TITLE: Alzheimer's dementia research: past approaches and future directions.

Abstract

The rising global incidence of dementia resulting from increased life expectancy is associated with growing personal, social, and financial burdens; yet, there is currently no disease modifying treatment for the condition. The last decade of dementia research has seen a shift in focus, with increased efforts being made to understand the early, asymptomatic phases of diseases like Alzheimer's in an effort to prevent, rather than just treat, cognitive decline. The present article provides an overview of the research in the area, where it is headed, and which challenges lay ahead.

Key Points

- Dementia research over the last three decades has failed to produce effective disease modifying treatments for the underlying causes of cognitive decline.
- Current research has shifted attention to the early, asymptomatic phases of diseases which lead to dementia, with the aim of allowing for early intervention and improving secondary prevention approaches.
- The identification of biomarkers that can help identify people at increased risk for or in the early stages of dementia is key to improving research quality and treatment efficacy.
- Health services are adjusting to the shift in focus to preclinical phases of dementia by implementing a 'brain health' approach and increased screening in high-risk groups.

Keywords: Dementia, Alzheimer's disease, biomarkers, prevention

Questions for reflective notes or discussion

- What has driven the focus for dementia research?
- What role could biomarkers play in preventing dementia?
- How could preventing or reducing risk of dementia work in the current clinical pathways?

Dementia is an umbrella term that describes a clinical syndrome characterised by a decline in a person's memory and cognitive abilities sufficiently severe to interfere with independence in daily living activities (American Psychiatric Association, 2013). Most dementias are the result of an underlying neurodegenerative condition—although in some rare cases there may be a

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non-neurodegenerative cause (eg, Knopman et al, 2006)—with Alzheimer's disease (AD) accounting for around 70% of all cases (Alzheimer's Disease International, 2018). Over the past 30 years the prevalence of dementia has more than doubled to an estimated 50 million people currently living with the disorder worldwide (GBD 2016 Dementia Collaborators, 2019); however, this number is expected to triple by 2050 (Alzheimer's Disease International, 2018). Similarly, while the global cost of dementia is currently thought to be around $1 trillion USD a year—which is more than 1% of the worldwide gross domestic product—this figure is rapidly rising and is anticipated to double over the next decade (Wimo et al, 2017). These numbers highlight the urgent need for effective treatments for dementia and its causes. However, while significant efforts have been made into developing such novel therapies, research in this area has thus far enjoyed very limited success, with one report showing that 99.6% of over 400 trials into AD run between 2002 and 2012 failed (Cummings et al, 2014).

The slow progress in the discovery of new pharmacological treatments and the introduction of innovative technologies have motivated a shift in the research landscape over the last decade, with the spotlight being shone on understanding the early, pre-symptomatic phase of the disorder, and on preventing (through both primary and secondary measures) rather than curing its causes. The present article aims to provide an overview of the current state of research in the field, focussing primarily on AD, the commonest cause of dementia, and how the approach taken to investigating and tackling it has evolved throughout the years.

Alzheimer's research: who, what, and when

Much of the research conducted on AD over the last three decades has been based on the amyloid cascade hypothesis (Hardy & Higgins, 1992). The key principle of this proposal is that tau-tangle formation, neuronal loss, vascular damage, and the consequent dementia which characterise the Alzheimer's pathology are the result of the deposition in the brain of a protein fragment called beta-amyloid (Aβ). Over the subsequent 20 years a wealth of clinical trials has been based on this hypothesis, for example, by testing medication intended to immunise Alzheimer's patients against the accumulation of amyloid plaques. Some of the drugs trialled as part of this line of research showed promise in lowering cortical Aβ load compared to placebo (eg, Gilman et al, 2008; Holmes et al, 2008); however, this reduction was either not accompanied by an improvement in the participants' cognitive symptoms, or the size of the effects were small and their duration short lived (Ricciarelli & Fedele, 2017).

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While the results generated by this approach have been generally disappointing, rarely leading to effective therapeutic solutions and as yet producing no disease modifying drugs, they have nonetheless been valuable both for refining theories on the role of Aβ and, importantly, for helping adjust the aim of subsequent research. In particular, the failure of these trials has raised questions as to which patient group should be the target of the next generation of studies, which aspect of the pathology the drugs tested in these studies should aim to modify, and crucially, at what stage of the disease the intervention should take place. Indeed, it may well be that previous trials were right in targeting amyloid but did so in the wrong population group (eg, people with cognitive impairment but without proven amyloidopathy, in part as it is now recognised that AD has multiple concurrent pathological pathways) or at too late a phase in the pathology for the drugs to work successfully.

For instance, one striking fact is that the accumulation of Aβ in the brain in AD begins decades before the first cognitive symptoms appear and cause the clinical syndrome of dementia (Lippa et al, 1998; Ritchie et al, 2015). Therefore, it may be that the accumulation of amyloid plaques is involved in the early period of the pathology, triggering a range of secondary processes, like the formation of tau-tangles, which, once set in motion, persist independently of Aβ, thus continuing to cause injury to neurons (St George-Hyslop & Morris, 2008). If this were the case, then removal of Aβ after these secondary events take hold would be expected to have little impact on the evolution of the disease. However, early immunisation to Aβ in people at high risk of developing Alzheimer's could halt the initiation of these processes, thus preventing the progression to dementia (Sevigny et al, 2016).

Other, more radical interpretations of the high failure rate in clinical trials have also been suggested. For example, some researchers propose that the role of amyloid may have been misinterpreted in the first instance. Perhaps, plaque formation is a response to internal processes, such as oxidative stress in the brain (Nunomura et al, 2001), or to external threats to the organism like viral infections (Itzhaki et al, 1997; Itzhaki et al, 2020), rather than the initial process of an independent pathology.

Early intervention: the importance of biomarkers

Irrespective of which hypothesis is correct, what has become increasingly apparent is the need for a better understanding not only of the later stages of AD, when the dementia is present and neurodegeneration is widespread, but of the earlier stages too. Two central questions in this

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respect are, how can asymptomatic people who are either at high risk of developing the disease or are already showing signs of the pathology (ie, the preclinical stage) be identified? And how would we know if any treatment was modifying the disease in this group? The answers to these questions rely on the discovery of biomarkers, which can help identify suitable individuals for inclusion in clinical trials, track disease treatment, and ultimately aid more accurate diagnosis in clinical settings. For instance, currently, amyloid and tau can both be measured by analysis of cerebrospinal fluid (CSF) and positron emission tomography (PET) scans (Ashton et al, 2018; Schöll et al, 2019). Although neither procedure is part of most current clinical pathways in UK memory clinics (who now more frequently see patients with mild memory symptoms, which may lead onto dementia), they do provide the ability to recruit with greater precision participants for studies aimed at those targets, reducing the risk of failure due to inclusion of amyloid- or tau-negative patients.

As discussed above, however, amyloid is only one aspect of the Alzheimer's pathology, it does not always predict cognitive decline, and its modification has rarely shown any benefits to patients. Furthermore, both CSF collection through lumbar puncture and PET scans are invasive and expensive procedures. Therefore, two major challenges lay ahead and need to be addressed: (1) the identification of biomarkers that can predict cognitive decline and disease progression; and (2) the development of quick and cheap techniques for the collection and measurement of such biomarkers (Zetterberg & Schott, 2019).

With regards to the first challenge, a significant push has been made in recent years to define the progression of Alzheimer's, from preclinical (before any symptoms of dementia are present) to prodromal (commonly referred to as mild cognitive impairment; MCI), up to dementia (Aisen et al, 2017; see Figure 1). A recent review listed nine studies focused on prevention of progression of early AD (Cummings et al, 2018). For instance, the PREVENT study (Ritchie & Ritchie, 2012) prospectively tests the children of parents with and without AD, categorising them as low-, medium-, or high-risk for developing the disease based on parental and genetic information. The objective of the study is to characterise changes in AD biomarkers (eg, amyloid, tau, pro-inflammatory cytokines, white matter lesions, cognitive performance) years before the development of any clinical symptoms.

A different, large-scale study aiming to further define the progression of the disorder is the European Prevention of Alzheimer's Dementia (EPAD) project (Ritchie et al, 2016). The study was collaboratively run out of multiple sites across Europe—recruiting both healthy people

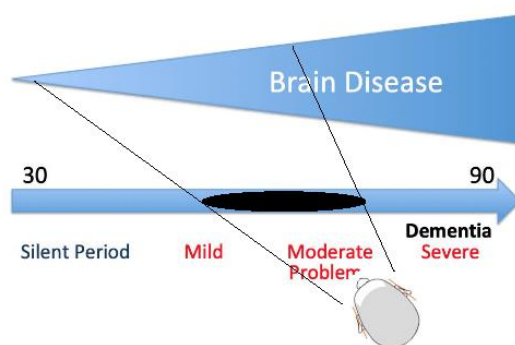**TITLE: Alzheimer's dementia research: past approaches and future directions.**

Figure 1. Dementia as it has been viewed thus far through a 'clinical eye'. The focus has been on the later stages of disease, with little attention paid to the earlier 'silent period'.

and people with MCI—and gathered data for designing prediction models of AD based on a combination of unmodifiable risk factors—like age and genetics—cognitive symptoms, and biological markers. The upshot of these models, it is hoped, will be the development of a full spectrum of dementia—rather than just the division into discrete disease categories—from which to quantify someone's risk of progressing to dementia, and enabling the implementation of early and targeted interventions.

Being able to quantify someone's likelihood of developing dementia far in advance is crucial. However, a second, equally important aspect in the development of more successful research is knowing which outcome measures to assess, particularly in studies targeting preclinical and prodromal patients. Indeed, when testing a therapy on people not yet exhibiting significant cognitive decline, evaluating the efficacy of an intervention would be virtually impossible without running impractically long and expensive drug trials. Even then, it would still be difficult to determine whether someone not progressing to dementia is a sign of a drug working or if their cognition was never going to deteriorate in the first place.

Projects such as the Deep and Frequent Phenotyping (DFP; Koychev et al, 2019) study propose to bridge this gap. The key benefit of DFP lies in the high frequency of assessments and the addition of some new ways of evaluating brain pathology, compared to studies with similar objectives like EPAD. Specifically, DFP consists of a year-long observation of participants with prodromal AD (ie, people without dementia but with signs of very mild cognitive impairment and of Alzheimer's pathology) and healthy controls, during which a wide range of very frequent cognitive and biological markers (eg, performance on memory and executive function tasks, neuroimaging, CSF, blood, saliva, and urine tests) are taken. Additionally, more novel methods are also employed, including magnetoencephalography (known as MEG; which

assesses magnetic fields produced by natural electrical currents in the brain), retinal imaging (which may provide a far less invasive and more cost effective way of detecting Alzheimer's amyloid pathology), and the use wearable devices (which provide continuous information about parameters like gait and movement tracking). The aim of such an intensive testing schedule is to enable the identification of rapid and subtle clinically relevant changes in the early stages of the disease. The identification of such changes will allow assessing over the short term whether an intervention is successful without the need to wait for slow and long-term outcomes to occur and may involve a combination of assessments. As a result, the speed and cost-effectiveness of future proof-of-concept trials will be improved.

Another related advantage of the increased focus on understanding the preclinical and prodromal stages of AD is the potential for implementing non-pharmaceutical primary and secondary prevention in high-risk individuals through lifestyle modifications. Cardiovascular disease, poor diet, low physical activity levels, extreme body-mass index, and diabetes, among other factors, have all been shown to impact the risk of developing dementia (Flicker, 2010; Xu et al, 2015). With biomarkers capable of predicting disease progression, it will be possible to devise more personalised preventative plans aimed at the most relevant risk factors for individual patients. In fact, clinical trials evaluating the impact of multidomain intervention through the modification of lifestyle risk variables have already shown encouraging results (eg, Ngandu et al, 2015).

In addition to progress in the identification of early biomarkers, a significant effort has also been made towards the development of cheap and accessible ways to measure those markers. As we have already mentioned, CSF collection through lumbar puncture and neuroimaging scanning are invasive and expensive procedures. Therefore, alternatives are being developed primarily in the form of blood tests, with promising results emerging for its use in the measurement of Aβ and neurofilament light—a biomarker of neuronal degeneration (Simrén et al, 2020). Similarly, amyloid and tau are both detectable in saliva, and early investigations are currently under way to evaluate the reliability and feasibility of using saliva samples for effectively measuring those biomarkers (Ashton et al, 2019).

Implications for care

The shift in the way dementia is being approached in the lab is also being followed by changes in the approach taken in the clinic. The American Academy of Neurology, for instance, has

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recently published a report recommending yearly cognitive health assessments for individuals at high risk—including all adults over the age of 65—much in the same way as routine assessments are already conducted for a range of other health conditions (Foster et al, 2019). In the UK, the Edinburgh Consensus paper (Ritchie et al, 2017) highlighted that clinical services will need to adapt to a new 'brain health' focussed model sooner rather than later, and a growing number of clinics are already developing such services.

As part of this new approach, Ritchie and colleagues (2017) envisage the emergence of a new, specialist nurse role—equivalent to that of Macmillan nurses in cancer treatment. Specifically, these nurses will be expressly trained under this novel model of dementia care, which emphasises prevention in at-risk individuals, thus complementing the skills of current nurses whose work presently centres predominantly on a symptomatic and palliative approach. One obvious consequence will be the widening of the age distribution of patients in care: on the one hand, healthy younger people will begin risk-based preventative interventions before the onset of cognitive impairment; on the other hand, it is hoped that effective early treatment will lead to increased life expectancy, as well as higher quality of life. Thus, the patient population with which nurses will work will be larger, yet on average higher functioning, than it currently is, likely boosting the need for lower intensity, community care, and, with time, reducing the need for dementia-specific acute care.

As hinted above, in addition to allowing for timely disease modifying pharmacological treatment (once it becomes available), early intervention also strengthens the case for implementing lifestyle modification programmes in middle adulthood, at a time when they still have a chance of being effective. Therefore, the training of specialist dementia nurses will likely take a more holistic approach to prevention, encompassing various aspects of the patient's life. For instance, knowing that conditions which cause chronic inflammation exacerbate the likelihood of developing AD (eg, Kinney et al, 2018) provides an easy target for motivating changes to a patient's dietary and physical activity habits. Importantly, previous research shows that older adults are especially diligent in their adherence to such lifestyle modification programmes (Bouchard, Baillargeon, & Langlois, 2013; Diabetes Prevention Program Research Group, 2006).

The transition to earlier treatment of healthier patients in the community, will carry significant benefits not only for the neural health of patients, but also for their own and, importantly, their carers' mental health. Embedded in the steep cost figures associated with dementia, are a

decrease in sufferers' independence and in their ability to contribute to communal life (eg, through employment), as well as the onerous time commitment required of close family members and friends who assist in their care. Indeed, past research identified increased autonomy, social confidence, and a sense of hope among outcomes patients and caregivers wished to improve through community care (Bamford & Bruce, 2000). Hopelessness and a loss of sense of agency, in particular, are significant sources of suffering for patients right from the time of diagnosis, as the condition is understood to be terminal and their cognition in steady decline (Bartlett et al, 2017). Intervening early and giving patients an active role in maintaining a healthy brain in the hope (and eventually promise) of retaining cognitive function, could thus alleviate suffering in both patients and carers, as well as limiting patients' reliance on caregivers.

Conclusion

Since the proposal of the amyloid cascade hypothesis three decades ago, progress in the development of novel therapies for AD has been slow and there is still no cure available. As a result, it has become increasingly clear that understanding the early stages of the disease might hold the key to the development of effective preventative and disease modifying interventions. Consistently, the last ten years have seen a shift in the research landscape, with growing emphasis being put on characterising and tracking the prodromal phase of Alzheimer's, prior to the presentation of cognitive symptoms. As such, the identification of early biomarkers and the development of accessible and cost-effective ways to measure them have been made a central focus of a number of recent large-scale studies. From a therapeutic perspective, primary and secondary prevention through a combination of lifestyle modification and drug therapies (when these will become available) are being prioritised over interventions aimed at disease modification in the later stages of the pathology. If we could reach a stage where we could realistically prevent or even just delay the onset of dementia, that would surely be one of the biggest health successes of this century.

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