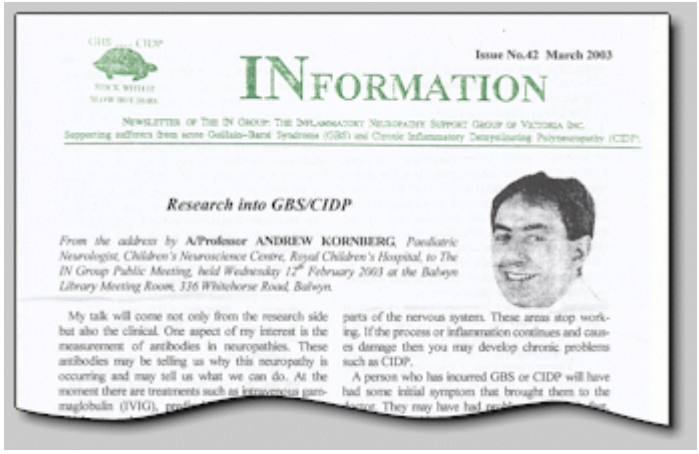
Newsletter No.42 - March 2003

See also: Newsletter No.42 Mail Wrapper

Research into GBS/CIDP


Issue No.42 March 2003

INFORMATION

Research into GBS/CIDP

From the address by **A/Professor ANDREW KORNBERG**, *Paediatric Neurologist, Children's Neuroscience Centre, Royal Children's Hospital, to The IN Group Public Meeting, held Wednesday 12th February 2003 at the Balwyn Library Meeting Room, 336 Whitehorse Road, Balwyn.*

My talk will come not only from the research side but also the clinical. One aspect of my interest is the measurement of antibodies in neuropathies. These antibodies may be telling us why this neuropathy is occurring and may tell us what we can do. At the moment there are treatments such as intravenous gammaglobulin (IVIG), predisolone and a few others, which are rather like a shotgun approach to sup-pressing the immune system. But if we can understand how these antibodies occurred, why they occurred and how they actually caused the damage to nerve we will be able to develop more specific treatments available for these conditions. Hopefully the treatments will be easier to get, more directed at the problem, not giving as many side effects, and even be given orally at home rather than coming to a hospital.

I will be talking about how a doctor goes about diagnosing one of the immune-mediated neuropathies, then using that diagnosis to pick the best treatment. This may involve using the antibody tests that I perform in my laboratory.

Neuropathies refer to conditions that affect the nerves. Immune-mediated neuropathies include disorders such as Guillain/Barr頓yndrome (GBS), Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and a few other conditions. These disorders occur when the person?s immune system gets confused between some trigger and the nerve itself. For example in 50-60% of people with GBS, and maybe a little higher in children, there is some sort of trigger before the development of the illness. This may be a vaccination, a virus, that in a susceptible person (this may be gene related), the immune system thinks the nerve is that virus or trigger and attacks the nerve with resultant problem being inflammation in the nerve or other parts of the nervous system. These areas stop working. If the process or inflammation continues and causes damage then you may develop chronic problems such as CIDP.

A person who has incurred GBS or CIDP will have had some initial symptom that brought them to the doctor. They may have had problems with their feet, "a footdrop", with them tripping over. For that reason, the doctor would have taken their history, examined them and maybe taken their history and found some pattern to the weakness. For example, in individuals with GBS, weakness tends to come on more rapidly, people would be weak in their proximal muscles (near the pelvis), they may have numbness or tingling as a symptom. A doctor that is aware of this condition would say "Aha, I think this is GBS". Then he would prescribe a treatment. With CIDP it can present like GBS but usually it is more of a chronic and slow process. People realise something is not right but it usually

takes longer to see the doctor. The doctor would need to recognise that the presentation is of a nerve condition and from the pattern of symptoms he may make a diagnosis. Investigations such as nerve conduction studies (where small electric shocks are given to "suspect" nerves, EMG (a needle test), a lum-bar puncture or an MRI may be performed.

Most research in neuropathies is focussed not on how people present but on what is causing the disease. Most of this research involves blood tests looking for antibodies in the blood or nerve tissue which are commonly seen in these conditions.

Q. Is it a specific antibody or is it a general elevation of types of antibodies?

A. We can now say due to the identification of more specific antibodies, "This is GBS, this may be Miller/Fisher Syndrome (MFS)". We have gone from saying "You have an elevation in this broad group of antibodies" to now picking out antibodies that are more specific.

Q. How about antibodies for CIDP?

A. In CIDP we have not yet identified specific anti-bodies. We are probably a a year or two away before we have more specific information. CIDP is probably a basket of conditions and we probably will be able to tease out those conditions in the CIDP basket. GBS was previously a basket but now we have at least four different types that we can determine clinically and from the tests and the antibodies. This is the way ultimately we may proceed with CIDP.

GBS and CIDP are the most common types of immune-related neuropathies Others include Multifocal Motor Neuropathy (MMN). People may be mis-diagnosed with Motor Neurone Disease (MND). If somebody is aware of the condition and measures antibodies, effective treatments are available. Rather than saying "Goodbye, I can?t do anything for your MND. You may pass away in three years" it may be "You have MMN and there are effective treatments available". We are able to diagnose many conditions earlier nowadays and we are trying to make these breakthroughs known to the wider community, and to doctors so appropriate treatment decisions can be made.

Research involving animal studies have shown that we are able to give animals "the disease" after administering some of these antibodies. Thus we suspect that they are related to the disease. We still have to get to the next step, that is, to understand why the process continues.

What causes the disease? Molecular mimicry is probably the answer. Essentially an infectious agent, some sort of trigger, shares something, or mimics, nerve tissue. In 1983 Brian Speed and Jaakov Kaldor at the Fairfield Infectious Diseases Hospital found that there was a particular bacteria in the bowel, campylobacter, which gives you diarrhoea, which was highly associated with GBS. We have proceeded a long way from this initial observation. Now we know this bacteria has a receptor on its coat which is also on nerve. We know that when we give that antibody or bacteria to a rabbit or a chicken you can give them the disease. We have gone from an observation, to measuring an antibody, to giving an animal that disease. So we know the antibody is pathogenic, ie it causes disease. But we still do not know why in an individual that action continues or why that person is susceptible in the first place.

Campylobacter has been found very important in the causation of GBS and of MFS. These disorders may be related to the production of antibodies.

People with GBS from campylobacter have not much in the way of sensory (feeling) problems, it is usually a motor problem. They may be paralysed, and weak. When I see a child with predominately motor weakness as confirmed by clinical and nerve tests, the first thing I do is examine the stools, the blood, look-ing for evidence of campylobacter infection. What is important is now we are getting an understanding of why this disease is occurring and so hopefully we will be able to pick it earlier

and treat it earlier. If treated earlier there are less problems later on.

Other clinical observations may lead to other break-throughs in understanding what causes disease. We have recently published in *Neuromuscular Disorders* the first case of a child with CIDP who also has a Multiple Sclerosis (MS) like illness, the two occurring in the one child. This has been described in adults but is not common. Five per cent of people in one series of CIDP had MRIs which showed the brain with areas that look like MS. Now MS is a central nervous sys-tem white matter disease. CIDP is a peripheral white matter disease. The question is why do they both occur? Although there are not many specific anti-bodies in CIDP identified, both disorders occurring in one person may lead to breakthroughs in which other pathways are involved. We are starting to explore different chemicals and inflammatory markers in CIDP and that may give us a clue as to why this disorder occurs. Hopefully this will lead to better treatments.

I saw this child today in the clinic ? unfortunately she is severely affected. She has two parts of the nervous system affected and now we have to pick a treatment which we can use to treat both. Hopefully treatment will do the trick and I may be able to report in a year or two?s time that the child is much better.

I am sure a number of people here initially went to their doctor and were told that it "it could be a virus, could be this, could be that. Go away and come back in a week, take an aspirin, then come and see me". If you have a test that can help the doctor to say "Yes, it is a nerve problem and it is this", treatment may be given earlier. When we first started in our laboratory we were maybe doing one or two antibody tests every other week. Nowadays we are overwhelmed ? there could be 20, 30, 40 50 of these tests in a week. This is hard because I don?t have a lot of funding for these tests. We are trying to set up a laboratory at St Vincent?s to carry out these tests as a routine. Importantly, this testing is becoming better known in the community and can be used to help diagnose specific clinical syndromes and with their treatment. We do know that some conditions respond to a medication and others don?t. For example, steroids can work with CIDP but don?t work in MMN, in fact they can make the condition worse.

The tests we and others perform revolve around measuring anti-gangliocide antibodies. Gangliosides "live" in nervous tissue and probably do something to signal nerve function. There are toxins and diseases which affect these signals and affect the function of the nerves. Gangliocides are normal parts of the nervous system but for some reason they act as an antigen. Gangliosides are close to the barrier between blood and nerve and blood and brain. If there is some leakiness of the barrier, antibodies may attach to the gangliocide and the nerve becomes affected. Treatment tries to break this cycle. Anti-gangliocide antibodies are very important and they are what we measure in our laboratory, one of many tests. The antibody finds the antigen and then causes the immune reaction to affect the nerves.

There is now good evidence to suggest that for example with MFS we have 95% of people who have identifying antibodies. This can be used as a diagnostic test. There is a condition, Ataxic GBS (ataxic meaning wobbliness) where the person appears to have GBS but is not necessarily very weak. Such persons have high amounts of particular antibodies. What is important is that these antibodies, and their associated antigens, certain gangliocides only "live" or are concentrated in certain parts of the nervous system. For example in acute opthalmoparesis, the muscle and nerve that controls eye movement have a high level of a particular antigen ? a gangliocide, and high levels antibodies are found. Another example is the Bickerstaff encephalitis (which affects the back of the brain). They also have high levels of another antigen antibody.

So it now appears that if you have an elevated antibody it will affect certain parts of the brain and give you a certain type of clinical picture. These antibodies are high when the person is sick and go away when well. So we now believe it is important to lower these antibody levels.

What treatments for GBS are there? You may get plasma exchange where you get your antibodies flushed out. Intravenous gammaglobulin (IVIG) does not affect the level of the antibodies but probably blocks the way the antibodies work so they don?t bind to the nervous tissue. We give a high dose of IVIG, it stops the binding and the person gets better. GBS happens and then goes away by itself. But CIDP happens and stays. So you have to re-treat and re-treat and re-treat. GBS is usually an one-off and goes away.

Q. How about treatment with cyclosporin?

A. Cyclosporin is a more specific therapy working on the T cells. It blocks one part of the system and so can be helpful. It is not helpful with all patients, it can be helpful with some patients with CIDP.

Q. How about Imuran?

A. It is a steroid sparing agent so it allows a lower dosage of steroid but in addition it has an effect on B and T cells. It is more of a shotgun approach but has some side effects.

Q. My wife was diagnosed with GBS in April 1984 and spent many months in Fairfield Hospital. How has treatment changed since then?

We have just reviewed one hundred children cases at the Royal Children?s Hospital. We had 50 kids with GBS before 1986 and 50 after 1986. 1986 was when plasma exchange and IVIG were first used for treatment at RCH. IVIG was first used in 1984, in the Netherlands. Nowadays we would recognise the condition early and treat it early, in the first seven days of the onset to get all those antibodies away. However there are some people, that despite whatever you do, nothing helps. They are a small subgroup of patients.

Nowadays we have a much wider spectrum of treatments. Some of the novel treatments are combination therapies. We may use cyclophosphamide, a more powerful immune suppressive, to target the parts of the immune system we think are causing the problem. Hopefully in the next five years we will have more specific therapies. This has already happened in MS. There are new treatments for MS coming on, which could translate to the peripheral nervous system.

The mainstay for treatment of GBS is still support. GBS is a disorder that usually gets better. There may be residual symptoms but from where they were, perhaps on a ventilator, the doctor can give support by telling them that they will get better and they will. You must have good intensive care and you must have fantastic nursing, probably the most important part of it all. You need good bowel care, good pressure care. Plasma exchange and IVIG may make a difference but they may not and you need to have good support to recover. Plasma exchange and IVIG are both equally helpful but plasma exchange is much harder to do, particularly for children, so IVIG is a godsend. It is very easy to administer. The difficulty is getting it, as it can be in short supply. For GBS we tend to get as much as we need. Steroids do not work for GBS and a combination of plasma exchange and IVIG does not add any benefit as shown by studies worldwide.

For CIDP, predisolone is a a standard treatment, plasma exchange can be helpful, IVIG can provide short term improvement in strength but not for 100% of people. We tend to give IVIG because it has few side effects but you can?t get it readily for recurrent treatments. If people don?t respond we use predis-olone and cyclosporin. The problem with predisolone is that taking it every day may give side effects, al-though now there are different ways of giving it. I don?t give children steroids as a daily dose any more. I give it once to twice a week in a big dose. They don?t have the side effects, the weight gain or other problems and it seems to be as helpful as a daily dose.

A big thing at the moment is a medication called Rituximab which is a monoclonal antibody which you give intravenously and targets B cells. The B cells pro-duce antibodies. So it knocks off all those

"bad" B cells, the antibodies fall dramatically and the person gets better. But you have to re-treat because the B cells come back.

Q. Is this new treatment useful for a longtime sufferer of CIDP?

A. It is only useful in a subgroup of patients who have measurable and high level antibodies. It is very good for MMN. I think Retuximab is the first of many drugs which will happen in the next few years.

Q. Where does your research fit in with other research being conducted in Australia and overseas?

A. I did my fellowship in research in St. Louis, USA, with a guy Alan Pestronk who is a world authority on MMN and other conditions. I have still ongoing collaborations with Alan. We have some active collaborations with the Sydney group under Professor John Pollard who has been doing a lot of the antibody studies. Unfortunately, I gather, they have had to close down a lot of their antibody evaluations. There is a Neuromuscular Centre in Europe. I was asked to be part of a panel some 2 years ago on childhood CIDP and we have planned studies. We now have collaboration on childhood CIDP with some Europeans and an Israeli group. We try and publish; we write grants and we see patients. I am not just a researcher. I have many patients. Ultimately we want to do our best for our patients and make sure they do better. America is a lot bigger and people are in competition. They tend not to share it around but in Australia we are lucky enough to share because we like each other.

Q. Is there more CIDP around or is it being better diagnosed?

A. It is probably a mixture of both. When you start to know what a condition is then more people are so diagnosed. As education and knowledge expands people are more adept at making a diagnosis. There appears to be a slight increase in the incidence of GBS and CIDP.

Q. GBS seems to be started by some trigger but not so for CIDP. Is this so?

A. If you have a chronic condition then you try to go back and ask what could have caused it. A small percentage of people with CIDP will have a viral trigger but it is much lower than for GBS. For CIDP you may have some symptom which is not "bad" but which gradually gets worse. You go to your doctor a few times and then ultimately it is diagnosed. GBS goes bang! If a process goes on for 6 or 9 months before you get diagnosed do you remember what happened in the weeks before?

Q. Is it still the case if the disorder develops within one month it is GBS or if more, then it is CIDP?

A. It is not development, it is progression. GBS should not progress, the weakness etc should not progress over four weeks. There is another group of conditions ? I have seen it a few times in children - which I call subacute inflammatory demyelinating polyneuropathy where there is progression for between four to eight weeks. This group responds to steroids. We are just writing a paper on how you can pick those kids when they come in looking like GBS. CIDP progresses over an 8 week period. If you have progression or fluctuation or episodic events beyond 8 weeks then it is CIDP. It is still based on clinical criteria and nerve conduction tests can be helpful. Antibodies at the moment are not that helpful for CIDP.

Q. If you had GBS some 5 years ago and not fully recovered is there any treatment now that would be beneficial?

A. If it is GBS then plasma exchange or IVIG won?t change it. Fatigue is a common long term problem with GBS. If you are left with "footdrop" or some weakness, that is because the nerves have become affected. Nerves grow back at 1mm per day but if they don?t grow in the right place or there

isn?t that nerve cell to sprout then the weakness will stay.

The IN Group awarded $875

The Victorian Department of Human Services has awarded The IN Group $875 under its Health Self Help Program 2002/2003 in recognition of our playing a "vital role" in the health care system. Last year The In Group was awarded $850 under this same Victorian government program.

These awards are a tribute to the help you members have contributed to assisting sufferers from the inflammatory peripheral neuropathies, mainly GBS and CIDP.

Support is the Name of our Game

Two persons suffering from GBS in Intensive Care were visited by member Pauline Whitelaw and James Gerrand. Alan Litchfield was in the ICU at St Vin-cent?s Hospital. He has mainly recovered after rehabilitation at the Albury Hospital. He is now back at home in Leeton NSW. Here is appreciation from his wife.

Dear James,

Thank you for the information about GBS. The booklet has helped Alan and myself understand about GBS. Alan is improving everyday.

We also appreciated the two of you coming to the hospital to visit us.

I?m enclosing a cheque for $50 to join The IN Group plus donation of $32.

Judith Litchfield

The other person is a lady who has been in the ICU at the Royal Melbourne Hospital for some months and is now making slow recovery. Her husband is keeping us advised of his wife?s progress. Their daughter has joined The IN Group also enclosing a donation of $32.

We continue to supply information to people seeking this usually via the Internet. Usually after obtaining a postal address we send them a booklet, either GBS or CIDP, plus The IN Group brochure (containing membership application form) and latest quarterly newsletter "INformation". Such enquiries are usually from persons diagnosed with GBS or CIDP or a variant. They come from overseas ? Hawaii and Illinois USA ? or interstate ? Stephens Qld, Ashby NSW ? or Victoria - Tangambalanga, Bendigo, Bun-yip, Dingley Village, Beaumaris. Some inquiries come from hospital staff such as an occupational therapist from the Melbourne Extended Care and Rehabilitation (RMH).

Here is one appreciation of such support.

James,

Thank you so much for your info forwarded to me by mail.

I appreciate your time taken to do this and "well" done for all who help you are obviously giving to

other neuropathy patients.

Colleen Wilson

North East Cluster

Our Group has grown from 3 to 12 this year which is in the main due to better and quicker diagnosis plus interested Health Staff in Wodonga. In the past we have been meeting for lunch alternating Wangaratta/Wodonga but now we are having our very first function in Rand at Bulganda Station. This is Nancy and Rob Wilson?s home and we have invited partners and family on Sunday 23rd February for lunch and a swim. People will be coming from far and wide ? Cooma, Wangaratta, Wooragee, Wodonga, Albury, Myrrhee.

Vilma Clarke

Survey of Rural Costs of Chronic Illness

Hi James,

I just wanted to thank you for getting behind this survey. Of the 36 surveys you sent out we have received replies from 12 households which is an excellent outcome. Usually the best you can hope for with mass mail-outs is 20%, so 33% is great. It just goes to show what an issue this is for rural people.

Obviously when the report is ready we will send you a copy and keep you informed about the project.

Jo-Anne Tamblyn, Project Coordinator,
Chronic Illness Alliance.

Internal Restructure of the Blood and Organ Donation Taskforce

We have been advised by Peter DeGraaff, Assistant Secretary of this Taskforce of the Commonwealth Department of Health and Ageing of this restructure. This is one outcome of the recent comprehensive review of the Australian blood banking and blood products needs.

Through working together with States and Territories, it is expected that a National Blood Authority will be established and become operational by mid-2003.

There is some expectation that the new Authority will lead to an increase in the supply of Intragam such that medically prescribed demands can be met.

---

vCJD Donor Deferral Workshop

The Taskforce has organised this Workshop to be held from 8.45am ? 5pm Friday 28 February at the

Melbourne Airport Hilton.

The Workshop is to review the validity of the rejection of blood donations from people who have lived in the United Kingdom for more than six months for fear that they may transmit through their blood donation the fatal "mad cow disease" Variant Creutzfeldt-Jacob Disease. This Disease has been transmitted to some 29 UK citizens by contact with cattle suffering from bovine encephalitis.

This rejection has decreased the amount of blood donations by some 5%.

The IN Group has been invited to attend and Director James Gerrand will be "showing The IN Group flag".

Entertainment Books for 2003

Victorians members will receive enclosed info including order form. We make $11 for every Book.

Last Updated: 15 Oct 2007 17:49