

# CFU Carers' Support Group



**For carers and relatives of people with fronto-temporal dementia and semantic dementia**

## **Newsletter**

**May 2009**

## Welcome

Welcome to the May issue of the Carers Support Group Newsletter!

Thanks to all of you who came along to the April meeting. We were joined by Professor David Mann, Senior Consultant Neuropathologist, who gave a fascinating talk on research into FTD and SD. Professor Mann has worked with Professor Neary and Dr Snowden for over twenty years, and has played an integral role in the department's breakthroughs and growth of the CFU's international research reputation. He spoke about Manchester's contribution to research into neurodegenerative disease, providing great insights into recent work and future plans. It was really interesting to hear how carers and patients too have made a huge contribution to scientific discoveries, simply by attending the CFU clinic.

If you find it difficult to attend the meetings, don't worry, we always provide a summary of the talks in the newsletter. Equally, if you have any ideas or questions about future talks, please feel free to get in touch, as we are always willing to consider new directions for the group:  
(Email: [cheryl.stopford@manchester.ac.uk](mailto:cheryl.stopford@manchester.ac.uk) or write to Cheryl at the Cerebral Function Unit, Department of Neurosciences, Salford Royal Hospital NHS Trust, Stott Lane, Salford, M6 8HD.)

## Housekeeping Notes

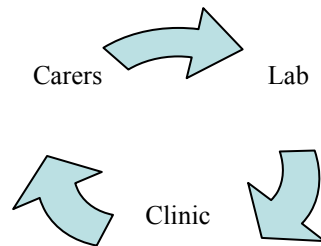
### The CFU carers support group website

It is easy to access any previous newsletters on our webpage by following the link below:

[www.cerebralfunctionunit.co.uk/carers.html](http://www.cerebralfunctionunit.co.uk/carers.html)

Our site also provides summaries of talks, carers questions and answers from previous meetings, links to useful resources such as Citizens Advice and Crossroads, and factsheets produced by the Alzheimer's Society that provide information about legal matters and looking after yourself. There is also a link to the general CFU website, where you can find information about our research and publications. There is also an 'Information for Clinicians' section produced specifically for doctors who may have limited knowledge of the conditions.

## Research into Frontotemporal Dementia – A Carer’s and Patient’s Contribution Professor David Mann, Senior Neuropathologist



The relationship between the CFU clinic, the research lab and the patients and carers is integral to develop research in the field of frontotemporal lobar degeneration (FTLD), which incorporates the syndromes of frontotemporal dementia (FTD), semantic dementia (SD) and progressive aphasia (PA).

The first case of FTD to be described in the literature was in 1892 by Arnold Pick, a Hungarian psychiatrist. It was known as ‘Pick’s disease’ for a long time thereafter.

**Appearance of the brain:** the frontal and temporal (side) regions of the brain are shrunken. The remainder of the brain remains relatively preserved, which gives rise to the term ‘frontotemporal atrophy’.

**Histology:** as you might imagine, it’s not just the outside appearance of the brain that changes – microscopically, the nerve cells inside also change. The appearance of these cells is shown by a process of ‘staining’, in which coloured chemicals (dyes) which have an affinity for particular structures in the brain are applied, which allows these structures to become visible under a microscope. Until the 1990s, these staining techniques were limited, but it was still possible to see that some of the cells contained rounded, ball-like structures – ‘Pick bodies’, while other cells appeared bloated and swollen – ‘Pick cells’.

In 1986, a study conducted by the CFU team examined the neuropsychology, neuropathology and neurochemistry of 24 of our patients by taking a sample, or biopsy, of the brain from patients while they were alive. They found that ¼ of these patients, who had until that point been assumed to have Alzheimer’s disease, had none of the clinical, histological or biochemical signs of Alzheimer’s disease. Instead, these patients appeared to have a different syndrome altogether. Following this discovery, the team here began to recognize more and more of these kinds of patients coming through the doors of the CFU.

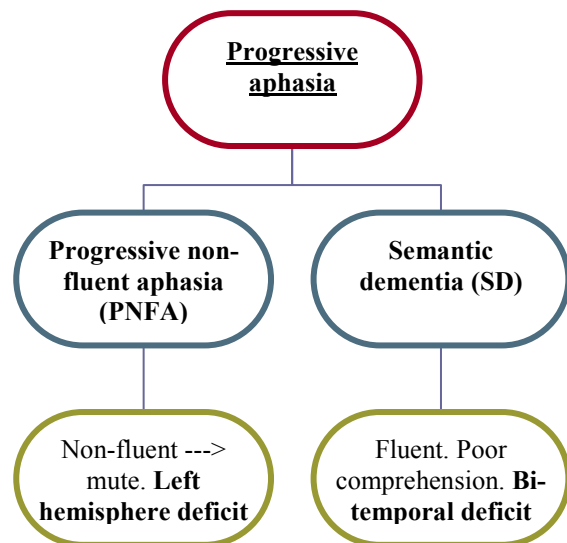
**Post 1986:** approximately 550 patients with FTLD have been reviewed in the CFU, and from these patients we have built what is probably the largest store of DNA blood and brain samples of any one centre world wide. Such donations by patients and their carers have been essential to the progress in our understanding of FTLD that we have been making over the past 20 years.

Because of this, we have been able to progressively refine our clinical assessment and neuropsychology methods to help in initial diagnosis. We have extended our neuropathological investigations which have helped us to understand the disease process. We have begun genetic analysis, which is helping us to understand what causes the disease, and how to predict the likelihood of an individual suffering with FTLD. We are also now looking at the role of biomarkers, which are changes in the proteins in the blood that can tell us what is happening in the brain at that point in

time. This may allow us to detect the disease at an earlier stage than can currently be achieved by clinical investigations.

**The Lund-Manchester criteria for FTD:** these criteria, based on our patients here at the CFU, were published in 1994 and are the gold standard in diagnosing FTD. They include the presence of early onset disease, sometimes with a strong degree of inheritance in families, changes in behaviour and personality but generally minimal effects on language, memory and vision in direct contrast with Alzheimer's disease.

**Progressive Aphasia:** These are primary disorders of language. Changes in behaviour and personality are present but are less marked than in FTD.



**PNFA:** patients experience problems in constructing language and communicating effectively.

**SD:** patients experience difficulties in understanding the meaning of words and objects. SD was first discovered by Dr Julie Snowden (Consultant Neuropsychologist).

**Tau pathology:** since the 1990s we have been able to use more sophisticated techniques to examine cells, including 'immunohistochemistry', in which antibodies which detect particular proteins are applied to the cell. The antibody will attach to its specific protein. We can then stain the cell with dyes and see the proteins of interest.

Tau is an important protein used in nerve cells to transport other proteins from where they are made to where they are needed. Other proteins vital to the health and wellbeing of the cell cannot reach their destination without the effective function of these tau proteins. When not working properly, tau proteins roll up into a clump thereby blocking the rest of the cell, stopping it from functioning properly. This kind of pathology is associated with mutations in the gene that produces the tau protein and is hereditary. 45% of patients with FTLD have tau pathology, about half of whom have a tau gene mutation. There are more than 30 different tau gene mutations which cause FTLD.

**TDP-43 (ubiquitin) pathology (2006):** ubiquitin is a protein which 'flags up' other proteins, which need to be degraded by the body, by binding to them and identifying them as 'rubbish' proteins. 18 months ago, in collaboration with scientists in Tokyo, we discovered which protein ubiquitin was signalling for destruction in FTLD – this is

called TDP-43. The normal function of the TDP-43 protein in the body is not well understood, and it is still not known how it becomes changed and accumulated in nerve cells in FTLD.

**Progranulin:** why are TDP-43 proteins targeted for destruction? In other words, why are TDP-43 proteins being incorrectly made in cases of FTLD? The cause was found accidentally. The function of TDP-43 proteins appears to be governed by another protein called progranulin which is made by the progranulin gene on chromosome 17. After scientists had been unable to find this disease causing gene by means of logical association, they took to randomly selecting genes present on chromosome 17 to analyse. One of the researchers, Jennifer Gass, first chose to look at the gene 'Adam-11', because her boyfriend was called Adam. When this was unsuccessful, she examined the gene 'Gastrin', because it sounded similar to her name. Again, this yielded nothing. She then chose to examine the gene 'Progranulin', because she liked to eat granola for breakfast and the name sounded similar. Bingo! So, mutations in the progranulin gene mean that TDP-43 proteins are not properly used. They are then signalled for destruction by ubiquitin. TDP-43 proteins are essential to the health and wellbeing of the cell – without this vital protein, the cell cannot function.

55% of patients with FTLD have TDP-43 pathology. So far more than 50 different progranulin gene mutations have been found to cause FTLD.

How do the tau pathologies and the TDP-43 pathologies result in the same disease?

- Progranulin gene mutations → protein deficiency.
- Tau gene mutations → disruption of the network used to transport proteins around the cell.

**Hypothesis:** failure to **produce** (progranulin mutation) or **deliver** (tau mutation) TDP-43 proteins → death of the cell.

Thanks to the discoveries of the role of malfunctioning tau and TDP-43 proteins there are now very strict guidelines in place to identify FTLD at post-mortem.

**Epidemiology of tau mutations:** Patients with one particular tau gene mutation have been found in the UK, USA, Canada and Australia. The patients with this mutation share the same genetic characteristics – they were all related. By a process of tracing back genetics across hundreds of years, it was discovered that an individual with this particular cause of FTLD first occurred in North Wales, on the Llwyn Peninsular near Anglesey, in approximately 1300AD. This person's genetic mutation has been passed on over 25 generations and has spread across the world thanks to emigration.

**Biomarkers:** through a simple blood test, researchers here and at the University of Lancaster are developing ways of measuring the level of tau and TDP-43 proteins in patients with FTLD. This may help to distinguish between the two types of pathology, which may one day be of therapeutic benefit – to be able to treat a disease, one first needs to know exactly what kind of disease one is dealing with.

**How to help future research:**

- **Continuation of clinic visits** allows us to understand more about how FTLD develops and refine diagnosis.
- **Blood samples** allow us to identify genetic mutations in patients. When more is understood about the impact of genetic mutations this will allow for genetic counselling, in which relations of a sufferer may be able to understand the potential risk of their developing FTLD.

- **Brain tissue donations** help us to identify the mechanisms of the disease, which is vital to discovering future methods of treatment and, possibly, prevention.

An interesting question was posed by one of our carers – why don't we tell the families of sufferers whether or not we have found a genetic mutation in their blood sample? The answer is that we do not yet understand the **penetrance** of a mutated gene, which is to say that we do not know how likely it is that a mutation will be expressed in an individual. It may be that having the mutation does not necessarily mean that a person will go on to develop FTLD. Without this understanding it would be irresponsible of us to provide this information if we are unable to offer any advice as to what a 'positive' result could mean. With further research into the genetics of FTLD and other types of dementia our understanding will grow.