

When dementia is misdiagnosed

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Structured Abstract

Objective

To explore and discuss the implications of diagnostic uncertainty within services that diagnose and treat people with dementia. In particular, the difficulties associated with false positive dementia diagnoses.

Methods

Narrative review written by an Old Age Psychiatrist and a Cognitive Neurologist.

Results

Both false-positive and false-negative dementia diagnoses are made. These are more likely when apparent dementia is mild and in less typical cases, including when the patient is under 60, the diagnosis is less common or diagnosis has depended largely on brain imaging. In such cases, the passage of time is generally helpful in revealing diagnostic status. Reversing a dementia diagnosis can be very difficult for patients.

Conclusion

Except in some rare situations, dementia diagnoses made in life are only “probable” and should be subject to review. Dementia diagnosis services should support patients through reversal of diagnoses.

Key words

Dementia diagnosis; misdiagnosis; reversal of diagnosis; functional cognitive disorder.

Key points

Dementia diagnoses are sometimes made incorrectly, particularly in younger patients.

Reversing a dementia diagnosis is difficult for clinicians and patients.

Dementia diagnosis pathways should include facility for review and possible reversal of diagnosis.

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Conflict of interest statement

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In the absence of treatments to slow neurodegeneration and in anticipation of inevitable deterioration in personal autonomy and identity, it is difficult to think of a diagnosis that is more life-changing to receive than dementia. The implications of an incorrect diagnosis; emotional and psychological damage to a patient and their family, unnecessary withdrawal from business, occupational and social activities, changes to financial planning, exposure to dementia treatments and failure to explore treatable alternative explanations for symptoms; are considerable. Dementia is by definition progressive, and implicit in making the diagnosis is both that there has been decline from a previous level of functioning, and that ongoing decline is inevitable. Alzheimer's disease studies show consistently that while there is considerable variation, on average patients will decline by 3 points on the 30 point minimal state examination per year (Han et al, 2000); and in a nationwide study of over 50,000 patients with dementia, median survival from diagnosis to death was 5.1 years for women, and 4.3 years for men (Haaksma et al 2020). Where the diagnosis is uncertain, for example, early in the disease course, serial assessment allowing for demonstration of decline in cognition and function adds confidence to the diagnosis, but is not routinely offered in many settings.

Dementia is a description of a clinical state with numerous underlying causes. Determining the subtype of dementia is not only important to guide treatment but also to inform prognosis, and is now included in NICE guidance (NICE 2018). However, because the vast majority of the causes of dementia can only be determined with certainty by neuropathological confirmation, diagnosis of syndromic subtype made in life (with a few notable exceptions) can only ever be *probable*, although clinical assessment, neuropsychological testing, brain imaging and pathology-specific biomarkers contribute to high levels of accuracy confirmed by eventual neuropathological examination.

Over the last 20 years, driven by increasing awareness of dementia as more than an inevitable accompaniment to ageing, availability of symptomatic drug treatments and conduct of disease-modification trials, expansion of services to diagnose dementia as early as practically possible in as many people as can be identified has been a notable achievement. In England, 65% of the population estimated to have dementia are currently diagnosed through NHS

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memory services (Department of Health, 2020). Although no benefits for patients in terms of subsequent disease progression, time to institutionalisation or death or for caregivers' burden, quality of life, depression and anxiety have been demonstrated, early or "timely" diagnosis of dementia has become standard (Dubois et al, 2016), and has many potential benefits including the opportunity to access relevant support, advice and benefits; receive appropriate symptomatic treatments; participate in clinical trials; plan for the future; and, in the future perhaps, be eligible to receive disease modifying therapies.

Diagnosing dementia at the point when individuals or those around them first become sufficiently concerned to seek help because of perceived changes in cognition, function or behaviour, however, is complex and difficult; not least as symptoms are likely to be mild. A measure of the inherent difficulty distinguishing between dementia and the effects of healthy ageing on cognitive function at this point is the high frequency of diagnoses of mild cognitive impairment (MCI) made in up to 40% of patients within some diagnostic services. MCI, a term introduced to delineate individuals with objective cognitive impairment but who remain functionally unimpaired, is not inevitably progressive. Although individuals have a higher risk of developing dementia than cognitively normal individuals (typically, 10-15% per year), 50% will show no decline over the subsequent five years (Dunne et al, 2020). In this group, there are increasing moves to use disease specific biomarkers to identify individuals with MCI due to specific neurodegenerative diseases (Alzheimer's disease in particular), who are most likely to progress to dementia (van Maurik et al, 2019). Inherent in this approach (although usually much less of a focus), is the potential opportunity to identify individuals who will not progress.

In the presence of such diagnostic imprecision it can be anticipated that significant numbers of patients will be misdiagnosed, with both over- and under-diagnosis of cases of dementia.

Clinicians will be more familiar with the implications of under-diagnosis. The progressive nature of the condition means that, over time, symptoms will inevitably worsen and the case for reversing a missed diagnosis becomes stronger as the months pass. However, once a dementia diagnosis has been made, any subsequent failure of symptoms to progress over following months and even years may be attributed to the effects of anti-dementia medication, cognitive stimulation or heterogeneity of decline patterns between individuals. Diagnosed individuals will often have made what were appropriate adjustments to their lives

and even be in receipt of some of the benefits associated with being a person with dementia, and many may not remain under regular review. Undiagnosing dementia is consequently very much more difficult than making the diagnosis, both for the diagnosing clinician and the patient.

Even if the proportion of people misdiagnosed with dementia is small, the large number of dementia diagnoses made (around 120,000 annually in England) (Matthews et al, 2016), would suggest that they constitute a significant number. While, anecdotally, dementia specialists routinely undiagnose patients with dementia, there are no research data to inform a precise estimate of the scale of false-positive dementia diagnoses, although illustrative case studies and reports have been published. Larner reported two cases where diagnoses of AD had been reversed after 9 and 14 years of non-progression of cognitive impairment (Larner 2004). Factors that contributed to misdiagnosis included lack of involvement of a specialist dementia clinic, failure to apply standardised diagnostic criteria, absence of supportive collateral history, presence of mood disorder symptoms, over-reliance on the results of structural brain imaging and lack of longitudinal follow-up data. Shipley reported 46 patients whose initial dementia diagnoses had been supported by FDG-PET and were subsequently reviewed in a tertiary clinic. Nine percent were found to be cognitively normal, 5% to have a reversible cause of cognitive impairment and 27% had some form of psychiatric disorder (Shipley 2013). The authors suggested that physicians often have a false sense of confidence in diagnoses made from PET beyond the evidence from a standard clinical evaluation and wrote: “our findings will come as no surprise to practising behavioural neurologists who frequently “undiagnose” AD diagnoses based on PET scans”.

An increasingly recognised group of people who have been diagnosed with mild cognitive impairment or early dementia have functional cognitive disorder. This is characterised by complaints of cognitive impairment symptoms that are internally inconsistent, show stability over prolonged periods of time and fail to respond to reassurance of evidence for lack of objective cognitive deficit (Ball et al, 2020). This diagnosis represents the most likely explanation for many individuals who have received a dementia diagnosis but show no discernible deterioration in cognitive functioning or disability over several years. Although there are no evidenced treatments for functional cognitive disorder, making the diagnosis is

important to protect patients from the potentially adverse effects of an incorrect dementia diagnosis.

The implications of a dementia diagnosis are sufficiently profound that it is important to attempt to be as certain as possible that the diagnosis is correct. In practice, this first requires the initial diagnosis – not just of dementia, but also its underlying cause – to be made with as much certainty as possible. This requires careful clinical assessment, and depending on the clinical situation may involve access to neuropsychology, expert neuroradiology, dementia biomarkers and genetic testing where appropriate and in line with NICE guidance (NICE 2018). While often, and particularly in the UK, there has been scepticism about the value of some of these more involved techniques, and particular those aimed at determining a molecular diagnosis, on the grounds that a positive test may be unlikely to change practice, the value of a *negative* or normal test result is underappreciated. This is particularly true in younger patients where the incidence of dementia is lower, the differential diagnosis may be wider (Rossor et al, 2010), the prevalence of incidental brain pathologies is lower; and at the earliest point at which the clinical symptoms of dementia manifest where the potential for a false positive dementia diagnosis will be strongest.

Sometimes, even following the application of all available aids to diagnosis, it may not be possible to determine with certainty whether or not a patient has dementia. Where such patients are labelled as having MCI, it is important that this is not viewed as a final diagnosis as this can absolve the clinician of further responsibility to investigate further and leaves the patient in a state of uncertainty about prognosis. In this situation, careful explanation; including acknowledging uncertainty is required, and utilising disease-specific biomarkers to determine the cause of MCI may be of benefit. In case of doubt, review of symptoms, neuropsychology and imaging after a further interval is usually helpful in distinguishing progressive neuropathology from less sinister explanations for symptoms.

All dementia diagnoses, and particularly those made at the earliest stages of the disease, those of rare or atypical dementia variants, those where the diagnosis has been largely based upon imaging or other biomarker evidence, and those in unusual groups such as those aged under 60, should be subject to routine review until it is clear from evidence of characteristic progression that the correct diagnosis has been made. As UK dementia diagnostic services

have grown to deliver population-based levels of diagnoses, they have tended to adopt a strategy of “diagnose and discharge” to cope with demand. This will inevitably make it more difficult to review those who may have been misdiagnosed with dementia and to reverse their diagnoses on the basis of non-progression of cognitive, functional or behavioural impairment.

All dementia services should include a clear pathway for the routine review and potential reversal of diagnosis where this is in doubt. At present, this tends to be available only within specialist Cognitive Neurology services and may be difficult for some patients to access. Any such service should include the provision of psychological support for patients, many of whom will find the reversal of their diagnosis extremely difficult along with their continuing anxiety about the cognitive symptoms that led them to present and that they will need to be able to understand and manage if they are to benefit from removal of their dementia diagnosis.

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