



FARA NEWS

Friedreichs Ataxia Research Association of Australasia newsletter

Issue 2 February 2005

FROM THE PRESIDENT

In its brief period as a national organization we have been able to establish FARA as a viable and relevant organization. The need for a strong, national entity is now more important than ever, given the need to gain access to the various funding authorities and government outlets in the face of greater demands from organizations similar to our own. The recent tsunami disaster, while resulting in a magnificent response from the Australian people, makes it even more difficult for small local groups such as ours to tap into the generosity of people. There is a limit on how many charities people and corporations are able to donate to.

Since our establishment in 2003 we have been able to establish strong relationships at the national and international levels. Without international assistance, and that of several generous individuals, we would not have been able to achieve what we have done. To maintain the existing clinic at Monash Medical Centre and the Bruce Lefroy Centre at the Royal Children's Hospital, Melbourne, in addition to speeding up the screening of chemicals that may assist in the uplifting of Frataxin levels in

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FA sufferers costs in the vicinity of \$ 100,000 per annum. In addition, FARA this year awarded its first post-graduate grant to a student working on FA research. To date the bulk of income from Australia has come from the Victorian group and individual donors and corporate sponsors. The tremendous input by groups such as Young Australians Fighting Friedreich Ataxia and the Friedreich Ataxia Association of Victoria should be a challenge to other states to muster resources that will enable us to provide the level of research funding that we require if we are to provide a therapy for our sufferers in the near future. It is important that we provide adequate funding to research that is carried on Australia-wide and in New Zealand. To do this we need a much wider source of contributions.

Recognition of the significant research in the field of Friedreich Ataxia is reflected in the recent awards by Australia's National Health and Medical Research Council from which body Professor Des Richardson of the University of New South Wales received a large grant for his work on the role of Frataxin and the capacity of iron-binding drugs that he has developed to lead to an eventual therapy. Such awards are not only a recognition of the relevance of the research and the prestige of the researcher, but they also demonstrate that Friedreich Ataxia is now a field of research that is widely recognized as of significant importance.

This year we hope to commence the long-awaited trials of Mitoquinone. We realize that sufferers believe that these have been too long in coming. However,

an article in this newsletter should enable readers to understand just why it takes so long for trials to take place. We thank Dr David Ketteridge of the Women's and Children's Hospital, Adelaide and the Lysosomal Diseases, Australia for their permission to publish this article. We wish to thank all those who have contributed to this edition, whether this be in the form of articles or personal assistance.

*Peter Rousch AM
Emeritus Professor*

Friedreich Ataxia Research Update.

November 2004

*Cell and Gene Therapy Research Group
Murdoch Childrens Research Institute
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The Cell and Gene Therapy Research Group at the Murdoch Childrens Research Institute has the largest group of researchers in Australia devoted to conducting basic medical research to develop a therapy for Friedreich ataxia. Throughout the past year, eight people were involved in performing research on various aspects of Friedreich. ataxia. The CAGT lab is focussing its efforts on the development of novel therapeutic strategies that benefit from the latest advances in the Human Genome Project. With the completion of the sequencing of the human genome, we are now able to grow a sequenced fragment of human DNA that carries the Friedreich. ataxia gene (ERDA) in unlimited amounts. We have

therefore been using the entire FRDA gene to develop a number of avenues of research for the therapy of Friedreich ataxia (FA).

Pharmacological upregulation of FRDA gene expression:
Individuals with FA have very low levels of the protein frataxin due to a reduction in FRDA gene expression caused by the GAA expansion. A several-fold increase in gene expression may slow or stop progression of symptoms. We are pursuing the identification of pharmacological agents that may increase the expression of the FRDA gene as a possible treatment. We have modified the normal FRDA gene by tagging it with what is known as "Enhanced Green Fluorescent Protein" (or EGFP). We have termed this a "Genomic Reporter". In this way we can easily measure how well the gene is functioning in response to various treatments. We have placed this modified FRDA gene in various cell types in culture and have begun testing compounds for their ability to increase the production of frataxin. We have identified several compounds which appear to increase gene expression; the largest effect being a doubling of FRDA expression. These particular compounds may not be suitable for treatment of people with FA, but demonstrate that we have the means to identify better drugs. We are now optimizing the format of our assay to screen a large number of compounds, including all approved drugs, to identify those compounds that may increase expression of frataxin to therapeutic levels in

Friedreich ataxia. This work will be done in collaboration with the High Throughput Screening Facility recently established by the Walter and Eliza Hall Institute with Bio21 support at the La Trobe University campus in Victoria.

Development of "frataxin-green" transgenic mouse models:
We have used the same human FRDA genomic reporter to generate "frataxin-green" mice in which we can easily follow the expression of frataxin in various tissues by measuring green fluorescence. We have also shown that we can make accurate measurements of the level of green fluorescence in different cell types, thus allowing us to examine the effects of inducers of FRDA expression directly in various tissues. It is anticipated that these mouse models will be invaluable in understanding what controls the level of FRDA expression in different tissues, thus helping us to understand why some tissues are more sensitive than others to damage in Friedreich ataxia. These mice will also greatly facilitate the preclinical testing of inducers of FRDA gene expression.

Humanised mouse models for Friedreich ataxia:
All of the available mouse models that have been developed in other labs involve the destruction or modification of the mouse Frda gene. However, this cannot accurately reproduce the disease as found in people with FA. We are therefore developing mice that carry the human FRDA gene with and without a large GAA expansion.

Such mice should more accurately reflect the disease in people, and allow the preclinical testing of new therapies. We have successfully generated transgenic mice containing the normal human FRDA gene. We have shown that the insertion into mice of the normal human FRDA gene can completely replace the mouse frda gene. This is an important result as it shows that human frataxin can substitute for mouse frataxin, and that the human DNA fragment used in our studies contains all sequences necessary for the correct function of the human gene.

After overcoming many technical challenges, we have also introduced a large GAA expansion into the normal human FRDA gene and used it to generate transgenic mice. This should allow us to generate mice dependent on the human FRDA gene with a disease-causing GAA expansion as the most accurate mouse model of FA. The mice should not only manifest the main traits or symptoms of the disorder but also provide the correct underlying molecular cause of the disease as found in people with FA. The mice are currently under careful observation for symptoms of FA.

Gene regulation studies:

Very little is currently known about the mechanisms which control when and where the FRDA gene is switched on, and off. Information about the regulation of expression of this gene may suggest ways in which to specifically increase its expression in a therapeutic manner. This year we commenced a new research project to develop a novel method for

the identification of regulatory elements which control the expression of the FRDA gene. Using our FRDA genomic reporter, information from the Human Genome Project, and genetic engineering techniques developed in our lab, we hope to rapidly identify important aspects of FRDA gene regulation.

The role of iron and oxidative stress in Friedreich ataxia:

In collaboration with Dr. Frank Petrat (Germany) and Dr. Brigitte Sturm (Austria and Australia) we have re-evaluated the role that iron and oxidative stress play in FA. New results appear to indicate that in cells of individuals with FA there is a decreased defence against oxidative stress caused by iron that is present outside of the mitochondria. These findings may suggest alternate targets for the treatment of FA.

We would sincerely like to thank FARA Australasia and the Friedreich Ataxia Associations of Victoria, New South Wales and Queensland for their continuing moral and financial support.

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Dr Joseph Sarsero, PhD

Dr. Brigitte Sturm, PhD

Timothy Holloway

Lingli Li

Novita Puspasari

Sanne van den Flengel

Marion Zanese

The Bruce Lefroy Centre: Friedreich ataxia clinical trials update

December 2004.

Since I last wrote to people, progress towards starting clinical trials with Mitoquinone has occurred. Most significantly Mitoquinone has been shown to be safe in animals and is therefore able to be tested in healthy human volunteers. This is called Phase 1 testing and is required before trials in Friedreich ataxia can take place. The human Phase 1 trials will take place in Christchurch, New Zealand, in the early part of 2005. Assuming this goes to plan, then trials in Friedreich ataxia can go ahead after this. Exactly when trials can begin is not possible to say due to the uncertainty of timing regarding the completion of Phase 1 studies and other necessary administrative requirements. I can assure you that this is all being done as quickly as possible with all parties being committed to testing this agent in Friedreich ataxia.

The exact format of clinical trials has not been decided. Therefore it is too early to let you know how people will be recruited and what will be required of them. As I have stated in previous correspondence, however, we are committed to undertaking the trial in a way that gives us the best chance of knowing whether or not Mitoquinone has any benefit, or conversely any harm for people with Friedreich ataxia.

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Clinical trials: what are they and

why do we need them?

By Dr David Ketteridge, Consultant Paediatrician, Women's and Children's Hospital, Adelaide

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When a new drug or therapy is developed, it must go through a rigorous evaluation process before it can be approved for use in humans. This process can take several years before sufficient information is obtained to satisfy those who are responsible for the approval of a new treatment that it is both safe and effectively treats the disorder for which it is designed.

In an ideal situation, any new treatment would have its effects predicted accurately using simple theoretical models, without exposing either animals or humans to risk. Unfortunately, people are very complex, so trials — both in animals and humans — are necessary to evaluate any new therapy.

The usual process involves some theoretical modelling (for example, antioxidants in Friedreich ataxia) followed by animal studies to provide some evidence that the theory being tested works; all being well, this is followed by trials in humans. At each step safety and ethics are important, but there are always common and conflicting needs that must be taken into consideration. For example, animal studies may take a year or more to complete, but these studies provide invaluable information on safety, dosage and effect, which can

be used when designing human clinical trials. However, even though the animal trials hugely improve our ability to predict the effect of treatment in humans, the same effects cannot be guaranteed 100%.

Thus, evaluation of new therapies in humans takes place in the context of what are known as *clinical trials*. Clinical trials are carefully designed and planned, and occur in a step-wise process. Each step in the process is identified as being a 'phase' and up to four 'phases' are common: phase I, phase I/II, phase III, phase IV. These are explained further below.

Many factors influence the design of a clinical trial. A clinical trial to evaluate a new treatment for migraine, for example, will be structured quite differently to a clinical trial for Friedreich ataxia. With migraine, many people can suffer from it and only one part of the body is affected. Unlike migraine, Friedreich ataxia is rare which means that patient numbers are quite small, and it affects the function of a variety of body systems (the nervous system and the heart for example). No two patients are affected in exactly the same way.

Because of this variation, clinical trials for Friedreich ataxia are quite complex and typically involve a number of tests on different parts of the body. An added complication is that because so many parts of the body can be affected, different symptoms may respond to treatment at different rates: some may take

several months to show improvement, whilst other symptoms may take a year or more, or not improve at all. A further complication in Friedreich ataxia is that symptoms are progressive, meaning that different problems become obvious at different ages, and become worse over time. However, not only is age important, but individuals with Friedreich ataxia also vary in the rate at which their symptoms progress. It is therefore important, in the interests of patients everywhere, that the clinical trial is designed very carefully so that the effect of the treatment can be measured accurately and in a way that shows very clearly that the improvement is directly related to the treatment and to nothing else.

Once the information is collected, it can then be presented to the appropriate regulatory authorities (e.g. the Australian Therapeutic Goods Administration, or the US Food and Drug Administration) for assessment of its safety and effectiveness before approving (or not) the marketing and use of the treatment.

Who is involved in a clinical trial?

There are many people involved in establishing clinical trials:

- the company that is developing the treatment;
 - the doctors~ nurses and others who will be involved in assessing the patient's response to the treatment;
 - the scientists, who have researched the treatment in the

laboratory and in animal models;

- the patients and their families; and
- the regulatory agencies who are responsible for assessing the treatment's safety and effectiveness

Each of these shares common interests:

- the company is interested in ensuring that the treatment works, and would like a return on its investment;
- the doctors are interested in seeing their patients get better;
- the scientists are interested in seeing their ideas applied to the patient and seeing the patients improve;
- the patients and families are interested in accessing the treatment as soon as possible to improve their or their child's quality of life; and
- the regulatory agencies are interested to ensure the therapy is safe and effective

All would like to ensure that the treatment is safe, both short term and long term.

However, there are also compromises that have to be made by all parties in the context of a clinical trial, particularly for Friedreich ataxia. For example, younger patients with more severe disease may show quicker improvement, but they are less able to understand and/or cooperate with the assessments and procedures required in the trial. Younger patients are still growing and so it is more

difficult to assess the effects of treatment in an individual who is constantly changing. How do we assess changes that may be due to growth, disease or treatment?

In individually rare disorders such as Friedreich ataxia, it is important to understand the progression and variability of the condition. Even though it may seem obvious to the patients, families and doctors that the symptoms of Friedreich ataxia become worse over time without treatment, careful documentation of individual variation in severity and progress is essential to allow the regulatory agencies to properly assess a treatment's effectiveness. The regulatory agencies are not experts in Friedreich ataxia and thus need to be convinced that improvement is directly related to treatment and not because the patient is improving on their own. Thus, natural history studies in the absence of treatment are not only valuable, but essential in the clinical trial process.

The *phases* of a clinical trial

Phase I trials are the first level of assessing a new treatment that will be given to humans for the first time. Many phase I trials are conducted in healthy volunteers. Phase I trials are primarily designed to assess the safety of a particular treatment, to determine the length of time it remains in the body's circulation, where it is distributed in the body, the preferred method of administration and assessing appropriate dosage levels.

Phase II trials are designed to assess both the safety and effectiveness of a proposed treatment. These trials are an extension of the phase I studies and usually compare the effects of treating patients with different doses of the same therapy to assess which is the more effective.

Phase III trials are also referred to as 'pivotal' trials. Phase III trials are held if the proposed treatment shows clinical benefit (and exceeds the potential harm caused by the treatment) in a phase II study. Usually a greater number of patients are involved in phase III trials and more than one treatment centre (sometimes in different countries) is involved. Again, because Friedreich ataxia is rare, the number of patients involved in a phase III trial is still quite small relative to other, more common disorders. Phase III trials for Friedreich ataxia may have as few as fewer than 100 patients, whilst phase III trials for common disorders such as diabetes may include tens of thousands of people. The information gained in phase III trials is submitted to the regulatory authorities for assessment of safety and effectiveness, and marketing approval.

Phase IV trials are usually conducted after a proposed therapy has received approval for clinical use (they can also be referred to as 'post-marketing studies'). These studies are primarily extension studies that involve using the approved treatment in a variety of different settings, for example, in studies that compare the approved

therapy with other potential treatments, or in combination with other therapies.

Because of the variability of Friedreich ataxia, in any clinical trial it is important to confirm that any changes being seen (either improvement or worsening) are due to the treatment and not due to the natural course of the disorder or other changes in treatment and general health care. There is also the so-called **placebo** effect, which is the very real effect in someone who is expecting a change (usually improvement) if they believe they are being given a treatment. This can be very significant, with some studies (e.g. anti-depressant therapy) showing up to 60-80% of people reporting an improvement when they receive only placebo and not the treatment being tested. These can be physical changes, such as temperature, growth etc. not just psychological. Effects of different doses also need to be considered.

Therefore there are different types of trials that can be conducted at each phase. In each type of trial different doses can be given, either **open** (the doctor and patient know the dose and whether it is drug or placebo) or **blinded** (the doctor and/or patient don't know). This allows more accurate assessment of responses and whether it is due to the new treatment or some other factor.

Open label trials: all patients involved in open-label trials receive the treatment that is being assessed. Both the patient and medical staff know that the patient is receiving the

treatment and the dosage.

Single-blind, placebo-controlled trials: patients involved in these trials are usually divided into two groups: some patients will receive the treatment that is being assessed and others will not. Those patients not being given the treatment will be given a 'placebo' instead. Patients involved in these types of trials do not know to which group they have been assigned, but the study doctor does ('single-blind'). Placebo-controlled trials enable the assessment of a treatment's effectiveness by comparing the results of patients receiving the treatment with those who are not. Usually, once the trial period is completed, patients who have been receiving the placebo are started on the therapy.

Double-blind, placebo-controlled trials: patients involved in these trials are usually divided into two groups: some patients will receive the treatment that is being assessed and others will not. A 'placebo' is given to those patients not receiving the treatment, as above, but in these trials neither the patients nor the doctors involved know which group each patient has been assigned to ('double-blind'). Double-blind placebo-controlled trials enable the most accurate assessment of a treatment's effectiveness by comparing the results of patients receiving the treatment with those who are not and eliminating any bias that may be potentially introduced by factors such as the "placebo effect", or other factors affecting outcome such as improvements in nutrition

and general health care (especially if comparisons are made with treatment outcomes from old data or if bias occurs in the reporting of results). These trials are often given the most "weight" when the regulatory authorities are looking at the evidence for or against a drug's effectiveness. Usually, once the trial period is completed, patients who have been receiving the placebo are started on the therapy.

Trial Design

Even with all the different phases and types of trials there must be compromise in trial design. For example, with conditions such as Friedreich ataxia, which are life-long and become worse over time, it is likely that treatment will be life-long. Long-term effects of treatments can be difficult to predict, so from a safety perspective a trial should be as long as possible (? lifelong). This would, however, delay the approval of treatment for use in all of those people not involved in the trial and it would also significantly increase the cost! Patients with more severe disease at the beginning of a trial may show more obvious or rapid improvement; on the other hand their disorder may have progressed to the extent that some effects may be irreversible. The importance of this will depend on the factors being assessed in a trial. The trial sponsors obviously want to show reasonably rapid improvement to allow marketing and more widespread use. Adult patients are usually preferable as they can make their own decisions regarding potential risks and benefits but they

may have disease that has progressed to the irreversible stage. Adults are usually more co-operative and often more motivated to volunteer, especially where effort-based assessments are involved (such as a walk test). Adults also have stopped growing so it can be easier to assess whether an improvement is due to treatment rather than growth.

In a placebo controlled, double blind trial there is also a need for some patients to receive the placebo. This can seem unfair so volunteers need to be prepared for this eventuality (again, often easier for adults to understand than children). Most trials have a monitoring panel who will stop the trial as soon as a benefit or otherwise is determined so that it is not too unfair for those on the placebo group, but again this is a difficult decision for those who may wish to take part in the process. In an ideal situation, the placebo group will include participants with as near as possible identical disease to those in the treatment group but unless there are a lot of identical twins or even triptets, this is not usually possible.

The aim, then, is to design a trial with careful selection of the type of tests, and selecting patients who may show improvement with the new treatment in as short a time as possible whilst still giving enough long term data to ensure safety and confirm ongoing benefit.

These and many other factors, e.g. availability of certain investigators, the geographical location of patients,

availability of tests, and the effects of disease, all need to be considered with the aim of providing proof of safety and effectiveness within the appropriate timeframe. This information can then be presented to the regulatory agencies so they can make an informed judgement about whether to approve the treatment for general use or not. Sometimes, approval is given subject to further studies (phase IV).

Patient Selection

As can be seen from the above, there are many factors to be considered in the design of a trial and the selection of patients. To those who are not selected, the process can seem arbitrary and unfair. The ultimate aim, however, is to ensure safety and provide appropriate treatment to all (including those not selected) as soon as reasonably possible.

- the company that is developing the treatment;
 - the doctors, nurses and others who will be involved in assessing the patient's response to the treatment;
 - the scientists, who have researched the treatment in the laboratory and in animal models;
 - the patients and their families; and
 - the regulatory agencies who are responsible for assessing the treatment's safety and effectiveness

Each of these shares common interests:

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However, there are also compromises that have to be made by all parties in the context of a clinical trial, particularly for Friedreich ataxia. For example, younger patients with more severe disease may show quicker improvement, but they are less able to understand and/or cooperate with the assessments and procedures required in the trial. Younger patients are still growing and so it is more difficult to assess the effects of treatment in an individual who is constantly changing. How do we assess changes that may be due to growth, disease or treatment?

In individually rare disorders such as Friedreich ataxia, it is important to understand the progression and variability of the condition. Even though it may seem obvious to the

patients, families and doctors that the symptoms of Friedreich ataxia become worse over time without treatment, careful documentation of individual variation in severity and progress is essential to allow the regulatory agencies to properly assess a treatment's effectiveness. The regulatory agencies are not experts in Friedreich ataxia and thus need to be convinced that improvement is directly related to treatment and not because the patient is improving on their own. Thus, natural history studies in the absence of treatment are not only valuable, but essential in the clinical trial process.

Friedreich Ataxia, the oxidative stress paradox.

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Friedreich ataxia (FRDA) results from a generalized deficiency of mitochondrial and cytosolic iron—sulfur protein activity initially ascribed to mitochondrial iron overload. Recent in vitro data suggest that frataxin is necessary for iron incorporation in [Fe—S] cluster (ISC) and heme biosynthesis. In addition, several reports suggest that continuous oxidative damage resulting from hampered superoxide dismutases (SODs) signaling participates in the mitochondrial deficiency and ultimately the neuronal and cardiac cell death. This has led to the use of antioxidants as

idebenone for FRDA therapy. To further discern the role of oxidative stress in FRDA pathophysiology, we have tested the potential effect of increased antioxidant defense using an MnSOD mimetic (MnTBAP) and Cu,ZnSOD overexpression on the murine FRDA cardiomyopathy. Surprisingly, no positive effect was observed, suggesting that increased superoxide production could not explain by itself the FRDA cardiac pathophysiology. Moreover, we demonstrate that complete frataxin—deficiency does not induce oxidative stress in neuronal tissues nor alters the MnSOD expression and induction in the early step of the pathology (neuronal and cardiac) as previously suggested. We show that cytosolic iron-sulfur (Fe-S) cluster assembly activity of IRP—1 progressively decreases while its apo-RNA binding form increases despite the absence of oxidative stress suggesting that in a mammalian system, the mitochondrial Fe-S assembly machinery is essential for cytosolic Fe-S biogenesis. In conclusion, our data demonstrate that in FRDA, mitochondrial iron accumulation does not induce oxidative stress and we propose that, contrary to the general assumption, FRDA is a neurodegenerative disease not associated with oxidative damage.

Frataxin deficiency in pancreatic islets causes diabetes due to loss of beta cell mass.

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Diabetes is caused by an absolute (type 1) or relative (type 2) deficiency of insulin-producing beta cells. We have disrupted expression of the mitochondrial protein frataxin selectively in pancreatic beta cells. Mice born healthy but subsequently developed impaired glucose tolerance progressing to overt diabetes mellitus. These observations were explained by impairment of insulin secretion due to a loss of beta cell mass in knockout animals. This phenotype was preceded by elevated levels of reactive oxygen species in knockout islets, an increased frequency of apoptosis, and a decreased number of proliferating beta cells. Hence, disruption of the frataxin gene in pancreatic beta cells causes diabetes following cellular growth arrest and apoptosis, paralleled by an increase in reactive oxygen species in islets. Our observations might provide insight into the deterioration of beta cell function observed in different subtypes of diabetes in humans.

Friedreich ataxia mouse models with progressive cerebellar ~ sensory ataxia reveal autophagic neurodegeneration in dorsal ganglia.

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Friedreich ataxia (FRDA), the most common recessive ataxia, is characterized by degeneration of the large sensory neurons of the spinal cord and cardiomyopathy. It is caused by severely reduced levels of frataxin, a mitochondrial protein involved in iron-sulfur cluster (ISC) biosynthesis. Through a spatiotemporally controlled conditional gene-targeting approach we have generated two mouse models for FRDA that specifically develop progressive mixed cerebellar and sensory ataxia, the most prominent neurological features of FRDA. Histological studies showed both spinal cord and dorsal root ganglia (DRG) anomalies with absence of motor neuropathological hallmark of the human disease. In addition, one line revealed a cerebellar granule cell loss, whereas both lines had Purkinje cell arborization defect; These lines represent the first FRDA models with a slowly progressive neurological degeneration. We identified an autophagic process as the causative pathological mechanism in the DRG, leading to removal of mitochondrial debris and appearance of lipofuscin deposits. These mice therefore represent excellent models for FRDA to unravel the pathological cascade and to test compounds that interfere with the degenerative process.

Hum Mol Genet. 2004 May 15;13(10):1017-24.

Idebenone delays the onset of cardiac functional alteration without correction of Fe-S enzymes deficit in a mouse model of Friedreich ataxia.

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Friedreich ataxia (FRDA), a progressive neurodegenerative disorder associated with cardiomyopathy, is caused by severely reduced frataxin, a mitochondrial protein involved in Fe-S cluster assembly. We have recently generated mouse models that reproduce important progressive pathological and biochemical features of the human disease. Our frataxin-deficient mouse models demonstrate time-dependent intramitochondrial iron accumulation. Here we report a more detailed pathophysiological characterization of our mouse model with isolated cardiac disease by echocardiographic, biochemical and histological studies and its use for placebo-controlled therapeutic trial with Idebenone. The Fe-S enzyme deficiency occurs at 4 weeks of age, prior to cardiac dilatation and concomitant development of ventricular hypertrophy, while the mitochondrial iron accumulation occurs at a terminal stage. From 7 weeks onward, Fe-S enzyme activities are strongly **decreased** and are associated with lower levels of oxidative stress marker as a **consequence of reduced respiratory chain activity.**

Furthermore, we demonstrate that the antioxidant Idebenone delays the cardiac disease from progression and death of frataxin deficient animals by 1 week, but does not correct the Fe-S enzyme deficiency. Our results support the view that frataxin is a necessary, albeit non-essential, component of the Fe-S cluster biogen and indicate that Idebenone acts downstream of the primary Fe-S enzyme deficit. Furthermore, our results demonstrate that Idebenone is cardioprotective even in the context of a complete lack of frataxin, which further supports utilization for the treatment of FRDA.

Trinucleotide repeats and neurodegenerative disease

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Major insights have been attained into the molecular pathology of the trinucleotide repeat neurodegenerative diseases over the past decade. Genetic definition has allowed subclassification into translated polyglutamine diseases, which are due to CAG repeat expansions, and a more heterogeneous group in which the trinucleotide repeat remains untranslated. The polyglutamine disorders are due to a toxic gain of function of mutant expanded proteins. Neuronal intranuclear inclusions (NIIs) characteristically occur. Protein misfolding, interference with DNA transcription and RNA processing, activation of apoptosis and dysfunction of

cytoplasmic elements have all been invoked in the toxic process. The end result is apoptotic cell death with many aspects of neuronal function being perturbed. Promising progress has been made into arresting and reversing neurodegeneration in both cellular and animal models. The molecular mechanisms underlying the untranslated group remain less clear. Impedance of gene transcription secondary to abnormal DNA structures formed by repeats, modification of chromatin gene packaging and dysfunction at the RNA level have all been suggested as possible pathological mechanisms. These diseases remain irreversible. It is hoped that clarification of the molecular pathogenic mechanisms will provide the tools for future therapeutic intervention.

LATE ONSET CEREBELLAR ATAXIA (LOCA) IN SOUTH WALES, UNITED KINGDOM

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Assessment of ataxia by clinicians is made difficult by widely variable clinical features and multiple causes. As a result, adult patients presenting with symptoms and signs of late onset cerebellar ataxia (LOCA) impose considerable diagnostic difficulties. In addition, the classification of this group of disorders remains controversial. However, LOCA may be subdivided into those patients with acquired, genetic and non-hereditary ataxias. Most cases are sporadic with an

underlying acquired aetiology such as toxins, malignancy or vitamin deficiency. The second most common group are those patients in whom ataxia is non-hereditary and degenerative in nature and remain idiopathic despite extensive investigations, whilst genetic or antibody-mediated causes represent a minority of patients. However, the number of patients affected and the frequency with which these aetiologies occur is poorly documented and information is usually limited to that derived from groups of patients seen in specialist clinics.

Scientific advances over last decade have created new opportunities for improving diagnostic accuracy for patients with ataxia and their families. These include identification of tandem repeat expansions in numerous spinocerebellar ataxias (SCA) and Friedreich's ataxia (FRDA), and detection of specific anti-neuron antibodies allowing earlier identification of patients with underlying occult malignancy or coeliac disease. As a result, patient management as well as clinical classification have benefited, and this has allowed some reduction in the large proportion of LOCA patients previously considered to be idiopathic (ILOCA). Previous epidemiological studies, both in the UK and wider afield have tended to focus on the inherited ataxias. Reported estimates from these populations suggest 1 to 40 per 100,000 are affected with this disorder. These studies have also identified wide geographical variations in the frequency of SCA mutations as well as between ethnic

groups. However, it remains the case that little is known about the numbers of patients affected with ataxia in the UK or what clinical or social impact the disorder has. This information is important since it contributes to public health mer. heine decisions on the allocation of health care resources, and provides information for the patient, the patient's family, health care workers and clinicians on how to manage the disease.

In an attempt to increase available information on ataxia in the UK, we are performing a detailed study of a large population in SE Wales as part of a larger study into the causes of ataxia. Patients were included in this study if they had a predominantly progressive cerebellar ataxia with onset of symptoms aged a 18 years and disease duration of a 1 year. Cases with known acquired ataxias, ataxic syndromes with associated prominent autonomic dysfunction and/or atypical parkinsonism suggestive of multiple system atrophy (MSA) and disorders with ataxia as a minor feature were excluded but some limited clinical data was also collected on these patients.

Our population-based study is examining a region with a population of 1.8 million (Office of National Statistics, 1999) comprising three health authorities [Bro Taf Health Authority (BTHA), Gwent Health Authority (GHA) and Iechyd Morgannwg Health Authority (IMHA)]. A preliminary study to establish data collection and sample storage has been completed in the BTHA which has a population of 742 400.

The BTHA serves a relatively large and stable population of SE Wales and has been proven to be an effective epidemiological resource for studies of other neurological diseases. It has well-established regional referral patterns for both neurosciences and medical genetics and we were able to achieve a high level of cooperation from GPs with 80% of practices participating in case notification. Multiple alternative sources were also used including hospital databases, consultants etc. to make sure we were able to identify all resident patients.

Overall we managed to identify 409 cases in a provisional register from multiple sources. After carefully checking clinical details of these patients from hospital records, 333 (81.4%) were excluded. This left 76 (18.6%) cases, of whom 13 had a family history of a similar disorder, in seven familial cases, no cause was identified but six had an established genetic basis [SCA 6 (n=2); FRDA (n=2); dominant episodic ataxias (EA) (n=2)]. This information provides disease frequency rates of 8.4 per 100 000 (95% CI: 7.2 to 11.6) for sporadic, idiopathic LOCA (ILOCA) and 1.8 per 100 000 (95% CI: 0.8 to 2.7) for inherited LOCA. If this pattern was mirrored in England, Northern Ireland and Scotland, our data would suggest that more than 6000 people are affected with this form of ataxia in the UK.

For those patients (36.7%) with acquired ataxia who were excluded from the main prevalence study, the commonest causes, in order of decreasing frequency were: multiple sclerosis (43.2%), isolated and

familial spastic paraparesis (29.5%), cerebellar tumours (13.6%) and alcoholic cerebellar degeneration (6.8%). Of the remaining 99 cases excluded from the study, 38 (38.8%) had a congenital and/or early onset form of cerebellar ataxia.

From these preliminary results we have been able to gain some insights into the phenotype, disability and impairment of idiopathic LOCA that makes up the majority of the prevalent cases with ataxia within our region. The average age of these patients was 61.8 ± 13.2 years (range: as to 88) with a male predominance 10 (M:F=2:1). Average age at onset of symptoms was 53.8 ± 14.1 years (range: 19 to 78) with mean disease duration of 8.7 ± 6.3 years (range: 1 to 31). In addition, there seemed to be two distinct clinical groups: one-third had a relatively pure form of ataxia and two-thirds had additional non-cerebellar neurological features. In most of our patients, the disorder was slowly progressive with disability related to the disease duration. However, the majority of patients (78.2%) had a mild degree of disability, irrespective of disease duration. The majority remained ambulant (92%) but use of a walking aid was common. Wheelchair dependence was rare and only seen in patients with disease duration greater than 20 years. Ninety nine percent of patients had some form of daily assistance from a carer (usually a close relative or employee of social services) and the remainder were self-caring.

Final comment and further studies:

Our experience from this comprehensive population-based study has provided an insight into the frequency and clinical profile of LOCA in the UK. It has allowed us to establish a serum and DNA bank. We have taken considerable steps to establish a detailed disease register which we will hope to expand further to include patients with a wide range of acquired, inherited and idiopathic ataxias. We hope that this will create opportunities for further epidemiological, clinical and molecular studies into ataxia cases from a well-demarcated population base.

We have also been able to collect objective measurements of the severity of ataxia and the impact on patients' activities of daily living (ADL). We have tested a Ataxia Rating Scale (ARS) for reliability and validity in a cohort of patients, which takes into account the recent European network of cerebellar ataxia researchers (EUROSCA) plan for the development of such a scale. We will continue to develop our ARS in the hope that our experience with this scale might contribute to assessing the impact of future therapeutic trials.

In the future we hope to extend our study into the neighbouring areas (GHA, IMHA) which have similar neurological referral patterns and resources. This is likely to expand the register considerably, and we aim to collect data on around 800 patients and their families. This will enable us to improve our prevalence estimate for all causes of ataxia including acquired, genetic and idiopathic causes, and to more

closely determine the significance of relevant genetic mutations. We also hope to investigate the frequency of antineuronal antibodies in sporadic ILOCA patients, provide data on the severity of the ataxia and its impact on patients' activities of daily living, establish detailed longitudinal

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SUBSCRIPTIONS

Subscriptions are now due for members of the former Friedreich Ataxia Association (New South Wales) and those who are not currently members of a state FA organisation. The New South Wales body has been replaced by the new national body. All members of the former New South Wales Association have been included as members of the new national body. All financial members of other state FA bodies are also included as members of the national body and do not need to pay an additional annual subscription to the national association.

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PLEASE RETURN THIS FORM TO:

Mr Mike Dwyer
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