Alzheimer's disease

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Introduction

In 1907, Alois Alzheimer described the case of a 51 year old woman with dementia and prominent behavioural disturbance. At autopsy, the brain was found to be atrophied and microscopic examination with silver staining revealed widespread senile plaques and neurofibrillary tangles. Senile plaques were seen as dystrophic neuritic processes around a central core and neurofibrillary tangles as intensely staining intraneuronal perikaryal inclusions. Both of these had been observed before but had not been related to the clinical picture of dementia. Doubt was expressed at the time about the nosological entity focusing upon the distinction or lack of it from old age. Although the concept of Alzheimer's disease rapidly became accepted as a presenile dementia, it was not until the studies in the 1960s from Newcastle¹ that Alzheimer-type changes, namely senile plaques and neurofibrillary tangles, were also shown to underlie cases of senile dementia. Recently, the term of Alzheimer's disease has been used irrespective of the age of the patient. Nevertheless, the presence of both plaques and tangles in certain areas of the brains of the very old without apparent dementia has continued to raise the question of whether Alzheimer's disease is really distinct from the ageing process.

Clinical features

The development of dementia, that is, a clinical syndrome characterized by multiple domains of cognitive impairment, reflects the predominant involvement of association cerebral cortices in Alzheimer's disease. Thus memory impairment together with some degree of dysphasia, usually with comprehension difficulties, and visuospatial disturbance, are the characteristic features. This clinical picture can be contrasted with the predominance of frontal lobe disturbance more commonly associated with either Pick's disease or a non-specific neuronal degeneration referred to as

frontal lobe dementia of the non-Alzheimer type.^{2,3} Further distinctions can be drawn from patients with subcortical dementia⁴ in whom memory impairment may be prominent but is accompanied by relative sparing of language and visuospatial function although patients often appear to be severely impaired due to a marked slowness of cognition.

The predilection for plaques, tangles and cell loss to involve the association cortex with sparing of primary motor and sensory cortex determines the pattern of cognitive impairment with sparing of basic sensory and motor functions. This pattern is also reflected in positron emission tomography (PET) using oxygen-15 or 2-fluoro-2-deoxyglucose to determine quantitatively regional cerebral metabolism. Posterior biparietal and bitemporal hypometabolism is a characteristic, although not necessarily specific, feature of Alzheimer's disease.⁵ This has been used increasingly as a diagnostic tool, particularly since the similar posterior pattern of hypometabolism can also be demonstrated using single photon emission computed tomography (SPECT), a considerably cheaper facility.

The diagnosis of Alzheimer's disease remains clinical unless histological confirmation is available at biopsy or autopsy. Diagnostic criteria have been developed, with which a characteristic pattern of cognitive impairment exists with exclusion of other causes of dementia, such as tumours, hydrocephalus and metabolic disturbance, allows a diagnosis of probable Alzheimer's disease. Definite Alzheimer's disease is established with histological confirmation and possible Alzheimer's disease is allowed in the presence of atypical features.⁶ These criteria give a reasonable accuracy of diagnosis.⁷⁻⁹ However, such data depend upon histological confirmation as the gold standard, and the presence of Alzheimer changes in normal old age impose a degree of uncertainty even on histological criteria.¹⁰

If one accepts the combination of cognitive impairment with widespread neocortical plaques and tangles as constituting Alzheimer's disease, then considerable heterogeneity can be observed within this rubric. Many classifications have been proposed based on age at onset, presence of a

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family history, the presence of extrapyramidal features and focal cortical disease. One of the most widely considered distinctions has been that based on age at onset. Originally using a somewhat arbitrary age, those starting below the age of 65 were considered to have presenile dementia in contrast to later onset cases of senile dementia of the Alzheimer type. It is now recognized that the underlying histopathological changes are qualitatively the same regardless of age, but some differences between these two groups have been observed. Clinically, it has been suggested that early onset cases have a more severe disease with rapid progression together with a predominance of language disturbance,¹¹ although this has not been confirmed in all studies. A family history is also more readily apparent in young onset cases but this may be a sampling bias. Neurochemically, the neurotransmitter defects are more circumscribed in late onset cases when compared with age-matched controls, being largely confined to the cholinergic projection system.¹²

Some patients with Alzheimer's disease show quite striking motor disturbance characterized as marked rigidity and occasional gait disturbance. On careful examination, many patients are found to have abnormalities of tone with prevalence figures for these 'extrapyramidal' features as high as 90%.¹³ This group of so-called extrapyramidal patients may themselves be heterogeneous. Some are found to have low concentrations of dopamine metabolites in the cerebrospinal fluid,¹⁴ and may be due to co-existent Lewy bodies both in the substantia nigra and in cerebral cortex; a feature found in a number of cases of Alzheimer's disease and referred to as the Lewy body variant of Alzheimer's disease.¹⁵ Other patients, however, are found to have *gegenhalten* rather than genuine cogwheeling and these patients have a normal gait and no apparent hypokinesia.¹⁶ Moreover, these patients have normal fluorodopa uptake into the basal ganglia unlike patients with Parkinson's disease.¹⁷ Since a number of patients with extrapyramidal features at autopsy have no discernible nigral pathology,¹⁸ it is likely that this subgroup reflects damage to a different neural system, for example, the corticostriatal projection from pyramidal cells.

A further source of variation is patients who present with focal neurological features. As discussed above, the disease is characterized by preferential involvement of the association cerebral cortices in a symmetrical pattern. Some patients, however, will present with strikingly asymmetric focal features. These have included patients with isolated dysphasia,¹⁹ cortical visual loss²⁰ and non-dominant sensory cortical dysfunction with hemiparesis and astereognosis.²¹ In general, these patients do progress to a dementia but late in the course of the illness. In addition, some rare patients

have been reported with prominent cerebellar or pyramidal tract involvement.²²

The above represent interesting examples of clinical variability, but may not necessarily reflect biological subtypes. More precisely delineated are groups based on the presence of a family history.

A number of large pedigrees with autosomal-dominant familial Alzheimer's disease have been described and, indeed, the prevalence figures for familial Alzheimer's may be as high as 50%.²³ No consistent clinical features distinguish these sporadic and familial cases, although language has been reported to be more prominent in familial cases. Familial cases tend to have a younger age of onset but this may be due mainly to the fact that genetic influences are less clearly discernible in late onset disease. A related group are patients with trisomy 21 Down's syndrome who develop Alzheimer histopathology and, in many instances, a super-added dementia in their third and fourth decade.

If Alzheimer's disease is defined as the presence of abundant plaques and tangles in the neo-cortex together with cognitive impairment, then any aetiological explanation has to explain the presence of the same histological changes albeit to a limited extent in ageing; it must also explain the clinical variability and the combination of sporadic and familial cases. Alternatively, rather than consider Alzheimer's disease as a single entity, the histological features may represent the final common pathway of degeneration from a number of different causes. Recent evidence from biochemical analyses of plaques and tangles, and molecular genetic studies of familial Alzheimer's disease, have come together to provide some of the answers to these questions.

Amyloid deposition as a final common pathway in Alzheimer's disease

The presence of amyloid within the brain of patients with Alzheimer's disease and, to a lesser extent, normal ageing has been known for a number of years. The designation amyloid refers to the formation of beta pleated insoluble fibrils which results in positive staining with congo red and birefringence under polarized light. The amyloid is predominantly within the core of the senile plaques and within blood vessels. This brain amyloid was shown to be distinct from systemic amyloidoses although the problems of isolation of senile plaques delayed purification. In the early 1980s, however, senile plaques were extracted in sufficient quantities to allow isolation of the amyloid protein and amino acid sequencing. The amyloid in senile plaque cores and blood vessels was shown to be similar and was referred to as beta

amyloid or A4 protein by different authors.²⁴ Specific immuno-staining with antisera against β A4 protein has shown that amyloid deposition is a consistent feature in Alzheimer's disease.

In 1987, a major advance was made using the techniques of reverse molecular genetics. A cDNA encoding for the known amino-acid sequence of the β A4 amyloid protein was isolated and the β A4 amyloid was shown to be part of a far larger precursor protein, the amyloid precursor protein (APP).²⁵ APP is a transmembrane molecule with a small cytoplasmic C-terminal tail and a large extracellular component (Figure 1). It is conserved throughout evolution and the extracellular domain shows homology to the protease nexin II.²⁶ It is expressed widely throughout the body, including platelets and T-lymphocytes. Although it is widely expressed, alternative mRNA splicing occurs to give a variety of mRNA species, some of which include a Kunitz protease inhibitor domain.²⁴ The APP mRNA expressed in the brain is predominantly that which lacks the protease inhibitor domain. The beta A4 domain straddles part of the membrane and the normal processing of APP involves cleavage close to the external surface of the membrane, that is, across the beta A4 domain.^{27,28} This suggests that in Alzheimer's disease alternative pathways must be utilized to release the beta A4 molecule (see below).

The APP gene is clearly a major candidate as the locus for familial Alzheimer's disease, supported by the fact that the APP gene is located on the long arm of chromosome 21.²⁹ Moreover, following the lead given by the development of Alzheimer's disease in trisomy 21 Down's syndrome cases, genetic linkage studies have concentrated on markers on the long arm of 21 and have demonstrated linkage of familial Alzheimer's disease to this region.³⁰ However, a series of publications subsequently demonstrated recombinations between the APP locus and the disease in a number of familial Alzheimer's disease pedigrees apparently excluding the APP gene.³¹ However, the possibility of genetic heterogeneity of familial

Alzheimer's became increasingly likely when a number of families failed to show chromosome 21 linkage.³² A large multinational collaborative linkage survey also supported the view that familial Alzheimer's disease was genetically heterogeneous with the majority of young onset cases contributing to the observed chromosome 21 linkage.³³ The published linkage studies had relied on the assumption that the disease was homogeneous thus allowing pooling of a number of pedigrees, which would no longer be valid if indeed familial Alzheimer's disease was genetically heterogeneous.

A familial Alzheimer's family studied by the group at St Mary's Hospital was sufficiently informative to be able to demonstrate linkage to markers on the long arm of chromosome 21 in that single family. Moreover the APP gene could not be excluded. Further interest in the APP gene was generated by studies of hereditary cerebral haemorrhage with amyloidosis of the Dutch type. In this autosomal dominant disease there is prominent cerebral amyloid angiopathy with recurrent cerebral haemorrhages in early middle age. A point mutation resulting in a glutamate to glutamine substitution at APP 693, that is, within the beta A4 domain, was demonstrated.³⁴ Direct sequencing of the corresponding exons 16 and 17 was therefore undertaken in the St Mary's Alzheimer family. This demonstrated a point mutation at APP 717 resulting in a valine to isoleucine substitution.³⁵ A similar mutation has been found in a US family, and subsequently in three Japanese families and a further UK family.³⁶ Subsequent to this, two other mutations at APP 717 have been reported, resulting in valine to phenylalanine³⁷ and valine to glycine³⁸ substitutions. Clinically the patients develop a widespread cognitive impairment with prominent memory deficit and histologically show plaques, tangles and amyloid angiopathy.^{39,40} The index case of the first UK family with APP 717 valine to isoleucine mutation also showed cortical Lewy bodies,⁴⁰ but this is not a consistent feature.

The number of families with APP mutations are few, indicating that these are rare. Nevertheless, they have clear implications for possible pathophysiological mechanisms of Alzheimer's disease in general. The demonstration of APP 717 mutations in familial Alzheimer's disease argues for a central role of amyloid deposition in these cases and by inference may also be important in other familial cases and sporadic cases of Alzheimer's disease. This is further supported by the recent report of Alzheimer type pathology in transgenic mice carrying extra copies of the C-terminal 100 amino acids of the APP molecule.⁴¹ These mice showed both amyloid senile plaques and neurofibrillary tangles. If amyloid deposition is important, the first question is how the mutations result in beta A4 deposition. Since constitutive processing of the

Figure 1 The amyloid precursor protein showing the location within the overall sequence of the β -amyloid sequence (hatched); sites of known mutations and the normal and presumed abnormal cleavage sites are included. (Courtesy of Professor B. Anderton, Institute of Psychiatry.)

APP results in cleavage across the A4 domain,^{27,28} then alternative pathways have to be implicated and mutations at APP 717 may alter the normal processing. Alternatively it has been speculated that this region of the mRNA causes a stem loop which is important in control of mRNA translation. This might result in excessive amounts of APP produced similar to the situation in Down's syndrome.⁴² Minor pathways of APP processing, which release the β A4 domain may then become quantitatively important if there is increased APP synthesis. It can be speculated that non-21-linked familial Alzheimer's disease involves genes whose products are involved at other sites in APP processing. The final step from β A4 deposition to cellular degeneration is unclear although there is evidence that the protein is neurotoxic.⁴³ In this model of

central amyloid deposition, the neurofibrillary tangles are seen as a secondary phenomenon.

The generation of transgenic mice as an animal model for Alzheimer's disease represents a major advance. The elucidation of the precise molecular pathology now paves the way for the development of drugs which might interact with the APP pathway. However, it is clear that Alzheimer's disease cannot be viewed as a single entity. There is certainly heterogeneity within familial Alzheimer's disease and no doubt this will be found in the sporadic disease. Whether all cases are seen to be amyloidopathies or this is only part of the story remains to be seen; nevertheless, these recent advances do create an optimistic climate for future therapeutic intervention.

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