A way out of the maze

Campylobacter jejuni gene polymorphisms define
Guillain–Barré syndrome

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In the last decade, experimental and clinical studies have laid a solid foundation under the molecular mimicry hypothesis to explain the pathogenesis of the Guillain–Barré syndrome (GBS). Bacterial or viral infections and genetic host factors are important. In brief, in the weeks following infection with known and unknown micro-organisms, previously healthy persons develop a devastating acute inflammatory disease of the peripheral nervous system. The immune system of the patient is apparently deceived by bacterial ganglioside-like epitopes that mimic peripheral nerve components, thereby triggering a cascade of inflammatory responses against peripheral nerves. Cross-reactive anti-ganglioside antibodies may be directed against myelin, Schwann cell components, and axonal membranes. Mechanisms by which damage is induced include activation of inflammatory cells by interaction of antibodies with Fcγ receptors (FcγRs) on macrophages and γδT cells. Efficient FcγR-IgG interactions increase efficacy of leukocyte effector functions such as phagocytosis, cellular cytotoxicity, and cytokine production. FcγRIII genotypes are host factors that could modify severity of GBS. Also, an association has been found between polymorphisms in genes that are involved in immune homeostasis and the presence of anti-ganglioside antibodies in GBS. Most of these host factors and many aspects of antecedent infections are not fully known or understood.

As the inflammatory process is self-limiting, GBS can be considered a hit-and-run disease of the peripheral nervous system. By definition, in 95% of patients, the nadir is reached within 4 weeks and in up to 70% within 2 weeks after onset. Treatment with plasma exchange or IV human immunoglobulins within 4 weeks of onset hastens recovery. Interestingly, early IV administration of methylprednisolone has no additional benefit.

In this issue of Neurology, Koga et al. provide important insight into the association between a bacterial gene that regulates the biosynthesis of cell surface lipo-oligosaccharides (LOSs) of Campylobacter jejuni and GBS subtypes. They hypothesized a relationship between polymorphisms in the Campylobacter cst-II gene and autoantibody reactivity and GBS subtypes. The cst-II gene is a likely candidate as it encodes sialyltransferase, an important determinant of the variation in expression of ganglioside epitopes, as the sialylation type determines ganglioside classification. cst-II polymorphisms leading to different enzyme activity could thus change the ganglioside epitopes on LOSs with consequences for autoantibody reactivity. They analyzed bacterial strains from 105 GBS patients and 65 enteritis control subjects for cst-II gene frequency and polymorphisms and further analyzed ganglioside epitopes on LOSs of C. jejuni. Next, these findings were correlated with the anti-ganglioside antibody profile and clinical features of the patients with GBS. The two main conclusions were a more frequent occurrence of the cst-II gene in the neuropathic bacterial strains and a relationship between cst-II gene polymorphisms and different ganglioside epitopes. The latter finding was clinically reflected by serum antibodies against these gangliosides and expected subtypes: GBS syndrome vs Fisher syndrome.

The study represents a new step in the unraveling of the molecular mimicry of GBS after C. jejuni infection. The results provide important evidence that genetic polymorphisms of antecedent infectious agents determine the production of specific autoantibodies and clinical manifestations in a postinfectious disorder. Previously, the same group demonstrated that different bacteria may cause the Fisher subtype of GBS with anti-GQ1b antibodies being present in most patients. In that study, they could link anti-
GQ1b autoantibody production and GQ1b-mimicking LOSs on *C. jejuni* and on *Haemophilus influenzae*.

However, for the current study, some caution seems justified. First, the strong points are positive correlations, but between neuropathic and enteritic strains, these were not always as strong as might have been theoretically expected. Also, some overlap between *cst-II* polymorphisms and ganglioside epitopes in *C. jejuni* and GBS subtypes was demonstrated. This could partly be explained by technical issues. Other explanations are involvement of other genes in sialylation of LOSs or currently unidentified host factors that could explain why not all GM1- or GQ1b-containing *C. jejuni* strains lead to GBS. Second, during the course of infection, *cst-II* genes of *C. jejuni* may undergo mutations, leading to amino acid substitution, change of sialyltransferase function, and different sialylation of LOSs.11 *C. jejuni* organisms have at least five mechanisms to vary the outer core of LOSs. Variation of cell surface structures could have a survival advantage for bacteria by evading the immune attack.11 It is not known whether this phenomenon could play a significant role in infections that precede GBS.10

Finally, for GBS, the rule of “infection gone, damage done” holds true. GBS is essentially a postinfectious disease where damage to the peripheral nervous system is initiated in the period of disappearance of the infection and before the occurrence of neuropathic signs. Immune modulation has no effect after 4 symptomatic weeks.7,8 To be more successful earlier, treatment strategies must counteract dysregulation of the immune system to prevent severe inflammation and to promote axonal regeneration. Such treatments are not yet on the horizon.

Yet, results of this study show the way out of the maze of the molecular mimicry in GBS. Implications are wider than for GBS alone. Variable cell surface glycoconjugates are present in many more bacteria including *Streptococcus* spp. and *Neisseria meningitidis*.11 If rapid analysis of the molecular structure of capsular polysaccharides of pathogenic microorganisms becomes available, patterns of virulence could be predicted and more specific treatment strategies for neurologic infections developed.

References