Journal of the Neurological Sciences 382 (2017) 1–9

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

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

José Berciano

University of Cantabria, Service of Neurology, University Hospital "Marqués de Valdecilla (IDIVAL)", Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Santander, Spain

ARTICLE INFO

Keywords:
Acute febrile polyneuritis
Acute motor or motor-sensory axonal neuropathy
Axonal degeneration
Demyelination
Endoneurial fluid pressure
Experimental allergic neuritis
Guillain-Barré syndrome
Haymaker Webb
Kernohan James
Landry's palsy
Nerve inflammatory oedema
Spinal nerves
Spinal roots
Ultrasonography

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*

E-mail address: jaberciano@humv.es.

http://dx.doi.org/10.1016/j.jns.2017.09.017
Received 21 August 2017; Received in revised form 5 September 2017; Accepted 11 September 2017
Available online 13 September 2017

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.