Antecedent infections and vaccinations in chronic inflammatory demyelinating polyneuropathy: a European collaborative study

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REVISED VERSION R3.

Key words: acute-onset; chronic inflammatory demyelinating polyneuropathy; infection; respiratory; gastrointestinal; vaccination.

Disclosures:

YAR has received speaker/consultancy honoraria from LFB and Polyneuron, has received educational sponsorships from LFB and CSL Behring and has obtained research grants from LFB and CSL Behring.
SP reports following conflicts of interest, unrelated to this work. He has received lecture honoraria from Pfizer, Teva Actavis, Berlin Chemie Menarini, Mylan, Worwag, Adoc and Salveo; research grants from Kedrion, Octapharma and Argenx; consultant fees from Argenx, Mylan and Roche; and travel grants from Octapharma, Kedrion, Teva Actavis, Sanofi Genzyme, Pfizer, Roche, Adoc and Berlin Chemie Menarini.
LKL reports no conflict of interest.
IBo reports following conflicts of interest, unrelated to this work. He has received lecture honoraria from Salveo; and travel grants from Kedrion, and Adoc.
AK reports no conflicts of interest.
AP reports no conflict of interest.
IBa reports following conflicts of interest, unrelated to this work. She has received lecture honoraria from Pfizer, Teva Actavis, Berlin Chemie Menarini, Mylan, and Adoc; research grants from Kedrion; and travel grants from Kedrion, and Teva Actavis.

"We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Funding: None

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mus.27374

Abstract.

Introduction/Aims: Chronic inflammatory demyelinating polyneuropathy (CIDP) may be rarely preceded by infection. A causative link remains unproven, in contrast to Guillain-Barré syndrome (GBS), which is commonly post-infectious with well-demonstrated pathophysiologic mechanisms of molecular mimicry following *Campylobacter jejuni* enteritis. Uncommonly, infections are reported before the onset of CIDP. We aimed to determine the frequency and characteristics of CIDP occurring after antecedent infections or vaccinations in two large European cohorts.

Methods: We reviewed the records of 268 subjects with "definite" or "probable" CIDP from the Inflammatory Neuropathy clinic, Birmingham, U.K. (129 subjects), and from the Serbian national CIDP database (139 subjects).

Results: Twenty-five of 268 (9.3%) subjects had a respiratory or gastrointestinal infection in the 6 weeks preceding CIDP onset and 3/268 (1.1%) had received an influenza vaccination. CIDP disease onset occurred at a younger age (44.25 years S.D. 17.36 vs. 54.05 years S.D. 15.19; $p<0.005$) and acute-onset CIDP was more common (42.9% vs. 12.1%; OR: 5.46; 95% CI: 2.35-12.68; $p<0.001$), in subjects with preceding infections or vaccinations. No differences in CIDP subtype, rates of cerebrospinal fluid protein level elevation, disability or likelihood of treatment response, were observed.

Discussion: Antecedent infections or vaccinations may precede about 10% of cases of CIDP and are more common in younger subjects. Acute-onset CIDP is more frequent after antecedent events. These findings may suggest specific pathophysiological mechanisms in such cases.

Introduction.

The post-infectious nature of Guillain-Barré syndrome (GBS) is today well-recognised in the majority of presenting cases. About 70% of cases of GBS are preceded by an infectious respiratory or gastrointestinal illness (1). GBS has also been reported after influenza vaccinations (2), although the risk appears extremely low, with studies since the original reports of association with swine flu vaccine having not confirmed a link. Molecular mimicry between microbial and axolemmal surface molecules after *Campylobacter jejuni* infection is known to represent the pathophysiological basis of neural involvement leading to symptoms of axonal GBS (2). In chronic inflammatory demyelinating polyneuropathy (CIDP), there is paucity as well as heterogeneity of data on preceding infections. Proportions as high as 30% have been reported in the earlier literature, although more recent studies have suggested 10-20% (3-9). A pathophysiological link between preceding infection and onset of CIDP remains unproven. No specific characteristics of post-infectious CIDP had been described from previous reports. However, a recent national Italian CIDP database study found that onset may follow an infectious illness in about 10% of cases, and vaccination in about 1.5% of cases (10). In addition, this study indicated that post-infectious CIDP may more commonly present as “acute-onset CIDP” (10), defined by disease onset over <8 weeks, as opposed to classic CIDP which, by definition, develops over > 8 weeks. This finding remains unconfirmed in other cohorts . It is otherwise also unknown whether post-infectious and post-vaccination CIDP may present with other clinical features or distinguishing characteristics on investigative tests. This may have diagnostic, prognostic and management implications for affected subjects.

We aimed to analyse our combined cohorts of patients with CIDP in relation to the frequency of infection and vaccination prior to disease onset and attempted to compare affected patients to those without antecedent events.

Methods.

We retrospectively studied electronic hospital records of adult patients aged 18 years or above with a diagnosis of "definite" or "probable" CIDP as per the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) Guidelines (11), attending the Inflammatory Neuropathy Clinic, University Hospitals Birmingham, U.K for the period 2013-2020. Similarly, we studied records for the period 2007-2016 of patients registered on the multinational Serbian CIDP database meeting requirements for "definite" or "probable" CIDP. Exclusion criteria included presence of IgM monoclonal protein with anti-myelin-associated-glycoprotein (MAG) activity, suspected or confirmed genetic neuropathy with classical slowly progressive course, clinical and electrophysiological picture compatible with multifocal motor neuropathy and clinical and immunological phenotype consistent with chronic ataxic neuropathy with ophthalmoplegia, M-protein and disialosyl antibodies.

The Birmingham Inflammatory Neuropathy Clinic is an adult U.K. tertiary regional referral centre for dysimmune neuropathies. The Serbian database includes CIDP patients diagnosed from tertiary centres from Serbia, Republic of Srpska (Bosnia and Herzegovina) and Montenegro.

Each case was characterised for pattern of motor weakness, disease symmetry, reflexes and sensory dysfunction, so as to establish the CIDP diagnosis and the subtype classification, as per the EFNS/PNS Guidelines (11). Electrophysiology had been performed as per routine procedures and fulfilment of electrodiagnostic subtype category had been determined in each case by was performed a physician with extensive experience in electrophysiology.

We determined demographic characteristics, CIDP subtype (typical vs. atypical [Lewis-Sumner syndrome, pure motor, pure sensory, distal type]), mode of presentation (acute-onset

vs. classic chronic onset), Inflammatory Neuropathy Cause and Treatment (INCAT) score, cerebrospinal fluid protein levels (normal ≤ 50mg/dL). Response to treatment was defined as a one-point or greater improvement of the INCAT score, based on the previously published minimum clinically important difference (12, 13) . The presence of a preceding infection, respiratory or gastrointestinal, or of any vaccination, was ascertained in the 6 weeks prior to symptom onset, from the medical records for the Birmingham patients and from a structured questionnaire, based on available records, at the time of retrospective inclusion for the Serbian patients. The 6-week time frame was arbitrarily decided in view of previous studies (5, 10). Disease onset, but not relapses, were considered in relation to antecedent events. Patients were not re-contacted for additional history-taking. We did not consider serological confirmation of recent infection for inclusion.

This study was approved by both relevant institutional boards, as part of wider retrospective analyses of these cohorts. This was by the Ethical Board of the Neurology Clinic, Clinical Centre of Serbia (No. 29/XII-24, 27th December 2017) and was part of a retrospective audit on CIDP approved by the University Hospitals of Birmingham Clinical Audit Office (CARMS no. 15747, December 2019).

Comparison of proportions were performed by Fisher Exact tests and odds ratios (OR) and 95% confidence intervals (CI) were calculated. Comparisons of means were performed by T-tests.

Results.

We included 268 patients with a diagnosis of "definite" or "probable" CIDP. Of those, 129 were from the Birmingham Inflammatory Neuropathy Clinic, selected from a total of 156 patients with at least "possible CIDP". One hundred and thirty-nine were included from the Serbian CIDP database, selected from 181 patients with at least "possible CIDP". We hence included 79.5% of our combined total cohort of subjects .

Six patients (2.2%) had "probable CIDP" and 262 (97.8%) had "definite" CIDP. A majority (174; 64.9%) had typical CIDP, and the remainder had atypical forms (Lewis-Sumner syndrome, pure motor and pure sensory). There were 84 females and 184 males (ratio of 1:2.19). Mean age at onset was 53.02 years (S.D.: 15.69).

Of the included subjects, 28 (10.4%) had an antecedent event in the 6 weeks prior to onset of CIDP. Twenty-five (9.3%) had a prior respiratory infection (20) or gastrointestinal infection (5), with documented symptoms as well as need for medical input and treatment. Three subjects (1.2%) had received influenza vaccination in the same time-frame prior to disease onset. None of the 28 subjects with an antecedent event had experienced neurological symptoms previously after infection or vaccination. In none was a specific previous infection confirmed. There was no difference between the rate of preceding infections or vaccinations between the 2 CIDP cohorts ($p = 0.20$ and $p=0.10$, respectively). The 2 studied cohorts were otherwise comparable in demographics and disease characteristics.

We compared the 28 patients with antecedent respiratory or gastrointestinal infection, or vaccination, with the 240 patients without such antecedent events. The results are detailed in Table 1. There were no significant differences between the groups with and without antecedent events with regards to gender distribution, CIDP disease subtype, association with

diabetes, frequency of other associated autoimmune disorders, cerebrospinal fluid (CSF) protein level elevation rates, mean Inflammatory Neuropathy Cause and Treatment (INCAT) disability scores pre-treatment and proportions of treatment-responders as defined by an improvement of the INCAT disability score of at least 1 point. However, a greater proportion of patients with antecedent events presented with acute-onset CIDP, than those without antecedent events. Onset of CIDP with antecedent events otherwise occurred earlier by about a decade compared to that without antecedent events.

Discussion.

In this study, we confirmed previous reports that a low proportion of about 10% of patients presenting with CIDP had a history of a previous infection or underwent a vaccination in the 6 weeks prior to disease onset. This consistent finding in multiple series suggests, but does not prove, the possibility of an association between the antecedent event and the onset of CIDP. The finding of a significantly greater proportion of subjects with antecedent events developing acute-onset CIDP is in keeping with the results from the recent Italian CIDP database study (10). That study described a greater proportion of cases with cranial nerve involvement, which we could not confirm in our study, as none of our patients with antecedent event demonstrated cranial neuropathies. It is noteworthy that a principal distinguishing clinical characteristic separating GBS and acute-onset CIDP is the usual absence of cranial nerve involvement in the latter (14). The details of the mode of onset in the Italian patients with cranial neuropathies amongst those with antecedent events was not detailed (10). We found that our CIDP patients with antecedent events presented about 10 years younger than those without antecedent events. The reasons for this are uncertain. Previous studies found a higher rate of antecedent events in children compared to adults, of 27% vs. 17% (5, 6). CIDP is a disease of increasing prevalence with greater age (15), and it is possible that post-infectious or post-vaccination auto-immunity affects predominantly younger patients as shown in some studies in post-*Campylobacter jejuni* enteritis-related axonal GBS (16). Similar descriptions of a higher incidence of infection in younger subjects have been made for GBS following cytomegalovirus (CMV) (17) and Mycoplasma pneumoniae (18). Immune tolerance with repeated exposure may be an explanation for lower rates of CIDP after antecedent events in older subjects. Lesser exposure to implicated pathogens in older patients represents another potential explanation to this finding. Post-vaccination GBS has been reported with a median age of 15 years in one study of Korean

patients (19). We are not however aware of multiple consistent reports of predilection for younger age groups with regards to GBS following vaccination, which remains an infrequent occurrence.

Of potential relevance and interest to the question of CIDP onset after antecedent events is the comparison with inflammatory central nervous system (CNS) disease, where post-infectious acute-disseminated encephalomyelitis (ADEM) is known to occur predominantly in children, whereas multiple sclerosis affects mainly adults (20). Although both fall within the spectrum of dysimmune polyradiculoneuropathies and demonstrate considerable overlap of clinical features, GBS and CIDP differ in their onset and course as well as by their therapeutic responses to corticosteroids, present in the latter but not in the former (21). There is an overlap between the 2 disorders in that subacute forms may evolve over a time course that is overlapping between that of GBS and CIDP (22), as GBS may occur with treatment-related-fluctuations mimicking CIDP (23), and as CIDP itself presenting on occasion with a GBS-like acute-onset (14). Hence, strict separation of GBS and CIDP, although desirable and straightforward in most cases, is not always easy in clinical practice. How this spectrum may relate to the underlying pathophysiological mechanisms remains unknown.

The current findings, consistent with previous reports and with a greater proportion of acute-onset cases in subjects with antecedent events from the Italian CIDP Database Study (10), suggest that the pathophysiological mechanisms involved in these cases may be different from those in CIDP without antecedent events. Our results highlight the infrequent occurrence of preceding vaccination prior to onset of CIDP, for which a definite link remains unlikely. This study may be limited by recall bias as CIDP is a chronic illness and documented preceding events depend often exclusively on patients' and/or relatives'

recollection when medical attention was not sought. Another limitation may relate to incomplete recording in the medical records on which the current findings rely.

Further prospective, multinational, longitudinal cohort studies may help compare the precise disease course of CIDP patients with and without antecedent events . Long-term follow up, both from the clinical and electrophysiological point of view, of patients with CIDP is also of interest. This would be useful from a prognostic and therapeutic perspective, if patients with antecedent events have higher remission rates, shorter remission times, or lesser need for long-term treatment.

Abbreviations: ADEM: acute disseminated encephalomyelitis; CIDP: chronic inflammatory demyelinating polyneuropathy; GBS: Guillain-Barré syndrome; INCAT: Inflammatory Neuropathy Cause and Treatment.

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Table 1. Comparison of patients with and without antecedent infection or vaccination from the combined Birmingham and Serbian CIDP cohorts.

	Patients with antecedent infection or vaccination	**Patients without antecedent infection or vaccination**	**Odds Ratio (95% CI)**	**p value**
Number of Subjects	28	240	NA	NA
Male: Female	15:13	168:72	0.49; (0.22-1.09)	p = 0.09
Mean age of onset (years) [SD]	44.25 [17.36]	54.05 [15.19]	NA	***p < 0.005***
Acute-Onset CIDP	12/28 [42.9%]	29/240 [12.1%]	5.46; (2.35-12.68)	***p < 0.001***
Atypical CIDP	12/28 [42.9%]	85/240 [35.4%]	1.37 (0.62-3.03)	p = 0.53
Associated Diabetes	2/28 [7.1%]	50/240 [20.8%]	0.29; (0.07-1.29)	p = 0.13
Other Associated Autoimmune Disease	5/28 [17.9%]	45/240 [18.8%]	0.94; (0.34-2.61)	p = 1
CSF protein > 50 mg/dL	18/19 [94.7%]	92/121 [76%]	(5.67; 0.73-44.36)	p = 0.07
Mean INCAT disability score at onset [SD]	4.07 [2.51]	3.90 [2.28]	NA	p = 0.70
Treatment responders	18/27 [66.7%]	140/184 [76.1%]	5.46; (2.35-12.68)	p = 0.34