An Update on Inflammatory Neuropathy

Newsletter No.15 - June 1996

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From the address to The IN Group at its meeting on 14th May 1996 at 4 Alandale Ave, Balwyn.

My brief talk tonight is about recent advances in inflammatory neuropathy discussed at the American Academy of Medicine meeting held in April/May at San Francisco. Most of the interest being dealt with the Chinese Paralytic Syndrome which has caused a review of our thinking about Guillain-Barr 銓yndrome. GBS is a disorder of the peripheral nerves and is due to inflammation affecting these nerves. Classicly we have tended to think that it is affecting the lining of the nerves, the myelin which is responsible for increasing the speed of conduction of the nerves and for a long time our understanding of GBS was following a viral or other infection the auto-immune system, the body's defence mechanism against that virus, for some reason or another, decides to recognise the lining of the nerve as being the same thing as the infection and starts to attack the lining. More recently it became apparent that some patients who looked to all the world as having GBS in fact seemed to have electrophysiologically, ie with diagnostic tests, a disorder that primarily affected not the lining but the centre part of the nerve, the axonal nerve, the part that is responsible for maintaining the integrity of the nerve and its ability to conduct impulses. This was of some concern because patients that had the axon affected had a much more protracted recovery than those where the lining was affected. So there was some debate as to whether those patients who had the axon affected could be predicted to have a worse outcome. Fairly soon after these observations were made there was some debate as to how accurately you could predict this from the electro-physiological studies. Cases became apparent in China and to some extent in Central America which occurred in an unusual epidemiological pattern in that they occurred primarily in the summer months, affected children and mainly in rural areas. Features suggested that the axonal nerve was primarily affected.

In 1992 a group of doctors, mainly from the Charles Hopkins Medical Center, travelled to China to further investigate in conjunction with Chinese doctors the conditions relating to the unusual occurrences of GBS. Although we tend to think of GBS as a rare condition in Australia and it is also so in China but because of the much greater population you see a huge number of cases in China. When they studied some of the children who had died they found at autopsy a certain percentage of these children had a disorder that didn't affect the lining of the nerve but primarily affected the centre of the nerve - the axonal. When they did serological studies - blood tests to determine what the body was trying to attack they found many of the children had been recently infected with campylobacter jejuni bacterium, an organism found primarily in undercooked chickens. The etiology is still not fully understood but it seems that these summer outbreaks were somehow related to exposure to campylobacter jejuni which affected the central part of the nerve. When we went back and looked at the incidence of campylobacter jejuni in GBS populations of places like Australia and more recently in great detail in the south of England by Professor Richard Hughes, it was found that this seemed to affect sporadically the Western population as well, although it does not share the same epidemiological features.

Now that brings us to the question as to whether the axonal variant can be predicted in life from the electrophysiological studies and whether these patients seem to have the worse outlook and whether possible alternative treatments should be considered. With regard to the ability to predict this condition in life, this has highly debated. Many of the changes that have been considered specific for axonal changes on the lack of physiological studies are in fact difficult to interpret. In addition it is rare to see a demyelinating patient that doesn't have at some stage in the illness some evidence that the axons have degenerated as well. It is also known that patients that have features that are classically say are due to the axon degeneration have shown remarkably rapid recoveries after interventions like plasma exchange or gammaglobulin. This is the opposite to which to what we would expect. This latter finding has puzzled people and there was some evidence presented at the meeting to explain this. One of the arguments was that although these patients have degeneration of the axons, this is a very peripheral phenomenon and the nerves can regrow relatively quickly which leads to the rapid recovery. There was a presentation of such a case - a patient that had the electrophysiological features of the so-called axonal variant of GBS. The researchers had managed to get a motor nerve muscle junction biopsy which showed that the end of this nerve was in fact undergoing regeneration of the axonal component. This looked fairly conclusive evidence. There were however some flaws in this presentation. The first one was that the patient had recovered their reflexes before any strength. We were told there was no sensory involvement but we know from first principles that if there recovery of reflexes before improvement in strength then this is almost certainly due to improvement of the sensory component of the reflex arc. So there was evidence in this patient that there was some rapid reverse of the sensory component that could not be easily explained by axonal degeneration. So there was much debate, back and forth, as to whether we were really looking at the whole of the conditions which affect different parts of the peripheral nerve or whether it was the case of the proverbial case of the blind men reporting on the elephant. One blind man feels the trunk and reports that it is sinuous and muscular but another blind man feeling the leg, says "No, it is like a tree". A third blind man feeling the tail, says "You are both wrong, it is like a brush."

So are we looking at different bits of the GBS and deciding different things about it. The whole of GBS is in fact a combination of all these different varieties of these manifestations.

So there was a lot of interest in the Chinese Paralytic Syndrome and the fact that it may open the door to GBS being regarded rather than one condition being a factor, as two or more conditions. This I think will be that path research takes in the future to try and sort this out and determine what makes these conditions different. If they are different should we be using different treatments?

Questions

Q. How can you tell which type you have?

A. Sometimes we can tell very definitely what type you have. If we do nerve conduction studies and the nerve conduction speed is down from a normal 60 to 12 or 18 metres per second then it is pretty clear that this is the type of condition where the lining of the nerve has been stripped away. In other types we do not see such unequivocal evidence. The slowing may be down to 30 metres per second and that the amplitude of response has dropped more tha the slowing. So we are left with the question, is this the slowing type or the axonal type where the centre of the nerve is damaged, or is it a combination of both. My own gut feeling is that the vast majority of GBS cases are a combination. We do see some rare ones that are purely demyelinating and some that are purely axonal.

Q. I was diagnosed some five months ago. The causes of mine came up about 2 years ago when I had a car accident. The car was a write-off and I started showing symptoms of loss of feeling in the feet and legs. I went to how many specialists and doctors and it was only five months ago that I was given the name of a neurologist who diagnosed me as having CIDP. He said it was caused by a virus. Is that what causes it or could it be a shock from an accident? I had no illnesses or viruses.

A. If we look at the viral hypothesis it is strongest for GBS. The incidence of an antecedent viral infection for GBS is high whereas for CIDP the incident is low. The question is whether there is areal difference or is it because the CIDP over a much longer period where it more difficult to recall. We know that it is not just viruses; there are bacterial infections such as the camphylobacter. We know that certain stresses precede GBS. The classic one is surgery. In recent years we have come to realise that in Intensive Care environment you can get a muscle disorder that looks very much like GBS but a biopsy shows a very unusual pattern of muscle degeneration. So we wonder just how strongly a stress like surgery preceding GBS holds up as its cause holds up after more detailed examination.

As regards stress, we know that the immune system is intimately related to the psychological status of the patient. We know that depressed patients have changes in their immune system. We should keep an open mind in this area.

There are a lot of mysteries in medicine; it is very hard to be definite about many things. We know that after the death of a spouse, the chance of one getting a serious illness is high.

Q. Was there any discussion at the meeting on CIDP?

A. There were a few papers but nothing significant emerged here.

Q. Is there any treatment for pain?

A. Some of you will recall we did discuss the treatment of pain at a previous meeting *("INformation"Jun'93)*. There a range of possible mechanisms for getting pain. There is also a range of possible therapies. Generally speaking the management of pain requires using one medication and if that doesn't work trying another and so on.

Q. GBS has left me with drooping eyelids that affects my vision. Can anything be done?

A. One has to be careful about surgery that might elevate the eyelids because the more important thing is that the eyes close, particularly when you sleep. Otherwise you will get ulceration. The issue with many of these residual symptoms is whether some further treatment may not result in improvement. I remember an early patient in New Zealand who made a good recovery. He was a keen pilot of antique planes. This requires a good judgment for controlling the foot pedals. He never really felt that his feeling in his feet was good enough to go back to his piloting. He was sitting there watching his planes rot in the hangars. He came down to visit us and thought he was making an imposition by asking for some more gammaglobulin, some six months after his recovery. We gave him some and remarkably this last bit of control of his feet came back and he went back to flying.

One problem is that these treatments are rationed, sometimes in short supply, considered to be expensive - although their expense has to be balanced against the expense of a person's continued disability. On top of that we know gammaglobulin will continue to be produced whether it is used or not. In fact our experience in New Zealand when we first started using it was that it was just being discarded, there was no need for it. Now there is much need for it for treatment of many conditions it is now scarce and we are told it is very expensive to manufacture.

Q. Does gammaglobulin boost the immune system?

A. Boosting is a crude term to cover a complex system. Certainly gammablobulin provides a balance of supply of one arm of the immune system. In that sense you could say it boosts the immune system. How gammaglobulin actually works is not clear. Sometimes your immune system is out of control because the attack part of the immune system is not working properly. There is one theory that gammaglobulin soaks up the overactive immune system. The immune system is being found to

be more and more complex. If you are not working in the area you can't even understand the scientific literature. I think we use words like boosting and depressing to cover up our ignorance.

Q. Are GBS and CIDP part of the same syndrome?

A. It is very rare for one type to change to the other. The difference is I think primarily clinical. GBS is classically taken to mean that type of inflammatory neuropathy where the patient goes from being normal to being bed-bound within a couple of days and then possibly having respiratory problems within a couple more days requiring a ventilator, then tending to have a period of a month or so where things are relatively stable, neither great improvement or deterioration, then slowly starting to recover. Young people seem to recover pretty well to normal. It is rare to get another attack or any form of residual disability.

CIDP tends to follow two courses. One is that it progressively gets worse and the other is that it gets worse for a couple of months then it seems to improve for a while perhaps for a year or two then deteriorates again, following a relapsing course. We don't tend to see this relapsing course any more because we tend to treat them with gammaglobulin which tends to keep people fairly stable. If anything, fluctuations now in CIDP are a manifestation of treatment. The course is dictated by the treatment.

Q. Are there any new promising treatments?

A. I don't think there are new therapeutic ideas coming in. We tend to use plasma exchange or gammaglobulin as the number one treatments. For CIDP we use steroids but not for GBS. The evidence seems to be against it. If we get desperate we may try other forms, such as immuno-suppressant agents such as Imuran and cyclosporin.

Q. Can there be a change from GBS or CIDP to Multiple Sclerosis?

A. It can occur but is quite rare. I have not seen one such ;patient since being in Melbourne.

Q. How importance is exercise to rehabilitation?

A. I think doing a certain amount of exercise is very valuable but there are hazards with overexercising when you have peripheral nerve problems. You can damage the muscle, the muscle not getting the right sort of messages to tell you that it is fatiguing. For example the muscles in the front of the leg are responsible for acting as a brake when you put your foot down as you walk or run so that the foot doesn't slap down. Occasionally young people that have weaknesses of the feet muscles, having slapping "foot-drop", feel that they just need more exercise to overcome the slapping, can do a lot of damage to the joints in the foot because the normal cushioning action of the muscles is impaired.

Q. I do an hour's hydrotherapy each week. Can that do any harm?

A. The advantage of hydrotherapy is that it takes body-weight out of the issue. It is a very effective form of exercise for anyone with neurological weakness problems.

Q. Has diet useful?

A. Not that I am aware although with some reservation. I read of an interesting observation that the American Indians when walking through a forest full of poison ivy would eat bits of it. In this way they tricked the immune system into seeing poison ivy as a non-inflammatory toxin. The reason for this is that you have to eat to live and you have to eat lots of foreign proteins and in the wild lots of bacteria so you develop an immune reaction to everything you ate. So the gut has a mechanism for

saying this is food, don't attack it. So the theory is that when you eat the poison ivy this teaches the body to see this as a food rather than an insulting toxin. This has promoted a whole lot of research in the US into multiple sclerosis and rheumatoid arthritis and other auto-immune disorders to see whether we can use this mechanism for dietary control of these conditions by tricking the immune system into switching off its attack on various types of protein. As far as I am aware nobody has done such a thing in demyelinating polyneuropathies but there is some research is being done into MS using this. They introduce small amounts of central nervous system myelin protein into the diet to try and get the MS under control. The results have been mixed and inconclusive to date.

Q. What does inflammatory mean?

A. Inflammatory does not mean spontaneous combustion. What it basically means is that the body's defence mechanism has been called into action. In a complex activity, proteins are produced to attack foreign organisms, and cells ....? Usually the most obvious thing from an infection is that there is a whole lot of swelling, redness, odema, these are all chemicals released by those cells going into the area to attack the bacteria. They release chemicals that increase the blood flow to the area and an increase in temperature. We tend to use the word inflammatory to basically cover any sort of condition that seems to have at its core some activation of this defence mechanism.

Q. Is inflammatory the basis for a burning sensation I get in my feet?

A. I think this is a different mechanism. I think the lining of the sensory nerves are being affected. I think what is happening there is that the other nerves, the nerves that measure touch are the ones primarily being attacked. As these nerves come into the spinal cord they tend to damp down any information coming up from the pain nerves. When you lose that dampening down effect then the pain nerves produce this burning sensation. You can actually block nerves by pressure. When you apply pressure say on the radial nerve you make this part of the arm numb and as you increase the pressure you block off the large nerves and the small nerves are the last to be blocked and you go through a phase of getting a burning sensation. If you stick a pin into your flesh you can still feel its sharpness.

Q. Now that Fairfield Hospital has been closed, will Melbourne's major hospitals be able to cope with GBS and CIDP patients?

A. For CIDP there should be no problem. Many CIDP patients go to major hospitals for diagnostic testing and management. They are usually still mobile and can be capably managed as outpatients. GBS patients should not be a problem either as all major hospitals in Melbourne have now a lot of experience with handling GBS. Where the problem may crop up is with the patient who is going to be on a ventilator for a long time, say for the order of a year. The unit at Fairfield was very skilled at managing these patients. There are a lot of complications that can arise, a lot of issues to deal with, frustrations of both the patients and the families, of staff when progress is not as expected. These require skills which other hospitals are probably not as adept at. It is something they will have to learn. Fortunately longterm patients are becoming somewhat rarer due to the new treatments. Recent tests have shown that immunoglobulin is at least as successful as plasma exchange. I must say it must be one of the most horrifying experiences to be on a ventilator for a year.

Q. What would determine the period between treatments of plasma exchange?

A. Once a patient has achieved a certain level of function one is often guided more by the patient. Probably many of you who have had immunoglobulin or plasma exchange will be aware that you will feel that you are improving or deteriorating before anybody can really detect it. I constantly see patients who on the second or third day of a course saying "I feel better" then you know in another two days there will be definite clinical evidence that they are getting better. Similarly if a patient says that he is getting weaker you will know that later this will show up. We tend to rely a lot on the

patient's assessment on how they feel themselves. I am not sure why the patient can feel the difference before there is evidence.Plasma exchange and gammaglobulin can have very dramatic effects. Some patients turn around dramatically.

Last Updated: 15 Oct 2007 17:49