Raised inflammatory markers and cognitive decline in older people with T2D

In this section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the focus is on the results of a cross-sectional study that looked at the association between raised inflammatory markers and cognitive decline in an older population with type 2 diabetes.

Association between raised inflammatory markers and cognitive decline in elderly people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study

Marioni RE, Strachan MW, Reynolds RM et al (2010)
Diabetes **59**: 710–3

DIABETES

Raised inflammatory markers associated with cognitive decline in T2D

1 In this cross-sectional study, the authors sought to determine whether three inflammatory markers were associated with cognitive ability and lifetime cognitive decline in an older population with T2D.

2 The Lothian Diabetes Register was used to select, at random, community-dwelling people with T2D aged 60–75 years.

3 Participants were given a range of cognitive assessments for memory, non-verbal reasoning, information processing speed, executive function and mental flexibility. Cognitive test results were used to derive a general intelligence factor (GIF). Vocabulary tests (the results of which are known to vary little with ageing) were used as a surrogate measure for peak prior cognitive ability.

4 Blood samples were taken from all participants and were assessed for circulating levels of the inflammatory markers C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-alpha (all assays performed at the Glasgow Royal Infirmary).

5 Invitations to participate in the study were sent to 5454 people from the Lothian Diabetes Register who met the inclusion criteria. While small population differences existed between recruits (n=1066) and non-responders, they were not considered to be clinically relevant.

6 Poorer age- and sex-adjusted scores on most individual cognitive tests, and for the GIF, were associated with higher IL-6 and TNF-alpha levels (all $P<0.05$). Associations between cognitive ability and CRP were weak.

7 Following adjustment for vocabulary, education level, cardiovascular dysfunction, duration of diabetes and glycaemic control, IL-6 showed the maximum effect size for age- and sex-adjusted GIF, with a 0.173 decrease in the GIF for every 2-fold increase in IL-6 levels.

8 The authors concluded that an association between cognitive decline and raised inflammatory markers was present in this representative T2D population, but that further study was required to determine the direction of the association and evidence of causality.

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Marc Evans, Consultant Physician, Llandough Hospital, Cardiff

This study (Marioni et al, 2010; summarised above) sought to determine whether circulating levels of the inflammatory markers C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-alpha were associated with cognitive ability and estimated lifetime cognitive decline in an older population with type 2 diabetes. Higher IL-6 and TNF- alpha levels appeared to be associated with poorer scores in the cognitive function measures used. Following adjustment for multiple confounding variables, including age, sex, vocabulary, education level, cardiovascular (CV) dysfunction, duration of diabetes and glycaemic control, IL-6 appeared to remain associated with cognitive dysfunction.

These observations suggest that elevated plasma concentrations of inflammatory makers are associated with poorer general cognitive ability among older people with type 2 diabetes. However, this study does not indicate whether some of the factors adjusted for (CV risk, glycaemic control, duration of diabetes, education) are confounders, or whether they could be mediators in the pathway to cognitive decline. Inflammatory markers are sensitive to acute illness, thus single measures of inflammatory markers are unlikely to be of clinical use in terms of defining the risk of life-time cognitive decline.

Although cross-sectional, this study provides some intriguing epidemiological evidence to support the concept of an inflammatory mediated pathogenesis of declining cognitive function in older people with type 2 diabetes. Further studies are clearly required to further address this issue and could include long-term prospective analyses defining the possible role of differing measures of inflammation as markers of future cognitive decline along with studies evaluating the effects of specific anti-inflammatory agents on cognitive decline in people with type 2 diabetes.

Clive Holmes, Professor in Biological Psychiatry, University of Southampton, Southampton

Joe Butchart, Specialist Registrar in Geriatric and General Medicine, University of Southampton, Southampton

A growing body of evidence links raised systemic inflammatory cytokines and poor cognition (Wilson et al, 2002). In animal models, raised systemic pro-inflammatory cytokines result in raised pro-inflammatory cytokines in the central nervous system (Perry et al, 2007). This effect is exaggerated in elderly animals, and in those with pre-existing neurodegenerative disease, resulting in neuro-inflammation, synaptic dysfunction and neuronal cell death (Cunningham et al, 2009). In Alzheimer's disease we have shown that raised systemic tumor necrosis factor-alpha – but, notably, not C-reactive protein – is associated with increased cognitive decline (Holmes et al, 2009).

Type 2 diabetes is associated with raised levels of circulating cytokines (Kolb and Mandrup-Poulsen, 2005). The study by Marioni et al (2010; summarised previous page) suggests that some of the increased risk of cognitive dysfunction in type 2 diabetes may be accounted for by this pro-inflammatory state.

Will therapies aimed at reducing systemic inflammation protect people with type 2 diabetes from cognitive decline and dementia? Clinical trials have yet to be carried out. Improved glycaemic control, particularly with thiazolidinediones, may reduce the inflammatory burden of type 2 diabetes, but whether this reduces the risk of cognitive harm remains to be seen.

In the eagerly-awaited follow-up to this study, it will be interesting to learn whether raised inflammatory markers predict cognitive decline and whether treatment with any particular class of drug confers cognitive protection in type 2 diabetes. This study highlights the importance of systemic inflammation as an independent risk factor for cognitive decline in type 2 diabetes.

Cunningham C, Campion S, Lunnon K et al (2009) Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biol Psychiatry* **65**: 304–12

Holmes C, Cunningham C, Zotova E et al (2009) Systemic inflammation and disease progression in Alzheimer disease. *Neurology* **73**: 768–74

Kolb H, Mandrup-Poulsen T (2005) An immune origin of type 2 diabetes? *Diabetologia* **48**: 1038–50

Perry VH, Cunningham C, Holmes C (2007) Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol* **7**: 161–7

Wilson CJ, Finch CE, Cohen HJ (2002) Cytokines and cognition – the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc* **50**: 2041–56

"In the eagerly-awaited follow-up to this study, it will be interesting to learn whether raised inflammatory markers predict cognitive decline and whether treatment with any particular class of drug confers cognitive protection in type 2 diabetes."

Alan Sinclair, Professor of Medicine and Dean, Bedfordshire and Hertfordshire Postgraduate Medical School, University of Bedfordshire, Luton

Inflammation has emerged as a relevant risk factor for several conditions including cardiovascular diseases and dementia (see, for example, McDermott et al, 2005; Malaguarnera et al, 2006). For both conditions, diabetes is a prominent risk factor, raising this as one of a number of attractive hypotheses in the aetiology of dementia. Marioni et al (2010; summarised previous page) make an important contribution to the literature on this topic.

When trying to understand the impact of the pro-inflammatory state on disease processes, a relevant factor – though usually neglected – is *ageing*. Increased age is associated with inflammation and may have special relevance in older people with disabilities or who are frail (Candore et al, 2010). Age-associated inflammation has been shown to be manifest in several organs and tissues, including brain and blood vessels (Rodríguez-Mañas et al, 2009).

Consequently, studies undertaken in older populations must account for age-associated increases in inflammation. This is because the association between the mechanism (inflammation), the risk factor (diabetes) and the outcome (cognitive decline) might have its origin not in the proposed risk factor (diabetes), but in the process of ageing itself.

Confounders are especially difficult to exclude in cross-sectional studies such as Marioni et al's, and failure to account for them can lead to false or weaker conclusions. The question we really need to ask is this: does the candidate mechanism (inflammation) cause specific neurodegeneration or vascular damage in older people with diabetes compared with older people without diabetes? In the absence of a control group, we cannot be certain that part of the effect of a pro-inflammatory state on cognition seen in Marioni et al's cohort is not attributable to ageing alone, and not diabetes.

Candore G, Caruso C, Jirillo E et al (2010) Low grade inflammation as a common pathogenetic denominator in age-related diseases: novel drug targets for anti-ageing strategies and successful ageing achievement. *Curr Pharm Des* **16**: 584–96

Malaguarnera L, Motta M, Di Rosa M et al (2006) Interleukin-18 and transforming growth factor-beta 1 plasma levels in Alzheimer's disease and vascular dementia. *Neuropathology* **26**: 307–12

McDermott MM, Guralnik JM, Corsi A et al (2005) Patterns of inflammation associated with peripheral arterial disease: the InCHIANTI study. *Am Heart J* **150**: 276–81

Rodríguez-Mañas L, El-Assar M, Vallejo S et al (2009) Endothelial dysfunction in aged humans is related with oxidative stress and vascular inflammation. *Aging Cell* **8**: 226–38

"In the absence of a control group, we cannot be certain that part of the effect of a pro-inflammatory state on cognition seen in Marioni et al's cohort is not attributable to ageing alone, and not diabetes."