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Commentary

Novel Therapeutic Avenues for Chronic Inflammatory Demyelinating Polyneuropathy: The Difficulties of Disease Diversity

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a relatively rare, treatable, peripheral nerve disorder of autoimmune basis. Its prevalence is probably only around 5 per 100,000, with an incidence of <1 per 100,000 per year (Rajabally et al., 2009). CIDP causes in its typical form, symmetrical proximal and distal weakness of the 4 limbs. There are several atypical forms. These are, importantly, not much more uncommon than typical CIDP and have varied presentations, including, pure motor, pure sensory, focal or multifocal subtypes (Van den Bergh et al., 2010). Onset is usually progressive >8 weeks although acute-onset forms are well documented. Available evidence-based treatments for CIDP include corticosteroids, immunoglobulins and plasma exchanges. There remains a proportion of patients who remain refractory to these therapies, individually or in combination. Although several immunosuppressant drugs have been tried, there is currently no evidence of efficacy for any of them. Newer therapies require consideration, particularly for refractory patients but also to provide more options generally for this patient population.

In this issue of *EBioMedicine*, Faucard et al. (2016) describe their work on 51 patients with CIDP from 2 centres, investigated for the pro-inflammatory protein MSRV-Env (Multiple Sclerosis Associated Retroviral element), encoded by the Human Endogenous Retrovirus HERV-W. MSRV-Env had been previously detected in a small number of patients with CIDP used as neurological controls in a study of patients with multiple sclerosis (MS). A heterogeneous group of patients with other neurological diseases as well as healthy blood donors was used as controls. Detailed clinical description was not available although the majority (24 subjects) had symmetrical sensory and motor deficits, 9 had Lewis–Sumner syndrome (LSS) and one pure sensory CIDP, of unspecified subtype. Nearly half received immunoglobulins, one in six was on immunosuppressants and over a quarter, were untreated, although their disease activity status was not specified. Mean disease duration was 7 years with however, a very wide range of 9 weeks up to 42 years. MSRV-Env expressions were found significantly higher in CIDP patients than in healthy blood donors and, of note, inversely correlating with disease duration. The expression was not high in neurological controls. IL6 and CXCL10 chemokine levels were both significantly higher in CIDP than in all controls, this being for the former, a contradictory finding in comparison to previous studies. MSRV-Env expression was raised in 5/7 sural nerve biopsies from CIDP patients but in neither of 2 control biopsies. In a further experiment, the authors found that the pro-inflammatory effects of MSRV-Env on human Schwann cells as measured by IL6 and CXCL10 concentrations, were inhibited by the humanized IgG4 subclass monoclonal antibody, GNbAC1. They concluded that the autoimmune reaction in CIDP may result from TLR4-driven activation of innate immunity by MSRV-Env protein, making it a possible therapeutic target and raising the possibility that GNbAC1 may represent a potential innovative treatment for CIDP. This is already the focus of phase II trials in MS (Derfuss et al., 2015).

These findings are interesting with conceivable implications for future CIDP research. One of the main issues with the study, partly acknowledged, is that of small numbers. Furthermore, the breakdown per CIDP subtype is imprecise, and leaves still lesser numbers which prevents any meaningful analysis per subgroup. This is however of paramount importance as different CIDP subtypes may have varying underlying pathophysiology, the disorder representing a spectrum of related conditions rather than an entity *per se* (Mathey et al., 2015). Although thought to be both implicated, relative contributions of T-cell and antibody-mediated mechanisms are uncertain. It has been suggested that Lewis–Sumner syndrome for instance may involve cellular immunity as opposed to typical CIDP which may instead relate to antibody-mediated mechanisms (Kuwabara et al., 2015). As a result, it is possible that Lewis–Sumner syndrome may be less responsive to main CIDP therapies (Kuwabara et al., 2015). In recent years, studies on antibody specificity in CIDP have focused on the node of Ranvier (Mathey et al., 2015). A minority of CIDP patients, some with specific phenotypes and lack of response to usual therapies, have been identified as demonstrating antibodies to a number of nodal proteins. As an illustrative example, anti-neurofascin-155 IgG4 antibody-positive cases, with a characteristic phenotype of early-onset ataxia, tremor

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and central nervous system involvement, are few in number (<10%), unresponsive to steroids or immunoglobulins (Devaux et al., 2016), although may show some response to the anti-CD20 monoclonal antibody, rituximab (Querol et al., 2015).

The heterogeneity of CIDP is becoming more and more evident and studies combining CIDP patients for search of biomarkers and potential therapeutic targets, are in these circumstances of uncertain value, particularly if numbers analysed are small. The tentation to use entire cohorts is understandable for a disorder of such low prevalence, although results obtained by combining cases of disorders, of ultimately different pathophysiological basis, will always be difficult to interpret.

The comparison with MS by Faucard et al. (2016) is interesting, although considerable progress has been achieved in MS itself in terms of phenotyping and subsequent differentiation of disease subtype pathophysiological differences. Studies in MS have otherwise shown that MSRV-Env expression correlates with plaque activity (Mameli et al., 2007), clinical progression and prognosis (Sotgiu et al., 2010). The same does not appear proven for CIDP, the current study demonstrating higher expression in early disease stages in a heterogeneously treated cohort with a proportion of untreated subjects possibly in remission, with very limited nerve histopathological samples. These samples themselves, as opposed to MS, furthermore originate from a nerve not necessarily affected by the disease. The results may suggest possible diagnostic utility as biomarker or marker of early disease activity and could also reflect efficacy of administered treatments, but whether they indicate a definite potential therapeutic target in CIDP is uncertain and will require further study in larger, well-defined and homogeneous patient cohorts.

The differentiation of the various forms of the CIDP entity, although previously felt of little importance for clinical practise, may become crucial in the initial essential task of delineating the different disease subtypes for such future research. Splitting rather than lumping appears the way forward to adequately understand CIDP pathophysiology in its likely wide diversity, although will clearly compound the difficulties of studying this low-prevalence disorder and may unfortunately as a result, also delay therapeutic progress.

Disclosure

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