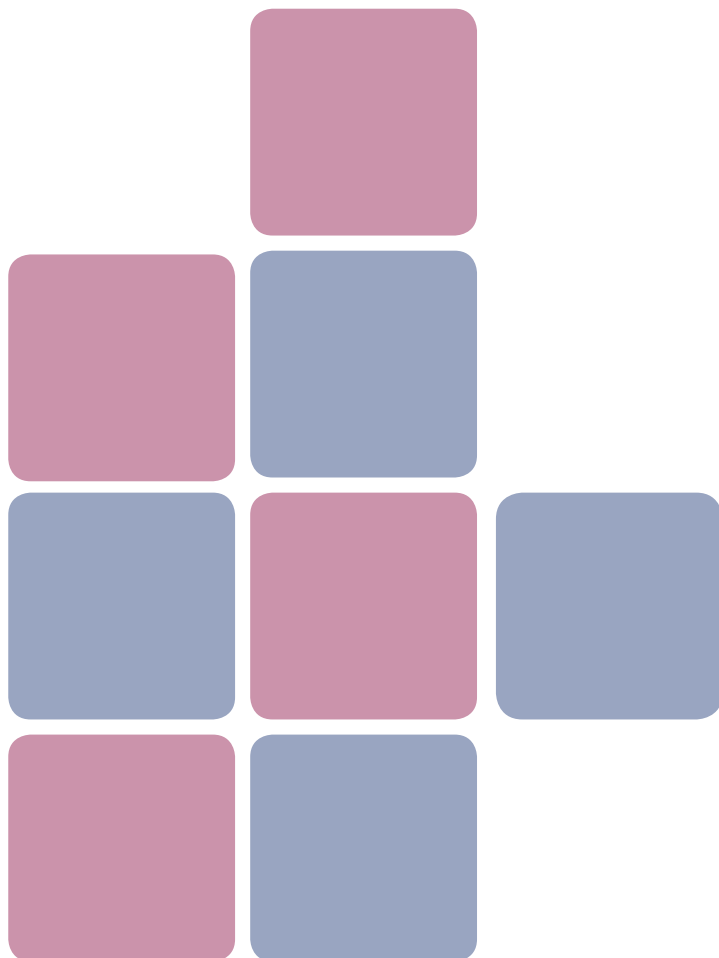


# Rare forms of dementia



*Final report of a project  
supported by the Community  
Rare Diseases Programme  
2000-2002*





Alzheimer Europe, Route de Thionville 145, L-2311 Luxembourg

# **Rare forms of dementia**

## **General Introduction**

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# Table of contents

<b>PREFACE</b>	<b>4</b>
<b>INTRODUCTION</b>	<b>8</b>
<b>DEMENTIA – DEFINITION - CONCEPT</b>	<b>12</b>
<b>EXPLANATION OF BRAIN</b>	<b>16</b>
<b>DIAGNOSTIC PROCEDURES</b>	<b>18</b>
<b>CARE AND TREATMENT</b>	<b>27</b>

## Preface

By Jean GEORGES

This report presents the results of the Alzheimer Europe project "Rare forms of dementia" which was financed in the framework of the rare diseases programme of the European Commission.

Rare diseases are described by the European Community Action programme as diseases of low prevalence "which is generally recognised as less than 5 per 10,000 in the Community".

While quite extensive work has been carried out on the prevalence of dementia, the same cannot be said for the various forms of dementia, which are covered in this report and for which epidemiological data are often either incomplete or missing. This presented us with an obvious problem at the outset of our project, in order to decide on which forms of dementia we should include and which fulfilled the criteria set out by the European Commission.

Although dementia does not only affect older people, the likelihood of developing dementia nevertheless increases with age. Thanks to the work of the European Community Concerted Action on the Epidemiology and Prevention of Dementia<sup>1</sup> group (EURODEM for short), it is possible to estimate how many people in a given country are likely to have dementia provided that accurate population statistics are available.

In the course of their work, members of the above-mentioned group pooled data on the prevalence of moderate to severe dementia in several European countries and came up with a set of prevalence rates for men and women in 9 different age groups.

Age group	Male	Female
30-59	0.16%	0.09%
60-64	1.58%	0.47%
65-69	2.17%	1.10%
70-74	4.61%	3.86%
75-79	5.04%	6.67%
80-84	12.12%	13.50%
85-89	18.45%	22.76%
90-94	32.1%	32.25%
95-99	31.58%	36.00%

By using the 2000 population figures of EUROSTAT and applying the EURODEM prevalence rates, it was possible to calculate the number of people with dementia living in the

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<sup>1</sup> For more details about this study, please refer to the article: Hofman, A. et al. (1991), The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings, International Journal of Epidemiology, Volume 20, No.3, pages 736-748.

European Union. Alzheimer Europe estimates this number at 4,731,576 in the current 15 Member States, which corresponds to a prevalence rate of 1.25% of the overall population of the European Union or, to use the Commission definition, 125 per 10,000.

It is clear that dementia in itself is not a rare phenomenon under the Commission definition and neither are the two most frequent causes of dementia, Alzheimer's disease or vascular disease.

While the EURODEM figures are generally accepted, it is far more difficult to find a breakdown of the various diseases covered by the definition of dementia. Often the percentages used vary quite considerably.

Alzheimer's disease is considered to be the main cause of dementia and according to the quoted research, should amount to between 50 and 75% of all causes. Vascular dementia is the second most common form of dementia and it is generally accepted that it accounts for between 25 and 50% of all cases of dementia.

For the purpose of our report, we have therefore concluded that all other forms of dementia account for maximum 25% of all forms of dementia, which would give us a prevalence rate of 31.25 per 10,000.

Fronto-temporal degeneration and Lewy body diseases would be the commonest of these rarer forms of dementia and it is generally accepted that they account each for about 5% of all cases of dementia or 7.81 per 10,000. Both of these categories though cannot be considered as one single disease, but rather as a spectrum of different diseases, which would individually fall under the Commission definition of "rare diseases".

Similarly, all other causes of dementia are even rarer and have been included in our report, as well as the rare forms of both Alzheimer's disease and vascular dementia. We found some 30 diseases or disease groups which are either rare in themselves or which lead to dementia in rare cases. For each disease we provide general outline, describe the symptoms and course, the causes and risk factors, the genetics, the frequency, the diagnostic procedures, as well as information on care and treatment, ongoing research and available services.

The expert group discussed possible ways on how to present these diseases and we ultimately opted for a classification system based on the causes of dementia, as this system had the advantage of grouping related diseases.

The biggest group of diseases is made up of **degenerative diseases**, which are characterised by a progressive loss of nerve cells and synapses. For most of these

diseases, the causes of this nerve loss are unknown and our knowledge about possible treatment or prevention remains limited.

**Infectious diseases** are caused by an infectious agent, such as a virus or prion.

**Metabolic diseases** are a group of often treatable diseases which may lead to dementia and which are caused by an under-activity or over-activity of a part of the human metabolism.

**Traumatic diseases** are caused by a trauma and in the disease described in this report by repeated head trauma.

**Toxic diseases** are caused by the consumption of substances, which are harmful to the human body.

**Cerebro-vascular diseases** are diseases of the blood vessels in the brain, which are the second most common cause for dementia.

When describing the various diseases, we have attempted to be as complete as possible, yet we also noted that for a lay reader some information may be too technical or that repetitions between various diseases would have become necessary.

For these reasons, the expert group decided to include some introductory chapters to the disease definitions.

In the introduction, **Clive EVERS** highlights the importance of dedicating a report to rare forms of dementia and reminds us of the very special needs and expectations of people suffering from rare forms of dementia and their carers.

In the chapter on "Dementia", **Alexander KURZ** reminds us that dementia is not a disease, but rather a syndrome which can be caused by a number of various diseases and provides a definition of dementia that is useful for the understanding of the following chapters.

The chapter on "The human brain" by **André DELACOURTE** gives an overview of how the brain functions and provides some information to link the apparition of symptoms to the areas of the brain which are affected.



To help us understand the information on diagnosis in the disease descriptions, **Giuliano BINETTI** has dedicated the chapter on “Diagnostic procedures” to an explanation of the various tools that doctors use to come to an accurate and differential diagnosis.

Similarly, the chapter on “Genetics of dementia” by **Jos van der POEL** is aimed at helping the reader to understand the information on genetics for the various diseases described by describing the various forms of transmission of genetic diseases. At the same time, she raises some of the ethical points involved in genetic testing.

In the final introductory chapter on “Care and treatment”, Clive EVERS addresses the impact of a diagnosis of dementia on a person and his/her family and highlights some of the care and treatment approaches which are relevant to the great majority of rare dementias covered in this report.

On behalf of Alzheimer Europe, I wanted to thank the above-mentioned experts for their contributions, as well as Sandrine LAVALLE, the Communication Officer for the coordination and support of the work carried out in the framework of the project and hope that the collected information will prove useful to all people interested in the rarer forms of dementia.

**Jean Georges**  
**Executive Director**

## Introduction

By **Clive EVERS**

By definition there are relatively low numbers of people affected by the extensive range of these diseases in any population. Despite this they have a major impact on health and social services, voluntary organisations, carers families and patients.

While most of the diseases have different symptoms and consequences they all have some features in common:

- They are characterised by severe and often progressive, cognitive, physical, psychological and behavioural impairments.
- They have a profound impact on the lives and capabilities of the people who develop the diseases.
- They require major long-term commitments in many cases from both health and social care services
- The majority require skilled specialised diagnosis and assessment
- A significant number of these diseases are treatable and need early identification

Whilst dementia is associated mainly with older people, in the range of rare diseases described here many patients may be 'younger' and below retirement ages. This will bring special needs.

At primary care level GPs, practice nurses social workers and other professionals may not have any experience of treating individuals with these disorders. Currently because of the low incidence of people with these diseases together with a lack of specialised hospital, residential or nursing home facilities, many people with rare dementias' receive inappropriate care. They are for example sometimes inappropriately placed in acute hospital wards (medical and psychiatric), nursing homes for elderly mentally ill people and private hospitals located far away from families.

Sometimes patients are categorised as having predominantly physical disorders and this can result in insufficient care for psychiatric, behavioural, emotional and cognitive problems that often develop. In fact people with brain diseases and brain damage are at greater risk of mental health problems and disorders than the general population. Their carers are also more liable to depression and other illnesses resulting from the stress of providing care to a close relative or friend whose life and personality has changed.

A significant number of these diseases are well represented in some European countries by nationally networked voluntary and charitable organisations such as the Huntington's Disease Association, Alzheimer's Societies, Motor Neurone Associations, Multiple Sclerosis Societies etc.

These organisations have played an increasingly important role in supporting people affected and their carers and in providing updated information about the disorders to primary healthcare teams.

Research and practice has shown that patients and carer's value a range of key skills and services to assist in treatment and management.

### **Expert assessment and accurate diagnosis especially of symptoms and behaviours**

In acquired brain injury, whilst health professionals can give good attention, the condition itself was often misunderstood. In frontal lobe dementia, carers wanted early diagnosis as in hindsight they felt guilty about their inappropriate responses to the patients behaviour when they were not yet diagnosed.

### **Need for appropriate facilities for rehabilitation, respite care and support**

Patients are often placed in facilities that do not offer rehabilitation. The only residential respite that is available is often a home for elderly people with dementia or on an acute psychiatric unit. These facilities do not meet the individual needs of people with rare dementias.

Specialist information and advice needs to be available about the range of rare dementia's and about what services and support may be available.

Employment and legal advice will be particularly important for patients still of working age

Individual and family counselling may be needed for patients and carers who have young children

Centres of expertise and specialism are much valued. For example there is evidence that there are growing numbers of such centres for people with Huntington's disease and carers. But the supply and availability of them remains limited in relation to demand.

Genetic counselling is much in demand for these diseases e.g. Frontal Lobe Type Dementia, Familial Autosomal Dominant AD, Familial Parkinson's Disease, Huntington's Disease, Familial CJD all require and benefit from prompt, expert and supportive genetic counselling services.

Continuity of care is much valued but rarely available. For example it is far preferable that a patient with Huntington's attending a specialist unit on a day care basis is enabled to become a resident when needed rather than being moved somewhere new.

Clearly defined care pathways are important especially at times of transition when a patient is passed from one service to another. The completion of comprehensive assessments and prompt and accurate referrals will avoid distress and confusion for patients and carers.

Where they exist community mental health teams can be very supportive. Regular visits from a community psychiatric nurse can provide continuity with the range of health services and provide opportunities for regular review of patients.

The best environment for improving and developing services for this group of people is where there already exists a clinical team with a special interest. When this happens the services in the area tend to focus their efforts on gathering information about requirements, providing advice and support to family carers and primary healthcare teams, and building links with other specialist services such as neurology, genetics, and psychiatry of old age. Such a setting is also likely to stimulate the development of new services in association with any leading charities for the conditions.

More outreach services are needed. Where specialist psychiatric services may exist for some of these diseases they tend to have a strong inpatient focus. This results in a limited impact on the local populations and services outside the immediate vicinity.

Effective commissioning of services for these groups is best achieved by proper assessments of local needs. Commissioning could be very effective because the target populations are small and well defined. In the main these diseases are well-defined clinical entities which can be diagnosed through specialist services. Although the exact course of an illness cannot be defined for each patient the general pattern of symptoms and needs are often similar within in group of conditions and this makes forward planning easier.

In some countries (UK) complex care programmes (within the Care Programme Approach CPA) have been found to be effective for these groups of patients when taken on by mental health teams.

The intervention of care co-ordinators, case managers and link nurses in the post diagnosis period is important. They can reduce the stress on carers and lead to more effective use of scarce health resources( e.g. by preventing crises, which result in lengthy hospital admission.)

Consulting service users and carers in order to develop effective provision should be seen as pivotal in the development of services and is now increasingly required by regulation in some countries.

It is important to recognise that patient and carers needs do not end with the acute stage of diagnosis and management. Many of these patients will have clinical needs over many years and continuity of care is essential.

Specialist neuropsychiatry posts have been established in some countries in which the psychiatrist has specialist neurological as well as behavioural and psychiatric expertise. Such posts can make a major contribution to the diagnosis, assessment, support and care of these patients.

Specialist memory clinics have developed in some countries e.g. UK and they are useful referral points for people with e.g. early onset dementia. They are run by many different disciplines and offer high quality assessment services. They can be particularly useful in identifying the treatable disorders that are present in up to 10% of people with early onset dementia. [www.memory.kingshill-research.org](http://www.memory.kingshill-research.org)

Multi-disciplinary working is also essential in the assessment, care and management of people in these client groups. Alongside medical and nursing staff, important contributions are made by clinical neuropsychologists, occupational therapists, speech and language therapists, social workers, rehabilitation technicians and others. The integration of specialist social workers in healthcare teams can provide individual workers with more specialised knowledge of these conditions and their consequences.

## Dementia – Definition - Concept

by **Alexander KURZ**

In Western countries approximately 6 % of the population at the age of 65 years or above is in a condition termed dementia [10]. Dementia is not a disease but a pattern of symptoms (or a syndrome, in medical language), which can be caused by an almost infinite number of cerebral and extra cerebral diseases. According to current diagnostic criteria the pattern is defined by changes of observable behaviour on three different levels.

- Patients perform significantly worse than their age peers on tests of cognitive ability including memory and at least one other domain such as attention, temporal and spatial orientation, language, and executive functions (planning, organising, problem solving, judgment) [21].
- Patients have a reduced ability to carry out activities of daily living. More complex activities such as managing the bank account, organising the household or arranging travel, are impaired first, while basic activities such as dressing, grooming, preparing simple meals, eating, or using the toilet are affected later [5].
- In addition to impairments of cognition and activities of daily living, patients with dementia show significant alterations of personality (loss of interests, apathy), social conduct (indifference to others, tactlessness, aggressiveness, disinhibition) and emotional control (outbursts of anger, tearfulness and mood swings) [3].

This definition of dementia is very broad and covers a number of different clinical presentations which depend primarily on the cerebral localisation of the underlying disease. The temporo-parietal type is characterised by impairments of memory, orientation, language, recognition and handling of objects [23]. Changes of personality and social conduct as well as impairment of judgement and problem solving, are the hallmarks of the frontal type which may be associated with either apathy or agitation [6]. In the subcortical type, slowing of information processing and changes of affect are associated with frontal symptoms [13]. It is important to note that the current definition links dementia to the presence of a significant impairment in activities of daily living, i. e. to a certain level of disability. In most diseases, which ultimately lead to dementia, this stage of clinical severity is only reached when a significant degree of brain damage has accumulated. Therefore, the goal of early diagnosis is to identify these diseases before dementia has developed [16].

Dementia must be distinguished from normal ageing and from two other symptom patterns (or syndromes), which occur relatively frequently in the elderly: amnesia and delirium. The deterioration of some cognitive abilities which can be associated with normal ageing is very slow and never shows the observable decline within one or two years as it is seen in dementia [17]. Furthermore, in normal ageing there is no significant loss of

activities of daily living due to impaired cognition. Amnesia is a state of relatively isolated memory impairment in the absence of significant changes in personality, social conduct, and emotional control [8]. Delirium is a symptom pattern which usually occurs in acute brain diseases. The characteristics of delirium are rapid onset, fluctuating course, and clouding of consciousness which becomes apparent in a reduced ability to focus and shift attention. Patients are usually disoriented: they may have vivid hallucinations, delusions, and agitation [9].

Dementia can be caused by a large number of diseases some of which affect only the brain while others affect the body as a whole. For the purposes of the present documentation we have classified these diseases into six main categories (neurodegenerative, infectious, traumatic, toxic, cerebro-vascular and metabolic). Of these categories, neuro-degenerative diseases represent the largest group [7]. They are characterised by a progressive loss of nerve cells and synaptic connections. The second largest category of dementia causes comprises diseases of brain blood vessels. By reducing or cutting off blood supply they result in large or small infarcts as well as in demyelination of the fibers connecting nerve cells [18]. Compared to these two categories, traumatic, toxic, infectious, and metabolic causes of dementia are rare. Nevertheless these categories are important because in several of these diseases dementia may be reversible by adequate treatment [22].

As mentioned above, neuro-degenerative and small-vessel cerebro-vascular diseases which account for the majority of dementias are gradually progressive. Over extended periods of their course they are clinically silent because the brain can compensate a remarkable amount of pathology. Only when nerve cell and synaptic loss has reached a certain threshold symptoms become apparent. Initial symptoms consist in minor impairments of memory, attention, and executive functions, or in slight changes of personality, social conduct, and initiative. These symptom patterns represent a pre-dementia stage of a number of diseases and are termed „mild cognitive impairment“ [14]. Different definitions of mild cognitive impairment have been proposed, some of which focus on memory impairment [15] while others are broader [4]. Follow-up studies have consistently demonstrated that patients with an amnesic type of mild cognitive impairment are likely to develop dementia at an annual rate of 12 to 15 % [12]. At post-mortem examination over 80 % of these subjects show neuro-pathological changes consistent with Alzheimer's disease, whereas fronto-temporal degenerations, Parkinson's disease, and cerebro-vascular disease are rare causes [11].

For the affected individual having dementia is associated with a progressive loss of abilities, personal autonomy, social roles and gratifications. Quality of life is further reduced by non-cognitive symptoms including depression, agitation, anxiety, delusions, illusionary misidentifications, and hallucinations. At later stages of dementia, physical symptoms such as epileptic seizures, difficulty swallowing, and gait disorder also occur. The management of dementia must therefore aim at maintaining cognition as well as

activities of daily living and physical well-being for as long as possible, and to minimise non-cognitive symptoms, combining pharmacological and non-pharmacological treatment strategies. For family members living with a demented person means a heavy and continuous burden which significantly increases the probability of psychological and physical morbidity [1]. The loss of a loved one, a change of roles and responsibilities, and withdrawal of relatives and friends all contribute to caregiver burden. Non-cognitive symptoms are more closely associated with caregiver distress than impairment of cognition or loss of activities of daily living [2]. Importantly, these symptoms frequently precipitate nursing home admissions [20]. Hence, providing advice and support to caregivers and improving their ability to cope with disease-related problems is another essential part of dementia management [19].

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## Explanation of brain

by **André DELACOURTE**

Our nervous system receives information from the outside world, via our eyes, ears, nose and other sensitive captors (from the skin for example). This information is processed in the brain by nerve cells, analysed and integrated with our own information, our knowledge and our experience. The result of the integration generates an adapted response, an action if necessary, a storage in our memory if the information is interesting or important. All this work is performed by different specialised nerve cells, also known as neurons, that are gathered in specific neuronal populations that have different and specialised roles and location. Their function is to transport and to store the information (memory), or to trigger the activity of other cells (muscle fibers for example).

The information is transported along neuronal extensions of nerve cells, called the axons. Information can jump and circulate to another neuron via a "synapse", which is located at the end of the axon. The synapse bridges the gap between each neuron and allows the next neuron in the chain to be activated.

### The brain: how it works

The brain works like a computer. Each neuron can be considered like a chip. But in a brain, we have billions of neurons. Each neuron receives thousands of information simultaneously from other neurons. All the information, received as micro-electric currents, is processed, analysed, integrated and then the resulting information is delivered to the appropriate neuron, via a synapse, for a specific task.

For example, for vision, the eyes receive the visual information through numerous and specialised photoreceptors distributed on the retina. The visual information is then transported along axons, via a subset of neuronal population (colliculus), towards the occipital cortex. This part of the brain is like a computer screen. The virtual image from the eye is reflected on this special screen. The information corresponding to the image is then transported to other brain areas to be analysed. The picture of the screen on the occipital pole (which is a primary visual area) is then analysed in secondary visual areas, and recognised as a specific object such as "an apple" for example. This recognition is the result of a comparison of the shape of the object with our knowledge of objects stored in the secondary visual areas (occipital regions around the occipital pole). Then the information is processed progressively (but very rapidly) by all other brain areas, at higher intellectual levels: the apple is recognised as a "golden" apple. The word will be pronounced, via a work of the language areas. If you do not like apples, you will be reminded of this by other brain areas involved in feelings and emotions, namely the limbic system. If you are hungry, the perception of an apple will push you to grab it. If you grab

the apple, you will activate your motor brain areas located in the upper part of the frontal cortex that will activate the nerves of your arms, then the muscles to grab the apple. In fact, the functioning of the brain is logical and easy to understand in its main lines. But to work properly, the mechanisms at the molecular levels are extremely complex and well regulated. Many aspects of the physiology of the brain are still poorly understood.

## **The transmission of the information from one nerve cell to the other**

The synapse is a specialised neuronal ending that connects one neuron to another one in order to relay information. When the micro-current arrives at the synapse level, it releases a special molecule, known as neuromediator or neurotransmitter, that activates the other neuron, which in turn transmits the information. The neuromediator is a specific key to activate the other neuron. There are different keys according to the different types of neurons. Acetyl-choline, serotonin, glutamate are different neuromediators. In Alzheimer's disease, neurons with acetyl-choline synapses die rapidly. A way to slow down the disease is to restore the normal levels of acetyl-choline. Drugs that stimulate the production of acetyl-choline are commercialised (Aricept ®, Exelon ®, Reminyl ®) for use in the treatment of Alzheimer's disease.

## **Brain regions and neuro-degenerative disorders**

Most brain diseases first affect specific vulnerable neuronal populations. The degenerating process will then progressively invade other brain areas. Clinical manifestations mostly reflect the brain areas affected. For instance, if subcortical nuclei are affected, motor problems appear. If the frontal pole is affected, the patient will likely present behaviour problems, while short-term memory problems result from a pathology of the hippocampal area.

But because different types of degenerative diseases can affect the fronto-temporal regions (behaviour or language impairment), the clinical diagnosis is sometimes difficult, especially during the early stages. Indeed, different brain diseases can generate similar cognitive impairments.

## Diagnostic procedures

By **Giuliano BINETTI**

The most important symptom that leads the patient and caregiver to a neurologist is a memory deficit. When memory impairment is suspected, it is important to review the clinical history and course of deterioration with both the patient and a knowledgeable informant (e.g. caregiver or family member).

The history should include an assessment of:

1. Clinical manifestation of the symptoms  
The age of onset, the symptoms presentation (such as memory, language, depression,...) and the impact of the symptoms on the daily life.
2. Mini-Mental State Examination (MMSE)  
A standard mental status exam routinely used to measure a person's basic cognitive skills, such as short-term memory, long-term memory, orientation, writing, language, judgment and abilities to solve problem.
3. Neurological Examination
4. Functional Status assessment  
Analysis of the basic activities (such as walking, bathing, dressing...), the instrumental activities (the use of the telephone, public services, house cleaning,...) and social, community and intellectual functions.
5. Non-cognitive symptoms  
Non-cognitive symptoms consist of behavioural disturbances (physical or verbal aggression, agitation, wandering, sexual disinhibition, incontinence, increase eating and screaming) and psychiatric symptoms (personality change, depression, visual and auditory hallucinations, paranoid ideas, misidentifications and mania).

Dementia presents a significant variability of clinical pictures. Despite having the same causes and origins, different presentations of the disease can be described and usually both cognitive and non-cognitive symptoms are present.

Memory impairment is necessary but not sufficient criterion for the diagnosis of dementia. Criteria for dementia require a person to manifest at least one additional cognitive deficit : aphasia, apraxia, agnosia or impairment of executive functioning. Moreover, these deficits must result in impairment of social or occupational functioning and represent a significant decline from a person's previous level of functioning.

Non-cognitive symptoms need to be assessed carefully as they are important for the diagnosis. They have an important impact on the quality of life and represent one of the primary outcomes of the pharmacological treatment. These symptoms can be present at the beginning of the disease and are a major cause of placement in care.

## Symptoms of dementia

### Cognitive symptoms

- Memory deficit
- Temporal and space disorientation
- Apraxia
- Aphasia
- Deficit logical and abstract reasoning
- Acalculia
- Agnosia
- Visuo-spatial deficit

### Non-cognitive symptoms

- Delusion
- Hallucination
- Depression
- Euphoria
- Anxiety
- Sleep, sexual and eating disorders
- Wandering
- Apathy, disinhibition and irritability

Several cognitive tests have been proposed in order to evaluate the impairment in the different cognitive areas in dementia. They are also used to follow the progression of the disease and the efficacy of drug treatments. Among the cognitive tests the Mini-Mental State Examination (MMSE) is one of the most used test for screening. In a short time (10-15 minutes), it facilitates the evaluation of global cognitive abilities. It is composed of 11 items that assess several cognitive functions: time and space orientation, short and long term memory, attention and calculation, language and apraxia.

The assessment of non-cognitive symptoms of dementia represents a methodological and clinical challenge. The presence of cognitive and non-cognitive symptoms in the same patient makes the observation and characterisation of the symptoms difficult. A recent evaluation scale, called Neuro Psychiatric Instrument (NPI) and proposed by Cummings et al., assesses the non-cognitive symptoms based on the information provided by caregivers. NPI evaluates the presence, the frequency and severity of several non-cognitive symptoms.

## Lab Test

In general most patients should undergo a complete blood count, thyroid function screening and routine blood studies for liver, kidney and endocrine function. Most dementia specialists also obtain a serum vitamin B12 level, which may be low despite the absence of anemia or macrocytosis.

## Brain scan

Imaging studies (computed tomography [CT SCAN] or magnetic resonance imaging [MRI]) may identify conditions other than neuro-degeneration that could explain or contribute to the dementia symptoms. Anatomic imaging reveals clinically unexpected lesions in up to 5% of patients. However, the greatest promise of MRI may lie in its ability to quantitate the degree of brain atrophy.

The role of single-photon emission computed tomography (SPECT) in the diagnosis of Dementia disease remains controversial despite more than 30 years of clinical experience. Only a few studies have compared the imaging changes to the findings at autopsy.

## Biochemical markers

Over the past several years, there has been an intensive search for structural and biochemical markers that can serve as diagnostic tests during the earliest stage of the disease.

MRI can document and quantify the presence of regional and whole-brain atrophy that exceeds age adjusted norms, and it may serve as an important "anatomical" biomarker of neuro-degenerative pathology. To date, MRI has been used only as a research tool for this purpose; however, if the method is shown to be reliable and valid in routine clinical use, the finding of cerebral atrophy on quantitative MRI in a patient with mild cognitive impairment may increase the certainty of a clinical diagnosis of Alzheimer's disease. Likewise, monitoring the rate of cerebral atrophy may provide a measure of disease activity and response to therapy.

Biochemical changes that reflect the presence of disease-related pathology also have the potential to serve as diagnostic biomarkers of Alzheimer's disease. To date, the most extensively studied biochemical markers are the cerebrospinal fluid (CSF) proteins tau and beta-amyloid. Both are particularly relevant to the pathology of Alzheimer disease and thus may provide diagnostically useful information.

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## Genetics of dementia

By **Jos VAN DER POEL**

In the description of the following diseases it may strike you that in every disorder genetics play a role. May it reassure you that up till now research has shown that only a minor part of all dementias, including the rare forms, is caused by genetic factors, so called strong genes. Most other (weak) genes are indicated as risk factors for developing dementia. This means that if one has this specific genetic material, one's susceptibility to developing dementia is heightened. Getting the disease or not in these cases is dependent on more than just hereditary factors.

### **Genetic material**

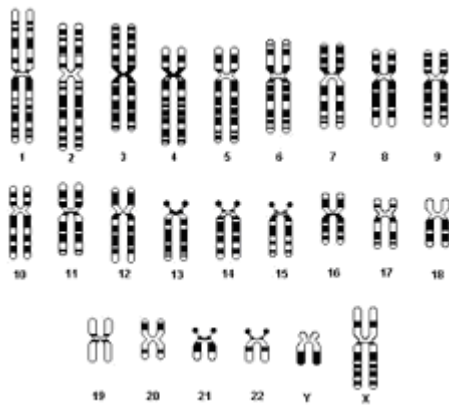
The human body consists of a large number of organs, which are built up from different tissues that contain millions of cells. These cells enable an organ to function well. Every cell contains a full copy of all genetic material, the chromosomes. The chromosomes contain the necessary information for the development, maintaining and reproduction of an individual.

Chromosomes can be imagined as long fibers, which consist of DNA (deoxyribonucleic acid). All our qualities and traits are described in codes or genes, which are found on these chromosomes. These genes determine our inherited traits. There are genes for hair colour, body length and other visible traits, but also for the production of substances our body needs for example for digesting food. Genes also play a role in the vulnerability for certain disorders.

Every human cell normally contains 46 chromosomes, more precisely 23 pairs of two identical chromosomes. Of each pair of chromosomes one comes from the mother and one from the father. The reason for this is that human reproductive cells have only 23 chromosomes. At insemination the 23 chromosomes of the male and female reproductive cell join to form a cell with 46 chromosomes. Every child inherits a unique combination of genetic properties from its parents. That is why brothers and sisters can be so different. On the other hand, some qualities can be very obvious in one family – certain parts of the DNA are then shared by grandparents, a parent, uncles, aunts and children.

The 23rd pair of chromosomes is made up of sex chromosomes, which determines the gender of an individual. Females have two X-chromosomes, one from their father and one from their mother. A male receives a X-chromosome from his mother and an Y-chromosome from his father. The other 22 pairs of chromosomes are also called autosomes.





In this chromosome map of a healthy man, it is visible that chromosomes differ in size, form and structure. On the basis of these characteristics the chromosomes are classified.

Genes (parts of the DNA) contain the information (code) for all hereditary properties. Every single gene contains the code for producing one of the many proteins in our body. Proteins form the basis for the properly functioning of our body. Because our chromosomes come in pairs, every gene is also present twofold: one gene from our mother and one from our father. For each trait two different genetic codes – one in each pair of chromosomes – are found in the DNA.

### **Genes: dominant, recessive or co-dominant**

At the moment of insemination a large number of personality traits and qualities are determined. Not only visible traits like gender or eye colour, but also traits, which appear only later in life. This for example is the case in the vulnerability for developing diabetes or muscular dystrophies. Which of the two genes will determine our eye colour, or whether a genetic disorder will be manifest, depends on the strength of the gene. If a gene is **dominant**, only one gene (from the father or the mother) is sufficient for having the genetic property. Traits, which are encoded in **recessive** genes, can only become manifest when the recessive gene is found on both chromosomes. **Co-dominant** genes are equally strong.

## **Deviations**

Deviations in the hereditary material can cause a genetic disorder. One can distinguish between three groups of genetic deviations: chromosomal deviations (in structure or number), monogenic disorders (deviations which are caused by a mutation in one gene) and multifactorial disorders (mutations in several genes in combination with environmental factors).

But not always do deviations in the hereditary material cause a genetic disorder. We all carry genetic properties without these bothering us. The deviation does not manifest itself, because there is a normal, healthy copy of the specific material present.

## **Hereditary patterns**

There are different ways of inheriting traits and qualities, but also of diseases. Some diseases often occur in one family, while other disorders seem to come out from nowhere. Other diseases affect males, while females stay healthy. These differences are due to different hereditary patterns.

## **Autosomal inheriting**

Some diseases can develop when a child receives a deviant gene from one parent, even when the other parent's gene is normal. Autosomal means that the sex chromosomes are not involved, so the gender of the child does not influence the chance of inheriting the disease. Huntington's disease is an example of an autosomal disorder.

## **Gender linked inheriting**

Females may carry certain properties that are connected to mutations on the X-chromosome, while males – with only one X-chromosome and no healthy copy gene on the Y-chromosome- will develop a disease. Colour blindness is an example of gender linked disorders.

## **Mutations**

Other diseases are caused by spontaneous changes (mutations) in the genetic material. The disease may develop later in life. In some cases dementia is caused by a mutation in a dominant gene. A small number of families is known where Alzheimer's disease is inherited in this way. Someone with a parent who has this disease has a 50 % chance to have the mutated gene too and to develop the same type of dementia. Research has shown that the risk of inherited dementia is highest in families where the disorder develops at a relatively young age.

## **Genetic testing**

When dementia occurs in a family often, the suspicion may rise that genetic factors play a role in the origin of the disorder. A clinical genetic centre can – by studying one's pedigree on the prevalence of the disease- estimate the chance of the person to develop it. A blood test can determine if one has a gene mutation that can cause or heighten the risk of developing dementia.

## **Diagnostic testing**

Familial early onset Alzheimer's disease (FAD) is associated with 3 genes. These are the amyloid precursor protein (APP), presenilin-1 and presenilin-2. These genetic mutations can be detected by genetic testing. However, it is important to note that the test only relates to those people with FAD (i.e. about 1% of all people with Alzheimer's disease). In the extremely limited number of families with this dominant genetic disorder, family members inherit from one of their parents the part of the DNA (the genetic make-up), which causes the disease. On average, half the children of an affected parent will develop the disease. For those who do, the age of onset tends to be relatively low, usually between 35 and 60.

## **Assessment for risk testing**

Whether or not members of one's family have Alzheimer's disease, everyone risks developing the disease at some time. However, it is now known that there is a gene, which can affect this risk. This gene is found on chromosome 19 and it is responsible for the production of a protein called apolipoprotein E (ApoE). There are three main types of this protein, one of which (ApoE4), although uncommon, makes it more likely that Alzheimer's disease will occur. However, it does not cause the disease, but merely increases the likelihood. For example, a person of 50, would have a 2 in 1,000 chance of developing Alzheimer's disease instead of the usual 1 in 1,000, but might never actually develop it. Only 50% of people with Alzheimer's disease have ApoE4 and not everyone with ApoE4 suffers from it.

There is no way to accurately predict whether a particular person will develop the disease. It is possible to test for the ApoE4 gene mentioned above, but strictly speaking such a test does not predict whether a particular person will develop Alzheimer's disease or not. It merely indicates that he or she is at greater risk. There are in fact people who have had the ApoE4 gene, lived well into old age and never developed Alzheimer's disease, just as there are people who did not have ApoE4, who did develop the disease. Therefore taking such a test carries the risk of unduly alarming or comforting somebody.

**Alzheimer Europe has developed the following positions with regard to genetic testing:**

1. Alzheimer Europe firmly believes that the use and/or possession of genetic information by insurance companies should be prohibited.
2. Alzheimer Europe strongly supports research into the genetic factors linked to dementia which might further our understanding of the cause and development of the disease and possibly contribute to future treatment.
3. Based on its current information, Alzheimer Europe does not encourage the use of any genetic test for dementia UNLESS such test has a high and proven success rate either in assessing the risk of developing the disease (or not as the case may be) or in detecting the existence of it in a particular individual.
4. Alzheimer Europe requests further information on the accuracy, reliability and predictive value of any genetic tests for dementia.
5. Genetic testing should always be accompanied by adequate pre- and post-test counselling.
6. Anonymous testing should be possible so that individuals can ensure that such information does not remain in their medical files against their will.

## Care and treatment

By **Clive EVERS**

### Patient perspectives

How does it feel to have dementia? Dementia is usually described in books as a list of neurological symptoms or is written about as a series of problems that need to be solved or skills that are gradually lost. But it is important that not to forget the individual behind the medical definition.

People with dementia often find that they have more than their physical neurological symptoms to cope with. They also have to deal with other people's reactions to dementia. They may be talked about as if they are not there or treated like a child.

If this happens people will lose their confidence and begin to doubt their sense of self and identity.

If they have a rare disease other people may regard them as an 'odddity' and be very wary of them.

A diagnosis of a rare disease that includes dementia can come as a shock even if the person is half expecting it.

Reactions may include:

- **Anger:** 'Why is this happening to me?' 'What did I do to deserve this?'
- **Worry:** 'how will I cope? How will my family cope?'
- **Sadness:** 'Things get too much for me. There doesn't seem any point in making an effort.'
- **Guilt:** 'I feel bad asking for help. I don't want to be a burden'
- **Alone:** 'Sometimes I feel I am tackling this on my own. No one seems to understand.'
- **Frustrated:** 'I just can't do the things I used to. Sometimes I feel like screaming.!'
- **Fear:** ' I am afraid of what will happen to me in the future. It seems just like darkness ahead.'
- **Relief:** ' I'm glad I know it's an illness. I wasn't having a breakdown. I will manage.'

People with rare diseases including dementia may feel isolated but they are not alone. Other people will have been through the experience and some of them have given the following tips:

- **Talking helps:** if you can talk to your friends and family about your worries. Don't bottle things up.'
- **Get support:** we all need extra help at some point in our lives- don't be afraid to ask for support. Think about contacting someone with the same disease through a support group.
- **Find out about your dementia:** you have a right to know about your illness and what will happen in the future. Patient organisations can provide much information and support.
- **Tell other people about dementia:** explain what you know about your dementia. Other people need to understand that you are going through.
- **Stay as active as you can:** maintain your interests, see your friends. Carry on with your life.

## Caregiver problems and needs

There has been extensive research into the needs of carers of people with dementia and the problems they may face. These needs have been described as :

- Early identification and diagnosis
- Assessment of need
- Active treatments when available
- Continuing support and review
- Information, advice, counselling and advocacy
- Emotional needs and support
- Respite care
- Financial support
- Appropriate residential care

Research also shows that there is a higher prevalence of the rarer dementias in younger people below the age of 65. This group and their carers have specific needs and will encounter particular problems.

- Rarer dementias are less likely to be recognised and addressed by services bringing extra burden to families.
- Younger people are more likely to have children and financial commitments dependent on them. The carer may have to give up work to look after them.
- The emotional impact of developing a dementia at a younger age is significant and has dramatic effect on life plans and expectations.
- Younger people with dementia will have a diverse range of needs. They may remain physically strong and fit and still have work related aspirations.
- The issues facing younger people with dementia and their families are complex and may change quickly. There is a need for ongoing specialist involvement and monitoring.

These needs and issues should be taken into account within the context of the specific dementia that is being investigated or has been diagnosed.

Having recognised these special needs there are a range of common problems that dementia presents which caregivers should be alert for.

### **Communicating with the person with dementia**

The person with dementia will gradually have problems communicating their thoughts and feelings using words. They will also have problems interpreting what other people say to them. But there are many ways to actively support people with dementia, enabling them to communicate as much as possible for as long as possible.

Some practical communication tips include:

- Listening carefully to what they say and taking time.
- Use words that are as simple and straightforward as possible
- Introduce one thought, idea or proposal at a time
- Avoid offering multiple choices when asking a question
- Be patient in waiting for a response
- Rephrase the question if necessary
- Use gestures and signs if you think they may help
- Avoid competing noises or activities e.g. television, radio

## **Understanding and coping with unusual behaviour**

In the middle or later stages of dementia a person may behave in ways that might be considered unusual. They may wander around, repeat questions or phrases, display a lack of inhibition or become suspicious, for example. Occasionally they may become angry or aggressive.

So-called 'unusual' behaviour can be caused by the physical neurological changes the person is experiencing. But much of the behaviour needs to be understood as a form of communication

In responding to such behaviour try not to take it personally and stay as calm as you can. Be as understanding and patient as possible. Don't try to argue or convince the person and acknowledge what you think they are trying to express.

It is essential to consider which rare dementia the person may have or is being investigated for.

People with Front-temporal- degeneration (FTD) are likely to present quite severe behavioural disturbance. This is due to the damage caused by the disease to the frontal lobes of their brain, which control social functioning and behaviour.

Sometimes the behavioural disturbance can be quite severe e.g. aggressive and antisocial behaviour including physical assault, theft, offensive language, public urination and masturbation.

This is the result of a loss of executive control and of insight and empathy.

Carers can often overlook the implications of a loss of insight and perceive the behaviour to be deliberate and when reasoning fails may think that they are being callous.

Specialist psychological help may be needed to consider possible application of techniques such as cognitive behavioural therapy, cognitive neuro-psychology, neurorehabilitation.

People with a dementia may present with one or some of the following symptoms and behaviours. There are techniques for identifying these and for minimising or managing their effects. Contact the appropriate patient group or organisation for further information and advice.



- Walking about or wandering
- Hallucinations
- Lack of inhibition
- Repetitive questioning
- Sleeplessness and sundowning
- Trailing and following
- Aggression
- Suspicion
- Extreme emotional reactions
- Laughing and crying
- Depression and dementia

## **Financial aspects**

Your financial situation is likely to be affected if you are caring for a person with dementia.

If a carer is working and has to give up work either temporarily or permanently they should check their pension position.

They should check to see whether they are entitled to any benefits and if so which ones.

It is important to find out the best way of managing the person's financial affairs when it becomes necessary. This will depend on the legal framework of the country concerned. In some countries like the UK it will be through appointeeship or enduring power of attorney. See below.

A carer should also check their position with regard to the person's home and finances if they go into long-term care or die.

## Legal issues

People with dementia will lose mental capacity as their dementia progresses. Each European country has its own legal structure and devices to respond to people who no longer have mental capacity to manage their own affairs. For details of these consult the Alzheimer Europe website [www.alzheimer-europe.org](http://www.alzheimer-europe.org) and view their **LawNet reports**.

Where possible it is advisable to adopt preventive measures. In some countries (UK) there is a device called Enduring Powers of Attorney (EPA) which enable a nominated individual to take over the **financial affairs** of a person who has become mentally incapacitated. These devices have to be set up in advance and with initial mutual agreement of both parties.

Legal devices to assist with decisions about the **care** of a person who has lost mental capacity are still very limited. Some countries (e.g. Scotland) have introduced a Care Power of Attorney, which does enable this to happen but this is an exception.

It is advisable for the patient to consider making an Advance Directive (Living Will/Advanced Statement) in which they can specify how they wish to be cared for when they no longer have capacity to express their wishes and needs. Different countries treat such devices differently. In the UK while they do not have the backing of statute law, doctors and others are required to take them into account when making decisions about patient care.

## Drug treatments:

Drug treatments for the rare dementias are not currently available. See the individual disease descriptions for information on drugs that may be beneficial or which should be avoided.

In recent years 3 drugs have been developed for Alzheimer's disease.

These are Aricept®, Exelon® and Reminyl®. They are all examples of a group of drugs known as the anticholinesterase inhibitors which may redress the imbalance in this neurochemical neurotransmitter in the brains of people with Alzheimer's disease. They are intended for people in the early to moderate stages of the disease. They will not be effective for everyone for whom they are prescribed. However those that do benefit usually experience an improvement in memory and/or behaviour for periods of 6, 12, or 18 months before the course of the disease resumes.

More recently another drug has been developed called Ebixa®, which works on a different neurochemical, glutamate and is intended for people in the moderate to late stage of Alzheimer's disease.

So far there is **no substantial research** into whether or not these drugs can effectively help with other forms of dementia. There is some limited research and anecdotal evidence that the anticholinesterase inhibitors may help some people with Lewy body dementia.

## Non-drug treatments

Effective non-drug treatments for the wide range of rare dementias discussed here are not available. However, there is an increasing amount of research into a range of psychological, behavioural and activity-based techniques with older people with Alzheimer's and vascular dementia. The evidence for their effectiveness in these former groups is limited and variable but promising in some cases.

Two helpful reviews of psychological therapies with older adults are available. The first was commissioned by the Department of Health in the UK as part of a strategic review of psychological therapies for all age groups (Woods, B and Roth, A Effectiveness of psychological interventions with older people in: *What works for whom? a critical review of psychotherapy research* (eds. Roth, A and Fonagy, P.), pp 321-340. Guildford Press New York).

In addition, specifically relating to dementia, the American Psychological Association's *1997 Practice Guideline* includes a section on psychotherapies and psychosocial interventions (ASP 1997).

Therefore health and care professionals and caregivers should be aware of these and consider their applications with those affected by rare diseases and dementia.

Nevertheless it will be important to take into account the type and subtype of rare dementia present; the pattern and course of impairment; the stage of progression the impairment has reached; the person's attempts at coping with what has happened (e.g. denial, self-blame etc); the person's previous lifestyle, experiences, abilities and interests; the support available to them and their relationship with caregivers; other disabilities they may have.

It is worth noting that in applied behaviour analysis and neuropsychological rehabilitation the use of small numbers of people is usual. The American Psychological Association criteria (Gatz et al 1998)(Gatz, M Fiske A Fox, LS et al 1998 Empirically validated psychological treatments for older adults: *Journal of Mental Health and Aging* 4(1), 9-46., simply require a series of 10 or more single cases with good experimental designs for a psychological treatment to be accepted as 'well-established' as long as certain other 'quality features' are present.

The following is a very brief overview of this range of techniques and treatments. For more information on these techniques consult *Woods, R Non-pharmacological techniques pp 428-446 IN (Evidenced based dementia practice Qizilbash, N editor, Blackwell 2002.)*

### **Reality orientation**

Reality orientation is a technique in which people caring for individuals with dementia take every opportunity to orientate people with dementia. For example a member of staff in a hospital may remind someone with dementia where they are and what time of day it is. Staff members would also disagree whenever someone with dementia says something that is incorrect.

Reality orientation has been shown to be effective in making some changes in the responses and behaviour of people with dementia. However in view of concerns about how significant these changes are and its insensitive use as a general approach, it is recommended that it be only used where there are important orientation aims for the person with dementia and as part of a person centred care plan.

**Reminiscence therapy**

Reminiscence therapy involves stimulating the recollection of events or memories from the past. This is achieved by using music, videotapes or pictures (for example films of trams or photographs of early cinema idols) or by providing items such as food packaging or articles of clothing from past times.

People with dementia appear to often enjoy this therapy although it probably does not prevent the memory getting worse in the long run. Knowledge of the person with dementia is a prerequisite of individualised care. It has not been adequately evaluated in dementia care but those who use it can be creative in its application.

**Validation therapy**

Validation therapy emphasises the emotional world of the person with dementia and offers some useful techniques for such communication. This may invoke 'tuning in' to the feelings and meanings behind the words, which are spoken. This approach stresses the importance of listening to the person's emotional expression but without getting into debates about facts, dates and reality. Essentially it is about trying to enter into the person's world seeking to understand their perspective rather than imposing our own reality.

The use of this approach may then bring sense out of less clearly articulated communication. Research into the effectiveness of validation therapy has been disappointing but there is evidence that more investigation is needed.

**Memory training**

In the early stages of dementia, some patients may wish to try to improve their memory function. Memory training approaches that have been mainly developed with people with static and specific memory difficulties may be of use.

These include the use of external memory aids, such as a watch or diary or a memory book with photos and text. Teaching mnemonics has been tried. Enhancing the learning process through special techniques such as 'spaced retrieval' and 'errorless learning' has shown some benefit in research.

The use of well preserved aspects of memory can be helpful. The time taken to complete self-care tasks with 10 people with dementia was reduced by using a procedural memory-training programme after 3 weeks of daily training sessions. The emphasis was on enacting and practising the tasks rather than memorising them

This is a developing approach and care should be taken in its application.

## **Stimulation**

Over the years a background level of stimulation and activity has come to be accepted as good practice in care and treatment of people with dementia. The current approach is on the effects of more specific forms of sensory stimulation and physical exercise.

There has been a lot of interest in multisensory stimulation known as 'Snoezelen'. This increases the amount of sensory stimulation by using lava and fibre optic lamps to provide changing visual stimulation, pleasant aromas, gentle music, and materials with interesting textures to touch and feel. Although often successful as form stimulation the calming effects of these activities are also important.

The effects of regular exercise have been discussed over many years. People with dementia in residential care who have taken part in regular exercises programmes have shown improvements in night-time sleep, less agitation and spending less time in bed each day.

## **Cognitive –behavioural therapy(CBT)**

CBT has been found to be useful for people with depression and it has now also been applied with some people with dementia with a lowered mood. This involves working with the caregiver of the patient included as much as possible. Weekly 1-hour sessions include teaching the caregiver to identify and develop pleasant events for the person with dementia and later for themselves as well as strategies for management of difficult behaviour. Additionally a flexible problem solving approach focussing on specific depressive behaviour is applied.

The results of these interventions have shown reduced levels of depression and improvements in the mood of the caregiver.

Progressive muscle relaxation techniques appear to be of some benefit and could be more widely applied with tense and anxious patients with dementia. This technique with its successive tensing and relaxing of muscle groups relies on procedural memory, which is relatively spared in dementia.

**Behavioural approaches**

These approaches can be divided into two types. First, there are the attempts to increase the patient's level of independence including re-learning apparently lost skills and maintaining existing skills. Secondly there are efforts to reduce the levels of behavioural disturbance and difficulty.

In promoting independence encouragement and support for continued self care may be helpful. Improvement in mobility including independent walking can come from prompting and praise for achievement.

Improvements in maintaining continence have been made through prompted voiding. The person with dementia is asked on a regular basis if they wish to be taken to the toilet and praised for using it and remaining dry.

Reinforcement and prompting can also be useful in increasing participation in purposeful activities.

Environmental changes in residential care can be beneficial. These include individualised care and a more homely environment; more choice and participation for residents; more time for people with dementia to go at their own pace and participate more in self-care. The benefits include less confusion and anxiety and improvements in mood and ability to carry out activities.

There is now much research activity underway to investigate ways of reducing problem behaviour as this is seen as the greatest clinical problem for caregivers, staff and patients themselves.

The four most challenging behaviours may be said to be noise making, wandering, aggression and agitation. There now exists a body of experience and techniques that may be applied to assist with each of these.

**Complementary and alternative medicine (CAM) and dementia**

Public interest in complementary therapies is growing at a significant rate, easily outpacing the research conducted into their safety and effectiveness.

The term complementary and alternative medicine (CAM) covers many therapies. There is no apparent connection between many of them and they often have diverse origins, theories and appearances.

There is no precise definition of what constitutes CAM. A good practical definition would be 'interventions that are neither taught widely in medical schools, nor available generally in hospitals.' What may be complementary medicine in one country may be conventional in another.

Common therapies encountered would include herbal medicine, aromatherapy, massage, music therapy, acupuncture, dietary supplements and melatonin and bright light therapy.

Further information on the possibilities of CAM may be obtained from patient organisations like the Alzheimer's Society Information Sheet 434 March 2003.

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Alzheimer Europe, Route de Thionville 145, L-2311 Luxembourg

# **Rare forms of dementia**

## Description of the diseases

*Final report of a project supported by the  
Community Rare Diseases Programme  
2000-2002*





# Table of contents

<b>NEURO-DEGENERATIVE DISEASES</b>	<b>5</b>
<b>1. FAMILIAL ALZHEIMER DISEASE (FAD) BY GIULIANO BINETTI</b>	<b>6</b>
<b>2. LEWY BODY DISEASES BY CLIVE EVERS</b>	<b>9</b>
2.1. DEMENTIA WITH LEWY BODIES (DLB)	9
2.2. DEMENTIA IN PARKINSON'S DISEASE (PDD) BY KURT JELLINGER	12
<b>3. FRONTO-TEMPORAL DEGENERATION (FTD) BY ANDRÉ DELACOURTE</b>	<b>14</b>
3.1. CLINICAL MANIFESTATION	15
3.1.1. Fronto-temporal dementia (FTD) by André Delacourte	15
3.1.2. Primary Progressive Aphasia (PPA) by André Delacourte	18
3.1.3. Semantic Dementia (SD) by André Delacourte	20
3.2. HISTOPATHOLOGICAL SUB-TYPES	22
3.2.1. FTD with parkinsonism linked to chromosome 17 (FTDP-17) by André Delacourte	22
3.2.2. Pick's disease (PiD) by André Delacourte	24
3.2.3. Dementia lacking distinctive histology (DLDH)	26
<b>4. PROGRESSIVE SUPRANUCLEAR PALSY (PSP) BY ANDRÉ DELACOURTE</b>	<b>28</b>
<b>5. CORTICOBASAL DEGENERATION (CBD) BY ANDRÉ DELACOURTE</b>	<b>31</b>
<b>6. ARGYROPHILIC GRAIN DISEASE (AGD) BY ANDRÉ DELACOURTE &amp; KURT JELLINGER</b>	<b>33</b>
<b>7. MULTIPLE SYSTEM ATROPHY (MSA) BY ANDRÉ DELACOURTE</b>	<b>35</b>
<b>8. AMYOTROPHIC LATERAL SCLEROSIS (ALS) BY GIULIANO BINETTI</b>	<b>37</b>
<b>9. ATAXIAS BY GIULIANO BINETTI</b>	<b>41</b>
<b>10. HUNTINGTON'S DISEASE (HD) BY GIULIANO BINETTI</b>	<b>44</b>
<b>11. DOWN SYNDROME BY JOS VAN DER POEL</b>	<b>47</b>
<b>12. FAMILIAL BRITISH DEMENTIA BY ANDRÉ DELACOURTE</b>	<b>49</b>
<b>INFECTIOUS DISEASES</b>	<b>51</b>
13.1. SPORADIC CJD BY ANDRÉ DELACOURTE AND CLIVE EVERS	54
13.2. TRANSMISSIBLE CJD	57
13.2.1. Iatrogenic CJD by André Delacourte and Clive Evers	57
13.2.2. Variant CJD (vCJD) by André Delacourte and Clive Evers	60
13.3. FAMILIAL CJD BY ANDRÉ DELACOURTE AND CLIVE EVERS	63
13.4. FATAL FAMILIAL INSOMNIA (FFI) BY ANDRÉ DELACOURTE	65
13.5. GERSTMANN-STRAUSSLER-SCHEINKER DISEASE BY ANDRÉ DELACOURTE	67
<b>13. AIDS DEMENTIA COMPLEX (ADC) BY JOS VAN DER POEL</b>	<b>69</b>
<b>14. SYPHILIS BY ALEXANDER KURZ</b>	<b>71</b>
<b>15. POSTENCEPHALITIC PARKINSONISM (PEP) BY KURT JELLINGER</b>	<b>74</b>
<b>16. HERPES ENCEPHALITIS BY KURT JELLINGER</b>	<b>76</b>
<b>METABOLIC DISEASES</b>	<b>78</b>
<b>17. THYROID DISORDERS BY CLIVE EVERS</b>	<b>79</b>
<b>18. NEURO-DEGENERATION WITH BRAIN IRON ACCUMULATION TYPE I (NBIA 1) BY KURT JELLINGER</b>	<b>82</b>
<b>19. CEREBRAL LIPIDOSES BY ALEXANDER KURZ</b>	<b>84</b>
20.1. TAY-SACHS DISEASE (TSD) BY ALEXANDER KURZ	84
20.2. SANDHOFF DISEASE BY ALEXANDER KURZ	86
20.3. GAUCHER DISEASE BY ALEXANDER KURZ	88
20.4. NIEMANN-PICK DISEASE (NPD) BY ALEXANDER KURZ	90
20.5. KRABBE DISEASE BY ALEXANDER KURZ	92
20.6. NEURONAL CEROID LIPOFUSCINOSES (NCL) BY ALEXANDER KURZ	94
20.7. CEREBROTENDINOUS XANTHOMATOSIS (CTX) BY ALEXANDER KURZ	96
<b>20. DEMENTIA IN HEPATIC AND RENAL FAILURE BY KURT JELLINGER</b>	<b>98</b>
<b>21. DEMENTIA DUE TO CHRONIC HYPOVITAMINOSIS</b>	<b>100</b>
<b>BY KURT JELLINGER</b>	<b>100</b>
<b>22. METACHROMATIC LEUKODYSTROPHY (MLD) BY ALEXANDER KURZ</b>	<b>102</b>
<b>23. ADRENOLEUKODYSTROPHY (ALD) BY ALEXANDER KURZ</b>	<b>104</b>

<b><u>TRAUMATIC DISEASES</u></b>	<b>106</b>
24. REPEATED HEAD TRAUMA BY ALEXANDER KURZ	107
<b><u>TOXIC DISEASES</u></b>	<b>109</b>
25. WERNICKE-KORSAKOFF SYNDROME (WKS) BY CLIVE EVERS	110
<b><u>CEREBRO-VASCULAR DEMENTIA</u></b>	<b>113</b>
26. CADASIL BY KURT JELLINGER	114
27. BINSWANGER DISEASE BY JOS VAN DER POEL	115
28. CEREBRAL AMYLOID ANGIOPATHY (CAA) BY KURT JELLINGER	116
<b><u>OTHER RARE CAUSES OF DEMENTIA</u></b>	<b>117</b>
29. COGNITIVE DYSFUNCTION IN MULTIPLE SCLEROSIS BY CLIVE EVERS	118
30. NORMAL PRESSURE HYDROCEPHALUS (NPH) BY JOS VAN DER POEL	121

## **NEURO-DEGENERATIVE DISEASES**

The biggest group of diseases is made up of **neuro-degenerative diseases**, which are characterised by a progressive loss of nerve cells and synapses. For most of these diseases, the causes of this nerve loss are unknown and our knowledge about possible treatment or prevention remains limited.

## 1. Familial Alzheimer Disease (FAD) by Giuliano Binetti

### General outlines

Alzheimer's disease where there is a family link, called familial Alzheimer's disease (FAD), is more common amongst younger people (under the age of 65).

Mutations in **three genes** were shown to be causative of familial Alzheimer's disease (FAD):

1. About 12 families worldwide have a genetic fault on chromosome 21 in a gene called **amyloid precursor protein (APP)**, which affects production of the protein amyloid. Amyloid build up in the brain has been linked to Alzheimer's.
2. A slightly larger number of families carry a fault on chromosome 14 ("presenilin-1") causing early onset familial Alzheimer's. Mutations in presenilin-1 (PS1) gene accounted for the majority of FAD cases and more than 70 mutations have been described.
3. A very small group of families (7 members of kin with FAD were described) carry a fault on chromosome 14 ("presenilin-2"). The presenilin-2 (PS2) gene is generally considered responsible for a variable penetrant clinical phenotype.

The three genes involve account for the 30-50% of all autosomal dominant early-onset cases, or around 10% of familial early onset cases.

The genetic link in some late onset cases of Alzheimer's disease (in people aged 65 and over) is more complex than the link for younger people. The presence of a positive family history in the late onset cases is considered as a risk factor, but a clear autosomal dominant pattern of inheritance is rare.

### Synonyms

Monogenic Alzheimer's disease

### Symptoms and course

#### **Mutations on the APP gene**

Age of onset: 40-65 years.

Aggressive form of dementia.

Duration of the disease: 9-16 years.

#### **Mutations on the PS1 gene**

Age of onset: 35-55 years.

These mutations are largely associated with early onset FAD, but at least two mutations have been observed with late onset FAD.

The clinical phenotype is characterised by early onset memory impairment, rapid global cognitive decline along with the presence of myoclonus and generalised seizures.

In a few (PS1) pedigrees, atypical clinical presentations, including spastic paraparesis and, more recently, fronto-temporal dementia (FTD) were reported.

Duration of the disease: 5.8-6.8 years.

#### **Mutations on the PS2 gene**

Age of onset: 45-88 years.

They show some overlaps with late-onset AD. The clinical features similar to those presented in the sporadic Alzheimer's disease patients.

Duration of the disease: 4.4-10.8 years.

## Causes and risk factors

These mutations in patients with early-onset AD appear to result in the increased production of Amyloid  $\beta$ 42 peptide (A $\beta$ 42), which is probably the primary neurotoxic species involving in the pathogenesis of the disease.

The mutations can shift the cleavage site to favor the  $\gamma$ -secretase site, and to favor increased production of the toxic A $\beta$ 42 peptide over the shorter, less toxic A $\beta$ 40 peptide.

## Frequency

1. About 12 families worldwide have a genetic fault on chromosome 21 in a gene called **amyloid precursor protein** (APP).
2. A slightly larger number of families carry a fault on chromosome 14 ("presenilin-1") causing early onset familial Alzheimer's. Mutations in presenilin-1 (PS1) gene accounted for the majority of FAD cases and more than 70 mutations have been described.
3. A very small group of families (7 members of kin with FAD were described) carry a fault on chromosome 14 ("presenilin-2").

## Diagnostic procedures

Genetic test: A genetic test is the analysis of human DNA, RNA, chromosomes, proteins, or certain metabolites in order to detect alterations related to a heritable disorder.

## Care and treatment

As yet, there is no preventative or curative treatment for Alzheimer's disease. A number of drugs exist, which can help alleviate certain symptoms such as agitation, anxiety, depression, hallucinations, confusion and insomnia. Unfortunately, these drugs tend to be effective for a limited number of patients, only for a short period of time and may cause undesirable side effects. It is therefore generally considered advisable to avoid medication unless really necessary.

It has been found that patients suffering from Alzheimer's disease have reduced levels of acetylcholine - a neurotransmitter (chemical substance responsible for transmitting messages from one cell to another) which plays a role in memory processes. Certain drugs have been introduced in some countries, which can inhibit the enzyme responsible for destroying acetylcholine. In some patients these drugs improve memory and concentration. There is additional evidence that they have the potential to slow down the progression of symptoms temporarily. But, there is no evidence that they halt or reverse the process of cell damage. Such drugs treat the symptoms, but do not cure the disease. As European countries have widely differing legislation, we recommend that you consult a specialist in all cases.

## Ongoing research

Studies demonstrating that accumulation and aggregation of the amyloid  $\beta$  protein within the brain is likely to cause Alzheimer's disease (AD) have provided the rationale for therapeutic strategies aimed at influencing A $\beta$  production, aggregation and clearance.  $\gamma$ -secretase catalyzes the final cleavage that releases the A $\beta$  from its precursor; therefore, it is a potential therapeutic target for the treatment of AD. Recent data show that the polytopic membrane proteins presenilin 1 and presenilin 2 are either catalytic components or essential co-factors of a membrane-bound proteolytic complex that possesses  $\gamma$ -secretase activity.

**Available services****Alzheimer Europe**

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Tel: +352 / 29.79.70  
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**Alzheimer's Disease International**

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[www.alz.co.uk](http://www.alz.co.uk)

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## 2. Lewy Body Diseases by Clive Evers

### 2.1. Dementia with Lewy Bodies (DLB)

#### General outlines

Dementia with Lewy bodies (DLB) is a form of dementia that shares characteristics with both Alzheimer's and Parkinson's diseases. Lewy bodies (named after FH Lewy who discovered them in 1912) are tiny spherical protein deposits found in nerve cells. Their presence in the brain disrupts the brain's normal functioning, interrupting the action of important chemical messengers including acetylcholine and dopamine.

Lewy bodies are also found in the brains of people with Parkinson's disease (PD), a progressive neurological disease that affects movement. Some people who are initially diagnosed with PD later go on to develop a dementia that closely resembles DLB.

#### Synonyms

Lewy body dementia, Lewy body variant of Alzheimer's disease, diffuse Lewy body disease, cortical Lewy body disease, senile dementia of Lewy body type.

#### Symptoms

DLB often starts quite rapidly or acutely, with quite a fast decline in the first few months although later there may be some levelling off. DLB tends to progress faster than Alzheimer's disease and can last from 5- 7 years, although this will vary from person to person.

People with DLB often experience memory loss, spatial disorientation and communication difficulties associated with Alzheimer's disease but also have some quite normal memory function. They may also develop the symptoms of Parkinson's disease, including slowness, muscle stiffness, trembling of the limbs, a tendency to shuffle when walking, loss of facial expression and changes in the strength and tone of voice.

Characteristic symptoms of people with DLB include fluctuation of abilities on a daily and even hourly basis; fainting, falls or experiencing vague weaknesses of arms or legs; experiencing detailed and convincing visual hallucinations, often people or animals; falling asleep easily by day and having restless disturbed nights with confusion, nightmares and hallucinations. Additionally at least 50% of people with DLB are over sensitive to the side effects of neuroleptic drugs which may be prescribed for people with severe mental illness.

Gradually progressive, symptoms gradually accumulate, average survival is 6 to 7 years. Age of onset 50 to 83, death 68 to 92, average survival from diagnosis 5 - 7 years.

#### Caregiver problems

Fluctuation of cognitive ability may cause problems, non-acceptance of disease, presence of hallucinations, probability of falls, safety of environment, possibility of falling asleep during the day.

#### Causes and risk factors

The cause of DLB remains unknown although there are overlaps with Alzheimer's and Parkinson's disease. Genetic research is looking at which genes may contribute to DLB but this is in its early stage. Some research has focused on the role of

certain proteins and the damage caused to nerve cells especially ubiquitin and alpha-synuclein.

### **Genetics**

Rare causes of familial DLB have been reported.

### **Frequency**

DLB is thought to be the second or third most common cause of dementia accounting for 15% to 25% of cases of dementia which start after the age of 65 (Perry et al 1990 and Jellinger 1996)

Male to female ratio is 1.5:1 but it is not clear if this represents increased male susceptibility to the disease or to reduced survival in men with DLB. Age at onset ranges from 50-83 years and 68-92 at death (Papka et al 1998)

### **Diagnostic procedures**

Consensus guidelines for the clinical and pathologic diagnosis of DLB have been published (McKeith et al, 1996)

The main requirement is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and frontal-sub-cortical skills and visuospatial ability may be especially prominent.

The main diagnostic issue is to distinguish DLB from the commoner Alzheimer's disease. A common diagnostic error is to attribute the clinical features of DLB to cerebral vascular disease such as multi-infarct dementia or Binswanger's disease.

There are no specific diagnostic tests for DLB. CT and MRI imaging can assist in the process (Ince, P et al Copyright Brain Pathology 1998).

### **Care and treatment**

For people with DLB neuroleptics may be particularly dangerous. This class of drugs induce Parkinson-like side effects, including rigidity and an inability to perform tasks or to communicate. Studies have shown that when prescribed for people with DLB it may cause sudden death.

If a person with DLB must be prescribed a neuroleptic it should be done with the utmost care and under constant supervision with regular monitoring. In certain cases some people with DLB are able to tolerate such treatment so that their hallucinations are reduced.

There is now some evidence to suggest that the more recently developed 'atypical' anti-psychotic drugs like olanzapine (Zyprexa), quetiapine (Seroquel) or risperidone (Risperdal), may be safe to use.

It is still reasonable to try to simplify anti-parkinsonian medication as a first step, particularly withdrawing drugs of lower potency (and particular tendency to cause confusion) such as anti-cholinergics and selegiline; where possible dopamine agonists should also be withdrawn, leaving most patients on levodopa alone. (Ince, P et al Copyright Brain Pathology 1998)

At present there is no cure for DLB. Recent research has suggested that the cholinesterase drugs used to treat Alzheimer's disease may also be useful in treating DLB, although they are not yet licensed for this use (Alzheimer Scotland-Action on Dementia 2002).

### Ongoing research / Clinical trials

The 35% diagnostic sensitivity reported by Lopez et al supports their call for improvements in the clinical criteria for diagnosing DLB.

Contemporary theories emphasise impaired cellular function due to protein aggregation, disrupted synaptic connections and critical neurochemical changes including alterations in the muscarinic and nicotinic receptors.

Recent recognition that antibodies to a-synuclein immunostain cortical Lewy bodies as well as those in the substantia nigra greatly enhances pathological diagnosis.

This advance coupled with the recognition that parkin (Shimura et al, 2001) and torsin (Sharma et al, 2001) co-exist with a-synuclein in Lewy bodies will likely open new molecular and genetic approaches to future research.

### Available services

#### **Institute for Ageing and Health**

Wolfson Research Centre

#### **Prof. Ian McKeith**

Newcastle General Hospital

Westgate Road

Newcastle upon Tyne

NE4 6BE

United Kingdom

i.g.mckeith@ncl.ac.uk

<http://www.ncl.ac.uk/nnp/staff/profile/i.g.mckeith>

#### **The Lewy Body Dementia Association, Inc.**

[www.lewybodydisease.org](http://www.lewybodydisease.org)

#### **Alzheimer Europe**

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[www.alz.co.uk](http://www.alz.co.uk)

### References

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2. Ince, P et al, Copyright Brain Pathology 1998
3. Lopez et al, arch Neurol 2002;59;43-46
4. McKeith, IG et al Neurology 1996 Nov.; 47(5) 1113-24
5. McKeith, I. G., D. J. Burn, et al. (2003). "Dementia with Lewy bodies." Semin Clin Neuropsychiatry 8(1): 46-57
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7. Sharma, N et al Am J Pathol 2001; 159: 339-344

## 2.2. Dementia in Parkinson's disease (PDD) by Kurt Jellinger

### General outlines

While people with Parkinson's disease have a higher risk of developing dementia than those without Parkinson's disease, the majority will remain unaffected.

Parkinson's disease is known as a movement disorder. The movement disorder is due to dopaminergic neurons mainly in the substantia nigra. Motor symptoms always precede cognitive impairment by several years signs with an involvement of cognitive impairment due to a degeneration changes in cortical structures with a general presence of Lewy bodies.

### Synonyms

Idiopathic parkinsonism plus dementia

### Symptoms and course

Symptoms of dementia associated with Parkinson's disease will vary from person to person. The most common are memory loss and the loss of the ability to reason and to carry out normal everyday tasks (planning, organising, solving problems).

Patients may become obsessional, and there may be a loss of emotional control with sudden outbursts of anger or distress.

Medications may cause or aggravate visual hallucinations.

Language problems (slower speech, not word finding difficulties).

Symptoms often fluctuate so that the person will seem better or worse at different times. Gradually progressive, symptoms accumulate progressively.

Duration of the disease: 4-5 years. Parkinson's disease plus dementia has shorter survival than Parkinson's disease without dementia (average between 5 to 10 years.)

### Caregiver problems

With movement disorder, slowness in information processing (difficulty of communication) may lead to carer frustration.

### Causes and risk factors

Abnormal aggregation of alpha synuclein in Lewy bodies. It is more than Lewy bodies accumulation (often associated with Alzheimer pathology).

### Genetics

Families with familial PD (Several chromosomes involved) There are inherited form of Parkinson's disease associated with mutation on chromosomes xxx.

### Frequency

Parkinson's disease is not RARE; however, only 10-30 % of the patients develop cognitive impairment / dementia. Prevalence 41:100,000

### Diagnostic procedures

Nothing specific

## Care and treatment

The movement disorder is treated by compounds augmenting dopamine transmission (dopaminergic substances and DA agonists). Medication may cause or aggravate hallucinations and psychotic symptoms. Antidementive drugs like in AD. Ongoing research/Clinical trials have been conducted on small patient samples demonstrating benefits of Cholinesterase inhibitors on cognitive ability.

## Available services

### European Parkinson's Disease Association (EPDA)

Lizzie Graham  
EPDA Liaison/Project Manager  
4 Golding Road  
Sevenoaks  
Kent TN13 3NJ  
United Kingdom  
Tel/Fax: +44 (0)1732 457683  
[admin@epda.eu.com](mailto:admin@epda.eu.com)  
[www.epda.eu.com](http://www.epda.eu.com)

Parkinson's disease associations provide services for the movement disorders but have less information on the cognitive problems associated with the disorder. In a case of dementia, please refer also to Alzheimer's disease associations.

### Alzheimer Europe

145 Route de Thionville  
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Tel: +352 / 29.79.70  
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[info@alzheimer-europe.org](mailto:info@alzheimer-europe.org)  
[www.alzheimer-europe.org](http://www.alzheimer-europe.org)

### Alzheimer's Disease International

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[info@alz.co.uk](mailto:info@alz.co.uk)  
[www.alz.co.uk](http://www.alz.co.uk)

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### 3. Fronto-Temporal Degeneration (FTD) by André Delacourte

#### Introduction

Fronto-temporal degeneration (FTD) refers to the parts of the brain that are preferentially affected: the frontal and temporal lobes (at the front and side of the brain respectively).

These areas are responsible for different clinical manifestations such as behaviour, emotional responses and language skills. According to the main location of damage, the different **clinical manifestations** evolve, giving rise to particular forms of frontal dementia and specific language disorders such as semantic dementia (SD) and primary progressive aphasia (PPA). This is why the classification of FTD is in part related to specific clinical manifestations.

However, the **pathological processes** responsible for the "FTD" clinical profile are heterogeneous, and mainly related to different dysfunctions of tau gene or tau protein (mutations, aggregation, abnormal production).

These different abnormal processes of tau are revealed by different types of brain lesions that accumulate in the cortex of patients, and more especially in fronto-temporal areas (Pick bodies, neurofibrillary tangles, astrocytic plaques).

All these histopathological features give rise to a complementary classification based on the types of lesions, or the types of molecular abnormalities responsible for the lesions. This classification is called **histological sub-types**.

Therefore this histological classification comprises Pick's disease with Pick bodies and FTDP-17. FTDP-17 is a mixed classification. "FTD" stands for the frontotemporal clinical symptoms, "P" for the additional parkinsonian manifestations and "17" stands for the number of the chromosome that bears tau gene with the pathological mutations responsible for this disease.

DLDH is characterised by the absence of tau lesions, but the main molecular defect is related to the sharp decrease of normal tau proteins.

### 3.1. Clinical manifestation

#### 3.1.1. Fronto-temporal dementia (FTD) by André Delacourte

##### General outlines

Fronto-temporal dementia (FTD) refers to the parts of the brain that are preferentially affected: the frontal and temporal lobes (at the front and side of the brain respectively).

FTD are generated by different pathological processes that provoke damage in the frontal or/and temporal parts of the brain. These areas are responsible for different clinical manifestations such as behaviour, emotional responses and language skills.

According to the main location of damage, the different clinical manifestations evolve, giving rise to particular forms of frontal dementia and specific language disorders such as semantic dementia (SD) and primary progressive aphasia (PPA).

The pathological processes responsible for the "FTD" clinical profile are heterogeneous, but mainly related to different dysfunctions of tau gene or tau protein (mutations, aggregation, abnormal production). All these features give rise to a classification which is either based upon specific clinical symptoms (PPA, SD) or to specific lesions (Pick's disease) or a mixed classification (FTDP-17), 17 being the chromosome that bears tau gene with the pathological mutations responsible for this disease.

##### Synonym

Lobar atrophy, fronto-temporal atrophy

##### Symptoms and course

Damage to the frontal and temporal lobe areas of the brain will cause a variety of different symptoms. Each person will experience the condition in his or her own individual way.

Typically, during the initial stages of fronto-temporal dementia, memory will still be intact, but the personality and behaviour of the person will change. The person may lose their inhibitions and become extrovert, or alternatively may become apathetic and withdrawn.

They may talk to strangers, make inappropriate remarks in public and be rude or impatient. They may become aggressive which may be quite out of character, and may develop fixed routines. Some people begin to hoard things and become obsessive. Behaviour may be sexually suggestive, though a loss of interest in sexual acts themselves is also common. Often the person with dementia will be unaware of the problems.

People may also develop a sweet tooth and overeat leading to gain in weight. Excessive alcohol intake may occur. Spending money and losing cash often causes problems. In the later stages people with the illness may compulsively put objects in their mouths.

In the early stages memory is not usually affected. However sometimes difficulties in organisation and concentration may lead to an apparent memory problem. People may be very distractible.

Later in the disease a more generalised dementia can develop, and symptoms will usually appear to be similar to those with Alzheimer's disease. Those affected may no longer recognise friends and family and may need nursing care, become incontinent and bed-ridden.

FTD is gradual progressive and leading to overt dementia.

The progression rate is similar to Alzheimer's disease, of several years.

The average age of onset is usually 55 (+/- 10 years).

Duration of the disease from diagnosis is 6 to 8 years. It is longer than Alzheimer's disease, which is of 4 years (Paquid study).

### **Causes and risk factors**

A number of different types of brain lesions can underlay FTD. Many FTD are characterised by tau lesions, such as the specific Pick bodies observed in Pick's disease or neurofibrillary tangles or tau accumulation in FTDP-17.

There is also a FTD without tau lesions named Fronto-temporal dementia lacking distinct histo-pathology (DLHD), characterised by a severe neuronal loss and a gliosis (glial cell reaction), but without tau lesions.

DLHD is also a tauopathy, in that the major abnormality is a dramatic decrease in the production of tau proteins. Together, most FTD are affected by tau abnormalities: mutations, aggregation or very low levels of normal tau.

### **Genetics**

There is a family history in about half of all cases of fronto-temporal degeneration. In these families 50 % can be caused by mutation in tau-gene. Some of these inherited forms have been linked to abnormalities on chromosomes 3.

The causes of non-inherited fronto-temporal dementia are so far unknown.

### **Frequency**

Prevalence of FTD in Minnesota: 24 / 100.000; in Switzerland: 30 - 60 / 100.000 (Ratnavalli et al, 2002).

### **Diagnostic procedures**

In order to differentiate FTD from AD, in addition to the clinical assessment, CT and MRI scans may be helpful demonstrating frontal atrophy.

Functional imaging (PET, SPECT) in typical cases show frontal / temporal hypometabolism, reflected by the decrease of blood flow in the affected areas (SPECT), as well as the decrease of glucose consumption (PET). CSF analysis of tau and Abeta levels help to differentiate AD (increase of phospho-tau and decrease of Abeta) from FTD (no modification).

### **Care and treatment**

As yet there is no cure for fronto-temporal dementia and the progression of the condition cannot be slowed.

Drugs that are designed for the treatment of Alzheimer's disease, such as Aricept ® and Exelon ®, may increase symptoms.

Symptomatic for disinhibition and behavioural problems.

Antidepressants for apathy.

Trazodone for agitation (Lebert et al, 2003).

No prevention.



**Ongoing research / clinical trials**

In selected cases, cholinesterase inhibitors have been tried and found ineffective. Research on the involvement of tau proteins in FTD.

**Available services**

The Association for Frontotemporal Dementias  
<http://www.ftd-picks.org/>

**References**

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2. Lebert F, Stekke W, Hasenbroekx Ch, Pasquier F. Fronto-temporal dementia. A randomized, controlled trial with trazodone. *Dem Cogn Disord*. (in press)
3. Ratnavalli et al, 2002, The prevalence of frontotemporal dementia. *Neurology* 58, 1615-1621

### 3.1.2. Primary Progressive Aphasia (PPA) by André Delacourte

#### General outlines

Primary progressive aphasia (PPA) is a focal dementia characterised by an isolated and gradual dissolution of language function. After several years, this disease develops into fronto-temporal dementia with severe language disorder.

#### Synonym

Slowly Progressive Aphasia

#### Symptoms and course

PPA may take a number of forms, it commonly appears initially as a disorder of speaking (an articulatory problem), progressing to nearly total inability to speak in its most severe stage, while comprehension remains relatively preserved. The disease starts with word-finding disturbances (anomia) and frequently proceeds to impair the grammatical structure (syntax) and comprehension (semantics) of language. The speech output in PPA can be fluent or nonfluent. Memory, visual processing, and personality remain relatively well-preserved until the advanced stages and help to distinguish PPA from Alzheimer's disease.

A less common variety begins with impaired word finding and progressive deterioration of naming and comprehension, with relatively preserved articulation.

Most people with PPA maintain ability to take care of themselves to pursue hobbies and in some instances to remain employed.

Average age of the onset: 50 to 60 years in general  
Duration of the disease: several years

#### Caregiver problems

People with primary progressive aphasia are fighting against a condition in which they will continue to lose their ability to speak, read, write and/or understand what they hear.

#### Genetics

There is a family history in about half of all cases of fronto-temporal degeneration. In these families 50 % can be caused by mutation in tau-gene. Some of these inherited forms have been linked to abnormalities on chromosome 3.

The causes of non-inherited fronto-temporal dementia are so far unknown.

#### Frequency

About 10% of fronto-temporal degeneration.

#### Diagnostic procedures

In order to differentiate FTD from AD, in addition to the clinical assessment, CT and MRI scans may be helpful demonstrating frontal atrophy. Functional imaging (PET, SPECT) in typical cases show frontal / temporal hypometabolism.

#### Causes and risk factors

Care and treatment  
No specific medication.  
Language rehabilitation has not been tried.

### **Available services**

#### **National Aphasia Association**

29 John St., Suite 1103  
New York, NY 10038

<http://www.aphasia.org/NAAppa.html>

### **References**

1. Sonty, S. P., M. M. Mesulam, et al. (2003). "Primary progressive aphasia: PPA and the language network." *Ann Neurol* 53(1): 35-49.

### 3.1.3. Semantic Dementia (SD) by André Delacourte

#### General outlines

Semantic dementia is characterised by the inability to match certain words with their images or meanings (semantic memory). However, patients with this disorder retain the ability to speak quite fluently, as well as the ability to remember day-to-day events (episodic memory). The cognitive locus of this syndrome appears to lie in the permanent store of long-term memory representing general world knowledge-semantic memory.

#### Symptoms and course

This begins with loss of knowledge about the world, which often presents as problems with language. Although people can still speak fluently they lose the words for certain items and also lose the knowledge of the meaning of the word. For example, someone may not only forget the word "hippopotamus" when shown a picture, but also loses all the knowledge they once had about this (e.g. that it is an African animal that lives in rivers). However, unlike Alzheimer's disease, memory for day-to-day events may be good. People may also have difficulty recognising what things are. At later stages, personality is often affected.

SD is gradually progressive and after 5 years, it develops into FTD. The average age of onset is usually 55 (+/- 10 years). The duration of the disease from diagnosis is 6 to 8 years (longer than AD).

#### Caregiver problems

People with primary progressive aphasia are fighting against a condition in which they will continue to lose their ability to speak, read, write, and/or understand what they hear.

#### Causes and risk factors

The causes and risk factors are unknown.

#### Frequency

Very rare disease.

#### Diagnostic procedures

Magnetic resonance imaging (MRI) of the brain can aid physicians in distinguishing semantic dementia from Alzheimer's disease, two neurodegenerative disorders that are hard to differentiate in their early stages.

In patients with semantic dementia, the loss of brain tissue was mostly confined to the left side of the brain and particularly to the front portion of the left temporal lobe.

In patients with Alzheimer's disease, the degree of atrophy was equivalent on both sides of the brain, with no evidence to suggest greater atrophy in the front portion, compared to the back portion, of the temporal lobes.

Semantic impairment, hypoperfusion of the temporal cortex, bilateral but with a left predominance.

### **Care and treatment**

Cholinesterase inhibitors are not useful.  
No prevention.

### **Available services**

#### **National Aphasia Association**

29 John St., Suite 1103  
New York, NY 10038

<http://www.aphasia.org/NAAppa.html>

### **References**

1. Garrard, P. and J. R. Hodges (2000). "Semantic dementia: clinical, radiological and pathological perspectives." *J Neurol* 247(6): 409-22.

## 3.2. Histopathological sub-types

### 3.2.1. FTD with parkinsonism linked to chromosome 17 (FTDP-17)

by André Delacourte

#### General outlines

Fronto-temporal clinical signs associated with Parkinsonism features. The Parkinsonian features are related to movement disorders such as rigidity, reduced speed and uncontrolled movements, including those of the eye (supranuclear palsy).

#### Symptoms and course

Clinical presentation is extremely variable, according to the type of mutation on tau gene, and heterogeneous inside a same family. Patients may have slowly progressive behavioural changes, language disturbances, and/or extrapyramidal signs. Some have with rigidity, bradykinesia, supranuclear palsy and saccadic eye movement disorders. Symptoms usually start between 40 and 60 years of age, but may occur earlier or later. Disease duration is usually between five and ten years, but occasionally may be up to 20-30 years. The disease progresses over a few years into a profound dementia with mutism.

#### Genetics

Familial autosomic dominant, with full penetrance (One child out of two inherits of the mutation of the parent, and this mutation will inevitably provoke the disease).

#### Frequency

FTDP-17 is extremely rare, but frequent in patients with FTD and a familial history (Rosso et al 2002).

#### Diagnostic procedures

Clinical (to observe frontotemporal and parkinsonian signs) and MRI (to observe atrophy of frontotemporal regions and to exclude other pathologies such as vascular pathology) (FTD phenotype). Familial cluster. Genetic test for the tau gene mutations.

#### Causes and risk factors

FTD is mainly due to abnormalities of tau gene or tau protein.

#### Care and treatment

As yet there is no cure for fronto-temporal dementia and the progression of the condition cannot be slowed.

Drugs that are designed for the treatment of Alzheimer's disease, such as Aricept and Exelon, may make symptoms worse and increase aggression.

Symptomatic for disinhibition and behavioural problems.

Antidepressants for apathy.

Trazodone for agitation.

No prevention.

#### Ongoing research / clinical trials

These mutations have generated the concept of "tauopathies", since the cause of the disease is tau mutations. Many other neurodegenerative disorders have also tau abnormalities.

**Available services**

The Association for Frontotemporal Dementias  
<http://www.ftd-picks.org/>

**References**

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2. Lebert F, Stekke W, Hasenbroekx Ch, Pasquier F. Fronto-temporal dementia. A randomized, controlled trial with trazodone. *Dem Cogn Disord.* (in press)
3. Rosso SM, van Herpen E, Deelen W, Kamphorst W, Severijnen LA, Willemsen R, Ravid R, Niermeijer MF, Dooijes D, Smith MJ, Goedert M, Heutink P, van Swieten JC (2002) A novel tau mutation, S320F, causes a tauopathy with inclusions similar to those in Pick's disease. *Ann Neurol* 51:373-6

### 3.2.2. Pick's disease (PiD) by André Delacourte

#### General outlines

Pick's disease (PiD) is a neuro-degenerative disorder that belongs to the group of "fronto-temporal dementia". This is a rare type of presenile dementia, with sometimes a familial character.

PiD is characterised by specific lesions named Pick bodies that are found in the hippocampus and in the neocortex. Pick bodies are made up of tau proteins.

Pick's disease is a form of dementia characterised by a slow deterioration of social skills and changes in personality, along with impairment of intellect, memory, and language.

#### Synonym

Dementia with Lobar Atrophy and Neuronal Cytoplasmic Inclusions , Diffuse Degenerative Cerebral Disease , Lobar Atrophy of the Brain, Pick Disease of the Brain

#### Symptoms and course

One of the first and most important warning signs of FTD is insensitivity to other people. This could be linked to difficulty in identifying emotions shown by their relatives.

Although the disease varies greatly in the way it affects individuals, there is a common core of symptoms among patients, which may be present at different stages of the disease. These symptoms include loss of memory, lack of spontaneity, difficulty in thinking or concentrating, and disturbances of speech. Other symptoms include gradual emotional dullness, loss of moral judgment, and progressive dementia.

Pick's disease usually has its onset between the ages of 40 and 60 years, but extreme cases have been reported with onset as early as 21 and as late as 80. In an analysis of 18 cases of Pick's disease average survival was reported to be 6.3 years for men and 8.4 year for women.

#### Causes and risk factors

A specific neurofibrillary degeneration, revealed by the presence of Pick bodies in the hippocampus and fronto-temporal cortex and an abnormal processing of tau proteins, is associated to this pathology.

#### Frequency

PiD defined as a disease with Pick bodies is extremely rare. This disease occurs sporadically. But some FTDP-17 with specific mutations have also Pick bodies, showing that there are probably two subsets for this rare disease.

#### Diagnostic procedures

Clinical with the specific features of fronto-temporal impairment. Imaging reveals a fronto-temporal atrophy and hyperperfusion.



**Care and treatment**

Symptomatic for disinhibition and behavioural problems.  
Antidepressants for apathy.  
Cholinesterase inhibitors are not useful.  
Trazodone for agitation.  
No prevention.

**Ongoing research / clinical trials**

Like most fronto-temporal dementia, tau proteins seem to be involved in the aetiology of the disease. Many laboratories are working on the molecular pathology of tau proteins.

**Available services****The Pick's Disease Support Group**

Brooksby Close  
Oadby  
Leicester  
LE2 5AB  
Tel : 0116 271 1414  
Fax : 0870 706 0958  
[carol@pdsg.org.uk](mailto:carol@pdsg.org.uk)  
[www.pdsg.org.uk](http://www.pdsg.org.uk)

**References**

1. Dickson, D. W. (2001). "Neuropathology of Pick's disease." *Neurology* 56(11 Suppl 4): S16-20.
2. Lebert F, Stekke W, Hasenbroekx Ch, Pasquier F. Fronto-temporal dementia. A randomized, controlled trial with trazodone. *Dem Cogn Disord.* (in press)

### 3.2.3. Dementia lacking distinctive histology (DLDH)

#### General outlines

Dementia lacking distinctive histology is a neuro-degenerative disorder that belongs to the group of "fronto-temporal dementia".

These FTD are also named FTD non-Alzheimer, non-Pick, to emphasize that there are no accumulation of tau proteins. However, levels of normal tau protein are dramatically decreased, suggesting that this fronto-temporal dementia is also a tauopathy ("tau-less tauopathy": Zhukareva et al, 2001).

#### Synonym

Fronto-temporal dementia, non-Alzheimer, non-Pick  
Frontal lobe degeneration

#### Symptoms and course

The symptoms are similar to FTD. Typically, during the initial stages of fronto-temporal dementia, memory will still be intact, but the personality and behaviour of the person will change. The person may lose their inhibitions and become extrovert, or alternatively may become apathetic and withdrawn. They may talk to strangers, make inappropriate remarks in public and be rude or impatient. They may become aggressive which may be quite out of character, and may develop fixed routines. Some people begin to hoard things and become obsessive. Behaviour may be sexually suggestive, though a loss of interest in sexual acts themselves is also common. Often the person with dementia will be unaware of the problems.

People may also develop a sweet tooth and overeat leading to gain in weight. Excessive alcohol intake may occur. Spending money and losing cash often causes problems. In the later stages people with the illness may compulsively put objects in their mouths.

In the early stages memory is not usually affected. However sometimes difficulties in organisation and concentration may lead to an apparent memory problem. People may be very distractible.

Later in the disease a more generalised dementia can develop, and symptoms will usually appear to be similar to those with Alzheimer's disease. Those affected may no longer recognise friends and family and may need nursing care, become incontinent and bed-ridden.

Average age of onset: 50 to 60  
Duration of the disease: several years

#### Causes and risk factors

Linked to tau protein metabolism

#### Genetics

DLDH is likely heterogeneous. Indeed, in addition to the previous description, there are DLDH not linked to tau.

1. non tau FTD linked to chromosome 3
2. FTD with Motor neuron disease: Amyotrophic Lateral Sclerosis (ALS) can be associated with FTD

Guam ALS is also a rare form of FTD and ALS found in the Chamorro population of Guam island. Tangles (tau pathology) is also well developed in neocortical areas

**Frequency**

Not rare among non-familial FTD cases

**Diagnostic procedures**

In order to differentiate FTD from AD, in addition to the clinical assessment, CT and MRI scans may be helpful demonstrating frontal atrophy. Functional imaging (PET, SPECT) in typical cases show frontal / temporal hypometabolism.

**Care and treatment**

As yet there is no cure for fronto-temporal dementia and the progression of the condition cannot be slowed.

Drugs that are designed for the treatment of Alzheimer's disease, such as Aricept® and Exelon® may increase symptoms.

Symptomatic for disinhibition and behavioural problems.

Antidepressants for apathy.

Trazodone for agitation.

No prevention.

**Ongoing research / clinical trials**

Research on the physiopathology of tau proteins, likely involved in the process

**Available services**

The **Association for Frontotemporal Dementias**

<http://www.ftd-picks.org/>

**References**

1. Lebert F, Stekke W, Hasenbroekx Ch, Pasquier F. Fronto-temporal dementia. A randomized, controlled trial with trazodone. Dem Cogn Disord. (in press)
2. Tolnay, M. and A. Probst (2001). "Frontotemporal lobar degeneration. An update on clinical, pathological and genetic findings." Gerontology 47(1): 1-8.
3. Zhukareva V., Vogelsberg-Ragaglia V., Van Deerlin V. M., Bruce J., Shuck T., Grossman M., Clark C. M., Arnold S. E., Masliah E., Galasko D., Trojanowski J. Q. and Lee V. M. (2001) Loss of brain tau defines novel sporadic and familial tauopathies with frontotemporal dementia. Ann Neurol 49, 165-175.

## 4. Progressive Supranuclear Palsy (PSP) by André Delacourte

### General outlines

Progressive Supranuclear Palsy is a disorder caused by damage to certain nerve cells in the brain, characterised by progressive lack of coordination, stiffness of the neck and trunk, difficulties with eye movement, slow movements, cognitive dysfunction, and difficulty walking that can result in falls. This disease is most often seen in people over 60 years old.

### Synonyms

Steele-Richardson-Olszewsky syndrome

### Symptoms and course

PSP is a very individual disease, affecting different people in different ways at different rates of progression.

Early symptoms in 'classical' PSP cases involve a tendency to fall unexpectedly, usually backwards. Other common symptoms include rigidity and backward arching of the neck, and - a key diagnostic feature - the "Supranuclear Palsy". This is a difficulty in 'willed' upgaze and downgaze, ie. the ability of the patient to voluntarily move their eyes up and down whilst keeping the head still.

The gait of a PSP patient is mildly unsteady and broad based. PSP is a disorder characterised by symptoms similar to Parkinson's disease (including unsteady gait, stiff movements and mild dementia). PSP can be easily misdiagnosed as Parkinson's disease in its early stages. Tiny, cramped handwriting and some changes in personality are often other indicators of the disease.

Cognitive symptoms include reduced verbal fluency, attention deficit, executive dysfunction, slowing of information processing and problems with complex and abstract thought. Nevertheless the patient is still very much aware of what is going on. Behavioural changes include emotional lability and temper outbursts.

Motor symptoms come first and always precede cognitive changes.  
The progression of the disease is slow between 5 to 10 years.  
The age of onset is typically over 50 years old.  
The duration of the disease is 7 years.

### Causes and risk factors

The cause of PSP is as yet unknown, though there may be a genetic, as well as an environmental, component. From a broad survey of various countries in the Western World, the probability of the disease being passed from one generation to the next within a family is extremely low. It may be that a combination of complex genetic susceptibility to PSP, together with an environmental trigger such as a blow on the head or exposure to toxins may cause the onset, but more research is required to confirm this theory. However, as observed in many neurodegenerative disorders, tau proteins or tau gene is likely a significant causal factor. Indeed, there is a genetic risk factor linked to H1H1 haplotype in the tau gene. PSP belongs to the 4R tauopathies (aggregation of tau isoforms with 4 repeats) (Sergeant N. et al, 1999).

### Genetics

A genetic risk factor linked to tau gene (Baker M. et al, 1999).

**Frequency**

Prevalence estimations vary between 1.4 /100.000 (Tolosa - E) to 6/100.000.

**Diagnostic procedures**

No specific tests. Brain imaging non specific. Poor response to Parkinsonian drugs argues against Parkinson's.

**Care and treatment**

Treatment is aimed at controlling symptoms. There is no known cure for progressive supranuclear palsy. Levodopa and anticholinergic medications may provide temporary reduction of symptoms.

These are not as effective as in Parkinson´s disease, however.

**Ongoing research / clinical trials**

Two multicentre European trials have been launched to evaluate the effects of riluzole (NNIPPS see in PSP file) and human recombinant growth hormone on disease progression in MSA.

Clinical trial on Riluzole (NNIPPS study: efficacy and safety of Riluzole (200 mg/day), in patients with multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).

A randomised, multicentric, double blind, placebo controlled, stratified, parallel group study. Acronym: NNIPPS (Neuroprotection & Natural History in Parkinson Plus Syndromes)

**Project coordinators:**

Dr G. Bensimon, Dept. de Pharmacologie, Hôpital de la Pitié-Salpêtrière, Assistance Publique - Hôpitaux de Paris, Paris, France

Prof. PN. Leigh, Dept Clinical Neuroscience, Institute of Psychiatry & Guy's, King's & Thomas's School of Medicine (GKT), London, UK

Prof. A. Ludolph, Dept of Neurology, Universitätsklinik and Rehabilitation Krankenhaus Ulm, Ulm, Germany )

**Available services****PSP Europe**

The Old Rectory, Wappenham  
Towcester  
Northants  
NN12 8SQ  
Tel: + 44 1327 860299  
Fax: + 44 1327 861007  
psp.eur@virgin.net  
<http://www.pspeur.org>

**References**

1. Baker M., Litvan I., Houlden H., Adamson J., Dickson D., Perez-Tur J., Hardy J., Lynch T., Bigio E. and Hutton M. (1999) Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet* 8, 711-715.
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5. Tolosa E., Valldeoriola F. and Marti M. J. (1994) Clinical diagnosis and diagnostic criteria of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *J Neural Transm Suppl* 42, 15-31.

## 5. Corticobasal degeneration (CBD) by André Delacourte

### General outlines

Corticobasal degeneration (CBD) is a rare neurological disease in which parts of the brain deteriorate or degenerate. CBD is also known as corticobasal ganglionic degeneration, or CBGD.

Several regions of the brain degenerate in CBD. The cortex, or outer layer of the brain, is severely affected, especially the fronto-parietal regions, located near the center-top of the head. Other, deeper brain regions are also affected, including parts of the basal ganglia, hence the name "corticobasal" degeneration.

### Synonyms

Corticobasal ganglionic degeneration (CBGD)

### Symptoms and course

Initial symptoms, which typically begin at or around age 60, may first appear on one side of the body (unilateral), but eventually affect both sides as the disease progresses. Symptoms include signs of parkinsonism such as poor coordination, akinesia (an absence of movements), rigidity (a resistance to imposed movement), and disequilibrium (impaired balance); and limb dystonia (abnormal muscle postures). Other symptoms such as cognitive and visual-spatial impairments, apraxia (loss of the ability to make familiar, purposeful movements), hesitant and halting speech, myoclonus, and dysphagia (difficulty swallowing) may also occur.

CBD is a progressive disease, meaning that the symptoms worsen over time. Over the course of one to several years, most people with CBD gradually worsen, with symptoms progressing to involve upper and lower extremities and other body regions. Symptoms of advanced CBD include:

- parkinsonism (rigidity, slow movements, postural instability)
- tremor
- myoclonus (sudden, brief jerky movements)
- dystonia, including blepharospasm
- speech difficulty
- mild-to-moderate cognitive impairment (memory loss, difficulty planning or executing unrehearsed movements, dementia)
- sensory loss
- "alien hand/limb" phenomenon (difficulty controlling the movements of a limb, which seems to undertake movements on its own, sometimes combined with a feeling that the limb is not one's own)

The age of onset is around 60 years old.

The duration of the disease is between 5 and 10 years.

### Causes and risk factors

CBD is essentially sporadic. A degeneration affecting many subcortical nuclei and spreading into the neocortex in the frontal and parietal areas with an aggregation of tau protein in affected areas within neurons and in astrocytes. Genetic risk factor is H1H1 in the tau gene. Belongs to the 4R tauopathies (aggregation of tau isoforms with 4 repeats) (Sergeant N. et al, 1999).

### Genetics

Genetic risk factor linked to tau gene (Baker M. et al, 1999).

## Frequency

Similar to PSP: 2-6/100.000.

## Diagnostic procedures

An EEG (electroencephalogram) may show changes in brain function over time that are consistent with the neuro-degeneration. CT or MRI scans can also be used in this way, providing images of asymmetric atrophy of the fronto-parietal regions of the brain's cortex, the regions most frequently involved in the disease. (Litvan I. Et al, 1997).

Clinical features. A difference between PSP and CBD is described at the neuro-pathological level (glial tufted plaques for PSP or astrocytic plaques for CBD).

## Care and treatment

Unfortunately, there are no drugs or other therapies that can slow the progress of the disease, and very few that offer symptomatic relief. Tremor and myoclonus may be controlled somewhat with drugs such as clonazepam. Baclofen may help reduce rigidity somewhat. Levodopa and other dopaminergic drugs used in Parkinson's disease are rarely beneficial, but may help some CBD patients.

## Ongoing research / Clinical trials

Search on risk factors. Analysis of tau protein involvement

## Available services

### Corticobasal ganglionic degeneration (CBGD) caregivers report

<http://www.tornadodesign.com/cbgd/index.htm>

## References

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## **6. Argyrophilic Grain Disease (AGD)** by André Delacourte & Kurt Jellinger

### **General outlines**

New disease, which is not fully characterised. A sporadic late-onset form of dementia characterised by a neuro-degenerative process, which mainly affects limbic structures (amygdala, hippocampus and mediobasal temporal/entorhinal cortex).

It is named after silver-staining (argyrophilic) grains or "coiled bodies" within the cytoplasm of neurons that consist mainly of tau protein isoforms with four microtubule-binding repeats (4-R tau).

### **Synonym**

Braak's disease

### **Symptoms and course**

Reduction of short-term memory, disorders of word finding, disorders of reading and writing, disorientation, behavioural disturbances (personality changes, emotional disorders with aggression and ill-temper) may precede or follow memory failure. Clinically it is hard to distinguish from late-onset AD.

The age of onset is around 70 years old.  
The duration of the disease is between 4 and 8 years.

### **Causes and risk factors**

Neuron degeneration likely associated with dysfunction of tau protein. Grains are composed of abnormally phosphorylated tau protein with 4 repeats. Recent studies indicate that tau protein dysfunction in AGD in contrast to other 4-R-tauopathies (progressive supranuclear palsy, corticobasal degeneration).

### **Genetics**

The disease arises irrespective of the genetic background regarding tau H1 or H2 haplotypes, at the opposite of PSP and CBD (Miserez A. R. et al, 2003).  
Lack of relationship with apolipoprotein E4.

### **Frequency**

1 to 5% of AD patients (Togo T. et al, 2002).

### **Diagnostic procedures**

It is almost impossible to distinguish from late-onset Alzheimer's disease.  
The diagnosis is almost entirely made by post-mortem examination. AGD lesions are found in about 5% of Alzheimer's disease (Togo T. et al, 2002).

### **Care and treatment**

Those related to patients affected by Alzheimer's disease.

**Ongoing research / clinical trials**

Continued research on tau protein.  
Subclasses of AGD may exist, with a more diffuse forms of grain pathology (Maurage C. A. et al, 2003).

**Available services**

Due to the recent characterization of this disease, there are no specific available services.

**References**

1. Botez G et al. Clinical aspects of "argyrophilic grain disease" (German). *Nervenarzt* 2000; 71:38-43.
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## 7. Multiple System Atrophy (MSA) by André Delacourte

### General outlines

Multiple system atrophy (MSA) is a progressive disorder of the central and sympathetic nervous systems. The disorder is characterized by postural (or orthostatic) hypotension—an excessive drop in blood pressure when the patient stands up, which causes dizziness or momentary blackouts. MSA does not provoke dementia but could impair some cognitive functions.

### Synonyms

Shy-Drager syndrome, olivopontocerebellar atrophy (OPCA), striatonigral degeneration

### Symptoms and course

MSA has been classified clinically into three types, olivopontocerebellar atrophy (OPCA), which primarily affects balance, coordination, and speech; a parkinsonian form (striatonigral degeneration), which can resemble Parkinson's disease because of slow movement and stiff muscles; and a mixed cerebellar and parkinsonian form. In all three forms of MSA, the patient can have orthostatic hypotension. Orthostatic hypotension and symptoms of autonomic failure such as constipation, impotence in men, and urinary incontinence usually predominate early in the course of the disease. Constipation may be unrelenting and hard to manage. Shy-Drager syndrome may be difficult to diagnose in the early stages. For the majority of patients, blood pressure is low when the patients stand up and high when the patients lie down. Other symptoms that may develop include impaired speech, difficulties with breathing and swallowing, and inability to sweat. Shy-Drager syndrome usually ends in the patient's death by 7 to 10 years after diagnosis. Breathing problems such as aspiration, stridor (high-pitched breathing sounds due to airway obstruction), or cardiopulmonary arrest are common causes of death.

### Causes and risk factors

Neurodegeneration in subcortical nuclei is mainly affecting oligodendrocytes. A simultaneous synucleopathy and tauopathy is observed.

### Frequency

The average annual incidence rate (new cases per 100,000 person-years) for ages 50 to 99 years is 3.0 for MSA (Bower 1997).

The age-adjusted prevalence for MSA is 4.4 per 100,000 (two probable and two possible cases) (Schrag, 1999).

**NEUROPATHOLOGY** Argyrophilic intracytoplasmic inclusions in oligodendrocytes (AGCIs) are widespread, not only in the olivopontocerebellar and striatonigral systems but also among fibers connecting their affecting lesions of MSA. Synuclein and tau proteins accumulate in AGCIs.

### Diagnostic procedures

The diagnosis is mainly based on the specific clinical manifestations (postural or orthostatic) hypotension, rigidity, balance, coordination, impaired speech, excessive drop in blood pressure, and in general autonomic/urogenital failure. (Wenning G.k. - 2003) MRI can help to precise the diagnosis (Yekhlef F - 2003)

## Care and treatment

Orthostatic hypotension in Shy-Drager syndrome is treatable, but there is not known effective treatment for the progression central nervous system degeneration. The general treatment course is aimed at controlling symptoms. Antiparkinsonian medication, such as L-dopa, may be helpful. To relieve low blood pressure while standing, dietary increases of salt and fluid may be beneficial. Medications to elevate blood pressure, such as salt-retaining steroids, are often necessary, but they can cause side effects and should be carefully monitored by a physician. Alpha-adrenergic medications, non-steroidal anti-inflammatory drugs, and sympathomimetic amines are sometimes used. Sleeping in a head-up position at night reduces morning orthostatic hypotension. An artificial feeding tube or breathing tube may be surgically inserted for management of swallowing and breathing difficulties.

## Available services

The Sarah Matheson Trust  
Contact: Pickering Unit  
St. Mary's Hospital, Praed Street  
London W2 1NY UK  
TEL: (44) 207 8 861 520  
FAX: (44) 207 8 861 540  
<http://www.msaweb.co.uk>

## References

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## 8. Amyotrophic Lateral Sclerosis (ALS) by Giuliano Binetti

### General outlines

Jean-Martin Charcot, a French Neurologist, described the ALS in 1874.

ALS is a disease of the motor nerve cells in the brain and spinal cord, causing progressive loss of motor control. ALS affects both upper and lower motor neurons throughout the brain and spinal cord.

A-myo-trophic comes from the Greek language. "A" means no or negative. "Myo" refers to muscle, and "Trophic" means nourishment - "No muscle nourishment." When a muscle has no nourishment, it "atrophies" or wastes away. "Amyotrophic" refers to the muscle atrophy, weakness and fasciculation that signify disease of the lower motor neurons.

"Lateral" identifies the areas in a person's spinal cord where portions of the nerve cells that nourish the muscles are located. As this area degenerates it leads to scarring or hardening ("sclerosis") in the region.

"Lateral sclerosis" refers to the hardness to palpation of the lateral columns of the spinal cord in autopsy specimens, where gliosis follows degeneration of the corticospinal tracts.

### Synonyms

Lou Gehrig Disease, Motor Neuron Disease and Charcot disease.

### Symptoms and course

In patients with typical ALS, the symptoms are primarily those of weakness, which may start in the hands or legs or be manifested by slurred speech and dysphagia.

The symptoms of lower motor neuron disease are muscular weakness, atrophy, fasciculation, cramps, slurred speech (dysarthria), difficulties in swallowing (dysphagia) and difficulties in mastication.

The symptoms of upper motor neuron disease are stiffness, slowness, clumsiness of movement, limb spasticity (a specific type of stiffness), abnormally brisk jaw jerk, Babinski's sign and diminished fine motor coordination.

On examination there are almost always lower motor neuron signs together with upper motor neuron signs.

Significant bulbar and respiratory weakness soon occurs in about one half of the patients.

Dementia and parkinsonism each occur in less than 5% of patients.

Dementia often antedates motor involvement. Cognitive dysfunctions are apathy, poor attention, poor motivation, altered social skills and behaviour abnormalities.

Familial cases are inherited as a dominant trait with variable penetrance and expressivities.

The rate at which ALS progresses can be quite variable from one person to another. Although the mean survival time with ALS is three to five years, many people live five, ten or more years. In a small number of people, ALS is known to remit or halt its progression, though there is no scientific understanding as to how and why this happens.

### **Caregiver problems**

A multidisciplinary care is necessary in ALS. Discussion of the diagnosis by sympathetic personnel may reduce anxiety in patients and relatives. Regular reviews by home health staff for family and psychosocial problems, crisis situations and the need for equipment or community services is vital.

Active management of patients by trained physical, occupational, and speech therapists is helpful.

### **Causes and risk factors**

The aetiology is likely multifactorial involving both genetic and environmental factors.

#### **Genetic factors**

Familial clustering of ALS has been recognised for many years and pedigrees of autosomal dominant inheritance of up to six generations recorded.

The incidence of individuals with ALS with another affected family member has been reported as around 5 to 10% in several studies. In some of these families, there is clear evidence of autosomal dominant inheritance and rarely of autosomal recessive inheritance. Many families may contain only two affected individuals in the same generation or more distantly related, and it is not possible immediately to say whether these reflect common genetic or environmental influences.

In 1993, Rosen et al. described mutations in gene encoding superoxide dismutase 1 (SOD1). These mutations account for 20 percent of cases of familial ALS. The remaining 80 percent are caused by mutations in other genes. Five percent of people with apparently sporadic ALS also have SOD1 mutations. More than 90 SOD1 mutations involve 40 of the 153 amino acid residues. All SOD1 mutations are dominant, except for the substitution of alanine for aspartate at position 90 (D90A), which can be either recessive or dominant.

#### **Environmental factors**

- Exposure to heavy metals
- Viral Infection and Prion Disease as Causes
- Autoimmunity

### **Genetics**

Familial clustering of ALS has been recognised for many years and pedigrees of autosomal dominant inheritance of up to six generations recorded.

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## Frequency

The worldwide annual incidence rates for classical ALS range between 0.4 and 1.8 per 100 000 population, and the prevalence rates between 4 and 6 per 100 000 population.

Several studies have shown an increasing incidence of ALS in individuals older than 60. The annual range of death is about 1 per 100 000.

The incidence and prevalence of ALS vary little worldwide, with notable pockets of higher prevalence, especially in Guam. During World War II, neuropathologist Harry Zimmerman noted an unusual frequency of ALS, parkinsonism and dementia in Guam.

Epidemiologic studies indicated that the prevalence of ALS in Guam was 50 times the prevalence anywhere else. Both the parkinsonism–dementia–ALS complex and ALS alone remain prevalent in Guam.

The cause of Guamanian ALS with parkinsonism and dementia is unknown. Heredity was discounted because the spouses of many patients were also affected, and no environmental causes or virus were found.

Most people who develop ALS are between the ages of 40 and 70, with an average age of 55 at the time of diagnosis. However, cases of the disease do occur in persons in their twenties and thirties. Generally though, ALS occurs in greater percentages as men and women grow older. ALS is 20% more common in men than in women. However with increasing age, the incidence of ALS is more equal between men and women. Half of all people affected with ALS live at least three or more years after diagnosis. Twenty percent live five years or more; up to ten percent will survive more than ten years.

## Diagnostic procedures

The clinical diagnosis of ALS is probably correct in more than 95 percent of cases.

Electromyographic demonstration of denervation in at least three limbs confirms the findings of lower motor neuron abnormalities.

Two methods are being used to document the involvement of upper neurons:

1. Magnetic resonance spectroscopy measures the number of surviving neurons in the motor cortex
2. Magnetic stimulation of the motor cortex assesses conduction in the corticospinal tracts.

The sensitivity and specificity of the two approaches seem to be equal and need to be improved. Magnetic resonance imaging may show high signal intensity in the corticospinal tracts.

## Care and treatment

Riluzole, a glutamate antagonist, is the only drug approved by the Food and Drug Administration for the treatment of ALS. In two therapeutic trials, riluzole prolonged survival by three to six months.

In one of these trials, treatment slightly slowed the decline in the strength of limb muscle; there was no benefit with respect to many measures of function in either trial. In one retrospective analysis, patients who received riluzole remained in a milder stage of disease longer than did controls. For patients, the effects are invisible.

## Ongoing research/Clinical trials

Fifteen years ago, a role for excitotoxic damage in the pathology of amyotrophic lateral sclerosis (ALS) was postulated. This stimulated the development of riluzole, the only available treatment for the disease. Since then, the identification of abnormal forms of superoxide dismutase as the genetic basis of certain familial forms of ALS has provided a huge impetus to the search for new effective treatments for this devastating disease.

Transgenic mouse models have been developed expressing these aberrant mutants that develop a form of motor neurone disease the progress of which can be slowed by riluzole. Studies in these mice have provided evidence for a role for excitotoxic, apoptotic and oxidative processes in the development of pathology. The mice can be used for testing molecules targeting these processes as potential therapies, to allow the most promising to be evaluated in humans. Several such agents are currently in clinical trials. Many previous clinical trials in ALS were insufficiently powered to demonstrate any relevant effect on disease progression. This situation has been to some extent remedied in the more recent trials, which have recruited many hundreds of patients. However, with the exception of studies with riluzole, the results of these have been disappointing. In particular, a number of large trials with neurotrophic agents have revealed no evidence for efficiency.

## Available services

### International Alliance of ALS/MND associations

PO Box 246  
Northampton NN1 2PR  
United Kingdom  
Tel: +44 1604 250 505  
Fax: +44 1604 611 85 29  
[alliance@alsmndalliance.org](mailto:alliance@alsmndalliance.org)  
[www.alsmndalliance.org](http://www.alsmndalliance.org)

### European Alliance of Neuromuscular Disease Associations

C/o Ysbrand Poortman  
Lt. Gen. Van Heulszlaan  
NL-3743 JN Baarn  
ypoortman@zonnet.nl  
<http://www.eamda.org/>

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## 9. Ataxias by Giuliano Binetti

### General outlines

The word "ataxia" comes from the Greek word "ataxis" meaning "without order" or "incoordination."

The Hereditary Ataxias are a group of rare diseases characterised by degeneration of the cerebellum, brain stem and spinal cord. They vary in age of onset, mode of inheritance and severity of the symptoms.

### Synonyms

Cerebellar Ataxia

### Symptoms and course

#### 1) Early Onset

Friedreich ataxia (FRDA) is the most common of the hereditary ataxias. It accounts for at least 50% of cases of hereditary ataxia; the prevalence of the disease in Europe and US is between 1 and 2 per 100 000.

Symptoms: classically presenting with gait ataxia, but with a number of additional features including dysarthria, and pyramidal tract involvement.

Initially this latter feature may be mild, with just extensor plantar responses, but almost invariably a pyramidal pattern of weakness in the legs occurs, which sometimes leads to paralysis.

A peripheral neuropathy is seen with absent reflexes, large fibre sensory abnormalities, and occasionally distal wasting, particularly in the upper limbs. Skeletal abnormalities are also commonly found including scoliosis and pes cavus. Additionally optic atrophy and deafness may be found. Nystagmus is seen in only about 20%, but the extraocular movements are nearly always abnormal. Mental retardation is described.

The other autosomal recessive ataxias are individually rare and often have a metabolic abnormality underlying the pathogenesis (sphingomyelin lipidoses, metachromatic leukodystrophy, galactosylceramide lipidosis (Krabbe's disease) and hexosaminidase deficiencies. Cholestanolosis (also called cerebrotendinous xanthomatosis (CTX)) is a rare autosomal recessive disorder caused by defective bile salt metabolism, resulting from a deficiency of mitochondrial sterol 27 hydroxylase. It gives rise to ataxia, dementia, spasticity, peripheral neuropathy, cataracts, and tendon xanthomata in the second decade of life. Treatment with chenodeoxycholic acid appears to improve neurological function.

#### 2) Late onset inherited ataxias

They are usually autosomal dominant. The dominant ataxias are a clinically and genetically complex group of neurodegenerative disorders. Autosomal dominant cerebellar ataxia (ADCA) type I is characterised by a progressive cerebellar ataxia and is variably associated with other extracerebellar neurological features such as ophthalmoplegia, optic atrophy, peripheral neuropathy and pyramidal/extrapyramidal signs.

The presence and severity of these signs is, in part, dependent on the duration of the disease. Mild or moderate dementia may occur but it is usually not a prominent early feature. ADCA type II is clinically distinguished from ADCA type I by the presence of pigmentary macular dystrophy, whereas ADCA type III is a relatively "pure" cerebellar syndrome and generally starts at a later age.

This clinical classification is still useful, despite the tremendous improvements in our understanding of the genetic basis, because it provides a framework that can be used in the clinic and helps direct the genetic evaluation.

### **3) Idiopathic degenerative late onset ataxias**

In the absence of a clear family history this is rarely genetic. There are a few reports with one or other of the SCAs (spino-cerebellar ataxia) or occasional FA but these are very infrequent. The main differential in this group of patients is whether or not it is the cerebellar presentation of multiple system atrophy. A frequent clinical problem is whether to test for the identifiable mutations.

### **Caregiver problems**

Depression in the patient and family members is common. Although no cures exist for most of the causes of cerebellar ataxia and there are as yet no proven ways to protect neurons from premature cell death or to restore neuronal populations that have been lost, symptomatic treatment can greatly improve the quality of life of these patients and prevent complications that could hasten death. Supportive interventions should always be offered: education about the disease itself, genetic counseling, individual and family counseling, referral to support groups and advocacy groups, and guidance to online resources. Misinformation, fear, depression, hopelessness, isolation, and financial and interpersonal stress can often cause more harm to the patient and caregiver than the ataxia itself.

### **Causes and risk factors**

#### **Friedreich ataxia (FRDA):**

The gene frataxin was cloned in 1996. The predominant mutation is a trinucleotide repeat (GAA) in intron 1 of this gene. Expansion of both alleles is found in over 96% of patients. The remaining patients have point mutations in the frataxin gene. The DNA test for the repeat is relatively simple and widely available. The length of the repeat is a determinant of age of onset and therefore to some degree influences the severity in that early onset tends to progress more rapidly.

#### **Late onset inherited ataxias**

The genetic loci causing the dominant ataxias are given the acronym SCA (spino-cerebellar ataxia). At the time of publication there are over 20 SCA loci identified. Of these genes are established for SCAs 1, 2, 3, 6, 7, 10, 12 and 17. Interestingly the "common" ones are all caused by a similar mutational mechanism, expansion of an exonic CAG repeat. The resultant proteins all possess an expanded polyglutamine tract and there are now at least eight conditions caused by these expansions. Other types of ADCA are exceedingly rare.

### **Genetics**

A simple clinical point when considering the nature of a possible inherited ataxia is the age of onset. As a general rule early onset (< 20 years) tends to be autosomal recessive, later onset (> 25 years) is usually autosomal dominant and X linked inheritance is very rare.

### **Frequency**

Friedreich ataxia (FRDA) is the most common of the hereditary ataxias. It accounts for at least 50% of cases of hereditary ataxia; the prevalence of the disease in Europe and US is between 1 and 2 per 100 000.

## Care and treatment

There is nothing more discouraging than for a patient to be given a specific diagnosis, then to be told that there is nothing that can be done.

Physicians are equally disheartened to see exponential progress being made in the understanding of the pathophysiology of a complex disorder but few direct benefits resulting for their patients.

Over the past 5 years, molecular genetic research has completely revolutionised the way in which the progressive ataxias are classified and diagnosed, but it has yet to produce effective gene-based, neuroprotective, or neurorestorative therapies.

The treatment of cerebellar ataxia remains primarily a neurorehabilitation challenge, employing physical, occupational, speech, and swallowing therapy; adaptive equipment; driver safety training; and nutritional counseling. Modest additional gains are seen with the use of medications that can improve imbalance, incoordination, or dysarthria (amantadine, buspirone, acetazolamide); cerebellar tremor (clonazepam, propranolol); and cerebellar or central vestibular nystagmus (gabapentin, baclofen, clonazepam).

## Ongoing research/Clinical trials

Pilot studies have shown the potential effect of antioxidant therapy based on idebenone or coenzyme Q10 plus Vitamin E administration in FRDA and provide a strong rationale for designing larger randomized clinical trials.

## Available services

### **European Federation of Hereditary Ataxias (EURO-ATAXIA)**

Ms Dagmar KROEBEL  
Haagwindelaan 19  
B – 3090 OVERIJSE  
Tel. : 32/2/657.15.10  
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[dagmar.kroebel@euro-ataxia.org](mailto:dagmar.kroebel@euro-ataxia.org)  
<http://www.euro-ataxia.org>

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## 10. Huntington's Disease (HD) by Giuliano Binetti

### General outlines

In 1872 G.Huntington described the variety of chorea that came to bear his name. His description contains all the essential features considered disgnostic of Huntington's Disease (HD): a progressive disorders combining chorea with behavioral disturbances and dementia, transmitted via an autosomal dominant inheritance pattern. Huntington's disease is the prototypic neurogenetic disorder, one of the first to be mapped (1983) and subsequently cloned (1993), and the model on which presymptomatic genetic testing is based.

### Synonyms

Huntington's chorea

### Symptoms and course

It is usually apparent in the forth or fifth decades, but may occur at almost any age. No clear sex preponderance is evident. Low prevalence rates have been noted in Japan and among African and American blacks, and most patients are of northern European ancestry.

The clinical triad of movement disorder, psychiatric features, and eventual dementia will be well known to neurologists. Chorea is the first manifestation in about two thirds of patients, initially a mild fidgetiness apparent only to the careful observer, which gradually progresses and may be the only clinical manifestation of HD for several years. Personality change and eye movement disorders including slow saccades, and head thrusting or blinking to generate saccadic eye movements, are also common early features. A wide range of movement disorders including parkinsonism, loss of postural stability, and dystonia eventually supervene, leading to increasingly functional impairment. Progressive weight loss, often resulting in cachexia, is common. The juvenile onset form of HD may present with parkinsonism, the so-called Westphal variant, while late onset forms may cause chorea alone.

The majority of the patients exhibit neuropsychiatric symptoms, the most prevalent being dysphoria, agitation, irritability, apathy, and anxiety. Symptoms range from mild to severe and are unrelated to dementia and chorea. The cognitive disturbances associated to HD may begin early in the disease course and include deficit in attention and concentration, memory retrieval, "executive" functions, and psychomotor speed. The constellation of cognitive and behavior deficits associated with HD forms a so called "subcortical dementia syndrome" tht is distinct from the frank amnesia, aphasia, apraxia, and agnosia that embodies the cortical dementia syndrome associated to disorders such as Alzheimer disease. Death most often results from dysphagia through aspiration pneumonia or suffocation, usually between 10 and 20 years after the onset of symptoms. Suicide is also a common cause of death. Juvenile onset patients have a distinctly poorer prognosis than adults, with a high incidence of seizure disorders late in the course and a much shorter life expectancy. The onset of HD at later life is associated with a slower progression of symptoms.

### Caregiver problems

The most important issue in the management of HD is the education of the patient and family about the disease and the implication of the diagnosis for other family members. The organisations are invaluable sources of information and support for HD families, as well as help with chronic care patients.

## Causes and risk factors

Huntington's disease results from a genetic mutation on the fourth chromosome. This abnormality causes the death of vital nerve cells in a region of the brain known as the basal ganglia. HD is an autosomal dominant disorder, which means that each child of a parent with the disease has a 50 percent risk of inheriting the illness.

The huntington gene (IT15 gene) is considered virtually 100 percent "penetrant," meaning that anyone who inherits the faulty gene will inevitably develop the disease. All "carriers" eventually become "patients."

## Frequency

Prevalence of HD: People Currently Living with Disorder (US data: 30.000).

## Diagnostic procedures

The IT15 gene is composed of 67 exons and encodes a protein of 3,144 amino acids, called huntington. Exon 1 contains a CAG trinucleotide repeat that encodes the amino acid glutamine, followed by another repeat that encodes proline. In unaffected individuals, there are 10–34 CAG repeats. In those affected by HD, there are more than 40 repeats. In those with 35–39 repeats, the disease is variably penetrant. The age of onset of the disease varies inversely with the number of CAG repeats. Individuals with juvenile onset usually have over 55 repeats, and they usually inherit the gene from their father.

The expansion is thought to occur via slippage during the DNA replication process. Expansion of a polyglutamine (CAG) trinucleotide repeat beyond the critical threshold of 36 repeats results in disease, and forms the basis of the polymerase chain reaction based genetic test. Inheritance is dominant with full penetrance, meaning that almost all mutation carriers will eventually develop the disease, except those with 36–39 repeats where penetrance is reduced. Predictive genetic testing of asymptomatic at-risk relatives of affected patients is governed by international guidelines. Prenatal testing in known mutation carriers is routinely available, while linkage based exclusion testing is available to those at-risk women who do not wish to know their own gene status. The latter depends on termination of a pregnancy where linkage shows the fetus to have the same 50% genetic risk as the mother.

## Care and treatment

Chorea may respond to dopamine antagonists, both presynaptic (Tetrabenazine or reserpin) and postsynaptic (neuroleptics such as haloperidol). The high incidence of serious adverse reactions to these agents limits their use where the movements disorder are truly disabling.

## Ongoing research/Clinical trials

Current research is exploring possible drug treatments, which would prevent the accumulation of anomalous proteins in cells. Other research efforts include the development of a mouse model for Huntington's disease and the CARE-HD study, a clinical drug trial underway at about 20 Huntington Study Group sites. Researchers are evaluating the combination of a medication (remacimide) and co-enzyme Q-10. Both basic (laboratory) and clinical (testing of medications and treatments) research continues to pursue avenues to facilitate new drug testing and experimental surgical techniques.

**Available services****International Huntington Association**

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The Netherlands

Tel: +31 - 573 - 431 595)

Fax: +31 - 573 - 431 719

[iha@huntington-assoc.com](mailto:iha@huntington-assoc.com)

[www.huntington-assoc.com/](http://www.huntington-assoc.com/)

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## **11. Down syndrome** by Jos Van der Poel

### **General outlines**

Down's syndrome is a genetic disorder (in stead of two these persons have three chromosomes 21) that besides a number of physical characteristics leads to intellectual impairment.

It occurs in one out of every 1.000 births. Life expectancy of people with Down's syndrome has increased substantially over the last century: about 50 % of them will reach the age of 60. Because of the trisomie 21 people with Down's syndrome have an overexpression of the amyloid precursor protein. Amyloid is the main ingredient of the plaques, which are found in the brains of people with Alzheimer's disease.

### **Symptoms and course**

Not all persons with Down's syndrome show evidence of cognitive deterioration or other clinical evidence of dementia even after extended periods of observation.

Clinical symptoms at first are increasing depression, indifference and a decline in social communication. Later symptoms are: seizures in previously unaffected persons, changes in personality, loss of memory and general functions, long periods of inactivity or apathy, hyperactive reflexes, loss of activity of daily skills, visual retention deficits, loss of speech, disorientation, increase in stereotyped behaviour and abnormal neurological signs.

Average age of onset is 54 years and average interval from diagnosis to death is less than 5 years.

### **Caregiver problems**

Especially for brothers and sisters who are confronted with the responsibility for (the care of) their sibling with Down's syndrome when their parents have died. It is distressing when this person develops Alzheimer's disease at a relatively young age. Not only are they losing the person they (often) love very much, but the burden of care gets heavier.

### **Causes and risk factors**

In Down's syndrome the development of Alzheimer's disease seems to be linked directly to the overexposure to APP. The ApoE2 gene seems to have a protective effect in Down's syndrome too, but whether ApoE4 increases the risk of Alzheimer's disease in Down's syndrome is not clear yet. Men and women seem to be equally susceptible.

### **Genetics**

Down's syndrome originates in an extra copy of chromosome 21.

### **Frequency**

At least 36 % of the people with Down's syndrome aged 50 – 59 years and 65 % aged 60 and older are affected by dementia. Brain changes associated with Alzheimer's disease are found in 96 % of all adults with Down's syndrome.

### **Diagnostic procedures**

Diagnosing dementia in people with Down's syndrome is very difficult, as the dementia symptoms are often masked by the existing intellectual impairment. Several screening and evaluation procedures have been developed. These evaluations must be performed at select intervals, thus comparing with the person's previous score. Definitive diagnosis is only available after death.

### **Care and treatment**

Because of limited personnel in small scale living settings for people with an intellectual impairment, persons with dementia often have to move (back) to an institution for mentally retarded people. Research has shown that donepezil (Aricept®) has a positive though not significant effect.

### **Ongoing research/Clinical trials**

Erasmus University Rotterdam (Evenhuis HM)

### **Available services**

European Down Syndrome Association  
<http://www.edsa.down-syndrome.org/>

### **References**

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## 12. **Familial British dementia** by André Delacourte

### General outlines

Familial British dementia (FBD) and Familial Danish dementia (FDD) are early-onset autosomal dominant disorders characterised by progressive cognitive impairment, spasticity, and cerebellar ataxia.

Hippocampal neurofibrillar degeneration and widespread parenchymal and vascular amyloid deposits are the main neuropathological lesions.

### Synonyms

Familial cerebral amyloid angiopathy-British type for FBD  
Heredopathia ophthalmoto-encephalica for FDD

### Symptoms and course

FBD is characterised by an impaired recognition and recall memory progressing to dementia, progressive spastic tetraparesis and cerebellar ataxia. The average age of onset is usually 60 years old.

FDD is characterised by cataracts, deafness, progressive ataxia and dementia. The average age of onset is usually 60 years old.

### Causes and risk factors

Pure familial disease, with genetic defects on BRI gene provoking the production of an abnormal protein fragment that accumulate in the brain tissue.

### Genetics

Familial British dementia (FBD) and familial Danish dementia (FDD) are associated with a stop codon mutation in the BRI gene located on chromosome 13, resulting in the production of an amyloidogenic fragment, amyloid-Bri (ABri) for FBD and ADan for FDD.

Patients with FBD have a single nucleotide substitution at codon 267 in the BRI2 gene, resulting in an arginine replacing the stop codon and a longer open reading frame of 277 amino acids instead of 266.

Patients with FDD have a presence of a 10-nt duplication (795-796insTTTAATTTGT) between codons 265 and 266, one codon before the normal stop codon 267. The decamer duplication mutation produces a frame-shift in the BRI sequence generating a larger-than-normal precursor protein, of which the amyloid subunit (designated ADan) comprises the last 34 C-terminal amino acids.

### Frequency

Six patients affected in England, and 52 persons at risk in one wellcharacterised family (Mead S. et al, 2000).

Familial British dementia with amyloid angiopathy: early clinical, neuropsychological and imaging findings.

### Diagnostic procedures

Familial cluster. Early clinical signs : impaired recognition and recall memory, abnormal MRI of the brain, consisting of deep white-matter hyperintensity (T(2)-weighted scans) and lacunar infarcts, but no intracerebral haemorrhage.

The corpus callosum can be severely atrophic. Cataracts and deafness for FDD. Genetic analysis to demonstrate the gene defect on BRI gene.

**Ongoing research/Clinical trials**

These pathologies could benefit from the research on proteopathies (most neurodegenerative disorders are characterized by an aggregation of specific proteins in the brain tissue that could have neurotoxic effects).

**Available services**

No specific services were found.

**References**

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## **INFECTIOUS DISEASES**

**Infectious diseases** are caused by an infectious agent, such as a virus or prion.

## 13. Human Prion Diseases

### General description of CREUTZFELDT-JAKOB DISEASE (CJD)

by André Delacourte and Clive Evers

#### General outlines

Group of rare and fatal brain disorders called the prion diseases. These occur in both humans and animals and designed as spongiform encephalopathies. All subgroups, sporadic or familial, result from a defect of a protein named prion, which aggregates in the nervous tissue and provokes a rapid neurodegeneration.

Prion aggregates make amyloid plaques in neocortex, cerebellum and subcortical nuclei. Neurodegeneration provokes a spongiosis, gliosis and neuronal loss.

Clinical subgroups are :

- sporadic CJD
- transmissible CJD
  - iatrogenic CJD
  - new variant form of CJD
- familial CJD
- Gerstmann-Straussler-Scheinker disease (GSS)
- fatal familial insomnia (FFI)

#### Symptoms and course

Prion diseases cause a progressive but generally rapid loss of mental abilities and is accompanied by neurological symptoms such as unsteadiness and clumsiness.

All forms have generally an early onset, between 20 to 50 years. The evolution is generally between 12 to 60 months.

#### Causes and risk factors

Prion diseases are transmissible in certain circumstances, but they are not infectious in the usual way. So they are not spread by airborne droplets, blood or sexual contact.

Contact with someone with CJD does not lead to increased risk of developing the conditions no special precautions are required.

The infectious agent is thought to be a prion, an abnormal form of a protein called PrP, which in its natural form occurs in the brain and parts of the body of humans.

Unlike bacteria and viruses, prions are not inactivated by heat, ultraviolet light or other standard sterilisation procedures. Normal Prp can convert into abnormal PrP, named PrPres, which leads to disease.

#### Genetics

Some forms are sporadic, others are clearly familial autosomic dominant, linked to mutations on prion gene.

#### Frequency

Rare disease.

## **Diagnostic procedures**

In general, EEG and MRI analysis are used to demonstrate an atrophy and the lack of other causes such as vascular pathology, genetic analysis of the prion gene, analysis of biological markers in the CSF, post-mortem examination of prion amyloid plaques help to diagnose and to type the different prion pathologies.

## **Caregiver problems**

Clear, accurate information about the disease is necessary, as there is still many stigmas attached to CJD. Prompt, coordinated multidisciplinary support for the patient and their family is important.

Social services should be involved early on to advise on financial benefits, day care, respite care and long-term care.

Although there is no evidence that CJD can be transmitted through blood, people with a history of CJD are asked not to give blood to minimise any potential risk.

Carers will need help from speech and occupational therapists and district nurses may provide general nursing care and advice. Carers may find that the person with CJD will behave in an aggressive way, which is uncharacteristic of their usual personality. It is important to try to identify any triggers for aggression and takes steps for prevention.

Keeping a diary may help to identify the pattern of events. The brain damage caused by prion disease can sometimes cause swallowing problems, which are distressing for the person with CJD and their carers. These problems may also lead to malnutrition if eating/swallowing become difficult. It is important to ask for a referral to a speech and language therapist for advice.

## **Ongoing research/Clinical trials**

New clinical approaches in development, such as vaccination or anti-aggregation drugs (beta-sheet breakers). Prof. Stanley Prusiner, California, USA, published a paper in the Proceedings of the National Academy of Science 14 August 2001 suggesting potential treatments. The research gave evidence of stopping the formation of the disease associated form of prion protein in scrapie (prion disease in sheep) infected cells by a number of compounds with quinacrine and chlorpromazine showing the greatest potency.

These drugs have been used in humans for many years as anti-malarial and anti-psychotic drugs and Prof. Prusiner suggested that they are immediate candidates for treatment of CJD and other prion diseases.

Clinical trials of these drugs are however needed and they are currently being planned. During 2002 there has been some publicity about the possible application of pentosan polysulphate for CJD. There is evidence of at least one person with CJD being administered with it. This is widely used in North America for the treatment of interstitial cystitis. It is unlicensed in the United Kingdom.

## **Care and treatment**

There is no treatment at present for CJD. However, there are a number of drugs, which can relieve the symptoms and make the patient more comfortable.

These include valproate and Clonazepam for jerking movements. The patient and their carers will also need much help from social services and nursing services.

### **13.1. Sporadic CJD** by André Delacourte and Clive Evers

#### **General outlines**

Sporadic CJD is one of different forms of Creutzfeldt Jakob Disease. CJD was first described in the 1920's by two German neurologists (Creutzfeldt and Jakob).

#### **Synonyms**

Classical CJD and CJD

#### **Symptoms and course**

Sporadic CJD usually comes out of the blue, although the pattern of symptoms may vary from person to person. Early symptoms may be like those of depression-mood swings, memory lapses, social withdrawal and lack of interest.

However rapid progression to dementia and neurological symptoms are distinctive. Within weeks the patient may become unsteady on their feet, lacking in coordination and clumsy.

Later symptoms may include blurred vision or even blindness, rigidity in the limbs, sudden jerky movements and incontinence. Difficulty in speaking, slurred speech and difficulty in swallowing may also occur.

Eventually the person will need full time care.  
70% of patients die within six months of the onset of symptoms.  
Rarely sporadic CJD lasts for several years.

#### **Caregiver problems**

Clear, accurate information about the disease is necessary, as there is still many stigmas attached to CJD. Prompt, coordinated multidisciplinary support for the patient and their family is important.

Social services should be involved early on to advise on financial benefits, day care, respite care and long-term care.

Although there is no evidence that CJD can be transmitted through blood, people with a history of CJD are asked not to give blood to minimise any potential risk.

Carers will need help from speech and occupational therapists and district nurses may provide general nursing care and advice. Carers may find that the person with CJD will behave in an aggressive way, which is uncharacteristic of their usual personality. It is important to try to identify any triggers for aggression and takes steps for prevention.

Keeping a diary may help to identify the pattern of events. The brain damage caused by prion disease can sometimes cause swallowing problems, which are distressing for the person with CJD and their carers. These problems may also lead to malnutrition if eating/swallowing become difficult. It is important to ask for a referral to a speech and language therapist for advice.

#### **Causes and risk factors**

Sporadic in that mutations on the prion gene are not found.  
The cause of the abnormal aggregation of prion protein is not known.

#### **Genetics**

No heredity

**Frequency**

The disease affects about one person in a million a year.

**Care and Treatment**

There is no treatment at present for CJD. However, there are a number of drugs, which can relieve the symptoms and make the patient more comfortable.

These include valproate and Clonazepam for jerking movements. The patient and their carers will also need much help from social services and nursing services.

**Diagnostic procedures**

At present Sporadic CJD can only be diagnosed for certain by post mortem examination of the brain. All GPs should be aware of Sporadic CJD although most will never have seen a case.

A prompt referral to a neurologist should follow reporting of suspicious pattern of symptoms. A number of investigations will be carried out including: blood and other biochemical tests are usually normal. Recent research suggests that the presence of three protein markers, 14-3-33, S 100, and NSE may also be diagnostic of Sporadic CJD; magnetic resonance imaging; electroencephalogram (EEG); a brain biopsy may be done to look for evidence of spongiform change.

**Available services****National CJD Surveillance Unit**

Western General Hospital  
Crewe Road  
Edinburgh, EH4 2XU  
Scotland  
[www.cjd.ed.ac.uk](http://www.cjd.ed.ac.uk)

In addition to surveillance and research they can organise intensive support for the person with CJD and their family

**CJD Support Network**

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Birchwood, Heath Top, Ashley Heath  
Market Drayton,  
Shropshire TF9 4QR  
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[www.cjdsupport.net](http://www.cjdsupport.net)

**Child Growth Foundation**

2, Mayfeld Avenue  
London, W4 1PW  
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Tel 020 8995 0257  
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[cgflondon@aol.com](mailto:cgflondon@aol.com)

**Prion Clinic**

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**References**

1. CJD and prion disease: an introduction and explanation. Alzheimer's Society CJD Support Network. December 1998.
2. Will, RG et al A new variant of Creutzfeldt Jakob disease in the UK. Lancet 1996; 347; pp 921-925
3. Douglas, MJ et al Patients with new variant CJD disease and their families: care and information needs. National CJD Surveillance Unit, Edinburgh, Feb 1999.
4. Variant CJD: Alzheimer's Society CJD Support Network. Information Sheet No 4. April 2001



## 13.2. Transmissible CJD

### 13.2.1. Iatrogenic CJD by André Delacourte and Clive Evers

#### General outlines

Iatrogenic CJD is a form of Creutzfeldt Jakob disease, which belongs to a group of rare and fatal brain disorders called prion diseases.

This form of CJD arises from contamination with tissue from an infected person, usually as the result of a medical procedure.

The first indication that human prion diseases might be transmissible through infected tissue came with the discovery of a strange disease called **Kuru** among the Fore people of Papua New Guinea in the 1950s.

Kuru mainly affected women and children. It began with unsteadiness of gait, shakiness and lack of coordination. Eventually the patient would become unable to move and death would occur within a year of onset of symptoms.

On examination the brain would show damage to the cerebellum and spongiform changes characteristic of prion disease. Kuru was eventually linked to the funeral practices of the Fore people in which it was common for women and children to handle the dead body of their relatives including the brain.

Kuru is almost extinct now since the Fore people abandoned their funeral rites. Kuru has been very important in assisting in the understanding of human prion diseases in particular their risks of being transmitted from person to person.

#### Synonyms

CJD

#### Symptoms and course

Iatrogenic CJD may be transmitted intracerebrally, i.e. directly into the brain (example: contamination of surgical instruments).

In this case the symptoms are like sporadic CJD: initially depression, memory lapses, maybe unusual fatigue. However rapid progression to dementia and obvious neurological symptoms distinguish CJD from depression.

Within weeks unsteadiness and lack of coordination are likely. Sometimes these symptoms appear first. There may be sudden jerky movements, rigid limbs, maybe blindness and incontinence; difficulty in speaking and swallowing.

Eventually the patient loses the ability to move or speak and will need full time nursing care. CJD has been transmitted by treatment with human growth hormone. This is known as peripheral transmission because the route to the brain of the infective agent is through the circulation not direct into the brain. Peripherally acquired CJD may be more like Kuru, with symptoms of ataxia (unsteadiness and lack of coordination) predominating and dementia being a rare feature.

#### Causes and risk factors

Brain tissue from a person with CJD contains an abnormal form of a protein called PrP. If this abnormal form comes into contact with normal PrP, which is present in the brains of unaffected people, it can change into the abnormal form and thereby transmit the disease. Unless precautions are taken some medical procedures carry a risk of transmitting CJD. For instance a few people contracted CJD from brain operations done with instruments, which were previously used on someone with CJD. In these rare cases the infection was delivered intracerebrally, that is directly

into the brain. The prion agent survives the disinfection procedures, which normally destroy bacteria and viruses, but this was not known at the time.

Instruments which have been used on the brain of someone with suspected CJD should be destroyed. Intracerebral transmission of CJD has also occurred with corneal transplants and with grafts of dura mater, the tough membrane that covers the brain and is used in various kinds of surgery. The incubation period for intracerebral iatrogenic CJD is 19-46 months. In tonsil surgery there is a theoretical risk of contracting CJD through unknowingly contaminated surgical instruments previously used on a patient with CJD.

CJD has been transmitted peripherally by treatment with human growth hormone. This drug for the treatment of children with short stature used to be prepared from human pituitary glands. The inclusion, unknowingly, of just one gland from someone with CJD has the potential to infect many people. The incubation period for this type of CJD is around 15 years.

There is no evidence that CJD has been transmitted through blood although there is a theoretical risk. Some countries like the UK have taken precautions with their blood transfusion service to minimise such risk.

The risk of contracting CJD from organ transplants is uncertain but believed to be small. There appears to be a genetic predisposition to contracting iatrogenic CJD. We all have two copies of the Prp gene, one from our mother and one from our father. These copies exist in different forms; people who inherit two identical forms appear to be at greater risk. It may be that this form of Prp is more susceptible to changing into the abnormal form of PrP.

### **Care and treatment**

There is no treatment at present for CJD. However, there are a number of drugs, which can relieve the symptoms and make the patient more comfortable.

These include valproate and Clonazepam for jerking movements. The patient and their carers will also need much help from social services and nursing services.

### **Diagnostic procedures**

In general, EEG and MRI analysis are used to demonstrate an atrophy and the lack of other causes such as vascular pathology, genetic analysis of the prion gene, analysis of biological markers in the CSF, post-mortem examination of prion amyloid plaques help to diagnose and to type the different prion pathologies.

**Available services****National CJD Surveillance Unit**

Western General Hospital  
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[www.cjd.ed.ac.uk](http://www.cjd.ed.ac.uk)

In addition to surveillance and research they can organise intensive support for the person with CJD and their family

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**Prion Clinic**

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**References**

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2. Will, RG et al A new variant of Creutzfeldt Jakob disease in the UK. Lancet 1996; 347; pp 921-925
3. Douglas, MJ et al Patients with new variant CJD disease and their families: care and information needs. National CJD Surveillance Unit, Edinburgh, Feb 1999.
4. Variant CJD: Alzheimer's Society CJD Support Network. Information Sheet No 4. April 2001

### 13.2.2. Variant CJD (vCJD) by André Delacourte and Clive Evers

#### General outlines

vCJD is a recent form of Creutzfeldt-Jakob disease, which belongs to a group of rare and fatal brain disorders called prion diseases.

vCJD is almost certainly caused by exposure to Bovine Spongiform Encephalopathy (BSE) a prion found in cattle. In 1996 ten teenagers in the UK had been diagnosed with vCJD. This was unusual and alarming. Also the occurrence of an epidemic of prion disease, BSE, among UK cattle from 1986 was thought to be no coincidence.

Like all other prion disease, vCJD is caused by a highly unusual infective agent called a prion, which is an abnormal form of a protein called PrP. However vCJD differs from sporadic CJD, which is far more common, in several respects:

- The majority of cases reported have been in young people with average age of onset of symptoms being 28.
- The course of illness is longer than sporadic CJD, being typically around a year
- The symptoms at the outset are often more psychiatric than neurological
- When the brains of people with vCJD are examined at post mortem the characteristic spongiform change was seen under the microscope but additionally alongside florid plaques.

It is still not clear how the young people may have been exposed to BSE. However it is known that spinal cord from infected animals may have ended up in the mechanically recovered meat, used in the manufacture of sausages, meat pies and hamburgers.

An investigation into a cluster of cases of vCJD in Leicestershire published in March 2001 produced additional information. Here 4 out of the 5 people with vCJD may have been exposed to the BSE agent through the purchase and consumption of beef from a butcher's shop where the meat could have been contaminated with brain tissue. Analysis of the exposure of cases to this practice suggests that the incubation period for the development of vCJD may be between 10 and 16 years.

#### Synonyms

Variant CJD, new variant CJD

#### Symptoms and course

The symptoms of vCJD differ from those of sporadic CJD. Initially there is typically anxiety, depression, withdrawal and behavioural changes.

The patient may be referred first to a psychiatrist, rather than a neurologist. It may be very difficult early on to determine that the illness is a neurological rather than a psychiatric one.

The patient may also report persistent pain and odd sensations in the face and limbs.

After several weeks or months more obvious neurological symptoms may begin including:

- unsteadiness in walking, sudden jerky movements
- Progressive dementia (loss of mental function and symptoms of memory loss)
- Eventually the patient typically loses the ability to move or speak and will need 24 hour nursing care.

Death occurs on average around one year after the onset of symptoms. Up to April 2003 there had been 134 definite or probable cases of vCJD dead and alive. In January 2003 statistical evidence emerged from the NCJDSU in Edinburgh that the epidemic of vCJD was no longer increasing at its previous rate. It may have or be reaching its peak. However this is still not certain.

### **Causes and risk factors**

It is not yet known what the likely route of transmission in vCJD is. It may be that young people consume more of whatever foodstuffs carried the most infectivity or it may be that young people are just more susceptible to the transmission of CJD via BSE. There is the same genetic susceptibility as found in sporadic CJD. BSE contaminated foodstuffs were also fed to sheep, pigs and poultry so exposure through their consumption cannot be ruled out. It is not known how many other people will develop vCJD without knowing the probable route of exposure. However as the incubation period is still uncertain there could still be many more cases in the future.

### **Frequency**

Up to April 2003 there had been 134 definite or probable cases of vCJD dead and alive. In January 2003 statistical evidence emerged from the NCJDSU in Edinburgh that the epidemic of vCJD was no longer increasing at its previous rate. It may have or be reaching its peak. However this is still not certain.

### **Diagnostic procedures**

Diagnostic procedures as described in the generic description. Also, a brain biopsy may be carried out to detect signs of spongiform change. It has been shown that infectivity can be detected in tonsil tissue in cases of vCJD so tonsil biopsy may be suggested. As with other forms of CJD at present a definite diagnosis is only possible by examining the brain during a post-mortem examination. The hallmarks of CJD, spongiform change and loss of neurons, are present but the most striking feature is the presence of so called florid plaques. These are deposits scattered throughout the brain, which are surrounded by spongiform change.

### **Care and treatment**

There is no treatment at present for CJD. However, there are a number of drugs, which can relieve the symptoms and make the patient more comfortable.

These include valproate and Clonazepam for jerking movements. The patient and their carers will also need much help from social services and nursing services.

**Available services****National CJD Surveillance Unit**

Western General Hospital  
Crewe Road, Edinburgh  
EH4 2XU Scotland  
[www.cjd.ed.ac.uk](http://www.cjd.ed.ac.uk).

In addition to surveillance and research they can organise intensive support for the person with CJD and their family.

**Human BSE Foundation**

A charity set up by and for people who have been affected by vCJD.

[www.hbsef.org](http://www.hbsef.org)  
[grahamsteel@hbsef.org](mailto:grahamsteel@hbsef.org)

**CJD Support Network**

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**References**

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2. Will, RG et al A new variant of Creutzfeldt Jakob disease in the UK. Lancet 1996; 347; pp 921-925
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4. Variant CJD: Alzheimer's Society CJD Support Network. Information Sheet No 4. April 2001

### 13.3. Familial CJD by André Delacourte and Clive Evers

#### General outlines

Familial CJD is an inherited form of Creutzfeldt-Jakob disease, resulting from several types of mutations on prion gene.

There are fewer than 5 new cases of familial CJD occurring in the UK each year. Like other forms of CJD, familial CJD is characterised by dementia and neurological problems such as unsteadiness.

#### Symptoms and course

The symptoms and course of familial CJD will vary depending on the type of Prp mutation involved. There may even be a great variation in the symptoms within affected members of the same family.

Sometimes, the symptom pattern is similar to that found in sporadic CJD, namely: early symptoms may be like those of depression-mood swings, memory lapses, social withdrawal and lack of interest.

However rapid progression to dementia and neurological symptoms are distinctive. Within weeks the patient may become unsteady on their feet, lacking in coordination and clumsy. Later symptoms may include blurred vision or even blindness, rigidity in the limbs, sudden jerky movements and incontinence. Difficulty in speaking, slurred speech and difficulty in swallowing may also occur.

Eventually the person will need full time care. Familial CJD often strikes at an earlier age than the sporadic form: the average age of onset is 52 compared to 65.

The course of the disease is often longer and the patient may survive for several years after the onset of symptoms.

#### Causes and risk factors

Human spongiform encephalopathy (TSE)

#### Genetics

Familial autosomal by a range of mutations within the open reading frame of the prion protein gene (PRNP) on chromosome 20. We all inherit two copies of the PrP gene- one from our mother and one from our father.

Familial CJD, GSS and FFI are all inherited in an autosomal dominant fashion. This means you need to possess just one mutated copy of the PrP gene to develop the disease. A person carrying the mutated gene has a 50% chance of passing it on to each child. Since CJD does not usually strike until late in life, when people have usually had their children, the gene has persisted in the population.

Mutations in the PrP gene can now be detected via blood test. At risk family members who do not have symptoms therefore can opt to find out whether they carry the mutation. In most (but not all) cases a person is certain to develop the disease eventually if they carry the mutation.

It may also be possible to tell, from the form of the PrP gene carried, whether the person will have early or later onset disease. Undergoing Prp gene testing is a serious matter and should not be done without full consent of the person involved and full pre- and post-test support and counselling by specialist staff.

The results will have an impact on other family members and they should be involved in discussions. Antenatal testing where a foetus is at risk of carrying the mutation is also possible. This gives the couple a chance to opt for termination,

and so avoids passing the disease on. However this also involves a difficult decision, for a child carrying a mutated PrP gene is likely to enjoy normal health for many years before the onset of the disease.

### Frequency

5 to 15% of all human spongiform encephalopathy.

### Diagnostic procedures

For people with symptoms of familial CJD the investigations are the same as for any other prion disease. However, in addition, a simple blood test should confirm the presence of a PrP gene mutation. E.g. often but not always show characteristic changes. MRI will be done to eliminate other conditions such as a tumour. Blood and other biochemical tests are likely to be normal. The only definite diagnosis comes by post mortem. However in the case of inherited prion disease, the family history of neurological disease will be a very important pointer in the diagnosis.

### Available services

#### **National CJD Surveillance Unit**

Western General Hospital  
Crewe Road, Edinburgh  
EH4 2XU Scotland  
[www.cjd.ed.ac.uk](http://www.cjd.ed.ac.uk).

In addition to surveillance and research they can organise intensive support for the person with CJD and their family.

#### **Human BSE Foundation**

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### References

1. Kovacs et al, Mutations of the prion protein gene. Phenotypic spectrum. J. Neurol (2002) 249:1567-1582.
2. CJD and prion disease: an introduction and explanation. Alzheimer's Society CJD Support Network. December 1998.
3. Will, RG et al A new variant of Creutzfeldt Jakob disease in the UK. Lancet 1996; 347; pp 921-925
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5. Variant CJD: Alzheimer's Society CJD Support Network. Information Sheet No 4. April 2001



### **13.4. Fatal familial Insomnia (FFI)** by André Delacourte

#### **General outlines**

Fatal familial Insomnia (FFI) is a Prion disease, a rare form of CJD.

#### **Symptoms and course**

Dementia associated with sleep disorders. FFI is reserved for patients manifesting prominent insomnia, generally in combination with dysautonomia, myoclonus, and eventual dementia, with the predominant pathologic changes lying within the thalami and a specific underlying mutation in PRNP.

Brain damage is confined to the thalamus, the area that is involved in relaying information to and from the brain and in controlling sleep-wake cycles.

Eventually FFI leads to a complete breakdown of the brain's bodily functions, coma and death. The average age of onset is 50 years and the average duration of the disease is 12 months.

#### **Genetics**

Associated with the mutation D178N and the polymorphism 129M. This polymorphism at codon 129 is supposed to discriminate between familial CJD (fCJD) and FFI

#### **Frequency**

Unknown.

#### **Diagnostic procedures**

For people with symptoms of FFI, the investigations are the same as for any other prion disease. However, in addition, a simple blood test should confirm the presence of a PrP gene mutation. E.g. often but not always show characteristic changes. MRI will be done to eliminate other conditions such as a tumour. Blood and other biochemical tests are likely to be normal. The only definite diagnosis comes by post mortem. However in the case of inherited prion disease, the family history of neurological disease will be a very important pointer in the diagnosis.

Post-mortem examination: Stripe-like deposition perpendicular to the surface in the molecular layer of the cerebellum, stained with antibodies against prion protein.

**Available services****National CJD Surveillance Unit**

Western General Hospital  
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In addition to surveillance and research they can organise intensive support for the person with CJD and their family.

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**References**

1. Gambetti P, Hereditary Creutzfeldt-Jakob disease and fatal familial insomnia., Clin Lab Med 2003 Mar;23(1):43-64
2. Kovacs et al, Mutations of the prion protein gene. Phenotypic spectrum. J. Neurol (2002) 249:1567-1582.

### **13.5. Gerstmann-Straussler-Scheinker disease** by André Delacourte

#### **General outlines**

Familial prion disease

#### **Symptoms and course**

GSS encompasses a diverse clinical spectrum ranging from progressive cerebellar ataxia or spastic paraparesis (both usually in combination with dementia), to isolated cognitive impairment resembling Alzheimer's disease.

The average age of onset is 46 years and the average duration of the disease is 60 months. GSS usually starts with clumsiness, unsteadiness and shakiness, together with rigidity in the limbs. Dementia sets in later and the patient may survive for several years.

#### **Causes and risk factors**

Due to different types of mutations on prion genes such as P102L, P105L, A117V, G131V, F198S, D202N, Q212P, Q217R, M232T.

#### **Diagnostic procedures**

For people with symptoms of GSS, the investigations are the same as for any other prion disease. However, in addition, a simple blood test should confirm the presence of a PrP gene mutation. EGG often but not always show characteristic changes. MRI will be done to eliminate other conditions such as a tumour. Blood and other biochemical tests are likely to be normal. The only definite diagnosis comes by post mortem. However in the case of inherited prion disease, the family history of neurological disease will be a very important pointer in the diagnosis.

Post-mortem examination: multicentric amyloid plaques stained with antibodies against prion protein.

**Available services****National CJD Surveillance Unit**

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In addition to surveillance and research they can organise intensive support for the person with CJD and their family.

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1. Kovacs et al, Mutations of the prion protein gene. Phenotypic spectrum. J. Neurol (2002) 249:1567-1582.

## 14. Aids Dementia Complex (ADC) by Jos van der Poel

### General outlines

Through the majority of patients with HIV do not develop dementia (due to treatment with AZT and combination therapy), the AIDS Dementia Complex may occur when a HIV-infection affects neurons in the brain. The disease mainly occurs in later stages of the infection, and appears to involve subcortical, rather than cortical, brain structures. There is more dysfunction than destruction of neurons. Characteristic are memory problems, slow and unsteady movements, anxiety and mood-swings.

### Synonyms

HIV/AIDS encephalopathy, HIV/AIDS related brain impairment, HIV dementia

### Symptoms and course

Symptoms, which may vary from person to person, are:

- Forgetfulness
- concentration problems
- anxiety
- language difficulties
- slowing down of thinking
- slow, unsteady movements
- difficulty keeping balance
- coordination problems
- jerky eye movements
- personality changes, mood-swings
- hallucinations
- sleep disturbances
- loss of appetite

The number of symptoms gradually increases. Sometimes psychosis, depression and suicide occur.

### Caregiver problems

ADC may begin at a relatively young age. At first symptoms resemble those of depression. Psychiatric symptoms.

### Causes and risk factors

The precise role of HIV in ADC is unknown. Probably the virus is included by macrophages, which take the virus to the brain where it infects microglia.

### Frequency

It is difficult to be precise about the incidence of Aids-related cognitive impairment. Estimates are from 5 – 15 % of all AIDS patients. Many of the studies into its incidence were carried out before the introduction of 'combination therapy'.

### Diagnostic procedures

- HIV test to demonstrate the viral infection
- CT and MRI scan to demonstrate the absence of opportunistic infections and tumors
- lumbar puncture to demonstrate HIV-1 p24 antigene
- neuropsychometric testing to demonstrate subcortical dementia

## Care and treatment

At the moment it is not possible to cure AIDS. Anti-HIV drugs however decrease the amount of the virus in the bloodstream, reducing the damage it can cause. The success of these drugs has meant that the focus of treatment has now shifted from palliative care to rehabilitation: relearn the skills the patient need to care for himself (like dressing, taking medication, cooking etc.).

## Ongoing research/Clinical trials

Development of therapeutic strategies to prevent neurological complications in AIDS and the role of macrophages in neurological diseases.

## Available services

### The **International HIV/AIDS Alliance**

Queensberry House  
104-106 Queens Road  
Brighton  
BN1 3XF  
United Kingdom  
Telephone: +44 1273 718 900  
Fax: +44 1273 718 901  
[mail@aidsalliance.org](mailto:mail@aidsalliance.org)  
[www.aidsalliance.org](http://www.aidsalliance.org)

AIDS associations provide information on HIV, but have less information on the cognitive problems associated with the disorder.

In a case of dementia, please refer also to Alzheimer's disease associations.

### **Alzheimer Europe**

145 Route de Thionville  
L- 2611 Luxembourg  
Tel: +352 / 29.79.70  
Fax: +352 / 29.79.72  
[info@alzheimer-europe.org](mailto:info@alzheimer-europe.org)  
[www.alzheimer-europe.org](http://www.alzheimer-europe.org)

### **Alzheimer's Disease International**

45-46 Lower Marsh  
London SE1 7RG  
United Kingdom  
Tel: +44 / 20 7620 3011  
Fax: +44 / 20 7401 7351  
[info@alz.co.uk](mailto:info@alz.co.uk)  
[www.alz.co.uk](http://www.alz.co.uk)

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5. *AIDS weekly plus magazine*, December 14, 1998
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## 15. Syphilis by Alexander Kurz

### General outlines

Syphilis is a systemic infectious disease caused by the spirochete *Treponema pallidum*. Involvement of the nervous system may occur at any stage of the infection.

A chronic meningitis is the pathological substrate of all forms of neurosyphilis which include meningovascular syphilis, progressive paralysis, and tabes dorsalis.

Syphilis is transmitted by sexual contact, rarely by sharing venous puncture needles in drug addicts. The percentage of patients with syphilitic CNS infection has been increasing since the advent of the human immunodeficiency virus (HIV) epidemic.

### Synonyms

Neurosyphilis, progressive paralysis, lues

### Symptoms and course

Psychiatric symptoms may evolve at any time during the development of syphilis. At the early stage non-specific depression and anxiety may occur. Later, common psychiatric symptoms include sleep disturbances, distractibility, irritability, disorientation, confusion as well as delusional or hypochondrical worries. However, spells of elation and confabulation may also be present.

There are three major variants of neurosyphilis. Meningovascular syphilis becomes manifest as a cerebral or spinal vascular syndrome caused by the occlusion of small vessels. Patients show intellectual decline accompanied by confusional states. Agitation or stupor and stroke-like neurological symptoms including hemiplegia, aphasia, or seizures, are also usually present. Meningovascular syphilis occurs 4 – 7 years after the infection. Without treatment it causes small vessel occlusions and persistent neurologic deficits.

With treatment remission of symptoms is usually satisfactory. Parenchymal neurosyphilis may present as progressive paralysis or as tabes dorsalis.

Progressive paralysis is the most important psychiatric complication of neurosyphilis. It usually develops 10 to 15 years after the infection. Clinical features include progressive dementia, which is frequently accompanied by psychotic symptoms, personality change, dysphoric or elevated mood and striking lapses in social functioning.

The dementia is of a frontal type with prominent apathy, elation, attentional deficits and memory impairment. Salient features are coarse movements, dull facial expression, increased muscle reflexes and pupil abnormalities.

At the late stage seizures may occur. The "classic" megalomaniac psychosis was always a rarity. In untreated cases, death usually occurs within 4 – 5 years. Progressive paralysis develops 10 – 20 years after the infection. The condition is rapidly progressive and leads to death after 2 – 5 years.

Penicillin therapy normalises the inflammatory changes in the cerebrospinal fluid and arrests the progression of symptoms. Improvements are seen in 60 % of the patients. Tabes dorsalis is the consequence of an infectious and degenerative destruction of the posterior horn cells and tracts. Classical symptoms are sharp pain in the legs, difficulty emptying the bladder, spinal ataxia and delayed pain recognition. Psychiatric symptoms are rare. More than 90 % of all patients show pupil abnormalities, which in half of the cases presents as a miotic pupil which fails to react to direct light (Argyll Robertson phenomenon). Tabes dorsalis occurs 10 – 20 years after the infection. Progression is slow and may end in a residual state without further worsening. Treatment stops progression and normalises cerebrospinal parameters. Incomplete remission is the most likely outcome.

### **Causes and risk factors**

Syphilis is caused by an infection with the spirochete *Treponema pallidum*. Neurosyphilis has two major forms: meningovascular syphilis, and parenchymal neurosyphilis. Meningovascular syphilis is a small-vessel disease with thickening of the intima, obliterations, and brain infarcts associated with focal neurological deficits which frequently involve the cranial nerves.

### **Frequency**

In European countries the incidence of newly identified syphilis fell below 10 per 1.000.000 inhabitants after 1980. The true frequency is not precisely known but is estimated to be 50 per cent higher. With the HIV epidemic the incidence of syphilis increased by 75 % between 1985 and 1990 in the US, but declined afterwards. Of patients with untreated syphilis, 4 to 9 % develop symptoms of neurosyphilis (2 – 3 % meningovascular syphilis, 2 – 5 % progressive paralysis, 1 – 5 % tabes dorsalis).

### **Diagnostic procedures**

There are two forms of laboratory tests for syphilis, non-specific and specific for *Treponema pallidum*. The non-specific Venereal Disease Research Laboratory (VDRL) test has been replaced by the simpler but also non-specific Rapid-Plasma-Reagin (RPR) test. Both tests use cardiolipin antigens for the identification of antibodies which are generated by the interaction of *Treponema pallidum* with human antigens. For the diagnosis of neurosyphilis at a late stage these tests are insufficient and must be complemented by tests which are specific for the infectious agent. The Fluorescent Treponemal-Antibody Absorption test (FTA-ABS), the *Treponema Pallidum* Hemagglutination test (TPHA), and the Microhemagglutination Assay for *Treponema Pallidum* (MHA-TP) are commonly used. They become positive before the cardiolipin tests and remain so for life, even after successful treatment. The cerebrospinal fluid usually shows typical signs of inflammation including proliferation of lymphocytes and an elevated total protein content.

### **Care and treatment**

Neurosyphilis is treated with high doses of penicillin G over 10 to 14 days intravenously (6 x 4 mio units per day). Alternatives are Doxycycline (2 x 100 mg per day intravenously for 30 days), and ceftriaxone (1 g per day for 14 days).



**Available services**

Departments of internal medicine, neurology or psychiatry.

**References**

1. M A Conde-Sendin, J L Hernandez-Fleta, M A Cardanes-Santana, R Amela-Peris. Neurosyphilis: forms of presentation and clinical management. *Rev Neurol* 35: 380-386, 2002
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## 16. Postencephalitic Parkinsonism (PEP) by Kurt Jellinger

### General outlines

PEP is a progressive neuro-degenerative disease with clinical features referable mainly to the extrapyramidal and oculomotor systems and cognitive deterioration. It represents a chronic complication of encephalitis lethargica (EL) or Economo's encephalitis or sleep sickness that emerged during and after World War I.

### Symptoms and course

Bradykinesia, rigidity, hypomimia, postural instability, gait disorders with falls and sialorrhea. Ophthalmoplegia and oculogyric crises. Elderly patients suffer from continuous deterioration of motor function with dysphagia, incontinence, Levodopa induced psychoses, dystonia, and cognitive impairment.

Neuropathology: multisystem neuronal degeneration and cell loss, with gliosis in many brainstem nuclei, in particular substantia nigra, locus ceruleus, and others with globular neurofibrillary tangles in residual neurons in many subcortical nuclei. Cortical pathology is common with frequent NFTs in hippocampus, entorhinal, frontal and insular cortices, differing in distribution from those in AD.

Immunohistochemical studies showed deposits of pathologic tau protein in subcortical fibrillary tangles and astroglia, indicating relationship to tauopathies. Ultrastructure and biochemistry of neuronal and glial deposits are similar to those in Alzheimer disease: Ultrastructurally NFTs are composed of 22 nm paired helical filaments and rare 15 nm straight tubules, Biochemistry of tau protein in PEP shows tau triplet with 3 prominent bands at 60, 64, and 68 kDa, differing from tau in PSP, CBD, Pick's disease, and argyrophilic grain disease.

### Caregiver problems

Similar to those in Parkinson's disease and its late complications.

### Causes and risk factors

The causes and risk factors are unknown. Recent microbiological methods were unable to demonstrate any virus, in particular, wild-type influenza virus, that caused influenza pandemic in 1918-21, simultaneously to LE, could not be detected in brain material of PEP patients. Relationship between EL/PEP and influenza remains enigmatic.

### Frequency

Frequency currently extremely rare; since 1970 only single cases reported. Main occurrence of EL between 1918 and 1924. Between 1925-38, PEP represented almost 50% of all cases of parkinsonism diagnosed at that time. Later on, incidence of PEP ranged from 4 - 30% (mean of 13%) of all cases of parkinsonism. In recent years, incidence of PEP in autopsy series dropped from 6% (1957-70) to almost zero in last decade.

### Diagnostic procedures

Similar to Parkinson disease (PD), but history of EL necessary. No diagnostic test available. Diff. diagnosis: mainly against PD, but significant differences: 1. onset of symptoms in younger age, including children and adults aged 25-40 yrs; 2. rare occurrence of rest tremor; 3. progression of disease in discontinuous spurts; 4. prior history of acute EL.

### Care and treatment

Similar to PD. Patients may variably respond to L-dopa therapy. Late complications to be treated like those in PD.

**Ongoing research/Clinical trials**

Trials to identify causing viral agent using modern molecular biologic and genetic methods. Due to almost total extinction of PEP, repository archival material represents the only source for modern investigations, that up to the present, failed to identify a causative or transmissible agent.

**Available services**

The **European Parkinson's Disease Association** (EPDA)  
Lizzie Graham  
EPDA Liaison/Project Manager  
4 Golding Road  
Sevenoaks  
Kent TN13 3NJ  
United Kingdom  
Tel/Fax: + 44 (0)1732 457683  
[admin@epda.eu.com](mailto:admin@epda.eu.com)  
[www.epda.eu.com](http://www.epda.eu.com)

**References**

1. J.M.Henry & K.A.Jellinger. Postencephalitic parkinsonism In: Neurodegeneration. The molecular pathology of dementia and movement disorders.
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3. Litvan I. et al.; Eur J Neurol 5:451-57 (1998)
4. Reid AH et al. J Neuropathol Exp Neurol 60:563-70(2001).

## 17. Herpes Encephalitis by Kurt Jellinger

### General outlines

With increasing survival of acute herpes simplex (HSV) encephalitis, (due to recent treatment with vidarabine® - adenine arabinoside and acyclovir), patients surviving acute disease develop persistent neurological and psychiatric dysfunctions, especially Kluver-Bucy syndrome, amnesia and memory dysfunctions, due to extensive necrosis of medial temporal lobes, cingulate gyrus, and thalamus, with cavitation and atrophy of the involved cerebral tissues and rare chronic HSV encephalitis due to persistent inflammatory reaction.

### Synonyms

Dementia after HSV encephalitis

### Symptoms and course

Frequent persisting symptoms are dysomnia, amnesia, Kluver-Bucy syndrome, impairment of memory which, in some cases, may be mild and evident only on neuropsychological testing. In addition, there may be seizures. In some patients, cognitive dysfunction and other psychiatric symptoms may resemble those in Alzheimer disease and Creutzfeldt-Jakob disease. A small proportion of patients experience a clinical deterioration or relapse weeks to months or even years, after cessation of antiviral therapy. Sometimes depression, hallucinations, and personality changes occur. The majority of late symptoms show a chronic course with little tendency for repair.

### Caregiver problems

HSV encephalitis may occur in young persons, but also in elderly subjects and in these may pose similar problems as in Alzheimer's disease patients. The duration of clinical residual symptoms may last many years.

### Causes and risk factors

HSV encephalitis is caused mainly by HSV type I virus spreading along olfactory nerve fibres and tracts via trigeminal ganglia into the brain. Reactivation of latent virus in the trigeminal ganglia and spread along centrally projecting nerve roots may also enter the brain. Reactivation of the virus has also previously established latent infection within the brain. Risk factors are concomitant HIV infection and immunological defects.

### Frequency

The incidence of acute HSV encephalitis is estimated as 1 in 250 000 - 500 000 persons per year. All age groups are involved. For dementia after survived HSV encephalitis no epidemiological data are available.

### Diagnostic procedures

Detection of HSV DNA in CSF using PCR; CCT and MRI can early demonstrate. Demonstration of HSV antibodies in CSF and serum are no useful for early diagnosis, but can confirm HSV infection in chronic or residual cases. CCT and MRI show severe destruction and atrophy of medial temporal lobes, hippocampus, cingulate gyrus (limbic structures) and thalamus; SPECT and PET scans show increased temporo-mesial flow. Brain biopsy (mainly stereotactic) may be used for histological and immunohistochemical diagnosis.

**Care and treatment**

In the acute phase, antiviral treatment with vidarbin and acyclovir, beginning as soon as possible. In the late or residual state only conservative and rehabilitation treatment possible. High dose immunoglobulin treatment can be tried.

**Ongoing research/Clinical trials**

HSV I vaccination to reduce risk of HSV-I encephalitis

**Available services****Encephalitis Information Resource**

7b Saville Street, Malton  
North Yorkshire, YO17 7LL  
United Kingdom

[mail@encephalitis.info](mailto:mail@encephalitis.info)

<http://www.esg.org.uk/ESG/Support/Default.asp>

**References**

1. H.Maravic & F.Berg-Dammer: Herpes simplex Virus-Enzephalitis, In: Henkers-Kölmel: Die entzündlichen Erkrankungen des ZNS. Handbuch u. Atlas, Ecomed Medizin, 1998.
2. Concon et al: Kluver-Bucy syndrome with severe amnesia secondary to herpes encephalitis. Can J Psychiatry 1988;33:754-6.

## **METABOLIC DISEASES**

**Metabolic diseases** are a group of often treatable diseases which may lead to dementia and which are caused by an under-activity or over-activity of a part of the human metabolism.

## 18. Thyroid disorders by Clive Evers

### General outlines

Hypothyroidism is one of the most important metabolic causes of reversible cognitive impairment. The term refers to thyroid underfunction within adults, which results in deficits of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). This underfunction may originate in the thyroid itself (primary type) or in the pituitary or hypothalamus which controls the thyroid gland (secondary type).

The main action of the thyroid hormones involves using up energy. This causes an increase in the metabolic rate of most tissues. It also appears to supplement and enhance the metabolic effects of the catecholamines (dopamine, noradrenaline and adrenaline) which have been associated with some major psychiatric illnesses e.g. Dopamine and Parkinson's disease.

The symptoms of hypothyroidism are therefore mainly due to decreased metabolism with an associated slowing of mental and physical activity.

### Synonyms

Myxoedema

### Symptoms and course

Hypothyroidism is more common after middle age; one per cent of the elderly population suffers from it.

There are more females than males affected on a ratio of 5:1. A picture of dementia develops as an extension of the mental impairment that is common. Due to its gradual progression it is often indistinguishable from a primary dementia. So when hypothyroidism has been long and severe, dementia can develop. The symptoms characteristically develop insidiously and almost every organ of the body is affected.

However dementia is not the only psychiatric symptom of hypothyroidism. It can also present with delirium, delusional disorder, schizophreniform psychosis or major depression. Difficulties will arise through the physical effects of the disease.

The skin can be dry, cold and thickened. A malar flush (reddening of the cheeks) may be seen against a generally pale face, known as 'strawberries and cream complexion.'

The lips are often thick and tinged purple. Hair is coarse and brittle. Neurological disturbances are often reported with deafness, slurred speech, a gruff husky voice, muscle cramps and muscle weaknesses and carpal tunnel syndrome at the wrists. This picture may be complicated with other commonly associated conditions e.g. Diabetes mellitus or pernicious anaemia.

### Caregiver problems

Psychological features include mental lethargy, dulling and slowing of all cognitive functions. The patient is readily fatigued and daily routines will take longer.

Memory is often affected from an early stage and the patient becomes apathetic and sluggish. Some patients may also show low mood and irritability. These features will all present demands on the immediate carer.

## Causes and risk factors

The thyroid gland, located in the front of the neck just below the larynx, secretes hormones that control metabolism. These are the T3 and T4 as above.

The secretion of both hormones is controlled by the pituitary gland and the hypothalamus, which is part of the brain. Thyroid disorders may result not only from defects in the thyroid gland itself but also from abnormalities of the pituitary or hypothalamus.

Hypothyroidism or underactivity of the thyroid gland, may cause a variety of symptoms and may affect many body functions. The body's normal rate of functioning is low. The symptoms may vary from mild to severe with the most severe form called myxedema, which is a medical emergency.

The most common cause of hypothyroidism is Hashimoto's thyroiditis, a disease of the thyroid gland where the body's immune system attacks the gland.

Failure of the pituitary gland to secrete a hormone to stimulate the thyroid gland (secondary hypothyroidism) is a less common cause.

Other causes include congenital defects, surgical removal of the thyroid gland, irradiation of the gland or inflammatory conditions.

Risk factors include age over 50 years, female gender, obesity, thyroid surgery and exposure of the neck to x-ray or radiation treatments.

## Frequency

Hypothyroidism is more common after middle age; one per cent of the elderly population suffers from it.

There are more females than males affected on a ratio of 5:1. A picture of dementia develops as an extension of the mental impairment that is common.

## Diagnostic procedures

A physical examination shows delayed relaxation of the muscles during tests of reflexes. Pale, yellow skin; loss of the outer edge of the eyebrows; thin and brittle hair; coarse facial features; brittle nails; firm swelling of the arms and legs; and mental slowing may be noted.

The diagnosis is confirmed by laboratory tests of serum T3 and T4. In hypothyroidism these concentrations will be low. However it is also necessary to measure serum TSH (thyroid stimulating hormone) which regulates this hormone production and is released from the pituitary gland.

If underfunction of the thyroid is mainly due to disease of the thyroid gland, TSH will be high while it will be low if it is due to secondary pituitary disease. Electrocardiogram (ECG) and electroencephalogram (EEG) measures may also assist.

Hypothyroidism is often confused with early dementia or depression that is resistant to treatment. Suspicions usually arise through the characteristic facial appearance or physical signs. Many old age services in the UK now do thyroid functions tests routinely in the initial assessment.



## Care and treatment

Replacement of the deficient thyroid hormone is the basis of treatment and Levothyroxine is the most commonly used medication. The lowest dose effective in relieving symptoms and normalising the TSH is used.

Life-long therapy is needed. Medication must be continued even when symptoms subside. Thyroid hormone levels need to be monitored yearly after a stable dose of medication is established. Patients can return to normal life with treatment but life long medication is necessary. It should be noted that myxedema coma, a medical emergency, can result in death.

## Available services

### International Thyroid Federation

[info@thyroid-fed.org](mailto:info@thyroid-fed.org)

<http://www.thyroid-fed.org/>

## References

1. Allardyce, J. The secondary dementias 2: hypothyroidism. Journal of Dementia Care July/August 1996; pp 28/29.
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## 19. Neuro-degeneration with brain iron accumulation type I (NBIA 1) by Kurt Jellinger

### General outlines

NBIA 1 is a rare familial and sporadic progressive autosomal recessive neurodegenerative disease. Condition in which extrapyramidal movement disorders are associated with a combination of neuroaxonal dystrophy and iron accumulation in basal ganglia.

### Synonyms

Hallervorden-Spatz disease, pantothenate kinase-associated neurodegeneration.

### Symptoms and course

Slowly progressive gait disorders, stiffness, cramps in legs, muscular hypotonia, rarely progressing into rigidity, clubfoot, stuttering, speech and visual disorders rare. Delay of psychomotor development often antedates neurologic symptoms.

Hyperkinesia in around 50% of classical cases, rare in infantile and late-infantile forms. These show choreatic, athetotic, dystonic disorders, tremor, occasional rest tremor. Frequent dystonia. Parkinsonism in late cases. Dysarthria, dysphagia, eye movement disorders.

Other symptoms include ataxia, nystagmus, optic atrophy and rare seizures. Early-infantile cases present with psychomotor retardation, seizures, followed by progressive rigidity, spasticity with/without dystonia.

Ataxia, terminating in stiffness and dementia.

Rare adult cases show ataxia, rigidity, athetosis, akinetic-rigid parkinsonism, with or without dementia, rarely early-onset dementia. According to onset of disorder, one distinguishes:

1. Infantile forms (onset 1st year of life);
  2. Late-infantile cases (onset 2-3 years; death at age 8-16 yrs);
  3. Juvenile "classic" HAD (onset between age 7-15 years; duration 6-20 yrs);
  4. Adult or late cases (onset between age 22-64 years, duration 3- months to 13 years with death up to age 70 years).
- Course with slow progression of clinical signs and symptoms.

### Causes and risk factors

Due to mutations of PANK 2 (pantothenate kinase), mapped on chromosome 20p13 or other mutations. PANK is a rate-determining enzyme in coenzyme A biosynthesis.

Another, similar disorder was mapped to chromosome 19q13.3 that contains the gene for ferritin light peptide (FTS). This "new" disease was called "neuroferritinopathy". In patients reported as HARP syndrome, changes in exon 5 of PANK 2 gene were seen. Risk factors are consanguinity in families, and missense mutations in PANK 2 gene.

### Frequency

Rare disorder, around 100 published cases. No incidence or prevalence data available.

### **Diagnostic procedures**

Laboratory tests and blood chemistry are unremarkable. CerebroSpinal Fluid (CFS) may show increased non-protein bound iron. Electromyograph (EMG) may show rigidospasticity. CCT shows high signal lesions in globus pallidus; MRI T-2 weighted images show marked decreased intensity in globus pallidus and nigra due to increased iron and ferritin content, and small hyperintensive area in internal segment (gliosis and tissue vacuolation).

This "eye-of-the-tiger" signal is of great diagnostic value, particularly in late-infantile forms. Familial cases may show acanthocytosis and retinitis pigmentosa. After IV iron application, decreased uptake of <sup>59</sup>Fe is seen in basal ganglia. <sup>β</sup>-CIT and IBZM-SPECT, in contrast to PD and MSA, shows normal basal ganglia; PET shows significant hypoperfusion in head of caudate nucleus, pons and cerebellum with normal dopaminergic function of basal ganglia.

### **Care and treatment**

Causal treatment is unknown. Symptomatic strategies include L-Dopa and dopamine agonists showing limited efficacy. Trials with iron-chelators gave negative results.

### **Ongoing research/Clinical trials**

To elucidate the pathogenic and molecular genetic backgrounds of HAD and related disorders and iron accumulation in brain.

### **Available services**

Departments of neurology.

### **References**

1. K.A.Jellinger, J. Duda: Hallervorden-Spatz disease. In; Neurodegeneration. DW Dickson et al. (eds) ISN edition, Los Angeles 2003 (in press). OMIM #234200 (update 09/18/2002)
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## 20. Cerebral lipidoses by Alexander Kurz

This chapter summarises a group of diseases caused by enzyme defects, which result in the accumulation of abnormal lipid materials. The enzyme defects are due to mutations with autosomal recessive inheritance. Usually, these storage diseases have an onset at an infantile or juvenile age, but there are rare variants with adult onset.

### 20.1. Tay-Sachs disease (TSD) by Alexander Kurz

#### General outline

Tay-Sachs disease (TSD) is an autosomal recessive, progressive neurodegenerative disorder, which, in the classic infantile form, is usually fatal by age 2 or 3 years.

The adult form of the disease is very rare. Tay-Sachs disease is approximately 100 times more common in infants of Ashkenazi Jewish ancestry (central-eastern Europe) than in non-Jewish infants

#### Symptoms and course

Classic TSD is characterised by the onset in infancy of developmental retardation, followed by paralysis, dementia and blindness, with death in the second or third year of life. A gray-white area around the retinal fovea centralis, due to lipid-laden ganglion cells, leaving a central "cherry-red" spot is a typical fundoscopic finding. Affected children show slowly progressive deterioration of gait and posture.

Muscular atrophy begins. There may be spasticity, mild ataxia of limbs and trunk, dystonia, and dysarthria. In young adults clinical features are progressive leg weakness and fasciculations consistent with anterior horn disease. Patients may also show cerebellar atrophy, dementia, and denervation motor neuron disease.

#### Causes and risk factors

The basic enzyme defect in TSD involves the enzyme hexosaminidase A (hex A). It results in the accumulation of a glycoprotein. More than 80 different mutations have been found in the hexosaminidase A gene (15q23-q24).

#### Diagnostic procedures

Reduced sphingomyelin in red blood cells may be used as a laboratory test to identify mutation carriers. Among Ashkenazi carriers identified by the enzyme test 82 % have one of the known hex A mutations. Today, DNA testing alone is considered as the most cost-effective and efficient approach to carrier screening for TSD in individuals of confirmed Ashkenazi Jewish ancestry. TSD was the first genetic condition for which community-based screening for carrier detection was implemented.

**Treatment and rehabilitation**

To date no effective treatment is available for TSD. Experimental strategies include bone marrow transplantation, enzyme replacement, and gene therapy.

**Available services**

Neurology and pediatrics departments

**References**

1. Barnes, D.; Misra, V. P.; Young, E. P.; Thomas, P. K.; Harding, A. E. : An adult onset hexosaminidase A deficiency syndrome with sensory neuropathy and internuclear ophthalmoplegia. *J. Neurol. Neurosurg. Psychiat.* 54: 1112-1113, 1991
2. Brady, R. O. : Cerebral lipidoses. *Ann. Rev. Med.* 21: 317-334, 1970
3. Hultberg, B. : N-acetylhexosaminidase activities in Tay-Sachs disease. (Letter) *Lancet* II: 1195, 1969
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5. F Kaplan: Tay-Sachs disease carrier screening: a model for prevention of genetic disease. *Genet Test* 2: 271-292, 1998
6. Suzuki, Y.; Suzuki, K. : Partial deficiency of hexosaminidase component A in juvenile Gm(2)-gangliosidosis. *Neurology* 20: 848-851, 1970

## 20.2. Sandhoff disease by Alexander Kurz

### General outline

Sandhoff disease is an autosomal recessive neurodegenerative disorder characterised by an accumulation of GM2 gangliosides, particularly in neurons, and is clinically indistinguishable from Tay-Sachs disease.

The biochemical deficit is the absence of beta hexosaminidase A and B activity which results in the abnormal storage of GM2 gangliosides.

Neurodegeneration begins in infancy and leads to death generally by 4 – 6 years of age. The ganglioside, which is abnormally stored, is different from Tay-Sachs disease. There are infantile, late infantile, juvenile, and adult variants of generalised gangliosidosis.

### Synonyms

GM2 gangliosidosis

### Symptoms and course

In the adult variant childhood development may be normal. In early adulthood patients may develop impairment in articulation or stuttering, and in limb coordination, hyperactive deep tendon reflexes, progressive dysarthria, moderate ataxia, and intention tremor. Intellectual impairment is usually mild.

Neurodegeneration begins in infancy and leads to death generally by 4 – 6 years of age.

### Causes and risk factors

While Tay-Sachs disease results from a mutation in the alpha subunit of the hexosaminidase gene (hex A), Sandhoff disease is caused by mutation in the beta subunit of the hexosaminidase A (15q23-q24, leading to a partial deficit of the enzyme) and B (5q11) enzymes. Therefore, hexosaminidases A and B are both deficient in Sandhoff disease.

### Diagnostic procedures

The diagnosis is established by an enzymatic test.

### Care and treatment

Most research effort has focused on strategies for augmenting enzyme levels to compensate for the underlying defect. These include bone marrow transplantation, enzyme replacement, and gene therapy. An alternative strategy is substrate deprivation which aims at balancing the rate of ganglioside synthesis with the impaired rate of ganglioside breakdown. Studies in humans are planned.

### Available services

Neurology and pediatrics departments

**References**

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## 20.3. Gaucher disease by Alexander Kurz

### General outline

Gaucher disease is a member of the group of inherited metabolic disorders known as sphingolipidoses.

It is characterised by a deficiency of the lysosomal enzyme glucocerebrosidase which results in the deposition of glucocerebroside in visceral organs, in the reticuloendothelial system, and in the nervous system.

The inheritance is autosomal recessive. Three forms of the disease, with differing age of onset, can be distinguished. In the infantile, neuronopathic form (Type 2) visceral and neurological involvement is prominent and infants with the disease typically die before the age of 2 years.

The adult non-neuronopathic form (Type 1) is particularly common among Ashkenazi Jews and presents with hepatosplenomegaly, pancytopenia, and bone pain with erosions. Type 3 is a subacute, intermediate form with frequent neurological involvement, which includes intellectual deterioration, behavioural disorders, psychosis, involuntary movements, and abnormality of eye movements.

### Symptoms and course

Hepatosplenomegaly usually precedes neurologic abnormality. The age at onset is variable. Neurologic symptoms include ataxia, spastic paraplegia, psychomotor seizures, supranuclear ophthalmoplegia and dementia.

### Causes and risk factors

Gaucher disease is a typical lysosomal storage disorder resulting from an inborn deficiency of glucocerebrosidase. This leads to the accumulation of glycolipids in macrophages, particularly those in the liver, bone marrow, spleen and lung. In addition, disease of the nervous system can arise as a result of the accumulation of glycosphingolipid metabolites in brain tissue. Approximately 150 mutations of the glucocerebrosidase gene (1q21) have been identified.

### Diagnostic procedures

Laboratory diagnosis of Gaucher disease is performed by measuring glucocerebrosidase activity using a fluorimetric assay.

### Care and treatment

A European consensus on the management of Gaucher disease recommended enzyme replacement therapy with macrophage-targeted recombinant human glucocerebrosidase and found that it ameliorates systemic involvement and enhanced quality of life. There was also evidence that enzyme replacement therapy reversed, stabilised, or slowed the progression of neurological symptoms in some patients.

### Available services

Neurology and pediatrics departments



**References**

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## 20.4. Niemann-Pick disease (NPD) by Alexander Kurz

### General outline

Niemann-Pick disease (NPD) refers to a heterogeneous group of disorders the common features of which include autosomal recessive inheritance, hepatosplenomegaly, and accumulation of variable amounts of sphingomyelin and other lipids in liver, spleen, and bone marrow.

NPD is separated into disorders associated with marked deficiency of sphingomyelinase and prominent storage of sphingomyelin (Types A, B, and F) and disorders in which sphingomyelinase activity is mildly reduced or normal (Types C, D, and E). Lipid accumulation in these patients was recently related to impaired esterification of intracellular cholesterol.

### Synonyms

Sphingomyelinosis

### Symptoms and course

The neurological features of NPD type C include organomegaly, dementia, ataxia, supranuclear ophthalmoplegia and dystonia. Onset usually occurs in childhood with psychomotor retardation most typically manifested as poor school performance. Focal or generalised seizures may occur as a late complication. Onset in adolescence or adulthood is associated with a slower rate of disease progression, and organomegaly is less prominent.

### Causes and risk factors

The central biochemical defect is a deficiency in sphingomyelinase which results in a blockade of cholesterol esterification. As a consequence, abnormal amounts of unesterified cholesterol is stored.

However, nerve cells demonstrate not only storage of cholesterol but also neurofibrillary tangles. Tangles are found in many parts of the brain. Tangles are silver-staining and react strongly with antibodies to tau protein. Ultrastructurally the tangles consist of paired helical filaments identical to those seen in Alzheimer's disease. Niemann-Pick disease is genetically heterogeneous. Type C1 is caused by mutations in the NPC1 gene on chromosome 18 (18q11.q12).

### Diagnostic procedures

The cranial CT may be normal despite significant neurological symptoms. The diagnosis can be confirmed by the demonstration of an impaired ability of cultured skin fibroblasts to esterify exogenous cholesterol or by the finding of elevated levels of sphingomyelin, cholesterol, or glycolipid in the spleen or liver. Bone marrow aspiration commonly shows the presence of foam cells.

### Care and treatment

There is no effective treatment.

**Available services**

Neurology and pediatrics departments

**References**

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## 20.5. Krabbe disease by Alexander Kurz

### General outline

Krabbe disease is an autosomal recessive disorder involving the white matter of the central and peripheral nervous system. The disease is caused by a deficiency of the enzyme beta-galactocerebrosidase. While most patients develop the disease within the first 6 months of life, others develop the disease later in life, including in adulthood.

### Synonyms

Globoid cell leukodystrophy

### Symptoms and course

Adults patients may show unsteadiness of gait, weakness of the legs postural tremor, limb paresis, and hyperreflexia

### Causes and risk factors

The major biochemical defect is a deficiency of the enzyme beta-galactocerebrosidase beta-galactosidase caused by mutations in the gene encoding the enzyme (14q31).

### Diagnostic procedures

The MRI may demonstrate changes of demyelination in the white matter of the brain, while nerve conduction can be normal. The diagnosis is established by demonstrating the deficiency of galactosylceramide beta-galactosidase in serum, white blood cells and fibroblasts. Skin biopsy shows typical sprage of galactocerebroside in globoid cells, in eccrise galnds, and in Schwann cells.

### Care and treatment

Hematopoietic stem cell transplantation has been tried in Krabbe disease with positive results.

### Available services

Neurology and pediatrics departments

**References**

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## 20.6. Neuronal ceroid lipofuscinoses (NCL) by Alexander Kurz

### General outline

The neuronal ceroid lipofuscinoses (NCL) are a group of autosomal recessive encephalopathies, which usually occur in children.

Infantile (Santavuori-Haltia-Hagberg disease, late infantile (Jansky-Bielschowsky disease), juvenile (Spielmeyer-Vogt-Sjögren disease) and adult variants (Kufs-Hallervorden disease) may be distinguished.

### Synonyms

Batten disease, Kuf disease

### Symptoms and course

NCL are characterised by psychomotor deterioration, visual failure, and the accumulation of autofluorescent lipopigment in neurons and other cell types.

In the adult form of NCL initial symptoms may occur in the third year of life. Clinical features include mental retardation and behavioural disturbance, which may be accompanied by extrapyramidal symptoms (facial dyskinesia) and myoclonus epilepsy.

### Causes and risk factors

The infantile variant of NCL (Santavuori-Haltia-Hagberg disease) is caused by mutations in the CLN1-gene on chromosome 1 (1p32).

The late infantile form (Jansky-Bielschowsky disease) is caused by mutations in the CLN2 gene on chromosome 11 (11p15 and 15q21-23). The adult variant (Kufs-Hallervorden disease) is caused by mutations on chromosome 13 (13q21.1-q32).

### Frequency

The incidence is estimated at 1: 12.500 in Finland.

### Diagnostic procedures

The cranial CT may be normal despite significant neurological symptoms. The diagnosis can be confirmed by the demonstration of an impaired ability of cultured skin fibroblasts to esterify exogenous cholesterol or by the finding of elevated levels of sphingomyelin, cholesterol, or glycolipid in the spleen or liver. Bone marrow aspiration commonly shows the presence of foam cells.

### Care and treatment

There is no effective treatment.

### Available services

Neurology and pediatrics departments

**References**

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3. J K Fink, M R Filling-Katz, J Sokol: Clinical spectrum of Nieman-Pick disease type C. *Neurology* 39: 1040-1049, 1989
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## 20.7. Cerebrotendinous Xanthomatosis (CTX) by Alexander Kurz

### General outline

Cerebrotendinous xanthomatosis (CTX) is a rare inherited lipid storage disease characterised clinically by cerebellar ataxia beginning after puberty, systemic spinal cord involvement and a pseudobulbar phase leading to death, premature atherosclerosis, and cataracts.

Large deposits of cholesterol and cholestanol (ac cholesterol derivative) are found in virtually every tissue, particularly in the Achilles tendons, in the brain and the lung. The enzymatic defect is a deficiency of hepatic mitochondrial 26-hydroxylase.

### Symptoms and course

The age of onset is variable, but symptoms usually begin in the second or third decade.

Presenting features include intellectual impairment, cataracts, extensor tendon xanthomas and signs of neurological deficit. Cerebellar ataxia, spasticity, pseudobulbar palsy and peripheral neuropathy are the common neurological manifestations.

Low intelligence or dementia is present in 70 % of the cases. In the later stages there may be evidence of a peripheral neuropathy with distal loss of pain and vibration sense.

Occasionally patients with onset of symptoms as late as the seventh decade have been reported. The course is variable, but patients tend to become incapacitated within 5 – 15 years of onset.

Death occurs from progressive pseudobulbar paralysis or myocardial infarction, the latter resulting from the premature atherosclerosis which commonly complicates the disease.

### Causes and risk factors

The disease is caused by mutation in the CYP27A1 gene, which encodes sterol 27-hydroxylase (2q33).

Pathologically the disease is characterised by xanthomatous lesions and demyelination in the cerebellar white matter, with similar but less severe lesions elsewhere in the central nervous system. The peripheral nerves may show evidence of demyelination and remyelination with the formation of „onion bulbs“.

### Diagnostic procedures

The diagnosis can be confirmed by the finding of elevated levels of cholestanol in serum, tendon, or nervous tissue. Plasma cholesterol concentrations are low normal. Cerebrospinal fluid examination may show an elevated protein content. Cranial CT characteristically shows a diffuse reduction in white matter density in the cerebral hemispheres and cerebellum.

### Care and treatment

Treatment with chenodeoxycholic acid has been shown to inhibit cholestanol synthesis and may reverse neurological and intellectual deterioration.



### **Available services**

Neurology and pediatrics departments

### **References**

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## 21. Dementia in hepatic and renal failure by Kurt Jellinger

### General outline

Among metabolic and toxic disorders leading to cognitive impairment, both acute and chronic hepatic and renal failure may have adverse effects on the CNS with serious repercussions for cerebral function causing both neurological and psychiatric signs and symptoms.

They result in "metabolic encephalopathies", a series of disorders that, although potentially reversible following appropriate therapy or organ transplantation, may ultimately lead to CNS changes. The best characterised of these disorders include those associated with liver and kidney failure.

### Synonyms

hepatic or portal-systemic encephalopathy; uremic encephalopathy

### Symptoms and course

Fulminant hepatic failure results from severe inflammatory or necrotic liver disease of rapid onset and progressive neurological signs from altered mental status, stupor and coma, often within hours or days. It is also seen in "failed" liver transplants.

Delirium and mania are encountered and, occasionally, seizures which may be multifocal before coma. No real dementia is seen.

Porto-systemic encephalopathy (PSE) is the most commonly encountered form of CNS disorder associated with hepatic failure. It accompanies the development of portal-systemic collaterals arising as a result of portal hypertension in liver cirrhosis.

Neurologically, it develops slowly, the onset is insidious starting with anxiety, restlessness, and altered sleep patterns. These symptoms are followed by shortened attention span and muscular incoordination, asterixis, and lethargy, progressing to stupor and coma.

Multiple episodes of PSE are not uncommon.

In uremic encephalopathy, occurring when the glomerular filtrating rate declines below 10% of normal, neurological symptoms tend to fluctuate, and although, variable include disturbances of memory and cognition. They may progress to delirium, convulsions, stupor and coma.

Acute hepatic encephalopathy shows a rapidly progressing course and death results in 70-80% of the patients, which reach grade IV (deep) coma. Clinical signs of increased intracranial pressure include increased muscle tone in the arms and legs, progressing to full decerebrate posture, marked hyperventilation and dilated pupils with final deep coma or brain death.

PSE shows a chronic progressive course, which may be lethal due to severe hepatic failure. The same applies for uremic encephalopathy.

### Causes and risk factors

Acute hepatic encephalopathy results from acute hepatic failure with severe brain swelling which varies according to the aetiology of liver disease, with patients with hepatitis B or non-A, non-B hepatitis having the highest incidence of this complication.

PSE frequently results from a precipitating factor, such as dietary protein overload, constipation or gastrointestinal bleeding. Other conditions are hypoglycaemia, hypoxia, or the use of sedative drugs, particularly benzodiazepines, may also precipitate PSE in cirrhosis patients.

The pathophysiology of uremic encephalopathy is complex and is considered a multifactorial process, and may initially reflect a neurotransmitter deficit. There is evidence that parathyroid hormone (PTH) plays a role (Fraser, 1993), since, in uremic patients, both the EEG abnormalities and the neuropsychiatric symptoms are improved by either parathyroidectomy or medical suppression of PTH (Cogan et al. 1978). The mechanism whereby parathyroid hormone disturbs CNS function is unknown but could relate to facilitation of Ca<sup>2+</sup> entry into the cell and consequent cell death.

### Diagnostic procedure

Continuous monitoring of liver and kidney functions

### Care and treatment

Treatment would be best in a potentially reversible stage with urgent liver and /or kidney transplantation. Treatment of PSE is prevention of variceal bleeding in cirrhotic patients, use of transjugular intrahepatic portal-systemic shunts (TIPS) which are safer and less expensive to perform than portocaval anastomosis surgery. However, a major complication of TIPS is PSE, which occurs in over 30% of patients, particularly those over 60 years of age (Conn, 1993).

Treatment of uremic encephalopathy, except kidney transplantation, is dialysis that may be associated with various clinical disorders of the CNS: dialysis disequilibrium syndrome resulting as a consequence of an osmotic gradient which develops between plasma and the brain during rapid dialysis, progressive intellectual dysfunction, and dialysis dementia that may be related to aluminium neurotoxicity. The frequency of dialysis dementia has been reduced with the use of aluminium-free dialysate (Burn & Bates, 1998).

### Available services:

Liver and kidney transplant services and dialysis services in many hospitals all over Europe.

### References

1. Burn DJ, Bates D. *J Neurol Neurosurg Psychiatry* 1998;65:810-21.
2. Conn HO. *Hepatology* 1993;1:148-58.

## 22. Dementia due to chronic hypovitaminosis

by Kurt Jellinger

### General outlines

Vitamin deficiency states can lead to a number of important neuro-psychiatric disorders. The most common disorders are associated with deficiencies of the B group of vitamins, particularly thiamine.

Although they are seen particularly in populations suffering from general malnutrition, there are specific groups of people who are particularly susceptible to specific deficiencies.

For example, thiamine deficiency is frequently seen in alcoholics. The possibility of multiple vitamin deficiencies should also be taken into consideration.

### Symptoms and course

People having dementia due to chronic hypovitaminosis have problems with the eyes include disorders of their control of direction, coordination and movement; problems with gait and a loss of balance or equilibrium called ataxia; and a global confusional state where the person is apathetic, has little awareness of their immediate situation and difficulties with space, attention and concentration.

The symptoms of amnesia fall into two broad categories of impaired memory function and retained memory function.

In impaired memory there is a profound difficulty or total inability to learn new material and the lack of a normal short term memory (where a person would be able to repeat a telephone number after looking it up). This is known as anterograde amnesia. Also the person cannot remember events in their past life particularly the period immediately before their amnesia. This is known as retrograde amnesia.

However, some memory functions can be well retained. Particularly early established skills and habits. The use of language, gesture, and well practised skills may remain unaffected.

However people can also show a tendency towards decreased initiative and spontaneity and a blunting of effect, so events, which would normally be of emotional significance are reacted to in a dull or apathetic manner.

Other psychiatric symptoms include depression, irritable spells and paranoia.

Stable if drinking is stopped, Wernicke-Korsakoff Syndrome shows a mortality of about 10-20% unless it is treated. Of the patients who survive, 70-80% develop Wernicke-Korsakoff Syndrome.

### Causes and risk factors

The main cause is chronic thiamine (vitamin B 1) and niacin deficiency.

**Frequency**

Studies of vitamin deficiencies show that there are significant variations in the prevalence of these disorders. For example, the highest prevalence of Wernicke-Korsakoff syndrome (WKS), which is caused by thiamine deficiency, has been reported in Australia, whereas in a study of a similar alcoholic population in France, the prevalence of pellagra, a disease caused primarily by niacin (nicotinic acid) deficiency was high (approximately 0.3% vs. WKS around 1.9%). This issue has been addressed in an analysis of the international prevalence of WKS (Harper et al., 1994).

**Caregiver problems**

Problem of drinking and of vitamin supplementation

**Care and treatment**

Treatment with vitamin substitution; memory rehabilitation programs may be successful.

**Available services:**

Treatment services for alcoholics; regular control of vitamin intake by general practitioners and specialists.

**References**

1. Harper C et al. *Metabol Brain Dis* 1994; 10:17-24.
2. Harper C et al.: *Brain Pathol* 1997; 7:1253-55.

## 23. Metachromatic leukodystrophy (MLD) by Alexander Kurz

### General outline

Metachromatic leukodystrophy (MLD) is an autosomal recessive disorder of myelin metabolism. Due to the deficiency of the enzyme arylsulfatase A sulfatides (cerebroside sulfate) accumulate in the white matter of the central and peripheral nervous system as well as in other body organs including kidney, liver, pancreas, testes, and retina.

The sulfatides show a peculiar staining which is called „metachromatic“. There are late infantile, juvenile, and adult variants of the disease.

### Symptoms and course

In the adult variant of MLD onset may occur from the mid-teens to the seventh decade. The most common signs are personality or behavioural change and signs of intellectual deterioration. Patients show impairment of memory and concentration, and their behaviour becomes childish. Atypical psychotic features are common and often lead to a misdiagnosis of schizophrenia. Progressive dementia is usually accompanied by spasticity, involuntary movements, emotional lability and involuntary movements. Evidence of peripheral neuropathy is variable, but occasionally this is the presenting feature. The disease may progress slowly over several decades; the mean survival time is 14 years. In the final stages patients are mute, blind, quadriparetic, and unresponsive.

### Causes and risk factors

The defect in MLD involves the lysosomal enzyme arylsulfatase. A number of mutations were identified in the arylsulfatase A (ARSA) gene (22q13.31). Inheritance is autosomal recessive. The arylsulfatase A deficit generates an abnormal storage of sulfatides. Microscopically there is diffuse demyelination in the white matter of the central nervous system, ventricular enlargement and atrophy of the corpus callosum with loss of oligodendroglia and accumulation of sulfatide-containing metachromatic granules in neurons and glial cells. Similar changes are seen in the peripheral nerves.

### Frequency

The prevalence is estimated at 1 : 40.000 (Ben-Yoseph and Mitchell, 1995).

### Diagnostic procedures

The diagnosis of MLD can be established during life by the demonstration of reduced activity of arylsulfatase A in peripheral blood leukocytes or by the finding of metachromatic lipid material in centrifuged urine or peripheral nervous tissue.

The cerebrospinal fluid may show an elevated protein content. Nerve conduction studies may reveal evidence of a peripheral neuropathy with slowed motor nerve conduction and absent sensory action potentials.

The CT shows symmetrical hypodensities of the white matter whereas brain atrophy is only mild. Abnormal signal in the periventricular white matter on T2-weighted MRI scanning appears to be more specific. Proton MRS shows reduced N-acetylaspartate and increased myoinositol in affected areas. Genetic test can be used to identify mutations in the arylsulfatase A gene on chromosome 22 or mutations in the sulfatid activator gene on chromosome 10 (rare).

## Care and treatment

Bone marrow transplantation is used in MLD to replace the deficient enzyme. After successful transplantation, enzyme activity increases to normal or heterozygote levels, and the correction is permanent without the need for further treatment.

The new enzyme levels prevent the accumulation of sulfatides and contribute to the removal of abnormal tissue deposits. In patients with MLD bone marrow transplantation slows down or even halts the progression of the disease and stabilises clinical, neurophysiologic, and neuroradiologic features. These favourable results occur when transplantation is performed early in the disease. At more advanced stages results have been disappointing.

Results in significant improvements in the clinical course of MLD. Outcomes based on neuropsychological tests indicate continued maintenance and in some cases increase in cognitive function.

## Available services

### UNITED LEUKODYSTROPHY FOUNDATION

2304 Highland Drive  
Sycamore, Illinois USA  
60178  
<http://www.ulf.org/>

You can also contact the Department of Neurology.

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9. G. Waltz et al. Adult metachromatic leukodystrophy. Value of computed tomographic scanning and magnetic resonance imaging of the brain. *Arch Neurol* 44: 225-227, 1987
10. Ben-Yoseph and Mitchell, *Am J. Med. Sci* 309: 88-91, 1995

## 24. Adrenoleukodystrophy (ALD) by Alexander Kurz

### General outline

Adrenoleukodystrophy (ALD) is an X-chromosomal recessive disorder which leads to adrenal gland dysfunction. The disease is characterised by an abnormal storage of very long chain fatty acids (VLCFA) in myelin and in almost all cells of the body.

A variant of ALD is adrenomyeloneuropathy (AMN) in which the spinal cord and peripheral nerves are mainly affected, resulting in spastic paraparesis, sensory abnormalities in the legs, and bladder or anal sphincter dysfunction.

### Synonyms

Adrenomyeloneuropathy

### Symptoms and course

The adult variant of ALD becomes manifest at the age of 28 to 30 years. Clinical features include behavioural disorders, psychotic symptoms, impaired sexual function, ataxia, pseudobulbar symptoms, progressive dyskinesia or polyneuropathy. Psychiatric and neurological symptoms are accompanied by adrenal gland dysfunction (fatigue, intermittent vomiting, arterial hypotension, hyperpigmentation of the skin) and hypogonadism.

### Causes and risk factors

ALD is caused by mutations in the ABCD1 gene (Xq28), which encodes a transporter involved in the import of very long-chain fatty acids (VLCFA) into the peroxisome. The storage of abnormally long fatty acids alters the properties of myelin and results in a destabilisation of myelin membranes followed by demyelination.

### Frequency

The prevalence is estimated at 1:42.000 (Van Geel et al, 2001). Juvenile, adolescent, and adult variants of ALD may be distinguished. The adult form of ALD accounts for approximately 3 % of all cases of ALD.

### Diagnostic procedures

Cranial CT demonstrates demyelination in 80 % of ALD patients which is parieto-occipital initially and later also extends to frontal areas. MRT shows hyperintensities in the parieto-occipital white matter and in the spinal cord. The cerebrospinal fluid shows inflammation with pleocytosis, elevated protein content and intrathecal immunoglobulin production. As a consequence of demyelination, evoked potentials are slowed. Skin biopsy shows macrophages with typical inclusions. The diagnosis of ALD is established by the demonstration of elevated levels of VLCFA in plasma.

### Care and treatment

Dietary restriction of VLCFA is not sufficient. Lorenzo's oil is used to increase the intake of unsaturated fatty acids in order to inhibit the generation of VLCFA. Lorenzo's oil, however, has no effect on demyelination and does not slow the progression of the disease. The combination of VLCFA-poor diet and Lorenzo's oil normalises VLCFA in some patients and slows the progression of symptoms. Adverse effects include thrombopenia, lymphopenia, liver enzyme elevation, and reversible cardiomyopathy. Immune suppressive therapy and high-dose intravenous immunoglobulin treatment had only minor effects. Recently bone marrow transplantation has been reported to improve neurological and neuropsychological symptoms if applied at the early stage of the disease.



**Available services****UNITED LEUKODYSTROPHY FOUNDATION**

2304 Highland Drive  
Sycamore, Illinois USA  
60178  
<http://www.ulf.org/>

You can also contact the Department of Neurology and department of Pediatric

**References**

1. P Aubourg, S Blache, I Jambaqué: Reversal of early neurologic and neuroradiologic manifestations of X-linked adrenoleukodystrophy by bone marrow transplantation. *N Engl J Med* 322: 1860-1866, 1990
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## **TRAUMATIC DISEASES**

**Traumatic diseases** are caused by a trauma and in the disease described in this report by repeated head trauma.

## 25. Repeated head trauma by Alexander Kurz

### General outlines

There are two lines of evidence linking traumatic brain injury with dementia. Firstly, chronic traumatic brain injury is associated with boxing. Although many boxers will develop mild neurocognitive deficits, it is not yet known how many of these mild presentations progress to diagnosable dementia pugilistica.

Secondly, remote head trauma has been identified in some studies as a risk factor for of Alzheimer's disease, particularly if associated with the loss of consciousness.

### Synonyms

Dementia pugilistica, punch-drunk syndrome

### Symptoms and course

The clinical symptoms of dementia pugilistica are different from those seen in Alzheimer's disease. They include movement disorder, ataxia, cognitive changes, and personality change. Patients perform poorly on neuropsychological tests, are frequently aggressive, and undergo a progressive social decline.

### Causes and risk factors

Risk factors associated with dementia pugilistica include increased exposure (duration of career, age of retirement, total number of bouts) and in individuals carrying the apolipoprotein E e4 allele. Initially it was believed that the brains of patients with dementia pugilistica show numerous neurofibrillary tangles in the absence of plaques, more recent studies have demonstrated that all cases with substantial tangle formation showed evidence of extensive diffuse beta amyloid protein immunoreactive deposits. It is therefore assumed that repeated head injury can trigger similar neurodegenerative mechanisms as in Alzheimer's disease. The increased risk of boxers carrying the apolipoprotein E e4 allele is explained by the finding that deposition of amyloid beta protein occurs after head injury particularly in individuals who carry the apolipoprotein E e4.

### Frequency

Chronic traumatic brain injury associated with boxing occurs in approximately 20 % of professional boxers.

### Diagnostic procedures

The diagnosis of dementia pugilistica is dependent upon documenting a progressive neuropsychiatric condition which is consistent with the clinical symptomatology of chronic traumatic brain injury attributable to brain trauma and unexplainable by an alternative process.

### Care and treatment

The mainstay of treatment of dementia pugilistica is prevention, however medications used in the treatment of Alzheimer's disease and / or Parkinson's disease may be utilised.

**Available services****Alzheimer Europe**

145 Route de Thionville  
L- 2611 Luxembourg  
Tel: +352 / 29.79.70  
Fax: +352 / 29.79.72  
[info@alzheimer-europe.org](mailto:info@alzheimer-europe.org)  
[www.alzheimer-europe.org](http://www.alzheimer-europe.org)

**Alzheimer's Disease International**

45-46 Lower Marsh  
London SE1 7RG  
United Kingdom  
Tel: +44 / 20 7620 3011  
Fax: +44 / 20 7401 7351  
[info@alz.co.uk](mailto:info@alz.co.uk)  
[www.alz.co.uk](http://www.alz.co.uk)

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## **Toxic Diseases**

**Toxic diseases** are caused by the consumption of substances, which are harmful to the human body.

## 26. Wernicke-Korsakoff Syndrome (WKS) by Clive Evers

### General outlines

Wernicke's encephalopathy (WE) is an acute neurological illness caused by severe deficiency of the vitamin thiamine (vitamin B 1).

It can occur suddenly and is characterised by problems with the eyes, problems with gait and balance, and an overall confusional state.

Alcoholism is usually the cause of thiamine deficiency but cases of WE can also be attributed to anorexia nervosa and disorders associated with high levels of vomiting.

WE can be reversed by dosage of thiamine. WE is a medical emergency and if left untreated will result in coma and death. Wernicke-Korsakoff syndrome is characterised by amnesia and a number of specific memory impairments.

Additionally there is a tendency towards confabulation. The confabulation can be momentary fantastic when they produce grandiose descriptions which are repeated.

### Synonyms

Wernicke's encephalopathy; Korsakoff's psychosis; Korsakoff's syndrome; Korsakoff's amnesic syndrome

### Symptoms and course

WE can occur suddenly and problems with the eyes include disorders of their control of direction, coordination and movement; problems with gait and a loss of balance or equilibrium called ataxia; and a global confusional state where the person is apathetic, has little awareness of their immediate situation and difficulties with space, attention and concentration.

The symptoms of amnesia fall into two broad categories of impaired memory function and retained memory function. In impaired memory there is a profound difficulty or total inability to learn new material and the lack of a normal short term memory (where a person would be able to repeat a telephone number after looking it up). This is known as anterograde amnesia. Also the person cannot remember events in their past life particularly the period immediately before their amnesia. This is known as retrograde amnesia.

However, some memory functions can be well retained. Particularly early established skills and habits. The use of language, gesture, and well practised skills may remain unaffected.

However people can also show a tendency towards decreased initiative and spontaneity and a blunting of effect, so events, which would normally be of emotional significance are reacted to in a dull or apathetic manner. Other psychiatric symptoms include depression, irritable spells and paranoia. Patients who have abused alcohol for many years are also likely to show some of the physical effects such as liver, stomach, and blood disorders.

### **Causes and risk factors**

The main cause of Wernicke-Korsakoff syndrome is chronic alcohol abuse which results in severe deficiency of the vitamin thiamine (vitamin B1).

However this deficiency can also arise as a result of forced or self-imposed starvation eg anorexia nervosa or from protein-energy malnutrition resulting from inadequate diet or malabsorption.

Conditions associated with protracted vomiting may also be a cause including severe vomiting during pregnancy. People with kidney conditions which may result in chronic renal failure may be at risk. The condition has been described in patients receiving dialysis. Consuming large quantities of carbohydrates when thiamine levels are very low can be a cause (feeding after starvation).

The condition has also been noted in patients with AIDS. Patients with a diagnosis or suspect diagnosis of delirium may also be at risk.

### **Frequency**

Total population figures for the prevalence have proved very difficult to estimate (Blansjaar et al, 1992). In the Hague, The Netherlands gave a prevalence figure of 48 per 100,000 total population while price (1985). In Queensland, Australia estimated there were 6.5 per 100,000 new cases each year.

### **Diagnostic procedures**

Doctors will look for an ALTERED MENTAL state in the patient and for other neurological abnormalities. They will take a careful history from the patient and relative/carer, undertake a physical EXAMINATION, laboratory tests and X-RAY to exclude other causes of neurological dysfunction.

We remain a clinical diagnosis with no abnormalities in eg cerebrospinal fluid, brain imaging or EEGs.

A complete blood count excludes severe anemias and leukemias as causes of altered mental state. Alterations in serum electrolytes like hyponatremia or hypercalcemia can cause altered mental status serum glucose will be determined to exclude hypoglycemia and hyperglycemia to exclude uremia BLOOD UREA NITROGEN AND creatinine will be tested.

Arterial blood gases may be tested to exclude hypoxia and hypercarbia toxic drug screening may be given to exclude some causes of drug induced altered mental status. A lumbar puncture may be considered a head CT scan is the definitive test for emergency diagnosis of focal neurologic disease. It may be necessary to consider EEG's for some patients to exclude an epileptic state as a cause of coma and altered mental state. (Source: P Salen www.emedicine.com)

## Care and treatment

Wernicke's encephalopathy must be viewed as a medical emergency even if there are other possible DIAGNOSES that are being considered. As the condition is potentially reversible, patients with any combination of the above symptoms should be treated with thiamine.

As little as 2mg of thiamine may be enough to reverse the eye problems but initial higher doses of at least 100mg are advisable. Thiamine solutions should be fresh as old solutions may be inactive. The problems of gait and acute confusional state may improve dramatically although improvement may not be noted for days or months. After thiamine has been started doctors may consider treatment with GLUCOSE.

They will carefully monitor the cardiovascular status of patients. Doctors will investigate the patients magnesium levels and correct any deficiency. Some drug treatments have been tried INCLUDING THE SELECTIVE SEROTONIN re-uptake inhibitor FLUOXAMINE AND a drug called clonidine to improve memory. HOWEVER THERE is still no satisfactory evidence that any of these or OTHER DRUGS should be used in ordinary clinical practice.

There is some evidence that good social supports can bring a good social outcome in alcohol misuse. There is some experience and evidence that memory rehabilitation and therapies may have be of some benefit to patients. These would include external aids like diaries and reminders; the use of mnemonics to help memory; attendance at memory groups. However only a few patients with WK have been tried with these techniques. Referral of patients with alcoholism to drinking cessation programmes and monitoring them for signs of alcohol withdrawal is a key step in outpatient treatment. There is some evidence of the effectiveness of specialist units for patients with WE syndrome.

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## **CEREBRO-VASCULAR DEMENTIA**

**Cerebro-vascular diseases** are diseases of the blood vessels in the brain, which are the second most common cause for dementia.

## 27. CADASIL by Kurt Jellinger

### General outlines

A disease of the endothelium in small vessels giving rise to small subcortical infarcts and hemorrhages as well as to extensive white matter changes

### Synonyms

Hereditary multi-infarct dementia

### Symptoms and course

In contrast to the common forms of vascular dementia, patients are usually not hypertensive. Migraine attacks with aura (visual misperceptions) precede the onset of cognitive impairment.

Cognitive impairment and dementia symptoms are different from AD Stepwise decline in cognitive ability associated with minor strokes and persistent focal neurological symptoms.

Death occurs 15-25 years after the patients' first stroke.

### Causes and risk factors

Mutations on the NOTCH-3 gene cause inclusions in the smooth arterial muscles, the arterioles walls are thickened which impedes blood supply to the subcortical brain areas

### Diagnostic procedures

MRI demonstrates lacunar infarcts and leukoencephalopathy. A skin biopsy can demonstrate granular osmiophilic material.

### Available services

#### **Association CADASIL France**

Brigitte LERBOURG

7, Les Marronniers

60240 Liancourt St Pierre

Tél : +33 3 44 49 16 34

<http://association.cadasil.free.fr/>

### References

1. Gertz et al: Nervenarzt 73 (2002) 393-404; Dichgans M: Cerebrovasc Dis 13 Suppl 2 (2002) 37-41.

## 28. Binswanger disease by Jos Van der Poel

### General outlines

Binswanger disease is a form of vascular dementia and was first described in 1894. The illness occurs mainly in middle-aged hypertensive patients who show evidence of systematic vascular disease and who develop insidious fluctuating dementia with special involvement of memory, mood and cognition; seizures and mild strokes. Pathological features: lacunes, subcortical white matter demyelination, neuronal loss, gliosis, ventricular dilatation and atheromatosis of the larger cerebral vessels.

### Synonyms

Subacute arteriosclerotic encephalopathy

### Symptoms and course

1. forgetfulness
2. disorientation
3. slowness of thought
4. apathy
5. lack of emotion
6. depression
7. aggression
8. mild intellectual impairment (difficulties to think or reason)
9. language difficulties
10. problems reading and writing
11. mood swings (sometimes extreme)
12. loss of inhibitions and unusual behaviour towards other people

### Causes and risk factors

The illness originates in an affection of small blood vessels in the brain, which leads to the loss of nerve cells. Risk factors are hypertension, atherosclerosis and cardiac problems.

### Diagnostic procedures

Visible brain loss can be seen by undergoing a CT-scan.  
Examination of the condition of heart and blood vessels.

### Care and treatment

Only the treatment of risk factors may have positive effect.

### Available services

**Alzheimer Europe**  
145 Route de Thionville  
L- 2611 Luxembourg  
Tel: +352 / 29.79.70  
Fax: +352 / 29.79.72  
[info@alzheimer-europe.org](mailto:info@alzheimer-europe.org)  
[www.alzheimer-europe.org](http://www.alzheimer-europe.org)

**Alzheimer's Disease International**  
45-46 Lower Marsh  
London SE1 7RG  
United Kingdom  
Tel: +44 / 20 7620 3011  
Fax: +44 / 20 7401 7351  
[info@alz.co.uk](mailto:info@alz.co.uk)  
[www.alz.co.uk](http://www.alz.co.uk)

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## 29. Cerebral Amyloid Angiopathy (CAA) by Kurt Jellinger

### General outlines

A rare form of cerebrovascular dementia caused by amyloid deposits in small-vessel walls which give rise to hemorrhages.

### Synonyms

Congophilic angiopathy

### Symptoms and course

A combination of neurological and psychopathological symptoms. Stepwise progressive, hemorrhages cause neurological symptoms accompanied by progressive dementia

### Causes and risk factors

Several mutations on the APP gene on Chromosome 21 have been identified in Dutch families

### Frequency

CAA at a subclinical level can occur in up to 98% of AD and 85% of aged brains.

### Diagnostic procedures

Imaging (CCT and MRI) demonstrates the multiple hemorrhages. Genetic testing is used as ApoE [epsilon] 4 is a risk factor.

### Care and treatment

Anticoagulants and thrombolysis; rehabilitation after stroke.

### Available services

Unknown.

### References

1. Greenberg: Neurology 51 (1998) 690-94.

## **OTHER RARE CAUSES OF DEMENTIA**

## 30. Cognitive Dysfunction in Multiple Sclerosis

by Clive Evers

### General outlines

There has been a lot of recent research into changes in cognition due to MS and it is now evident that such changes do occur and that they are more common than was previously thought. Cognition is about our abilities in thinking things through and how well our memory works.

Cognition is also about how to focus and to maintain our attention; the way we learn and remember new things; how we think reason and solve problems. It also concerns how we plan and carry out our activities; the way we understand and use language and how well we recognise objects, assemble things together and judge distances.

The brain damage in MS is different to that in e.g. Alzheimer's type dementia and so the problems shown are different. Although the problems may not amount to full dementia they can cause significant disruption to the lives of patients. In studies of MS patients with and without cognitive dysfunction, those with have been shown to be more significantly impaired with respect to work, sexual and social functioning and basic activities of daily living.

### Synonyms

Multiple Sclerosis (MS)

### Symptoms and course

Cognitive decline in MS generally does not correspond with either disease duration or physical ability. This may be explained by the unpredictable nature of damage to the myelin. Some patients may have had MS for many years without physical disability but others will be severely affected and confined to a wheelchair early on. Current research shows that the main determinant of the rate of cognitive decline is not the course of the disease but the extent of the development of brain lesions to the myelin. This can vary in patients with relapse/remission and those with a progressive condition. Cognitive dysfunction can be an early sign of MS and of brain lesions but progression is difficult to predict. Follow up studies of patients' show that in some people there has been no or little further cognitive decline after 2, 4 or 5 years.

### Caregiver problems

When someone with MS has cognitive problems their family and friends may be affected as well. There are a range of issues that may arise. The key to coping with them is to understand and to accept what is happening as a result of the disease process and possibly make some changes to make life easier. Carers may become frustrated if the person doesn't respond to a question as quickly as the person is being awkward but in fact they just cannot remember or think straight.

The person may express anger about what is happening to them and take this out on the carer. Similarly the carer may also be angry or depressed about he person and possibly become irritable and withdrawn.

### Causes and risk factors

MS is the most common disabling neurological condition among young adults (in the UK) and around 85,000 people are affected. MS is the result of damage to the myelin-a protective sheath surrounding nerve fibres of the central nervous system. This is part of the 'white matter' of the brain as opposed to the grey matter, which contains the nerve cells themselves. For some people MS is characterised by period of relapse and remission while for others it has a progressive pattern.

It is now accepted that approximately 45-60% of patients with MS have evidence of cognitive decline. For the majority of these people the changes are mild to moderate rather than severe. Whilst brain lesions can result in more permanent cognitive problems there are a several factors that can interfere with or impair cognition temporarily. Depression, stress, pain, tiredness and relapses can create temporary cognitive difficulties.

Additional circumstances that can affect concentration, memory and learning include high alcohol consumption, poor nutrition and illnesses as well as medication that affects the central nervous system like tranquillisers, sleeping pills and painkillers.

Lifestyle change can also affect cognition. When patients experience cognitive problems it does not mean that they will experience all of them. There is much variation in the difficulties people experience and the impact it they will have on their lives. Learning and memory: the most common types of memory problems are remembering recent events and the need to do things. Some people say that it may take more time and effort to remember this affecting recall.

However, problems with language, recognition and spatial judgements e.g. distances are not so frequent in people with MS. People with MS rarely have problems with other types of memory and can remember skills, general knowledge or things about the past. Their memory problems are different to those who experience Alzheimer's disease. Most often people with memory problems due to MS will continue to know who they are have no difficulties with communication and are able to carry out normal daily activities. Attention, concentration and mental speed: some people find it more difficult to concentrate for long periods of time or have trouble keeping track of what they are doing if interrupted. Problem solving: some people experience difficulties when making plans and solving problems. They know what they want to do but find it difficult to know where to start and what steps to take to achieve their aims. Word finding: people with MS may also experience some difficulties in finding the right word at the appropriate time in discussion.

### **Diagnostic procedures**

Patients and their carers are encouraged to report repeated cognitive problems to their doctor as it may be a symptom of MS or due to other causes. MRI is the favoured brain imaging technique used to identify the brain lesions. It is safe and does not have an adverse effect on cognition. Studies that have looked for links between brain abnormalities and cognitive dysfunction have used two approaches in analysing the MRI data. These have been the use of rating scales and direct computer assisted lesion volume measurement. Little use has been made of PET scanning for diagnostic purposes and this reflects the difficulties in using this technique when the damage to the brain white matter is so widespread. Comprehensive neuropsychological testing can be complex for the purpose of cognitive screening. However combinations of tests (4, Rao) have been developed to examine long-term verbal and spatial memory, verbal fluency and speed of information processing.. These tests have been shown to have high sensitivity (71%) and specificity (94%) in detecting cognitive impairment in people with MS.

## Care and treatment

A neuropsychological assessment will assist in identifying the problems the person is experiencing and make potential treatment easier. The assessment will consist of an interview about the past and present social functions and abilities of the person; a number of different verbal and written tests on attention, memory, problem solving and giving feedback on the results. The assessment will usually take between two and three hours with a follow-up session for feedback. The assessment should aim to identify the specific problems of the person and also their personal strengths to help them overcome and manage any weaknesses. Rehabilitation will aim to minimise the effects of problems with memory and thinking. It will include encouraging the person to practise and improve weakened skills; make better use of strengths; learn alternative and compensatory techniques; cope with limited abilities practically and emotionally and offer counselling to relatives. Goals may be set for the person based on the outcome of the assessment. Rehabilitation may be carried out in an individual or group setting. Voluntary agencies have further information of hints and tips for coping with cognitive problems.

## Ongoing research/Clinical trials

There is a lot of research taking place in to Multiple Sclerosis and considerable research has been undertaken on cognitive function and MS. Worthy of note here is a major international review of research published in November 2002 which was highly critical of three decades of research effort. The review led by Prof. Peter Behan concluded that there is little evidence to support the accepted scientific assumption that MS is an autoimmune disease. The review offered further clarification to the effect that MS is a neurodegenerative and metabolic disorder, with the predominant genes being on chromosome 17, thus assisting in the hunt for the cause of the disease.

## Available services

Voluntary organisations can provide advice, support and practical help in a range of areas:

### **Multiple Sclerosis International Federation**

[www.msif.org](http://www.msif.org)

### **MS Society**

[www.mssociety.org.uk](http://www.mssociety.org.uk)

## References

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5. Kujala, P et al The progress of cognitive decline in multiple sclerosis. Brain 120, pp.289-297



## **31. Normal Pressure Hydrocephalus (NPH)**

by Jos Van der Poel

### **General outlines**

NPH is an accumulation of cerebrospinal fluid, which causes the ventricles of the brain to enlarge. This is thought to stretch the brain tissue, causing a triad of symptoms. Whether NPH is a disease-entity, is disputable.

### **Symptoms and course**

1. gait disturbances (swaying, with stiff leggs)
2. urinary incontinence
3. mild dementia

### **Causes and risk factors**

In most cases, the cause of this disorder is unknown. In some patients a brain operation or infection has led to the condition.

### **Frequency**

6 – 10 % of all dementia patients

### **Diagnostic procedures**

1. CT-scan to detect enlarged ventricles
2. MRI to detect enlarged ventricles and oedema at sides of ventricles
3. Lumbar puncture to estimate CSF pressure and analysis of the fluid

### **Care and treatment**

Placement of CSF shunt.

### **Available services**

The Hydrocephalus Association  
<http://www.hydroassoc.org/>

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2. Tans J, Boon A; How to select patients with normal pressure hydrocephalus for shunting *Acta Neurochirurgica Supplement*, 2002, 81, 3-5
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Alzheimer Europe, Route de Thionville 145, L-2311 Luxembourg

# **Rare forms of dementia**

## Glossary

*Final report of a project supported by the  
Community Rare Diseases Programme  
2000-2002*





## **A**

### **acalculia**

Inability to perform mathematical computations.

### **acetylcholine**

One of a group of chemicals known as neuro-transmitters. Found throughout the brain, acetylcholine enables nerve cells to communicate with each other. In Alzheimer's disease, the levels of acetylcholine are lower than usual.

### **activities of daily living**

Activities necessary for everyday living, such as eating, bathing, grooming, dressing and toileting. Also referred to as basic activities of daily living (BADLs). Differs from instrumental activities of daily living (IADLs).

### **AD**

See Alzheimer's disease

### **ADL**

See activities of daily living

### **ADLs**

See activities of daily living

### **aetiology**

The cause or origin of a disease or disorder.

### **agonist**

A chemical or drug that mimics the action of a neurotransmitter by stimulating the target site or receptor

### **Alzheimer's disease**

A progressive, neurodegenerative disease characterised by loss of function and death of nerve cells in several areas of the brain, leading to loss of mental functions such as memory and learning. Alzheimer's disease is the most common cause of dementia.

### **amyloid**

A protein that is found in the brains of people with Alzheimer's disease. It is deposited throughout the brain in microscopic clumps known as plaques. Its function is unknown and it may be the cause of the deterioration of brain function.

### **amyloid plaque**

Abnormal cluster of dead and dying nerve cells, other brain cells, and amyloid protein fragments. Amyloid plaques are one of the characteristic structural abnormalities found in the brains of individuals with Alzheimer's. Upon autopsy, the presence of amyloid plaques and neurofibrillary tangles is used to positively diagnose Alzheimer's.

### **amyloid precursor protein**

A protein found in the brain, heart, kidneys, lungs, spleen, and intestines. The normal function of APP in the body is unknown. In Alzheimer's disease, APP is

abnormally processed and converted to beta amyloid protein. Beta amyloid is the protein deposited in amyloid plaques.

**antibodies**

Specialised proteins produced by the cells of the immune system that counteract a specific foreign substance. The production of antibodies is the first line of defense in the body's immune response.

**anticholinergic drugs**

A term for drugs that reverse or inhibit the action of acetylcholine on nerve cells.

**anticholinesterase**

A class of drugs frequently prescribed to patients with Alzheimer's disease.

**anticholinesterase drugs**

Also known as cholinesterase inhibitors, these dementia drugs, stop the breakdown of acetylcholine. They may help to slow down the progression of Alzheimer's disease in some people. Aricept and Exelon are examples.

**anti-inflammatory drugs**

Drugs that reduce inflammation by modifying the body's immune response.

**anxiety**

A feeling of apprehension, fear, nervousness, or dread accompanied by restlessness or tension.

**apathy**

Lack of interest, concern, or emotion.

**aphagia**

Not able to swallow.

**aphasia**

Difficulty understanding the speech of others and/or expressing oneself verbally.

**apolipoprotein E**

A protein whose main function is to transport cholesterol. The gene for this protein is on chromosome 19 and is referred to as APOE. There are three forms of APOE: e2, e3, and e4. APOE-e4 is associated with about 60 percent of late-onset Alzheimer's cases and is considered a risk factor for the disease.

**APP**

See amyloid precursor protein.

**Aricept**

An dementia drug whose generic name is donepezil.

**atrophy**

Shrinking of size; often used to describe the loss of brain mass seen in Alzheimer's disease during autopsy.

**autoimmunity**

Autoimmunity is when the body's natural defences (the immune system) mistakenly attacks the body's own tissue. "Auto" is derived from the Greek auto, meaning self, and autoimmune means attacking self.

**autonomy**

A person's ability to make independent choices.

**autopsy**

Examination of a body organ and tissue after death. Autopsy is often performed (upon request) to confirm a diagnosis of Alzheimer's disease.

**autosomal**

Pertaining to a chromosome not involved in sex determination. The gender does not influence the chance of inheriting the disease.

**autosome**

A chromosome not involved in sex determination. The diploid human genome consists of 46 chromosomes, 22 pairs of autosomes, and 1 pair of sex chromosomes (the X and Y chromosomes).

**axon**

The arm of a nerve cell that normally transmits outgoing signals from one cell body to another. Each nerve cell has one axon.

## **B**

**Babinski's signs**

When the sole of the foot is scratched, the big toe goes up instead of down.

**behavioural symptoms**

In Alzheimer's disease, symptoms that relate to action or emotion, such as wandering, depression, anxiety, hostility and sleep disturbances.

**beta amyloid**

A specific type of amyloid normally found in humans and animals. In Alzheimer's disease, beta amyloid is abnormally processed by nerve cells and becomes deposited in amyloid plaques in the brains of persons with the disease.

**biomarker**

Used to indicate or measure a biological process (for instance, levels of a specific protein in blood or spinal fluid, genetic mutations, or brain abnormalities observed in a PET scan or other imaging test). Detecting biomarkers specific to a disease can aid in the identification, diagnosis, and treatment of affected individuals and people who may be at risk but do not yet exhibit symptoms.

**brain**

One of the two components of the central nervous system, the brain is the center of thought and emotion. It is responsible for the coordination and control of bodily activities, and the interpretation of information from the senses (sight, hearing, smell, etc.). The other component of the central nervous system is the spinal cord.

**brain scan**

A general term to mean any investigation that produces pictures of the brain. A CT scan or MRI scan shows slices through the brain. A SPECT scan shows the brain's blood supply.

**Bradykinesia**

Slowness of all voluntary movement and speech.

**BSE**

Bovine Spongiform Encephalopathy

**bulbar**

The bulbar region of the brain is the brainstem, the nerves coming out of the brainstem are the bulbar nerves and the muscles they innervate are the bulbar musculature. Bulbar functions include eye movements, muscle of facial expression, speaking, and swallowing.

**C****caregiver**

The primary person in charge of caring for an individual having dementia, usually a family member or a designated health care professional.

**cataract**

The development of cloudiness of the human lens due to discoloration of cells.

**cell**

The fundamental unit of all organisms; the smallest structural unit capable of independent functioning. In the brain and nervous system important cells are the neuronal cells, which make up the nerves and brain.

**cell body**

In nerve cells, the central portion from which axons and dendrites sprout. The cell body controls the life-sustaining functions of a nerve cell.

**cell membrane**

The outer boundary of the cell. The cell membrane helps control what substances enter or exit the cell.

**central nervous system (CNS)**

The part of the human nervous system consisting of the brain and spinal cord. The CNS is the control network for the entire body.

**cerebellum**

The portion of the brain in the back of the head between the cerebrum and the brain stem. The cerebellum controls balance for walking and standing, and other complex motor functions.

**cerebral cortex**

The outer layer of the brain, consisting of nerve cells and the pathways that connect them. The cerebral cortex is the part of the brain in which thought processes take place. In Alzheimer's disease, nerve cells in the cerebral cortex degenerate and die.

**cerebrospinal fluid (CSF)**

The fluid that fills the areas surrounding the brain and spinal cord. It contains substances that when analyzed can help in the diagnosis of Alzheimer's disease. Collected by lumbar puncture.

**choline**

A natural substance required by the body that is obtained from various foods, such as eggs; an essential component of acetylcholine.



**choline acetyltransferase (CAT)**

An enzyme that controls the production of acetylcholine; appears to be depleted in the brains of individuals with Alzheimer's disease.

**cholinergic system**

The system of nerve cells that uses acetylcholine as its neurotransmitter and is damaged in the brains of individuals with Alzheimer's.

**cholinesterase**

An enzyme that breaks down acetylcholine, into active parts that can be recycled.

**chromosome**

The structures within cells made up of DNA. Each chromosome carries many individual genes. Normally, human cells contain 22 pairs of chromosomes and one X and one Y or two X chromosomes depending on gender.

**clinical trials**

Human experiments conducted by researchers that test the value, safety and efficiency of various treatments, such as drugs.

**clonus**

Involuntary movement of rapidly alternating contraction and relaxation of a muscle. Ankle Clonus is the most common form of Clonus.

**coexisting illness**

A medical condition that exists simultaneously with another, such as arthritis and dementia.

**Cognex**

An anticholinesterase drug whose generic name is tacrine.

**cognition**

Brain functions involving thinking, remembering, learning, reasoning and planning.

**cognitive abilities**

Mental abilities such as judgment, memory, learning, comprehension and reasoning.

**cognitive symptoms**

Dysfunction of cognition, in Alzheimer's disease patients these are the defining early symptoms such as loss of memory, confusion and aphasia.

**computed tomography scan (CT scan)**

(pronounced "cat scan") - A type of imaging scan (X-ray) that shows the internal structure of a person's brain. In diagnosing dementia, CT scans can reveal tumors and small strokes in the brain.

**D****deficits**

Physical and/or cognitive skills or abilities that a person has lost, has difficulty with, or can no longer perform due to his or her dementia.

**delirium**

A temporary condition with rapid onset consisting of cognitive dysfunction, different from dementia in its time course.

**dementia**

The loss of intellectual functions (such as thinking, remembering and reasoning) of sufficient severity to interfere with a person's daily functioning. Dementia is not a disease itself but rather a group of symptoms that may accompany certain diseases or conditions. Symptoms may also include changes in personality, mood and behaviour. Dementia is irreversible when caused by disease or injury but may be reversible when caused by drugs, alcohol, hormone or vitamin imbalances or depression.

**dendrites**

Branched extensions of the nerve cell body that receive signals from other nerve cells. Each nerve cell usually has many dendrites.

**deoxyribonucleic acid**

The basis of all genetic material. Nucleotides are the building blocks of deoxyribonucleic acid (DNA). Specific patterns of nucleotides represent particular genes.

**diagnosis**

The process by which a physician determines what disease a patient has by studying the patient's symptoms and medical history and analysing any tests performed (blood, urine, brain scans, etc.).

**disinhibition**

Loss of the feelings of shame or embarrassment that normally help control a person's actions. Disinhibition results in inappropriate or improper behaviour.

**disorientation**

A state in which someone loses their awareness of time and place. For example, they may fail to recall the date or even the year, and may not be able to say where they are.

**DNA**

The basis of all genetic material. Nucleotides are the building blocks of DNA. Specific patterns of nucleotides represent particular genes.

**dominant**

Dominant gene (or dominant allele) is a gene which, when present, produces a certain trait, and "dominates" over a recessive allele in the gene pair.

**Donepezil**

An anticholinesterase drug whose generic name is Aricept.

**dopaminergic**

Relating to nerve cells or fibres that employ dopamine as their neurotransmitter

**dysarthria**

a neurologic speech disorder caused by paralysis, weakness, improper muscle tone or incoordination of the muscles of the mouth. Dysarthria is not a disorder of language.

**dysphagia**

Difficulty in swallowing.

**dysphasia**

Lack of coordination in speech, and failure to arrange words in an understandable way; due to brain lesion. Aphasia is the complete or near complete absence of speech, and is used to describe a more severe situation than dysphasia.

**E****early-onset Alzheimer's disease**

An unusual form of Alzheimer's in which individuals are diagnosed with Alzheimer's before the age of 65. Less than 10 percent of all Alzheimer patients have early-onset. Early-onset Alzheimer's is associated with mutations in genes located on chromosomes 1, 14 and 21.

**early stage**

The beginning stages of dementia when an individual experiences very mild to moderate cognitive impairments.

**enzyme**

A protein produced by living organisms that promotes or otherwise influences chemical reactions.

**estrogen**

A hormone produced by the ovaries and testes. It stimulates the development of secondary sexual characteristics and induces menstruation in women. Estrogen is important for the maintenance of normal brain function and development of nerve cells. Estrogen is used therapeutically to treat breast and prostate cancer, osteoporosis and to relieve the discomforts of menopause. Some research suggests that estrogen may be beneficial in preventing Alzheimer's disease. More studies are needed to confirm this.

**excitotoxic**

Exciting neurons which can over time lead to neuronal death.

**executive function**

The ability to plan actions and change plans when adaptation is necessary

**F****familial Alzheimer's disease (FAD)**

A form of Alzheimer's disease that runs in families.

**fasciculation**

A small local contraction of muscles, visible through the skin

**free radicals**

Highly reactive molecules capable of causing damage in brain and other tissue. Free radicals are common by-products of normal chemical reactions occurring in cells. The body has several mechanisms to deactivate free radicals.

## G

### **gait**

A person's manner of walking. People in the later stages of Alzheimer's often have "reduced gait," meaning they may lose the ability to lift their feet as they walk.

### **gene**

The basic unit of heredity; a section of DNA coding for a particular trait.

### **gene linkage**

A group of genes located closely together on a chromosome. Used by researchers to related diseases to specific genes.

### **gene regulation**

The control of the rate or manner in which a gene is expressed as a protein.

### **genetic susceptibility**

The state of being more likely than the average person to develop a disease as a result of genetics.

### **genome**

All the genes of an organism. The Human Genome Project is currently trying to map all of the genes of the human genome by the year 2003.

### **glial**

Pertaining to the supporting cells of neural tissue.

### **glial cells**

Glial cells are maintenance and support cells in the central nervous system (CNS). There are a number of different types of glial cell in the CNS including: oligodendrocytes, astrocytes and microglia.

### **gliosis**

In the brain, scars are formed by glial cells and are called glial scars or gliosis.

### **glucose**

A simple sugar that is a major energy source for all cellular and bodily functions. Glucose is obtained through the breakdown or metabolism of food in the digestive system.

### **glutamate**

An amino acid neurotransmitter normally involved in learning and memory. Under certain circumstances it can be an excitotoxin and appears to cause nerve cell death in a variety of neurodegenerative disorders.

## H

### **hallucination**

A sensory experience in which a person can see, hear, smell, taste or feel something that isn't there.

### **heavy metals**

The term heavy metal refers to any metallic chemical element that has a relatively high density and is toxic, highly toxic or poisonous at low concentrations. Examples of heavy metals include mercury (Hg), cadmium (Cd), arsenic (As), chromium (Cr), thallium (Tl), and lead (Pb).

**hippocampus**

A part of the brain that is important for learning and memory.

**hypokinesia**

Decreased muscular activity.

**I****immune system**

A system of cells that protect a person from bacteria, viruses, toxins and other foreign substances that enter the body.

**incontinence**

Loss of bladder and/or bowel control.

**inflammatory response**

The immune system's normal response to tissue injury or abnormal stimulation caused by a physical, chemical or biological substance. Immune system cells, if abnormally stimulated, can often cause further tissue damage while responding to the injured site.

**L****lability**

Unstable, easily changed. The word is usually applied to rapid mood swings.

**lack of coordination**

Uncoordinated movement is an abnormality of muscle control or an inability to finely coordinate movements, resulting in a jerky "to-and-fro" unsteady motion of the trunk or the limbs.

**late-onset Alzheimer's disease**

The most common form of Alzheimer's disease, usually occurring after age 65. Late-onset Alzheimer's strikes almost half of all people over the age of 85 and may or may not be hereditary.

**late stage**

Designation given when dementia symptoms have progressed to the extent that a person has little capacity for self-care.

**lumbar puncture**

A procedure used to collect cerebrospinal fluid, which can help in the diagnosis of Alzheimer's disease, also called spinal tap.

**M**

**magnetic resonance imaging**

A brain scanning technique that generates cross-sectional images of a human brain by detecting small molecular changes. MRI scans reveal a contrast between normal and abnormal tissues. The image produced is similar to those generated by CT scans. There are no side effects or risks associated with MRI scans, although MRI can affect electrical devices like pacemakers and hearing aids.

**mania**

A state characterised by a pervasive and abnormally expansive mood, elation, irritability, flight of ideas, pressured speech and increased motor activity.

**memory**

The ability to process information that requires attention, storage and retrieval.

**metabolism**

The complex chemical and physical processes of living organisms that promote growth, sustain life and enable all other bodily functions to take place.

**Mini-Mental State Examination**

A standard mental status exam routinely used to measure a person's basic cognitive skills, such as short-term memory, long-term memory, orientation, writing, and language.

**mitochondria**

Components found in cells that serve as primary energy sources for all cellular functions.

**model system**

A system used to study processes that take place in humans or other living organisms.

**monogenic**

Controlled by or associated with a single gene.

**muscular dystrophies**

A group of genetic degenerative myopathies characterized by weakness and muscle atrophy without nervous system involvement.

**mutation**

A sudden change in the genetic constitution.

**myoclonus**

A brief, shock like contraction of a single muscle or of one or more muscle groups, rarely of a part of a muscle.

**myopathy**

Disease of the muscle tissues, which include the muscles over our bones (skeletal muscle) and the heart (cardiac muscle).

**N****nerve cell (neuron)**

The basic working unit of the nervous system. The nerve cell is typically composed of a cell body containing the nucleus, several short branches (dendrites), and one long arm (the axon) with short branches along its length and

at its end. Nerve cells send signals that control the actions of other cells in the body, such as other nerve cells and muscle cells.

**neuro-degenerative disease**

A type of neurological disorder marked by the loss of nerve cells.

**neurofibrillary tangle**

Accumulation of twisted protein fragments inside nerve cells. Neurofibrillary tangles are one of the characteristic structural abnormalities found in the brains of Alzheimer patients. Upon autopsy, the presence of amyloid plaques and neurofibrillary tangles is used to positively diagnose Alzheimer's.

**neurological disorder**

Disturbance in structure or function of the nervous system resulting from developmental abnormality, disease, injury, or toxin.

**neuron**

See nerve cell.

**neuropathology**

Changes in the brain produced by a disease.

**neurotransmission**

Passage of signals from one nerve cell to another via chemical substances or electrical signals.

**neurotransmitter**

Specialised chemical messenger (e.g., acetylcholine, dopamine) that sends a message from one nerve cell to another. Most neurotransmitters play different roles throughout the body, many of which are not yet known.

**nucleotides**

The different building blocks of DNA, represented by the letter A, T, G and C.

**nucleus**

The central component of a cell. It contains all genetic material.

## O

**onset**

Defines time of life when disease begins (e.g., early-onset, late-onset).

**overvalued ideas**

Unreasonable and persistent beliefs, held with less than delusional intensity, which are not generally held in the patient's culture. Overvalued ideas may have a basis in reality, such as preoccupations that one's nose is too large, that only diet can cure cancer, or that "having a baby is the only way I'll ever be happy." Ideas of reference are one type of overvalued idea.

## P

**paranoia**

Suspicion of others that is not based on fact.

**paranoid idea**

An overvalued idea that one is being persecuted.

**paraparesis**

Weakness affecting the lower extremities (the hip, thigh, leg, ankle, and foot)

**parkinsonism**

A group of neurological disorders characterised by hypokinesia, tremor and muscular rigidity.

**Parkinson's disease**

A disorder of the brain characterised by shaking (tremor) and difficulty with walking, movement, and coordination. The disease is associated with damage to a part of the brain that is involved with movement.

**penetrance**

An individual who carries a dominant gene may show a variable degree of the symptoms of the disorder.

**PET scan**

See positron emission tomography scan.

**phenotype**

Expression of any of those genes as a physical, biochemical or physiological trait.

**plaques**

See amyloid plaque.

**positron emission tomography scan (PET scan)**

An imaging scan that measures the activity or functional level of the brain by measuring its use of glucose.

**presenilins**

Proteins that may be linked to early-onset Alzheimer's disease. Genes that code for presenilin 1 and presenilin 2 have been found on chromosomes 14 and 1, respectively, and are linked to early-onset familial Alzheimer's disease.

**prions**

Protein segments that may cause infection that may lead to some forms of dementia.

**Protein**

The product of gene expression. Proteins are the molecules that do much of the work in the body such as creating structures, utilising and storing energy and transmitting signals.

**psychosis**

A general term for a state of mind in which thinking becomes irrational and/or disturbed. It refers primarily to delusions, hallucinations, and other severe thought disturbances.

**R****recessive**



Recessive gene (or recessive allele) is a gene, which must be present on both chromosomes in a pair to show outward signs of a certain characteristic.

**repetitive behaviors**

Repeated questions, stories and outbursts or specific activities done over and over again, common in people with dementia.

**riluzole**

A drug that has been shown to have energy buffering and anti-glutamate properties

**risk factors**

Factors that have been shown to increase one's odds of developing a disease. In Alzheimer's disease, the only established risk factors are age, family history and genetics.

## S

**senile plaque**

See amyloid plaque.

**side effect**

An undesired effect of a drug treatment that may range in severity from barely noticeable, to uncomfortable, to dangerous. Side effects are usually predictable.

**SPECT scan**

A painless procedure that takes a picture of a person's brain, which can help in the diagnosis of Alzheimer's disease, yields somewhat different information from MRI.

**Spinal cord**

One of the two components of the central nervous system, the spinal cord carries signals between the brain and the rest of the body to allow a person to sense the environment and react to it. The other component of the central nervous system is the brain.

**sporadic**

Occurring occasionally in a random or isolated manner.

**stages**

Course of disease progression defined by levels or periods of severity: early, mild, moderate, moderately severe, severe.

**synapse**

The junction where a signal is transmitted from one nerve cell to another, usually by a neurotransmitter.

## T

**Tacrine**

An anticholinesterase drug, also called Cognex.

**tangles**

See neurofibrillary tangles.

**tauopathies**

Mutations on tau gene are directly causing a disease named "fronto-temporal dementia with parkinsonism linked to chromosome 17" (FTDP-17). These mutations (more than 30) have demonstrated the important role of tau pathology in neurodegenerative disorders. Indeed, more than 20 neurodegenerative disorders have a tau pathology, generally with an accumulation of tau proteins in neurons or glial cells, or both. The fact that tau can be directly responsible of diseases and that most dementing disorders have a tau pathology has generated this concept. Tauopathies comprise primary and secondary tauopathies. Primary tauopathies are the diseases with tau playing a major role, such as FTDP-17, PSP, CBD and most fronto-temporal dementia. Secondary tauopathies are diseases like Alzheimer's disease, which is likely a true tauopathy, but fuelled by defects of the APP metabolic pathway.

**tau protein**

The major protein that makes up neurofibrillary tangles found in degenerating nerve cells. Tau is normally involved in maintaining the internal structure of the nerve cell. In Alzheimer's disease, tau protein is abnormally processed.

**tissue**

A group of similar cells that act together in the performance of a particular function.

**toxin**

A substance that can cause illness, injury or death. Toxins are produced by living organisms.

**trigger**

An environmental or personal stimulus that sets off particular and sometimes challenging behavior.

## U

**upper motor neuron signs**

Signs and symptoms that result from damage to descending motor systems. These include paralysis, spasticity and a positive Babinski sign (reflex).