Alzheimer's Disease

An overview of the past and present developments in the diagnosis of the disease

— M F Rosin

Summary

In the last 6 years interest and research in Alzheimer's Disease has leapt into prominence and brought much hope for sufferers. The author describes the clinical symptoms and different phases of the disease, gives the incidence, some diagnostic help, etiologies and the advances in recent research. She also introduces ARDA, a very recently established organisation in the RSA. This organisation fosters research and help for AD sufferers.

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Curriculum vitae

Mickey Rosin was born in Pietersburg, grew up and was educated in Johannesburg. She obtained the degree BA Social Studies from Wits in 1943 and worked as a social worker until her marriage in 1947. In 1962 she returned to Wits and in 1974 she graduated: MA (Clin Psych). Since 1974 Mrs Rosin has been in practice as a clinical psychologist in Johannesburg, and worked part-time at Phoenix House - Drug Addicts' Rehabilitation Centre for 5½ years. She became interested in Alzheimer's Disease as her husband - a lawyer - was severely afflicted with the disease about 7 years ago. (Mr Rosin passed away in August 1986.)

Mrs Rosin was a co-founder of ARDA (Alzheimer's and Related Diseases Association) and is presently vice-chairperson of the organisation. She is an active participant in the support groups which have been formed to assist the caregivers (usually the spouses) of AD victims. She has taken the opportunity of visits to New York City and Toronto to obtain advice and assistance for the local organisation.

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Until as recently as six years ago, few people, (including many health workers) had ever heard of Alzheimer's Disease (AD). In the short interim period, interest in AD has leapt into prominence, especially in the Western world. The main reason for the meteoric rise of interest in AD has been that the life expectancy of people has greatly increased. Many more people are living to a 'ripe old age' and AD has been identified as being the major psychiatric disorder of old age.

AD is believed to affect one in ten people over the age of 65 and according to Dr Peter Davies[1], Associate Professor of the Albert Einstein College of Medicine, one in seven people over the age of 90. AD presently affects more than 2,5 million Americans and is the fourth leading cause of death in the USA, causing 150 000 deaths annually. Within the next ten years, it is expected that one out of three families in the USA will be touched by AD. It is estimated that $34 billion is spent annually on the costs of caring for AD victims, both at home and in institutions. The cost of care could rise to $750 billion annually by the end of the century. Huge costs are incurred, both to society and to individual families, because the span of the illness from onset until death could be as long as from seven to twelve years. It can be seen that the actual cost of medical care and support for AD sufferers has become a mind-boggling exercise. The financial cost of the disease has spurred the immense amount which is now being spent on research.

In South Africa there are few statistics available concerning the incidence of the disease, but it would be reasonable to infer that the incidence would largely follow the trends observed in the USA and elsewhere. The disease not only seriously affects its victims, but also the "hidden" victims: their families - spouses and children.

History

In 1838 an eminent French physician, Dr Jean Esquirol, described a condition "démence sénile" as an illness that came on gradually and resulted in the loss of short-term memory, drive and will power[2]. AD was first described by Alois Alzheimer in 1907, after a female patient aged 55 years had died following the onset of severe dementia. Alzheimer defined AD as a progressive pre-senile dementia with prominent aphasia, amnesia and cognitive impairment but with relatively intact motor function until the final stages of the disease.

AD is not a part of normal ageing – as has been believed for centuries

Another fifty years was to elapse before three British scientists studied 50 demented patients who were over the age of 65 through to the end of their lives. After their deaths autopsies were performed and comparisons were made with the brain matter of 28 non-demented age-matched adults who had died during the same period. It was found that half the demented brains showed pathological changes indicative of AD. They concluded that in most cases, senile and pre-senile dementia were the same disease: Alzheimer's Disease.

Definition

AD is defined as a progressive chronic cognitive dysfunction usually afflicting those in the 65-year and over age group. However, there are many cases of younger people being afflicted as well. The disease is accompanied by cognitive, behavioural, motoric and bodily symptoms. The seriousness of the symptoms depends on the stage of the disease. These symptoms lead to the onset of severe dementia, medically defined as a profound loss of memory and intellectual functioning and an inability to take care of social and bodily needs[2].

Clinical syndrome

There are three major phases in the progress of the disease:

Phase 1: The individual and the spouse may notice that the patient has a tendency to forget where things are placed, has difficulty in remembering names or appointments or he may get lost on a trip to a familiar place. (One writer distinguishes the difference between an entity called "benign senescent forgetfulness" and the malignant form of the amnestic syndrome.)[3] The cognitive ability of the patient is also affected – he may have difficulty in paying bills, performing complex familiar tasks such as playing bridge; and work efficiency may be reduced. Motor coordination skills may be slightly affected; the patient begins to manifest slow reaction time and driving efficiency is impaired. There may be signs of change in mood and behaviour. The person becomes socially withdrawn, may show less initiative and may suffer from depression. At this stage the patient carries out activities of daily living without assistance. Speech is generally unaffected at this stage[4].

Phase 2: This is considered to be the 'confusional' phase. This phase is characterised by an impairment of cognitive functioning. The patient has difficulty with computations of the simplest kind, has difficulty in concentrating, loses sense of time and place and forgets where he is. There is severe loss of memory for recent events and a lack of ability to form new memories or to learn. Motor coordination skills begin to weaken progressively. The patient becomes unsteady and weak, may have difficulty in walking and loses the ability to write legibly. The patient experiences frequent mood swings, becomes agitated and may suffer from delusions or hallucinations. There may also be sleep disturbances. At this time the patient starts needing assistance in activities associated with daily living such as dressing, bathing or showering. Incontinence of urine appears, followed by incontinence of faeces. In this phase the patient begins to talk less, or repeats words and phrases continuously, and may begin to experience difficulty in recalling appropriate words.

AD affects one in ten people over the age of 65

Phase 3: Late Alzheimer's. This is known as the 'dementia phase'. In this phase the patient has no recent or remote memory, no observable cognitive functioning, almost total atrophy of coordination and motor skills, is most often oblivious to the environment and others, may not recognise the primary caregiver, needs extensive assistance to carry out activities of daily living and must be bathed, dressed, groomed, toileted and fed. There is also an almost complete loss of language skills. In some cases severe emaciation has been observed.

Diagnosis

Great care needs to be taken in making the diagnosis, as other etiologies of dementia include such conditions as:

- toxic conditions – alcohol abuse and barbiturate intoxication
- infections
- nutritional disorders
- endocrine disorders
- cerebral disease – such as slow-growing tumours
- depression
- metabolic disturbances.

Many of the latter can be reversed if identified and given early treatment - and this avoids a diagnosis of AD which could leave the patient with 'a grim diagnosis implying irreversible damage and a grim prognosis'[3].

Pathology

Up to the present AD has usually been definitely diagnosed only at post mortem. However, using the CAT scan the extent of brain atrophy can be seen. While brain atrophy is a prominent feature in AD, a large number of patients have no evidence of atrophy. 'In vivo studies of gross brain pathology using CT brain scans have shown significant correlations between measurements of the ventricular size and cognitive impairment in early mild to moderate cases of AD'[3]. Because of the generalised atrophy observed in AD, loss of cortical neurons has been hypothesised. EEG and PET scans are also instruments used in diagnosis.

The major pathological changes in the brains of AD sufferers identified in the past on post mortem examination of the tissues, revealed:

1. Changes occurring in the nerve cells of the cortex, leading to an accumulation of abnormal fibres called neurofibrillary tangles (paired helical filaments) which are found predominantly in the cerebral cortex and especially in the hippocampus.

These are found not only in the neuronal cell body, but also in the synaptic terminals and the senile plaques.

2. The second major microscopic lesions observed are the senile plaques (neuritic plaques). These are found chiefly in the cerebral cortex, although they may also occur in the basal ganglia, white matter,

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brain stem and cerebellum. Many studies have demonstrated that the degree of intellectual deterioration in AD is correlated with an increasing number of senile plaques per area of the brain. 'Ultrastructurally, the senile plaque contains a central core consisting of amyloid surrounded by abnormal neurites.'[3] However, senile plaques have also been observed in the brains of the normal elderly.

3. The third major lesion is the granulovacuolar body, said to be present in large numbers in the hippocampus of AD patients. A slight increase in granulovacuolar body formation is found in normal elderly individuals. However, patients with AD had a 2 to 100 times greater incidence of granulovacuolar degeneration than age-matched control subjects.

4. In AD patients a shrinkage of the dendritic tree has been described by some investigators.

5. Employing biochemical techniques, researchers have examined the brains of AD patients and determined the levels of various neurotransmitters. Researchers have reported large reductions in the levels of choline acetyltransferose and acetylcholinesterase enzymes in AD patients. While both these enzymes show an age-related decline, the decline is significantly greater in AD patients than in aged control subjects. The neurochemical findings have led to attempts to manipulate the cholinergic neurotransmitter system as a possible

Until recently AD has only been diagnosed post mortem

treatment approach to AD patients. Most of the aforegoing data relates to work carried out before February 1982.

The April 25, 1986 edition of *Science* reported a discovery made by workers at the Albert Einstein College of Medicine, led by Dr Peter Davies. A protein was found in the brains of AD patients, which does not appear to exist in normal brains[6]. This appears to be the first protein discovered that differentiates abnormal changes in the AD patient's brains from changes that occur in normal ageing. The discovery is important, firstly because it will enable more certain diagnosis. Secondly, there is now hope of shedding some light on the cause of this 'mysterious' disease. The protein was found in nerve cells that had not yet been demonstrably damaged and seems to appear relatively early in the destructive process. This could mean that the protein is involved in the causative process. The protein was found in relative abundance in areas of the brain known to be affected in AD, including the cerebral cortex and the hippocampus (centre of memory functioning). The search is now on to find this protein in the spinal fluid. An analysis of the protein may be a step toward finding the gene that causes it to be produced. It is not yet known whether the protein causes the disease or is a result of it. The new protein is distinct from amyloid which is a major constituent of the neurofibrillary tangles mentioned earlier. The protein was also found in the autopsied brain of an adult who had Down's Syndrome. (Most Down's Syndrome patients develop AD if they live long enough). The new protein has been designated ALZ-50 antigen.

6. The principal difficulty in the clinical recognition of AD stems from the lack of diagnostic criteria that discriminates AD from other dementing disorders. In the absence of specific radiologic or laboratory findings, more accurate clinical recognition of AD depends on a constellation of characteristic symptoms or signs present in AD, but not in other dementias. In recent years, psychological testing has greatly improved the accuracy of

diagnosing AD. There are a number of instruments in use in the USA, most of which provide global measures of personal and social functioning or of intellectual abilities distinguishing the demented from non-demented control subjects and thus aiding in the clinical diagnosis of dementia. There are tests such as the Mini-Mental State Examinations (MMSE); the Dementia Scale of Blessed, Tomlinson and Roth; Sandoz Clinical Assessment – Geriatric, and some others[6].

AD seriously affects the families of the victim – and probably one in every three families in the USA will be touched in the next decade

Cummings and Benson devised the DAT Inventory (Dementia of the Alzheimer Type)[5] in an effort to improve diagnostic accuracy and identify 'operational criteria that distinguish DAT (AD) from other dementias'[5]. The DAT Inventory includes six categories: memory, visuospatial, cognition, personality, language and motor functions (includes psychomotor speed, posture, gait and movements). Cummings and Benson characterised a dementia syndrome as 'an acquired persistent compromise' in at least three of the above areas[5]. The 10 subscales of the DAT Inventory provides a profile in which the highest scores represent classical AD features and the lowest scores represent the greatest deviation from the score syndrome.

Etiologies

1. A major current hypothesis centres on viral etiology. It is commonly known that viral infections affect the brain, sometimes many years after the acute infectious attack.

2. Atoxic agents, more specifically aluminium have been associated with AD in several studies quoted by Schmeck, Reisberg and Ferris[3]. However, other investigators have published contradictory results. On the basis of findings obtained using the scanning electronic microscope, some researchers have reported the presence of aluminium in the nuclear region of the neurofibrillary tangles.

3. A third possibility is that there is a defect in the immune system of AD patients.

4. A fair amount of controversy exists as to whether AD can be related to a specific chromosome or genotype. As yet, although many studies have been undertaken, there are no definite or conclusive answers except as may have been suggested by the latest findings at the Albert Einstein College.

Treatment

In the USA a whole body of information and techniques are being developed to help the victims of AD and the 'victim's victims – the most closely associated caregivers'[2]. At the International Council for the Disabled (ICD) in NYC, there is a Centre where AD victims can go for therapy on a daily basis. There they take part in physiotherapy exercises, art therapy, and especially useful and important: music therapy. Much emphasis is placed on the issue of 'reality orientation', that is trying to keep the patient in touch with aspects of everyday life such as the day and the date, the season of the year and so on. Rooms are labelled so that the patient can avoid the confusion of going in the wrong direction. Communication strategies have been developed to enable others to converse with the language-impaired adult.

Help and research has been directed towards the caregivers. Support groups have been formed and there is a great deal of research into their mode of functioning and also research on how the support group structure can be optimalised to assist the caregivers.

In the Republic of South Africa an organisation known as Alzheimer's Disease and Related Disorders Association (ARDA) was founded in April 1984. The aim of ARDA is to establish an assessment clinic to help in the diagnosis of AD, to foster research into the epidemiology of the disease in the RSA and to establish support groups for the caregivers of AD sufferers. Several support groups are already functioning, but much work needs to be done to establish the society so that optimum help can be given to both sufferers and caregivers.

Conclusion

The emergence of AD from the mystery which has enshrouded the disease from time immemorial has at last begun. Senile dementia was once regarded as an inevitable part of the ageing process, but it has now been shown that AD is not a part of normal ageing, that it is a disease process which is reflected in specific changes in brain anatomy and functioning reflected in specific symptoms of behavioural and cognitive degeneration.

For sufferers and future sufferers, there is some hope now that mental and physical decline may no longer be inevitable. The vigorous research programmes now underway, may one day produce a way of avoiding or coping or of even curing the disease.

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