Ageing, cognition and dementia

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Age-related changes in cognitive function

Most of us are aware, as we grow older, that our memory is not as good as it used to be, especially our memory for names. Our mental speed also slows down as we age. Most elderly people also find it harder to adjust to new technology. Anecdotal evidence of age-related cognitive decline is amply supported by a wealth of objective data. Experimental and epidemiological studies demonstrate the presence of age-related decline in a wide range of cognitive functions, including memory and learning, language, visuo-spatial function, attentional resources, mental speed and the group of abilities known as 'executive function' (e.g. reasoning and abstraction, mental flexibility).

However, different abilities decline at different rates. One aspect of memory which declines very rapidly is the ability to remember the context in which an event occurred, although the details of the event may be well remembered. One consequence of this difficulty in everyday life is the embarrassing situation of repeating a joke or story to the person from whom you heard it. Prospective remembering is another type of memory which is particularly vulnerable to the effects of ageing. Prospective memory involves remembering to perform a task, such as posting a letter or taking medication. Older people often compensate for this by using diaries, making lists of 'to do' items, etc.

Likewise, different aspects of language function decline at different rates. In tests of vocabulary where subjects have to provide the meaning of words, ability tends to hold up with age and even to increase slightly. In contrast, if asked to provide a word in response to a description, elderly people are more likely than the young to fail to produce a word they actually know, often having a feeling that the word is on the tip of their tongue.

Individual variation in cognitive skills

Not only do different cognitive functions decline at different rates, but also the rate at which they decline differs from one individual to another. What determines individual differences in rate of cognitive decline is not yet known, but several factors have been implicated. Individuals with a high level of intelligence or education generally continue to perform relatively well throughout their lives, but we await definitive evidence about whether they have a slower rate of decline. ApoE genotype, a major risk factor for late-onset dementia, has also been implicated. The presence of the E4 allele is associated with a faster rate of cognitive decline in nondemented individuals from a population study [1]. Another factor influencing rate of decline is survival. In longitudinal studies with long-term follow-up, long-term survivors show much less decline than intermediate- and short-term survivors [2].

An intriguing finding is that the performance of elderly people on a wide range of cognitive tests is strongly associated with normal variations in visual and auditory acuity [3]. The authors dismiss the possibility that performance on cognitive tests is directly attributable to small differences in sensory function, suggesting instead that brain ageing is the common cause of cognitive, sensory and motor impairment. Vascular changes in the brain, in particular the microvascular changes that increase with age, are likely to play a causal role in all three types of impairment.

In addition to age differences in a wide range of cognitive abilities, there are other socio-demographic differences. Gender, education and socio-economic status each exert independent effects on cognitive performance [4]. These effects make it difficult to develop a simple screening test to separate normal from abnormal cognitive function. Since most clinicians cannot undertake an exhaustive battery of cognitive tests, the usual solution is to administer a test such as the Mini Mental-State Examination (MMSE) [5] which aims to provide a global assessment of cognitive function.

Leaving aside the question of whether global measures encapsulate the most important aspects of cognitive function, a standard cut-off point on such a scale is clearly an untrustworthy guide to cognitive impairment in an individual. An entirely new approach to dementia screening is proposed here, based on the new generation of epidemiological studies.

Assessment of cognition—the way forward

In order to diagnose an individual as being demented, we need to show that their cognitive decline exceeds that expected for their age and socio-demographic
characteristics. We therefore need longitudinal data on expected rates of decline in the normal elderly population. Such data are currently being obtained in ongoing longitudinal studies of representative samples of the elderly population in the UK [6, 7] and elsewhere.

The availability of normative data such as these will lead to a revolution in the accurate detection of dementia based on cognitive assessment. First, the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), while including the MMSE, assesses a broader range of cognitive abilities, using the CAMDEX cognitive examination (CAMCOG) [4, 8] and additional measures of memory, reasoning and speed of information processing. Discriminant analysis of scores will provide a powerful indicator of which measures are the most sensitive for dementia detection. Second, because of the enormous sample size, cognitive norms can be provided for all possible combinations of socio-demographic characteristics. Where an individual’s observed scores are significantly lower than their expected scores, the cause of their impairment should be further investigated.

The presence of physical illness, sensory impairment, depression and some forms of medication may contribute to lowered scores. At present, we have no way to estimate the extent to which an individual’s cognitive state can be explained by these factors, but from the normative population sample we could determine the expected scores for people with particular disorders such as diabetes, hypertension or depression. If an individual’s obtained score remains below the score expected even after taking account of these conditions, then that individual is very likely to have dementia.

In the very near future, one can imagine a dementia-sensitive cognitive assessment being routinely administered to an elderly patient and the results entered into a computer, along with key information about that person’s socio-demographic characteristics and other relevant health conditions. From its normative database, the computer will calculate the difference between the expected and observed results, on the basis of which a likely diagnosis may be made. More refined information could also be obtained by examining the pattern of scores. For example, if the individual showed a disproportionate impairment on measures of expressive language and executive function, abilities which depend particularly on the integrity of the frontal lobes, one might suspect a dementia of the frontal lobe type.

While these are very exciting developments, and will undoubtedly assist diagnosis in the future, they cannot replace the need for a full clinical examination and a detailed history, which are needed to obtain a full understanding of the cause and progression of the disorder.

In summary, decline across a wide range of cognitive functions is widespread, if not universal, in the ageing population. A novel approach has been suggested for differentiating this normal cognitive decline from abnormal or pathological decline associated with dementia.

Relevance of ageing-related changes in cognition to the diagnosis of dementias

It is clear from the foregoing that there are very definite age-related changes in many aspects of cognitive function, and that these present a fairly consistent pattern within an ageing population. This would appear to be a sound foundation upon which to base attempts to separate abnormal, i.e. dementia-related, changes from the norm. In practice, however, this has proved disappointing and we have not yet been able to develop a tool that clearly distinguishes between normal ageing and the cognitive deficits that are a feature of one or other of the dementias, although the knowledge gained from large community studies may change this.

The same difficulties are found in the differential diagnosis between different causes of dementia, whether working with clinical parameters or laboratory tests. In general, a range of results is obtained when exploring the value of a potential test, with overlap between the results in normal people and those with whichever of the different causes of dementia is being examined. Although there have been claims to the contrary, usually based on small numbers of subjects, when a potential test is examined in a larger cohort that includes subjects with different types of dementia, the apparent ability to discriminate begins to disappear. At the time of writing, there are one or two exceptions, e.g. laboratory-based tests such as the protein p97 about which further information is awaited [9].

Our inability, especially early in the disease course when it matters most, to use the well documented pattern of cognitive change associated with age to discriminate normal from abnormal ageing of the brain, let alone identifying discrete causes of dementia, i.e. Alzheimer’s disease (AD), vascular dementia, etc., poses important questions as to why this should be. The need to explore these issues further is emphasized by the similar inability of ‘harder’ parameters such as laboratory tests to improve discrimination.

Possible reasons for the difficulty in identifying early dementia and its causes

These are many and may include the difficulty of identifying that part of impaired cognition that may actually be age-related rather than caused by disease. It may also be that disease affects similar parts of the brain to the ageing process, aggravating such changes.

One could also ask whether these diseases exist as discrete clinical entities in the way that we apply them
to our patients. The individual pathological processes undoubtedly exist, but in many people the clinical manifestations of a disease may result from a combination of signs and symptoms that have a number of different underlying aetiologies. One example of this is the contribution made by white matter low attenuation, as shown on a CT or MRI scan, to disease symptoms. It is found in 12% of normal people, 30% of those with AD, 32% of those with isolated memory loss and 80% of people with vascular dementia [10]. Could it be a separate entity contributing to normal ageing in some, AD in others and vascular dementia in a greater number, or is it really an integral part of each of these conditions, with a different underlying pathogenesis in each?

Heterogeneity of the underlying pathology

Many of the diseases causing dementia exhibit heterogeneity of clinical presentation and pathology. AD is perhaps the best model of this as it is the most explored.

There are clinical subgroups with different underlying pathological changes [11], variation in clinical features associated with the different genotypes in familial AD [12, 13], differences in physiological parameters, e.g. in cerebral blood flow patterns as revealed by SPECT scanning [14], and even neurochemical heterogeneity—some AD sufferers do not have the expected pattern of neurotransmitter deficits [15].

As well as a small number of potential ‘environmental’ risk factors, a number of protective factors are also now beginning to emerge, e.g. the use of oestrogens in women, anti-inflammatory medication and vitamin E. Whether these protect against other acquired, rather than genetic, influences is uncertain. Nor do we yet know whether they benefit the same individuals, or work differentially within the population of people with AD.

Why do only 40-50% of people with AD respond to anticholinesterases? Even taking into account the inaccuracy of the clinical diagnosis, this is a strangely low response rate for a condition where traditionally all those affected are considered to have a primarily cholinergic deficit.

Is there a different way forward?

Are we being constrained by nosological concepts that may be comfortable to us as clinicians but which are scientifically inadequate? We still talk about Alzheimer’s disease rather than diseases, but clinical, pathological and genetic differences clearly exist. The uniformity of the pathological findings does not necessarily mean that all brains that look the same at autopsy have suffered an identical disease process. The pathology may actually represent a final common pathway for different disease entities.

Perhaps the time has come to use our increasing knowledge of the genetic basis of AD and, in due course, some of the other dementias, as an opportunity to re-focus our thoughts about the nosology of these disorders. This will become easier as the biological mechanisms associated with different genetic aberrations or polymorphisms become clearer. The latter may also provide clues as to how acquired, i.e. non-genetic, factors may contribute to different dementias, eventually helping to unravel the interaction between genetic and acquired mechanisms.

Conclusions

This paper is trying not to provide answers but to stimulate thought. It is possible that the current approach to classifying the dementias, and its consequences, is the correct way forward. On the other hand, perhaps the time has come to develop our present concepts further. These are mainly based on a historical, descriptive approach to classifying and treating disease, although this has been as important to our present understanding as the firm foundation contributed to this field by the study of the cognitive changes associated with normal ageing.

Whichever nosology we adopt—whether we retain the existing one or modify it in light of our increased knowledge of the clinical and basic science of these conditions—what really matters is how our increasing understanding contributes to alleviating the problems of people with dementia.

References


