GBS, CIDP OR WHAT?
And Does It Matter?

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Introduction

Guillain Barré syndrome (GBS) is defined and separated from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) by the time people take to reach their worst. By an arbitrary definition, patients who reach their worse within four weeks are said to have GBS. Patients who reach their worst in more than eight weeks are diagnosed as having CIDP. In between are a small group of patients who reach their worst between four and eight weeks and are said to have subacute inflammatory demyelinating polyradiculoneuropathy (SIDP). GBS and CIDP have also been divided up by their clinical features into different sub-types. Finally, related disorders, the Fisher syndrome and Bickerstaff's brainstem encephalitis, and overlap syndromes have been described. My talk will describe these different syndromes and how they dictate the type of treatment and final outcome.

Guillain Barré syndromes

- Acute inflammatory demyelinating polyradiculoneuropathy
- Acute motor axonal neuropathy
- Acute motor and sensory axonal neuropathy
- Fisher syndrome
- Bickerstaff's encephalitis
- Overlap syndrome

Acute inflammatory demyelinating polyradiculoneuropathy

This is by far the commonest form of GBS in the USA and Europe. It causes the rapid development of weakness and loss of feeling. The tendon reflexes disappear. It affects the limbs and may affect the swallowing muscles and breathing muscles. It is caused by damage to and loss of the myelin sheath which insulates the core or axon of the nerve fibre. Inflammatory cells invade the nerve tissue and cause phagocytic cells, called macrophages, to digest myelin sheaths leaving the axons naked. The process is triggered by infections with bacteria like Campylobacter which causes diarrhoea, and cytomegalovirus or Epstein-Barr virus, which cause glandular fever. According to one hypothesis the T-lymphocytes react to an antigen on the surface of the bacterium, become activated and get into the nerve fibre where they release chemicals called cytokines. These cytokines cause the macrophages to attack the myelin sheath. Fortunately, the cells which make the myelin sheath, called Schwann cells, have an immense capacity to repair the damage so that substantial recovery is the rule. Unfortunately, severely affected patients also have damage to the central conducting part of the nerve fibre called the axon. This damage is the reason why some patients are left with permanent weakness.

Acute motor axonal neuropathy

In the early 1990s, the Hopkins Group described acute motor axonal neuropathy occurring in summer epidemics in northern China. These patients are very similar to ordinary GBS in having rapidly developing weakness and lost tendon reflexes but they do not have any loss of feeling. As in AIDP, the cerebral spinal fluid (CSF) protein is increased, but the neurophysiology tests are different. They show normal nerve conduction speed whereas the speed of conduction is slowed in AIDP. These and other features indicate that it is the axons and not the myelin sheaths which are damaged in AMAN. Post mortem studies of the pathology establish that the axon and not the myelin sheaths are the target of the immune attack.

These patients usually have had a preceding Campylobacter infection. Campylobacter is the commonest cause of diarrhoea throughout the world. On its coat it has a special sequence of sugars called ganglioside GM1. The axon has the same GM1 sugar pattern. Consequently when the immune system generates antibodies against GM1 on the Campylobacter these antibodies are able to attack the axons and cause the axons to degenerate. We also encounter patients with similar axonal pathology who have sensory loss. These are called acute motor and sensory axonal neuropathy.

Related and overlap syndromes

In 1956, Miller Fisher in Boston described an acute illness which he compared to GBS, characterised by loss of eye movements, in-coordination and loss of tendon reflexes. Some patients had face or swallowing weakness but none had limb weakness. As in GBS, the CSF protein was raised. Chiba in Japan was the first to show that antibodies to the GQ1b pattern of sugars are present in most patients with Fisher syndrome. Willison in Glasgow has shown that these antibodies will damage motor nerve terminals and are the likely cause. Some Campylobacter bacteria have the GQ1b sugars in their coats.

About the same time, Edwin Bickerstaff in Birmingham described similar patients who had other features indicating that the pathology was not just in the peripheral nerves but also in the brain stem which joins the cerebral hemispheres to the spinal cord. These patients differed from Fisher syndrome in having drowsiness, extensor plantar responses (an abnormal reflex which tells us that the central nervous system is involved) and raised CSF cell counts. Yuki in Japan has shown that many of these patients also have antibodies to GQ1b.

In real life, these syndromes may overlap. So we see patients with GBS who lose their eye movements and overlap with Fisher syndrome. We also see patients who have a combination of brain stem encephalitis and peripheral neuropathy, thus overlapping either with GBS or with Fisher syndrome.

How common are these sub-types?

In the USA and Europe, Fisher syndrome accounts for about 7% of patients. In a large European-American trial in the 1990s we were able to characterise 68% of patients as having AIDP, 3% as having AMAN or AMSAN, but another 3% had inexcitable nerves which might have been due to either. We also found that the most common antecedent infection was Campylobacter jejuni at 30%, with cytomegalovirus accounting for 10%, Epstein-Barr virus for 6% and mycoplasma for 6%.

Does it matter?

On average, the rate of recovery from AIDP and AMAN is about the same. There are some patients with AMAN who recover fast, as AIDP usually does. There may be slightly more who recover slowly. AMAN is so uncommon in the USA and Europe that it is difficult for us to study. Most people in series of patients with GBS actually had AIDP. On average patients remain bed-bound for four weeks, remain unable to work for three months, have only minor disability after six months and have recovered completely by one year. Unfortunately some patients still die and as many as 20% may be left with significant disability after a year. In Fisher syndrome, on the other hand, recovery is the rule and giving treatment probably does not make any difference.

Plasma exchange was first used for treating GBS in London in 1978. The Cochrane review summarised the results of all four trials undertaken and showed unequivocally that plasma exchange hastens recovery. Subsequent trials have shown that intravenous immunoglobulin has the same affect. We do not know whether they work better for AIDP than for AMAN or AMSAN and we do not really know whether they work at all in AMAN and AMSAN.

Subacute inflammatory demyelinating polyradiculoneuropathy
This is a less common and less studied group of patients. In my experience and in the published series such patients often have a monophasic illness which gets better on its own. Steroids have often been used in its treatment but some neurologists use intravenous immunoglobulin.

Chronic inflammatory demyelinating polyradiculoneuropathy
Typical patients with CIDP have a chronic progressive or relapsing remitting illness, with weakness and loss of feeling in the limbs which develop over at least two months and continues for many years and often lifelong. Randomised trials have shown that corticosteroids, IVIg and plasma exchange are all beneficial. Unfortunately the benefit from IVIg and plasma exchange is short lived, so that the treatments have to be repeated. Immunosuppressive drugs are often used in its treatment but are not of proven benefit. We are currently undertaking the randomised methotrexate CIDP trial (RMC trial), part funded by the GBS-CIDP Foundation International, to discover whether methotrexate is beneficial. We intend to randomise 62 patients in Great Britain and Europe to methotrexate or placebo. We will be following the patients up for 40 weeks. The conclusion of the trial will not be known until January 2008.

Parenthetically trials like this take a huge effort to mount and undertake. We need to start planning now the next trial to follow the RMC trial so that we can accelerate progress in discovering the best treatments for CIDP. We hope the Foundation will help us plan this trial.

Disorders related to CIDP
Rich Lewis and Austin Sumner were the first to describe a variant of CIDP which is not symmetrical but may affect one or one or two nerves in a focal fashion. It is called the **Lewis-Sumner Syndrome** or **multifocal acquired demyelinating sensory and motor neuropathy** (MADSAM). The multifocality may be retained throughout the course of the illness. It seems to respond to the same treatments as the conventional form of CIDP.

On the other hand, another related condition, **motor focal motor neuropathy**, has some important differences from CIDP. Firstly it is purely motor. Secondly the nerve damage occurs at one or two discrete points, usually in upper limb nerves and nerve conduction in other nerves remains normal. It can cause loss of muscle bulk and be confused with amyotrophic lateral sclerosis. Distinguishing this condition really does matter because steroid treatment may make it worse whereas it usually responds well to IVIg. Whether it responds to plasma exchange is uncertain. It is also uncertain whether immunosuppressive drugs help.

Paraproteins may occur with CIDP. **Paraproteins** are abnormal proteins circulating in the blood produced by bone marrow cells. One clone of bone marrow cells multiplies excessively and churns out huge amounts of the same paraprotein molecule. The molecule is in fact an antibody. **In some patients the presence of the paraprotein is a coincidence** because paraproteins may be found in 5% of the elderly population.

There are some defined syndromes in which the paraprotein is itself an antibody against a constituent of the nerve. In the commonest of these patients with an **IgM paraprotein** have a slowly progressive peripheral neuropathy affecting the sensory nerve fibres. They often have shaking of their hands as well. The nerve damage is caused by the antibody properties of the paraprotein. The antibodies are directed against a myelin protein called **MAG**. These antibodies latch on to the MAG protein and cause disruption of the myelin sheath. This condition is usually only slowly progressive, it is difficult to treat and may be best left untreated.

Another example of CIDP associated with a paraprotein is the **POEMS syndrome**. This acronym stands for polyneuropathy, organomegaly (enlarged organs like the liver), endocrinopathy, monoclonal protein (a paraprotein) and skin changes (such as increased pigmentation and hairiness). It is often associated with cancer like changes in the bone marrow. Local forms of the disease can be treated with irradiation which is followed by gratifying improvement in the peripheral neuropathy. More widespread forms of the disease need to be treated with chemotherapy or even stem cell transplantation.

Conclusion

The recognition of different types of GBS and CIDP has been key to working out the causes of the many different diseases which they represent. It is already clear that some respond better to different forms of immunotherapy than others. It is likely that further research into their mechanisms will allow us to design tailor-made treatments for individual patients or groups of patients. The GBS-CIDP Foundation International can play a key role in developing a strategy for conducting the clinical trials needed to demonstrate the efficacy of existing and new treatments.