 1927, the illness was recognized with the eponym Guillain-Barré syndrome [35].

It is worth noting that the original report by Guillain and colleagues did not contain any assessment of the literature [34]. At that time, however, two comparable nosological entities, Landry's palsy and acute febrile polyneuritis (AFP), had already been reported, which are briefly commented on below.

In 1859, Octave Landry described 10 cases of acute ascending paralysis and sensory tingling with sparing of bowel and bladder function [36]. Two patients died, their autopsies failing to demonstrate the cause of illness after examination of brain and spinal cord and muscles; apparently the peripheral nerves were not examined. The remaining eight patients exhibited remission of the illness. These cases fitted well with the modern concept of GBS, but necessarily lacked the defining features of tendon areflexia and CSF albumino-cytological dissociation [37].

AFP is an entity introduced by Osler in 1892 to designate an illness starting with a temperature rapidly rising to 103°F or 104°F (39.5°C or 40°C) and causing aching limbs and back, tingling and ascending or descending paralysis with respiratory involvement, some patients dying and others remaining stable for several weeks and then slowly recovered [38]. According to the author the clinical picture is not to be distinguished, in many cases, from Landry's paralysis. Holmes described 12 patients of AFP coming from British Army in France, who were attended in winter of 1916–1917 [39]. In this series invariably there was facial paresis, deep tendon areflexia and sphincter disturbances, though the use of a catheter was never necessary. CSF in three cases was normal. Two patients died, one from bronchitis and the other from bronchopneumonia, the remaining 10 patients showing rapid improvement. Autopsy in both fatal cases revealed no findings in the central nervous system, and demyelination of the sciatic nerve in the only case with sampled peripheral nerves. Wisely, Holmes wrote: “Unavoidable circumstances made a more complete examination of the nervous system impossible, but these changes are sufficient to confirm the diagnosis of peripheral neuritis”. Holmes' report did not contain any assessment of the literature either.

The nosology of “radiculoneuritis with acellular hyperalbuminosis of the CSF” was updated by Georges Guillain himself, reviewing 27 reports published between 1916 and 1936, and describing 10 further personal cases [40]. According to Guillain, pronounced CSF hyperalbuminosis is a constant feature, which characteristically ranges “From 1 to 2 Gm/100 cm^3… Cases with slight hyperalbuminosis, with an albuminoid content from 0.3 to 0.4 Gm., do not belong to the syndrome or must be regarded as instances of an abortive form”. As stated by Wiederholt and colleagues, in all probability the values reported by Guillain as grams per 100 ml were meant by the author to be grams per litre [41]. Additional features of the syndrome would be abolition of tendon reflexes, and favourable clinical course; in fact, Guillain considered that two previously reported fatal cases “did not belong to this group”. Furthermore, Guillain considered that Landry's paralysis and AFP are dissimilar entities.

5. The Landry-Guillain-Barré syndrome: the landmark contribution by Haymaker and Kernohan

In an 82-page paper with 225 references, Haymaker and Kernohan carried out an exhaustive review of the literature of GBS, Landry's paralysis and AFP, and described 50 fatal GBS cases, 32 of them having died between 2 and 10 days after symptomatic onset, received in the U.S. Army Institute of Pathology during World War II [1]. For the first time in the literature, GBS, Landry's paralysis and AFP were considered to fall into a single category; in fact, the name of Landry was included in the title of their paper. Worthy of note is that this terminology met with the opposition of some French authors who wrote: "Cette terminologie qui est. apparue depuis la publication de Haymaker et Kernohan [1] est erronée et elle fait perdre à chacun des éponyms toute leur signification" (this terminology appeared after Haymaker and Kernohan's publication is wrong, since each eponyms lose their significance) [42]. The authors carried out an update of the significance of the increase in protein in the CSF, as set out by Guillain (*vide supra*). Shrewdly, Haymaker and Kernohan indicated that CSF may be normal at the onset of the illness, protein becoming elevated in the course of the disease. Furthermore, they added: "were Guillain's criteria strictly adhere to, one would be obliged to remove from consideration many cases in the literature designated by the term Guillain-Barré syndrome".

Concerning mortality, Haymaker and Kenohan quoted a sentence by Guillain, who, in a symposium on the subject held in Brussels in 1938, stated that the disorder described by him might be fatal; very pertinently the authors wrote "a concession which seems to have escaped the notice of most subsequent workers on the subject" [1].

Detailed clinical data, including positive, negative and not available information, is summarized in Table 4 occupying 12 pages [1]. In their autopsy studies, the authors found that the most profound GBS alterations were encountered in the peripheral nervous system. Starting from the 32 early GBS histological studies, they were able to describe the topography and evolution of initial lesions as follows: "As a whole, the observed pathological changes were more prominent in the region where motor and sensory roots join to form the spinal nerve. Oedema of the more proximal part of the peripheral nervous system constituted the only significant alteration the first 3 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, but whether or not peripheral nerves also bore the brunt of the attack could not be determined because of the paucity of peripheral nerve material. Where motor symptoms were most prominent the lesions tended to predominate in the anterior roots, and where widespread anaesthesia accompanied the paralysis the lesions were found in anterior and posterior roots". Given that lymphocytes tended to increase in number as time went on, they were originally regarded as part of a reparative process; in fact, the disorder was characterized by a "polyradiculoneuropathy", in which changes in the amount of protein and in the number of cells in the CSF were regarded as incidental to the disorder. Central chromatolysis was observed in spinal motor neurons and dorsal ganglion neurons, a feature that would be widely confirmed in further works; worthy of note is the observed presence of inflammatory cells in spinal and sympathetic ganglia. Separately, the authors reported two clinico-pathological studies in GBS patients [43,44], which are briefly analysed hereafter.

Gilpin, Moersch and Kernohan analysed 35 cases of acute polyneuritis, 15 of them being removed from consideration because of lack of CSF complete examination [43]. Clinical data of the remaining 20 cases are fully and timely tabulated. Most patients had an increase of CSF proteins (100 to 800 mg/100 cm^3), cells, mostly lymphocytes, varying between 1 and 80 per cubic millimetre (average 12). Although the authors recognized closely similarity to AFP and without referring to the paper by Guillain and colleagues [34], they used the term "neuronitis" to designate the disease. Such designation generated sharp comments (see remarks following the Discussion of the paper): i/ Adolph Meyer (Baltimore) stated: "To speak of neuronitis is a little awkward. One ought to have the term for the primary alterations of nerve elements"; and ii/and Israel Wechsler (New York) annotated: "Therefore, I think that the name polyneuritis -not neuronitis, which is a barbarous word- should be applied in these cases and not in others". Mortality in this series occurred in 4 (20%) patients. I will focus on their fatal patient 3, showing a typical GBS with facial diplegia, who died one month after admission, and whose histological study included central nervous system, spinal roots, cranial, phrenic, intercostal, sciatic and femoral nerves, brachial plexus, sympathetic nervous system, and gasserian and dorsal root ganglia. As a whole, there was widespread and patchy demyelination of peripheral nerves with marked endoneurial oedema separating the fibres. It is worth noting the presence of beautiful images of fragmentation and vacuolation of axis-cylinders stained by a modified silver impregnation method. The authors wrote that "there were a few lymphocytes in the nerves, but seemed to us that these could be accounted for on basis of degeneration rather than on true inflammation". In this regard, it should be pointed out that paraffin sections, at that time used, may reveal minor or no inflammatory changes [45,46]. Be that as it may, Gilpin and colleagues described that "in the bundles distal to the ganglia there were collections of lymphocytes, and many were also scattered diffusely throughout the connective tissue which presented marked oedema"; furthermore their Fig. 4 shows marked subacute inflammatory process involving the fifth cranial nerve just distal to the gasserian ganglion. In retrospect, this study shows many of the pathological features characterizing the modern concept of AIDP.

In 1955, Waskman and Adams described EAN produced by injecting rabbits with rabbit sciatic nerve or spinal ganglia [47]. The authors indicated that this experimental disease is of importance because it represents one of the first laboratory models of non-infectious inflammatory disorder of peripheral nerves; they rightly noted resemblances between EAN and GBS. Thereafter, Matsuyama and Haymaker reported a clinico-pathological study in a fatal GBS case died on day 15 after onset, corroborating the topography of changes in peripheral nervous system including sympathetic white rami communicantes [44]. They found endoneurial and epineurial inflammatory infiltrates with presence of myelin debris in enlarged Schwann cells, though failed to interpret the primary pathogenic role of nerve inflammation.

In short, the contributions by Haymaker and Kernohan could be summarized as follows: i/ascending Landry's paralysis, AFP and GBS are similar disorders; ii/neither absence of albumino-cytological CSF dissociation nor fatal evolution is a criterion of exclusion of GBS; iii/in early GBS the brunt of pathology relies on proximal nerve trunks, and particularly where motor and sensory roots join to form the spinal nerve; and iv/ initial lesions consist of endoneurial oedema, reparative inflammatory cells not appearing till later stages of the clinical course.

6. Krücke corroborates the relevance of spinal nerve pathology in GBS

In his GBS autopsy material (3 infantile cases and 4 adult cases), Krücke carried out a systematic study of the central and peripheral nervous system, including proximal and distal nerve trunks and sympathetic system (Fig. 1A) [48]. In this material, endoneurial infiltrates occurred as of 24 h and were prominent as of the third day. Endoneurial oedema was accompanied by cellular infiltrates; given that there were no isolated serous exudates, as previously reported [1,43], the author interpreted that oedema was an integral part of the inflammatory

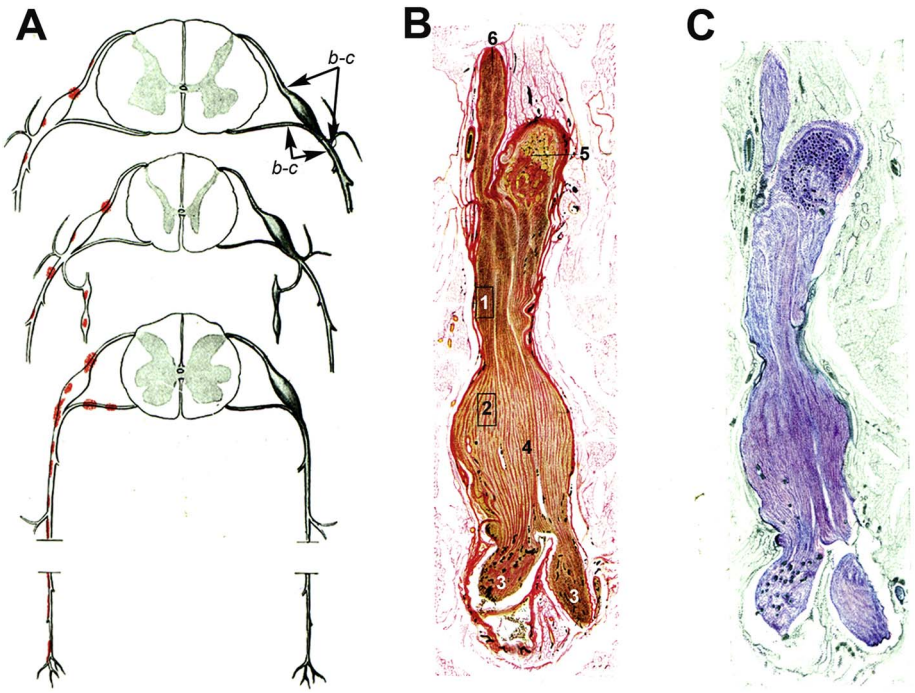

Fig. 1. Reproduction of Figs. 65 to 67 by Krücke [48] with minimal modifications. (A) Diagram of GBS lesions at cervical (upper row), thoracic (middle row) and sacral (lower row) levels; note that they mainly rely on proximal nerves including ventral and dorsal spinal roots, spinal root ganglia, sympathetic ganglia and ventral rami of spinal nerves (red dots). Lettering *b-c* indicates nerve segment illustrated in the following two figs. (B) Longitudinal section of the nerve segment between ventral spinal root and spinal nerve from a GBS patient who died on day 18, original numbering being as follows: (1 and 2) areas illustrated by the author in other figures (specially his Fig. 68b showing abundant endoneurial inflammatory oedema, which was designated as "mucoid exudate"); (3) rami of the spinal nerve (undoubtedly, ventral and dorsal rami); (4) spindle-shaped swelling of the spinal nerve; (5) spinal root ganglion; and (6) ventral spinal root (Van Gieson, magnification not specified). (C) The same longitudinal section showing a purplish discoloration of the spindle-shaped swelling of the spinal nerve (Cresyl violet, magnification not specified). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

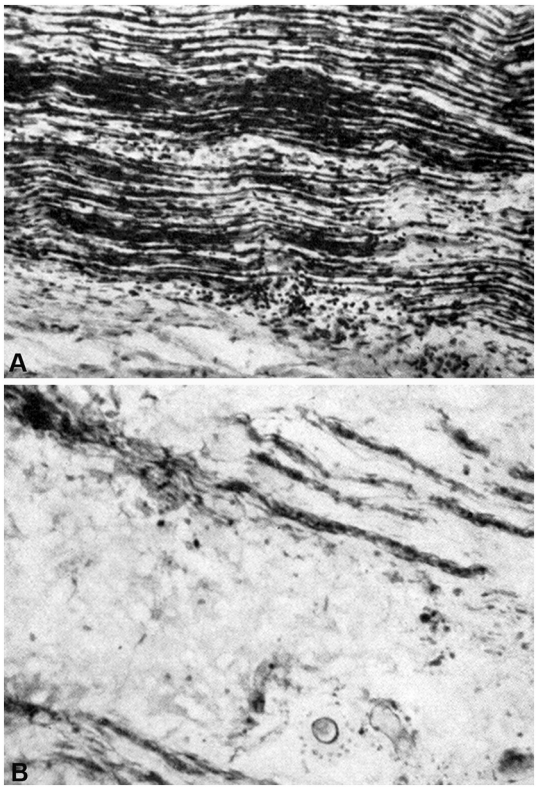

Fig. 2. Reproduction of Fig. 68 by Krücke [48]. This figure includes two sections of spinal nerve (see lettering *b–c* in Fig. 1A). (A) Focal inflammatory infiltrates with preservation of myelinated fibres (Heindenhain-Wolcke, magnification not specified). (B) Extensive "mucoid" exudate separating myelinated fibres, which appear largely disrupted (Hotchkiss reaction, magnification not specified).

process. Parenchymal destruction, namely, demyelination, was most prominent as of day 14. Initially, lesions were focal predominating in proximal nerve trunks, particularly in spinal nerves where oedema was severe enough to cause their swelling visible to the naked eye (Fig. 1B, 1C). As illustrated in Fig. 2, the severity of spinal nerve inflammatory lesions was variable. It is worthy of note that comparable inflammatory infiltrates involved sympathetic nerves, which, according to Krücke, could account for vegetative symptoms occurring in the illness.

7. Neither pre-inflammatory nor oedema stage in GBS?

Asbury and colleagues reported another comprehensive clinico-pathological series of 19 GBS patients, cases 1–5 being autopsied within 9 days after onset [8]. The authors established that the pathologic hallmark of the disease is a spotty perivenular mononuclear inflammatory infiltrate with segmental demyelination being the predominant form of nerve fibre damage. According to the authors, all levels of the peripheral nervous system are vulnerable to attack, including the anterior and posterior roots, ganglia, proximal and distal nerve trunks and terminal twigs, cranial nerves, and sympathetic chains and ganglia. In contrast to what described Haymaker and Kernohan (*vide supra*), no pre-inflammatory or oedema stage was recognized either in the gross or microscopic state. They stated that some of the emphasis on root pathology doubtlessly reflects the fact that roots have been taken at the autopsy table far more frequently than have peripheral nerves; no level or site in the peripheral nerve is indemnified. Although this notion is probably true in the long run of the clinical course [9], it is worth noting that in 2 cases (Nos. 2 and 3) presenting with motor clinical manifestations, lesions predominated in anterior roots, peripheral nerves being minimally involved. Moreover, case 2 showed prominent axonal retraction bulbs on silver stains in lumbar roots, which pertinently the authors related with intense inflammatory changes. This patient, that had had an influenza-like illness 10 days prior to admission, probably represents the first description of AMAN. Finally, Asbury and colleagues underlined the similarities between EAN and GBS, which are helpful in understanding the events surrounding the onset of GBS and interpreting its pathology.

In the Foreword of a recent book on peripheral neuropathy, Asbury commented on the influential paper by Haymaker and Kernohan [1], stating that the gist of their observations was that no inflammation was observed in the available bits of spinal roots they studied until the eighth day of illness, this being interpreted as a reparative change [49]. Asbury argues as follows: "This was in accord with the prevailing English-language view of the pathology of the Landry-Guillain-Barré

syndrome in the mid-20th century, namely that GBS was an acute, bland process, affecting mainly the spinal roots but that did not excite an inflammatory response. In contrast, some French and German neuropathologic observers had long noted widespread inflammatory changes in peripheral nerve, ganglia and spinal roots, but the inflammatory changes were either not recognized or were misinterpreted by many others, especially by English and North American observers". Even though Asbury was well aware of the aforementioned paper by Krücke [48], he avoided discussing the relevance of florid spinal nerve pathology reported in GBS (*vide supra*).

8. Inflammatory oedema of proximal nerve trunks is a relevant feature of EAN

In the seminal paper on EAN mediated by T cell lines specific for bovine P_2 protein, Izumo and colleagues reported that the initial lesion, appearing on day 4 post-inoculation (pi), is marked oedema with or without cellular infiltrates in the sciatic nerve and lumbosacral nerve roots [50]. On the following day, extensive, disseminated lesions were observed in the sciatic nerve, these being more severe and advanced proximally. They consisted of marked oedema, cellular infiltrates, and perivascular cuffs not only in the endoneurial space but also in the epineural connective tissue; there appeared incipient demyelination that was more obvious as of day 7 pi. Between days 7 and 8 pi and independent of demyelination, there were some nerve fibres showing distinct evidence of axonal degeneration. Potential mechanisms of axonal degeneration in EAN and GBS were discussed by Izumo and colleagues, who wisely wrote: "In our animal model of EAN, marked axonal degeneration was observed just 1–2 days after intense endoneurial oedema. This observation would support the possible role for ischemia in the development of axonal degeneration". Our pathological studies in GBS prove the validity of such proposal (next paragraph).

9. Spinal nerve epi-perineurium contributes to axonal damage in GBS

In three clinico-pathological studies carried out in severe AIDP patients, we have demonstrated that the lesional pattern drastically changes in the transition from preforaminal nerve roots to post-foraminal nerve trunks [51–53]. Our contributions are summarized herebelow.

In a fulminant AIDP patient, aged 67 years, who died on day 18, electrophysiology showed universal nerve inexcitability on days 3, 10 and 17 [51]. Histological study showed widespread inflammatory demyelination of spinal roots, and predominantly axonal degeneration of peripheral nerve trunks (Fig. 3). This dissociated pattern of pathology between spinal roots and more distal nerve trunks, which was hitherto unheard-of in human pathology, had already been reported in EAN induced by P_2 peptide [54]. In EAN, the severity of lesions correlates with the dose of peptide inoculates; low doses result in pure demyelination, whereas axonal degeneration occurs with high doses of antigen. In spite of widespread inflammation, axonal damage in this EAN model was severe in sciatic nerve and almost absent in lumbosacral roots, just as we had observed. Furthermore, in this EAN model axonal degeneration was centrofascicular [55], namely, a feature characteristic of ischemic neuropathy [56]. Based upon these features and Izumo's insights into the mechanisms of axonal damage in EAN (*vide supra*), we proposed the hypothesis of increased EFP in nerve trunks possessing epi-perineurium as the cause of axonal pathology in early stages of severe GBS, an issue that called for performing proximal-to-distal analysis of spinal roots and more distant nerve trunks to establish whether or not the appearance of epi-perineurium determines any change in the degree of axonal degeneration. It is timely to remember that spinal roots traverse the subarachnoid space covered by an elastic multicellular root sheath derived from the arachnoid angle (Fig. 4) [57]. External to this angle, nerve roots (spinal nerves) possess epi-perineurium and endoneurium as in the peripheral nerve trunks [58]. We hypothesized that if Haymaker and Kernohan [1] were right in their appreciation of maximum oedema (inflammatory oedema according to Krücke [48]; *vide supra*) on spinal nerves in early GBS, this could result in focal increase of EFP leading to ischemic changes and proximal conduction failure. This question was addressed in two clinico-pathological studies [52,53]; briefly, I will focus on the first one in the next paragraph.

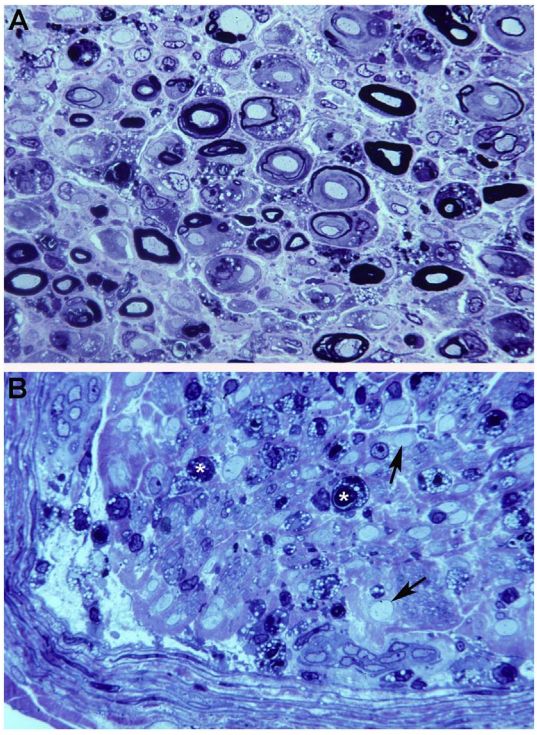

Fig. 3. Pathology in fulminant GBS with universal nerve inexcitability. (A) Semithin section of L5 ventral root showing massive demyelination and numerous lipid-laden macrophages (Toluidine blue; × 630 before reduction). (B) Semithin section of femoral nerve illustrating marked axonal degeneration (asterisks). Note the presence of denuded axons (arrows), and endoneurial and subperineurial macrophage infiltrates (Toluidine blue, × 630 before reduction).
Taken from Berciano et al. [51].

A patient, aged 79 years, presented with 2-day history of distal paresthesias and ascending weakness culminating in quadriplegia and mechanical ventilation; he died 60 days after onset [52]. Serial electrophysiological studies (days 4, 17 and 50) initially showed normal nerve conduction velocities with further slowing down to the demyelinating range, progressive attenuation of compound motor action potentials (CMAP), absent sensory nerve action potentials, and profuse muscle denervation. Pathological study included preforaminal anterior and posterior L5 spinal roots, third and fifth lumbar spinal nerves and their branches, and femoral and sural nerves. Mild de/remyelination was noted in lumbar roots. Axonal degeneration was the predominant lesion in sural nerve. In both lumbar nerves and their branches, there were extensive de/remyelination, and centrofascicular or wedge shaped areas with marked loss of large myelinated fibres (Fig. 5). Such focal endoneurial lesions are characteristic of nerve ischemia involving watershed zones of poor perfusion [56]. In EAN, axonal damage in sciatic nerve is preceded by a significant increase of the endoneurial extracellular space, which is correlated with an increase of EFP causing constriction of transperineurial vessels with pathogenic diminution of nerve blood flow [59]. We argued that the absence of epi-perineurium in spinal roots probably prevents their having an increase of EFP and ischemic injury in spite of inflammatory demyelination. Perineurium is relatively inelastic and has only a limited ability to expand. Small increases of EFP, as caused by endoneurial inflammation [50,56,59], can

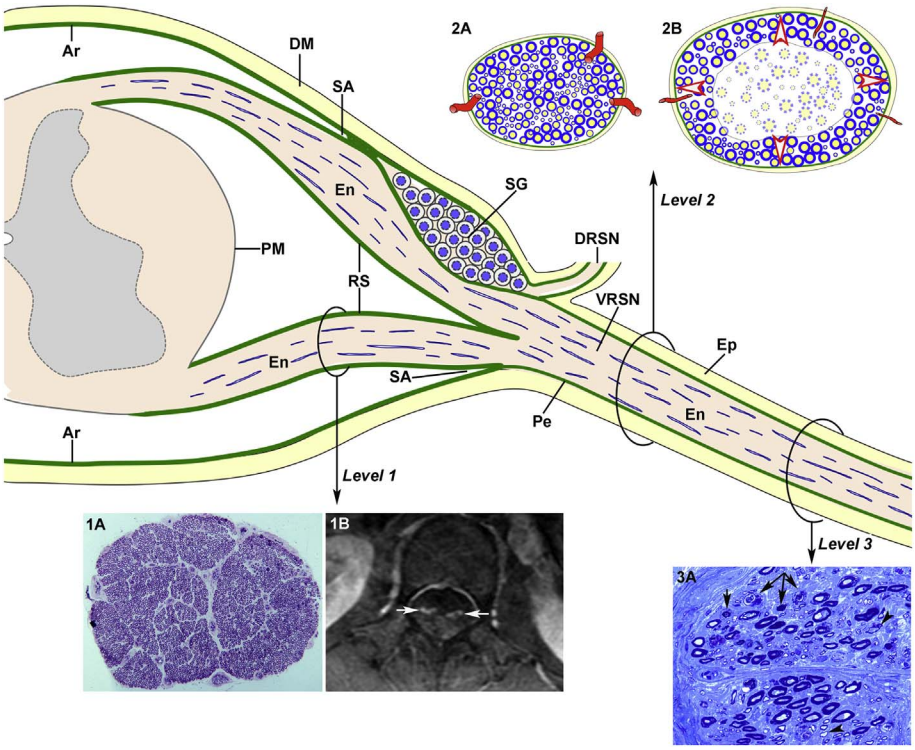

Fig. 4. Diagram of spinal root and spinal nerve microscopic anatomy. As of subaracnoid angle (SA), the epineurium (Ep) is in continuity with the dura mater (DM). The endoneurium (En) persists from the peripheral nerves through the spinal roots to their junction with the spinal cord. At the SA, the greater portion 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 unite to form the spinal nerve, which emerges through the intervertebral foramen 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 ventral L5 root shows preservation of the density myelinated fibres (1A), though inflammatory lesions, observable at higher augmentation (not shown), may account for increased surface area, and thickening and contrast enhancement of ventral roots on spinal MRI (1B, arrows). Both cartoons at *level 2* illustrate the following features: i/normal anatomy of spinal nerve, usually monofascicular with epi-perineurial covering (2A), which account for its sonographic appearance usually consisting of a hypoechoic oval structure surrounded by hyperechoic perineurial rim; and ii/endoneurial inflammatory oedema may cause a critical elevation in EFP that constricts transperineurial vessels by stretching the perineurium beyond the compliance limits (2B, arrowheads), which could result in areas of endoneurial ischemia, here centrofascicular. As illustrated here (2A vs 2B), despite low spinal nerve compliance, early inflammatory events in GBS may cause an increase of cross sectional area; moreover, perineurial inflammation accounts for loss of hyperechoic perineurial rim. At *level 3*, this cross semithin section of sciatic nerve from a fatal AIDP patient shows several myelinated fibres exhibiting wallerian-like degeneration (myelin collapse, arrows) secondary to more proximal demyelinating lesions; note the presence of remyelinated fibres (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. Diagram inspired by Fig. 3–6 from Berthold et al. [58].
Taken from Berciano et al. [57].

be accommodated, but any increase beyond these limits, as presumably occurs in early stages of severe or fulminant forms of GBS, will produce an increase in EFP, leading to distal axonal degeneration (see Fig. 4). Parallel to the distribution of endoneurial inflammatory changes, nerve ischemia could account for early partial or complete conduction block or even for universal inexcitability [51,60]. Despite accumulation of ischemic areas distally, it is conceivable that just partial preservation of one or several nerve fascicles could explain attenuated CMAP with normal motor conduction velocity, as occurred at first electrophysiological evaluation of the current patient. Quick clinical recovery, occasionally reported in other GBS cases, could be related to the fact that conduction is rapidly re-established with restoration of nerve flow in nerves suffering ischemic axonal dysfunction, but without getting Wallerian-like degeneration [56]. Obviously, our pathogenetic proposal does not exclude the contribution of primary myelin or axonal pathology to early electrophysiological abnormalities. Later

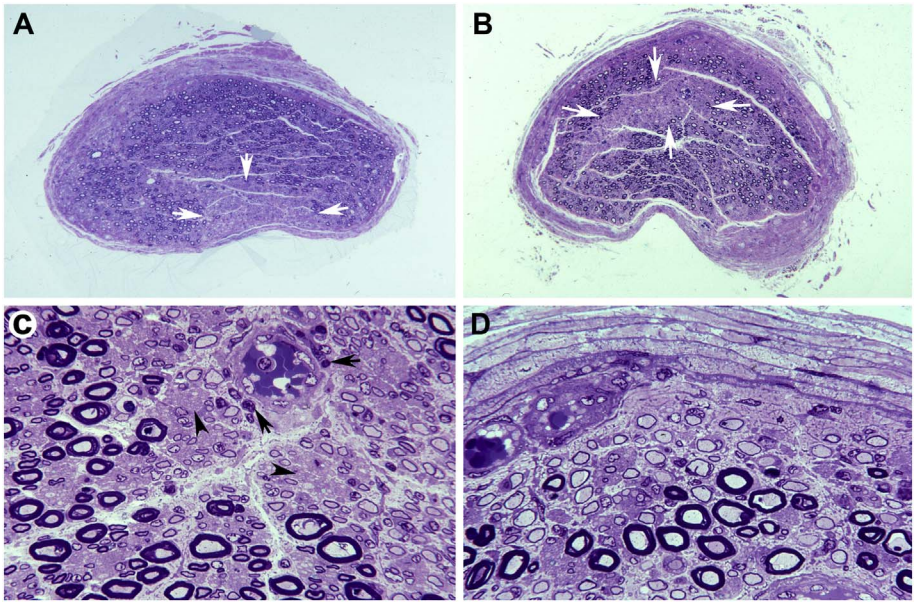

Fig. 5. Proximal nerve ischemic lesions in AIDP. (A) Semithin cross-section of the third lumbar nerve showing a wedge-shape area (arrows) with marked loss of myelinated fibres (Toluidine blue; × 62 before reduction). (B) Semithin cross-section of the lumbosacral trunk with a centrofascicular area (arrows) also exhibiting marked loss of myelinated fibres (Toluidine blue; × 62 before reduction). Both in A and B note apparent widespread diminution of myelinated fibres. (C) This high-power view of the central region of the lumbosacral trunk illustrates severe reduction of large myelinated fibres, thinly myelinated small axons, preserved unmyelinated axons (arrowheads), and widespread 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 fibres and mononuclear cells; such extensive demyelination accounts, to some degree, for the apparent widespread loss of myelinated fibres observed in A and B (Toluidine blue; × 475 before reduction). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
Taken from Berciano et al. [52].

electrophysiologic features will rely on such myelin, axonal, or both pathologies.

10. Spinal nerve involvement in early GBS: a frequent finding in nerve US

Spinal magnetic resonance imaging (MRI) studies have demonstrated in the great majority of early GBS patients contrast enhancement and thickening of cauda equina, which selectively involved anterior roots in AMAN series [57]. The main limiting factor of MRI is that it is not always applicable in severe patients, particularly those under mechanical ventilation. Nerve US has emerged as promising technique in the diagnosis of peripheral nervous system disorders [61]. One advantage of nerve US is its applicability and repeatability even in severe patients. With colleagues, I carried out a prospective study in all consecutive early GBS patients, admitted in our Hospital over one year [62]. The series comprised six GBS patients, four categorized as AIDP and the remaining two as AMSAN. Patient's ages ranged from 37 to 80 years. Five patients required mechanical ventilation, two of them having died, 9 and 28 days after onset. US protocol included scanning of representative nerves of upper and lower limbs. Since the brunt of pathology may rely on spinal nerves (*vide supra*), we also scanned ventral rami of C5-C7 nerves. Upper and lower limb nerve sonograms showed abnormal findings in just 9% of scanned peripheral nerves. Conversely, US of the fifth to seventh cervical nerves showed abnormal features in 4 (67%) of cases consisting of nerve enlargement, blurred boundaries of the corresponding ventral rami, or both (Fig. 6). Such features are in good correlation with our autopsy study showing evident endoneurial inflammatory oedema extending to the epi-perineurium (Fig. 7). Furthermore, we have reported similar US findings in an AMAN patient presenting with paraparetic GBS [63]. Our US cervical nerve findings have been replicated by others [64–66].

11. Final comments and conclusions

Corroborating pathological findings by Haymaker and Kernohan [1], our US and histological studies have demonstrated that inflammatory changes of ventral rami of spinal nerves may be a glaring feature in early GBS. Fig. 4 summarizes our pathogenic proposals for early stages of GBS. Severe inflammatory oedema of ventral rami of spinal nerves in any GBS subtype, either AIDP or AMAN, conceivably has a double consequence: i/loss of hyperechoic epineurial rim as a result of epineurial inflammation; and ii/a compressive effect with variable increase of cross sectional area, which would imply an increase of EFP that stretches the perineurium constricting the transperineurial microcirculation, compromising blood flow and producing potential ischemic injury [59]. Such ischemic injury could induce failure in proximal conduction manifested with abnormal late electrophysiological responses and relative preservation of motor and sensory conduction velocities. This mechanism helps explain the pathogenesis of GBS cases with severe paralysis and short-lived clinical course whose autopsy studies, not including spinal nerves, showed no prominent structural changes along the nerve [17], and cases with demonstrated early attenuated M responses after electrical root stimulation and preserved conventional electrophysiological studies [67]. Concerning early AMAN/AMSAN, we have proposed that there may be a dual mechanism of muscle weakness: distal motor conduction block induced by antiganglioside antibodies, and proximal conduction block induced by inflammatory oedema [57]. Accepting the pathogenic role of endoneurial oedema in the first few days of the clinical course, there is a pressing need for new therapeutic strategies to stop its rapid impact on the axons, which in EAN appears at the height of the inflammatory process at 7 days immunogen postinoculation [59,68].

Other outstanding Haymaker and Kernohan's contributions were to clarify the complex nosology of GBS bringing under the same rubric Landry's paralysis, AFP and GBS, and critically analyzing the GBS exclusion criteria by then prevailing.

12. Postcript: Haymaker's and Kernohan's obituaries

As renowned authorities in the field of neurology and neuropathology, Webb Edward Haymaker (1902–1984) and James W.

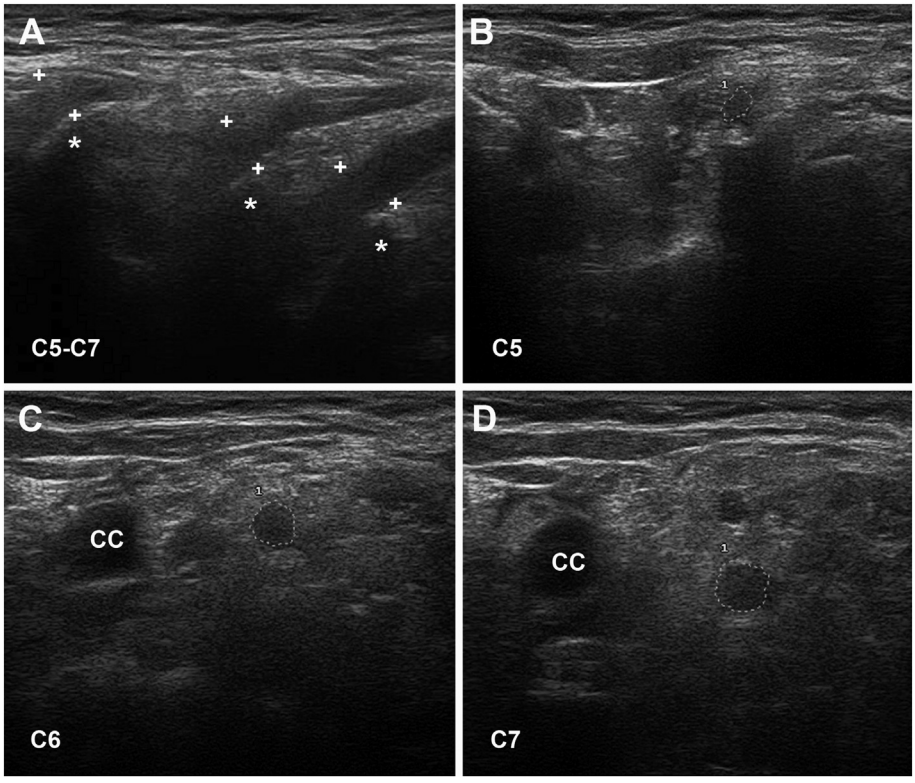

Fig. 6. Cervical nerve US in a severe AIDP patient. US study in this 80-year-old patient was done on day 5 after onset. For pathological data of ventral rami of C6 nerve see Fig. 1 in Gallardo et al. [62]. (A) Sagittal sonogram showing blurred boundaries of the 3 scanned cervical nerves (callipers). Asterisks indicate transverse vertebral processes. (B–D) Short-axis sonograms showing the cross sectional area of each cervical nerve (dotted green tracings; for values see Gallardo et al. [62]); note that perineurial hyperechoic rims are not identified and that the edge between the nerve and the surrounding fat is not clear. CC indicates common carotid artery.
Taken from Gallardo et al. [62].

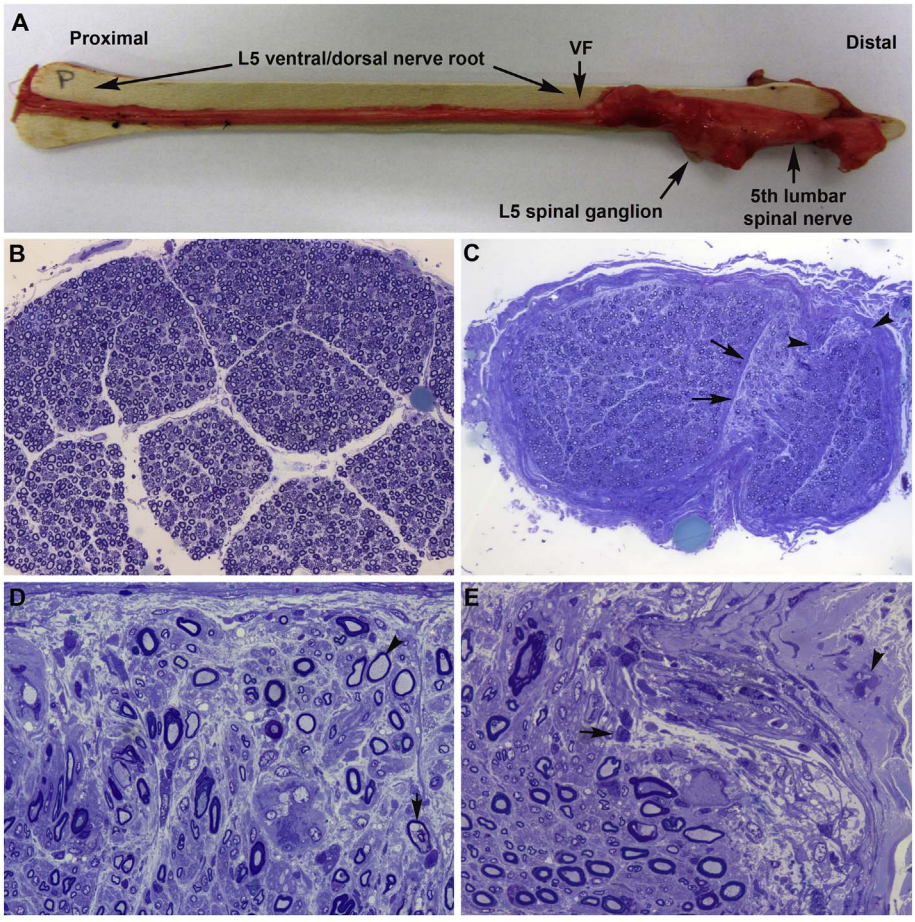

Fig. 7. L5 root and fifth lumbar nerve in a severe AIDP patient. This is the patient whose nerve US is illustrated in Fig. 6; she died 9 days after onset. (A) After being dissected down, macroscopic appearance of the right L5 spinal root, L5 spinal ganglion and fifth lumbar spinal nerve. Whereas the preforaminal root shows normal morphology, as of the vertebral foramen (VF) note visible nerve enlargement (for comparison, see Fig. 1B, C). (B) Semithin cross-section of L5 ventral root, taken 1 cm above its entrance to the VF, showing that the density of myelinated fibres 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 trough intervertebral foramen, showing widespread endoneural oedema, which is more conspicuous in some subperineurial areas (arrows and arrowheads); such oedema results in a spacing out phenomenon giving an observer the false impression of reduced density of myelinated fibres (Toluidine blue; original magnification ×65 before reduction). (D) High-power view of the subperineurial area arrowed in C. Note the presence of inflammatory oedema with numerous mononuclear cells, fibres with inappropriately thin myelin sheaths (arrowhead), and fibres exhibiting myelin vacuolation (arrow) (Toluidine blue; original magnification ×630 before reduction). (E) High-power view of the epi-perineurial and subperineurial area indicated with arrowheads in C. Conspicuous oedema is accompanied by the presence of endoneurial (arrow) and epi-perineurial (arrowhead) mononuclear cells (Toluidine blue; original magnification ×630 before reduction).
Partly taken from Gallardo et al. [62].

Kernohan (1896–1981) were recognized with laudatory obituaries [69–71]. Neither Sayre [69,70] nor Earle [71] mentioned the immense contribution of the authors to GBS. It is a shame because Haymaker and Kernohan's findings, as proven here, play an irreplaceable role to understanding the physiopathology of early GBS.

Conflict of interest

The author declares that I have no conflict of interest.

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References

[1] W.E. Haymaker, J.W. Kernohan, The Landry-Guillain-Barré syndrome; a clinicopathologic report of 50 fatal cases and a critique of the literature, Medicine (Baltimore) 28 (1949) 59–141.
[2] R.A. Hughes, D.R. Cornblath, Guillain-Barré syndrome, Lancet 366 (2005) 1653–1666.
[3] P.A. van Doorn, L. Ruts, B.C. Jacobs, Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome, Lancet Neurol. 7 (2008) 939–950.
[4] N. Yuki, H.P. Hartung, Guillain-Barré syndrome, N. Engl. J. Med. 366 (2012) 2294–2304.
[5] S. Kuwabara, N. Yuki, Axonal Guillain-Barré syndrome: concepts and controversies, Lancet Neurol. 12 (2013) 1180–1188.
[6] B.R. Wakerley, A. Uncini, N. Yuki, GBS Classification Group, Guillain-Barré and Miller Fisher syndromes-new diagnostic classification, Nat. Rev. Neurol. 10 (2014) 537–544.
[7] J.W. Griffin, C.Y. Li, T.W. Ho, M. Tian, C.Y. Gao, P. Xue, et al., Pathology of the motor-sensory axonal Guillain-Barré syndrome, Ann. Neurol. 39 (1996) 17–28.
[8] A.K. Asbury, B.G. Arnason, R.D. Adams, The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis, Medicine (Baltimore) 48 (1969) 173–215.
[9] M. Honavar, J.K. Tharakan, R.A. Hughes, S. Leibowitz, J.B. Winer, A clinicopathological study of the Guillain-Barré syndrome. Nine cases and literature review, Brain 114 (1991) 1245–1269.
[10] J.W. Albers, P.D. Donofrio, T.K. McGonagle, Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy, Muscle Nerve 8 (1981) 528–553.
[11] T.E. Feasby, J.J. Gilbert, W.F. Brown, C.F. Bolton, A.F. Hahn, W.F. Koopman, et al., An acute axonal form of Guillain-Barré polyneuropathy, Brain 109 (1986) 1115–1126.
[12] T. Kanda, H. Hayashi, H. Tanabe, T. Tsubaki, M. Oda, A fulminant case of Guillain-Barré syndrome: topographic and fibre size related analysis of demyelinating changes, J. Neurol. Neurosurg. Psychiatry 52 (1989) 857–864.
[13] W.J. Trigss, D. Cros, S.C. Gominak, G. Zuniga, A. Beric, B.T. Shahani, et al., Motor nerve inexcitability in Guillain-Barré syndrome. The spectrum of distal conduction block and axonal degeneration, Brain 115 (1992) 1291–1302.
[14] T. Yokota, T. Kanda, F. Hirashima, K. Hirose, H. Tanabe, Is acute axonal form of Guillain-Barré syndrome a primary axonopathy? Muscle Nerve 15 (1992) 1211–1213.
[15] G.M. McKhann, D.R. Cornblath, T. Ho, C.Y. Li, A.Y. Bai, H.S. Wu, et al., Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China, Lancet 338 (8767) (1991) 593–597.
[16] G.M. McKhann, D.R. Cornblath, J.W. Griffin, T.W. Ho, C.Y. Li, Z. Jiang, et al., Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China, Ann. Neurol. 33 (1993) 333–342.
[17] J.W. Griffin, C.Y. Li, T.W. Ho, P. Xue, C. Macko, C.Y. Gao, C. Yang, et al., Guillain-Barré syndrome in northern China. The spectrum of neuropathological changes in clinically defined cases, Brain 118 (1995) 577–595.
[18] T.W. Ho, B. Mishu, C.Y. Li, C.Y. Gao, D.R. Cornblath, J.W. Griffin, et al., Guillain-Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies, Brain 118 (1995) 597–605.
[19] M.J. Sedano, J. Calleja, E. Canga, J. Berciano, Guillain-Barré syndrome in

Cantabria, Spain. An epidemiological and clinical study, Acta Neurol. Scand. 89 (1994) 287–292.
[20] A.K. Asbury, D.R. Cornblath, Assessment of current diagnostic criteria for Guillain-Barré syndrome, Ann. Neurol. 27 (Suppl) (1990) S21–4.
[21] S. Vucic, K.D. Cairns, K.R. Black, P.S.T. Chong, D. Cros, Neurophysiologic findings in early acute inflammatory demyelinating polyradiculoneuropathy, Clin. Neurophysiol. 115 (2004) 2329–2335.
[22] D. Dubey, M. Kapotic, M. Freeman, A. Sawhney, J.C. Rojas, W. Warnack, et al., Factors contributing to delay in diagnosis of Guillain-Barré syndrome and impact on clinical outcome, Muscle Nerve 53 (2016) 384–387.
[23] R.D. Hadden, D.R. Cornblath, R.A. Hughes, J. Zielasek, H.P. Hartung, K.V. Toyka, et al., Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome, Ann. Neurol. 44 (1998) 780–788.
[24] A. Hiraga, S. Kuwabara, K. Ogawara, S. Misawa, T. Kanesaka, M. Koga, et al., Patterns and serial changes in electrodiagnostic abnormalities of axonal Guillain-Barré syndrome, Neurology 64 (2005) 856–860.
[25] A. Uncini, C. Manzoli, F. Notturno, M. Capasso, Pitfalls in electrodiagnosis of Guillain-Barré syndrome subtypes, J. Neurol. Neurosurg. Psychiatry 81 (2010) 1157–1163.
[26] C. Fokke, B. van den Berg, J. Drenthen, C. Walgaard, P.A. van Doorn, B.C. Jacobs, Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria, Brain 137 (2014) 33–43.
[27] A.H. Ropper, E.F.M. Wijdicks, B.T. Truax, Guillain-Barré syndrome, FA Davis Company, Philadelphia, 1991.
[28] A.K. Asbury, H.L. Fields, Pain due to peripheral nerve damage: an hypothesis, Neurology 34 (1984) 1587–1590.
[29] A.H. Ropper, B.T. Shahani, Pain in Guillain-Barré syndrome, Arch. Neurol. 41 (1984) 511–514.
[30] A.E. de Jager, H.J. Sluiter, Clinical signs in severe Guillain-Barré syndrome: analysis of 63 patients, J. Neurol. Sci. 104 (1991) 143–150.
[31] L. Ruts, R. van Koningsveld, B.C. Jacobs, P.A. van Doorn, Determination of pain and response to methylprednisolone in Guillain-Barré syndrome, J. Neurol. 254 (2007) 1318–1322.
[32] S. Kuwabara, K. Ogawara, K. Mizobuchi, M. Koga, M. Mori, T. Hattori, et al., Isolated absence of F waves and proximal axonal dysfunction in Guillain-Barré syndrome with antiganglioside antibodies, J. Neurol. Neurosurg. Psychiatry 68 (2000) 191–195.
[33] P.H. Gordon, A.J. Wilbourn, Early electrodiagnostic findings in Guillain-Barré syndrome, Arch. Neurol. 58 (2001) 913–917.
[34] G. Guillain, J.A. Barré, A. Strohl, Sur un syndrome de radiculo-névrite avec hyperalbuminose du liquide céphalo-rachidien sans réaction cellulaire. Remarques sur les caractères cliniques et graphiques des réflexes tendineux, Bull Soc. Méd. Hôp. Paris 40 (1916) 1462–1470.
[35] S. Draganescu, J. Claudian, Sur un cas de radiculo-névrite curable (syndrome de Guillain-Barré) apparue au cours d'une osteomielite du bras, Rev. Neurol. 2 (1927) 517–519.
[36] D.A. Rottenberg, F.H. Hochberg, A Note on Acute Ascending Paralysis (Landry O), Hafner Press, New York, Neurological Classics in Modern Translation, 1977, pp. 298–308.
[37] R.A.C. Hughes, D.R. Cornblath, H.J. Willison, Guillain-Barré syndrome in the 100 years since its description by Guillain, Barré and Strohl, Brain 139 (2016) 3041–3047.
[38] W. Osler, The Principles and Practice of Medicine, D. Applenton and Company, New York, 1892, pp. 776–778.
[39] G. Holmes, Acute febrile polyneuritis, Br. Med. J. 2 (1917) 37–39.
[40] G. Guillain, Radiculoneuritis with acellular hyper-albuminosis of the cerebrospinal fluid, Arch. Neurol. Psychiatr. 36 (1936) 975–989.
[41] W.C. Wiederholt, D.W. Mulder, E.H. Lambert, The Landry-Guillain-Barré-Strohl syndrome or polyradiculoneuropathy: historical review, report on 97 patients, and present concepts, Mayo Clin. Proc. 39 (1964) 427–451.
[42] J. Cambier, P. Brunet, Le syndrome de Guillain et Barré, Baillière et C[ie], Éditeurs, Paris, 1970.
[43] S.P. Gilpin, F.P. Moersch, J.W. Kernohan, Polyneuritis. A clinical and pathological study of a special group of cases frequently referred as instances of neuronitis, Arch. Neurol. Psychiatr. 38 (1936) 937–963.
[44] H. Matsuyama, W. Haymaker, Distribution of lesions in the Landry-Guillain-Barré syndrome, with emphasis on involvement of the sympathetic system, Acta Neuropathol. 8 (1967) 230–241.
[45] J.W. Prineas, Pathology of the Guillain-Barré syndrome, Ann. Neurol. 9 (Suppl) (1981) 6–19.
[46] C. Brechenmacher, C. Vital, C. Deminiere, L. Laurentjoye, Y. Castaing, G. Gbikpi-Benissan, et al., Guillain-Barré syndrome: an ultrastructural study of peripheral nerve in 65 patients, Clin. Neuropathol. 6 (1987) 19–24.
[47] B.H. Waksman, R.D. Adams, Allergic neuritis: an experimental disease of rabbits induced by the injection of peripheral nervous tissue and adjuvants, J. Exp. Med. 102 (1955) 213–236.
[48] W. Krücke, Die primär-entzündliche Polyneuritis unbekannter Ursache, in: O. Lubarsch, et al. (Ed.), Handbuch der speziellen pathologischen Anatomie und Histologie, Vol XIII/5, Erkrankungen des peripheren und des vegetativen Nerven, Springer-Verlag, Berlin, 1955, pp. 164–182.
[49] A.K. Asbury, Foreword, in: P.J. Dyck, et al. (Ed.), Companion to Peripheral Neuropathy, Illustrated Cases and New Developments, Saunders Elsevier, Philadelphia., 2010, pp. xix–xxi.
[50] S. Izumo, C. Linington, H. Wekerle, R. Meyermann, Morphologic study on experimental allergic neuritis mediated by T cell line specific for bovine P2 protein in Lewis rats, Lab. Investig. 53 (1985) 209–218.
[51] J. Berciano, J. Figols, A. García, E. Calle, I. Illa, M. Lafarga, et al., Fulminant Guillain-Barré syndrome with universal inexcitability of peripheral nerves: a clinicopathological study, Muscle Nerve 20 (1997) 846–857.
[52] J. Berciano, A. García, J. Figols, R. Muñoz, M.T. Berciano, M. Lafarga, Perineurium contributes to axonal damage in acute inflammatory demyelinating polyneuropathy, Neurology 55 (2000) 552–559.
[53] J. Berciano, A. García, N.T. Villagrá, F. González, C. Ramón, I. Illa, et al., Severe Guillain-Barré syndrome: sorting out the pathological hallmark in an electrophysiological axonal case, J. Peripher. Nerv. Syst. 14 (2009) 54–63.
[54] A.F. Hahn, T.E. Feasby, D. Wilkie Lougren, P_2-peptide induced experimental allergic neuritis: a model to study axonal degeneration, Acta Neuropathol. 82 (1991) 60–65.
[55] A.F. Hahn, T.E. Feasby, A. Steele, D.S. Lovgren, J. Berry, Demyelination and axonal degeneration in Lewis rat experimental allergic neuritis depend on the myelin dosage, Lab. Investig. 59 (1988) 115–125.
[56] P.G. McManis, P.A. Low, T.D. Lagerlund, Nerve blood flow and microenviroment, in: P.J. Dyck, et al. (Ed.), Peripheral Neuropathy, WB Saunders, Philadelphia, 1993, pp. 453–473.
[57] J. Berciano, M.J. Sedano, A.L. Pelayo-Negro, A. García, P. Orizaola, E. Gallardo, et al., Proximal nerve lesions in early Guillain-Barré syndrome: implications for pathogenesis and disease classification, J. Neurol. 264 (2017) 221–236.
[58] C.H. Berthold, J.P. Fraher, R.H.M. King, M. Rydmark, Microscopical anatomy of the peripheral nervous system, in: P.J. Dyck, P.K. Thomas (Eds.), Peripheral Neuropathy, WB Saunders, Philadelphia, 2005, pp. 35–91.
[59] H.C. Powell, R.R. Myers, A.P. Mizisin, T. Olee, S.W. Brotoff, Response of the axon and barrier endothelium to experimental allergic neuritis induced by autoreactive T cell lines, Acta Neuropathol. 82 (1991) 364–377.
[60] G.N. Fuller, J.M. Jacobs, P.D. Lewis, R.J. Lane, Pseudoaxonal Guillain-Barré syndrome: severe demyelination mimicking axonopathy. A case with pupillary involvement, J. Neurol. Neurosurg. Psychiatry 55 (1992) 1079–1083.
[61] E. Gallardo, Y. Noto, N.G. Simon, Ultrasound in the diagnosis of peripheral neuropathy: structure meets function in the neuromuscular clinic, J. Neurol. Neurosurg. Psychiatry 86 (2015) 1066–1074.
[62] E. Gallardo, M.J. Sedano, P. Orizaola, P. Sánchez-Juan, A. González-Suárez, A. García, et al., Spinal nerve involvement in early Guillain-Barré syndrome: a clinico-electrophysiological, ultrasonographic and pathological study, Clin. Neurophysiol. 126 (2015) 810–819.
[63] J. Berciano, E. Gallardo, P. Orizaola, E. Marco de Lucas, A. García, A.L. Pelayo-Negro, et al., Early axonal Guillain-Barré syndrome with normal peripheral conduction: imaging evidence for changes in proximal nerve segments, J. Neurol. Neurosurg. Psychiatry 87 (2016) 563–565.
[64] A. Grimm, B.F. Décard, H. Axer, Ultrasonography of the peripheral nervous system in the early stage of Guillain-Barré syndrome, J. Peripher. Nerv. Syst. 19 (2014) 234–241.
[65] A. Grimm, B.F. Décard, A. Schramm, A.K. Pröbstel, M. Rasenack, H. Axer, et al., Ultrasound and electrophysiologic findings in patients with Guillain-Barré syndrome at disease onset and over a period of six months, Clin. Neurophysiol. 127 (2016) 1657–1663.
[66] S.N. Razali, T. Arumugam, N. Yuki, F.I. Rozalli, K.J. Goh, N. Shahrizaila, Serial peripheral nerve ultrasound in Guillain-Barré syndrome, Clin. Neurophysiol. 127 (2016) 1652–1656.
[67] T. Kurt Incesu, Y. Secil, F. Tokucoglu, N. Gurgor, T. Özdemirkiran, G. Akhan, et al., Diagnostic value of lumbar root stimulation at the early stage of Guillain-Barré syndrome, Clin. Neurophysiol. 124 (2013) 197–203.
[68] H.C. Powell, R.R. Myers, The axon in Guillain-Barré syndrome: immune target or innocent bystander? Ann. Neurol. 39 (1996) 4–5.
[69] G.P. Sayre, In memoriam. James W. Kernohan (1896–1981), J. Neuropathol. Exp. Neurol. 41 (1982) 337–339.
[70] G.P. Sayre, In memoriam. James W. Kernohan (1896–1981), Am. J. Clin. Pathol. 85 (1983) 753–754.
[71] K.M. Earle, In memoriam: Webb Edward Haymaker, M.D. (1902–1984), Acta Neuropathol. 66 (1985) 1–2.