Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an uncommon but treatable cause of acquired peripheral neuropathy affecting at least 1 to 2 per 100,000 people.1,2 The concept of the disease has grown since Austin reported cases of recurrent steroid responsive neuropathy,3 aided by the description of increasingly large series by Dyck,4 McLeod,5 and later authors.6-8 In the absence of a diagnostic laboratory test, arbitrary clinical, neurophysiological, and pathological criteria have been published,9 found excessively restrictive, and made more liberal.10

The resemblance of CIDP to Guillain-Barré syndrome and its response to immunosuppressive treatment led inevitably to the proposal that it has an autoimmune cause, but supportive evidence has remained elusive.11 Circumstantial evidence came from the demonstration that the model experimental autoimmune neuritis sometimes develops into a chronic relapsing form in rats and especially in rabbits.12,13 These models faithfully reproduced the chronic inflammatory changes in the endoneurium and onion bulb formation seen in CIDP. They were induced with whole myelin. Acute experimental autoimmune neuritis can be induced by P2 protein, which does not have an extracellular domain, and by P0 glycoprotein and peripheral myelin protein 22, both of which do. The presumption is that one of these or possibly another myelin antigen can induce chronic experimental autoimmune neuritis and is therefore a candidate autoantigen for CIDP. Previous attempts to identify immune responses to any of these candidate autoantigens in CIDP have been relatively unsuccessful with responses being identified in 16% or fewer patients.11,14

In this issue, Yan and colleagues provide persuasive evidence that antibodies to P0 glycoprotein are present in the serum of a respectable minority of patients with CIDP (6 of 21 cases or 28%) and, when present, have the potential to cause demyelination (four of six sera).15 The positive CIDP sera produced intense labeling on a Western blot of a 30 kDa band that had the N terminal sequence of P0 and four also bound the myelin sheath. The positive staining pattern could be absorbed with the 30 kDa band cut from the immunoblot. The four sera that stained the presumed P0 band and the myelin sheath also produced partial conduction block and demyelination following injection into the rat sciatic nerve. These observations strongly support the authors’ conclusion that P0 is the autoantigen responsible for CIDP in these patients. Three factors may have contributed to their success: (1) They selected sera from untreated patients with active disease; (2) they produced commendably clean immunoblots on myelin proteins; and (3) they have unique experience of performing injections of 20 µL volumes via a 30-gauge needle into the rat sciatic nerve without producing unacceptable amounts of artefactual damage. Their results confirm that antibodies against P0 glycoprotein are present in a minority of patients with CIDP and demonstrate for the first time that these human antibodies have demyelinating ability and so are likely to play a part in the pathogenesis of CIDP.

Like all good experiments, that of Yan and colleagues raises as many questions as it answers. Are the antibodies a response to, or the primary cause of the demyelination? Are they present in sera from patients with other inflammatory neuropathies such as vasculitic neuropathy or noninflammatory demyelinating neuropathies? What happens to the antibody tier during the course of the disease and in response to treatment? What are the epitopes against which the responsible antibodies are directed? The heavily glycosylated extracellular domain is the likely target and must be shared by rat myelin. Antibodies alone are not a sufficient explanation for the production of demyelination because they would not penetrate the blood-nerve barrier unless it were first rendered leaky. It is likely that a T-cell response is also involved. Biopsies demonstrated T cells in active lesions in CIDP,8,16,17 and circulating T cells responded to a P0 peptide in 3 of 13 cases.18 The antibodies to P0 glycoprotein in Yan and colleagues’ study were mainly IgG1, a subclass that implies T-cell activation. Presumably, as in most immunological reactions, both B- and T-cell mechanisms are involved. The search must continue for autoantibodies to additional myelin antigens that might account for the pathogenesis of other cases of CIDP. Among possible candidates, peripheral myelin protein 22 is a favorite since it also has a glycosylated extracellular domain and induces experimental autoimmune neuritis.19 Immunoblot and ELISA identified antibodies to PMP22 or its extracellular domain peptides in 7 of 17 patients with CIDP.20 However, in another study antibodies were found not only in three of six sera from CIDP patients but also in the sera of patients with Charcot-Marie Tooth disease types 1 and 2,21 so this requires further investigation.

During the past decade research into the pathogenesis of inflammatory neuropathy has largely focussed on antibodies to glycolipids. Fisher syndrome is almost always associated with IgG antibodies to ganglioside GQ1b which is preferentially located on ocular motor nerves.22 Acute motor axonal neuropathy is associated with IgG antibodies to ganglioside GD1a which is
preferentially recognized by monoclonal antibodies on motor rather than sensory axons.\textsuperscript{23} While in these special situations the evidence for the importance of antibodies to gangliosides is indeed strong, such antibodies are not found in most patients with the common acute inflammatory demyelinating polyradiculoneuropathy form of Guillain-Barré syndrome or in CIDP. In multifocal motor neuropathy some but by no means all patients have IgM antibodies to ganglioside GM1, but their role in pathogenesis is far from clear. In other variants of CIDP the search for antibodies to gangliosides has been largely negative.\textsuperscript{11}

The study by Yan and colleagues should refocus attention on the potential role of cell-mediated immunity to myelin proteins in peripheral nerve demyelinating disease. The goal should be to identify immune responses that will identify homogeneous groups. This might provide a logical classification of types and variants of CIDP, which now include (in addition to multifocal motor neuropathy) predominantly sensory forms,\textsuperscript{24} distal acquired demyelinating symmetric neuropathy,\textsuperscript{25} multifocal acquired demyelinating motor and sensory motor neuropathy,\textsuperscript{26} and multifocal inflammatory demyelinating neuropathy.\textsuperscript{27,28}

Defining epitopes that make sense of these CIDP variants will be a necessary preliminary to discovering what breaks tolerance and causes autoimmune neuropathy. If this problem cannot be solved for peripheral nerve demyelinating disease, what hope is there for discovering the cause of multiple sclerosis?

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parkin and parkinson’s: more than homonymy?

the existence of monogenic forms of parkinson’s disease (pd) is now well established.1 at least 6 loci/genes have already been identified, including parkin, initially described as responsible for autosomal recessive juvenile parkinsonism in japanese families.2 research so far has shown that parkin mutations are the major cause of a clinically variable form of parkinsonism, similar to idiopathic pd but characterized by the absence of lewy bodies.3 its function, recently elucidated, is related to the ubiquitin-proteasome pathway.4,5 the study by farrer’s group6 in this issue complicates the matter. it not only suggests the possibility of dominant inheritance of parkin-related pd but also shows the neuropathological features of idiopathic pd in a parkin case.

the autosomal recessive juvenile parkinsonism patients originally described had early-onset (before age 40 years) parkinsonism and mild dystonia, slow disease progression, marked response to levodopa (l-dopa), early and severe l-dopa-induced dyskinesias, hyperreflexia, and sleep benefit.3 neurodegeneration was restricted to the dopaminergic neurons in the substantia nigra pars compacta; and lewy bodies, the histopathological hallmarks of idiopathic pd, were absent.7 a wide variety of parkin mutations has since been found in nearly 50% of familial cases with early-onset autosomal recessive parkinsonism and in isolated early-onset cases in populations of different ethnic origins.8–12 onset as late as age 58 years has, however, been observed. the clinical spectrum, broader than that initially described in japanese families, includes phenotypes similar to dopa-responsive dystonia or resembling idiopathic, although slow-progressing, pd.11–15 the possibility that the parkin gene may play a role in the cause of the more frequent typical late-onset pd was raised by klein and collaborators14 in a study of a large parkin pedigree from south-tyrol, in which onset occurred in adults as old as 64 years. the few autopsy reports published so far have confirmed the absence of lewy bodies in parkin-related disease cases and support the hypothesis that parkinsonism due to parkin gene mutations and idiopathic pd result from distinct etiological causes.15–17

farrer and colleagues6 describe a novel 40 bp deletion in exon 3 of the parkin gene in 2 families (ph and pw) with both atypical and classic parkinsonism and apparently autosomal dominant inheritance. furthermore and more importantly, the authors report the presence of lewy bodies in a parkin-related proband with compound heterozygous mutations, diagnosed as having typical pd. this is the first evidence indicating that compound heterozygous parkin mutations may lead to early-onset pd with lewy body pathology.

the novel deletion in exon 3 is thought to be dominant because disease transmission is autosomal dominant in both families. furthermore, to postulate the existence of recessive mutations implies that each family carries at least four different parkin-related disease haplotypes. this is very unlikely. however, pseudodominance has already been observed in at least 3 families, 1 from japan and 2 from italy, in which three different mutant parkin alleles were detected in patients from two successive generations.18–20 thus, although a second mutation was not found in any of the affected individuals described by farrer and colleagues6 (with the exception of the neuropathological case pw3), the possibility that such mutations exist in the yet unexplored promoter and/or intronic regions of the parkin gene cannot be formally excluded. previous family studies have also shown that heterozygous carriers of parkin mutations in families in which patients are compound heterozygotes are not affected.12 this argues against dominance at least for known mutations. in both families described by farrer and colleagues,6 several unaffected subjects carried the exon 3 deletion, raising doubts about its dominance. however, except for proband ph1, who died at age 93 without any clinical or neuropathological signs of parkinsonism, this may reflect the variability in age at onset (24–64 years) associated with the mutation. follow-up studies of healthy carriers in families ph and pw will help to resolve this ambiguity. it has been speculated that some parkin mutations might be more deleterious than others and might even be dominant.14,19,20 this has been observed in other disorders with both autosomal dominant and autosomal recessive inheritance. farrer and colleagues6 suggest that the hemizygous 40 bp exon 3 deletion, unlike other parkin gene mutations, may confer increased susceptibility to both atypical and typical parkinsonism in combination with other genetic or environmental factors. two noncarrier members of family ph indeed have essential tremor, which might be a sign of an additional genetic risk factor in this family.

positron emission tomography has provided some evidence that parkin mutations may have dominant effects on metabolism. [18f]-6-fluoro-dopa uptake in caudate and putamen, a measure of the integrity of dopaminergic neurons, was reduced in asymptomatic carriers of heterozygous deletions in the parkin gene, showing for the first time the presence of pre- or subclinical disease that may confer increased susceptibility to parkinsonism.21,22 interestingly, striatal [18f]-6-fluoro-dopa uptake decreases to a similar extent in patients with mutations in the parkin gene and in those with idiopathic pd.21,22 in the study by hilker and colleagues,21 the decrease was greater in the posterior
part of the putamen, a pattern considered to be fairly specific for the idiopathic form of PD. Thus, the degeneration of dopaminergic neurons seems to be the same in parkin-related patients and classic PD cases, although effects of parkin mutations on postsynaptic dopaminergic neurons are also observed.21 Given the striking overlap of the clinical and metabolic features of parkin-related parkinsonism and idiopathic PD, the report by Farrer and colleagues6 of a compound heterogeneous parkin-related case presenting Lewy body pathology should not necessarily be surprising. It needs to be confirmed, however, by complementary neuropathological studies, particularly in late-onset parkin cases, but adds a further element to an increasing body of evidence suggesting that parkin-induced parkinsonism and idiopathic PD are more closely related than previously imagined.

Elucidation of the physiological role of Parkin, the protein encoded by the parkin gene, may provide essential information. The structural motifs of this protein, its N-terminal ubiquitin-like motif, and its C-terminal RING-IBR-RING domain, identified in several proteins involved in the ubiquitin-proteasome pathway, provided the first hints to its function.2 Parkin is today known to have E3 ubiquitin-ligase activity, which mediates the ubiquitylation and subsequent degradation of specific, but for the most part unknown, proteins.4,5 The ubiquitin-proteasome pathway has long been suspected of playing a role in the cause of PD. Lewy bodies are heavily ubiquitylated cytoplasmic inclusions reactive to antibodies against ubiquitin carboxyl-terminal hydrolase L1.24 A missense mutation in the ubiquitin carboxyl-terminal hydrolase L1 gene appeared to be associated with PD in a single family.25 α-Synuclein, another major component of Lewy bodies, is responsible for some cases of autosomal dominant parkinsonism.26 These findings together with the recent exciting discovery of the direct involvement of Parkin in the ubiquitylation of a glycosylated form of α-synuclein,27 converge toward the idea that Parkin may be a component of a complex pathogenetic pathway leading to PD. However, it remains to be elucidated how different mutations in the parkin gene, which apparently result in a similar loss of function, can lead to different genetic and neuropathological features.

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