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Professor Clive Ballard

Professor of Old Age Psychiatry, King's College London and Director of Research, Alzheimer's Society

It has been a very exciting year for dementia research. Researchers have discovered a new gene (progranulin), which accounts for a substantial proportion of people who develop fronto-temporal dementia. It is the first new major dementia gene identified this decade and may have relevance for all types of dementia.

In another important discovery, a factor promoting the development of new blood vessels (MEOX-2) has been shown to be reduced in people with Alzheimer's disease and may also have important implications for people with vascular dementia. Both of these developments offer new opportunities to develop novel treatments for people with dementia.

Cutting edge research over the last year has extended our understanding of current treatments and lifestyle approaches that may help to prevent Alzheimer's disease. For example, studies have demonstrated that cholinesterase inhibitors are effective for the treatment of people with severe Alzheimer's disease and impact upon pathological changes in the brain. In addition, important new research has provided further evidence that a healthy lifestyle can reduce the risk of developing Alzheimer's disease; research related to vaccine therapies has made important steps forward; and an evolving literature has highlighted the potential importance of heavy metals in the development of the changes of Alzheimer's disease in the brain.

Research supported by the Alzheimer's Society has also made a significant contribution over the last year. The FITS study, published in the BMJ, demonstrated that a package of training and



psychological intervention can reduce the need for sedative neuroleptic medication in people with dementia residing in care facilities. An important study (reviewed in this issue of this online journal), led by Professor Murna Downs, evaluated different approaches to improving the diagnosis of dementia by primary care physicians. Our ongoing work continues to cover a diverse range of topics, including the potential value of aromatherapy for the treatment of behavioural symptoms in people with dementia.

Many of these key issues are discussed in what we think is an exciting issue of this online journal.

Aromatherapy for the treatment of Alzheimer's disease

Professor Elaine Perry (FmedSci)

Professor of Neurochemical Pathology, Institute for Ageing and Health, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE Telephone 0191 444 4416. Fax 0191 444 4402. Email E.K.Perry@ncl.ac.uk Elaine Perry also runs Dilston Physic Garden, Northumberland (<http://www.dilstonphysicgarden.com/>)

Linda Cawley, Secretary to the Cerebrovascular Group, Institute for Ageing and Health, assisted in the preparation of this article.

Abstract

While essential oils from plants have been used therapeutically for centuries to improve physical and mental health, there is little confirmed scientific proof of their efficacy. A limited number of clinical trials have concluded that they provide a potentially effective and safe treatment for psychiatric disorders, including Alzheimer's disease and related dementias, but further research is needed.

Professor Perry is currently involved in a multicentre trial of aromatherapy for people with Alzheimer's disease and agitation, and also new laboratory studies on the mechanism of action of the essential oils, funded by the Alzheimer's Society.

Introduction

Aromatherapy uses essential oils from plants, either applied in a lotion and absorbed by the skin or inhaled and absorbed into the lungs and nasal passages, to improve physical and mental health. Aromatic oils from plants have been used for over 5,000 years: ancient Egyptians used them as perfumes and there are many references in the Bible to their use in mental and physical healing. Modern aromatherapy, which began in Germany during the 16th century, was also used successfully to treat wounded soldiers in the two World Wars.

Aromatherapy is the fastest growing complementary therapy amongst nurses. In the USA it has recently been recognised as a legitimate part of holistic nursing. Yet there is very little confirmed scientific evidence to prove its value in the modern world. A limited number of clinical trials have concluded that essential oils do provide a potentially effective treatment for psychiatric disorders, including Alzheimer's disease and related dementias. However, judging by the clinical trials' literature, the use of aromatherapy is only rarely considered by the medical profession. Moreover, controlled trials of its use in the field of psychiatry have been conducted only in relation to dementia. This may reflect the lack of prescription drugs for this disorder (until recently), and the particular need for treatments for some of the symptoms that accompany the advanced stages of dementia.

Trials of aromatherapy in dementia

Controlled clinical trials of aromatherapy in dementia were initiated following promising results from open trials of historical medical remedies. In folklore linen bags were filled with lavender flowers and placed under pillows in order to facilitate sleep: one trial showed that use of lavender increased sleep patterns of dementia patients who were in residential care.[1] In a trial involving 122 non-demented patients in intensive care, massage aromatherapy using lavender oil was well received, the greatest improvements being in mood and reduction in anxiety.[2] In another trial, lavender, geranium and mandarin essential oils in an almond oil base were applied to the skin of 39 patients over an unspecified period. This resulted in increased alertness, contentment and sleeping at night; and reduced levels of agitation, withdrawal and wandering.[3] In a recent open-labelled trial on people with dementia, the use of a range of essential oils, including ylang ylang, patchouli, rosemary, peppermint and others, produced a marked decrease in disturbed behaviour in the majority of participants. This led to a reduction in prescribed conventional medicines, thereby delivering cost savings.[4]

Results of placebo-controlled clinical trials using *Lavendula* (lavender) and *Melissa Officinalis* (lemon balm) for the treatment of residential care residents with advanced dementia

1. Lemon balm and lavender aroma were introduced to six patients and compared to a control group using sunflower oil for one week. The treatment increased functional abilities and communication, and decreased difficult behaviour.[5]
2. Lavender aroma and massage with 21 patients were compared to aroma or massage alone for one week. Aromatherapy with massage significantly reduced frequency of excessive motor behaviour.[6]
3. Lavender aroma oil was given to 15 patients and placebo (water) on alternate days for ten days. The aromatherapy significantly reduced agitated behaviour (as assessed using the Pittsburgh Agitation scale) versus placebo.[7]
4. Lemon balm (Melissa) lotion was applied to the face and arms of 36 patients, whilst another 36 patients had sunflower oil applied. Melissa was associated with highly significant reductions measured on the Cohen-Mansfield Agitation Inventory (CMAI) and social withdrawal, together with an increase in constructive activities (dementia care mapping).[8]
5. Lavender, marjoram, patchouli and vetivert were applied as a cream to the body and limbs of 36 patients and compared with inert oil. The essential oil combination significantly increased the Mini Mental State Examination (MMSE) but also increased resistance to care (considered to be due to increase in alertness), compared to inert oil.[9]

What is remarkable is that all treatments resulted in significant benefit, including (in most instances) reductions in agitation, sleeplessness, wandering and unsociable behaviour.

How does it work?

It might be thought that aromatherapy works by providing a pleasing smell, but many patients with advanced dementia have lost their sense of smell.

According to Snow et al, a purely olfactory form of lavender aromatherapy had no effect on agitation in people with dementia, while application as a skin lotion is effective.[10] A recent study from Korea also reported that lavender hand massage reduces aggression.[11]

Safety and efficacy

In general, the essential oils chosen for use in aromatherapy are those that are known to be least

harmful, with fewest potential risks for users. Lavender is considered to be the safest, along with others such as basil, chamomile, coriander, lemon, lemon balm and neroli. Essential oils should be used with the same precautions as any other type of medication, in this instance on the advice of a qualified aromatherapist, medical herbalist, or practising physician experienced in this type of treatment.

Widespread current use of aromatherapies, together with contemporary clinical data, indicate that if these oils are used carefully within the directions suggested, they can provide treatment for Alzheimer's disease, dementia and other psychiatric disorders, without any of the adverse effects associated with some of the conventional drugs already in use. Aromatherapy may therefore be a much safer option than conventional drugs such as antipsychotics or SSRIs, which are often used to treat agitation or other non-cognitive symptoms that accompany dementia.

Challenges for further research

There are many challenges for further research into the use of essential oils for treating psychiatric disorders.

Standardisation

There is a need for trials to facilitate standardisation of commercial preparation, type of application and dose delivery, and developing other criteria to establish clinical effectiveness.

Contraindications

Since aromatherapy potentially affects all systems in the body, it is vital to develop awareness of which essential oils do, or do not, have contraindications that interact with other medications, and assess adverse reactions that are likely to occur.

Convincing health professionals

There is a pressing need for more scientific evidence, clinical trial data and relevant pharmacology, in order to persuade general practitioners and nursing staff to consider using aromatherapy (either on its own or alongside conventional medicine) wherever appropriate when dealing with psychiatric disorders. Such information could usefully be included in medical student education.

Chemical investigation

From a basic scientific view, there is the need to discover how the chemicals in the essential oils relieve symptoms. There is already evidence that some of these chemicals (terpenes) have effects on receptor molecules in the brain. More research is needed here, both to encourage acceptance of aromatherapy as a valid treatment in the 21st century, and to promote investigation into chemicals with novel mechanisms of action that could provide new drug treatments in the future.

Conclusion

It may not be possible to fully assess the clinical value of aromatherapy in psychiatry without knowing the general (systemic and beyond the central nervous system) effects of the oils that contribute to general physical well being. However, based on the relevant neuropharmacological and limited clinical evidence so far available, it may be a treatment with major but unexplored potential in the field of clinical psychiatry. While lavender is the most widely used essential oil, there is great scope for

exploring other oils that may help with the treatment of various clinical aspects of disease, such as Alzheimer's disease and dementia in general, in order to give people the chance to make an informed choice between conventional medicine and aromatherapy, based on reliable evidence.

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Cholinesterase inhibitor treatments for Alzheimer's disease

Samantha Sharp

Policy Officer, Alzheimer's Society, Gordon House, 10 Greencoat Place, London SW1P 1PH
Telephone 0207 423 3580. Email ssharp@alzheimers.org.uk

Professor Clive Ballard

Professor of Old Age Psychiatry, King's College London and Director of Research, Alzheimer's Society, The Wolfson CARD, The Wolfson Wing, Hodgkin Building, Guy's Campus, London SE1 1UL
Tel: 020 7848 8054. Fax: 020 7848 6145. Email clive.ballard@kcl.ac.uk

Abstract

There are currently three cholinesterase inhibitors licensed for the treatment of mild to moderate Alzheimer's disease. Despite evidence of their clinical effectiveness and beneficial impact on the disease process, a dispute over cost-effectiveness is threatening continued availability.

This review summarises the research evidence base and assesses the implications for dementia care, should prescription restrictions be imposed.

Background

There are 25 million people with Alzheimer's disease worldwide, and more than 500,000 in the UK alone.[1] Currently there are three cholinesterase inhibitor treatments licensed for mild to moderate Alzheimer's disease: donepezil (Aricept), rivastigmine (Exelon) and galanthamine (Reminyl). There is a considerable evidence base around the clinical effectiveness of the cholinesterase inhibitors and emerging evidence for their impact on the disease process. However, a dispute over their cost-effectiveness means their continued availability within the NHS during the mild stages of Alzheimer's disease is under threat.

What is the evidence for clinical effectiveness?

The development of cholinergic therapies for people with Alzheimer's disease emerged from groundbreaking studies in the 1970s, which demonstrated a significant correlation between the severity of dementia and loss of cholinergic innervation to the cerebral cortex.[2] A number of different approaches aiming to enhance cholinergic function were evaluated, the most successful of which was based upon inhibiting acetylcholinesterase - the enzyme that breaks down acetylcholine in the neuronal synapse. The symptomatic benefits of cholinesterase inhibitor therapy for people with Alzheimer's disease are evident from the results of more than 30 placebo-controlled trials, demonstrating improvement in cognition and stabilisation of everyday function over the six to twelve

month period of treatment investigated in these studies.[1,2,3] Individuals improve on average by about 10 per cent on standardised cognitive assessments, which is the equivalent of six months of usual decline in cognitive function, and the level of performance remains above baseline for nine to twelve months for most people.[3,4,5] Emerging work suggests benefits for people with other dementias, such as dementia with Lewy bodies (DLB) and Parkinson's disease dementia.[6,7]

Longer term benefits

Although only a handful of studies have maintained a placebo-controlled design for more than six months, the initial evidence is encouraging. Several placebo-controlled trials show continued benefit over 12 months or longer.[8,9] The majority of trials have focused on people with mild-to-moderate Alzheimer's disease, although work examining the value of cholinesterase therapy in people with more severe Alzheimer's disease has confirmed the significant benefits associated with treatment.[10,11] These improvements are consistent with what would be expected, given the increased severity of cholinergic deficits in people with severe Alzheimer's disease. All three cholinesterase inhibitors licensed for the treatment of mild-to-moderate disease show similar evidence of efficacy, confirmed by a recent large study comparing donepezil and rivastigmine over two years.[12]

Impact on quality of life

It has been more difficult to assess the impact of cholinesterase inhibitors on quality of life, not least because of the lack of formal quality of life measures in the majority of clinical trials, and the difficulty of capturing many aspects of quality of life in dementia. A survey by the Alzheimer's Society found that people reported benefits in a number of areas that are difficult to quantify in clinical trials, such as social functioning and confidence (Table 1).

Table 1: Reported benefits of treatment

Benefit	No of responses	Percentage of all responses	Percentage of people reporting
Slowed/stabilised illness	1045	25%	39%
Happier/brighter/more aware/more active	550	13%	21%
Improved/helped memory loss	491	12%	18%
Calmer/less aggressive	324	8%	12%
More independent/taking care of personal needs	238	6%	9%
Showed an interest in things	219	5%	8%
Improved conversation/speech	187	4%	7%
Less confused/better understanding	183	4%	7%
Better quality of life			

	137	3%	5%
Restored/more confident	105	2%	4%

Rockwood has developed a methodology that looks at the drug treatments' impact on outcomes of importance to the individual. A random controlled trial using this method found that people treated with galantamine were more likely to achieve key goals identified by people with Alzheimer's disease than placebo-treated individuals.[13]

Emerging evidence around impact on disease progression

A key question is whether cholinesterase inhibitors do more than just improve symptoms and also impact upon the disease process in people with these dementias.

Impact on b-amyloid (Ab) deposition

The impact of cholinesterase inhibitors on b-amyloid (Ab) deposition has been the most widely studied potential influence of treatment upon mechanisms underlying disease progression. Ab is one of the core pathological substrates of Alzheimer's disease. It is seen as diffuse deposits throughout the brain, and at the core of the senile plaques that are one of the hallmarks of the disease, and therefore represents a key treatment target. There are several strong pieces of evidence from experimental studies showing that cholinesterase inhibitors and other cholinergic therapies reduce the accumulation of amyloid in cultured neurones and in rodent models.[14,15,16]

Evidence utilising cerebrospinal fluid (CSF) biomarkers supports this. A double-blind placebo-controlled trial of forty patients found Ab concentrations were reduced two-fold after four weeks of the administration of the muscarinic M1 receptor, agonist talsaclidine. A further study found increases in CSF Ab were prevented by both rivastigmine and tacrine treatment.

Autopsy studies

Autopsy studies are an additional viable method of examining the impact of cholinesterase inhibitor therapy upon amyloid pathology in the brain. In the first human autopsy study examining this, fifteen DLB patients treated with cholinesterase inhibitors as part of placebocontrolled trials were compared with 15 matched untreated patients. The DLB patients treated with cholinesterase inhibitors had 68 per cent less parenchymal A, deposition in the cerebral cortex than untreated patients, an impact similar to that of the Alzheimer vaccine. Consistent with these data, a recent clinical trial demonstrated a reduction in the progression of hippocampal atrophy on MRI in cholinesterase inhibitortreated patients. [17]

R isomer as a treatment target

Acetylcholinesterase, the enzyme that is the main treatment target of cholinesterase inhibitors, has a number of variations, including different isomers and subtypes. Most cholinesterase inhibitors increase the release of the R isomer of acetylcholine, which appears to be neuroprotective and increases stem cell activity in animal studies.[18] In people with Alzheimer's disease, an increase of the R isomer appears to be associated with a slower illness progression. While further research is needed to clarify the importance of the R isomer as a treatment target, this highlights the potential disease modifying properties of cholinesterase inhibitors.

Possible additional benefits

Different agents within the cholinesterase inhibitor class may also have additional beneficial properties. Galanthamine also acts as an allosteric modulator at α -7 nicotinic receptors. While it is not confirmed whether this action confers any neuroprotective properties, there is evidence indicating that nicotine has neuroprotective properties. Rivastigmine inhibits a different cholinesterase enzyme (butyrylcholinesterase), as well as acetylcholinesterase, which appears to contribute to the symptomatic benefits. There is also some emerging evidence that butyrylcholinesterase activity is related to the rate of disease progression in Alzheimer's disease, but it has not yet been established whether the butyrylcholinesterase inhibitor actions of rivastigmine have any direct impact on the progression of disease pathology.[19,20,21]

Cost-effectiveness: ongoing access to cholinesterase inhibitors is under threat

There has been considerable controversy around continued NHS prescription of the anticholinesterase drugs. The National Institute for Clinical Excellence (NICE), the body charged with providing guidance on the use of new and existing licensed medicines within the NHS, issued its first guidance on anticholinesterase drugs for Alzheimer's disease in 2001.[22] Its recommendation was that the drugs should be prescribed for people in the mild and moderate stages of Alzheimer's; an assessment should be made two to four months after initiation of treatment; and the drug should only be continued if there has been an improvement, or no deterioration, in MMSE score, and there is evidence of global improvement on the basis of behavioural and/or functional assessment. This guidance is now being reviewed: memantine (a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA)-receptor antagonist), licensed for the treatment of moderate to severe dementia, is being appraised for the first time.

NICE's final appraisal determination (FAD), published in June 2006, stated that anticholinesterase drugs should be restricted to individuals with a Mini Mental State Examination (MMSE) of between 10 and 20. The prescription of Ebixa is not recommended outside clinical trials.[23] NICE has confirmed that the anticholinesterase drug treatments are clinically effective, but questions their cost-effectiveness for people in the mild stages of the illness. It suggests that, contrary to a recent Cochrane review, that there is limited evidence of the clinical value or cost-effectiveness of Ebixa.[24]

Patient and professional groups, as well manufacturers, have lodged appeals against the FAD based upon some of the fundamental inaccuracies in the assumptions underpinning the assessment of cost-effectiveness (outlined in Table 2).

Table 2: Key points in the appeal against the NICE FAD for cholinesterase inhibitors for Alzheimer's disease

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Duration of treatment is a key issue

A key issue in the economic analysis undertaken as part of the NICE appraisal is the assumption that all patients receive the drugs for a period of three years. As stated above, the current NICE guidance ensures that only people who respond to the drugs remain on them after an initial three to four month period. In response to concerns raised around this issue, NICE requested an analysis of patient level data to examine the proportion of responders (as defined by the 2001 NICE guidance) and the magnitude of benefit in responders, compared with the overall treatment group. Based on this, NICE recalculated cost-effectiveness based on a 'responder analysis'.

NICE's analysis of patient level data found the overall proportion of responders to anticholinesterase drugs was 39 per cent. When considering just those who were classed as responders, the magnitude of change was 6.6 ADAS-Cog points (99 per cent CI 5.9-7.1). This compares to a magnitude of change of 2.05 (Rivastigmine), 3.01 (Donepezil) and 3.37 (Galantamine) ADAS-Cog points, when comparing the treatment group as a whole to placebo.

Despite the better reflection of clinical practice created by the responder analysis, the NICE appraisal committee concluded that there was too great a risk of bias with this type of analysis, and stated that it was not clear whether it would result in a cost-effective estimate that was within their usual threshold of £30k per QALY.

Grave concerns if the FAD is implemented

There is grave concern around the implications for dementia care should NICE implement the current FAD.

The inflexible use of the MMSE to govern access to drugs would discriminate against people with: a learning disability; a first language other than English; language problems; a particularly high or low level of education; and people who are from a culture other than English

Restricting access to the anticholinesterase drugs to people in the moderate disease stages will discourage early diagnosis and counteract all the positive work that has gone on in recent years to encourage early diagnosis

Stabilisation in the early stages of Alzheimer's should be the goal of treatment, as it allows the best possible quality of life to be maintained for as long as possible

While specialist services such as memory clinics have a role beyond initiation and monitoring of drug treatments, there is a concern that increased restrictions on access to drugs will threaten their funding, particularly in light of the current climate of spending cuts in mental health services

Lack of access to memantine will result in neuroleptics being the only pharmacological treatment for behavioural symptoms in severe Alzheimer's disease.

Conclusion

There is now a substantial evidence base demonstrating that cholinesterase inhibitors are a clinically effective treatment for people with Alzheimer's disease. There is also emerging evidence which

strongly indicates that cholinesterase inhibitors have a range of beneficial impacts on mechanisms that influence the development of core disease pathology in Alzheimer's disease. If research confirms this hypothesis, it is likely that the ongoing benefits of long-term treatment have been underestimated. Further research to clarify the mechanisms of action and their impact is necessary to inform optimal use of these agents.

Access to cholinesterase inhibitors in the mild stages of Alzheimer's disease is currently under threat. If the NICE guidance is unchanged, it will entail a huge setback for dementia care, and will have a significant negative impact on the lives of those in the early and late stages of Alzheimer's disease.

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Diet can improve mental health and well-being

Sarah Day

Hearts and Brains Project Manager, Alzheimer's Society, Gordon House, 10 Greencoat Place, London SW1P 1PH. Telephone 0207 423 3605. Email sday@alzheimers.org.uk

Abstract

There is increasing evidence that diet could play a role in the development of vascular dementia. The Hearts and Brains project, which aims to raise general awareness of vascular dementia (VaD), has a particular focus on the potential for both prevention of dementia and slowing deterioration through a healthy lifestyle.

This review summarises the findings of some major studies, examines how dietary habits have changed over the years, and discusses the implications for the future of dementia care and research.

Background

The popular media is now full of references about the influence of food on the way our bodies look, the way we feel about ourselves, and the way we act. Correlations have also been established between a healthy diet and a reduced risk of coronary heart disease. There appears to be much less awareness that what we eat and drink can affect our brain health. Yet there is an increasing body of evidence which indicates that our diet could play a role in the development of dementia. That is not to say that it is the only factor: but that those who lead an unhealthy lifestyle could be at increased risk of developing the disease.

The Hearts and Brains project

Over the last few years, the Alzheimer's Society has dedicated increasing resources to understanding and communicating the benefits of a healthy diet. In 2004, the three-year Hearts and Brains project was launched. The main objective was to raise awareness of vascular dementia, but it also set out to find ways of reducing people's risk of developing dementia on the premise that 'what is good for your heart is good for your brain'. Vascular risk factors (eg hypertension, high cholesterol, diabetes and heart conditions) have traditionally been associated with vascular dementia. However, research now indicates these are also risk factors for Alzheimer's disease, and this underlines the importance that attention is focused on ways we might prevent the two most common forms of dementia in the UK.

The following sections highlight key areas of our diet, with the links that research indicates they have with dementia.

Fat

The brain is composed of about 60 per cent fat. The transfats and saturated fats we eat are known to make brain cell membranes less flexible and fluid, affecting the ability of brain cells to communicate with one another. Saturated fat also increases the amount of cholesterol in our blood. Excess cholesterol is deposited on the walls of blood vessels, contributing to atherosclerosis and increasing the risk of heart disease and stroke. A number of studies have investigated whether our fat intake also increases the risk of dementia. In 2004, Morris reviewed three studies.[1] In one study, those in the highest fat intake group had a risk 2.2 times as high as those in the lowest intake group.[2] Higher intake of monounsaturated and polyunsaturated fats was associated with a lower risk of Alzheimer's disease. Other studies have not reached a consensus - one found a greater risk associated with total fat and saturated fat intake but no benefit from polyunsaturated fats.[3] Finally, a Dutch study found initial increases in risk associated with total and saturated fats, but that this risk was not sustained at the six-year follow-up stage.[4]

Salt

Salt has been the target of a high-profile government health promotion campaign, following the realisation that, in the UK, most adults consume far more than the recommended 6 grammes a day. There is a positive correlation between the amount of salt we eat and our blood pressure, which is one of the biggest risk factors for dementia.[5] Much of the salt we eat is concealed in processed foods, such as bread. But the proposed 'traffic light' signposting system - which is being developed by the Food Standards Authority - should influence shoppers' purchasing decisions and, in turn, influence the efforts manufacturers go to in order to reduce this ingredient.

Oily fish

UK guidelines recommend consumption of one portion of oily fish a week. The benefits of the constituent omega-3 oils have long been recognised in the context of prevention of heart disease. It is logical that they should play a part in brain health too, since it is an essential fatty acid which is crucial to normal functioning. Omega 3 has to be obtained from the food we eat, since it cannot be made in the body.

Surveys conducted by the Mental Health Foundation indicate that people in the UK eat 59 per cent less fish than they did 60 years ago.[6] This is significant, bearing in mind that several studies have confirmed the benefits of eating fish. One American study found a 60 per cent reduction in risk of Alzheimer's disease in people who ate oily fish at least once a week, compared with those who rarely or never ate fish.[7] A further study reinforced this; those who ate fish twice a week had a 13 per cent lower rate of annual cognitive decline than those who rarely or never ate fish.[8] Another study found that elderly people who ate fish or seafood at least once a week had a 66 per cent reduction in risk of developing dementia.[9] However, a recent study published in April 2006 received much press coverage and cast doubt on the benefits associated with oily fish.[10] Furthermore, one of the 89 studies reviewed identified a worrying association with increased risk of heart attack in men with stable angina.

Clearly, more research is required, but the evidence accumulating is encouraging.

Antioxidants - vitamin C and vitamin E

Over the last 60 years there has been a 34 per cent decline in UK vegetable consumption, with currently only 13 per cent of men and 15 per cent of women eating at least five portions of fruit and vegetables per day. Fruit and vegetables are an important source of antioxidants such as vitamins C and E, which are thought to combat the harmful effects of free radicals on the brain.

The question that has exercised researchers is: could an increase in the levels of antioxidants through vitamin supplements provide any protection against this brain insult, and consequent risk of Alzheimer's disease? A six-year study in Rotterdam [11] found that a high intake of vitamin E reduced the risk of Alzheimer's disease by 43 per cent, compared with those with a low intake. They also found a small association between vitamin C and risk of Alzheimer's disease. However, Luchsinger et al [12] found no association. In a four-year study of 815 people [13], it appeared that there was a difference between the risk of Alzheimer's disease in those people who derived antioxidants from the diet compared with those who took supplements. Those with a high intake from food had a 70 per cent lower risk of Alzheimer's disease. However, this reduced risk was only observed in the absence of the ApoE4 gene. Vitamin C was not protective. Finally, the Heart Protection study, a randomised intervention study run in collaboration with the Medical Research Council and the British Heart Foundation, published in the Lancet in 2002, found supplements of vitamins A, C and E did not protect against cognitive decline.[14]

These studies are promising in identifying the link between antioxidants and dementia, but there is insufficient evidence to recommend that people take supplements to boost their levels. However, Patrick Holford, a high profile nutritionist, asserts that it is a misconception to assume that you get everything you need from a well-balanced diet as we age.[15] Instead, he suggests a programme of vitamin supplementation is required that well exceeds the recommended daily allowance. However, large daily doses (400mg or above) of vitamin E were associated with increased mortality in a meta-analysis, and vitamin E can also detrimentally interact with other medication.[16] Therefore, the Alzheimer's Society recommends that the best source of antioxidants is a diet rich in fruit and vegetables.

Folate (folic acid) and vitamin B12

Folic acid (folate) and vitamin B12 deficiencies in the diet can cause levels of the amino acid homocysteine to build up. Moderate levels of homocysteine are needed for the growth and maintenance of healthy tissue. However, excess levels are strongly associated with vascular and heart disease, and a number of studies have found a link with cognitive impairment.

One recent study found that eating more than the UK recommended daily allowance of folate reduced the risk of Alzheimer's disease by 55 per cent. [17] Another studied 370 people aged 75 or over living in Sweden, where seventy-eight people had gone on to develop some form of dementia when they were followed up three years later. In this group, 46 with Alzheimer's disease had low levels of vitamin B12 or folate, so the researchers concluded that those with lower B12 or folate levels were twice as likely to have developed Alzheimer's disease.[18] Other large-scale studies also followed people over a period of years and made similar conclusions.

Need for further research

Although this evidence is convincing, further research is required in order to clarify whether high levels of homocysteine and low levels of these B vitamins are a cause or effect of Alzheimer's disease. While there is not sufficient evidence (and some contraindications) to state that one should take vitamins B12 or folic acid supplements, the findings do illustrate the importance of ensuring one's diet does contain the recommended daily allowance, especially since many older people do not consume enough folate.

Of course, these studies were looking at individual risk factors, rather than a combination of issues. This raises the question 'how much of the benefits obtained from one part of the diet could be counteracted by the effects of another element?' To tackle this question, people consuming the so-called 'Mediterranean diet' have been studied.[19] Those who had the highest intake of foods characteristic of this diet had a 40 per cent lower risk of dementia than the people with the smallest intake. This adds further weight to the theory that lifestyle factors could play a significant part in the

development of dementia.

Role of nutrition for people with dementia

It is also important to state that good nutrition is a vital part of providing good care for someone with dementia. The Alzheimer's Society Food for Thought project highlighted the fact that people with dementia were often malnourished, and this can have a significant effect on the person's well-being. Much has been written on the topic of eating and dementia; we know what quality care in this area should look like. However, the results from the Food for Thought survey show that much of what is known to be good practice is still not being widely applied. Publications were developed as part of this project and the dissemination process now continues as part of the Quality Care Programme, the training and resources business of the Alzheimer's Society.

Conclusion

Dementia currently affects over 800,000 people in the UK. It is estimated that, by 2050, there will be over 1.8 million people with this condition. It is a progressive and debilitating disease with great financial, social and personal costs. However, the prevalence of dementia could be reduced by 50 per cent if the onset could be delayed by five years.[20] While further research is required, we know enough to say that a healthy diet benefits our physical and emotional health and may also reduce our risk of developing dementia. Much more attention needs to focus on changing people's behaviour and attitudes now, in order to maximise the chances of healthy ageing later.

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Genetics and Alzheimer's disease

Dr Clive Holmes

Senior Lecturer and Hon Consultant Old Age Psychiatry, Memory Assessment and Research Centre, Moorgreen Hospital, Botley Road, West End, Southampton, SO30 3JB Telephone 02380 475216. Fax 02380 463022. Email ch4@soton.ac.uk

Abstract

Four genes have been identified and confirmed as contributing to the genetic aetiology of Alzheimer's disease: amyloid precursor protein (APP), presenilin 1, presenilin 2, and apolipoprotein E (ApoE).

This review details the role of these known genetic factors in the development of Alzheimer's disease and outlines what has to be done to identify new genetic risk factors.

Introduction

To date, four genes have been identified and confirmed as contributing to the genetic aetiology of Alzheimer's disease. Mutations in three of these genes, amyloid precursor protein (APP), presenilin 1 and presenilin 2, were identified by linkage analysis in families that develop predominantly early onset Alzheimer's disease in an autosomal dominant pattern.

The importance of the identification of these genes has largely been in developing a greater understanding of the molecular biology of Alzheimer's disease. It has been shown that the processing of beta amyloid (A β) is a key event in the development of the pathological features.

Familial early onset Alzheimer's disease accounts for less than 1 per cent of total cases, the vast majority having a late onset (defined as over 65 years). Such individuals have no clear autosomal dominant pattern of inheritance. However, twin studies of non-autosomal dominant late onset Alzheimer's also show evidence that genetics has an important role to play in influencing whether these individuals will develop the disease. Studies comparing the risk of developing late onset Alzheimer's disease in identical twins compared with non-identical twins show a heritability of around 0.6. Thus the genetic component of late onset Alzheimer's disease is around 60 per cent with the other 40 per cent coming from environmental factors.[1]

Family studies of late onset Alzheimer's disease also show that having a first degree family member with the disease increases your risk of developing it later in life about threefold: although, importantly, not all people with a family history go on to develop Alzheimer's disease.[2]

Complex mechanism of inheritance in late onset Alzheimer's disease

The mechanism of inheritance in late onset Alzheimer's disease is complex. Thus, whilst some rare cases of recessive inheritance have been observed [3,4], in the majority of cases whether one develops late onset Alzheimer's disease is likely to depend on a mixture of genetic and environmental

factors. The identification of the genetic risk factors for late onset Alzheimer's disease has, in fact, proved to be much more difficult than originally anticipated. Thus, the ϵ 4 allele of the apolipoprotein E (ApoE) gene remains the only accepted genetic risk factor for late onset Alzheimer's disease, despite numerous studies reporting other genetic risk factors.

The amyloid precursor protein (APP) gene

The APP gene is located on the long arm of chromosome 21 and was the first gene implicated in the development of Alzheimer's disease to be discovered. Interest in chromosome 21 was aroused because of the recognition of the development, at least neuropathologically, of Alzheimer's disease in Down's syndrome patients, who have three copies of chromosome 21.

APP produces a transmembrane protein that is found in most cell types, including neuronal and glial cells. This large transmembrane protein contains within it a smaller protein called beta amyloid ($A\beta$), which is known to be one of the main constituents of neuritic plaques - a core histological feature of Alzheimer's disease. APP undergoes proteolytic cleavage by α , β and γ secretase activity to produce $A\beta$ protein of varying lengths. The length of the $A\beta$ protein determines, to some extent, whether $A\beta$ remains as a monomer or aggregates to form oligomeric or fibrillogenic $A\beta$. The $A\beta$ protein levels are regulated by amyloid degrading enzymes that degrade $A\beta$ in its various aggregated or non-aggregated forms.

Under normal circumstances, APP is cleaved by β -secretase that cuts the $A\beta$ peptide in half between amino acids 16 and 17, resulting in a soluble non-amyloidogenic fragment (sAPP β) and a membrane bound C-terminal fragment (C83). Further cleavage of the C83 fragment by γ secretase produces P3, a 3kDa protein, and the APP intracellular domain (AICD).[5]

Cleavage of APP by α secretase at the N terminus of $A\beta$ between amino acids 671 and 672 yields a soluble nonamyloidogenic fragment (sAPP α) and a different membrane bound C-terminal fragment (C99). Cleavage of the C99 fragment by γ secretase produces a variety of different versions of full length $A\beta$ between 37 to 43 amino acids.[5] The longer versions of $A\beta$, eg the $A\beta$ 42 or $A\beta$ 43 moieties, are considered to be more fibrillogenic and are deposited early in disease, compared with the shorter $A\beta$ 40.

Approximately 15 disease-causing mutations have been identified in APP to date, accounting for a small proportion of familial early onset Alzheimer's disease (approximately 5 per cent), with most individuals developing symptoms between the ages of 40 to 60. All of the known pathological mutations in APP occur close to the major APP cleavage sites, suggesting that these mutations alter the processing of APP. Thus, mutations close to the β secretase site are thought to enhance the production of both $A\beta$ 40 and $A\beta$ 42, while mutations close to the γ secretase site cause impaired β secretase activity with an increase in α and γ secretase activity, and a consequent increase in secreted $A\beta$. Mutations next to the β secretase site lead to a selective increase in $A\beta$ 42 over the $A\beta$ 40 isoforms.[6,7]

Presenilin 1

Presenilin 1 protein is a transmembrane protein expressed in many tissues, including the brain, where it is enriched in neurones. Over 100 different mutations have been found in presenilin 1 (present on chromosome 14), which account for around 30 per cent to 50 per cent of all presenile familial Alzheimer's disease. Presenilin is a cofactor for γ secretase and also appears to alter $A\beta$ processing. Thus, presenilin 1 mutations have been shown to increase the ratio of $A\beta$ 42 to $A\beta$ 40, probably by increasing $A\beta$ 42, rather than decreasing $A\beta$ 40, in transfected cell lines and transgenic mice expressing mutant forms of presenilin 1. This may be because PS1 mutations lead a greater amount of C99 protein to be in contact with γ secretase, which preferentially cleaves at residue 42.[8] Presenilin 1 mutations lead to the early development of Alzheimer's disease, with an average onset age of around

40 years, although cases as young as 24 years have been identified.

Presenilin 2

The other member of the presenilin family, presenilin 2, is present on chromosome 1 and is highly homologous to presenilin 1. However, in comparison to presenilin 1 mutations, the frequency of presenilin 2 mutations is very low with around 6 mutations identified. Age of onset in these individuals is more variable and shows some overlap with late onset Alzheimer's disease, raising the possibility that families with these mutations may have been overlooked. Presenilin 2 appears to decrease A β 40 levels, suggesting a partial loss of function.[9]

Apolipoprotein E

Linkage analysis in late onset Alzheimer's disease families initially suggested the existence of a genetic susceptibility factor on the long arm of chromosome 19. Subsequent association studies confirmed an increase in the ϵ 4 allele of Apolipoprotein E (ApoE) found in this region in subjects with late onset Alzheimer's disease compared with controls. Apolipoprotein E is a plasma protein involved in cholesterol uptake, storage, transport and metabolism. The ApoE gene has three common allele types, ϵ 2, ϵ 3, and ϵ 4. In the Caucasian population, the presence of one ϵ 4 allele (found in about 15 per cent of the population) approximately doubles the risk of Alzheimer's disease, while two ϵ 4 alleles (ϵ 4/ ϵ 4) increase the risk 10 to 15 fold, compared to subjects with the ϵ 3/ ϵ 3 genotype. Interestingly, the increased risk period is at its greatest between the ages of 60 to 80 years, suggesting that very late onset Alzheimer's disease has a relatively smaller genetic component.[10,11] In contrast to the ϵ 4 allele, the ϵ 2 allele appears to have a protective effect. Differential expression of ApoE may also be affected by the presence of polymorphisms in the promoter region of ApoE, with some studies showing these polymorphisms to have an additional effect on disease risk.[12]

In terms of cholesterol efflux, the E4 isoform is the least, and E2 the most biologically efficient form of ApoE. Interestingly, this differential effect is also present with regards to the binding and clearance of A β , with individuals carrying the ϵ 4 allele having an increased deposition of fibrillar A β . [13]

Identification of new genetic risk factors

Studies have suggested that there may be a further four susceptibility loci for late onset Alzheimer's disease, with a magnitude equal to, or greater than, the APOE ϵ 4 allele.[14] Identification of future genes will be dependent on the investigation of biological candidate genes, usually in association studies and/or by the identification of genes in proximity to regions showing linkage with Alzheimer's disease.

Positive associations have been found with numerous genes, including γ secretase and various components of the γ secretase complex. Associations have also been found with A β degradation proteins, including angiotensin-converting enzyme, endothelin-converting enzymes, neprilysin and insulin-degrading enzyme. However, association studies of plausible biological candidates can be difficult to interpret because of problems inherent in the study design, including: inadequate power to detect moderate effects; inappropriate statistical testing with a lack of correction for multiple testing; and the past reliance on only one polymorphism which may, or may not, be linked to the genuine pathological variant. These problems, and others, have led in many cases to large numbers of false positive and potentially false negative findings.

Linkage studies

Linkage studies have the advantage that no *a priori* assumptions about the function of a protein have to be made. This method allows a chromosomal region of interest to be identified that has a high likelihood of containing within it a gene that is related to the development of Alzheimer's disease. At present, 13 genome scans have been carried out to identify genomic regions that may contain susceptibility genes.[15,16] The most consistent evidence has been found with markers on three chromosomes - the short arm of chromosome 9; the long arm of chromosome 10; and the short arm of chromosome 12.

Presently work is focusing on a mixed model, combining association studies that screen the most biologically plausible candidate genes found in these regions of interest, with a greater emphasis on highly powered studies and the recognition of the need for independent replication.

Recent research (Baker et al. 2006; Cruts et al. 2006) has shown that mutations leading to a reduced transcription of a gene coding for a secreted growth factor called progranulin appear to be responsible for the development of Fronto-Temporal Dementia in some individuals. Progranulin is located close to the tau gene, mutations in which are already known to lead to Fronto-Temporal Dementia, and is involved in multiple processes including development, wound repair and inflammation and has also been strongly linked to tumorigenesis. Interestingly progranulin is also increased in activated microglial cells in many neurodegenerative diseases including AD. It is thus highly likely that the progranulin gene and its protein will now receive a great deal of attention from the AD research community.

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Iron and Alzheimer's disease: the good, the bad and the ugly

Dr Joanna F Collingwood

Alzheimer's Society Research Fellow, Institute of Science and Technology in Medicine, Keele University, Staffordshire ST4 7QB Telephone 01782 554253. Fax 01782 717079. Email j.f.collingwood@keele.ac.uk

Professor Jon Dobson

Professor of Biophysics and Biomedical Engineering, Institute of Science and Technology in Medicine, Keele University, Staffordshire ST4 7QB Telephone 01782 554 253. Fax 01782 717 079. Email: jdobson@keele.ac.uk

Abstract

The study of iron in the human brain is particularly important in the context of Alzheimer's disease. Iron is both essential for healthy brain function and is implicated as a factor in neurodegeneration. The chemical form of the iron is particularly critical, as this affects its toxicity and disrupted iron metabolism is linked to regional iron accumulation and pathological hallmarks, such as senile plaques and neurofibrillary tangles.

This review aims to clarify the forms in which iron is present in order to gain an improved understanding of iron's role in disease pathogenesis. Aspects of disrupted iron metabolism may also be helpful: iron has been identified as a potential MRI biomarker for early detection and diagnosis, while iron chelation therapies are under development.

Brain iron metabolism

Iron is the most abundant transition metal in the human brain. We depend on it, not only for oxygen transport, but also for the underlying formation and maintenance of the neuronal network, as well as for numerous aspects of DNA and enzyme processes, including neurotransmitter synthesis. Iron is present in vivo in both the ferrous (Fe²⁺) and ferric (Fe³⁺) valence states. The ease with which iron converts between Fe²⁺ and Fe³⁺ is critical for metabolism. Its uptake and transport across membranes, and release from transporter proteins such as transferrin (Tf), is dependent on reduction to Fe²⁺. As Fe²⁺ is highly redoxactive (and thus more toxic), the majority of non-haem iron that is not immediately utilised is prevented from participating in harmful reactions through uptake, oxidation, and storage in the iron-storage protein, ferritin. Some Fe²⁺ is thought to remain as free iron in the 'labile iron pool', which to an extent defines cellular iron levels. Free iron is readily bound by Tf, and the 'supply and demand' response to the labile iron pool is thought to determine the expression of Tf receptors and ferritin to maintain iron homeostasis within the brain.

Highly specialised proteins are involved in brain iron metabolism. Tf transports iron into the brain across the blood-brain-barrier via endocytosis, and ferritin sequesters iron in the cytosol. Ferritin is the

primary iron storage protein and consists of a spherical cage containing a maximum of 4,500 iron atoms as a ferrihydrite-like core, up to 8nm in diameter. Additional iron transport proteins such as DMT1 (a transmembrane iron transporter observed in mammals) and iron stores (for example, haemosiderin) have been demonstrated. The extent to which Tf and ferritin dominate brain iron transport and storage is a matter of ongoing investigation.

Disrupted brain iron metabolism

While being essential to maintain a healthy brain, iron can play a toxic role. It exacerbates damage to brain tissue following processes such as stroke or trauma. Regional increase of iron within Alzheimer's diseased brains, compared with healthy controls, is considered a key factor in neuronal atrophy.[1] In stroke and trauma, the iron implicated in tissue damage is predominantly thought to be from haemoglobin, but this is not necessarily the case for iron-mediated damage in neurodegenerative disease. Regional accumulation and deposition of iron within the brain; altered iron transport and storage-protein regulation and the association of iron with neuropathology are evident in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease and several others.[2,3,4]

Iron in the Alzheimer's brain

In Alzheimer's disease, regions exhibiting extensive lesions and plaque-related pathology show iron accumulation. The cellular distribution of iron accumulations is yet to be fully determined, although there is evidence for increased intra-neuronal levels of iron in the ageing mammalian brain,[5] raising the possibility that some aspect of disrupted iron metabolism is responsible for a decrease in the capacity of neurones to export iron. What is clear is that the homeostasis of iron, and of the respective iron-binding proteins, is significantly altered in the brains of people with Alzheimer's disease.[6]

Iron accumulations occur in the cerebral cortex, the hippocampus and the basal nucleus of Meynert, colocalising with lesions, neurofibrillary tangles and plaques. These are particularly important areas in the clinical picture of Alzheimer's disease, being associated with the centres of memory and thought processes that are gradually lost as the disease progresses. Various studies have shown altered levels of ferritin and transferrin in affected regions of the Alzheimer's brain. There is evidence that the ratio of the ferritin protein to iron decreases in affected regions,[7] implying either increased loading of the ferritin core or failure to store the iron.

Iron concentrations are most apparent in the regions affected by Alzheimer's disease pathology, and are thought to be involved in the generation of an excess of reactive radical species, leading to the observed cell and tissue damage. One possibility is that iron is not properly taken up and oxidised in the ferritin core, leading to an excess of Fe²⁺, either as 'free iron' or as a component of the ferritin mineral core. Given that Fe²⁺ is highly reactive, an excess of Fe²⁺ may stimulate the overproduction of reactive chemical species, such as the hydroxyl radical (OH[•]). Such free radicals are responsible for oxidative stress, considered to be a primary contributing factor to neurodegeneration.[8,9]

What do we know about unusual iron accumulations in the brain?

While iron is present in both soluble and insoluble forms in the normal human brain, certain insoluble deposits may be indicative of disrupted iron metabolism. In addition to the normal ferrihydrite-like ferritin core, iron is also found as insoluble deposits of haemosiderin. Results from various studies suggest that haemosiderin may be a degradation product of intracellular ferritin agglomerations [10,11]. There is also evidence for mixed-valence species in brain tissue in the form of magnetite (a ferrimagnetic cubic iron oxide more commonly associated with magnetotactic bacteria) that contains alternating lattices of Fe²⁺ and Fe³⁺ and was first found in human brain tissue by Kirschvink and

co-workers.[12] It has been suggested that the presence of magnetite may indicate a failure to fully oxidise Fe²⁺ in the ferritin core.[13] Its chemical and magnetic properties make it a candidate for mediating free radical generation, and therefore oxidative stress damage, via both Fenton chemistry and the low field triplet state stabilisation.[14]

How could this information be applied?

We do not know whether, or to what extent, iron plays a role in Alzheimer's disease pathogenesis, but the accumulation of iron related to Alzheimer's disease may provide a mechanism for early detection of disease.[11,13] Iron has been identified as a potential MRI biomarker, which may aid screening, early detection, and diagnosis for a wide variety of neurodegenerative disorders, including Alzheimer's disease.[11,15,16] A key objective is to identify altered regional iron concentrations and to differentiate between iron compounds in vivo. To do this it is first necessary to establish which iron compounds are present, both in healthy tissue and in neurodegenerative disorders. In our research, we are exploring ways to quantify, map and characterise various iron accumulations associated with Alzheimer's disease.

Why don't we have this information already?

Histochemical iron staining methods and various microprobe techniques have been used to identify regions of iron overload and the distribution of non-haeme iron, [17,18] to obtain certain information about the redox state of the iron, [8,19] and to quantify elemental concentrations of iron and other metal ions in brain tissue samples, including Alzheimer's.[20] These approaches can only provide limited information about the state of precipitated iron. Much remains to be understood about the precise location, form and role of iron accumulations in pathogenesis, despite more than five decades of research in this area.

What techniques are we using?

SQUID magnetometry

To quantify various iron oxides in brain tissue, we are using superconducting quantum interference device (SQUID) magnetometry, a technique that is very sensitive to tiny quantities of magnetic material. The magnetic properties of iron in brain tissue depend on the structural form of the iron that is present: for example, the magnetic properties of magnetite are distinct from the ferrihydrite-like mineral present in normal ferritin. Appropriate combinations of measurements can be used to quantify components in freeze-dried tissue, including normal ferritin, superparamagnetic ferrimagnetic material and larger magnetically blocked particles.[21] This approach has been applied to brain tissue from human Alzheimer's disease cases and age-matched controls,[22] where preliminary results indicated a possible correlation between the amount of nanoscale biogenic magnetite in diseased brain tissue and the onset and progression of Alzheimer's disease. They also demonstrated that magnetite is a contributing factor to the elevated levels of iron observed in Alzheimer's disease tissue.

It is necessary to extract these iron-rich particles from tissue to determine their morphology and enable detailed subsequent examination by transmission electron microscopy. But while these approaches are useful for quantifying various iron oxides and determining their crystal structure and size distribution, information about the relationship between unusual iron accumulations and extra/intracellular structures is not available. For this, we turn to alternative methods.

Synchrotron X-ray spectroscopy

We have developed a synchrotron X-ray approach that allows us both to locate and characterise iron compounds in autopsy tissue sections at sub-cellular resolution.[23,24,25] This builds on previous research involving both microfocus X-ray fluorescence mapping techniques [26] and X-ray absorption near edge spectroscopy (XANES) to look at the valence state of iron in neurodegenerative tissue.[27] It is the combination of these techniques with an intense microfocused beam that allows the distribution and chemical species to be discovered in conjunction with anatomical structure and pathology. An essential component of the mapping and characterisation technique has been developing sample preparation and mounting techniques that minimise disruption of the iron oxidation state.[23]

We can now map large areas (to the order of a few cm²) of tissue in a matter of hours to identify dispersed nanoscale iron particles. The composition of the iron compounds located in low-resolution scans is determined by collecting a XANES spectrum from the region of interest with a beam microfocused to ~ 3 mm x 3 mm, and fitting the spectrum with pre-measured standards for the various biogenic and synthetic iron compounds, such as ferrihydrite, magnetite, haemosiderin, haeme iron, metallic iron and so forth. A more detailed outline of this technique, along with a discussion of the information that can be obtained about metal ion accumulations associated with pathological hallmarks, can be found elsewhere. [24,25] Interestingly, many of the iron-rich spectra obtained during synchrotron mapping and characterisation work with autopsy tissue sections exhibit co-localised ferritin-like ferrihydrite and magnetite at the micron resolution limit of the technique. [24] Continued research in this area should provide insights concerning the formation and role of various iron oxides in the human brain.

Conclusion

The application of combined techniques from the physical sciences, including SQUID magnetometry and synchrotron X-ray spectroscopy, is allowing progress to be made in locating and identifying the nature of iron accumulations in Alzheimer's disease. This research should contribute to our understanding of the role of iron in Alzheimer's disease and to the development of early detection and diagnosis, while also providing clues as to the potential impact of iron chelation treatment on affected regions of the brain.

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Primary care and dementia

Professor Murna Downs

Head of Dementia Studies Group, Bradford Dementia Group, Division of Dementia Studies, School of Health Studies, University of Bradford, Bradford BD5 0BB Telephone 01274 233996. Fax 01274 236395. Email m.downs@bradford.ac.uk

Abstract

Effective primary care response is essential to quality of life for people with dementia and their families. Causes for inadequate response have been identified and a variety of approaches adopted to address the problems. These centre on education and training for both professionals and consumers, and efficient partnership working between key health and social care professionals.

This review describes how a study to develop educational interventions for practitioners, funded by the Alzheimer's Society, a consumer initiative by the Alzheimer's Association in California, and research into improving partnership working offer reasons for optimism.

Role of primary care in supporting people with dementia and their families

Primary care plays a key role in supporting people with dementia and their families throughout their journey living with dementia. This has been generally acknowledged for some time and has recently been enshrined in government policy and guidance [1-3]. While much emphasis has been placed on the role of primary care in early detection and diagnosis of dementia, its role in regular assessment, support and referral is no less important. In addition, the role of primary care for people with advanced dementia and those at the end of life is critical to quality of life.

Barriers to effective primary care

It is widely acknowledged that the primary care response to people with dementia and their families is an area of concern. Primary care services have been criticised for failing to provide timely detection or diagnosis, sufficient information or appropriate referral [1, 4-7]. Several barriers to effective primary care have been identified [8- 11] including:

- Ageism
- Lack of information and training for primary care professionals about the importance of diagnosis and ongoing support [1,8]
- The stigma associated with having a diagnosis of dementia [12, 13]
- Lack of information about dementia and available services and supports for people with dementia and carers

- Lack of suitable supports and services
- Strategies for improving primary care

A variety of efforts have been made to improve primary care responses to people with dementia and their families. These have included education for primary care professionals [14,9], education for consumers [15,16] and partnership between key professionals across the medical and social divide [17, 18]. While most of these have demonstrated some success, the combined effect of these approaches has yet to be determined.

Education and training for professionals

Considerable attention has been paid to the needs for training and education [1,5,19]. Curricula have been proposed and a variety of approaches adopted, including seminars and workshops, CD-ROM, academic detailing and audit. With funding from the Alzheimer's Society QRD Programme through the Alexander and Christina Dykes Project Grant, a multisite study and multidisciplinary collaborative study developed and tested three educational interventions for primary care practitioners. The educational interventions, using a standard curriculum designed by a multidisciplinary expert group, reflected different approaches to adult learning [20]:

- **A CD-Rom for self-directed learning used clinical case studies encouraging professionals to reflect on knowledge.** This 'electronic book' has an indexing system that allows easy access to different themes and hypertext links for easy movement from one subject to another.
- **Decision support software for real-time, real-case learning.** The software was written inside the existing electronic medical record software and produces prompts to assist clinical reasoning and care planning [21,22]. It has been incorporated into the Egton Medical Information Systems (EMIS) electronic medical record for its subscribers and is now available to about 5,000 medical practices in the UK.
- **Practice-based workshops for peer discussion and reflection.** The workshops provide an opportunity for small, multidisciplinary groups to consider real cases. The curriculum for practice-based workshops for general practitioners and the electronic tutorial is available to download from the Alzheimer's Society website (<http://www.alzheimers.org.uk/>).

Study outcome

Recently reported in the *British Medical Journal* [14], the study demonstrated that both decision support software and practice-based workshops led to increased rates of detection of dementia, as compared to control practices.

Education and training for people with dementia and their families

Consumer initiatives directed at people with dementia and their families have received less attention than interventions targeting professionals. One such approach is the Partnering with your Doctor (PWYD) programme developed by the Alzheimer's Association in California, which aims to educate people with early stage dementia and their family carers through three elements.

1. **A 90-minute workshop** focusing on eight strategies to guide consumers through the partnership process. These include:
Planning for the visit

Asking for a diagnosis
Reporting recent or sudden changes, and other changes
Talking to the doctor about your role in the partnership
Naming your community resources
Engaging in the partnership
Restating and agreeing on a plan
Scheduling the next visit.

2. **A booklet** that includes information on the diagnosis, treatment, and management of dementia and a list of community resources.
3. **Resource logs** to use in consultations, including a care log, a medication log, and an appointment log

Such an initiative fits well within a modernised healthcare system committed to user and carer involvement [23,24]. The NHS Expert Patients programme recognises patients and their carers as experts in their own right [3], albeit focusing mostly on those with physical health problems. With pilot funding from the Selby and York NHS R&D Committee, a multidisciplinary group from the University of Bradford, York NHS and the Alzheimer's Society Bradford branch are currently involved in examining the relevance of this US PWYD model for use within the NHS [15].

Importance of partnership working

It is important to note that consumer involvement in primary care for dementia involves the person with dementia and their carer, as well as the doctor. All three of the partners need appropriate information and communication skills in order to achieve successful partnership working [25]. Yet we know from general practitioners' self-reports that the information given to people with dementia is often different to the information given to their family carers [26,27]. Euphemistic terms, such as 'memory problems', are more likely to be used with people with dementia; while medical terms, like 'dementia' and 'Alzheimer's disease', are used with carers [26]. Furthermore, we know that people with dementia and their family carers may hold differing views and preferences [28]. Such differences in experiences, information and views will need to be addressed in order to achieve true partnership working. Although developing opportunities for user involvement for people with dementia may present particular challenges, evidence indicates that these can be constructively addressed [29,30,28].

Partnership between key professionals across the medical and social divide

A further approach to improving primary care services for people with dementia and their families is to develop partnerships that cross the health and social care divide. Most of the research on these approaches has been conducted in the USA. Fortinsky and colleagues [18] describe one such programme, whereby a service coordinator based with the Alzheimer's Association partners with a local primary care doctor. The client and their family are referred to the named service co-ordinator, who provides an individualised consultation about the psychosocial aspects of living with dementia, and describes relevant social services. Such an approach has led to increased diagnoses, increased reported self-efficacy, and increased knowledge about available services among primary care doctors. A related partnership between Managed Care and Alzheimer's Association Chapters as part of a National Chronic Care Consortium is also available (www.nccconline.org/about/alzheimers.htm). The components include early identification, initial assessment, care plans (both medical and social), and carer information and support. A robust research design leads the authors to conclude that such an approach holds promise for improving outcomes for people with dementia and their carers [17].

Conclusion

An adequate primary care response is essential to quality of life for people with dementia and their families. Barriers to an effective primary care response can be addressed using a variety of approaches. Our developing evidence base suggests we can be optimistic about the ability for primary care to fulfil its true potential for people with dementia and their families.

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