REVIEW

Young onset dementia

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Young onset dementia is a challenging clinical problem with potentially devastating medical and social consequences. The differential diagnosis is wide, and includes a number of rare sporadic and hereditary diseases. However, accurate diagnosis is often possible, and all patients should be thoroughly investigated to identify treatable processes. This review presents an approach to the diagnosis, investigation, and management of patients with young onset dementia, with particular reference to common and treatable causes.

Dementia in younger people (young onset dementia, YOD) is increasingly recognised as an important clinical and social problem, with frequently devastating consequences for both the sufferer and those who care for them.[1] Prevalence rates of YOD have been estimated between 67 to 81 per 100 000 in the 45 to 65 year old age group[2 3]; thus there are currently approximately 10 000 patients with YOD in the United Kingdom alone. YOD poses a diagnostic challenge and may present with a wide variety of subtle behavioural, cognitive, psychiatric, or neurological symptoms. While the degenerative dementias characteristically affect older patients, they are also an important cause of YOD: indeed, Alzheimer's disease is the commonest single cause of YOD with an estimated 3000 cases in the United Kingdom, followed by vascular dementia and the frontotemporal lobar degenerations (table 1). The young onset forms of these diseases are frequently familial.[4] Some degenerative dementias such as variant Creutzfeldt-Jakob disease typically occur in the young patient. In contrast, Lewy body dementia, which accounts for 20% of cases in patients over 65 years of age, accounts for only a small proportion of YOD.

The differential diagnosis of YOD is wide (tables 2 and 3). Dementia is very rare before the age of 40: in young adults and adolescents, genetic and metabolic disorders predominate and many present as a ''dementia-plus'' syndrome, where cognitive impairment occurs in the setting of more widespread neurological disturbance. The additional features of pyramidal, extrapyramidal, cerebellar, or peripheral nerve involvement are key diagnostic clues in this group (table 3) and help to direct investigations. Most inherited disorders of metabolism are autosomal recessive: in these diseases, the absence or partial inactivity of the affected enzyme leads to accumulation of abnormal material in lysosomes or peroxisomes.[5] Mitochondrial diseases have variable inheritance, as components of the respiratory chain are encoded both by nuclear DNA and maternally inherited mitochondrial DNA.[6] Many of the dementia-plus syndromes and metabolic disorders have ''subcortical'' cognitive impairment that may be misinterpreted as a pseudodementia. Changes in personality and mood, apathy and cognitive slowing are common, whereas memory may be relatively spared. In addition, drugs and toxic exposures should always be considered in younger adults: in approximately 10% of cases, YOD is a consequence of chronic alcohol abuse.[2]

This review will focus on common and treatable causes of YOD and outline general principles of investigation and management.

PRIMARY NEURODEGENERATIONS

Alzheimer's disease

Presenile Alzheimer's disease may manifest as early as the fourth decade, and it is frequently familial. Inheritance in familial Alzheimer's disease is autosomal dominant with essentially complete penetrance. It is genetically heterogeneous (see table 3): the majority of cases are due to mutations in the presenilin (PS)1 gene on chromosome 14[7]; rarely, pathogenetic mutations occur in the β-amyloid precursor protein gene on chromosome 21 (initially targeted because of the strikingly increased incidence of young onset Alzheimer's disease in Down's syndrome[8]) or in the PS-2 gene on chromosome 1.[9] The identification of these mutations has greatly advanced our understanding of the molecular pathology of Alzheimer's disease. Amyloid precursor protein is a trans-membrane protein that undergoes alternative proteolysis, either by α-secretase to generate a non-amyloidogenic product, or by the sequential action of β- and γ-secretase to generate Aβ peptides including highly amyloidogenic Aβ1–42 (the most abundant species in neuritic plaques). According to the ''amyloid hypothesis'', Alzheimer's disease results from a pathogenetic cascade driven by the accumulation of abnormally aggregated β-amyloid that leads to secondary neuronal injury and accumulation of tau in neurofibrillary tangles.[10] A central role for

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Abbreviations: BSE, bovine spongiform encephalopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CJD, Creutzfeldt-Jakob disease; FLAIR, fluid attenuated inversion recovery; FTDP-17, frontotemporal dementia-parkinsonism linked to chromosome 17; FTLD, frontotemporal lobar degeneration; MRI, magnetic resonance imaging; nvCJD, new variant Creutzfeldt-Jakob disease; PrP, prion protein; PS, presenilin; YOD, young onset dementia

Table 1 Epidemiology of young onset dementia (onset 30–64 years) (after Harvey *et al*[2])

Young onset dementia	Prevalence/ 100 000	Proportion of total (%)
Alzheimer's disease	21.7	30
Vascular dementia	10.9	15
Frontotemporal lobar degenerations	9.3	13
Alcohol related dementia	8.3	12
Dementia with Lewy bodies	6	4
Huntington's disease	4.7	25
Dementia in multiple sclerosis	4.1	
Dementia in Down's syndrome	1.6	
Corticobasal degeneration	1.0	
Prion disease	1.0	
Dementia in Parkinson's disease	1.0	
Dementia due to carbon monoxide poisoning	0.5	
Other causes	4.1	

amyloid, though contentious,[11] is consistent both with the location of the pathogenetic amyloid precursor protein mutations, which are all clustered near protease cleavage sites within the β-amyloid domain, and with evidence implicating the PS genes in γ-secretase cleavage of amyloid precursor protein, leading to overproduction of Aβ1–42.

The neuropathological hallmarks of Alzheimer's disease are neuritic (senile) plaques and neurofibrillary tangles. Neuritic plaques are extracellular and composed of dystrophic axons and dendrites clustered round a central core, predominantly consisting of β-amyloid (Aβ). Neurofibrillary tangles are intracellular and composed of abnormally phosphorylated microtubule associated tau protein. Involvement of basal forebrain nuclei leads to a widespread deficit in cholinergic transmission in cortical projection areas.

The clinical phenotype is similar in young onset and older onset Alzheimer's disease, and in familial and sporadic cases. Typically, early involvement of medial temporal lobe structures (hippocampus and entorhinal cortex) leads initially to forgetfulness for daily events (episodic memory loss). The patient may become lost in a familiar area (topographical memory impairment). Parietal dysfunction manifests as dyspraxia and visuospatial defects including visual disorientation: typically, parietal signs appear after memory loss, however in a subgroup of patients with posterior cortical atrophy they are the presenting features. In contrast to the frontotemporal lobar degenerations, language and social functioning are generally preserved until late in the course. Delusions, hallucinations, and aggression commonly occur later in the illness and often precipitate admission to institutional care. In familial Alzheimer's disease, myoclonus tends to be more florid and naming may be spared until later in the course.[12] Age at onset and age at death vary widely within the same kindred.[13] Specific mutations may give rise to characteristic clinical features such as early behavioural change,[14] a speech production deficit,[15] or spastic paraparesis with white matter changes.[16]

In familial cases, genotyping may enable Alzheimer's disease to be diagnosed at an early stage. As is true of the neurodegenerative dementias generally, definitive diagnosis in sporadic cases must still await histopathological examination. However volumetric magnetic resonance imaging (MRI) techniques can identify and quantify patterns of regional atrophy,[17] in particular medial temporal lobe structures (fig 1A), that reflect neuronal destruction. Studies of ''at risk'' members of familial Alzheimer's disease pedigrees indicate that increased rates of tissue loss and neuropsychological deficits (in particular, verbal recognition memory and performance IQ) precede symptoms by several years.[18]

Frontotemporal lobar degenerations

The frontotemporal lobar degenerations (FTLD) are a group of disorders characterised by focal degeneration of frontal and temporal lobes. The recent development of consensus diagnostic criteria for FTLD[19] has led to an increase in the number of cases diagnosed, and the recognition that FTLD and Alzheimer's disease have similar prevalence in YOD populations.[3] However FTLD remains a source of considerable nosological confusion, largely on account of its histopathological and genetic heterogeneity.

The usual age at onset is 45–60 (range 20–75 years); males may be more frequently affected.[3] Family history is positive in up to 50% of patients[4] and a number of genetic causes have been identified (table 3). The largest single group has mutations in the tau gene on chromosome 17: FTDP-17 (frontotemporal dementia with parkinsonism linked to chromosome 17).[20] The clinical phenotype is often highly variable within a kindred.

A wide variety of histopathological findings have been described in FTLD. Mild spongiform change with neuronal loss and non-specific gliosis may occur without inclusion bodies (dementia lacking distinctive histopathology).[21] Many cases are associated with tau inclusions; microtubular instability secondary to tau dysfunction may contribute to the pathogenesis of such ''tauopathies''.[20] The number of microtubule binding domains in the tau isoform provides a partial basis for classifying the tauopathies; thus, inclusions with three-repeat tau isoform are associated with classical Pick's disease with Pick bodies, while inclusions with four-repeat tau are associated with corticobasal type inclusions. Ubiquitin positive, tau negative inclusions similar to those in motor neurone disease may occur without motor neurone involvement.[22] New histopathological patterns continue to be defined.[23] There is no consistent relationship between histopathology and the clinical phenotype, which is largely determined by the distribution rather than the type of pathology.

In frontotemporal dementia, the clinical presentation is variable and often subtle, and may be dominated by behavioural disturbances, personality change, loss of empathy or motivation.[24] Loss of planning and judgment may force early retirement. Families and carers may attribute behavioural changes to marital difficulties or ''mid-life crisis'' and misdiagnoses as treatment resistant depression or Alzheimer's disease are frequent. As the disease advances, behavioural rigidity, disinhibition, loss of social skills, fatuousness, emotional lability and impulsivity often develop, accompanied by executive dysfunction, decreased verbal fluency, impaired abstraction, difficulty shifting set and motor and verbal perseveration and stereotypies. Hyperorality and development of a sweet tooth are characteristic. Disproportionate frontal atrophy may be evident on MRI (fig 1C), however this is often subtle.

Semantic dementia resembles a progressive fluent aphasia, with increasingly empty and circumlocutory (but grammatically correct) speech due to loss of semantic knowledge about the meanings of words and objects.[25] Anatomically, it is characterised by focal, predominantly left anterior temporal lobe atrophy (fig 1B): this asymmetry and the existence of an anteroposterior gradient of atrophy can distinguish semantic dementia from Alzheimer's disease on MRI.[26] For unknown reasons, selective right anterior temporal atrophy is observed much more rarely; it presents as a progressive difficulty interpreting facial expressions and emotions, facial impassivity, loss of empathy, and behavioural symptoms.[27] Primary progressive non-fluent aphasia manifests as an insidious deterioration in speech production with phonemic and syntactic errors and word-finding difficulties, frequently accompanied by orofacial apraxia. It is associated with circumscribed left perisylvian atrophy.[28] In these focal

Table 2 Causes of young onset dementia: sporadic and acquired (bold, treatable condition; * , often absent)

	Clues to diagnosis	
Disease	**Clinical features**	**Investigations**
Primary neurodegenerations		
Alzheimer's disease	History of becoming lost, biparietal signs	EEG: absent α rhythm MRI: early hippocampal atrophy
Frontotemporal lobar degenerations:		
Frontotemporal dementia	Early behavioural change, frontal features	EEG: preserved α rhythm
Semantic dementia[25]	Early circumscribed semantic impairment	MRI: selective anterior left temporal atrophy
Primary progressive non-fluent aphasia[28]	Progressive speech production impairment	MRI: circumscribed left perisylvian atrophy
Frontal dementia (motor neurone disease)[29]	Orofacial apraxia, bulbar features, fasciculations (especially deltoid), amyotrophy	EMG: changes of denervation*
Dementia with Lewy bodies[30]	Visual hallucinations, extrapyramidal syndrome, fluctuation	
Multiple system atrophy[71]	Dysautonomia, cerebellar, extrapyramidal features	MRI: midbrain atrophy, ''hot cross bun sign''* (increased signal in cerebellum, middle cerebellar peduncles, pons)
Corticobasal degeneration[72]	Early asymmetric apraxia and rigidity, dystonia, cortical sensory deficit, alien limb	
Parkinson's disease[73]	Established typical parkinsonian syndrome predating cognitive decline	
Progressive supranuclear palsy (Steele-Richardson-Olszewski)[72]	Early falls, vertical supranuclear gaze palsy, axial rigidity, no tremor	MRI: midbrain atrophy/hyperintensity*
Neurofilament inclusion body disease[23]	Rapidly progressive frontotemporal or corticobasal syndrome, early falls, mutism	
Vascular		
Strategic infarct[42]	Discrete thalamic, basal ganglia, or capsular infarct	Computed tomography/MRI: discrete infarction
Multiple cortical infarcts	Stepwise cognitive decline; predisposing factors	
Small vessel disease	Predisposing factors, brisk facial reflexes, frontal gait disorder	Computed tomography/MRI: lacunar state (generally involving basal ganglia and brainstem)
Prion		
Classical Creutzfeldt-Jakob disease[34]	Rapid, florid myoclonus, cortical blindness	EEG: triphasic periodic complexes MRI: basal ganglia high signal
Iatrogenic Creutzfeldt-Jakob disease[36]	History of dural or corneal grafts, exposure to donor human growth hormone; features as in sporadic Creutzfeldt-Jakob disease	CSF: positive 14-3-3 protein
New variant Creutzfeldt-Jakob disease[38]	Rapid, early psychiatric symptoms, dysaesthesiae	MRI: pulvinar sign
Inflammatory		
Multiple sclerosis[52]	History of acute demyelinating episodes*, frontal-subcortical features, absent abdominal reflexes	VERs/BAERs/SSEPs: delayed MRI: demyelinating changes in brain (corpus callosum involved) and/or spinal cord CSF: unmatched oligoclonal bands
Vasculitis associated with systemic disorders	Rapid course, headache, fluctuation, seizures, systemic features	EEG: slowing of rhythms MRI: ischaemic lesions CSF: >3 cells, oligoclonal bands
Primary angiitis of central nervous system*[47]	Rapid course, headache, seizures, fluctuation	EEG: slowing of rhythms MRI: ischaemic lesions CSF: >3 cells, oligoclonal bands
Neurosarcoidosis[74]	Systemic features, uveitis, hypothalamic dysfunction, cranial nerve signs, or polyradiculopathy	CXR: various patterns MRI: white matter lesions ± meningeal enhancement CSF: chronic lymphocytic meningitis
Behçet's disease[75]	Racial predilection (especially Turkish/Japanese), oral and genital ulcers, uveitis, skin lesions; posterior circulation strokes	MRI: brainstem, basal ganglia lesions CSF: chronic lymphocytic meningitis
Neoplastic/paraneoplastic		
Tumours (especially frontal/callosal, midbrain)[76]	Signs of raised intracranial pressure*, focal neurological signs, frontal disconnection syndromes	Computed tomography/MRI: mass lesion(s)
Limbic encephalitis[56]	Often smoker, constitutional upset, weight loss, rapid course, prominent behavioural changes, hallucinations, seizures	MRI: abnormal temporal lobe signal CSF: oligoclonal bands Serum: positive antineuronal/antivoltage gated potassium channel antibodies
Infections		
Tuberculosis/fungal/''atypical'' meningitis[77]	Risk factors* (including racial origin in tuberculosis, immunosuppression); systemic features, chronic meningitis ± cranial nerve signs	CXR: frequently abnormal Computed tomography/MRI: may have mass lesions (tuberculoma) CSF: lymphocytic meningitis
HIV (AIDS-dementia complex)[53]	Risk factors; systemic features, AIDS related illnesses, advanced immunosuppression, gait disorder, seizures	MRI: confluent white matter changes Serum: positive HIV serology, low CD4 count
Whipple's disease[78]	Arthralgia, gut symptoms, facial movement disorder (oculomasticatory myorrhythmia)	CSF: positive Whipple's polymerase chain reaction
Lyme disease[79]	Suspicion of tick bite/travel to endemic area, skin lesion, arthritis, radiculopathies/ mononeuropathies	CSF: lymphocytic meningitis Serum: positive Lyme serology*

Table 2 Continued

Disease	Clues to diagnosis: Clinical features	Clues to diagnosis: Investigations
Neurosyphilis[62]	Risk factors (now rare); chronic meningitis, multiple strokes, Argyll Robertson pupils (light-near dissociation), tremor, seizures, dorsal column signs (tabes dorsalis)	CSF: mononuclear pleocytosis, oligoclonal bands Serum: positive syphilis serology
Subacute sclerosing panencephalitis[80]	Usually child or adolescent; history of measles, rapid course, florid myoclonus and seizures	EEG: periodic burst suppression CSF: oligoclonal bands (measles specific antibody)
Progressive multifocal leukoencephalopathy[81]	Immunosuppression/haematological malignancies, posterior cortical syndrome	MRI: confluent posterior white matter changes CSF: positive JC virus polymerase chain reaction
Metabolic[62]		
Endocrinopathies	Clinical and/or biochemical features of specific diagnosis	
Nutritional deficiency	History of food faddism, features of malabsorption	
Uraemia	Usually obvious from clinical setting	
Hepatic encephalopathy	Usually obvious from clinical setting	
Epilepsy[61]	Discrete episodes, fluctuating course, topographical amnesia	EEG: epileptiform discharges (especially temporal lobe origin) MRI: abnormal mesial temporal signal
Alcohol[50]	Usually obvious from clinical setting; may be associated nutritional deficiency	
Toxic (including carbon monoxide poisoning,[82] lead,[83] prescribed drugs including lithium,[84] interferon α[85]	Suspicion of overt or covert exposure (for example, occupational/environmental, recreational drug use)	Specific screens if available
Post-irradiation[86]	History of cranial irradiation (may be delayed), corticospinal signs, ataxia, seizures	MRI: confluent white matter changes
Other		
Obstructive sleep apnoea[87]	Obesity, morning headaches, daytime somnolence, excessive snoring	Sleep study: findings consistent with obstructive sleep apnoea
Chronic subdural haematoma[62]	History of head trauma*, frontal-subcortical signs	Computed tomography: subdural haematoma (may be isodense depending on chronicity; may be bilateral)
Hydrocephalus (any cause)[62]	History of meningitis, subarachnoid haemorrhage or neurosurgical procedure; gait apraxia, urinary incontinence	Computed tomography/MRI: findings of hydrocephalus (disproportionate ventricular enlargement) and/or causative lesion
Dementia pugilistica[88]	History of repeated head trauma; parkinsonism	

BAERs, brainstem auditory evoked potentials; CSF, cerebrospinal fluid; CXR, chest radiograph; EEG, electroencephalography; EMG, electromyography; MRI, magnetic resonance imaging; SSEPs, somatosensory evoked potentials; VERs, visual evoked potentials.

syndromes, other cognitive functions are typically well preserved at presentation; generalised intellectual decline tends to occur only at the later stages of the illness. FTLD may be associated with motor neurone disease; the age of onset is similar to that of classical motor neurone disease, and frontal dementia (often associated with expressive language difficulties) commonly precedes the development of amyotrophy. Dysarthria and dysphagia caused by progressive bulbar palsy may develop rapidly, and progression is more rapid than in FTLD alone.[29]

Lewy body dementia

Lewy body dementia appears to be relatively uncommon in younger populations; the clinical presentation is similar to that in older patients, with fluctuating cognitive impairment, vivid visual hallucinations, parkinsonian symptoms, frontal-subcortical features, and autonomic instability.[30] The tempo of evolution is usually similar to Alzheimer's disease; occasional patients show a rapid clinical course. Lewy bodies are neuronal inclusions, composed of abnormally phosphorylated neurofilament proteins aggregated with ubiquitin and α-synuclein, that are deposited widely in brainstem nuclei, paralimbic, and neocortical areas. Neuritic plaques similar to those in Alzheimer's disease are frequent. Involvement of cholinergic projection pathways produces a profound cholinergic deficit.

Huntington's disease

Huntington's disease is caused by the expansion of a CAG trinucleotide repeat sequence on the short arm of chromosome 4.[31] It is inherited in autosomal dominant fashion, penetrance is complete, and new mutations are very rare; most apparently sporadic cases reflect an incomplete family history or non-paternity. The prevalence in Europe is approximately 0.5–8/100 000.[32] The gene encodes a protein, huntingtin, of unknown function. Pathologically, there is neuronal loss and gliosis mainly affecting the frontal lobes and the caudate nucleus; polyglutamine nuclear inclusions are present. Onset is generally in middle life, with relentless progression of cognitive and behavioural decline in most cases. Neuropsychiatric symptoms of depression, apathy, aggression, disinhibition, and social disintegration are common and may predate chorea and other extrapyramidal signs[33]; a subcortical dementia with gaze apraxia typically develops. Bilateral atrophy of the head of the caudate nucleus may be seen on brain imaging. Diagnostic and predictive genetic testing is now widely available.

Prion dementias

The prion diseases are transmissible neurodegenerations characterised pathologically by diffuse brain spongiosis and deposition of an abnormal fibrillar prion glycoprotein, PrP, which is encoded by the PRNP gene on chromosome 20.[34]

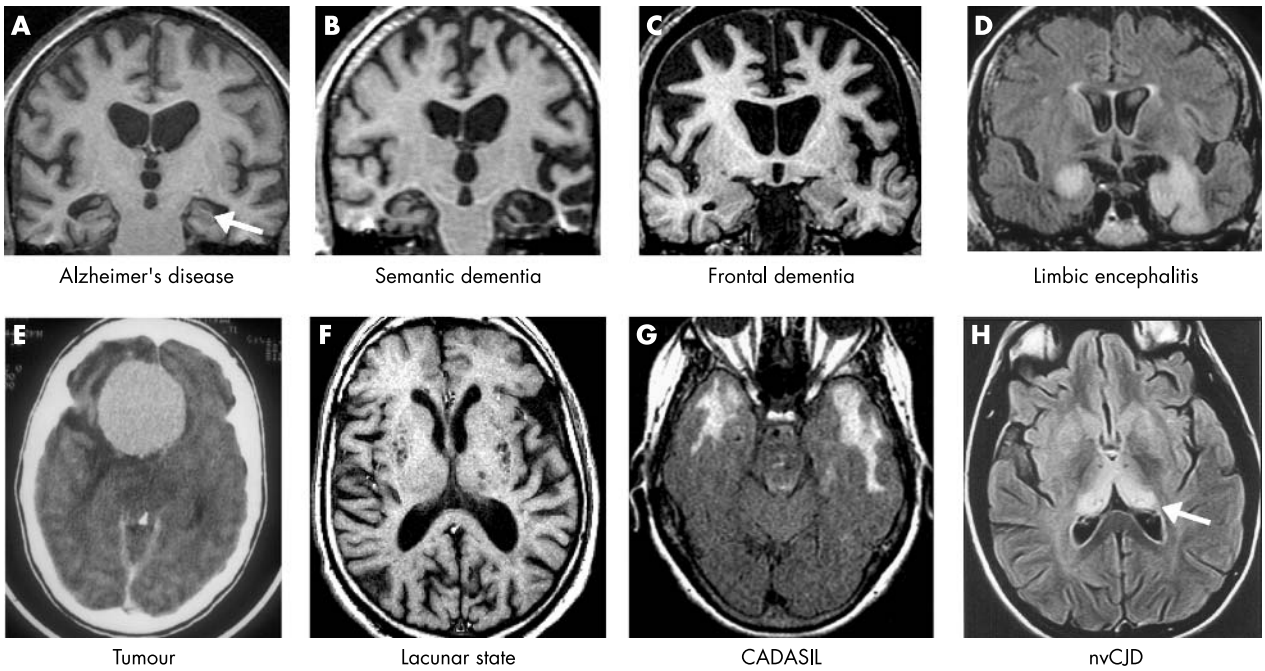

Figure 1 Coronal (above) and axial (below) views of brain imaging findings in selected young onset dementias (images reproduced by kind permission of Dr Hadi Manji and Dr Nick Fox, Institute of Neurology). All images are presented in radiological convention (the left hemisphere is on the right). (A) Magnetic resonance imaging (MRI), T1 sequence of Alzheimer's disease: disproportionate bilateral atrophy of hippocampi (white arrow). (B) MRI, T1 sequence, semantic dementia variant of frontotemporal lobar degeneration: disproportionate, asymmetric atrophy of anterior left temporal lobe. (C) MRI, T1 sequence, frontal variant of frontotemporal lobar degeneration: diffuse bilateral frontal atrophy relatively sparing temporal lobes. (D) MRI, fluid attenuated inversion recovery (FLAIR) sequence, paraneoplastic limbic encephalitis: focal bilateral alteration in mesial temporal lobe signal. (E) Computed tomogram, large frontal meningioma. (F) MRI, T1 sequence, small vessel disease: multiple lacunes in cerebral white matter and basal ganglia. (G) MRI, FLAIR sequence, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL): bilateral abnormal high signal in anterior temporal lobes. (H) MRI, FLAIR sequence, new variant Creutzfeldt-Jakob disease (nvCJD): bilateral abnormal high signal focally affecting posterior thalami (''pulvinar sign''; white arrow).

Different PrP conformations and glycosylation patterns give rise to various strains, which show species specificity. The paradigm for these disorders is scrapie, a disease of sheep and goats, for which analogues exist in a number of other species. Human prion diseases, occur in sporadic (approximately 90% of cases), acquired (generally iatrogenic), and inherited forms. Creutzfeldt-Jakob disease (CJD) is the most common, with an approximate incidence of one case per million worldwide. Kuru, described in the Fore linguistic group of New Guinea highlanders, was transmitted by ritual cannibalism; the disease has largely disappeared since this practice was abolished in the 1950s, although occasional new cases may occur, suggesting a very long presymptomatic phase. The inherited prion diseases comprise familial CJD, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, and atypical Alzheimer-like illnesses. All have autosomal dominant inheritance.

Prion diseases are examples of ''conformational dementias'',[35] arising from the aggregation of a conformational isomer (PrP^{Sc}) of the native prion protein, PrP^{C}. Sporadic disease results from rare spontaneous post-translational conversions of PrP^{Sc} to PrP^{C}, whereas the inherited prion diseases arise from mutations in the PRNP gene. Due to its relative insolubility, resistance to digestion by intracellular proteases and propensity to self aggregate, the PrP^{Sc} isomer accumulates in neurones as β-sheet amyloid fibrils (quite distinct from the amyloid deposited in Alzheimer's disease, which is composed of Aβ peptide). The mechanisms by which accumulation leads to cell death remain unclear. There are approximately 270 well documented cases worldwide in which CJD has been transmitted to humans by neurosurgical procedures, dural and corneal grafts, and pooled donor pituitary extract before the advent of recombinant human growth hormone[36]; presumably such iatrogenic cases result from ''seeding'' of the conformational conversion by introduced PrP^{Sc}. Susceptibility to acquired and sporadic CJD is determined by a common polymorphism (valine or methionine) at codon 129 of the PRNP gene, heterozygotes being relatively protected against development of disease.

Intense interest in the human prion diseases has been generated by growing concern that so-called new variant Creutzfeldt-Jakob disease (nvCJD), first identified in the United Kingdom in 1996,[37] was transmitted by ingestion of beef products contaminated with central nervous tissue from cattle with bovine spongiform encephalopathy (BSE), then epidemic in Britain. A number of lines of evidence including molecular strain typing and transmission studies in animals, indicate that BSE and nvCJD are caused by the same prion strain.[38] To date, a small but steadily increasing number of cases have appeared in the United Kingdom; the full public health implications are yet to be realised. New variant CJD is histopathologically distinct from the sporadic disease, with characteristic ''florid plaques''. All patients so far have been homozygous for methionine at codon 129 of the PRNP gene (compared with approximately 40% of controls and 80% of patients with sporadic CJD), and no mutation has been identified.

Clinically, classical (sporadic) CJD is a rapidly progressive dementia of middle life, generally proceeding relentlessly to death within six months, although some patients have a more prolonged course. Prodromal insomnia, depression, and general malaise are common. Myoclonus generally becomes prominent, and may be accompanied by seizures, extrapyramidal signs, cerebellar ataxia, and cortical blindness. In

Table 3 Causes of young onset dementia: inherited (bold, treatable condition; *, various combinations possible; †, neurological manifestations usually treatment resistant)

Disease	Chromosome and inheritance pattern	Protein	Cardinal features*				
			Ataxia	Pyramidal signs	Extrapyramidal syndrome	Peripheral neuropathy	Other
Neurodegenerations							
Alzheimer's disease[7]	21	APP (rare)	−	−	−	−	Biparietal signs, myoclonus
	14	Presenilin 1					EEG: loss of α rhythm
	1	Presenilin 2 (Volga Germans)					MRI: early hippocampal atrophy
FTDP-17[20]	17 AD	Tau	−	−	+	−	May have amytotrophy EEG: preserved α rhythm
Familial frontotemporal dementia	17[89] or NK AD	NK	−	−	−	−	EEG: preserved α rhythm
	9[90] AD	NK	−	−	−	−	Association with inclusion body myopathy and Paget's disease
Familial non-specific dementia[91]	3 AD	NK	−	+	+	−	Danish kindred FTLD, neurological signs late
Dementia (motor neurone disease)[92]	9 AD	NK	−	+	−	−	Orofacial apraxia, bulbar features, fasciculations (especially deltoid), amyotrophy
Huntington's disease[33]	4 CAG triplet repeat AD	Huntingtin	+	−	+	−	Various movement disorders possible, gaze apraxia MRI: atrophy of caudate head
Dentato-rubro-pallido-luysian atrophy[93]	12 AD	Atrophin 1 CAG triplet repeat disorder	+	−	+	−	Seizures More common in Japanese
Neuroacanthocytosis[94]	9 or X-linked	Chorein (chromosome 9) XK protein (X-linked)	+	−	+	+	Orofacial movement disorder, seizures Acanthocytes on wet smears Raised serum creatine kinase
Familial encephalopathy with neuroserpin inclusion bodies[95]	3 AD	Neuroserpin	−	−	−	−	Frontal-subcortical dementia Collins bodies (intraneuronal inclusions)
Neuroferritinopathy[96]	19 AD	Ferritin light polypeptide	−	−	+	−	Palatal tremor MRI: iron in basal ganglia
Hallervorden-Spatz (PKAN)[97]	20 AR	Pantothenate kinase (PANK2)	+	+	+	+	Seizures MRI: ''eye of the tiger'' (iron in globus pallidus)
Spinocerebellar ataxias[98]	Various CAG triplet repeats AD	Various	+	+	+	+	Often abnormal saccades; predominant executive dysfunction, usually mild
Metabolic							
Wilson's disease[55]	13 AR	Human copper-transporting ATPase ATP7B	+	−	+	−	Psychiatric disturbances, corneal Kayser-Fleischer rings Cirrhosis, haemolytic anaemia MRI: ''face of the giant panda'' sign Decreased serum copper and caeruloplasmin, increased urinary copper excretion

Table 3 Continued

Disease	Chromosome and inheritance pattern	Protein	Cardinal features*				
			Ataxia	Pyramidal signs	Extrapyramidal syndrome	Peripheral neuropathy	Other
Cerebrotendinous xanthomatosis[99]	2 AR	Mitochondrial sterol 27-hydroxylase	+	+	+	+	Tendon xanthomas, cataracts Characteristic MRI features Raised levels of cholestanol (bile acid intermediate) in serum, nervous tissue, tendons
Ornithine transcarbamylase deficiency[100]	X-linked	Ornithine transcarbamylase (urea cycle enzyme)	+	+	−	−	Episodes of unexplained vomiting and stupor, hyperammonaemia
Prion							
Creutzfeldt-Jakob disease[34]	20 (PRNP) AD Mutation codon 178 (codon 129 val)	Prion protein	+	+	+	−	Florid myoclonus, cortical blindness Periodic triphasic complexes on EEG MRI: basal ganglia high signal
Gerstmann-Sträussler-Scheinker	Mutation codon 102		+	+	+	−	May have gaze palsy, deafness, pseudobulbar palsy, cortical blindness
Fatal familial insomnia	Mutation codon 178 (codon 129 methionine)		+	+	−	−	Disordered sleep, oneiric behaviour, dysautonomia, myoclonus
Vascular/arteriopathies							
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[43]	19 AD	Notch3	In context of vascular events			−	Psychiatric disturbances, migraine, strokes Lack of conventional risk factors MRI: anterior temporal and external capsule high signal Osmophilic perivascular material on electron microscopy of skin, muscle, peripheral nerve, brain
Fabry's disease[101]	X-linked	Alpha-galactosidase A	In context of vascular events			+	Small vessel disease Renal disease, skin changes (angiokeratoma corporis diffusum), extremity pain
Cerebral amyloid angiopathies:[46]							
British (Worster-Drought)[45]	13 point mutation AD	BRI	+	+	−	−	MRI: prominent white matter disease (no haemorrhages)
Danish	13 duplication AD		+		−	−	Cataracts, deafness
Dutch (HCHWA-D)	21	APP	−	−	−	−	Recurrent lobar cerebral haemorrhages
Icelandic (HCHWA-I)	20	Cystatin C	−	−	−	−	
Meningovascular	18	Transthyretin	+	+	−	−	
Lysosomal storage disorders							
Adult GM2 gangliosidosis[102]	15/5 AR	Hexosaminidase A	+	+	+	+	Amyotrophy Particularly common in Ashkenazi Jews
Globoid cell leukodystrophy (Krabbe's)[103]	14 AR	Galactocerebrosidase	+	+	−	+	Visual loss Characteristic MRI features
Niemann-Pick type C[104]	18 AR	NPC1 protein	+	−	+	−	Psychosis, vertical supranuclear gaze palsy, seizures Organomegaly Sea-blue histiocytes on bone marrow biopsy Abnormal cholesterol esterification in cultured fibroblasts

Table 3 Continued

Disease	Chromosome and inheritance pattern	Protein	Cardinal features* Ataxia	Pyramidal signs	Extrapyramidal syndrome	Peripheral neuropathy	Other
Metachromic leukodystrophy[105]	22	Arylsulphatase A	+	+	+	+	May have early behavioural changes; wide range of age at onset
	AR						MRI: white matter changes
							Urinary metachromatic deposits
Gaucher's type 3[106]	1	Glucocerebrosidase	+	+	+	−	Horizontal supranuclear gaze palsy, progressive myoclonic epilepsy†
	AR						Bone pain, hepatospenomegaly, anaemia, thrombocytopenia
							Increased plasma non-prostatic acid phosphatase
							Gaucher's cells in bone marrow
Ceroid lipofuscinosis (Kufs')[107]	NK various	NK	+	−	+	−	Psychiatric features, progressive myoclonic epilepsy, facial dyskinesias
Sialidosis (mucolipidosis I)[108]	6	Sialidase (alpha-*N*-acetyl neuraminidase)	+	−	−	−	Progressive myoclonic epilepsy, retinal cherry red spot
	AR						
Adult Pelizaeus-Merzbacher[109]	X-linked	Proteolipid	+	+	+	−	MRI: cerebral demyelination
Peroxisomal storage disorders							
Adrenoleukodystrophy[110]	X-linked	Adrenoleukodystrophy protein	+	+	−	+	Adrenal insufficiency
							MRI: diffuse cerebral white matter change
							Increased plasma very long chain fatty acid esters
Other storage disorders							
Lafora body disease[111]	6	Laforin	+	−	−	−	Progressive myoclonic epilepsy
	AR						Lafora bodies on axillary skin biopsy
Adult polyglucosan body disease[112]	Various	Various (including glycogen branching enzyme)	+	+	+	+	Urinary incontinence
	AR						Polyglucosan bodies on axillary skin biopsy
Mitochondrial disorders[6]							
	mtDNA or nuclear DNA	Respiratory chain components	+	+	+	+	Various phenotypes (mixtures common); brain infarcts, cerebral white matter disease, seizures, myopathy, CPEO, sensorineural hearing loss, fundal abnormalities
	Various (often maternal)						Diabetes mellitus, lactic acidosis, short stature
							May have ragged red fibres on muscle biopsy
Novel mechanisms							
Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy: Nasu-Hakola[113]	19 or NK	DAP12	−	+	−	−	Frontal dementia and bone cysts, postural dyspraxia
	AR						MRI: atrophy, periventricular high signal

AD, autosomal dominant; APP, amyloid precursor protein; AR, autosomal recessive; CPEO, chronic progressive external ophthalmoplegia; EEG, electroencephalography; FTDP-17, frontotemporal dementia parkinsonism linked to chromosome 17; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NK, not known.

Table 4 Differential diagnosis of rapidly progressive dementia

Reversible processes
Non-convulsive status epilepticus
Cerebral vasculitis/other inflammatory conditions
Non-inflammatory cerebrovascular disease
Drug toxicities (especially lithium)
Tuberculosis/fungal meningitis
Parenchymal Whipple's disease
Chronic subdural haematoma/cerebral tumour
Paraneoplastic limbic encephalitis (may improve with treatment of tumour)
Antivoltage gated potassium channel antibody syndrome[59]
?Hashimoto's encephalopathy
Irreversible processes
Rapidly progressive neurodegenerative variants:
Dementia with Lewy bodies, multiple system atrophy, Alzheimer's disease
Dementia (motor neurone disease) syndromes
Neurofilament inclusion body disease[23]
Prion diseases:
Sporadic, familial, and new variant Creutzfeldt-Jakob disease
Progressive multifocal leukoencephalopathy
Subacute sclerosing panencephalitis (sequela of measles)

nvCJD, psychiatric disturbances and limb dysaesthesiae are often early features, and the spectrum of cognitive and neurological deficits is similar to sporadic disease, however patients as a group have been younger and the course tends to be more indolent, with a median survival of 14 months. Familial CJD is clinically indistinguishable from sporadic CJD; the other inherited prion diseases have characteristic clinical features (early prominent cerebellar ataxia in Gerstmann-Sträussler-Scheinker syndrome and progressive insomnia with dysautonomia in fatal familial insomnia), although genotype:phenotype correlation is problematic.

The differential diagnosis is limited but includes a number of potentially treatable causes of rapidly progressive dementia (table 4). In advanced sporadic (though not new variant) CJD, the electroencephalogram frequently shows characteristic triphasic periodic (1–2 Hz) complexes superimposed on a slow, disorganised background cerebral rhythm. Routine examination of cerebrospinal fluid is generally unremarkable; markers of rapid neuronal destruction such as the 14-3-3 protein are frequently raised in sporadic CJD, though not in nvCJD. A number of brain MRI abnormalities have been described[39]: in sporadic CJD, high signal changes in putamen and caudate head and cortical hyperintensity on FLAIR sequences, and in nvCJD, increased signal in the pulvinar (fig 1H). In nvCJD, prion protein immunostaining is positive in lymphoid tissue, and the diagnosis can be made reliably on tonsillar biopsy.[40] Lymphoid staining is negative in sporadic CJD, and a brain biopsy is required to exclude a potentially treatable, inflammatory disorder if there are atypical features. After discussion with the patient's relatives, genetic typing of prion proteins in peripheral white blood cells for epidemiological and research purposes should be undertaken in sporadic and nvCJD, and mutation analysis with formal genetic counselling in familial cases.

VASCULAR DEMENTIA

Vascular dementia is a common cause of YOD.[2] Patients developing young onset vascular dementia may lack conventional vascular risk factors, and unusual haematological, metabolic, and genetic causes (tables 2 and 3) should always be considered. Diagnosis is based on the clinical picture, brain imaging findings, and the identification of predisposing factors; however, no standard diagnostic criteria, even for neuropathology, are yet available.[41] Three broad clinicopathological syndromes have been described. Strategic infarcts especially involving the thalamus, basal ganglia, or internal capsule may produce a frontal-subcortical disconnection.[42] Multiple cortical infarcts lead to stepwise erosion of cognitive function with a mixture of cortical and subcortical impairments. Small vessel disease produces a clinical syndrome of subcortical frontal executive dysfunction, gait ''apraxia'', pseudobulbar palsy and urinary incontinence, associated with brain imaging findings (fig 1F) of lacunes in deep grey matter nuclei and leukoaraiosis (diffuse white matter ischaemic changes) and histopathological features of deep periventricular ischaemic demyelination (''Binswanger's disease''); this form of vascular dementia presents insidiously, often without a history of stroke.

A number of genetic arteriopathies are recognised. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)[43] is an uncommon cause of young onset subcortical strokes and dementia (mean age of onset 45 years) associated with migraine and psychiatric symptoms, which may be the presenting feature. The clinical picture is highly variable within families. MRI reveals diffuse white matter lesions of the cerebral hemispheres, notably the anterior temporal lobes and external capsules (fig 1G). CADASIL is caused by mutations of the Notch3 gene on chromosome 19. Light microscopy of skin biopsies may reveal non-specific periodic acid Schiff staining of vessel walls and electron microscopy frequently demonstrates characteristic granular osmophilic material of uncertain origin in proximity to vascular smooth muscle cells in skin, muscle, peripheral nerve, and brain. Genetic testing may be diagnostic; immunostaining of skin biopsies using Notch3 monoclonal antibody is a promising alternative diagnostic test.[44] Various hereditary cerebral amyloid angiopathies have been identified (table 3): these include the familial British and Danish dementias associated with mutations in the BRI gene on chromosome 13 which produce complex neurological syndromes.[45 46]

CEREBRAL VASCULITIS

Vasculitis rarely affects the central nervous system in isolation but must always be considered as it is a potentially treatable cause of YOD.[47 48] The differential diagnosis is wide (table 4) and includes primary vasculitides such as Wegener's granulomatosis, temporal arteritis, polyarteritis nodosa, and Churg-Strauss syndrome; systemic diseases that may produce vasculitis such as systemic lupus, sarcoidosis, Behçet's disease and cryoglobulinaemia; infectious agents such as herpes zoster; and other rare conditions such as intravascular lymphoma. Special mention should be made of primary angiitis of the central nervous system, which is almost exclusively confined to brain and less commonly spinal cord; the aetiology remains unknown, however pathologically there is patchy inflammation (which may be granulomatous, necrotising or lymphocytic) preferentially affecting small leptomeningeal and parenchymal vessels. Clinical presentations are highly variable, ranging from an acute encephalopathy and multiple sclerosis-like illnesses to an indolent subcortical dementia. Headache is common but not universal; symptoms may fluctuate, and seizures may occur. Findings on investigation that suggest cerebral vasculitis include raised inflammatory markers and/or autoantibodies, vascular lesions on brain imaging, an encephalopathic electroencephalogram, cerebrospinal fluid pleocytosis with unmatched oligoclonal bands, and beading of vessels on cerebral angiography; however, none in isolation can substitute for histopathology, and unconfirmed suspicion of cerebral vasculitis remains one of the few indications for biopsy of brain and meninges before committing the patient to immunosuppressive therapy.

Table 5 Investigation of the young patient with suspected dementia (* , specific counselling required; †, see table 3)

Investigation		Rationale
Routine		
Neuropsychometry		Delineation of cognitive syndrome, identification of ''subclinical'' areas of impairment
Haematology	Full blood count	Screen for anaemia, polycythaemia, eosinophilia
Inflammatory markers	Erythrocyte sedimentation rate/C-reactive protein	Screen for inflammatory process
Biochemistry	Urea and electrolytes, renal function, liver function, thyroid function, B12 and folate, lipids	Screen for treatable causes of dementia and vascular risk factors
Treponemal serology		Exclude tertiary syphilis
Immunology	ANCA , thyroid antimicrosomal, antigastric parietal, antiphospholipd, antineuronal, VGKC, serum electrophoresis	Screen for vasculitides, atrophic gastritis, Hashimoto's encephalopathy, paraneoplastic syndromes
Imaging	Chest radiography	Screen for pulmonary neoplasm, tuberculosis, some systemic disorders (for example, sarcoid)
	Brain computed tomography	Generalised atrophy, large space occupying lesions
	Brain MRI	Visualisation of regional atrophy and signal change
Neurophysiology	Electroencephalography	May help distinguish Alzheimer's from frontotemporal dementia (loss of α rhythm); diagnosis of CJD, epilepsy, acute encephalopathies
Cardiac	Electroencephalography, echocardiography	May reveal cardiac arrythmia or sources of emboli
For specific indication		
Copper studies	Slit lamp examination, serum caeruloplasmin, serum copper, 24 hour urine copper excretion	Wilson's disease where clinical suspicion or patient <age 40
Thrombophilia screens		Unexplained cerebrovascular disease
White cell enzymes†		Metabolic disorder/patient <age 40
Plasma long chain fatty acids		Metabolic disorder/patient <age 40
Heavy metal screens		Chronic intoxication
Drug screens		Chronic illicit drug use
HIV serology		Risk factors*
Genetic testing†		For mutation analysis where specific genetic disorder suspected*
Imaging	Computed tomography of chest/abdomen, whole body PET	To identify neoplasm in suspected paraneoplastic syndrome
	Brain SPECT/PET	Occasionally if normal structural imaging (usually suspected frontal dementias)
	Gallium scan	Some inflammatory disorders (for example, sarcoidosis)
	Gadolinium brain MRI	Meningeal enhancement after contrast
Neurophysiology	EEG telemetry	Frequent covert seizures
	EMG	Motor neurone disease/amyotrophy
	Sphincter EMG	Multiple system atrophy
	VERs/BAERS/SSEPs	Demyelination; characteristics of myoclonus
Sleep study		Obstructive sleep apnoea
Cerebrospinal fluid examination	Glucose, cell count, protein, electrophoresis for oligoclonal bands	Any rapidly progressing or unusual dementia and/or patient <age 55
	Human herpes virus serology	Infection (especially if complex partial seizures)
	Whipple's polymerase chain reaction	Infection (especially if oculofacial movement disorder)
	Measles antibodies	Subacute sclerosing panencephalitis
	JC virus polymerase chain reaction	PML
	Neuronal marker proteins	14-3-3 in setting of rapid neuronal destruction (for example, CJD); S100, tau in research settings
Tissue biopsy	Skin	CADASIL; some storage diseases (for example, Kufs'; must have axillary skin for apocrine sweat glands)
	Muscle	Vasculitis; mitochondrial disease
	Small bowel	Whipple's disease; coeliac disease
	Bone marrow	Niemann-Pick type C; lymphoma/other haematological malignancies
	Tonsil	New variant CJD
	Brain (cortex, white matter + meninges)	Cerebral vasculitis

ANCA, antineutrophil cytoplasmic antibodies; BAERs, brainstem auditory evoked potentials; EEG, electroencephalography; EMG, electromyography; PET, positron emission tomography; PML, progressive multifocal leukoencephalopathy; SPECT, single photon emission tomography; SSEPs, somatosensory evoked potentials; VERs, visual evoked potentials; VGKC, voltage gated potassium channel antibodies.

OTHER CAUSES

Alcohol related dementia

Progressive intellectual deterioration is part of the spectrum of neurological and psychiatric sequelae of chronic alcohol abuse and represents a substantial social burden (table 1)[2]; improvement may occur if abstinence is achieved.[49] Executive function and autobiographical memory appear especially vulnerable and confabulation may occur. However, the concept of alcohol related dementia has raised considerable nosological difficulties: many patients have clinical features of Wernicke-Korsakoff syndrome (thiamine deficiency), other nutritional deficiencies, or hepatic encephalopathy.[50] Brain imaging often shows generalised cerebral atrophy with frontal predominance; however, appearances are non-specific. Neuropathological findings have been variable and heterogeneous, consistent with a multifactorial aetiology.[50]

Multiple sclerosis

Cognitive impairment may be the presenting feature of multiple sclerosis and it is common late in the course[51 52]; most cases have predominantly frontal executive dysfunction, resulting from frontosubcortical disconnection with extensive cerebral white matter disease. Intellectual deterioration generally progresses slowly, however cognitive

impairment is more severe in chronic progressive than in relapsing-remitting disease. Cognitive impairment correlates with total lesion load and degree of atrophy of the corpus callosum on MRI,[52] and probably reflects axonal loss rather than demyelination *per se*.

AIDS dementia complex

AIDS dementia complex should not be overlooked as a cause of YOD. It generally presents as a subcortical dementia associated with gait ataxia and seizures. Brain MRI reveals diffuse cerebral atrophy with white matter hyperintensities. It is probably the direct result of central nervous HIV infection, and it is a diagnosis of exclusion in patients with known AIDS who develop cerebral symptoms. It is associated with a relatively low CD4 count[53] and is seen less frequently since the advent of highly active antiretroviral therapy.[54]

Wilson's disease

Wilson's disease is a treatable cause of YOD. It is an autosomal recessive disorder of copper transport with a prevalence of approximately 1/50 000.[55] Accumulated tissue copper causes progressive toxicity to the nervous system, liver, blood, and other organs. Abnormalities in behaviour and personality, depression, and cognitive deterioration are common. Neurological manifestations include tremor, dystonia, chorea, ataxia, dysarthria, a characteristic grimacing facial expression, and the pathognomonic corneal Kayser-Fleischer ring (which may require slit lamp examination for detection). The diagnosis is confirmed by low serum caeruloplasmin and total copper levels and increased 24 hour urinary copper excretion. Treatment is based on copper chelation. Copper studies should be part of the routine work-up of any patient presenting with psychiatric illness, dementia, or a movement disorder before the fifth decade.

Paraneoplastic limbic encephalitis

The rare entity of paraneoplastic limbic encephalitis arises from an autoimmune response to tumour antigens and usually precedes diagnosis of the underlying malignancy. It is characterised by mood and personality changes, hallucinations, seizures and dementia,[56] often coupled with symptoms and signs referable to other areas of the nervous system (ataxia, sensory neuronopathy). Mesial temporal involvement is typical, however extralimbic areas (including hypothalamus and brainstem) are also frequently affected; histopathological features include inflammatory infiltrates and neuronal loss. Clues may include an inflammatory cerebrospinal fluid (with oligoclonal bands in the cerebrospinal fluid but absent in serum, indicating local immunoglobulin synthesis, in a high proportion), and focal temporal lobe abnormalities on MRI (fig 1D) and electroencephalography. Approximately 60% of cases have positive antineuronal antibodies (predominantly anti-Hu), and this finding mandates an exhaustive search for malignancy, usually including thoracoabdominal computed tomography or whole body positron emission tomography if available. The most common associated cancers are lung, testis, and breast. Therapeutic options are limited but some patients improve after treatment of the underlying malignancy.

Table 6 Voluntary societies offering advice and support to patients and carers

Society	Web address
Alzheimer's Society	http://www.alzheimers.org.uk
Pick's Disease (FTLD) Support Group	http://www.pdsg.org.uk
Huntington's Society	http://www.hda.org.uk
Gaucher's Association	http://www.gaucher.org.uk

''Steroid-responsive'' and autoimmune encephalopathies

A small proportion of patients with YOD improve with immunosuppressive therapy. The ''steroid-responsive encephalopathies'' are likely to represent a heterogeneous group of disorders which produce tissue damage via autoimmune mechanisms. This group is currently the focus of considerable interest and nosological controversy. Some patients may have an underlying cerebral vasculitis. Circulating autoantibodies can sometimes be identified (notably thyroid autoantibodies in ''Hashimoto's encephalopathy''), however their pathogenetic role remains undefined.[57] Similar reservations apply to dementia in association with antigliadin antibodies and coeliac disease.[58] The recent identification of autoantibodies directed against voltage gated potassium channels in patients with reversible dementia[59] raises the possibility that ion channel dysfunction plays a part in some cases.

AN APPROACH TO DIAGNOSIS IN YOUNG ONSET DEMENTIA

Clinical assessment

All young patients presenting with suspected dementia need specialist referral. As in any patient with dementia, a corroborating history should always be obtained, exploring different cognitive domains (not simply memory) and impact on work and daily life. It is particularly important to establish the mode of onset and tempo of evolution. A psychiatric history is mandatory because behavioural symptoms are frequently the presenting feature. Issues of safety need to be considered,[60] for example, whether the patient is still driving, or whether they have they developed aggressive or sexually disinhibited behaviours. The past medical and family history must be detailed; relatives who develop ''mental instability'' or personality change in younger life or unaccountably ''disappear'' may indicate a previously undiagnosed familial dementia. The physical examination must be thorough: although the neurological examination is often normal in the early stages of many degenerative dementias, the presence of additional pyramidal, extrapyramidal, and cerebellar signs will direct the diagnosis towards one of the ''dementia-plus'' syndromes (tables 2 and 3). The general examination may provide specific clues such as hepatosplenomegaly and evidence of treatable comorbidity such as hypertension. Where available, neuropsychometry is very valuable in delineating the cognitive syndrome in detail and in identifying involvement of cognitive domains that may not have been evident clinically, indicating a more widespread impairment.

It is sometimes difficult to distinguish between organic and functional cognitive symptoms. This applies to diseases in which behavioural and emotional disturbances are integral to the disease process (such as FTLD) or where neurological symptoms may appear bizarre (as in some biparietal presentations of Alzheimer's disease), as well as disorders in which prominent mood symptoms may be a manifestation of retained insight. The opposite error is also frequent, for example misdiagnosing Alzheimer's disease in a depressed patient whose presenting complaint is poor memory, or FTLD in schizophrenia with prominent negative symptoms. The mode of onset of the symptoms and previous psychiatric history are of particular importance. Certain symptoms and signs should always arouse suspicion of an organic process (for example, isolated visual hallucinations, incontinence, ataxia, micrographia, or frontal phenomena such as utilisation behaviour, perseveration, or echolalia). Clues to a psychiatric disorder include a relatively abrupt onset, the

Table 7 Acetylcholinesterase inhibitors currently licensed in United Kingdom

Drug	Dosage schedule		Side effects
	Start	Maintenance	
Donepezil (Aricept)	5 mg at night	10 mg at night	Usually minor; may include gastrointestinal upset, sedation, agitation, sleep disturbance, headache, muscle cramps, urinary incontinence, atrioventricular block
Rivastigmine (Exelon)	1.5 mg twice a day	Up to 6 mg twice a day	
Galantamine (Reminyl)	8 mg/day	Up to 12 mg twice a day	

presence of an identifiable emotional precipitant, and lack of progression. There may be inconsistencies on formal testing and performance inferior to that expected from the history (for example, the patient who, having found his way to clinic unaccompanied, is quite unable to recall test material or gives ''Don't know'' responses): in contrast, many FTLD patients perform well on formal testing despite social disintegration. However, in practice, the distinction between organic and psychiatric disease may be difficult and the possibility of an elaborated, underlying organic impairment should always be considered. Clinical reassessment over time is the key to resolving this dilemma.

Investigations

The first priority of investigation is the identification of a treatable process (table 5). In addition, accurate diagnosis has implications for prognosis and possibly genetic counselling of other family members. The standard dementia screen used in older patients needs to be supplemented by additional investigations (table 5). This applies particularly to dementia in young adults and adolescents: accurate diagnosis is worthwhile in this group, as some of these disorders are treatable or have substantial genetic implications, however specialised techniques such as white cell or fibroblast enzyme assays, tissue histochemistry, and electron microscopy and molecular genetic studies are often required (table 5).

Certain investigations, such as HIV serology and diagnostic genetic testing, require the consent of the patient and family after detailed discussion, and predictive genetic testing of family members requires formal genetic counselling in collaboration with a clinical genetics service. All patients with suspected YOD should have electroencephalography: this may assist diagnosis in the neurodegenerations (it is usually normal in FTLD) and is particularly important in detecting unrecognised complex partial seizures that may produce an epileptic pseudodementia.[61] The brain imaging modality of choice in YOD is MRI, which provides more accurate visualisation of regional atrophy (fig 1) and signal change than computed tomography. Computed tomography can however exclude hydrocephalus or large mass lesions (fig 1E). Cerebrospinal fluid examination is recommended for all younger patients and in cases where there is an unusual presentation or rapid course.[62] Tissue biopsies can be of value in a number of diagnoses such as skin in CADASIL and Lafora body disease, and muscle in mitochodrial cytopathies and Kufs' disease. Tonsillar biopsy can provide a definitive diagnosis in nvCJD.[40] Rarely cerebral biopsy (usually non-dominant frontal and including cortex, white matter, and meninges) is required if vasculitis is suspected. Quarantining of instruments is necessary if CJD is in the differential diagnosis.

PRINCIPLES OF MANAGEMENT

The management of the patient with YOD is complex and a multidisciplinary approach is essential. However, many areas in the United Kingdom lack specific services for YOD. Many patients with YOD lack insight and judgment and associated behavioural disturbances often place a heavy burden on carers. Patients with cognitive impairment who wish to drive are legally obliged to inform their car insurance company and the Driver Vehicle Licensing Agency, which will then make a decision as to whether the patient should hold a driver's license. Early diagnosis of YOD and a comprehensive social

Multiple choice questions (answers at end of references)

Q1. Regarding the epidemiology of young onset dementia
A. Lewy body dementia is the commonest cause
B. Alzheimer's disease is rare
C. Approximately 10% is alcohol related
D. Prion disease is rare

Q2. Characteristics of early onset Alzheimer's disease include
A. Early disinhibition and personality change
B. 75% of patients have a family history of dementia
C. Supranuclear gaze palsy
D. Parietal signs

Q3. Patients with frontotemporal lobar degeneration present with
A. Lack of insight
B. Hepatosplenomegaly
C. Disinhibition
D. Cerebellar ataxia

Q4. Which of the following investigations are mandatory in YOD
A. EEG
B. Genetic testing
C. Cerebral biopsy
D. Tonsillar biopsy

Q5. Cholinesterase inhibitors may be of symptomatic benefit in
A. Frontotemporal lobar degeneration
B. Vascular dementia
C. Alzheimer's disease
D. Huntington's disease

needs assessment allow patients and carers to plan for the future and make pre-emptive decisions such as living wills or enduring power of attorney while they still have legal capacity. Volunteer support groups for YOD patients and their carers are an important resource (table 6).

Non-pharmacological management

All behavioural problems need thorough assessment and an ''Antecedent, Behaviour, and Consequences'' (ABC) chart can be useful in documenting and then formulating management. Techniques include distraction by engaging the patient in activities (jigsaws and word puzzles may be particularly effective in FTLD), or environmental modifications such as restricting access to food. Occupational and speech therapists may be able to suggest alternative ways in which patients can communicate. In the later stages, physical dependency may increase greatly such that patients need intensive nursing from district nurses or residential nursing care; in this phase a palliative care approach may be appropriate. The question of brain donation should be visited sensitively with the family wherever practical.

Pharmacological management

Depression frequently occurs in YOD; mood symptoms should be inquired about specifically, and there should be a low threshold for treatment with antidepressants. Selective serotonin reuptake inhibitors are the class of choice as tricyclic compounds have anticholinergic effects and may worsen cognition. If the patient is severely agitated, there are psychotic symptoms, there is danger to the patient or others or all other behavioural measures have failed, the use of sedative or neuroleptic medication may be appropriate, however many patients (notably those with Lewy body dementia and FTLD[63]) are exquisitely sensitive to neuroleptics and can develop life threatening extrapyramidal syndromes. If absolutely necessary, atypical neuroleptics such as risperidone or olanzapine are preferable; these agents should be used for the shortest time possible, under close supervision, and at low dosage (for example, risperidone 0.5 mg twice a day).

Few specific therapies are available for most forms of YOD. Close attention to vascular risk factors can modify the course of vascular dementia and may also have a role in preventing progression of Alzheimer's disease. The prevalence of Alzheimer's disease is lower in patients receiving statins,[64] suggesting that these lipid lowering drugs may be protective against Alzheimer's disease, although the mechanism is unclear. Based on observations that raised plasma homocysteine is associated with an increased risk of developing Alzheimer's disease, it has been suggested that folate may have a protective effect; however this remains unproven.[65] The acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine (table 7) can be effective as symptomatic therapies to partly redress the cholinergic deficit in Alzheimer's disease and may delay entry to residential care, however they have not been shown to influence the underlying disease process. Overall probably fewer than 50% of patients will experience an improvement in cognitive function, however the drugs may also have benefits for activities of daily living, mood, and general wellbeing which are difficult to quantify. The drugs should be prescribed according to the current United Kingdom National Institute of Clinical Excellence[66] guidelines (for patients with Mini-Mental State Examination Score 12–26/30 and arrangements for recommended follow up and monitoring). Acetylcholinesterase inhibitors may also be helpful in Lewy body dementia[67] and vascular dementia,[68] although they are not currently licensed for use in these diseases. They may worsen behavioural disturbance in FTLD.[69] The *N*-methyl-D-aspartate receptor antagonist, Memantine (Ebixa) may reduce glutamate-mediated neuronal excitotoxicity and has produced modest symptomatic benefit in severe Alzheimer's disease[70]; it is now licensed for this indication in the United Kingdom.

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ANSWERS

1. C and D; 2. D; 3. A and C; 4. A; 5. B and C.