Volume 20 Issue 62
Originally issued as A3



Global Journal of Medical Research: A
Neurology and Nervous System
Volume 20 Issue 3 Version 1.0 Year 2020
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Axonal Degeneration in Guillain-Barré Syndrome: A Reappraisal

By José Berciano
University of Cantabria

Abstract- The aim of this review was to analyse the pathophysiology of axonal degeneration in Guillain–Barré syndrome (GBS) with emphasis on early stages (≤ 10 days after onset). An overview of experimental autoimmune neuritis (EAN) models is provided. Originally GBS and acute inflammatory demyelinating polyneuropathy were equated, presence of axonal degeneration being attributed to a "bystander" effect. Afterwards, primary axonal GBS forms were reported, designated as acute motor axonal neuropathy/acute motor–sensory axonal neuropathy. Revision of the first pathological description of axonal GBS indicates the coexistence of active axonal degeneration and demyelination in spinal roots, and pure Wallerian-like degeneration in peripheral nerve trunks. Nerve conduction studies are essential for syndrome subtyping, though their sensitivity is scanty in early GBS. Serum markers of axonal degeneration include increased levels of neurofilament light chain and presence of anti-ganglioside reactivity.

Keywords: AIDP · AMAN · AMSAN · Axonal degeneration · Complement · Demyelination · Eculizumab · Electrophysiology · Endoneurial fluid pressure · Experimental autoimmune neuritis · Ganglioside · Guillain–Barré syndrome · Inflammatory oedema · Methylprednisolone · Pain · Spinal nerve · Ultrasonography.

GJMR-A Classification: NLMC Code: WL 140



Strictly as per the compliance and regulations of:



© 2020. José Berciano. This is a research/review paper, distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License http://creativecommons.org/licenses/by-nc/3.0/), permitting all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Axonal Degeneration in Guillain–Barré Syndrome: A Reappraisal

Ref: Journal of Neurology (DOI: 10.1007/s00415-020-10034-y)

José Berciano

Abstract- The aim of this review was to analyse the pathophysiology of axonal degeneration in Guillain–Barré syndrome (GBS) with emphasis on early stages (≦ 10 days after onset). An overview of experimental autoimmune neuritis (EAN) models is provided. Originally GBS and acute inflammatory demyelinating polyneuropathy were equated, presence of axonal degeneration being attributed to a "bystander" effect. Afterwards, primary axonal GBS forms were reported, designated as acute motor axonal neuropathy/acute motor–sensory axonal neuropathy. Revision of the first pathological description of axonal GBS indicates the coexistence of active axonal degeneration and demyelination in spinal roots, and pure Wallerian-like degeneration in peripheral nerve trunks. Nerve conduction studies are essential for syndrome subtyping, though their sensitivity is scanty in early GBS. Serum markers of axonal degeneration include increased levels of neurofilament light chain and presence of anti-ganglioside reactivity. According to nerve ultrasonographic features and autopsy studies, ventral rami of spinal nerves are a hotspot in early GBS. In P_2-induced EAN models, the initial pathogenic change is inflammatory oedema of spinal roots and sciatic nerve, which is followed by demyelination, and Wallerian-like degeneration in nerve trunks possessing epiperineurium; a critical elevation of endoneurial fluid pressure is a pre-requisite for inducing ischemic axonal degeneration. Similar lesion topography may occur in GBS. The repairing role of adaxonal Schwann cytoplasm in axonal degeneration is analysed. A novel pathophysiological mechanism for nerve trunk pain in GBS, including pure motor forms, is provided. The potential therapeutic role of intravenous boluses of methylprednisolone for early severe GBS and intractable pain is argued.

Keywords: AIDP · AMAN · AMSAN · Axonal degeneration · Complement · Demyelination · Eculizumab · Electrophysiology · Endoneurial fluid pressure · Experimental autoimmune neuritis · Ganglioside · Guillain–Barré syndrome · Inflammatory oedema · Methylprednisolone · Pain · Spinal nerve · Ultrasonography.

Author: Professor Emeritus of Neurology, Service of Neurology, University Hospital "Marqués de Valdecilla (IDIVAL)", "Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED)", University of Cantabria, Santander, Spain. e-mail: joseberciano51@hotmail.com

I. Introduction

Guillain–Barré syndrome (GBS) is an acute-onset, postinfectious and immune-mediated disorder of the peripheral nervous system, which is currently divided into several subtypes based on electrodiagnostic, pathological and immunological criteria [1, 2]. GBS includes at least four disease patterns: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor–sensory axonal neuropathy (AMSAN) and Miller Fisher syndrome (MFS) [3]. Patients with AMAN or AMSAN frequently have serum antibodies against GM1 or GD1a, whereas reactivity against GQ1b occurs 80–95% of patients with MFS [4–6]. Conversely, in ADIP, no consistent anti-ganglioside reactivity has been found. In Europe and North America, GBS is usually caused by AIDP, whereas in Asia (China, Japan and Bangladesh), a considerable number of GBS patients have AMAN [4, 7]. In a detailed histological study of ventral spinal roots in 15 Japanese patients with GBS, 5 (33%) had predominantly axonal pathology [8]. Worthy of note is that two recent European GBS surveys, conducted in Italy and Spain, have demonstrated a substantial and unexpected proportion of axonal GBS cases, 35% and 28.5%, respectively [9, 10].

According to GBS autopsy data, axonal degeneration in GBS may be primary or secondary to inflammatory demyelination in proximal nerve trunks [11]. Delimitation between primary and secondary axonopathy is not an easy task, quite often requiring serial nerve conduction studies (NCS) [12], and in fatal cases, adequate nerve sampling with use of immunocytochemistry, fibre teasing and plastic sections [13, 14]. Imaging techniques (magnetic resonance imaging [MRI] and ultrasonography [US]) have provided valuable guidance to delimitate the topography of nerve changes [11]. Certain known biological markers, presence of anti-ganglioside reactivity and elevated serum neurofilament light chain (sNfL) concentration may point to underlying axonal pathology in GBS [4, 6, 15]. Experimental autoimmune neuritis (EAN), a widely accepted model of GBS, has provided some important information regarding the pathogenesis of any GBS subtype, and particularly the mechanisms of axonal degeneration [16].

© 2020 Global Journals

Bearing in mind all of the above-mentioned considerations, the aim of this review was to critically analyse the pathophysiology of axonal degeneration in GBS with emphasis on initial stages of the disease, conventionally divided into two groups: early GBS (≤ 10 days after onset) and very early GBS (VEGBS; ≤ 4 days after onset). For a better pathophysiological understanding of axonal damage, an overview of EAN models will be provided.

II. Selected Electrophysiological and Imaging Considerations in GBS

In a serial electrophysiological evaluation of 70 AIDP patients, Albers and colleagues found that two of them, both with multiple serial NCS (5 and 8, respectively), showed axonal degeneration only [17]. At that time, Wallerian degeneration was a known epi-phenomenon in EAN, which may represent a "bystander" effect associated with inflammatory demyelination [18–20]. Electrophysiological criteria of GBS diagnosis have been in a state of constant flux providing an increasing accuracy for subtyping in the established disease [12, 21–23]. This is not the case of VEGBS where initial electrophysiology allows subtyping in just 20% of cases [24, 25]; so low electrodiagnostic sensitivity relies on the fact that, at early stages of the disease, its pathologic background is neither demyelination nor Wallerian-like degeneration, but inflammatory oedema causing conduction failure (see below). The pathogenic role of inaugural inflammatory nerve oedema, leading to increased endoneurial fluid pressure (EFP) as a potential cause of axonal dysfunction, has been to a large extent overlooked. Such forgetfulness makes it difficult to accurately interpret early and subsequent electrophysiological and pathological events both in GBS and EAN [11, 25].

In recent times, several advances have added accuracy for GBS diagnosis. It is well known that histopathological changes in any early GBS subtype often predominate in proximal nerve trunks [11], their detection having been improved by means of electrophysiological measurement at Erb's point [26], motor root conduction time [27], lumbar root stimulation [28] and triple stimulation technique (TST) [29]. Intriguingly in 6 AMAN patients, examined between days 1 and 6 (median, 4.5) and whose conventional NCS did not fulfil the electrophysiological criteria of GBS, TST demonstrated that all 6 patients had proximal conduction block situated between root emergences, namely ventral rami of spinal nerves and the Erb's point [29]. Therefore, these electrophysiological features correlate extremely well with pathological and US studies showing that spinal nerves are a hotspot in any early GBS subtype (see below).

Imaging techniques, including MRI and nerve US, have provided better topographic delineation of early changes in GBS [30–33]. Using post-contrast T1 sequences, MRI regularly (around 80% of scanned cases) shows cauda equina nerve root enhancement usually predominating in ventral roots [30, 32]. The MRI series by Byun and colleagues included eight GBS patients, six of them with the pure motor subtype; two enhancement patterns were noted [31]: (i) one was enhancement of both anterior and posterior spinal nerve roots, which occurred in their two patients presenting with sensorimotor neuropathy; and (ii) the other one was enhancement of the anterior spinal roots, observed in the remaining six patients presenting with pure motor GBS, which is in good correlation with the pathological background of either demyelinating or axonal pure motor syndromes [34–36].

Nerve US is a routine technique in the diagnosis of peripheral nervous system disorders [37]. In our US nerve studies, main early lesions relied on ventral rami of C5–C7 nerves, these occurring equally in patients categorized as axonal GBS or AIDP [25, 33]. Figure 1 illustrates sonograms of C5–C7 nerves (day 5 after onset) in a severe GBS patient, aged 80 years, who died on day 9 (case 1 in reference [33]). In our series, only a minority of patients showed abnormal peripheral nerve sonograms, essentially restricted to proximal median and ulnar nerves. In a previous early GBS study, there was significant enlargement in all measured nerves, except the sural nerves [38]. The obvious discrepancy calls for new US studies.

a) GBS classic pathological hallmark

Over the ensuing seven decades after its original description [39], GBS was regarded pathologically as a primary inflammatory demyelinating disease [40–44]. Autopsy studies in early GBS established that initial histological changes are characterized by endoneurial oedema, more prominent where motor and sensory roots joint to form the spinal nerve [40, 45]. It is worthy of note that Haymaker and Kernohan [45] did not identify inflammatory cells until the course was well-advanced and, therefore, then they were regarded

© 2020 Global Journals

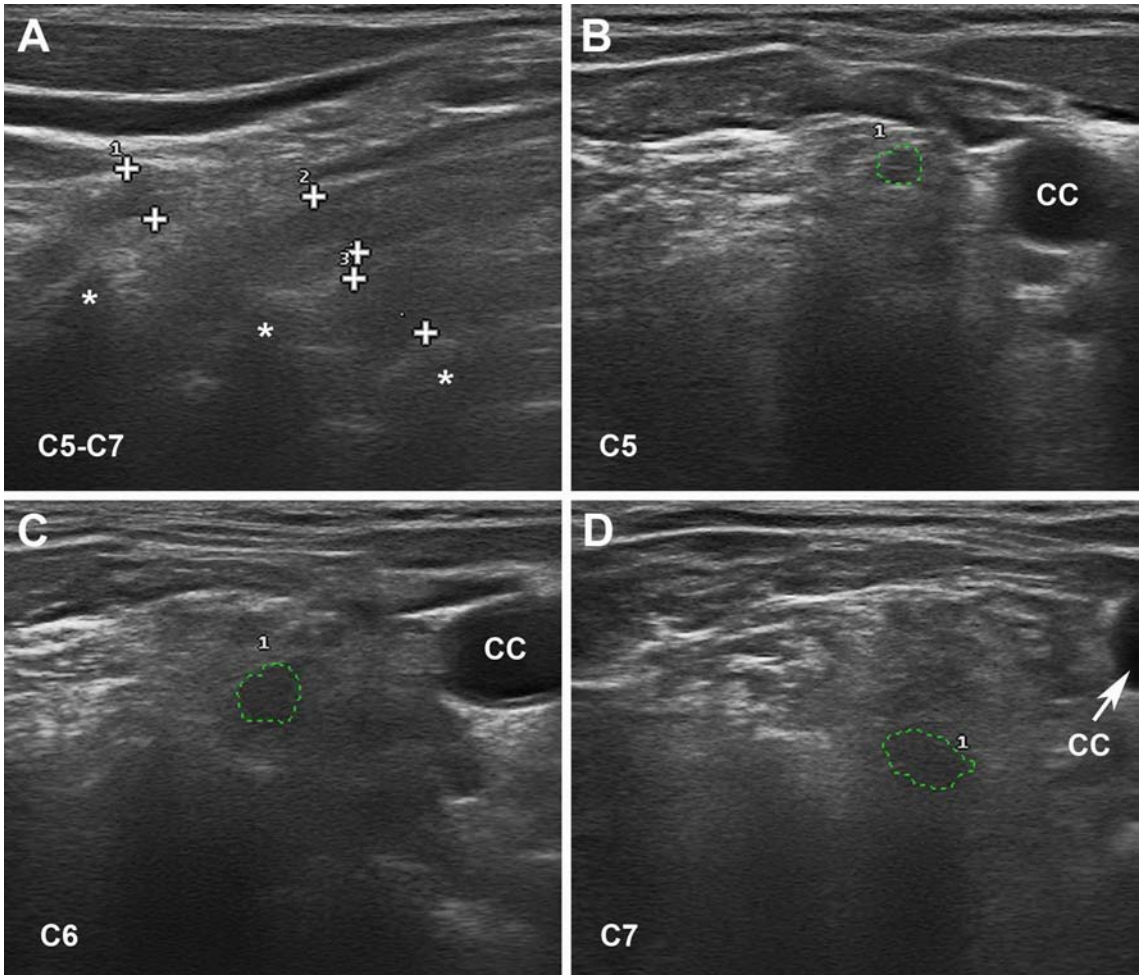


Fig. 1: US of ventral rami of C5-C7 nerves in early AIDP. Taken from reference [33]. a Sagittal sonogram showing blurred boundaries of the 3 scanned cervical nerves (callipers). Asterisks indicate transverse vertebral processes. b–d Short-axis sonograms showing the cross sectional areas of each cervical nerve(dotted green tracings), whose values are as follows: C5 = 9 mm^2 (control mean 6.22; SD 2.75), C6 = 18 mm^2 (control mean 9.63; SD 4.21) and C7 = 23 mm^2(control mean 12.29; SD 5.33). CC indicates common carotid artery

as part of a reparative process. Contrariwise, Krücke [40] recognized that endoneurial infiltrates occurred as of 24 h and were prominent as of the third day. Be that as it may, it should be noted that on traditional light microscopic study of GBS nerve biopsies, endoneurial mononuclear infiltration is visible in a minority of cases [46]; for an accurate detection of inflammatory cells, immunochemistry or thin sections are necessary [13, 14]. The outstanding lesions of ventral rami of spinal nerves are illustrated in Figs. 2 and 3.

In their seminal clinical–pathological paper comprising 19 autopsy studies, Asbury and colleagues found that the common denominator in all cases was an inflammatory demyelinative neuritis marked by focal, perivascular, lymphocytic infiltrate, affecting any level of the peripheral nervous system [41]. These authors indicated that varying amounts of Wallerian degeneration were also present, depending upon the intensity and destructiveness of lesions. They also suggested that, on the basis of the pathologic features of GBS and EAN, both disorders are a cell-mediated immunologic disorder, in which the peripheral nervous system, particularly myelin, is attacked by specifically-sensitized lymphocytes, but stating "that no oedema was observed in our series strengthens rather than weakens the homology between EAN and idiopathic polyneuritis".

b) Recognizing a distinct form of axonal GBS

Identification of an axonal form of GBS can be chronologically divided in three steps, which are analysed below.

First, a variant of GBS characterized by an acute axonal neuropathy was created by Feasby et al. [47] (for further details, see below). Not without lively debate and much controversy, the proposal of a primary axonal GBS subtype was

© 2020 Global Journals

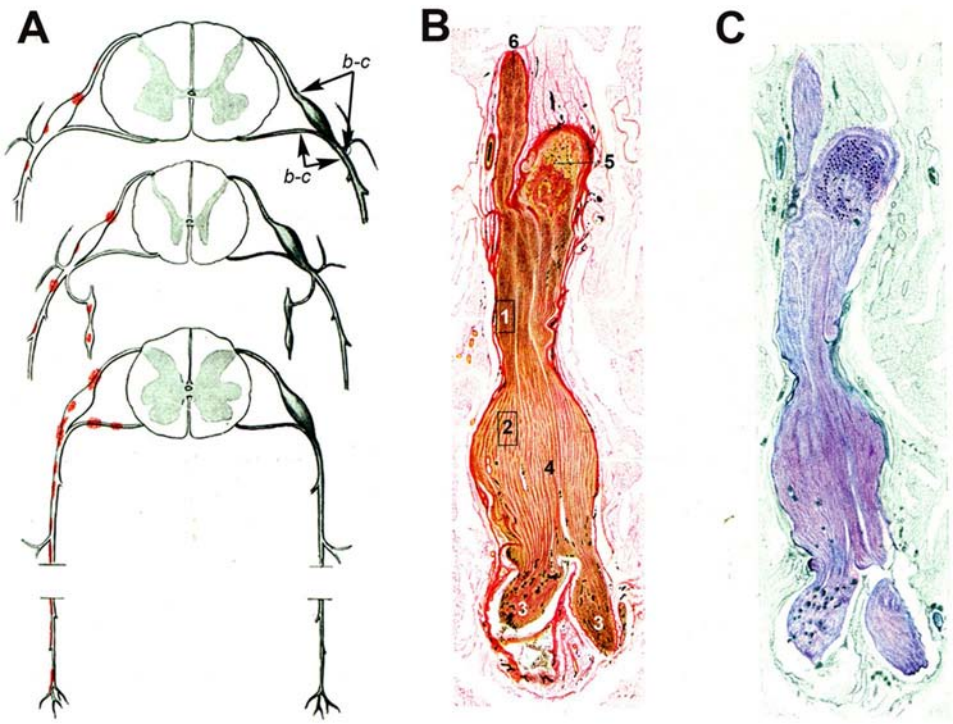


Fig. 2: Pathology of GBS. Adapted from Figs. 65 to 67 by Krücke [40] with minimal modifications. a Diagram of GBS lesions at cervical (upper row), thoracic (middle row) and sacral (lower row) levels; note that they mainly rely on proximal nerves including ventral and dorsal spinal roots, spinal root ganglia, sympathetic ganglia and ventral rami of spinal nerves (red dots). Lettering b-c indicates nerve segment illustrated in the following two images. b Longitudinal section of the nerve segment between anterior 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) splinded shaped swelling of the spinal nerve; (5) spinal root ganglion; and (6) anterior 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)

accepted in the literature [34, 48–54]. It is worthy of note that the earliest axonal GBS report was probably case 2 by Asbury and colleagues presenting a pure motor semeiology [41]. Three days after onset, autopsy revealed intense inflammatory lesions of ventral roots with prominent axonal retractions on silver staining; intriguingly, peripheral nerve trunks showed minimal changes. This patient, that had an influenza-like illness 10 days prior to admission, probably represents the first description of AMAN.

Second, Yuki and colleagues reported severe pure motor GBS in two adult patients, following *Campylobacter jejuni* enteritis, whose electrophysiology indicated that the predominant process was axonal degeneration of motor nerves; in both cases, there were high titres of IgG antibody against GM1 ganglioside considered pathogenic by selective motor axon involvement [55]. Soon after, Gregson and colleagues reported the case of a 52-year-old patient presenting with an acute-onset purely motor neuropathy in upper arms and thighs, though previously he had severe aching pains in the neck [56] (see below for the mechanism of neuropathic pain in pure motor GBS). There were high titres of polyclonal serum antibody to GM1, GD1b, asialo-GM1 and lacto-*N*-tetraose. Electrophysiology showed normal motor conduction velocities (MCV) and normal distal motor latencies (DML), reduced compound muscle action potentials (CMAP) without evidence of conduction block and denervation on muscle sampling. Wisely, the authors commented on "factors in favour of the pathophysiology being in part due to proximal conduction block with segmental demyelination at the root level would be the absence of F wave responses, the inflammatory cerebrospinal fluid changes and the relatively rapid recovery in the early stages of the disease. On the available evidence, it is not possible to distinguish the relative contribution of axonal versus demyelinating pathology further". As argued in this paper, such comment remains as relevant as ever.

Third, originally recognized under the rubric of Chinese paralytic syndrome, McKhann and colleagues reported 36 patients from rural areas of northern China, aged from 15 months to 37 years (median 7 years), who were admitted during a 2-week period in August 1990 with acute paralytic disease, whose electrophysiology showed CMAP amplitude

© 2020 Global Journals

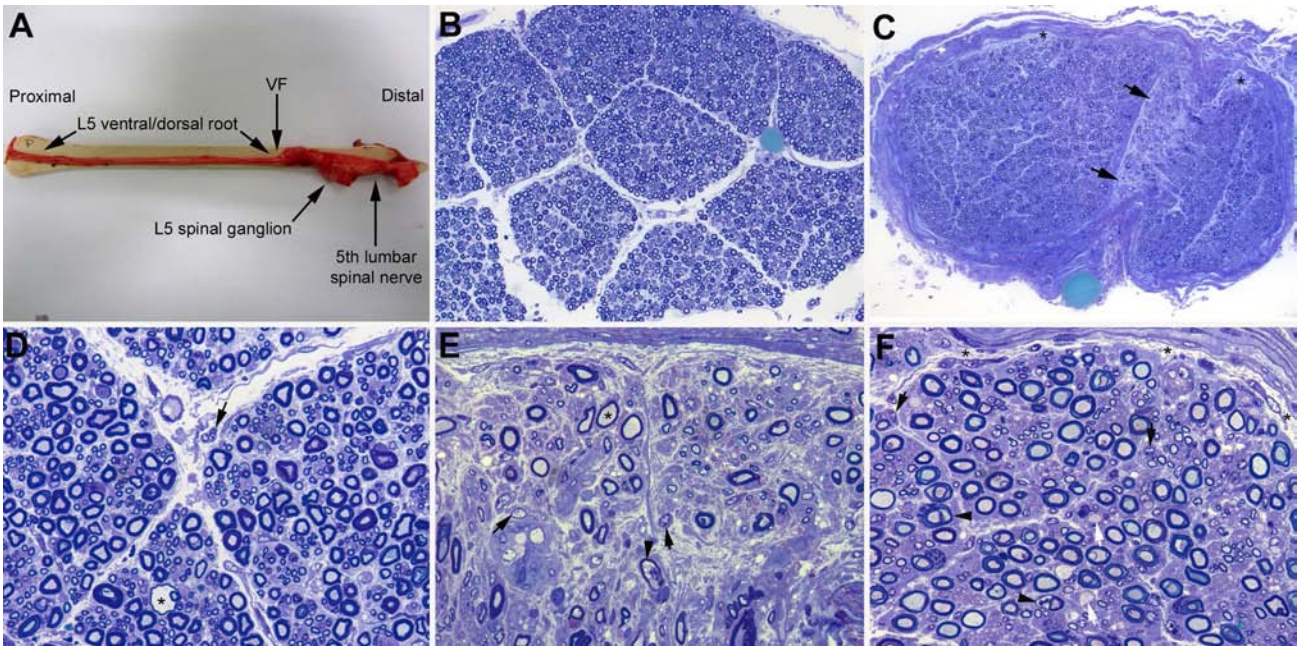


Fig. 3: Pathological features in early AIDP (adapted from case 1 by Gallardo et al. [33]). a After being dissected down, macroscopic appearance of the right L5 spinal root, L5 spinal ganglion and fifth lumbar spinal nerve. Whereas the pre-foraminal root shows normal morphology, as of the vertebral foramen (VF) note visible nerve enlargement. 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 endoneurial oedema, which is more conspicuous in septum adjacent areas (arrows) and subperineurial areas (asterisks); 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 L5 ventral root showing preservation of the density of myelinated fibres with occasional presence of mononuclear cells arrow and a fibre exhibiting myelin vacuolization (asterisk). e High-power view of the sub-septum area arrowed in C. Note the presence of florid inflammatory oedema with numerous mononuclear cells (arrows), fibres with inappropriately thin myelin sheaths (asterisk), and fibres exhibiting myelin vacuolation (arrowhead). Having in mind the spacing out phenomenon, there is reduced density of myelin fibres in comparison with L5 ventral root and sciatic nerve (previous and next images) (Toluidine blue; original magnification ×630 before reduction). f Semithin section of sciatic nerve showing some demyelinated axons (white arrows), fibres with vacuolar degeneration (arrowheads), and widespread but discreet endoneurial oedema more marked in subperineurial areas (asterisks) with presence of monuclear cells (black arrows) (Toluidine blue; original magnification × 630 before reduction)

reduction and normal MCV [57]. The disorder was considered a type of reversible distal motor nerve terminal or anterior horn lesion; intriguingly, shortly after such distal motor nerve lesion would be confirmed [58, 59]. A 4-week precedent illness occurred in 47% of patients. Worthy of note is that, despite being a pure motor syndrome, many patients had pain (see below). Two years later and under the rubric of AMAN, McKhann and colleagues reported the results of 10 autopsy studies showing non-inflammatory Wallerianlike degeneration of motor fibres in 5, demyelination in 3 and absence of lesions in 2 [35]. Afterwards, these histopathological features were reassessed in other seminal studies by the John's Hopkins Group and Chinese collaborators (reviewed in reference [60]). High IgG and IgM antibody titres to *Campylobacter jejuni* were observed. The series comprised now 12 post-mortem studies, lesions being categorized as follows: 3 AMAN, 3 AMSAN, 3 AIDP, and 3 exhibiting minimal pathology [30, 36, 59–63]. AMSAN pattern was considered similar to that originally reported in axonal GBS [47]. In AMAN, the major pathological finding was extensive Wallerian-like degeneration of the ventral roots and, usually a lesser degree, of motor fibres within the peripheral nerves; the proportion of degenerating radicular fibres increased distally toward the ventral root exit from the dura where 80% of fibres were degenerating [35], namely maximal pathology occurred in spinal nerves. A prominent feature of axonal patterns was the early presence of macrophages within the periaxonal space, surrounding or displacing the axon, and surrounded by an intact myelin sheath with the presence of IgG and the complement C3d and C5b-9 (membrane attack complex [MAC]) [64]. The authors suggested that AMAN is an antibody- and complement-mediated disorder in which relevant epitopes are present on the nodal and internodal axolemma. This notion was the starting point to create the new nosological category of nodo-paronodopathy encompassing various acute and chronic neuropathies

© 2020 Global Journals

associated with anti-ganglioside antibodies that share a common pathogenic mechanism of dysfunction/ disruption at the node of Ranvier [65].

c) Original description of axonal GBS: only axonal pathology?

The series by Feasby and colleagues consisted of five patients, who showed severe clinical picture and electrically inexcitable motor nerves [47]. One patient (case 1) died, and 3 of the 4 survivors exhibited poor recovery. Pathological study was done in case 1. Nerve inexcitability, recorded on day 3 after onset in case 1 and on day 2 in case 4, was attributed to axonal degeneration [47, 53, 54]. However, such interpretation is questionable given that in Wallerian degeneration motor-evoked responses amplitudes are reduced by 50% at 3 to 5 days after injury, the responses being absent by day 9 [66]. Retrospectively, three alternative pathophysiological explanations could be considered here:

- First, accepting that we are confronted with a primary axonal process, so very early nerve inexcitablity could be due to distal motor conduction block induced by antiganglioside antibodies [4]; at that time, however, the pathogenic role of such antibodies in axonal GBS was unknown.
- Second, one could argue distal demyelinating conduction block [58, 67], but again this interpretation is questionable since autopsy studies in VEGBS have shown that incipient demyelination, preceded by nerve inflammatory oedema, usually appears as of day 5, florid demyelination settling down later on [11, 40, 45].
- The third pathophysiological mechanism is ischemic neuropathy to be addressed later.

Feasby and colleagues carried out a detailed autopsy study in their case 1 [47]. This patient was a 64-year-old woman presenting with ascending weakness and paresthesiae over the course of several hours. Next morning, there was are flexic tetraplegia and bulbar palsy requiring mechanical ventilation. She died on day 28. Tissue sampling included central nervous system, nerve roots and peripheral nerves, whereby conventional neuropathological examination was undertaken complemented with semithin and thin sections, and fibre teasing. Pathological features are summarized as follows: "severe axonal degeneration in nerve roots and distal nerves without inflammation or demyelination." According to the authors, macrophages containing myelin debris were common, but few scattered lymphocytes were observed; there was no perivascular cuffing with inflammatory cells, and there was minimal endoneurial oedema; it is worth noting that their Fig. 3, corresponding to a transverse semithin section of the deep peroneal nerve, shows a phenomenon of spacing out of myelinated fibres probably due to endoneurial oedema, particularly prominent in subperineurial areas (on the bottom of the image). On fibre teasing, done in deep peroneal and superficial peroneal nerves but not in lumbar roots, the main finding was axonal degeneration.

With colleagues, I reported a severe case of pure motor GBS, died on day 29 after onset, whose pathological background was macrophage-associated demyelination of ventral roots with secondary axonal degeneration [34]. At that time, we compared our pathological findings with those reported by Feasby et al. [47] concluding as follows: "We have observed, however, an apparent similarity between our pathological findings on transverse sections of ventral root and those illustrated in Feasby's work (cf our Fig. 3 and their Fig. 2). Certainly without teased fiber preparation, semithin longitudinal sections, and ultrastructural study we would have overlooked the relevance of segmental demyelination and remyelination. In fact, 24% of teased fibres from L5 ventral root exhibited de-remyelination, and this percentage might have been substantially greater at the onset of symptoms if we assume that demyelination precedes axonal degeneration." These two mentioned images are reproduced in Fig. 4; note that in Feasby's material together with active axonal degeneration, there are also signs of evident demyelination including widespread vesicular dissolution of myelin that by then had already been recognized as an elementary lesion in demyelinating GBS [42–44]; afterwards, it was demonstrated that vesicular dissolution is seen before the invasion of macrophages into myelin, and is the predominant change in the subject with symptoms for 3 days [63]. Consequently, the question arises as to whether such radicular axonal degeneration is primary or secondary to inflammatory demyelination. Although there is no exact response, what we now know is that axonal GBS may result from a proximal demyelinating process with secondary axonal degeneration [33, 68–70]. Furthermore and accepting that Feasby's case 2 might be categorized retrospectively as AMSAN (see above), the presence of demyelinating lesions could be accounted for by the fact that peripheral nerve myelin contains many glycolipids and gangliosides that are important antigens for antibody responses [71]. Concerning pathology in AMSAN, Griffin and colleagues wisely indicate that "there were rare but unequivocal examples of demyelinated internodes with intact axonal and lipid nearby filled macrophages. Definite but rare patches containing scattered lymphocytes were identified in spinal roots by immunohistochemistry and plastic sections. There was oedema in the subperineurial and endoneurial spaces in regions with numerous degenerating fibres… Strictly speaking, these cases are neither non-demyelinating nor non-inflammatory, but rather predominantly axonal and minimally inflammatory [3]." In short, separation

© 2020 Global Journals

between AIDP and axonal GBS does not seem absolute, a fact already suggested by the heterogeneity of pathological background of the Chinese paralytic syndrome, encompassing AMAN/AMSAN, AIDP, or even minimal changes [36].

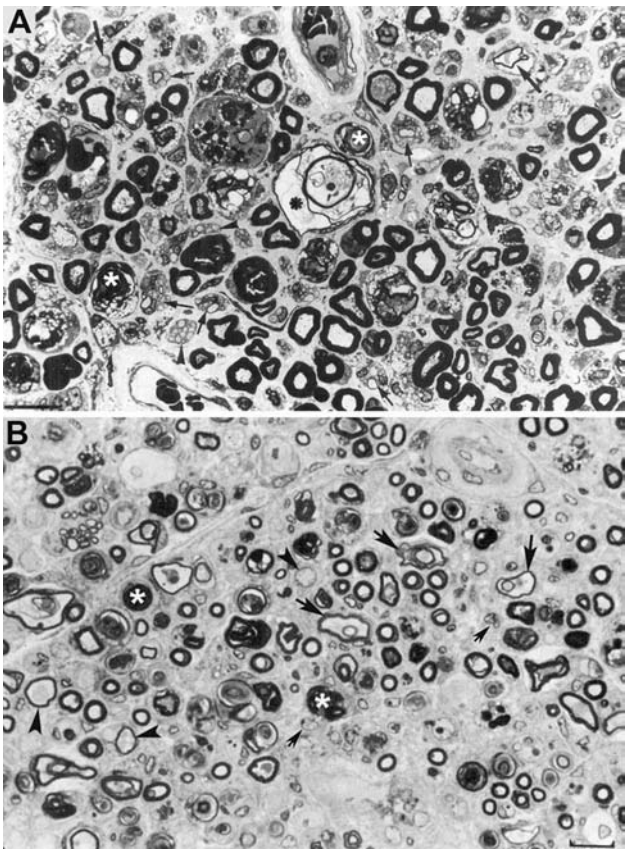


Fig. 4: Composite image to compare lesions in anterior spinal roots. Taken from Fig. 3 by Berciano et al. [34] (a) and Fig. 2 by Feasby et al. [47] (b). Both pictures correspond to transverse semithin sections of ventral lumbar roots. a Keeping up original graphic resources, note the presence of numerous endoneurial lipid-laden macrophages, sometimes encircling degenerated fibres with myelin collapse (white asterisks). There are clusters of regeneration containing either non-myelinated axons (arrowheads) or non-myelinated and thinly myelinated axons (small arrows), and also occasional demyelinated or remyelinated axons (large arrows). Black asterisk indicates a fiber exhibiting vesiculo-vacuolar dissolution of myelin (Toluidine blue; bar = 19 μm). b The original figure legend, with no graphic resources, is as follows: "Transverse section showing severe axonal degeneration". My interpretation is keeping with this criterion, as there are numerous fibers showing myelin collapse (white asterisks), which is indicative of acute axonal degeneration [13, 14]. But note also the presence of fibres with inappropriately thin myelin sheaths (arrowheads) and frequent fibres exhibiting vesiculo-vacuolar dissolution of myelin (large arrows), both features suggesting primary demyelination. In my view, there are frequent endoneurial ovoid or reniform nuclei (small arrows), which most probably correspond to macrophages (Toluidine blue; bar = 20 μm). (Reproduced with permission from Brain, Oxford University Press)

d) Axonal pathology in demyelinating models of EAN

Wallerian degeneration was already reported in the original EAN induced by the injection of peripheral nervous tissue and adjuvants [72], which were soon after correlated with a "bystander" effect (see above).

In a model of EAN passively induced in Lewis rats by intravenous injection of T line cells specific for bovine P_2 myelin protein, Izumo and colleagues reported serial animal semiology and detailed pathological changes [73]. The first signs of clinical disease, a flaccid tail and weakness of the hindlimbs started between 3.5 and 4 days postinoculation (pi), which rapidly progressed to a peak (flaccid paraplegia and forelimb paresis) between days 7 and 9. On day 4 pi, the first pathological change was marked oedema with or without cellular infiltrates in the sciatic nerve and lumbosacral nerve roots. On day 5, extensive, disseminated lesions were observed in the sciatic nerve, these being more severe and advanced proximally; they consisted of marked oedema, cellular infiltrates (granulocytes and mononuclear cells), and perivascular cuffs not only in the endoneurial space but also in the epineurium. At this time, no evidence of the characteristic changes observed in peripheral demyelination could be observed. Between days 7 and 9 pi, while inflammatory oedema declined, there appeared florid demyelination; independent of this, there were some nerve fibres showing distinct axonal

© 2020 Global Journals

degeneration. Between days 14 and 20 pi, inflammatory oedema subsided, and the lesions were composed of advanced demyelination and axonal degeneration. An overview of their tabulated morphological findings indicates that initial inflammatory oedema predominated in sciatic/femoral nerves and lumbosacral nerve roots, late demyelination is almost widespread, and marked axonal degeneration is almost restricted to sciatic/femoral nerves. Concerning the exact mechanism of axonal degeneration in EAN, the authors commented on the possible "bystander damage", though they wisely proposed the pathogenic role of ischemia, given that in their histological material marked axonal degeneration was observed just 1 to 2 days after intense endoneurial oedema.

In the same previous P_2-EAN model, Heininger and colleagues carried electrophysiological studies after injection of graded doses of freshly activated T cells, 10^6 (lower dose) and 2×10^6 (higher dose) [74]. The severity of the electrophysiological changes correlated with severity of the clinical disease and was dependent on the number of P_2-specific T cells transferred. As might have been expected in a demyelinating disorder, injection with lower T cell dose resulted in slowing of motor and sensory nerve conduction parameters over days 4 to 7 pi. Conversely, injection of higher dose induced fulminant paraplegia on day 4 pi, and complete conduction failure in peripheral nerves and roots within 24 h, which the authors attributed to severe axonal damage at the root level. Against this proposal, it can be argued that in Wallerian degeneration, motor nerve inexcitabilty does not occur till day 9 after nerve transection [66]; an alternative pathophysiological interpretation will be addressed below.

Using residue 53–78 (SP26) of bovine P_2 myelin protein, Hahn and colleagues induced EAN in Lewis rats [75]. At low peptide dose (25 or 50 μg), scattered pathological changes (demyelination, inflammation and oedema) were observed in lumbosacral roots and sciatic nerves; there was no axonal degeneration. At higher peptide dose (75 or 100 μg), lumbosacral roots showed very active inflammatory demyelination without axonal degeneration, while sciatic nerves exhibited similar signs of inflammatory oedema and almost total axonal destruction. The authors argued that axonal degeneration occurred only with high doses of antigen and in association with very active mononuclear inflammation, but they did not address the blatant discrepancy of axonal changes between spinal roots and sciatic nerves. A few years later, in a clinical–pathological study of a fulminant GBS patient with inexcitable nerves, we also reported a different framework: almost pure demyelination in spinal roots and predominantly Wallerian-lile degeneration in peripheral nerve trunks [67]. It is worthy of note that the Canadian group had reported a centrofascicular pattern of axonal degeneration in the sciatic nerves, which was rightly correlated with possible endoneurial ischemia [76].

Inflammatory oedema and increased EFP of sciatic nerve are changes initially detected in early EAN induced in Lewis rats with intradermal inoculation of an emulsion of peripheral nerve in complete Freund's adjuvant [77]. Several years later, the same American group re-examined the issue in Lewis rats by inoculation with autoreactive T cell lines sensitized to residue 57–81 of P_2 myelin protein [78]. Both oedema and inflammation in sciatic nerves paralleled the time of the EFP increase, reaching peak levels at 7 days pi and declining to near-normal values after 11 days. Intriguingly, axonal damage appeared at the height of the inflammatory process, when oedema and increased EFP were maximal, which are believed "to stretch the perineurium and constrict the transperineurial microcirculation, compromising nerve blood flow and producing the potential for ischemic nerve injury". In AIDP, this pathogenic proposal was corroborated with further description of peripheral nerve trunks (ventral rami of lumbar roots and lumbosacral trunk) showing centrofascicular or wedge-shaped regions with marked loss of large myelinated fibres, which are characteristic of nerve ischemia [69, 79] (Fig. 5).

Finally and continuing with adoptive transfer of P_2-EAN, L5 root histological study at peak disease (day 6) showed inflammation with a mean number of demyelinated axons of 79/mm^2 (0.7% of the total number), and a mean number of degenerating axons of 121/mm^2 (1.0% of the total) [80]; certainly, such low percentage of nerve fibre degeneration does not seem sufficient to explain maximal neurologic deficit (complete limb paralysis). Once again, these findings give strong support to the pathogenic role of inaugural inflammatory oedema.

e) Axonal pathology in EAN induced by anti-ganglioside antibodies

EAN models mediated by antibodies against glycolipids, either demyelinating or axonal, have recently been reviewed [16, 81]. I will focus on selected EAN studies resulting in early Wallerian-like degeneration.

Yuki and colleagues developed an AMAN model in rabbits after administering bovine brain ganglioside (BBG) or GM1 with Freund's complete adjuvant (CFA) [82]. Both experiments resulted in flaccid limb weakness of acute onset. In peripheral nerves, there was Wallerian-like degeneration, macrophage invasion and endoneurial oedema (see their Fig. 1c), with neither lymphocytic infiltration nor demyelination. IgG was deposited on the axons of the anterior roots that apparently exhibit lesser degree of axonal degeneration than that of sciatic nerves (cf. their Fig. 1c and d). The protocol used by Yuki and colleagues was severely criticized, as repeated injection CFA they used could lead to systemic inflammatory response that

© 2020 Global Journals

contributed to the success of the model [83]. A few years later, Moyano and colleagues validated the Yuki's rabbit model of axonal neuropathy induced by immunization with gangliosides [84]. Interestingly, the authors carried out five different experiments during a period of two years by different operator, using different batches of drugs, in a total of 26 rabbits. A serious objection to this paper is interpretation of their Fig. 3c, semithin section of sciatic nerve, from a rabbit immunized with BBG/Cronassial©/Keyhole limpet hemocyanine, which is described as follows: "note that fibres with axonal degeneration (arrows)", when the great majority of myelinated fibres (around 120 in this image) show normal axons sometimes surrounded by myelin with plumping appearance (just the two arrowed fibres exhibiting myelin collapse suggest active axonal degeneration). There are several endoneurial lipid-laden macrophages. I am persuaded that a diagnosis of axonal neuropathy cannot be accepted without reserve; quite to the contrary, I would suggest that the observed histological changes point to a primary demyelinating process.

Susuki and colleagues provided an AMAN model in rabbits immunized with BBG or GM1, which included the presence of macrophages in the periaxonal space, and IgG deposited on nerve root axons. Initial lesions were located

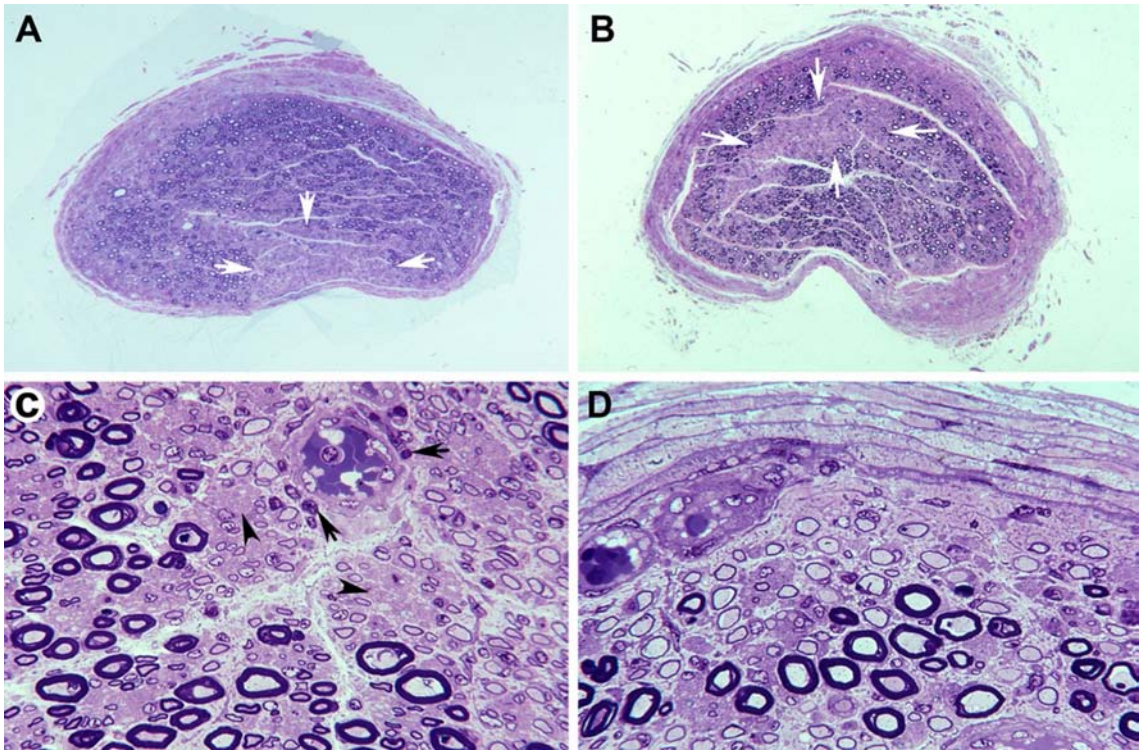


Fig. 5: Ischemic nerve lesions in AIDP. Adapted from Berciano et al. [69]. Semithin sections of the ventral ramus of the third lumbar nerve (a) and lumbosacral trunk (b) illustrating wedge-shaped and centrofascicular areas with marked loss of myelinated fibres (arrows) (Toluidine blue; original magnification × 62 before reduction). c This semithin section of the central region of the lumbosacral trunk illustrates severe reduction of large myelinated fibres, thinly myelinated small axons, preserved unmyelinated axons (arrowheads), and endoneurial mononuclear cells and lymphocytes (arrows) (Toluidine blue; original magnification 470 before reduction). d This semithin section of the subperineurial area of the lumbosacral trunk shows numerous thinly myelinated fibres and occasional mononuclear cells; such extensive de-remyelination accounts, to some degree, for the apparent widespread loss of myelinated fibres perceptible in image B (Toluidine blue; original magnification × 375 before reduction)

mainly on nerve roots, as in AMAN (see above) [85]. Electrophysiology showed that distal motor conduction was preserved, whereas F wave latency could be absent or exceptionally delayed. As wisely indicated by the authors, this electrophysiological finding may indicate demyelination, remyelination, or a wide-paranodes, consistent with the pathology of nerve root specimens. Subsequently, the authors examined the molecular organizations of nodes in this same EAN model associated with antiGM1 antibodies [86]. At the acute phase with progressing animal limb weakness, Na_v channel clusters were disrupted or disappeared at abnormally lengthened nodes concomitant with deposition of IgG and complement; paranodal axoglial structures were also disrupted. The nodal molecules disappear in lesions with complement deposition but not in association with macrophagic infiltration. During recovery, complement deposition at nodes decreased,

© 2020 Global Journals

and Na_v channels redistributed on both sides of affected nodes. In short, these findings give strong support to the notion that AMAN is a disease that specifically disrupts the nodes of Ranvier.

Using a rabbit EAN model, Yuki and colleagues verified that carbohydrate mimicry between GM1 and the *Campylobacter jejuni* lipooligosaccharide induces the production of pathogenic autoantibodies, and the development of axonal GBS [87]. Although the antecedent of *Campylobacter jejuni* infection and GBS, particularly AMAN/AMSAN, is well established, the concordance between disease in humanbeings and domestic animals, suffering from such infection, is less clear. Li and colleagues analysed the occurrence of spontaneous paralytic neuropathy induced by *Campylobacter* infection in five chicken flocks, whose farm families had recently developed GBS [88]. The only two paralyzed chickens showing florid Wallerian-like degeneration in sciatic nerve belonged to a flock whose farmer had AIDP.

The Willison's Group extended EAN studies focusing on the motor terminal as target site, using both MFS-associated anti-GQ1b antibodies, and AMAN-associated anti-GM1 and -GD1a antibodies [6, 12, 89, 90]. The authors demonstrated that the motor terminal is indeed a vulnerable site for anti-ganglioside antibody attack that resulted in complement fixation. Deposition of MAC pores would allow uncontrolled calcium ingress triggering a sequence of destructive events, including calpain activation, with subsequent paralysis. Undoubtedly, such biological events represent the basis of distal nerve conduction block or RCF reported in AMAN (see above). Nevertheless, the hypothesis that anti-GM1 or -GD1a antibodies alter the presynaptic motor nerve terminal at the neuromuscular junction has not entirely been supported by axonal-stimulating single-fibre electromyography studies. While Spaans and colleagues reported increased jitter and intermittent blocking of muscle fibre action potentials to a varying degree in all 9 examined GBS patients in the acute stage of illness [91], Kuwabara and colleagues found normal jitter in all 23 GBS patients, 13 of them categorized as AMAN [92]. Furthermore, in early axonal GBS, Brown and colleagues carried out electrophysiological recording of M responses in several motor nerves advancing the site of stimulation closer to the point motor [93]. Particularly illustrative is their Fig. 1 showing changes in the extensor digitorum brevis maximum M potentials in response to supramaximal stimulation of the deep (anterior) tibial nerve at 20, 40, 60, 80 and 100 mm proximal to the innervation zone. The greatest M amplitude is that obtained with most distal stimulation. So, this electrophysiological study points to failure, not in terminal motor segments but in pre-terminal ones.

In the context of experimental ganglioside-induced neuromuscular synaptopathy [90], ex vivo and in vivo nerve–muscle preparations exposed to anti-ganglioside antibodies have revealed that peri-synaptic Schawnn cells rapidly become phagocytic and engulf axonal debris [94]. Intriguingly, in proximal nerve trunks of patients died with AIDP harbouring secondary axonal degeneration, we have reported large myelinated fibres with apparently normal myelin sheath that surrounded a dark content often with a light core [69, 70], bringing to mind dark swollen axons [95, 96] (Fig. 6). Ultrastructural study revealed, however, that dark areas corresponded not to swollen axons but to ridges of adaxonal Schwann cells replete with degenerated organelles; axons, though sometimes attenuated, were preserved. Comparable Schwann cell/axon interactions had been reported in other neuropathies and likely represent a nonspecific mechanism by which the Schwann cell clears debris and help maintain the integrity of the axon under normal and pathologic conditions [97].

f) Topography of initial GBS lesions: pathophysiological considerations

As aforementioned, in any GBS subtype, early lesions predominate in spinal roots and spinal nerves; furthermore, in ganglioside-mediated EAN, the outstanding early finding is nerve terminal damage. As a whole, this is so because blood–nerve interface is less efficient in several important structures in the peripheral nervous system, including from the spinal cord to root-nerve junction (spinal nerve), dorsal root ganglia and neuromuscular junctions [98, 99]. Variations in permeability between such areas are presumably important for the distribution of lesions caused by various blood-borne agents of a toxic, immunologic or infectious nature [100], as is the case of GBS and EAN.

Knowledge of the microscopic anatomy of the peripheral nervous system is essential for an adequate understanding of the pathogenic relevance of early pathological events in GBS [101]. Spinal roots traverse the subarachnoid space covered by an elastic multicellular root sheath derived from the arachnoid and penetrate the dura at the subarachnoid angle. As of the subarachnoid angle, where motor and sensory roots join to form the spinal nerve, dura mater is in continuity with epineurium, whereas the arachnoid turns into perineurium. Therefore, intrathecal nerve roots are covered by an elastic root sheath, whereas spinal nerves and more distant nerve trunks till their pre-terminal segments possess epi-perineurium that is relatively inelastic. Conceivably, initial inflammatory oedema may be accommodated in intrathecal nerve roots enlarging their size but without this implying significant increase of EFP. Conversely, in nerve trunks surrounded by epi-perineurium, such oedema may cause a critical elevation of EFP that constricts transperineurial vessels by stretching the perineurium beyond the compliance limits, which lead to ischemic conduction failure, and eventually to Wallerian-like

© 2020 Global Journals

degeneration [11]. Although this phenomenon may occur in any segment of peripheral nerve trunks, pathological and US studies indicate that spinal nerves are the hotspot in any early GBS subtype, thus explaining the high prevalence of electrophysiological changes pointing to pathology in proximal nerve segments (see above and Fig. 3). In any case, inflammatory oedema is also a histological feature of intermediate and pre-terminal nerve segments, potential cause of partial conduction block, nerve inexcitability or RCF [67, 69] (see Fig. 3).

g) Neurofilament light chain concentration and GBS

Neurofilament light chain (NfL) is a neuronal cytoplasmic protein highly expressed in large calibre myelinated axons. Its levels increase in cerebrospinal fluid and serum (sNfL) proportionally to the degree of axonal damage in a variety of neurological disorders, including inflammatory, neurodegenerative, traumatic and cerebrovascular diseases [102].

Altmann and colleagues recently reported sNfL concentrations in 27 GBS patients, 17 being categorized as AIDP, 5 as primary axonal GBS, and the remaining 5 as equivocal [15]. Serum samples were obtained within 5 days after onset. The median sNfL concentration in GBS patients on admission was 85.5 pg/ml versus 9.1 pg/ml in controls. High sNfL levels correlated with poor outcome, but, intriguingly, no significant differences were observed between AIDP and primary axonal GBS. Wisely, the authors commented on that "though sample size is too small to draw any conclusions, we believe that sNfLs are elevated even in primarily demyelinating disease which might be attributed to axonal damage below the threshold detectable by nerve electrophysiology. Neurophysiology may not represent what is really happening at the pathology level". Although agreeing with this assertion, I wish to propose that so very early sNfL elevations might be associated with inflammatory oedema with subsequent ischemic endoneurial events mainly occurring in proximal nerve trunks, which may cause conduction failure and eventually Wallerian-like degeneration. Detection of such pathologic hallmark calls for further ultrasonographic or special electrophysiological studies (see above). Furthermore, in very early AMAN, there may be a dual mechanism of muscle weakness and elevation of sNfL: ganglioside-mediated distal motor conduction block implying axonal dysfunction and potential Wallerian-like degeneration; and (ii) conduction block at ventral rami of spinal nerves caused by above-mentioned endoneurial ischemia [69].

© 2020 Global Journals

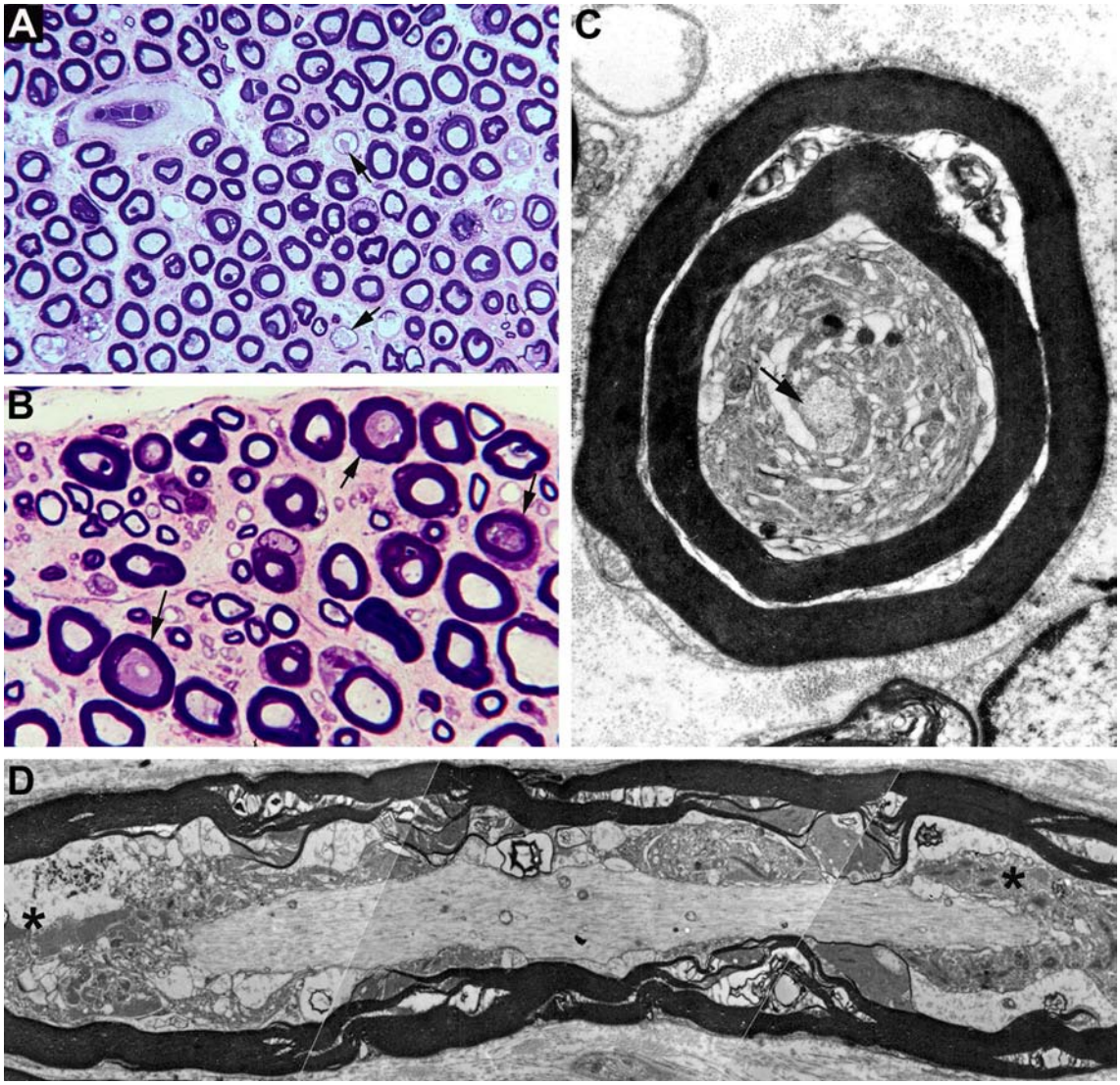


Fig. 6: Axonal repair in AIDP. Adapted from Berciano et al. [69]. a This semithin section of L5 ventral root shows that the density of myelinated fibres is preserved, although there are thinly myelinated fibres and fibres with vacuolated myelin (arrows) (Toluidine blue; original magnification ×375 before reduction). b This semithin section of L5 dorsal root illustrates three dark fibres (arrows) (Toluidine blue; original magnification ×750 before reduction). c This electron micrograph shows the morphology of a dark fibre characterized by an attenuated axon (arrow) surrounded by complex adaxonal Schwann cell processes and normal myelin (×5900 before reduction). d This longitudinal electron micrograph section shows extensive accumulation of vacuoles, degenerated organelles, and amorphous material in the adaxonal Schwann cell cytoplasm. Such accumulation is more pronounced in the paranodal regions (asterisks), though involving the internodal regions. Note that the axon is variably displaced but otherwise preserved (×2200 before reduction)

III. Therapeutic Considerations

GBS treatment is based upon the use of either intravenous high doses of human immunoglobulin (IVIG) or plasmapheresis [1, 2]. The rationale of both treatments is their capacity to remove pathogenic antibodies.

New complement inhibitors successfully prevented damage by anti-GQ1b antibodies at mouse neuromuscular junctions [103, 104]. Eculizumab, a humanized monoclonal antibody against terminal complement protein C5 that inhibits terminal complement activation, is an effective therapy for paroxysmal nocturnal hemoglobinuria [105]. All these data were the rationale for trials with eculizumab in GBS [106]. Regrettably, a recent meta-analysis of two trials comparing eculizumab and placebo demonstrated uncertain results [107].

As already stated, inflammatory oedema is pathogenic in early stages of GBS and EAN; in this regard, timely comment is made by Powell and Myers [108], "whereas brain edema is universally understood as a medical emergency, the destructive impact on the peripheral nervous system of endoneurial edema is less appreciated. Measures to inhibit edema and to ameliorate its effects have potential importance in protecting nerve fibers from ischemic injury". Given the

© 2020 Global Journals

narrow therapeutic window to avoid the impact of oedema on axons, such measures should be implemented as soon as possible, including the use of boluses of intravenous methylprednisolone in subgroups with severe early GBS.

a) Pain in pure motor GBS including AMAN

Asbury and Fields distinguished two major forms of neuropathic pain: (i) dysesthetic pain (ie, causalgia, small nerve neuropathy and post-herpetic neuralgia); and (ii) nerve trunk pain (eg, spinal nerve compression and inflammatory neuritis including GBS) [109].

In the original AMAN description [57], it is stated that "many patients had neck and back stiffness and pain; one father said that his son seemed as though he had a rod up his spine" (their composed Fig. 1 is an impressive picture displaying weakness of neck flexor muscles and displaying resistance to passive neck flexion).

In a series of 55 consecutive GBS patients, 49 (89%) described pain during the course of their illness; in around half of them, it was described as excruciating [110]. Back and leg pain was commonly exacerbated by straight leg raising, which provides indirect evidence that traction on inflamed nerve roots could be responsible for some of the pain. The authors argued that irritation of the nervi nervorum, which innervates nerve trunks, may also refer pain to the paraspinal region via dorsal rami of spinal nerves.

Ruts and colleagues described that a high proportion of GBS patients with pure motor neuropathy reported pain, mostly localized in the extremities, and sometimes referred to as severe pain [111]. The authors proposed that pain in the acute phase of pure motor GBS is likely of nociceptive origin, probably due to activation of nervi nervorum. In the IGOS study, 77 (62%) of 125 patients from Bangladesh reported pain at the entry; worthy of note is that 74 (69%) of them had pure motor GBS [7].

Based on our sonographic and autopsy studies (see above), we offered an alternative pathophysiological explanation for acute pain in pure motor GBS/AMAN: early inflammatory oedema, located in the anterior spinal roots at the vertebral foramina entrance, the ventral rami of spinal nerves or both, could involve abutting dorsal rami, thus causing nerve trunk pain referred to their innervation territories, from neck to buttocks, eventually accompanied by neck and back stiffness [112].

Therapy of nerve trunk pain in GBS includes the use of non-steroidal anti-inflammatory drugs, simple analgesics, parental opioids, or even epidural morphine [110]; in spite of their combined use, pain may remain intractable. There have been at least 13 well-documented GBS patients with severe backache and rapid response to steroids (reviewed in reference [11]). In a randomized placebo-controlled study of 223 GBS patients, methylprednisolone had no significant effect on the presence and intensity of pain [113]. Given that this series included only 10 patients with radicular pain, wisely, the authors concluded that this number is too small to conclude about a possible favourable effect of methylprednisolone on this type of pain in GBS. Be that as it may, there appears to be an area of potential further therapeutic study.

IV. Conclusion

The analysis of GBS and EAN data allows for drawing the following conclusions:

- Both in severe AIDP and P_2-induced EAN, the pathologic background may be divergent: pure demyelination in intrathecal spinal roots, and a combination of Wallerian-like degeneration and demyelination in more distant nerve trunks.
- Initial pathogenic lesion in AIDP and P_2-induced EAN is inflammatory oedema mainly involving proximal nerve trunks, particularly spinal nerves. In nerve trunks pos- sessing epi- perineurium, such oedema may increase EFP causing nerve ischemia with conduction failure and eventually Wallerian-like degeneration accompanying demyelination. Having this in mind, serial NCS studies seem to be necessary for accurate GBS subtyping. Imaging techniques help delineate the topography of lesions.
- Revision of the original description of the axonal form of GBS strongly suggests that its pathologic background consists of a divergent pathology: demyelination and axonal degeneration in spinal roots, and pure axonal degeneration in more distant nerve trunks.
- In AMAN, Wallerian-like degeneration also predominates at the ventral root exit from the dura, namely in spinal nerves. Therefore, spinal nerve is an ultrasonographic and pathological hotspot in any GBS subtype.
- In ganglioside-induced axonal EAN, there may be demyelinating changes; consequently, separation between axonal and demyelination patterns does not seem to be absolute. In ganglioside-induced EAN, neuromuscular synaptopathy promotes a repair phenomenon from the perisynaptic Schwann cells. Similar features act on AIDP with secondary axonal damage, where proximal nerve trunks may exhibit exuberant proliferation of adaxonal Schwann cell cytoplasm.
- Knowledge of the microscopic anatomy of the peripheral nervous system and the variable efficiency of the blood–nerve barrier is essential for an accurate understanding of the topographic distribution of lesions both in GBS and EAN.

© 2020 Global Journals

- There may be a potential therapeutic role of boluses of methylprednisolone in early severe GBS patients, or those with intractable pain.

Acknowledgements I thank my colleagues of the Service of Neurology, Drs Antonio García y Pedro Orizaola (Service of Clinical Neurophysiology), Dr. Elena Gallardo (Service of Radiology), Dr. Nuria Terán-Villagrá (Service of Pathology), and Professors Miguel Lafarga and María T. Berciano (Department of Anatomy and Cell Biology, UC) for their help in clinical, electrophysiological, imaging and pathological studies. I wish also to thank Dr José Gazulla (Service of Neurology, University Hospital Miguel Servet, Saragosse) for his comments on the manuscript, and Mr Mario Corral (Director of "Marquesa de Pelayo" Library) for his technical support.

Compliance with ethical standards

Conflicts of interest The author declare no conflict of interest.

References Références Referencias

1. van Doorn PA, Ruts L, Jacobs BC (2008) Clinical features, pathogenesis, and treatment of Guillain–Barré syndrome. Lancet Neurol 7:939–950.
2. Willison HJ, Jacobs BC, van Doorn PA (2016) Guillain Barré syndrome. Lancet 388:717–727.
3. Griffin JW, Li CY, Ho TW, Tian M, Gao CY, Xue P, Mishu B, Cornblath DR, Macko C, McKhann GM, Asbury AK (1996) Pathology of the motor-sensory axonal Guillain Barré syndrome. Ann Neurol 39:17–28.
4. Kuwabara S, Yuki N (2013) Axonal Guillain–Barré syndrome: concepts and controversies. Lancet Neurol 12:1180–1188.
5. van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA (2014) Guillain–Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 10:469–482.
6. Goodfellow JA, Willison HJ (2016) Guillain–Barré syndrome: a century of progress. Nat Rev Neurol 12:723–731.
7. Doets AY, Verboon C, van den Berg B, Harbo T, Cornblath DR, Willison HJ, Islam Z, Attarian S, Barroso FA, Bateman K, Benedetti L, van den Bergh P, Casasnovas C, Cavaletti G, Chavada G, Claeys KG, Dardiotis E, Davidson A, van Doorn PA, Feasby TE, Galassi G, Gorson KC, Hartung HP, Hsieh ST, Hughes RAC, Illa I, Islam B, Kusunoki S, Kuwabara S, Lehmann HC, Miller JAL, Mohammad QD, Monges S, Nobile Orazio E, Pardo J, Pereon Y, Rinaldi S, Querol L, Reddel SW, Reisin RC, Shahrizaila N, Sindrup SH, Waqar W, Jacobs BC, IGOS Consortium (2018) Regional variation of Guillain-Barré syndrome. Brain 141:2866–2877.
8. Sobue G, Li M, Terao S, Aoki S, Ichimura M, Ieda T, Doyu M, Yasuda T, Hashizume Y, Mitsuma T (1997) Axonal pathology in Japanese Guillain–Barré syndrome: a study of 15 autopsied cases. Neurology 48:1694–1700.
9. Benedetti L, Briani C, Beronio A, Massa F, Giorli E, Sani C, Delia P, Artioli S, Sormani MP, Mannironi A, Tartaglione A, Mancardi GL (2019) Increased incidence of axonal Guillain– Barré syndrome in La Spezia area of Italy. A 13-year follow-up study. J Peripher Nerv Syst 24:80–86.
10. Sedano MJ, Orizaola P, Gallardo E, García A, Pelayo-Negro AL, Sánchez-Juan P, Infante J, Berciano J (2019) A unicenter, prospective study of Guillain–Barré syndrome in Spain. Acta Neurol Scand 139:546–554.
11. Berciano J, Sedano MJ, Pelayo-Negro AL, García A, Orizaola P, Gallardo E, Lafarga M, Berciano MT, Jacobs BC (2017) Proximal nerve lesions in early Guillain–Barré syndrome: implications for pathogenesis and disease classification. J Neurol 264:221–236.
12. Uncini A, Ippoliti L, Shahrizaila N, Sekiguchi Y, Kuwabara S (2017) Optimizing the electrodiagnostic accuracy in Guillain–Barré syndrome subtypes: criteria sets and sparse linear discriminant analysis. Clin Neurophysiol 128:1176–1183.
13. Midroni G, Bilbao JM (1985) Biopsy diagnosis of peripheral neuropathy. Butterworth-Heinemann, Newton.
14. King R (1999) Atlas of nerve pathology. Arnold, London.
15. Altmann P, De Simoni D, Kaider A, Ludwig B, Rath J, Leutmezer F, Zimprich F, Hoeftberger R, Lunn MP, Heslegrave A, Berger T, Zetterberg H, Rommer PS (2020) Increased serum neurofilament light chain concentration indicates poor outcome in Guillain–Barré syndrome. J Neuroinflammation 17:86.
16. Soliven B (2014) Animal models of autoimmune neuropathy. ILAR J 54:282–290.
17. Albers JW, Donofrio PD, McGonagle TK (1985) Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 8:528–539.
18. Madrid RE, Wiśniewski HM (1978) Peripheral nervous system pathology in relapsing experimental allergic encephalomyelitis. J Neurocytol 7:265–281.
19. King RHM, Thomas PK, Pollard JD (1977) Axonal and dorsal root ganglion cell changes in experimental allergic neuritis. Neuropathol Appl Neurobiol 3:471–486.
20. Said G, Saida K, Saida T, Asbury AK (1981) Axonal lesions in acute experimental demyelination: a sequential teased nerve fiber study. Neurology 31:413–421.
21. Asbury AK, Cornblath DR (1990) Assessment of current diagnostic criteria for Guillain–Barré syndrome. Ann Neurol 27(Suppl):S21–S24.

© 2020 Global Journals

22. Ho TW, Mishu B, Li CY, Gao CY, Cornblath DR, Griffin JW, Asbury AK, Blaser MJ, McKhann GM (1995) Guillain– Barré syndrome in northern China. Relationship to Campylobacter jejuni infection and anti-glycolipid antibodies. Brain 118:597–605.
23. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, Swan AV (1998) Electrophysiological classification of Guillain–Barré syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group. Ann Neurol 44:780–788.
24. Albertí MA, Alentorn A, Martínez-Yelamos S, Martínez-Matos JA, Povedano M, Montero J, Casasnovas C (2011) Very early electrodiagnostic findings in Guillain–Barré syndrome. J Peripher Nerv Syst 16:136–142.
25. Berciano J, Orizaola P, Gallardo E, Pelayo-Negro AL, Sánchez-Juan P, Infante J, Sedano MJ (2020) Very early Guillain–Barré syndrome: a clinical-electrophysiological and ultrasonographic study. Clin Neurophysiol Pract 5:1–9.
26. Ye Y, Zhu D, Liu L, Wang K, Huang K, Hou C (2014) Electrophysiological measurement at Erb's point during the early stage of Guillain–Barré syndrome. J Clin Neurosci 21:786–789.
27. Temuçin CM, Nurlu G (2011) Measurement of motor root conduction time at the early stage of Guillain–Barre syndrome. Eur J Neurol 10:1240–1245.
28. Kurt Incesu T, Secil Y, Tokucoglu F, Gurgor N, Özdemirkiran T, Akhan G, Ertekin C (2013) Diagnostic value of lumbar root stimulation at the early stage of Guillain–Barré syndrome. Clin Neurophysiol 124:197–203.
29. Sevy A, Grapperon AM, Salort Campana E, Delmont E, Attarian S (2018) Detection of proximal conduction blocks using a triple stimulation technique improves the early diagnosis of Guillain–Barré syndrome. Clin Neurophysiol 129:127–132.
30. Gorson KC, Ropper AH, Muriello MA, Blair R (1996) Prospective evaluation of MRI lumbosacral nerve root enhancement in acute Guillain–Barré syndrome. Neurology 47:813–817.
31. Byun WM, Park WK, Park BH, Ahn SH, Hwang MS, Chang JC (1998) Guillain–Barré syndrome: MR imaging findings of the spine in eight patients. Radiology 208:137–141.
32. Yikilmaz A, Doganay S, Gumus H, Per H, Kumandas S, Coskun A (2010) Magnetic resonance imaging of childhood Guillain–Barre syndrome. Childs Nerv Syst 26:1103–1108.
33. Gallardo E, Sedano MJ, Orizaola P, Sánchez-Juan P, González-Suárez A, García A, Terán-Villagrá N, Ruiz-Soto M, Álvaro RL, Berciano MT, Lafarga M, Berciano J (2015) Spinal nerve involvement in early Guillain–Barré syndrome: a clinico-electrophysiological, ultrasonographic and pathological study. Clin Neurophysiol 126:810–819.
34. Berciano J, Coria F, Montón F, Calleja J, Figols J, LaFarga M (1993) Axonal form of Guillain–Barré syndrome: evidence for macrophage-associated demyelination. Muscle Nerve 16:744–751.
35. McKhann GM, Cornblath DR, Griffin JW, Ho TW, Li CY, Jiang Z, Wu HS, Zhaori G, Liu Y, Jou LP et al (1993) Acute motor axonal neuropathy: a frequent cause of acute flaccid paralysis in China. Ann Neurol 33:333–342.
36. Griffin JW, Li CY, Ho TW, Xue P, Macko C, Gao CY, Yang C, Tian M, Mishu B, Cornblath DR (1995) Guillain–Barré syndrome in northern China. The spectrum of neuropathological changes in clinically defined cases. Brain 118:577–595.
37. Gallardo E, Noto Y, Simon NG (2015) Ultrasound in the diagnosis of peripheral neuropathy: structure meets function in the neuromuscular clinic. J Neurol Neurosurg Psychiatry 86:1066–1074.
38. Grimm A, Décard BF, Schramm A, Pröbstel AK, Rasenack M, Axer H, Fuhr P (2016) Ultrasound and electrophysiologic findings in patients with Guillain–Barré syndrome at disease onset and over a period of six months. Clin Neurophysiol 127:1657–1663.
39. Guillain G, Barré JA, Strohl A (1916) 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 40:1462–1470.
40. Krücke W (1955) Die primär-entzündliche Polyneuritis unbekannter Ursache. In: Lubarsch O, et al. (eds) Handbuch der speziallen pathologischen Anatomie und Histologie, Vol XIII/5, Erkrankungen des peripheren und des vegetativen Nerven. Springer-Verlag, Berlin, pp 164–182.
41. Asbury AK, Arnason BG, Adams RD (1969) The inflammatory lesion in idiopathic polyneuritis. Its role in pathogenesis. Medicine (Baltimore) 48:173–215.
42. Wiśniewski H, Terry RD, Whitaker JN, Cook SD, Dowling PC (1969) Landry–Guillain–Barré syndrome. A primary demyelinating disease. Arch Neurol 21:269–276.
43. Carpenter S (1972) An ultrastructural study of an acute fatal case of the Guillain–Barré syndrome. J Neurol Sci 15:125–140.
44. Prineas JW (1972) Acute idiopathic polyneuritis. An electron microscope study. Lab Invest 26:133–147.
45. Haymaker WE, Kernohan JW (1949) The Landry–Guillain–Barré syndrome; a clinicopathologic report of 50 fatal cases and a critique of the literature. Medicine (Baltimore) 28:59–141.
46. Brechenmacher C, Vital C, Deminiere C, Laurentjoye L, Castaing Y, Gbikpi-Benissan G, Cardinaud JP, Favarel-Garrigues JP (1987) Guillain–Barré syndrome: an ultrastructural study of peripheral nerve in 65 patients. Clin Neuropathol 6:19–24.

© 2020 Global Journals

47. Feasby TE, Gilbert JJ, Brown WF, Bolton CF, Hahn AF, Koopman WF, Zochodne DW (1986) An acute axonal form of Guillain–Barré polyneuropathy. Brain 109:1115–1126.
48. Thomas PK (1992) The Guillain–Barré syndrome: no longer a simple concept. J Neurol 239:361–362.
49. Triggs WJ, Cros D, Gominak SC, Zuniga G, Beric A, Shahani BT, Ropper AH, Roongta SM (1992) Motor nerve inexcitability in Guillain–Barré syndrome. The spectrum of distal conduction block and axonal degeneration. Brain 115:1291–1302.
50. Cros D, Triggs WJ (1994) There are no neurophysiologic features characteristic of "axonal" Guillain–Barré syndrome. Muscle Nerve 17:675–677
51. Yuki N (1994) Pathogenesis of axonal Guillain–Barré syndrome: hypothesis. Muscle Nerve 17:680–682.
52. Feasby TE, Hahn AF, Brown WF, Bolton CF, Gilbert JJ, Koopman WJ (1993) Severe axonal degeneration in acute Guillain–Barré syndrome: evidence of two different mechanisms? J NeurolSci 116:185–192.
53. Feasby TE (1994) Axonal Guillain–Barré syndrome. Muscle Nerve 17:678–679.
54. Feasby TE (2016) Axonal Guillain–Barré syndrome. In: Willison HJ, Goodfellow JA (eds) GBS100 Celebrating a centenary of progress in Guillain–Barré syndrome. PNS, La Jolla, pp 120–124.
55. Yuki N, Yoshino H, Sato S, Miyatake T (1990) Acute axonal polyneuropathy associated with anti-GM1 antibodies following Campylobacter enteritis. Neurology 40:1900–1902.
56. Gregson NA, Jones D, Thomas PK, Willison HJ (1991) Acute motor neuropathy with antibodies to GM1 ganglioside. J Neurol 238:447–451.
57. McKhann GM, Cornblath DR, Ho T, Li CY, Bai AY, Wu HS, Yei QF, Zhang WC, Zhaori Z, Jiang Z et al (1991) Clinical and electrophysiological aspects of acute paralytic disease of children and young adults in northern China. Lancet 338:593–597.
58. Hall SM, Hughes RA, Atkinson PF, McColl I, Gale A (1992) Motor nerve biopsy in severe Guillain–Barré syndrome. Ann Neurol 31:441–444.
59. Ho TW, Hsieh ST, Nachamkin I, Willison HJ, Sheikh K, Kiehlbauch J, Flanigan K, McArthur JC, Cornblath DR, McKhann GM, Griffin JW (1997) Motor nerve terminal degeneration provides a potential mechanism for rapid recovery in acute motor axonal neuropathy after Campylobacter infection. Neurology 48:717–724.
60. McKhann G, Ho TW (2016) The Chinese paralytic syndrome. Recollection of participants. In: Willison HJ, Goodfellow JA (eds) GBS100 Celebrating a centenary of progress in Guillain–Barré syndrome. PNS, La Jolla, pp 78–88.
61. Griffin JW, Li CY, Macko C, Ho TW, Hsieh ST, Xue P, Wang FA, Cornblath DR, McKhann GM, Asbury AK (1996) Early nodal changes in the acute motor axonal neuropathy pattern of the Guillain–Barré syndrome. J Neurocytol 25:33–51.
62. Hafer-Macko C, Hsieh ST, Li CY, Ho TW, Sheikh K, Cornblath DR, McKhann GM, Asbury AK, Griffin JW (1996) Acute motor axonal neuropathy: an antibody-mediated attack on axolemma. Ann Neurol 40: 635–644.
63. Hafer-Macko CE, Sheikh KA, Li CY, Ho TW, Cornblath DR, McKhann GM, Asbury AK, Griffin JW (1996) Immune attack on the Schwann cell surface in acute inflammatory demyelinating polyneuropathy. Ann Neurol 39:625–635.
64. Willison HJ (2012) The translation of the pathological findings described in humans to experimental models of acute motor axonal neuropathy. J Peripher Nerv Syst 17(Suppl 3):3–8.
65. Uncini A, Susuki K, Yuki N (2013) Nodo-paranodopathy: beyond the demyelinating and axonal classification in anti-ganglioside antibody-mediated neuropathies. Clin Neurophysiol 124:1928–1934.
66. Chaudhry V, Cornblath DR (1992) Wallerian degeneration in human nerves: serial electrophysiological studies. Muscle Nerve 15: 687–693.
67. Berciano J, Figols J, García A, Calle E, Illa I, Lafarga M, Berciano MT (1997) Fulminant Guillain–Barré syndrome with universal inexcitability of peripheral nerves: a clinicopathological study. Muscle Nerve 20:846–857.
68. Kanda T, Hayashi H, Tanabe H, Tsubaki T, Oda M (1989) A fulminant case of Guillain–Barré syndrome: topographic and fibre size related analysis of demyelinating changes. J Neurol Neurosurg Psychiatry 52:857–864.
69. Berciano J, García A, Figols J, Muñoz R, Berciano MT, Lafarga M (2000) Perineurium contributes to axonal damage in acute inflammatory demyelinating polyneuropathy. Neurology 55:552–559.
70. Berciano J, García A, Villagrá NT, González F, Ramón C, Illa I, Berciano MT, Lafarga M (2009) Severe Guillain–Barré syndrome: sorting out the pathological hallmark in an electrophysiological axonal case. J Peripher Nerv Syst 14:54–63.
71. Goodfellow JA, Willison HJ (2018) Gangliosides and autoimmune peripheral nerve diseases. Prog Mol Biol Transl Sci 156:355–382.
72. Waksman BH, Adams RD (1955) Allergic neuritis: an experimental disease of rabbits induced by the injection of peripheral nervous tissue and adjuvants. J Exp Med 102:213–236.
73. Izumo S, Linington C, Wekerle H, Meyermann R (1985) Morphologic study on experimental allergic neuritis mediated by T cell line specific for bovine P_2 protein in Lewis rats. Lab Invest 53:209–218.
74. Heininger K, Stoll G, Linington C, Toyka KV, Wekerle H (1986) Conduction failure and nerve conduction

© 2020 Global Journals

slowing in experimental allergic neuritis induced by P_2-specific T-cell lines. Ann Neurol 19:44–449.
75. Hahn AF, Feasby TE, Wilkie L, Lovgren D (1991) P2-peptide induced experimental allergic neuritis: a model to study axonal degeneration. Acta Neuropathol 82:60–65.
76. Hahn AF, Feasby TE, Steele A, Lovgren DS, Berry J (1988) Demyelination and axonal degeneration in Lewis rat experimental allergic neuritis depend on the myelin dosage. Lab Invest 59:115–125.
77. Powell HC, Braheny SL, Myers RR, Rodriguez M, Lampert PW (1983) Early changes in experimental allergic neuritis. Lab Invest 48:332–338.
78. Powell HC, Myers RR, Mizisin AP, Olee T, Brostoff SW (1991) Response of the axon and barrier endothelium to experimental allergic neuritis induced by autoreactive T cell lines. Acta Neuropathol 82: 364–377.
79. McManis PG, Low PA, Lagerlund TD (1993) Nerve blood flow and microenviroment. In: Dyck PJ, et al. (eds) Peripheral neuropathy. WB Saunders, Philadelphia, pp 453–4731.
80. Hadden RD, Gregson NA, Gold R, Smith KJ, Hughes RA (2002) Accumulation of immunoglobulin across the 'blood-nerve barrier' in spinal roots in adoptive transfer experimental autoimmune neuritis. Neuropathol Appl Neurobiol 28:489–497.
81. Kusunoki S (2016) Animal models: antiganglioside antibodies as causative factor of GBS. In: Willison HJ, Goodfellow JA (eds) GBS100 Celebrating a centenary of progress in Guillain–Barré syndrome. PNS, La Jolla, pp 365–371.
82. Yuki N, Yamada M, Koga M, Odaka M, Susuki K, Tagawa Y, Ueda S, Kasama T, Ohnishi A, Hayashi S, Takahashi H, Kamijo M, Hirata K (2001) Animal model of axonal Guillain–Barré syndrome induced by sensitization with GM1 ganglioside. Ann Neurol 49:712–720.
83. Nachamkin I (2002) (2002) Rabbit model of Guillain–Barré syndrome. Ann Neurol 52:127–128.
84. Moyano AL, Comín R, Lardone RD, Alaniz ME, Theaux R, Irazoqui FJ, Nores GA (2008) Validation of a rabbit model of neuropathy induced by immunization with gangliosides. J Neurol Sci 272:110–114.
85. Susuki K, Nishimoto Y, Yamada M, Baba M, Ueda S, Hirata K, Yuki N (2003) Acute motor axonal neuropathy rabbit model: immune attack on nerve root axons. Ann Neurol 54:383–388.
86. Susuki K, Rasband MN, Tohyama K, Koibuchi K, Okamoto S, Funakoshi K, Hirata K, Baba H, Yuki N (2007) Anti-GM1 antibodies cause complement-mediated disruption of sodium channel clusters in peripheral motor nerve fibers. J Neurosci 27: 3956–3967.
87. Yuki N, Susuki K, Koga M, Nishimoto Y, Odaka M, Hirata K, Taguchi K, Miyatake T, Furukawa K, Kobata T, Yamada M (2004) Carbohydrate mimicry between human ganglioside GM1 and *Campylobacter jejuni* lipooligosaccharide causes Guillain–Barre syndrome. Proc Natl Acad Sci USA 101:11404–11409.
88. Li CY, Xue P, Tian WQ, Liu RC, Yang C (1996) Experimental *Campylobacter jejuni* infection in the chicken: an animal model of axonal Guillain–Barré syndrome. J Neurol Neurosurg Psychiatry 61: 279–284.
89. O'Hanlon GM, Humphreys PD, Goldman RS, Halstead SK, Bullens RW, Plomp JJ, Ushkaryov Y, Willison HJ (2003) Calpain inhibitors protect against axonal degeneration in a model of anti-ganglioside antibody-mediated motor nerve terminal injury. Brain 126:2497–2509.
90. Plomp JJ, Willison HJ (2009) Pathophysiological actions of neuropathy-related anti-ganglioside antibodies at the neuromuscular junction. J Physiol 587:3979–3999.
91. Spaans F, Vredeveld JW, Morré HH, Jacobs BC, De Baets MH (2003) Dysfunction at the motor end-plate and axon membrane in Guillain–Barré syndrome: a single-fiber EMG study. Muscle Nerve 27:426–434.
92. Kuwabara S, Kokubun N, Misawa S, Kanai K, Isose S, Shibuya K, Noto Y, Mori M, Sekiguchi Y, Nasu S, Fujimaki Y, Hirata K, Yuki N (2011) Neuromuscular transmission is not impaired in axonal Guillain–Barré syndrome. J Neurol Neurosurg Psychiatry 82: 1174–1147.
93. Brown WF, Feasby TE, Hahn AF (1993) Electrophysiological changes in the acute "axonal" form of Guillain–Barre syndrome. Muscle Nerve 16:200–205.
94. Cunningham ME, Meehan GR, Robinson S, Yao D, McGonigal R, Willison HJ (2020) Perisynaptic Schwann cells phagocytose nerve terminal debris in a mouse model of Guillain–Barré syndrome. J Peripher Nerv Syst. https://doi.org/10.1111/jns.12373.
(Online ahead of print)
95. Korthals JK, Korthals MA, Wisniewski HM (1978) Peripheral nerve ischemia: Part 2. Accumulation of organelles. Ann Neurol 4:487–498.
96. Nukada H, Dyck PJ (1987) Acute ischemia causes axonal stasis, swelling, attenuation, and secondary demyelination. Ann Neurol 22:311–318.
97. Spencer PS, Thomas PK (1974) Ultrastructural studies of the dying-back process. II. The sequestration and removal by Schwann cells and oligodendrocytes of organelles from normal and diseases axons. J Neurocytol 3:763–783.
98. Olsson Y (1968) Topographical differences in the vascular permeability of the peripheral nervous system. Acta Neuropathol 10:26–33.

© 2020 Global Journals

99. Kanda T (2007) Biology of the blood-nerve barrier and its alteration in immune mediate neuropathies. J Neuro Neurosurg Psychistry 84:208–212.
100. Olsson Y (1975) Vascular permeability in the peripheral nervous system. In: Dyck PJ, Thomas PK, Lambert ED (eds) Peripheral neuropathy (volume 1). WB Saunders, Philadelphia, pp 190–200.
101. Berthold CH, Fraher JP, King RHM, Rydmark M (2005) Microscopical anatomy of the peripheral nervous system. In: Dyck PJ, Thomas PK (eds) Peripheral neuropathy. WB Saunders, Philadelphia, pp 35–91.
102. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H (2019) Neurofilament light chain as a biomarker in neurological disorders. J Neurol J Neurosurg Psychiatry 90:870–881.
103. Halstead SK, Humphreys PD, Goodfellow JA, Wagner ER, Smith RA, Willison HJ (2005) Complement inhibition abrogates nerve terminal injury in Miller Fisher syndrome. Ann Neurol 58: 203–210.
104. McGonigal R, Rowan EG, Greenshields KN, Halstead SK, Humphreys PD, Rother RP, Furukawa K, Willison HJ (2010) Anti-GD1a antibodies activate complement and calpain to injure distal motor nodes of Ranvier in mice. Brain 133:1944–1960.
105. Hillmen P, Young NS, Schubert J, Brodsky RA, Socié G, Muus P, Röth A, Szer J, Elebute MO, Nakamura R, Browne P, Risitano AM, Hill A, Schrezenmeier H, Fu CL, Maciejewski J, Rollins SA, Mojcik CF, Rother RP, Luzzatto L (2006) The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med 355: 1233–1243.
106. Davidson AI, Halstead SK, Goodfellow JA, Chavada G, Mallik A, Overell J, Lunn MP, McConnachie A, van Doorn P, Willison HJ (2017) Inhibition of complement in Guillain–Barré syndrome: the ICA-GBS study. J Peripher Nerv Syst 22:4–12.
107. Doets AY, Hughes RA, Brassington R, Hadden RD, Pritchard J (2020) Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain–Barré syndrome. Cochrane Database Syst Rev 1(1):008630.
108. Powell HC, Myers RR (1996) The axon in Guillain–Barré syndrome: immune target or innocent bystander? Ann Neurol 39:4–5.
109. Asbury AK, Fields HL (1984) Pain due to peripheral nerve damage: an hypothesis. Neurology 34: 1587–1590.
110. Moulin DE, Hagen N, Feasby TE, Amireh R, Hahn A (1997) Pain in Guillain–Barré syndrome. Neurology 48: 328–331.
111. Ruts L, Rico R, van Koningsveld R, Botero JD, Meulstee J, Gerstenbluth I, Merkies IS, van Doorn PA (2008) Pain accompanies pure motor Guillain–Barré syndrome. J Peripher Nerv Syst 13:305–306.
112. Berciano J (2018) Neuropathic pain in early Guillain–Barré syndrome. Pain Physician 21:E279–E280.
113. Ruts L, van Koningsveld R, Jacobs BC, van Doorn PA (2007) Determination of pain and response to methylprednisolone in Guillain–Barré syndrome. J Neurol 254:1318–1322.

© 2020 Global Journals