NEUROLOGICAL MANAGEMENT

Management of neurological disorders: dementia

M N Rossor

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Dementia is the clinical syndrome of impairment in multiple domains of cognitive function occurring in an alert patient. Some definitions of dementia demand that the cognitive impairment is progressive but for the clinician the static cognitive impairment arising after an encephalitic illness or head injury shares many of the problems of management encountered with the progressive dementias such as Alzheimer's disease. The dementias as a group constitute one of the commonest problems presenting to neurologists and psychiatrists and comprise the third leading cause of death.

The commonest causes of dementia—namely, Alzheimer's disease and vascular dementia—are predominantly diseases of elderly people. Recent epidemiological studies suggest a low prevalence of dementia in populations below the age of 70, being in the region of 1% in those aged between 50 and 70 years with a dramatic rise to about 50% in very elderly people.[1–3] Because dementia by definition means that cognitive impairment is sufficient to result in a loss of previous skills to the extent that the patient's normal, social, or work activity is compromised the dementing illnesses represent a major burden on society.

With an ageing population the number of patients with dementia is expected to rise. Based on demographic trends of those above the age of 80 in the United States it is anticipated that there may be 10–15 million people affected by Alzheimer's disease by the middle of the next century.[4] Estimates that include the rapidly ageing population in Japan and other Asian countries give global figures that may exceed one hundred million.[5] The same trend can be anticipated in the United Kingdom; there are currently over half a million people predicted to have Alzheimer's disease and a larger total with dementia. It should, however, be recognised that about 18 000 people below the age of 65 are believed to have Alzheimer's disease and if one considers the number of neurological illnesses in which cognitive dysfunction may also feature, such as multiple sclerosis or the extrapyramidal diseases, then the figure is clearly far higher.

A recent systematic cost of illness analysis of Alzheimer's disease in England has been undertaken.[6] This included estimates of inpatient/outpatient day care as well as residential care costs and arrived at a total figure of 1144 million pounds for 1992. Comparison with other burden of illness analyses and adjustment for overall United Kingdom costs makes Alzheimer's disease more expensive than epilepsy although less than stroke if community and non-NHS care costs are excluded. If these are included then the comparable figures are 1373 million pounds for Alzheimer's disease and 838 million pounds for stroke. Moreover, this analysis did not include the indirect costs to family carers over and above the benefits they received from Government agencies. The burden of informal care from family members is substantial.

Diagnosis

Published definitions of dementia all include the involvement of multiple domains of cognitive impairment with intact arousal mechanisms to distinguish the patient with dementia from one with a confusional state. Moreover, the cognitive impairment should be of sufficient severity to result in the loss of previously acquired skills such that this interferes with normal social or employment function.

The most widely used criteria are those of the American Psychiatric Association Diagnostic and Statistical Manual of which the latest (DSM IV) has just been published.[7] Such criteria can provide a useful guide to the identification of the syndrome but not to the cause. The syndrome of dementia is of grave significance, as it usually reflects progressive degenerative disease that threatens the very integrity of the patient. Moreover, dementia occurs in the setting of many neurological disorders necessitating a broad differential diagnosis and wide ranging investigations. In this group, the clues to the diagnosis and direction of subsequent investigations are usually provided by the additional neurological abnormalities, although some disorders—for example, multiple sclerosis—can present as cognitive impairment with little else to find on examination.

Alzheimer's disease is the commonest of the degenerative dementias (table). Characteristically, the disease starts with impairment

Dementia Research Group, Department of Neurology, St Mary's Hospital, Praed Street, London, W2 1NY, UK and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1 3BG, UK
M N Rosser

Correspondence to:
Dr M N Rossor,
Dementia Research Group,
Department of Neurology,
St Mary's Hospital, Praed Street, London, W2 1NY, UK.

Differential diagnosis of degenerative dementia

Alzheimer's disease:	
Sporadic	Early onset
Familial	Late onset
	Chromosome 14-linked
	APP mutations
	Apolipoprotein E4
	Non-chromosome 14, 19, 21
Cortical lewy body disease	Pure
	With senile plaques
Prion disease	Sporadic
	Iatrogenic
	Familial—PrP gene mutations
Pick's disease	
Frontal lobe degeneration	With motor neuron disease
Focal degenerations, for example, primary progressive dysphasia	Corticobasal degeneration
Progressive subcortical gliosis	

Differential diagnosis of patients presenting with dementia or progressive isolated cognitive deficits on a degenerative basis. It is not exhaustive and does not include diseases in which dementia is not commonly the presenting feature.

of memory, at which time, if this is an isolated cognitive impairment, the patient would not fulfil the dementia criteria of multiple domains of cognitive dysfunction. Language impairment with both word finding and comprehension difficulties and visuospatial dysfunction, however, soon emerge. Neuropathologically, the disease is identified by senile plaques and neurofibrillary tangles (fig 1). The plaques consist of dystrophic neurites clustered around a core of β amyloid protein, which is derived from a larger precursor protein, the amyloid precursor protein (APP).[8] Neurofibrillary tangles are derived from the microtubule associated protein tau, which is in an abnormally hyperphosphorylated state.[9] The definitive diagnosis of Alzheimer's disease depends on histological confirmation, usually at necropsy, although as the histological abnormalities of senile plaques and neurofibrillary tangles are also found to a lesser extent in aged normal subjects, neuropathological quantitative criteria have been developed for the diagnosis.[10]

Criteria for the clinical diagnosis have been published by the National Institutes of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA).[11] Three levels of diagnostic certainty are provided by these criteria: definite Alzheimer's disease requires histological confirmation in a patient who fulfils the criteria for dementia; probable Alzheimer's disease can be diagnosed without histology in the presence of a typical history and dementia; possible Alzheimer's disease is reserved for those patients with atypical features or in whom additional potential causes for dementia, such as vascular disease, are present. These criteria have been assessed against subsequent neuropathology and in some studies have provided very high rates of accuracy.[12 13] Tierney *et al* assessed the clinical criteria against various neuropathological criteria and derived figures of 0·64–0·86 for sensitivity (cases clinically diagnosed as Alzheimer's disease with histopathological confirmation as a proportion of all cases with histologically proved Alzheimer's disease) and of 0·89–0·9 for specificity (cases clinically diagnosed as *not* Alzheimer's disease without Alzheimer histopathology as a proportion of all non-Alzheimer cases).[14]

Within the degenerative dementia group clinical diagnoses are becoming more refined although there is still a poor correlation between histology and phenotype. Thus although identification of regional patterns of deficits can define a group of patients with frontal lobe dementia,[15] the underlying histology can include a non-specific mild cell loss with white matter change, Pick's disease, plaques and tangles, or spongiform change.

Similarly, the focal degenerations such as progressive dysphasia can be associated with a variety of histopathologies such as occur in Pick's disease, Alzheimer's disease, neuronal achromasia, and focal spongiform change.[16]

The other main group is vascular disease, usually due either to multiple cortical infarcts, to small vessel disease, or both.[17] Occasionally, a discrete small infarct—for example, in the paramedial thalamus—can cause appreciable cognitive impairment.[18]

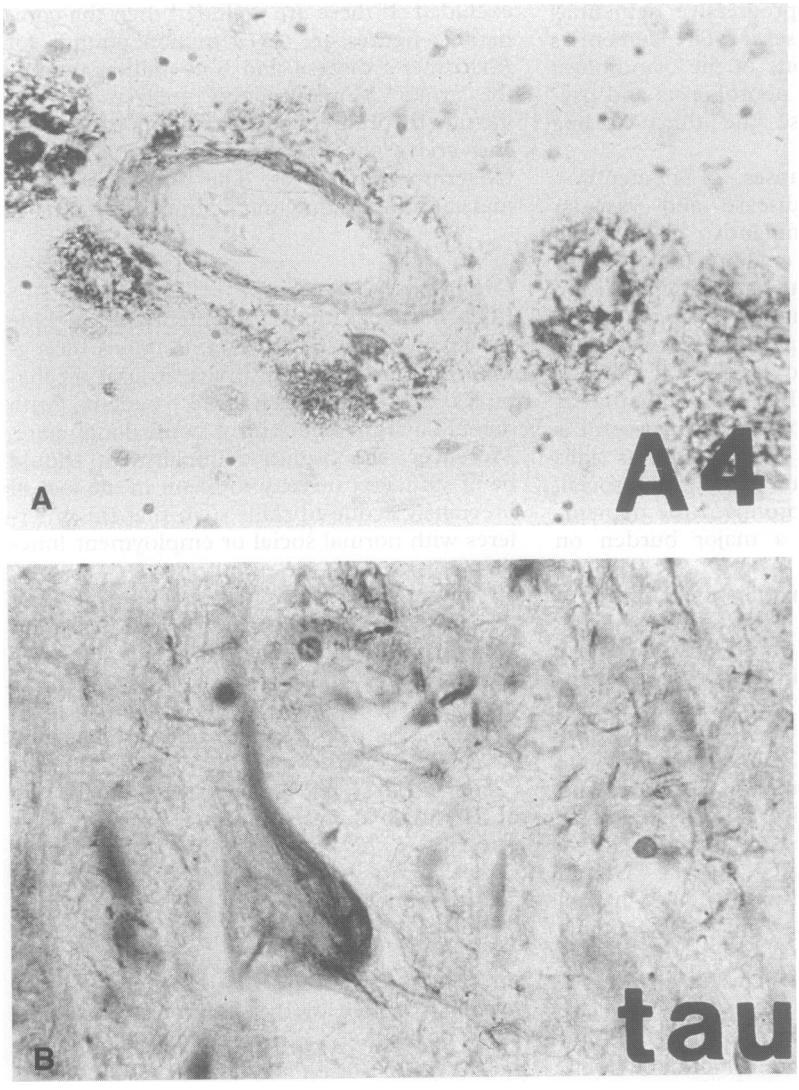

Figure 1 (A) Beta A4 immunohistochemistry illustrating a senile plaque and vascular amyloid in a case of Alzheimer's disease. (B) Anti-tau immunohistochemistry illustrating a neurofibrillary tangle in the same case (courtesy of Dr T Revesz, Institute of Neurology, London).

The criteria developed by Hachinski *et al*[19] provide a relatively poor guide when assessed against neuropathology, with an accuracy of only about 60%.[20] Recently, more detailed criteria, which utilise additional information from neuroimaging, have been published.[20 21]

Diseases with subcortical pathology, such as Parkinson's disease, progressive supranuclear palsy, and hydrocephalus are associated with cognitive slowing, referred to as subcortical dementia.[22] Although the concept has been challenged, the pattern of pronounced slowing of cognition is useful clinically to identify with relatively low error a group of patients, some of whom (for example, those with hydrocephalus) can be amenable to treatment.

History and examination

It is essential to obtain a history from an independent carer, usually the spouse, as well as from the patient, particularly as anosognosia for cognitive impairment occurs often in Alzheimer's disease and frontal lobe dementias. This should be done when the patient is not present as carers are often unwilling to be open in front of the patient. Details of the history that suggest deficits in specific areas of cognition should be explored and enquiries about activities of daily living such as shopping, cooking, housework, and household administration must be included. A useful clue is a change in the role of a patient within the family although this may be due to factors other than cognitive impairment, and features of a depressive illness causing a pseudodementia should be excluded. Pseudodementia should be suspected if the patient complains more of the memory impairment than the spouse, although depressive symptoms are a common accompaniment to early Alzheimer's disease.[23] Changes in sexual behaviour should be sensitively discussed as this is an area that can cause considerable distress but is rarely mentioned by the spouse.

A general medical history must be obtained including current and previous medications. A family history of dementia is often present if carefully and specifically sought as most of the degenerative dementias can occur as autosomal dominant as well as sporadic disease. With the younger patient it is necessary to enquire about employment and all patients should be asked about driving, not only because it gives a guide to cognitive function but also because of the medicolegal implications (see later). It is important to emphasise that whereas dementia is defined by the presence of multiple domains of cognitive impairment, patients will often start with a single deficit and this may not always be memory; Alzheimer's disease may occasionally present with visuospatial dysfunction, visual disorientation, dysphasia, or dyspraxia. A focal presentation may be characteristic of other dementias such as Pick's disease.

Examination should ensure adequate exploration of the major domains of cognitive function and must involve some simple tests of function of the non-dominant hemisphere. The mini mental state examination[24] is a brief bedside test of cognitive function that is now widely used and although not designed to provide any detail of neuropsychological function it is easy and rapid to give to outpatients.[25] The clinical dementia rating scale provides an overall staging of the functional deficit.[26] CAMDEX and its associated cognitive assessment CAMCOG, provide a more comprehensive diagnostic assessment,[27] but take time and can be inflexible. The US Consortium to Establish a Registry of Alzheimer's disease (CERAD) has attempted to develop a battery of tests useful for the early diagnosis of Alzheimer's disease[28] but these are more appropriate to the detailed investigation of neuropsychological function than as simple bedside tests.

On general neurological examination the presence of pyramidal signs, extrapyramidal features, or peripheral neuropathy may suggest a diagnosis other than a simple degenerative dementia. Many patients with Alzheimer's disease may have extrapyramidal features, however, most commonly rigidity but occasionally bradykinesia, which may relate to additional Lewy body formation.[29 30] A careful general medical examination is essential as this may provide important clues to secondary causes of dementia—for example, cardiac murmurs in vascular dementia or cytomegalovirus retinitis in a young patient with cognitive impairment due to HIV infection.

Investigation

Ideally all patients should undergo formal neuropsychological assessment to determine the extent and severity of the cognitive deficit. Routine investigations of haematology and biochemistry should also include treponemal serology, thyroid function, vitamin B12 and red cell folate, chest radiograph, and neuroimaging. Scanning by CT will exclude space occupying lesions and hydrocephalus and may also indicate changes in white matter associated with demyelination or vascular disease. Special orientation of the plane of CT can show medial temporal lobe atrophy in Alzheimer's disease.[31] Magnetic resonance imaging is of greater value than CT and regional volumetric studies may increasingly aid the diagnosis of specific degenerative dementias (fig 2).[32] It is recognised that in elderly demented patients routine neuropsychology and neuroimaging may not be practical; nevertheless, this is the ideal that should be sought. An EEG can be valuable; early slowing would favour Alzheimer's disease by contrast with a normal EEG commonly found with Pick's disease and other frontal lobe dementias; periodic complexes may be important in the diagnosis of prion disease.

In some patients a wider range of investigations is necessary. Specific blood tests might include screening for metabolic disorders such as Wilson's disease, metachromatic

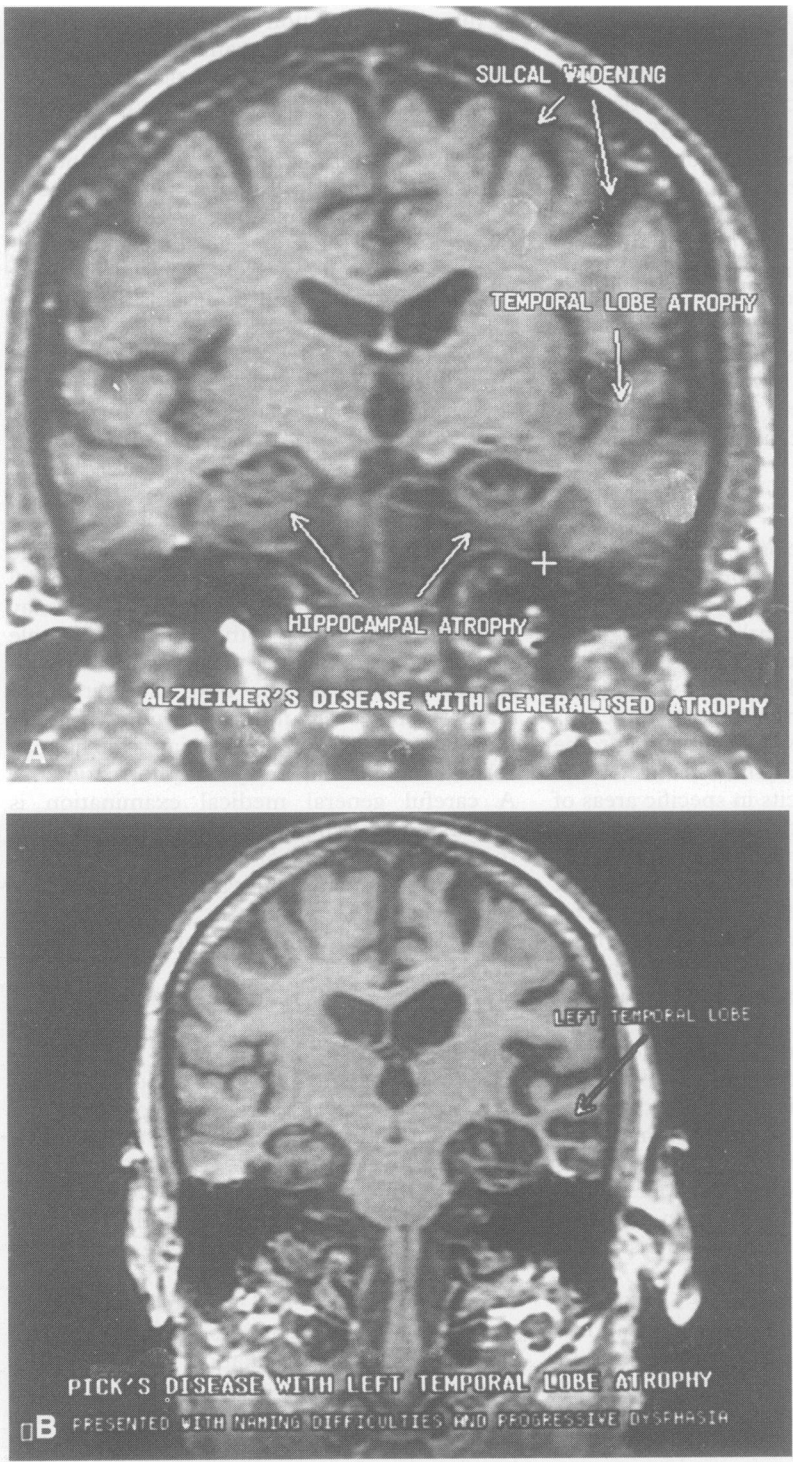

Figure 2 (A) MRI showing bilateral hippocampal and temporal lobe atrophy in a case of Alzheimer's disease. (B) MRI showing asymmetric anterior hippocampal, amygdala, and temporal lobe atrophy in a case of Pick's disease (courtesy of Dr N Fox, St Mary's Hospital, London).

leucodystrophy, and GM2 gangliosidoses; Tests for HIV should always be considered in unexplained cognitive impairment, particularly in young patients. Examination of CSF is often carried out in patients with presenile dementia but is usually normal in degenerative dementia: a raised protein or cell count would suggest the possibility of a vasculitis or other inflammatory disorder and, in view of the potential treatable nature of these diseases, may be an important finding. It is nevertheless uncommon to find an abnormal CSF in the presence of a normal MRI. Muscle biopsy may be indicated to look for ragged-red fibres in association with mitochondrial cytopathies. Very occasionally a brain biopsy may be indicated if a treatable cause such as cerebral vasculitis is suspected. In hereditary disease appropriate genetic screening for the Huntington mutation, amyloid precursor protein mutations, and prion protein gene mutations are all available; whether apolipoprotein e4 allele genotyping will prove to be of use in diagnosis and management remains to be seen.[33] Functional imaging with PET is still largely a research investigation, but single photon emission computed tomography (SPECT) is now more widely available and may be valuable in showing a posterior (common with Alzheimer's disease) as opposed to anterior pattern of hypometabolism.[34]

Prevention

At present there are few causes of dementia that are preventable. Control of hypertension may prevent some of the cases of vascular dementia although there is no simple relation between the development of dementia and vascular risk factors. With the discovery of the Huntington's mutation, amyloid precursor protein mutation, and prion protein mutations, prenatal testing is likely to become more important in young onset dementias.

Prognosis

The diagnosis of dementia carries a grave prognosis. Prompt treatment of some underlying diseases such as neurosyphilis, cerebral vasculitis, and metabolic disturbances can result in stabilisation and even reversal. Unfortunately most follow a relentless progression. This may vary from the devastatingly rapid deterioration measured in months in some cases of sporadic Creutzfeldt-Jakob disease to a deterioration measured in 10-15 years for some of the focal degenerations. The median survival from diagnosis in Alzheimer's disease is in the range of seven to 10 years, although some patients may have a prolonged mild stage.[35] Average rates of decline are in the order of 3–4 points on the mini mental state examination per year.

Communication and counselling

Although grave and tragic information often has to be imparted a frank discussion when the diagnosis and prognosis are known is essential. Commonly, however, the diagnosis may be unclear in the early stages. Thus when first seen the patient may show only mild changes in cognition and in the absence of a specific clinical test there is a natural reluctance to make a diagnosis such as Alzheimer's disease: inevitably there is a burden of uncertainty that has to be shared between the patient, the family, and the doctor. Nevertheless, there is still a reluctance to discuss Alzheimer's disease and its implications

that is comparable with that associated with a diagnosis of cancer 10 to 20 years ago. Early discussion of the implications and how help can be offered, together with appropriate counselling, is vital. The disease affects not only the patient but the entire family: in young onset dementia the illness can be devastating for the children and in older patients disruption of the shared plans for retirement can present a considerable sense of loss.

Memory clinics can provide diagnosis, counselling, and advice but most longer term support is provided in the community by the social work and community psychiatric services. The Alzheimer's Disease Society provides additional information and support. Some smaller patient support groups are now being established for some of the rarer disorders such as Pick's disease and Creutzfeldt-Jakob disease (see appendix).

Neurological follow up of cases of dementia is indicated when the diagnosis is unclear or when specialist advice is needed for some of the rarer diseases. In general, however, management is shared between the general practitioner, hospital, and community psychiatric services.

Management

The specific treatment of dementia relates to the underlying condition. There are the rare instances of reversible dementia such as those associated with hydrocephalus, hypothyroidism, cerebral vasculitis, neurosarcoid, or neurosyphilis. For most, there are no specific treatments although there is now the emerging prospect of symptomatic treatment. Where there is any doubt about the diagnosis or the presence of depressive symptoms, patients should be given a trial of an antidepressant, commonly one of the selective serotonin uptake inhibitors that avoid the anticholinergic side effects of tricyclic antidepressants and are better tolerated. This will help to identify patients with depressive pseudodementia and may also improve cognitive function in depressed patients early in the course of Alzheimer's disease.

Attention has recently been directed towards enhancing cholinergic transmission, which is reduced in Alzheimer's disease due to disruption of the subcorticocortical cholinergic projection. Most attention has been directed towards the acetylcholinesterase inhibitors after the report of a beneficial effect of tetrahydroaminoacridine (tacrine). Recent studies have confirmed this. The study of Farlow *et al* using a parallel design with 468 Alzheimer patients given tacrine in doses of 20–80 mg or placebo for 12 weeks showed improvement both on a global clinical impression of change and the cognitive subset of the Alzheimer's Disease assessment scale (ADAS-COG).[36] About half the patients on the highest dose had an improvement of 4 points on the ADAS-COG, which is equivalent to about six months of normal spontaneous decline. The most recent study[37] comprised 653 patients on treatment for 30 weeks with doses of tacrine up to 160 mg per day and improvement was seen at the higher dose in about 40% of patients who were able to complete the study with an improvement of more than 4 points on the ADAS-COG; however, 43% withdrew due to cholinergic side effects. Changes in transaminases reflecting the hepatotoxicity of the drug are commonly seen, with 29% of patients developing abnormal transaminases of more than three times the upper limit of normal and about half showing some abnormality. This is normally reversible on cessation of the drug and patients can often be successfully rechallenged.

Tacrine (Cognex) has received a licence for use in Alzheimer's disease in the United States and more recently in France, but not in the United Kingdom. Further acetylcholinesterase inhibitors are likely to become available over the next few years and there is intense activity within the pharmaceutical industry to develop other symptomatic treatments for Alzheimer's disease and, in the longer term, drugs that may alter the underlying disease process. Thus efforts are being directed towards drugs that might inhibit the hyperphosphorylation of protein tau, which leads to neurofibrillary tangle formation and the deposition of β amyloid protein associated with senile plaques.

As well as these exciting developments in Alzheimer's disease, treatment of behavioural disturbance is important and is common to many of the dementias. Hallucinations, aggressive behaviour, and psychoses can be difficult to treat as many patients are very sensitive to the effects of neuroleptics, particularly patients with diffuse Lewy body disease in whom rapid deterioration in motor and cognitive function can occur. The judicious and closely monitored introduction of a neuroleptic drug, however, particularly one with less extrapyramidal side effects, may be beneficial. Sleep disturbance is also common but can respond to small doses of a rapidly acting benzodiazepine such as temazepam.

Liaison

In the United Kingdom neurologists tend to see younger patients presenting with presenile dementia or cases of dementia with additional neurological abnormalities. Most cases of dementia that occur in elderly people and which are due to Alzheimer's disease are seen by psychiatrists and geriatricians. By contrast, in the United States and in many European countries, Alzheimer's disease is predominantly seen by neurologists. Dementia encompasses many disciplines and good management will involve care by neurologists, psychiatrists, and geriatricians as appropriate, together with neuropsychologists and specialist nurse counsellors. Liaison with general physicians, surgeons, and other professionals is also important to ensure that the patient gets appropriate care for other medical problems. Untreated or inadequately managed conditions can often exacerbate confusion

and behavioural disturbance, yet there is sometimes reluctance to treat if there has been a diagnosis of dementia.

As well as medical and paramedical liaison other agencies are important, particularly when patients are still in employment. We have clear guidelines for employment of those with epilepsy or cardiac disease who are airline pilots, public service vehicle drivers, etc. For those with cognitive impairment the opportunities for harm are far greater but the guidelines fewer. Even for driving the information is unclear.[38] Once a diagnosis of dementia has been made then the Driver and Vehicle Licensing Authority should be informed by the patient but there are few guidelines as to whether the patient is able to drive or not. Unfortunately for many patients driving is seen as important for maintaining independence in society and self esteem.

Although the ideal is for seamless care from the initial neurological assessment and diagnosis through the longer term management within the community and on to long term hospital care, this is often not achieved and one is faced with crisis management of the patient who is unable to be managed at home. This makes the early diagnosis, explanation, and prognosis all the more important.

Appendix

Alzheimer's Disease Society (Creutzfeldt-Jakob Group), Gordon House, 10 Greencoat Place, London, SW1P 1PH, UK.

Pick's Disease Self Help Group, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK.

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