The discovery of the Guillain–Barré syndrome and related disorders

Richard Hughes¹, Jean-Marc Léger²

1. Cochrane Neuromuscular Disease Group, MRC Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom
2. Referral Center for Rare Neuromuscular Disease, Hôpital de la Salpêtrière, Bâtiment Babinski, Paris, France

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The clinical picture of Guillain–Barré syndrome (GBS) was first clearly described by Landry in 1856 [1]. Although he examined the nerves post-mortem, he did not find any abnormalities. The causative inflammation of the peripheral nerves was not identified until Leyden’s description in 1880 [2]. During the second half of the 19th century, confusion continued whether acute ascending paralysis was “multiple neuritis” or myelitis. In 1916, Guillain, Barré and Strohl reported the characteristic albumino-cytological dissociation in the CSF and undertook graphical recordings of the reduced and delayed tendon reflexes [3,4]. They deduced that the spinal roots were involved and distinguished their syndrome from poliomyelitis. The frequent association of GBS with infections led to the suspicion, never confirmed, that GBS was a viral infection. The occurrence of autoimmune encephalitis following rabies vaccine led Waksman and Adams to experiment with injecting peripheral nerve and adjuvant into animals producing experimental autoimmune neuritis [5]. In 1969 Asbury, Arnason and Adams described severe inflammatory changes in the peripheral nerves of their 19 personal cases of GBS and noted their similarity to those in experimental autoimmune neuritis [6]. This experimental disease is now known to be caused by T helper cells responding to epitopes on myelin proteins. PO, P2 and PMP22 have been the most implicated inducing antigens. The identity of the autoantigen causing the common form of GBS, acute inflammatory demyelinating polyradiculoneuropathy, remains a mystery [7].

The description by Feasby et al. in 1986 of a clinical picture resembling GBS but electrophysiologically and pathologically due to an axonal neuropathy [8] led to the realisation that GBS is a syndrome with more than one pathological substrate. Study of the axonal form of the disease in China by investigators from Johns Hopkins Medical School in the 1990s led to the distinction of a purely motor form of GBS, acute motor axonal neuropathy [9]. Investigation of this homogeneous subtype has enormously enhanced our understanding of autoimmune neuropathy. It is usually preceded by Campylobacter jejuni infection and affected patients have antibodies to gangliosides, especially GM1 and GD1α, whose carbohydrate epitopes resemble those on the axolemma and perisynaptic Schwann cell. Yuki in Japan has produced a rabbit model of the human disease by immunising animals with ganglioside-GM1. Willison in Scotland has produced elegant mouse models and shown that these are caused by complement-fixing antibodies directed against ganglioside-GM1 or GD1α epitopes [10]. Another related neuropathy, Fisher syndrome, consisting of ophthalmoplegia, tendon areflexia and ataxia, turns out to be due to
similar antibodies directed against ganglioside-GQ1b. Which sort of neuropathy a patient develops depends on whether the preceding infection is caused by an organism which has the genes coding for the production of ganglioside-GM1 or GQ1b. It probably also depends on whether the patient has the appropriate susceptibility genes but these are not yet identified [10]. The clinical features and treatment of GBS are authoritatively described in this issue [11].

The concept of chronic inflammatory demyelinating polyradiculoneuropathy was slower to emerge than that of GBS. The clinical concept was established by Austin’s detailed description in 1958 of a patient with a relapsing steroid responsive neuropathy accompanied by a review of 30 previous cases from the literature [12]. The reasons for the delay included the initial limited availability of pathology and the lack of neurophysiology to demonstrate demyelination and of steroids to show a response to anti-inflammatory treatment. During the 1970s increasingly large series of patients were published, notably by Dyck et al. at the Mayo clinic and Prineas and McLeod in Sydney [13,14]. These papers described the neurophysiological abnormalities of slowed conduction and partial conduction block suggestive of demyelination and reported a frequent response to corticosteroids. The pathology of acute lesions involved lymphocytic infiltration of the endoneurium and macrophage invasion and stripping of the myelin sheaths to produce demyelination. The pathogenesis of the disease remains unclear although recent investigations point to abnormalities of T- and B-cell regulatory mechanisms and involvement of CD8+ T-cells [15].

Beginning in the 1980s, there was a realisation that more patients with chronic demyelinating neuropathy have a paraprotein than would be expected by chance. In some cases the paraprotein was caused by a malignant plasma cell dyscrasia but often the clinical picture was a slowly progressive predominantly sensory demyelinating neuropathy, frequently associated with tremor, combined with an IgMkappa paraprotein [16]. Latov in 1980 showed that this picture was almost always associated with high titres of complement-fixing antibodies to myelin which react with myelin-associated glycoprotein [17]. Pathologically there is characteristic widening of the lamellar spacing and the IgM antibodies label these parts of the myelin sheath. These antibodies also react with carbohydrate epitopes on other myelin proteins and glycolipids and induce demyelination following intraneural injection into feline nerve and in neonatal chicks. This syndrome accounts for about half of patients with IgM paraprotein-associated neuropathy while the other half and most of the patients with IgG and IgA neuropathies have a neuropathy which resembles CIDP whose pathogenesis is poorly understood. Since paraproteins occur in 1% of the population older than 50 years, the association may often be coincidental. However there are two other interesting homogeneous neuropathic syndromes associated with paraproteins. One, chronic axatic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies (CANOMAD), is probably due to the antiganglioside antibody properties of the paraprotein [18]. The other, POEMS syndrome, consists of a mixed axonal-demyelinating neuropathy with plasma cell dyscrasia, increased vascular endothelial growth factor, sclerotic bone lesions or Castleman disease and often organomegaly, endocrinopathy, skin changes, papilloedema, thrombocytosis and oedema or ascites [16]. The pathogenesis and the role of the paraprotein in the POEMS syndrome are not understood. It is likely that the associations between neuropathy and paraproteins will reveal further homogeneous subgroups with informative pathogenic mechanisms.

There are symmetrical pure motor and pure sensory and asymmetrical sensory and motor variants included under the rubric of atypical CIDP but in the 1980s a related but subtly different condition, multifocal motor neuropathy, was described [19–21]. In this, there are multifocal areas of persistent conduction block affecting motor but not sensory nerve fibres. The condition is slowly progressive and is usually markedly improved by treatment with intravenous immunoglobulin [22]. Unlike CIDP it does not relapse and remit spontaneously and does not respond to treatment with corticosteroids [23]. At least half of patients have circulating antibodies to ganglioside-GM1 [22] and Willison et al. have recently found antibodies to a ganglioside-GM1 galactocerebroside mixture in all their MMN cases [24]. This finding implicates an antibody-mediated mechanism with a glycolipid antigen in the pathogenesis but the persistence of multifocal lesions over many years still defies explanation.

Guillain, Barré and Strohl could not have foreseen the variety of different syndromes of which their syndrome was the harbinger. This Quarterly Medical Review brings the reader up-to-date with the latest research findings in these and other inflammatory neuropathies.

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References


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