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Evolving Embodiment of Risk:

The case of Alzheimer's Disease

Dr C J Ball MRCPsych
Consulting Medical Officer
Gen Re Life Health London

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Dr. C J Ball *MRCPsych*

Consulting Medical Officer, Gen Re London

Critical update: One disease. Millions of lives permanently disrupted.

The Alzheimer's Association *Alzheimer's Disease 2015 Facts and Figures*, released today, highlights the devastating human and economic costs of the Alzheimer's epidemic. Alzheimer's disease is taking more than memories — it's taking lives. (24/3/15)

It's a fact that Alzheimer's disease is an escalating epidemic.
The number of Americans with Alzheimer's disease and other dementias will grow each year as the size and proportion of the U.S. population age 65-and-older continue to increase. By 2050, the number of people with Alzheimer's may rise as high as 16 million. (8/4/15)

No time to lose in this fight (21/4/15)

Alzheimer's disease is an escalating epidemic. Imagine the future of our children and grandchildren: The loss of memories. The loss of the capacity to communicate, to think clearly and eventually, the ability to lead an active, engaged life.
(17/4/2015).

Introduction

It is predicted that the numbers with dementia in the UK will rise from 850,000 in 2015 to 'over one million' in 2025 (Alzheimer's Society 2014) and the commonest cause of dementia is Alzheimer's disease (AD).

The three extracts from e-mails sent by the American Alzheimer's Association paint an alarming, if simplistic picture, of a single devastating disease that will rob the elderly of their faculties, create financial instability and threaten the very core of American values. Whatever the threat, the language of crusade echoes that used against terrorism; a morally neutral disease has become invested with evil.

This rhetoric conceals the complex way in which AD (first described in 1906) has emerged over the last hundred years from a rare disease of relatively young people (Alois Alzheimer's first patient was only 54) to one, it is believed, that almost everyone will develop as they age. This happened despite accurate individual clinical diagnosis being a difficult process, fraught with problems at both national and international level where formal definitions of the disease are continually debated and revised.

The psycho-social considerations of what constitutes 'normal' for age 80 or age 90 are so varied that subjective clinical judgment inevitably plays a part in diagnosis. In order to fix the diagnosis more firmly, neuropathology is the gold standard. Alzheimer described the presence of plaques and tangles in the brain but identification of their constituent proteins (amyloid and tau respectively) only came later. The relationship between these brain changes and the clinical presentation of the patient (the phenotype) remains imperfectly understood.

Scientists investigating how the plaques and tangles come about have been dominated by the 'Amyloid Cascade Hypothesis' (Hardy & Higgins 1992) as a paradigm for understanding the deposition of amyloid and tau in the brain. However the failure of the hypothesis to deliver effective treatments has led to a rethink. It is now argued that intervention only after the patient has memory problems is too late in the neuropathological process to be of value. Dubois et al (2007) marshaled the evidence that the processes leading to cognitive decline start many years before the clinical presentation, calling upon the scientific community to identify 'biological footprints', or biomarkers, of the disease. Thambisetty and Lovestone (2010) suggest that the identification of such markers is less an issue of making a clinical diagnosis but rather that they will serve to identify candidates for early intervention trials and help track the effects of intervention on the underlying disease processes.

The rise of genetic sequencing has allowed a number of illnesses, for example Huntington's disease, to be identified well before symptoms arise. However, single gene illnesses like these are relatively rare. Developments in neuroimaging and the measurement of proteins in bodily fluids, particularly cerebral spinal fluid and blood make identification of biomarkers a real possibility and significantly shift the ways in which our bodies are recognized as expressing risk.

Neuroimaging

Lock (2013) describes the changes in neuroimaging as 'embodied risk made visible'. The earliest Computed Tomography (CT) studies showed the brain shrinkage (atrophy) present in severe AD but the findings were non-specific. Although they could be used to rule out other causes of dementia, such as stroke or tumour, there was a significant overlap with the scans of people with normal cognition (Jacoby & Levy 1980).

More detailed Magnetic Resonance Imaging (MRI) studies offer closer focus on those regions of the brain specifically affected by AD. The earliest changes are seen in a structure called the hippocampus. The ability to measure the volume of this structure and compare it to age matched cohorts has the potential to improve the diagnostic certainty in a given case. Evidence of hippocampal atrophy is a strong predictor of progression to dementia in people with subjective cognitive impairment (Mild Cognitive Impairment or MCI) but who do not yet meet the clinical criteria for a dementia diagnosis (e.g. Devenand et al 2007).

Sophisticated functional imaging techniques, Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT), allow the identification of patterns of decline in brain activity that correlate with the presence of AD. There is evidence that these patterns can be seen in cognitively normal people and those who have MCI who later develop AD (Silverman et al 2001, De Leon et al 2001).

In addition to these general findings, the development of tracers that bind specifically to the proteins amyloid and tau adds potential for early diagnosis and measuring the impact of therapeutic interventions. Amyloid PET is the best characterized technique but it is expensive and so not widely available. It also has a number of limitations. About one third of older people who do not have cognitive impairment have amyloid

positive PET scans. So while PET scanning is unhelpful as a screening tool (even if it was to become cheap and readily available) it may have a place as a diagnostic technique in cases where problems have already developed. More recently tau tracers have been introduced. Villemagne et al (2015) celebrate the progress made, but acknowledge that more needs to be done before its utility is established. Many other changes are beginning to be investigated using PET biomarkers, including the activity of other types of brain cells such as astrocytes and glia, inflammatory changes and neurotransmitters such as Acetylcholine, Serotonin and Dopamine.

Cerebrospinal Fluid

Cerebrospinal fluid (CSF) is an obvious target for measuring changes in the brain. The CSF bathes the brain and spinal cord but is difficult to get at. Samples can only be obtained by passing a needle between the lumbar vertebrae and into the space around the spinal cord; an invasive and uncomfortable procedure, requiring specialist training and not without complications (see Technical Glossary).

Amyloid and tau have received the most attention but a multitude of other biomarkers have been investigated. Levels of CSF amyloid show an inverse relationship to the number of plaques in the brain. Both the total of the tau protein and, more specifically a subset know as phosphorylated tau (p-Tau), are elevated in proportion to pathological change. There is little variation in these markers once dementia is established. It is suggested that these changes happen in the preclinical phase of the disease possibly 10 to 15 years before the onset of symptoms. The utility of these biomarkers remains in question as techniques to obtain, measure and report results are not standardized but they are increasingly available in specialist settings (see Blennow et al 2015 for a review).

Genetics

Diseases that have their onset late in life are not generally thought of as strongly genetic in origin. The family histories of people being assessed for AD are often incomplete, both because their parents and grandparents did not live long enough to get the illness and because there was less recognition of the disease in the past. The development of genetic techniques has changed this position. In AD the process began with identification of genes involved in familial, or dominantly inherited,

disease that affects people between the ages of 40 and 60. The *Presenillin 1* gene has over 30 variations and is estimated to account for 15% of familial AD. The *Presenillin 1* gene is associated with a very early age of onset. Carriers of the *Presenillin 2* gene have a later age of onset (over age 55) and some do not actually progress to dementia. The Amyloid Precursor Protein Gene (APP) is the third of these early onset genes. Together they account for fewer than 1 in 1,000 cases. The first genetic risk factor for late onset AD was identified in 1993. The *APOE* gene is located on chromosome 19 and has a number of variations (*APOEε2*, *ε3* and *ε4*). Each person has two *APOE* variations. Those with two *APOEε4* variations are most likely to develop AD between the ages of 60 and 80. A person with one *APOEε4* has approximately 3 times the risk, whilst a person with two has between 8 and 30 times the risk (Lock 2013). *APOEε4* is a susceptibility gene as it is neither necessary nor sufficient to develop AD. Between one third and half of those diagnosed with AD do not carry *APOEε4*. The exact way in which the gene is involved in the neurodegenerative process remains opaque.

Genome-wide association studies, the rapid sequencing to areas of interest that may be associated with a particular condition, have changed perceptions of the genetic influence in late onset AD. Lambert et al. (2013) reported 11 new AD susceptibility loci and confirmed 8 previously reported loci in addition to *APOE*. Together they account for 61% of the population-attributable risk (Medway & Morgan 2014). These findings suggest complex interactions between multiple genes and the environment (epigenetics) must take place in order to arrive at symptomatic AD. Understanding the role of these different genes leads to new ideas for therapeutic interventions – to the immune system or cholesterol metabolism for example. Good diet and exercise can alter the way these genes are expressed changing the long-term outcome. Currently genetic testing is reserved for specialist and research settings and is of value only in early onset cases.

Blood

However good a biomarker might be, if it is not cheap and acceptable then it has little clinical utility. Most people find blood tests acceptable from a practical perspective but because blood is separated from the brain by the blood-brain barrier, it is not a direct reflection of the organ's status. Thambiseety and Lovestone (2010)

stress the complexity of blood compared to CSF presents an opportunity as well as a challenge.

Early blood studies measured single molecules related to amyloid and tau but the overlap between controls and those with AD meant they had little utility as a diagnostic aid. The ability to identify multiple proteins in blood (proteomics) quickly and cheaply, allowed investigators to develop the protein signature of AD subjects. Kiddle et al. (2014) identified 163 candidate proteins from the literature and replicated the studies for 94 of these. Only 9 were found to associate with AD and none was associated with conversion from MCI to dementia. More promisingly, Hye et al (2014) identified 10 proteins that predicted the conversion of MCI to AD with 87% accuracy. The study opens real possibility that a cheap, acceptable biomarker of pre-symptomatic AD is not that far away. Despite these encouraging results, Chiam et al. (2015) argue that the majority of AD candidate proteins could be involved in other brain disorders and more research into their specificity is required.

Living with embodied risk

Early speculation has proved unfounded that the identification of the whole genome would lead to a clear vision of the biological life of an individual, detecting the 'pre-symptomatically ill' (Yoxen 1982). Even in single mutation disorders relatively small numbers (5% to 25%) of those potentially affected decide to undergo genetic testing (Lock 2013). Such testing enumerates risk objectively and statically, divorced from a person's biography and society. Concerns about the impact testing could have on the availability of life insurance appears to have some influence on these decisions (Apse et al. 2004).

For AD, this is the situation for a small number of familial cases with single gene mutations but the position is very different when the information given is about the susceptibility gene *APOE*. The *Risk Evaluation and Education for Alzheimer's Disease* (REVEAL) study sought to understand these processes in more detail. A cohort of volunteers agreed to have an educational session about AD following which their blood was taken for *APOE* testing. The participants were then informed of their results and seen three times over the next 12 months. One year on from the testing, 27% remembered the information, 50% had the broad gist correct whilst 23% either remembered nothing or were incorrect in their recall. A qualitative study of this

group revealed the difficulties of imparting and understanding probabilistic information about susceptibility (Lock 2013). The information was largely 'eclipsed' by the persons 'lay understanding' based on information from many sources, their individual experiences of the disease, a sense of the person they most resembled in the family and if this person had AD.

Although a small number had made changes to their insurance as a result, very few made long-term changes as a result of the experience. In a separate study, people with at least one *APOEε4* variation were 2.3 times more likely than those with two *APOEε3* variants to have increased their Long Term Care Insurance (LTCI) or to have had plans to do so. The absolute probability of making a change to their insurance for people with at least one *APOEε4* variant was 0.237 compared to 0.087 for those with two *APOEε3* variants (Taylor et al 2010).

Insurance

The attempt to define the 'pre-symptomatically' ill in AD has been driven by the failure to develop treatments, the growth in the elderly population in developed countries with the attendant financial risk, and the development of new technologies in imaging, genetics and proteomics. For the moment AD holds center stage politically but in many other areas of medicine similar developments are underway.

This provides some significant challenges for the insurance industry not only in the areas of life, critical illness and long term care (on which this paper concentrates) but also for products such as vehicle insurance, public liability and employer's liability. Not least of these challenges is appreciating the risks when complex susceptibility genes are identified but likely to be modified by epigenetic factors. Clearly the lay person struggles to understand these in the context of their own biographies and personal circumstances and instead use a wide variety of information to decide what to do with the information.

Managing this understanding is likely to improve with time but currently very few doctors would be comfortable with exploring the intricacies of this kind of risk with their patients. The dangers of the information being filtered through the doctors' understanding, and their taking too little time to explore the repercussions in detail,

could lead to false perceptions and ill-advised actions. Lock (2013) points out the potential complex effects of this knowledge which….. ”can initiate or inhibit action, and increase or reduce, or transform anxiety about genetic embodiment”. Understanding the individual’s driver to action will go a long way to understanding why particular people seek insurance at a particular time.

Approaches to accessing genetic information in a Life insurance context vary greatly across the globe. In the UK, a voluntary moratorium has been in effect since 2001 and extends to 2019. The restriction applies only to predictive genetic tests – done before any symptoms or abnormal non-genetic tests results suggest a condition is present. UK insurers may access “appropriate” family medical history. The response to other predictive tests such as proteomics or neuroimaging is not yet articulated.

The EU has not legislated on genetic testing but the Council of Europe’s *Convention on Human Rights and Biomedicine* prohibits genetic discrimination. Insurers may not ask an applicant to undergo a predictive genetic test (but may ask for a diagnostic one). The convention does not prohibit insurers asking for existing test results. Thereafter, access to gene testing by European insurers is governed, to a greater or lesser extent, by some (or all) of human rights legislation, limitation by national law, moratorium or blanket bans. Some countries prohibit all use by law. Others limit use by sum assured. The different approaches arise from the context of insurance; the UK operates a private market with voluntary enrolment for example while in other places insurance is tax funded or forms part of state health provision.

The impact of these developments upon insurers depends a great deal on the regulatory framework in which they must operate and the extent they are allowed to use this information. Where knowledge is held by one party and not the other the possibility of anti-selection becomes much more real. Discussing the impact of *APOE* testing on prefunded LTCI, Taylor et al (2010) outline a number of scenarios where various parties know the *APOE* status of the applicant raising the possibilities of anti-selection and adverse selection. They argue that only where both the insurer and the client know their *APOE* status is it likely that a fair premium could be charged and has the greatest possibility of increasing long term care coverage.

As the traditional causes of mortality decline – from cardiovascular disease for example –and people live longer, the assessment of dementia risk will become increasingly important in the design of insurance products and in risk assessment at underwriting (Ford & Capwell 2011). The potential to obtain preferable rates on retirement annuities for those with pre-clinical diagnoses becomes a real possibility, albeit with significant trend risk for insurers. The hope that treatments will follow from identifying the pre-clinical phase of disease raises the possibility of interventions that will improve the life expectancy of this group after an annuity has been purchased.

In contrast to many other causes, dementia and AD are making up an increasing proportion of deaths. In England and Wales the proportion of all registered deaths with dementia and AD reported as their primary cause rose by 4.2% for males over the period 2003 to 2013 (from 2.0% to 6.2%), and by 7.5% for females (from 4.7% to 12.2%). (ONS Statistical Bulletin Deaths Registered in England and Wales 2013). The *Global Burden of Disease Study 2013* concluded that age-standardised death rates for dementia and AD increased by 3.2% over the period 1990 to 2013, after modelled adjustments to allow for under-reporting of dementia as a cause of death historically. As outlined in this paper advances first need to be made in the understanding of pre-clinical dementia before treatment and associated gains in life expectancy become a reality and a consideration for pricing of mortality and longevity risk.

Existing disease definitions in some Critical Illness (CI) Insurance policies may be inadequate unless clear severity measures are included, with claims being made for diseases that may never actually become a problem to the person. The current model definition requires there be a “definite diagnosis of Alzheimer’s disease by a Consultant Neurologist, Psychiatrist or Geriatrician”. There must be permanent, clinical loss of the ability to do all of the following: remember, reason and perceive, understand, express and give effect to ideas. At present, this represents a relatively high level of severity and if maintained it is unlikely that there will be an increase in CI claims.

Conclusion

The creation of the ‘pre-symptomatically ill’, embodying risk in novel ways is increasingly possible in many areas of medicine. Assessment of this group is fraught with difficulty for the clinician articulating the risk, the individual in comprehending it and deciding how to act and also for insurance companies in responding to these changes.

AD provides a particularly pertinent example of this phenomenon with developments in genetics, neuroimaging and proteomics. The likelihood of a blood test that functions as a useful biomarker for the disease is not too distant. Effective treatments, however, are much further away. Until they come, developing a fair and proportionate approach to pre-symptomatic diagnosis is an urgent priority.

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Technical Glossary

Alzheimer’s Disease

Alzheimer's disease (AD) is a slowly progressive degenerative disease of the brain. It is recognised by impairment of memory and disturbances in reasoning, planning, language, and perception.

The brain changes are characterised by the deposition of abnormal proteins as plaques (amyloid) and tangles (tau).

APOE

APOE is a susceptibility gene for AD. Each person has two copies of this gene located on chromosome 19. The gene comes in three forms ϵ2, ϵ3 and ϵ4.

Biomarker

A biological characteristic that can be used to measure the presence or progress of disease or the effects of treatment.

Blood-Brain Barrier

The blood-brain barrier is a semi-permeable membrane that separates blood from the cerebrospinal fluid. It prevents the transfer of cells and large molecules including many drugs.

Computerised Tomography

A Computerised Tomography (CT) scan uses multiple X-rays and computer modeling to create detailed images of the inside of the body.

Epigenetics

Epigenetics is the study of environmental, external factors that influence the expression of genes, turning them on and off. These factors do not change the basic DNA sequence.

Functional Imaging

Unlike CT or MRI, functional imaging (PET and SPECT scanning) uses radioactive tracers to identify any abnormalities in functioning of the brain rather than structure.

PET; An acronym that stands for Positron Emission Tomography: In PET imaging, the patient receives a small intravenous injection of a radio-active chemical (sugar, amyloid etc) to identify areas of reduced function

SPECT: An acronym that stands for Single Photon Emission Computed Tomography, a nuclear medicine procedure in which a gamma camera rotates around the subject providing information to a computer that constructs a cross sectional image.

Lumbar Puncture

A lumbar puncture is a medical procedure where a needle is inserted into the lower part of the spine to test for conditions affecting the brain, spinal cord or other parts of the nervous system. Samples of Cerebrospinal Fluid are removed for analysis.

Possible side-effects include:- Back Pain, Headache, Swelling and bruising, bleeding inside the head, infection, numbness and tingling in the legs, and double vision.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a scan that uses magnetic fields and radio waves to produce detailed images of the inside of the body.

Mild Cognitive Impairment

A condition in which a person has subjective cognitive problems that do not meet the criteria for a dementing illness. People who experience this are more likely to develop dementia but this is not inevitable.

Neuropathology

Neuropathology is the study of diseases of the nervous system at the level of anatomical change. This may include visible changes but also those revealed by manipulation of samples of tissue at a microscopic level.

Proteomics

The study of the complete set of proteins in a cell (the proteome), their structure and function, is known as proteomics.

Institute and Faculty of Actuaries

London

7th Floor · Holborn Gate · 326-330 High Holborn · London · WC1V 7PP
Tel: +44 (0) 20 7632 2100 · Fax: +44 (0) 20 7632 2111

Edinburgh

Maclaurin House · 18 Dublin Street · Edinburgh · EH1 3PP
Tel: +44 (0) 131 240 1300 · Fax: +44 (0) 131 240 1313

Oxford

1st Floor · Park Central · 40/41 Park End Street · Oxford · OX1 1JD
Tel: +44 (0) 1865 268 200 · Fax: +44 (0) 1865 268 211

Hong Kong

2202 Tower Two · Lippo Centre · 89 Queensway · Hong Kong
Tel: +11 (0) 852 2147 9418 · Fax: +11 (0) 852 2147 2497

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