Uncommon neurodegenerative causes of dementia

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ABSTRACT

A group of neurodegenerative diseases is outlined that affect cortical and subcortical areas of the brain. These diseases give rise to atypical forms of dementia and, unlike Alzheimer's disease (AD), are often associated with neurological symptoms. Clinical symptoms reflect the localization of the degenerative process rather than the nature of the underlying histopathology. Degeneration of the frontal and anterior temporal lobe presents initially with behavioral alterations, but later in the course, impairment of cognition and activities of daily living develops. Posterior cortical atrophy affects the parietal and occipital association cortices and causes complex visual disturbances. In corticobasal degeneration (CBD) the focus of pathology includes the frontoparietal cortex and several subcortical nuclei, causing symmetrical rigidity, bradykinesia, myoclonus and dystonia. Progressive supranuclear palsy (PSP) involves the frontal, temporal and parietal cortex as well as parts of the brain stem. Clinical features include a hypokinetic rigid syndrome with nuchal dystonia and vertical gaze palsy. Huntington's disease is a prototypical autosomal dominant disorder that affects the extrapyramidal system and causes choreatic movements in combination with personality changes and cognitive deterioration. Amyotrophic lateral sclerosis (ALS) with dementia is a neurodegeneration of the frontotemporal cortex and of the anterior horn of the spinal cord. Behavioral change similar to frontotemporal dementia (FTD) is paralleled or followed by the classic features of motor neuron disease.

Key words: frontotemporal degenerations, posterior cortical atrophy, corticobasal degeneration, progressive supranuclear palsy, Huntington's disease, amyotrophic lateral sclerosis with dementia

Overview

This paper deals with a group of rare central nervous system (CNS) diseases that affect neuronal populations in cortical and subcortical areas of the brain.

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The underlying histopathology varies but often includes abnormal folding, aggregation, and deposition of tau protein. These disorders are associated with atypical forms of cognitive impairment and dementia that are rarely seen in Alzheimer's disease (AD) and are often accompanied by neurological symptoms. With the exception of rare familial cases and Huntington's disease, which are caused by gene mutations, the etiology is not known. No specific pharmacological or psychological treatment is available and no systematic study has been carried out on the burden of family carers. As the rate of diagnostic misclassification is high, specialist referral should be sought in suspect cases. Clinical management often requires psychiatric and neurological skills, and interdisicplinary cooperation is recommended.

Frontotemporal lobar degenerations (FTLD)

Introduction

The FTLD are a group of non-Alzheimer, non-Parkinson neurodegenerative diseases that primarily affect the frontal and anterior temporal lobes. The parietal cortex and the basal ganglia are involved to a variable extent. There are several types of underlying histopathology. Their topographical distribution rather than their specific nature determines the clinical presentation. Three clinical syndromes are usually distinguished: frontotemporal dementia (FTD), semantic dementia (SD) and progressive aphasia (PA). During the course of these syndromes, the motor symptoms of corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and amyotrophic lateral sclerosis (ALS) may occur. Prevalence estimates of FTD range from 9.4 to 53.4 per 100 000 in the 60–69-year-old population (Knopman *et al.*, 2004).

Signs and symptoms

FTD is the most prevalent clinical manifestaton of FTLD and is characterized by changes of personality and social conduct. Behavioral alterations may include loss of interest, lack of empathy, blunted affect and apathy, but also disinhibition, hyperorality, impulsivity and irritability. In many patients, behavior becomes increasingly stereotyped and ritualistic. Among cognitive abilities attention, executive function and verbal output are primarily affected, whereas memory and orientation remain relatively well preserved until late stages (Greicius *et al.*, 2002). Activities of daily living are also maintained over long periods of the course. Gradually, however, symptoms progress to profound dementia. The most prominent symptom of SD is a peculiar disturbance of language. Patients exhibit a progressive loss of meaning of words, objects and faces that contrasts with fluent verbal output. Over a number of years, everyday memory, general intellectual functioning and activities of daily living remain unimpaired,

but gradually the symptoms of FTD emerge (Hodges *et al.*, 1998). PA is another disorder of language, characterized by nonfluent aphasia with hesitant speech, word-finding difficulty, phonological and grammatical errors, frequently accompanied by buccofacial apraxia and dysarthria. Patients retain their ability to carry out daily routines, social roles and occupational tasks for many years (Sonty *et al.*, 2003). Ultimately, however, they also develop the symptoms of FTD, and the language disturbance progresses to complete mutism. Survival from diagnosis is approximately 6 years and similar to AD, but more rapid clinical deterioration has also been observed.

Classification and diagnosis

The diagnosis of FTD can be difficult. Patients often perform normally on standard cognitive tests, and unusual behavior may suggest depression, mania, schizophrenia or obsessive–compulsive disorder rather than a neurodegenerative disease. A careful history from an informant is essential to identify the change of behavior from the premorbid personality. At early stages, computed tomography (CT) or magnetic resonance imaging (MRI) scans may be normal. With further progression of the disease, however, atrophy – often asymmetrical – usually becomes apparent, affecting the orbital and dorsolateral frontal lobe, the anterior cingulate area, and the anterior temporal lobe including the hippocampus (Rosen *et al.*, 2002). Imaging of brain perfusion using single photon emission computed tomography (SPECT) or brain glucose metabolism using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) reveals regional deficits in the mediofrontal, ventrolateral, orbitofrontal and anterior cortex as well as in the anterior cingulate area and sometimes in the striatum (Diehl *et al.*, 2004). The syndrome of SD can be identified by the peculiar, fluent disorder of language with loss of meaning of words, objects, tastes, odours or faces. Structural imaging reveals bilateral, although asymmetric, atrophy of the medial temporal lobe, amygdala and anterior hippocampus. Functional imaging demonstrates left temporal deficits of brain perfusion and metabolism (Diehl *et al.*, 2004). PA may be suspected in patients with neurologically unexplained progressive nonfluent aphasia who are capable of fulfilling their social and occupational roles despite severe communication problems.

Differential diagnosis

To distinguish between FTD and AD, the sequence of symptoms during the clinical course is important. In FTD changes of personality, social conduct and emotional control clearly occur before significant cognitive impairment. There is disproportional behavioral change relative to minor deterioration of activities of daily living. Furthermore, executive abilities as assessed using

standard tests (Stroop Test, Trailmaking Test, Tower of Hanoi, Wisconsin Card Sorting Test) are significantly more impaired than memory, orientation and visuoconstructional ability (Diehl and Kurz, 2002). Differentiation between FTD and AD is assisted by functional brain imaging, demonstrating frontotemporal hypoperfusion or hypometabolism in typical cases of FTD, which contrasts with temporo-parietal deficits in AD. The role of cerebrospinal fluid (CSF) protein measurements in differential diagnosis has not been studied extensively. Available results suggest that CSF total tau (Riemenschneider *et al.*, 2002) and hyperphosphorylated tau (Hampel *et al.*, 2004) are lower in FTD than in AD. SD can be distinguished from FTD at early stages by the typical and prominent language disorder with severely impaired semantics but intact syntax and phonology, in the absence of significant behavioral change. Differential diagnosis may be assisted by functional brain imaging showing hypoperfusion or hypometabolism bilaterally in the temporal lobes. PA can be separated from SD and FTD by the prominent nonfluent aphasia with intact semantics and impaired syntax and phonology that stands in contrast to preserved executive ability and unimpaired activities of daily living (Mesulam, 2003). Differential diagnosis may be enhanced by functional imaging showing deficits around the Sylvian fissure in the language-dominant hemisphere.

Pathophysiological mechanisms of causation

Genetic factors play a role in the etiology of FTD. In 30–50% of the patients there are secondary cases among first-degree relatives (Chow *et al.*, 1999), suggesting autosomal dominant transmission in approximately one-third of these pedigrees. The apolipoprotein E e4 allele is not a risk factor for FTD (Riemenschneider *et al.*, 2002). In rare familial cases, FTD is caused by mutations of the tau gene on chromosome 17 (Sobrido *et al.*, 2003). These mutations are associated with the histopathological feature of tau-positive intraneuronal inclusions and with a clinical presentation of pronounced behavioral alterations, L-dopa-resistant parkinsonian features and frequent psychotic symptoms (FTDP-17). It is assumed that the mutations change the binding of tau to microtubules.

In a Danish family, linkage of autosomal dominant FTD with chromosome 3 was found but the molecular mechanism is not clear. The FTLD share the neuropathological characteristic of a lobar neuronal degeneration that is confined to the frontal and temporal lobes with variable involvement of the parietal and motor cortex. The neurodegeneration may affect subcortical structures including amygdala, striatum, hypothalamus, substantia nigra, brain stem motor nuclei and anterior horn cells of the spinal cord (Munoz, 1998). Histopathologically, there are several patterns that may be associated with any one of the clinical syndromes. The most frequent pattern is characterized by atrophy, spongiform change and nerve cell loss, and was considered "unspecific" (dementia lacking

distinct histopathology) until recently, when ubiquitin-positive and tau-negative inclusions were identified. The Pick type is less frequent, featuring severe atrophy of the frontal and anterior temporal lobe, massive neuronal loss and gliosis, tau-positive inclusions in neurons (Pick bodies) and glial cells, and achromatic swollen ("ballooned") neurons (Pick cells). The PSP type is characterized by tau-positive intraneuronal tangles in subcortical nuclei and in the cerebellum, and by tau-positive astrocytic plaques in the basal ganglia. For the CBD type, swollen neurons with tau- and ubiquitin-positive inclusions as well as tau-positive astrocytic plaques in the white matter are typical. The motor neuron type is characterized by ubiquitin-positive, tau-negative inclusions in anterior horn cells, frontal lobe neurons and dentate gyrus cells. There is severe nerve cell loss in the substantia nigra and in the hypoglossal nucleus.

Management

There is no approved treatment for FTD, SD or PA. Cholinergic replacement therapy seems to be ineffective. Glutamate receptor antagonists (memantine) have not been studied systematically. Small trials have been conducted with serotonergic antidepressants showing clinically meaningful improvements in behavior, including disinhibition, depression, carbohydrate craving, obsessive–compulsive and stereotyped behavior (Ikeda *et al.*, 2004). Irritability, agitation, depression and overeating in FTD were improved with the antidepressant trazodone. Neuroleptics may be used with caution for the treatment of aggression and disinhibition. Behavioral modification strategies include daytime structuring, token rewards, and taking advantage of the ritualistic tendency of the patients. The management of FTD must include counseling and support of carers.

Posterior cortical atrophy (PCA)

Introduction

PCA is a rare progressive dementia with usually presenile onset and a mean duration from symptom onset between 1 and 9 years. Clinically it is characterized by early neurological and neuropsychological dysfunctions attributable to the occipital and parietal association cortices. In most, but not all cases, PCA is a posteriorly shifted variant of AD. To accommodate early cases without evident atrophy, the term "progressive posterior cortical dysfunction" has been introduced (Renner *et al.*, 2004).

Signs and symptoms

Patients usually present with visuospatial complaints, and many are initially seen by an ophthalmologist (Tang-Wai *et al.*, 2004). On examination they

may show complex visual disturbances including visual agnosia, environmental disorientation, dressing apraxia and pure alexia. The clinical picture is frequently dominated by elements of Balint's syndrome (simultagonosia, oculomotor apraxia, optic ataxia). Patients are also prone to Gerstmann's syndrome (agraphia, acalculia, finger agnosia and right/left disorientation) and ideomotor apraxia. Long-term follow-up of patients with PCA usually documents progression of memory and language problems, as well as loss of insight (Mendez *et al.*, 2002).

Classification and diagnosis

PCA may be assumed in patients with progressive decline in complex visual processing out of proportion to other cognitive difficulties and without evidence of basic motor or sensory dysfunction. Upon standard neuropsychological testing, visuoconstructive difficulties are prevalent in drawing to copy or to command, and a large discrepancy in verbal and performance IQ is often apparent. Some patients may not fit the diagnosis of dementia because they present with visuoperceptual difficulties in the apparent absence of other signs of dementia such as poor memory or judgment (Black, 1996).

Differential diagnosis

In comparison to AD, psychometric evaluation reveals disproportionate visuospatial impairment but similar or slightly better performance on memory and verbal tests. Patients with PCA also show more depression and better insight into their condition than patiens with AD. Atrophy of posterior cortical regions is the typical finding on structural brain imaging but may be absent in early cases. Functional imaging demonstrates parieto-occipital hypoperfusion or hypometabolism (Nestor *et al.*, 2003), which is different from the temporoparietal deficits usually described in AD. There are no differences between PCA and AD regarding family history of dementia and apoE genotype. Early in the disorder, PCA may be clinically indistinguishable from dementia with Lewy bodies. However, the early presence of visual hallucinations, symmetric parkinsonism and the lack of features of Balint's syndrome distinguish dementia with Lewy bodies from PCA.

Pathophysiological mechanisms of causation

Although PCA is etiologically nonspecific, AD pathology is the most likely underlying cause. The apoE allele distribution is similar to AD (Tang-Wai *et al.*, 2004). Typically, the visual association areas are heavily affected and the frontal regions are spared. In addition, the mesiotemporal regions are relatively preserved. Other pathologies that may underlie PCA include AD

plus Parkinson's disease, Lewy body disease, progressive subcortical gliosis, corticobasal degeneration and prion-associated diseases (Creutzfeldt–Jakob disease, fatal familial insomnia).

Management

Specific recommendations for pharmacological treatment of PCA are not available. Given the likelihood of AD as the underlying pathology, a cholinesterase inhibitor should be tried. Management of these patients also includes visual aids, referral to services for the blind, participation in rehabilitation programs, and early consideration of antidepressant medication.

Corticobasal degeneration (CBD)

Introduction

CBD, also termed corticobasal ganglionic degeneration, affects frontal and parietal regions of the cerebral cortex as well as several subcortical nuclei, and is clinically characterized by the combination of motor sympoms with symptoms reflecting cortical involvement.

Signs and symptoms

Initial symptoms usually begin at an average age of 60 years. Pathology in subcortical nuclei is reflected in motor symptoms, which include progressive, asymmetrical and L-dopa-resistant rigidity, bradykinesia, tremor, dysphagia and myoclonus (Boeve *et al.*, 2003). Painful dystonia of one hand often develops, which distinguishes CBD from other bradyhypokinetic syndromes (Litvan *et al.*, 1997). Patients may complain of one hand feeling strange or being difficult to control ("alien limb sign"). Involvement of the cortex is reflected in cognitive impairment, which may be present early in the course, and typically includes memory disorder, executive dysfunction, reduced verbal output and apraxia.

In many patients, motor and cognitive symptoms are accompanied by changes of behavior similar to those seen in FTD such as apathy, social withdrawal, personality alteration and irritability. With progression of the disease, symptoms gradually spread to the upper and lower extremities and to other body regions. The average duration is between 5 and 10 years.

Classification and diagnosis

CBD is difficult to diagnose at early stages even for the experienced examiner. In particular, it may be impossible to differentiate CBD from PSP. A clue to the diagnosis of CBD is the combination of an asymmetrical bradyhypokinetic syndrome with dystonia and early features of cortical involvement. CT or MRI

typically reveals asymmetric atrophy of the frontal and parietal cortex and of the basal ganglia (Boeve *et al.*, 2003). Functional imaging demonstrates reduced cerebral perfusion and metabolism in dorsolateral and medial frontal, lateral temporal and sensorimotor cortex as well in striatum and thalamus (Hosaka *et al.*, 2002). Lack of improvement with L-dopa treatment differentiates CBD from idiopathic Parkinson's disease.

Pathophysiological mechanisms of causation

CBD is a sporadic disorder. A genetic risk factor is the H1H1 haplotype in the tau gene (Sergeant *et al.*, 1999). Histopathologically there is an aggregation of tau isoforms with four repeats in neuronal and glial cells. The tau pathology is associated with marked gliosis and ballooned achromatic neurons indistinguishable from Pick cells (Grimes *et al.*, 1999).

Management

There is no treatment available to slow the course of CBD, and the symptoms of the disease are usually resistant to therapy. Antiparkinsonian drugs do not produce any significant or sustained improvement. Clonazepam may ameliorate myoclonus. Occupational, physical and speech therapy may help in managing disability.

Progressive supranuclear palsy (PSP)

Introduction

PSP, also termed Steele–Richardson–Olszewski syndrome or dementia-nuchal dystonia, is the most frequent hypokinetic-rigid syndrome next to Parkinson's disease. It causes serious and permanent problems with control of posture, gait and balance. The most obvious symptom of this disease is an inability to aim the eyes properly. Patients are usually middle-aged or elderly, and men are affected more often than women.

Signs and symptoms

The most frequent initial symptom of PSP is a loss of balance while walking. Patients may experience unexplained falls or a stiffness and awkwardness in gait. Neurological examination typically reveals axial rigidity, bradykinesia, neck extension, and postural instability with proneness to backward falls. Motor symptoms of PSP respond poorly to L-dopa (Litvan *et al.*, 1996). In many patients the movement disorder is accompanied or even preceded by cognitive impairment including slowness, inattention, reduced verbal fluency and perseveration in contrast to relatively well-preserved memory, language and praxis (Esmonde *et al.*, 1996). In addition, significant alterations of

behavior may occur including apathy, loss of interest in ordinary pleasurable activities, increased irritability, cantankerousness, compulsions or stimulus dependence. As the disease progresses, most patients will begin to develop a blurring of vision and problems controlling eye movement. Typically, they have trouble voluntarily shifting their gaze downward (vertical gaze palsy). Speech usually becomes slurred and swallowing solid foods or liquids can be difficult. Average survival from first symptoms is 10 years. The most common complications are choking and pneumonia, head injury and fractures caused by falls.

Classification and diagnosis

Early diagnosis of PSP is always difficult. Primary complaints may be grouped into symptoms of dysequilibrium (unsteady walking, abrupt and unexplained falls without loss of consciousness), of vision (blurred vision, difficulties in looking up or down, double vision), speech or cognition (slowness of thought, memory impairment). PSP is often misdiagnosed because many of its symptoms are similar to Parkinson's disease or AD. The key to diagnosing PSP is identifying early gait instability and difficulty moving the eyes. PSP is different from Parkinson's disease with respect to several features. Patients with PSP usually stand straight or occasionally tilt their head backward (and tend to fall backward) while those with Parkinson's disease usually bend forward. Problems with speech and swallowing are much more common and severe in PSP than in Parkinson's disease, and tend to show up earlier in the course of the disease. Patients with PSP respond poorly and transiently to L-dopa and other dopaminergic drugs. Structural imaging demonstrates atrophy of the frontal, temporal and parietal cortex and of the brain stem (Foster *et al.*, 1992). Functional imaging reveals bilateral perfusion or metabolic deficit in the medial and dorsolateral frontal lobe, anterior cingulate, caudate, thalamus and midbrain (Hosaka *et al.*, 2002). The involvement of the mesencephalon is specific to PSP.

Pathophysiological mechanisms of causation

The symptoms of PSP are caused by a gradual degeneration of neurons in the brain stem including the substantia nigra. The probability of the disease being passed from one generation to the next within a family is extremely low. There is a genetic risk linked to the H1H1 haplotype in the tau gene. PSP belongs to the 4R tauopathies (Sergeant *et al.*, 1999).

Management

There is currently no effective treatment for PSP. In some patients bradykinesia and balance problems may respond to antiparkinsonian agents, but the effect is

usually temporary. Nonpharmacological treatment of PSP can take many forms including walking aids and special glasses (prisms).

Huntington's disease (HD)

Introduction

HD is a fatal neurodegenerative disorder that involves the extrapyramidal system and is characterized by uncontrolled movements (chorea), progressive dementia and behavioral change. HD is transmitted as an autosomal dominant disorder; the gene is known as IT 15 and is located on chromosome 4. The prevalence of HD is estimated at 1/10 000.

Signs and symptoms

HD produces symptoms in the areas of movement, cognition and behavior (Davies and Ramsden, 2001). The sequence in which symptoms develop varies from person to person. The most characteristic feature of the disease are involuntary, uncontrolled, rapid and ceaseless movements that may develop in the fingers, feet, face or trunk. This abnormality is referred to as *chorea* and can become more intense when the person is anxious or disturbed. Gradually, other motor symptoms emerge, such as clumsiness, jaw clenching, loss of coordination and balance, slurred speech, swallowing and/or eating disorder, dystonia, and walking difficulty leading to stumbling and falls. Cognitive impairment in HD may begin early in the disease course and includes deficit in attention and concentration, executive function, psychomotor speed and memory.

The most common behavioral symptom of HD is depression, which often develops early in the course. Patients with HD may also show delusions, hallucinations and aggressiveness. The rate of disease progression and the age at onset vary from person to person. The earlier the onset, the faster the disease seems to progress. A minority of patients (about 10%) develop symptoms of HD before the age of 20. This "juvenile" or *Westphal* variant of the disease may become manifest in slowness, rigidity, tremor and myoclonus accompanied by seizures and mental disability and may be associated with a survival of less than 10 years. A few individuals develop HD after the age of 55 years.

Classification and diagnosis

The diagnosis of HD is based on a thorough personal and family medical history, a neurological examination and laboratory tests to exclude other causes (Vonsattel and DiFiglia, 1998). It should be noted, however, that in 1–3% of the patients no family history of HD can be found. A CT or MRI scan typically demonstrates shrinkage of the brain in the caudate nucleus and putamen with a consecutive enlargement of the ventricles. Atrophy of the striatum may begin

long before the onset of motor symptoms. However, the presence of structural changes in the striatum is not conclusive for HD, nor does their absence rule it out. ^{18}F-FDG PET can demonstrate metabolic reduction in the caudate and putamen at early stages of HD and even in presymptomatic mutation carriers. Using specific markers of dopamine receptors such as ^{11}C-raclopride, a significant reduction in postsynaptic receptor binding can be demonstrated in the striatum and also in extrastriatal areas including amygdala, temporal and frontal cortex (Pavese *et al.*, 2003).

The discovery of the HD gene in 1993 resulted in a direct genetic test to make or confirm a diagnosis of HD in an individual exhibiting HD-like symptoms. Using a blood sample, the genetic test analyzes DNA for the HD mutation by counting the number of repeats in the HD gene region. Individuals who do not have HD usually have 28 or fewer CAG repeats. Those with HD usually have 40 or more repeats. A small percentage of individuals, however, have a number of repeats that fall within a borderline region. Presymptomic testing is available for those who are at risk for carrying the HD gene (Potter *et al.*, 2004).

A positive genetic test result can have a profound, unanticipated impact on patients and their families. Anyone contemplating genetic testing should obtain testing guidelines from the testing center or from an organization devoted to the interests of HD patients and their families. These guidelines recommend that counseling should be provided before and after the test, and before the results are communicated. Test results should be strictly confidential and should be disclosed only in person, regardless of the outcome. To protect the interests of minors, testing should not be conducted for persons under the age of 18 years without a compelling medical reason, such as the appearance of HD symptoms in a child.

Pathophysiological mechanisms of causation

The cause of HD is the expansion of a CAG repeat in the first exon of the gene IT 15 on chromosome 4, which encodes the protein *huntingtin*. The expanded CAG repeat is transmitted predominantly through the male germ line in humans. Although HD usually runs in certain families as a dominant trait, the disorder may occur as the result of a sporadic change in the gene for HD. Mutations in the IT 15 gene are characterized by increased numbers of trinucleotide (CAG) repeats, resulting in the production of an abnormal *huntingtin* protein. The length of the expanded trinucleotide repeats is thought to have some association with the age of symptom onset. Patients with a large number of repeats tend to develop symptoms at an earlier age. Extremely large CAG repeats of 80 or more are found in the juvenile variant of HD. Both normal and variant huntingins are localized chiefly in the cytoplasm of neurons.

In HD, ubiquinated fragments of *huntingtin* form insoluble deposits in both the cytoplasm and the nucleus. It is thought that these deposits interfere with glucose metabolism and cause degeneration of GABAergic striatal neurons, which results in atrophy of the caudate nucleus, putamen and globus pallidus accompanied by marked gliosis. There is also pronounced atrophy of the cerebral cortex (Davies and Ramsden, 2001).

Management

Current treatment for HD is only symptomatic (Bonelli *et al.*, 2004). For the treatment of movement disorder in HD, riluzole, olanzapine and amantadine may be recommended. Benzodiazepines such as clonazepam may help to alleviate choreic movements and may also be used to help control agitation, anxiety, hallucinations, delusions and violent outbursts. For the treatment of depression in HD, selective serotonine reuptake inhibitors or mirtazapine are preferred. Psychosis and behavioral problems may respond to atypical antipsychotics. Adjuvant psychotherapy, physiotherapy and speech therapy should be supplied.

It is important for people with HD to maintain physical fitness as much as possible, as individuals who exercise and keep active tend to do better than those who do not. A daily regimen of exercise can help the person feel better physically and mentally. Although their coordination may be poor, individuals should continue walking, with assistance if necessary. Those who want to walk independently should be allowed to do so for as long as possible, and careful attention should be given to keeping their environment free of hard, sharp objects. This will help ensure maximal independence while minimizing the risk of injury from a fall. Individuals can also wear special padding during walks to help protect against injury from falls.

Amyotrophic lateral sclerosis (ALS) with dementia

Introduction

ALS with dementia is characterized by both frontotemporal degeneration and motor neuron disease, causing progressive muscular atrophy, weakness and fasciculation in association with cognitive impairment resulting in a frontotemporal type of dementia. The prevalence of ALS is between 4 and 6/100 000, and males are more commonly affected than females. The mean onset is around 63 years. Over 50% of the patients die within 3 years of the first symptom.

Symptoms and signs

Initial clinical symptoms include changes in personality, behavior, cognition, speech and language, followed or paralleled, or sometimes preceded, by the

classic features of ALS. Involvement of the central (upper) motor neurons leads to spasticity, weakness and hyperreflexia, while lower motor neuron impairment causes fasciculation, atrophy, weakness and hyporeflexia (Yoshida *et al.*, 2004). Bulbar symptoms as well as wasting and fasciculations of the tongue, shoulder girdle and proximal upper limbs are prominent, whereas wasting and weakness of the lower limbs remain mild, and patients can often walk even in the terminal stage. As many as 50% of ALS patients may have neuropsychological deficits that often take the form of frontotemporal dementia.

Classification and diagnosis

According to revised criteria of the World Federation of Neurology, the diagnosis of ALS requires the presence of upper and lower motor neuron signs as well as progression of the disease. Sensory signs, neurogenic sphincter abnormalities, and other clinically evident CNS diseases need to be excluded. Electrophysiology studies are required to confirm the diagnosis and these will show evidence of acute denervation and reinnervation without conduction block.

MRI of the brain and spinal cord may be necessary to exclude a structural lesion, and a cerebrospinal fluid examination can exclude an infective or inflammatory cause (Howard and Orrell, 2002). Structural brain imaging may reveal atrophy of the precentral gyrus, the frontal and temporal cortex, and the anterior cingulate. Functional imaging may demonstrate bilateral impairment of brain perfusion and metabolism in the frontal and anterior temporal lobe (Strong *et al.*, 2003).

Pathophysiological mechanisms of causation

Symptoms of ALS are caused by neurodegeneration in ALS, resulting in atrophy of the anterior roots in the cervicothoracic spinal cord. In ALS with dementia there is also atrophy of the frontotemporal cortex. Histological changes include neuronal loss and gliosis with sponginess in the frontotemporal cortex and in the limbic system, ubiquitin-positive and tau- and alpha-synuclein-negative intraneuronal inclusions, as well as ubiquitin-positive inclusions in lower motor neurons. In approximately 10% of the cases a strong familial aggregation is found. A minority of familial ALS is caused by mutations in the superoxide dismutase gene on chromosome 21 (SOD1). Sporadic cases of ALS are sometimes due to novel mutations in this gene. In addition to SOD1, several other mutations have been identified that cause familial ALS (Majoor-Krakauer *et al.*, 2003). A specific linkage of ALS with frontotemporal dementia with a locus on chromosome 9 has been found in a set of families (Hosler *et al.*, 2000).

Management

The only disease-modifying treatment is riluzole, which inhibits glutamate release and prolongs survival by several months but has no effect on functional deterioration. Respiratory impairment is common in ALS and may require respiratory support. Physical therapy and special equipment can enhance patients' independence and safety throughout the course of ALS.

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