



## **FRONTOTEMPORAL DEMENTIA – FACT SHEET**

### **Causes of dementia other than Alzheimer's disease**

There are many causes of dementia, other than Alzheimer's disease, involving degenerative disease (shrinkage) of the brain. Most common among these is frontotemporal dementia, and other important causes are Creutzfeldt-Jakob disease, Lewy body dementia, and Huntington's disease. All of these disorders result in shrinkage of key parts of the brain due to damage to, and loss of, nerve cells and their connections. The pattern of brain damage is however not the same as that seen in Alzheimer's disease, and this explains why persons suffering from these other conditions show different symptoms.

### **What is frontotemporal dementia?**

This illness was initially given the name "Pick's disease", following the first cases to be examined at post mortem, in 1923, by the German psychiatrist and pathologist, Alois Alzheimer. Alzheimer named the condition Pick's disease after the German Physician Arnold Pick who had studied, and written about, the patients while they were alive. This term is still sometimes used today, though mostly the name frontotemporal dementia is preferred.

### **What are the signs and symptoms of frontotemporal dementia?**

Frontotemporal dementia involves a disturbance of behaviour and personality such that patients suffer a change in their character from their previous selves. Initially, they may become disinhibited and restless, having to give up work through failure to concentrate or as a result of unsocial attitudes and actions towards their fellows. As the disorder progresses, the patient becomes less interested in their environment and may adopt a limited range of behaviours, often of a repetitive and ritualistic nature frequently involving hoarding, gluttony and food fads. There is lack of insight into their illness and the

person adopts an uncaring and unsympathetic attitude towards previous friends and family. In late stages, the person becomes apathetic and there is paucity of speech, this being limited to a few words or expressions often out of context of the situation. Finally, the person becomes mute. Nonetheless, in some instances a disturbance of language appears early, this presenting either in the form of a loss of the meaning of words and failure to recognise and name objects or people, or as an inability to generate speech with proper construction of phrase and sentence. These language changes may dominate the clinical picture for a long part of the illness and occasionally may remain the only symptoms. In other patients the clinical changes of motor neurone disease, involving a wasting and weakening of the limb muscles with (eventual) problems in swallowing and breathing, may occur in conjunction with the frontotemporal dementia – a condition called frontotemporal dementia with motor neurone disease.

### **Who is affected by frontotemporal dementia?**

Overall, frontotemporal dementia occurs in about 1 in 5000 people but because the onset of the illness usually occurs well before 65 years of age, it is the second most common cause of dementia amongst that age group. After 65 years of age the disorder occurs only rarely. Patients as young as 20-30 years of age have occasionally been seen. Men and women are both affected equally. A family history of a similar illness is common, as many as half the number of patients have been reported as having affected brothers or sisters, cousins or parent and grandparent. This is known as an autosomal dominant pattern of inheritance. The duration of the illness is often long, as much as 10-15 years is common.

### **How is frontotemporal dementia diagnosed?**

Clinical observations and tests of intelligence and concentration can suggest a likely

diagnosis but it is well known that personality changes and altered behaviour and attitude can often accompany the memory deficits of Alzheimer's disease, and that language disturbances can also sometimes occur in the latter condition. Nevertheless, careful psychological testing can usually distinguish the pattern of changes in frontotemporal dementia. Brain scanning will show a loss of tissue, and a reduction in its activity, in front parts of the brain, which over the years leads to considerable shrinkage and loss of brain weight in that area.

At post mortem, the brain shows massive loss of nerve cells from the brain. In patients where behavioural changes predominate, this cell loss is mostly from the frontal lobes of the brain, though in those patients where language changes principally occur, the cell loss may be mostly from the temporal lobes of the brain, or mainly from the left side of the brain involving both the frontal and temporal lobes. When motor neurone disease is present there is additional loss of the large nerve cells in the brain stem and spinal cord which regulate and produce muscular activity. In many instances of frontotemporal dementia there are specific structural changes in the nerve cells, which can be used to confirm the diagnosis. These take the form of bundles of accumulated but unusable proteins. In some instances the accumulated protein is one known as tau. This is a protein that is vital for making and maintaining proper channels of transport within nerve cells, through which other proteins essential for correct function can be distributed from the sites where they are formed in the cell to the sites where they are used. Without tau protein this intracellular transport is impossible and nerve cells eventually "run out" of the vital substances they need to live and function correctly. Sometimes these bundles are quite similar in structure to those seen in Alzheimer's disease (neurofibrillary tangles), whereas on other occasions they have a rounded appearance, quite different from tangles, and are known as Pick bodies. Nonetheless, in about half of all patients, including many of those patients who show an additional motor neurone disease, the accumulated protein is not tau but is composed of a different protein called ubiquitin. Ubiquitin protein forms a key part of the cell's mechanisms for the destruction of unwanted or unusable proteins. These findings suggest that cell death in frontotemporal dementia may be due to a toxic effect on nerve cells induced by the accumulation of these useless proteins.

## What causes frontotemporal dementia?

In some of the cases where frontotemporal dementia is inherited as an autosomal dominant disorder (ie in families where a close relative is also affected), a change (mutation) in a gene on chromosome 17 is now known to be responsible. This is the gene that makes the tau protein. So far, at least 30 different mutations in tau gene causing frontotemporal dementia have been identified. Some of these tau gene mutations alter the structure of the tau protein in such a way as to prevent it from carrying out its normal function, and also cause it to bundle up into the tangles and Pick bodies seen under the microscope. In other patients, the mutations cause the cell to make more tau protein than it can use, with the excess again being bundled into unusable tangles that choke the cell. However, in that half of patients who do not show such changes in tau protein, the cause of the illness is still unknown. It is likely that there are several other genetic changes responsible for causing the disease, and current research is concentrating on identifying changes in at least two other genes on different chromosomes, and also changes in a gene on chromosome 17 other than tau. Such genetic changes may be responsible for causing the pathological accumulations of ubiquitin protein seen in many patients where the accumulation of tau protein is absent. Nevertheless, there are still many patients with frontotemporal dementia for whom no close relative is known to have suffered from the illness, and in these individuals it is uncertain as to whether any genetic changes increasing susceptibility to disease are involved, or whether there are non-genetic or environmental causes for the illness.

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