Rare forms of dementia:
Description of the diseases

This project has received financial support from the European Commission.

. Alzheimer Europe . Route de Thionville 145 . L- 2611 Luxembourg .

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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 β42 peptide (Aβ42), which is probably the primary neurotoxic species involving in the pathogenesis of the disease.

The mutations can shift the cleavage site to favor the γ-secretase site, and to favor increased production of the toxic Aβ42 peptide over the shorter, less toxic Aβ40 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 β protein within the brain is likely to cause Alzheimer's disease (AD) have provided the rationale for therapeutic strategies aimed at influencing Aβ production, aggregation and clearance. γ-secretase catalyzes the final cleavage that releases the Aβfrom 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 γ-secretase activity.

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
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
www.alz.co.uk

References

1. Goate AM. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 1991;349:704-706.
2. Sherrington R, Rogaev EI, Liang Y, et al. Cloning a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995;375:754-760.
3. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature 1995;376:775-778.
4. Crutz M, van Duijin CM, Backhovens H, et al. Estimation of the genetic contribution of presenilin-1 and –2 mutations in a population-based study of presenile Alzheimer disease. Hum Mol Genet 1998;7:43-51.
5. Finckh U, Alberici A, Antoniazzi M, et al. Variable expression of familial Alzheimer disease associated with presenilin 2 mutation M239I. Neurology 2000;54:2006-2008.

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 disrupt's the brain's normal functioning, interupting 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 guidlelines 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 dugs like olanzapine (Zyprexa), quetiapine (Seroquel) or respiridone (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 selegeline; 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

Alzheimer Europe
145 Route de Thionville
L- 2611 Luxembourg
Tel: +352 / 29.79.70
Fax: +352 / 29.79.72
info@alzheimer-europe.org
www.alzheimer-europe.org

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

References

1. Diagnostic criteria (McKeith), Lancet paper on treatment
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
6. Shimura et al Science 2001; 293:263-269
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 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
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
L- 2611 Luxembourg
Tel: +352 / 29.79.70
Fax: +352 / 29.79.72
info@alzheimer-europe.org
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
www.alz.co.uk

References

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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 responsable 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 (DLDH), characterised by a severe neuronal loss and a gliosis (gial cell reaction), but without tau lesions.

DLDH 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

1. McKhann, G. M., M. S. Albert, et al. (2001). "Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease." Arch Neurol 58(11): 1803-9.

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 movemements, 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 parkinsoninan 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

1. Ingram, E. M. and M. G. Spillantini (2002). "Tau gene mutations: dissecting the pathogenesis of FTDP-17." Trends Mol Med 8(12): 555-62.

2. Lebert F, Stekke W, Hasenbroekx Ch, Pasquier F.Fronto-temporal dementia. A randomized, controlled trial with trazodone. Dem Cogn Disord. (in press)

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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
www.pdsg.org.uk

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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/

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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 liability 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: efficacity and safety of Rulizole (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

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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

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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 repeates (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.

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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

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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 multidiciplinar care is necessary in ASL. 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.

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.

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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.

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
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/

References

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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 commonlyfound 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 ofpublication 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 polyglutaminetract 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
Fax : 32/2/657.61.76
dagmar.kroebel@euro-ataxia.org
http://www.euro-ataxia.org

References

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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 mambers. 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 postynaptic (neuroleptics such as haloperidol). The high incidence of serious adverse reactions to these agents limits their use where the movements disorder are truly disambling.

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
Callunahof 8
7217 ST Harfsen
The Netherlands
Tel: +31 - 573 - 431 595)
Fax: +31 - 573 - 431 719
iha@huntington-assoc.com
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 loosing 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 personel 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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5. Dementia an Intellectual Disabilities; Fact sheet Alzheimer's Disease International (s.a.)

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 ophthalmo-oto-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 beneficiate of 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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2. Vidal, R., B. Frangione, et al. (1999). "A stop-codon mutation in the BRI gene associated with familial British dementia." Nature 399(6738): 776-81.

3. Vidal, R., T. Revesz, et al. (2000). "A decamer duplication in the 3' region of the BRI gene originates an amyloid peptide that is associated with dementia in a Danish kindred." Proc Natl Acad Sci U S A 97(9): 4920-5.

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 insomania (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 heridity

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

CJD Support Network
Gillian Turner
Birchwood, Heath Top, Ashley Heath
Market Drayton,
Shropshire TF9 4QR
England
www.cjdsupport.net

Child Growth Foundation
2, Mayfeld Avenue
London, W4 1PW
United Kingdom
Tel 020 8995 0257
Fax 020 8995 9075
cgflondon@aol.com

Prion Clinic
Department of Neurology
St Mary's Hospita
Praed St.
London, W2 1NY
United Kingdom
Tel 020 7886 6883

References

1. CJD and prion disease: an introduction and explanation. Alzheimer's Society CJD Support Network. December 1998.
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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 (exemple: 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 rote 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 are 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
Crewe Road
Edinburgh, EH4 2XU
Scotland
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
Gillian Turner
Birchwood, Heath Top, Ashley Heath
Market Drayton,
Shropshire TF9 4QR
England
www.cjdsupport.net

Child Growth Foundation
2, Mayfeld Avenue
London, W4 1PW
United Kingdom
Tel 020 8995 0257
Fax 020 8995 9075
cgflondon@aol.com

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Department of Neurology
St Mary's Hospita
Praed St.
London, W2 1NY
United Kingdom

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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 form 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 form 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 form 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.
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
grahamsteel@hbsef.org·

CJD Support Network
Gillian Turner
Birchwood, Heath Top, Ashley Heath
Market Drayton
Shropshire, TF9 4QR
England
www.cjdsupport.net

Prion Clinic
Department of Neurology
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London, W2 1NY
United Kingdom

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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 autosomic 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 posses 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

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Western General Hospital
Crewe Road, Edinburgh
EH4 2XU Scotland
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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Market Drayton
Shropshire, TF9 4QR
England
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London, W2 1NY
United Kingdom

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4. Douglas, MJ et al Patients with new variant CJD disease and their families:care and information needs. National CJD Surveillance Unit, Edinburgh, Feb 1999.
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

Unkown.

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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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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Market Drayton
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England
www.cjdsupport.net

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Department of Neurology
St Mary's Hospital, Praed St.
London, W2 1NY
United Kingdom

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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
Western General Hospital
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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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References

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
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
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
www.alz.co.uk

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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, personallity 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” megalomanic 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 probression 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 parenchmymal 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 incidenced 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 cardioloipin antigenes 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. The 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 intravenuously (6 x 4 mio units per day). Alternatives are Doxycycline (2 x 100 mg per day invtravenously for 30 days), and ceftriaxone (1 g per day for 14 days).

Available services

Departments of internal medicine, neurology or psychiatry.

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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, Levo-Dopa induced psychoses, dystonia, and cognitive impairment.

Neuropathology: multisystem neuronal degeneration and cell loss, with gliosisin many brainstem nuclei, in particular substantia nigra, locus ceruleus, and others with globous 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 sucortical fibrillary tangesand astroglia, indicating relationship to tauopathies. Ultrastructure and biochemistry of neuronal and glial deposits are similar to those in Alzheimer diseaase: Ultrastructurally NFTs are composed of 22 nm paired helical filaments and rare 15 nm straiht tubules, Biochemistry of tau protein in PEP shows tau triplet wit h 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 influenzy remains enigmatic.

Frequency

Frequency currently extremely rare; since 1970 only single cases reportedMain occurrence of EL between 1918 and 1924. Between 1925-38, PEP reporesented 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 austopsy 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 occurence of rest tremor; 3. progression of disease in discontinous spurts; 44. 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 causaive 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
www.epda.eu.com

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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 develope 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 additon, 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 experiences 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
http://www.esg.org.uk/ESG/Support/Default.asp

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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 triodothyronine (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 T 4 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 thryoiditis, 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 concessions.

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

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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 wich extrapyramidal movement disorders are associated with a combination of neuroaxonaly dystrophy and iron accumulation in basal ganglie.

Synonyms

Hallervorden-Spatz disease, pantothenace kinase-associated neurodegeneration.

Symptoms and course

Slowly progressive gait disorders, stiffness, cramps in legs, muscular hypotonia, rarely progressing into rigidity, clubfoor, 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 parkinonism, 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 casses (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.

Causesand risk factors

Due to mutations of PANK 2 (pathothenate 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 fertitin 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 highs signal lesions in globus pallidus; MrI T-2 weighted images show marked decreased intensity in globus pallidus and nigra due to increased iron and feritin 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 cass may show acanthocytosis and retinitis pigmentosa. After IV iron application, decreased uptake of 59 Fe is seen in basal ganglia. ß-CIT and IBZM-Spect, in contras to PD and MSA, shows normal bbasal ganglia; PET shows significant hypoperfusion in head of caudat enucleus, pons and cerecbellum with normal dopaminergic function of basal ganglia.

Care and treatment

Causal treatment is unknown. Symptomatic strategies include L-Dopa and dopamine agonists showing limitied 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.

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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 arount the retinal fovea centralis, due to lipid-laden ganglion cells, leaving a central "cherry-red" spot is a typical fundoscopical finding. Affected childred show slowly progressive deterioraion 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 fo 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

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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 sotrage 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 tha alpha subunit of the hexosaminidase gene (hex A), Sandhoff disease is caused by mutaion in the beta subunit of the hexosaminidase A (15q23-q24, leading to a partial deficit of the enzyme) and B (5q11) enzymes. Therefore, hxosaminidases A and B are both deficient in Sandhof 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 replacementt, 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 sphigolipidoses.

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.

Symtoms 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 gylcolipds in pacrophages, particularly those in the liver, bone marrrow, 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 mutation of the glucocerebrosidase gene (1q21)s have been identified.

Diagnostic procedures

Laboratory diagnosis of Gaucher disease is performed by measuring glucocerebrosidase activity using a fluorimetric asssay.

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 pogression of neurologica 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

Nieman-Pick disease (NPD) refers to a heterogenous 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 spingomyelinase 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 opthalmoplegia 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 culutred 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

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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-galatosidase 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

1. Andrews, J. M.; Cancilla, P. A.; Grippo, J.; Menkes, J. H. : Globoid cell leukodystrophy (Krabbe's disease): morphological and biochemical studies. Neurology 21: 337-352, 1971

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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

Symtoms and course

NCL are characterised by psychomotor deterioriation, 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 behavoural distubance, 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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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 virtualy 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 vibraion 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.

Deatz 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 bulbs2.

Diagnostic procedures

The diagnosis can be confirmed by the finding of elevated levels of cholestanol in serum, tendon, or nervous tissue. Plasma cholesteros 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, particulary 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 Ca2+ 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 tranplantation. 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 patiens, particularly those over 60 years of age (Conn, 1993).

Treatment of uremic encephalopathy, except kidney tranplantation, 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.

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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 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 niacine (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.

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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, unvoluntary 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 demyelinisation 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 Mittchell, 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 sufatid activator gene on chromosoms 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 permament without the need for further treatment.

The new enzyme levels prevent the accumulation of sulfatades 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 result 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.

References

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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, psudobulbar symptoms, progressive dyskinesia or polyneuropathy. Psychiatric and neurological symptoms are accompanied by adrenal gland dysfunction (fatigue, intermittend 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 demyelinisation.

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 demyelinisation in 80 % of ALD patients which is parieto-occipital initally 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 demyelinisation, 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 acits in order to inhibit the generation of VLCFA. Lorenzo's oil, however, has no effect on demyelinisation 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 supressive therapy and high-dose intravenous immunoglobuline 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
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
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 vitamine thiamine (vitaminE 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 remains a clinical diagnosis with no abnormalities in eg cerebrospinal flui, brain imaging or EEGs.

A complete blood count excludes severe anemias and leukemias as causes of altered mental state. Alterations in serum electrolytes like hypernatremia or hypercalcemia can cause altered mental statusserum glucose will be determined to exclude hypoglycemia and hyperglycemiato exclude uremia BLOOD UREA NITROGEN AND creatinine will be tested.

Arterial blood gases may be tested to exclude hypoxia and hypercarbiatoxic drug screening may be given to exclude some causes of drug induced altered mental status.a lumbar puncture may be considereda 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 cardiovasculatr 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 misue. 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 subcortial brain areas

Diagnostic procedures

MRI demonstrates lacunar infarcts and leukoencephalopathy. A skin biopsy can demonstrate granular osmiophilic material.

Available services

Association CADASIL France
Brigitte LEREBOURG
7, Les Marronniers
60240 Liancourt St Pierre
Tél : +33 3 44 49 16 34
http://association.cadasil.free.fr/

References

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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, atheriosclerosis and cardiacproblems.

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
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
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

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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 severeWhilst 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 sped: 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

MS Society
www.mssociety.org.uk

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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 discutable.

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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