Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 26 (2016) 825–836

www.elsevier.com/locate/nmd

Nodo-paranodopathy, internodopathy and cleftopathy: Target-based reclassification of Guillain–Barré-like immune-mediated polyradiculoneuropathies in dogs and cats ☆

Simone Gross [a], Andrea Fischer [b], Marco Rosati [a], Lara Matiasek [c], Daniele Corlazzoli [d], Rodolfo Cappello [e], Laura Porcarelli [d], Tom Harcourt-Brown [f], Konrad Jurina [b], Laurent Garosi [g], Thomas Flegel [h], Pia Quitt [b], Jessica Molin [a], Velia-Isabel Huelsmeyer [b], Henning Schenk [i], Gualtiero Gandini [j], Kirsten Gnirs [k], Stéphane Blot [l], Aurélien Jeandel [l], Massimo Baroni [m], Shenja Loderstedt [n], Gianluca Abbiati [o], Carola Leithaeuser [p], Sabine Schulze [q], Marion Kornberg [r], Mark Lowrie [s], Kaspar Matiasek [a,*]

[a] *Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-Universität München, Munich, Germany*
[b] *Section of Neurology, Clinic of Small Animal Medicine, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-Universität, München, Munich, Germany*
[c] *Neurology Referral Service, Tierklinik Haar, Haar, Germany*
[d] *Clinica Veterinaria Roma Sud, Rome, Italy*
[e] *North Downs Specialist Referrals, Bletchingley, Surrey, UK*
[f] *Section of Neurology, Langford Veterinary Services, University of Bristol, Bristol, UK*
[g] *Neurology Referral Service, Davies Veterinary Specialists, Manor Farm Business Park, Higham Gobion, UK*
[h] *Neurology Unit, Department of Small Animal Medicine, University of Leipzig, Leipzig, Germany*
[i] *Neurology Service, Tierklinik Lueneburg, Lueneburg, Germany*
[j] *Department of Veterinary Medical Science, University of Bologna, Italy*
[k] *Section of Neurology & Neurosurgery, Advetia Clinic for Small Animal Medicine, Paris, France*
[l] *Section of Neurologie, Ecole Nationale Vétérinaire d'Alfort, University of Paris Est, Maisons Alfort, France*
[m] *Section of Neurology, Clinica Veterinaria Valdinievole, Monsummano, Italy*
[n] *Section of Neurology, Clinic of Small Animal Medicine, University of Berlin, Berlin, Germany*
[o] *Clinica Veterinaria Malpensa, Samarate, Italy*
[p] *Small Animal Clinic Magunna-Magunna-Nickel, Norderstedt, Germany*
[q] *Small Animal Clinic Fuerstenwalde, Germany*
[r] *Small Animal Clinic Trier, Germany*
[s] *Dovecote Veterinary Hospital, Castle Donington, UK*

Received 15 March 2016; received in revised form 14 July 2016; accepted 29 August 2016

Abstract

Recent views on Guillain–Barré syndrome (GBS) question the accuracy of classification into axonal and demyelinating subtypes that represent convergent neurophysiological phenotypes rather than immunological targets. Instead it has been proposed to clarify the primarily affected fibre subunit in nerve biopsies. As nerve biopsies rarely are part of routine work-up in human patients we evaluated tissues taken from companion animals affected by GBS-like polyradiculoneuropathy to screen for distribution of immune cells, targeted fibre components and segregating non-inflammatory lesions. We identified that immune responses were directed either at Schmidt-Lanterman clefts, the paranode–node complex or both. Based on infiltrative and non-inflammatory changes, four subtypes and/or stages were distinguished, some of which indicate localisation of primary target antigens while others represent convergent late stage pictures, as a consequence to epitope spreading. The impact of histological subtyping onto clinical management and prognosis remains to be evaluated in future clinical trials. Natural development and clinical manifestation of large animal dysimmune neuropathy may reflect human Guillain–Barré syndrome more accurately than experimental models and therefore provide complementary clues for translational research.

Keywords: Polyradiculoneuritis; Polyneuritis; Immune-mediated; Coonhound paralysis; Canine; Feline; Peripheral nerve; Teasing; Subtype

☆ This paper is dedicated to the 90th birthday of Prof. Dr. Dr. h.c. Erwin Dahme, a groundbreaking pioneer of comparative neuropathology in Germany.

* Corresponding author. Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-Universität München, Veterinarstr. 13, D-80539 Munich, Germany. Fax: +49 89 2180 99 3313.
E-mail address: kaspar.matiasek@neuropathologie.de (K. Matiasek).

http://dx.doi.org/10.1016/j.nmd.2016.08.015
0960-8966/

1. Introduction

Guillain–Barré Syndrome (GBS)-like neuropathy resembles the most common cause of sporadic acute non-traumatic limb paralysis amongst citizens of developed countries [1]. Similar syndromes are seen in dogs and cats in which they comprise important differentials to infectious polyradiculoneuritis, tick paralysis, fulminant myasthenia gravis, snake envenomation and botulism [2–6].

To avoid confusion by different terms and acronyms used for individual species (e.g. GBS, Acute Canine Polyradiculoneuritis (ACP)), the term Immune-mediated Polyradiculoneuropathy (IMPN) has been used in this manuscript when referring to the group of dysimmune neuropathies.

IMPN in people [7], dogs [2,8] and cats have all been hypothesised to originate from a redirected immune response addressing myelin components or axolemmal antigens [9]. While Coonhound Polyradiculoneuritis in dogs indeed can be reproduced by inoculation of raccoon saliva, the molecular mimicry responsible for sporadic IMPN in dogs, cats and humans is assumed to result from preceding antigen challenges in the course of infection, vaccination and exposure to environmental pathogens [2,10].

Once the immune reaction has been redirected to nerve fibres, IMPN in people are diagnosed and characterised by their clinical course, pattern of neurological impairment, albuminocytologic dissociation on CSF analysis and electrodiagnostic abnormalities, while nerve biopsies are not part of standard algorithms [11]. Even though not considered relevant for its clinical diagnosis, lack of insights into pathomorphological characteristics may render the understanding of GBS aetiopathogenesis and prediction of clinical course incomplete [12]. For its revelation and conclusions on disease progression it may be essential to have a closer look onto topography and distribution of fibre lesions and their segregation with cellular and humoural effector mechanisms in vivo. Currently, IMPN classification only aims to discriminate axonal and demyelinating subtypes via electrophysiology as axonal neuropathies should be associated with less favourable prognosis [12].

The most common GBS variant identified via electrophysiology is Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) [13,14]. AIDP is characterised by axons stripped free of myelin by macrophages [15,16]. This, however, does not rule out secondary axonal degeneration [17] resulting from lack of neurotrophic Schwann cell factors at advanced stages. Quite the opposite has been proposed for its axonal counterpart Acute Motor Axonal Neuropathy (AMAN). It is represented by immune attack of the nodes of Ranvier, leaving the myelin sheath initially unaffected. Demyelination however may kick-in at later stages [15,16]. Because of this convergence and equivocal electrodiagnostic features, distinction of axonal and demyelinating GBS variants, in particular at advanced stages, is difficult to achieve without nerve biopsy [13]. The same appears to be true for ACP [18]. As in GBS, serological evidence of anti-ganglioside antibodies often does not provide a clue as to whether the underlying disease is axonal or demyelinating [8]. In this regard, comparative data obtained from clinical biopsies of IMPN-affected animals should add to our understanding.

First analogies of veterinary cases and GBS have been recognised in Coonhound Polyradiculoneuritis, a paralytic syndrome incited by inoculation of raccoon saliva [2,19,20]. These similarities later on were reproduced in other immune-mediated canine polyradiculoneuritides without preceding raccoon contact and with successful application of similar treatments as in people [21], summarised as ACP [2,21,22].

Similar to GBS, ACP exhibits ventral root predominance with distally decreasing gradient of functional and electrodiagnostic impairment (muscle spontaneous activity, decreased compound muscle action potential (CMAP) amplitudes and increased minimum F-wave latencies or absent F-waves, increased F-ratios, decreased F-wave amplitudes) as well as with protein increase in cerebrospinal fluid (CSF) with albuminocytologic dissociation [2,20].

Dysimmune neuropathies of yet unclear cause (idiopathic) and less stereotypic clinical presentation have been also reported in cats [3,23–27]. The rather sparse literature on feline immune-mediated neuropathies, however, states features similar to ACP [3,25,28,29] albeit their resemblance to GBS remained to be clarified.

Insights from nerve biopsies in IMPN-affected dogs and cats imply some recurrent patterns that allow for subclassification of clinically indistinguishable patients in support of Uncini et al. [12]. Whether morphological subtypes might be associated with different courses and outcomes remains to be clarified. In order to base this assumption on scientific grounds, we reevaluated IMPN biopsies by screening for consistent damage patterns and addressed the pathomorphology with regard to the reported clinical history.

2. Materials and methods

2.1. Case selection

Nerve biopsies of a two-year period were screened for evidence of mononuclear nerve fibre invasion. Biopsies underwent additional nerve fibre processing as described below. Only cases that (1) exhibited infiltration of pre-degenerate fibres and (2) that lacked histopathological, serological and polymerase chain reaction (PCR) indications of neurotropic infection (e.g. *Neospora caninum*, *Toxoplasma gondii*) and systemic vasculitis were included.

2.2. Nerve processing

Nerve fascicles were freed from epineurial and mesoneurial tissue, gently separated from each other and fixed in 2.5% glutaraldehyde for 1–2 hours. Thereafter, they were rinsed with and immersed in 0.1 M Soerensen's phosphate buffer (pH 7.4) containing 0.2 M buffered D (+)-saccharose until further processing. Four segments of 2 mm length were harvested from proximal and distal edges using a razor blade. They were postfixed for 2 hours in 2% osmium tetroxide followed by repeated buffer rinses and ascending alcohol series ensued by embedding