Proinflammatory cytokines, sickness behavior, and Alzheimer disease

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ABSTRACT

Background: In Alzheimer disease (AD), systemic inflammation is known to give rise to a delirium. However, systemic inflammation also gives rise to other centrally mediated symptoms in the absence of a delirium, a concept known as sickness behavior. Systemic inflammation is characterized by the systemic production of the proinflammatory cytokines tumor necrosis factor–α (TNFα) and interleukin-6 (IL-6) that mediate immune to brain communication and the development of sickness behavior.

Objective: To determine if raised serum TNFα or IL-6 are associated with the presence of sickness behavior symptoms, independent of the development of delirium, in a prospective cohort study of subjects with AD.

Methods: A total of 300 subjects with mild to severe AD were cognitively assessed at baseline and a blood sample taken for inflammatory markers. Cognitive assessments, including assessments to detect the development of a delirium, and blood samples were repeated at 2, 4, and 6 months. The development of neuropsychiatric symptoms in the subject with AD over the 6-month follow-up period was assessed independently by carer interview at 2, 4, and 6 months.

Results: Raised serum TNFα and IL-6, but not CRP, were associated with an approximately 2-fold increased frequency of neuropsychiatric symptoms characteristic of sickness behavior. These relationships are independent of the development of delirium.

Conclusions: Increased serum proinflammatory cytokines are associated with the presence of symptoms characteristic of sickness behavior, which are common neuropsychiatric features found in AD. This association was independent of the presence of delirium. *Neurology*® 2011;77:212–218

GLOSSARY

AD = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale Cognitive subscale; **CAM** = Confusion Assessment Method; **ChEI** = cholinesterase inhibitor; **CI** = confidence interval; **CRP** = C-reactive protein; ***DSM-III-R*** = *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition, revised; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **IL-6** = interleukin-6; **IQR** = interquartile range; **MSD** = Meso Scale Discovery; **NINCDS-ADRDA** = Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association; **NPI** = Neuropsychiatric Inventory; **OR** = odds ratio; **SIE** = systemic inflammatory event; **TNFα** = tumor necrosis factor–α.

Systemic inflammation is characterized by the production of C-reactive protein (CRP) and the proinflammatory cytokines tumor necrosis factor–α (TNFα) and interleukin 6 (IL-6). TNFα and IL-6 play a role in immune to brain communication by activating the central innate immune response to initiate a behavioral response known as sickness behavior.[1,2] Sickness behavior refers to a coordinated set of behavioral changes that develop during the course of raised systemic inflammation.[3] These behaviors include increased anxiety, depressed mood, and apathy, and are adaptive protective mechanisms aimed at conserving energy and reducing further exposure to systemic inflammatory insults[4] (table e-1 on the *Neurology*® Web site at www.neurology.org). In animal models of neurodegeneration, systemic inflammation results in a markedly increased central proinflammatory cytokine profile and the development of sickness

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behavior and neuronal cell loss.[5,6] In Alzheimer disease (AD), we have shown that systemic inflammation, associated with raised serum proinflammatory cytokines, is associated with a marked increase in cognitive decline that is independent of acute cognitive deterioration associated with delirium.[7,8] We hypothesized that in AD raised serum TNFα and IL-6 would also be associated with an exacerbation of neuropsychiatric symptoms characteristic of sickness behavior independent of the development of the behavioral symptoms of delirium.

METHODS

Study design. A total of 300 community-dwelling subjects with mild to severe dementia and their caregivers were recruited between November 2003 and May 2006 from clinical referrals to memory assessment services in Southampton, UK. Following consent procedures, all subjects fulfilling National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[9] criteria for probable or possible AD were tested using the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog).[10] Immediately following cognitive assessment, a blood sample for assaying CRP and the proinflammatory cytokines TNFα and IL-6 was taken. At the end of the interview, the main caregiver was given a once-weekly checklist diary based on the Neuropsychiatric Inventory (NPI)[11] and the Confusion Assessment Method (CAM)[12] (see table e-1) in which to enter the presence of behavioral symptoms over the following 2 months and to alert the study coordinator if a delirium was suspected. The subjects' main caregiver was then formally interviewed 2 months later by a separate research nurse, blind to the initial cognitive assessment of the subject, using the NPI to determine (with cross-reference to the checklist) the presence of neuropsychiatric features and acute systemic inflammatory events (SIEs) over the preceding 2 months. An SIE was defined as a short-lived (less than 2 months duration) infection or trauma not directly involving the CNS with a minimum serum CRP level of 1 μg/mL after the event. The NPI is a carer-based interview that assesses 10 behavioral disturbances in the subject. Based on animal and human clinical studies,[13–17] we identified 3 core symptoms from the NPI as being a priori compatible with the concept of sickness behavior (i.e., increased depression/dysphoria, increased anxiety, and increased apathy). The main caregiver was revisited at 4 and 6 months with the NPI reassessed in an identical manner to that at 2 months.

All patients were cognitively reassessed 2, 4, and 6 months after baseline (within 2 days and independently of the NPI carer assessment) by the original patient assessor using the ADAS-Cog and the CAM to assess of the development of a delirium with additional blood sampling for inflammatory markers. The CAM operationalizes the core symptoms of delirium as defined by *DSM-III-R*[18] and has a high concordance with the *DSM-IV* diagnosis of delirium.[19–21] Additional assessments using the CAM were carried out if a delirium was suspected by the main carer in between scheduled visits.

Standard protocol approvals, registrations, and patient consents. This study received approval from the South and West Hampshire Local Research Ethics Committee (ref 237/03/w). Written informed consent was obtained from all patients (or guardians of patients) participating in the study.

Systemic inflammation assays. Blood sera were immediately placed on ice and stored within 2 hours at −80°C. CRP was assayed using ELISA and had a detection limit of 1 μg/mL. TNFα and IL-6 was assayed using sandwich immunoassay multispot cytokine assay (Meso Scale Discovery [MSD]). A protocol provided by MSD for custom assays was used with no major modifications. The lowest detectable limit was 1.1 pg/mL for TNFα and 0.7 pg/mL for IL-6.

Statistical analysis. Normality of continuous variables was determined by quantile-quantile plots of the residuals. Baseline age and ADAS-Cog were normally distributed. Serum CRP, TNFα, and IL-6 levels were not normally distributed. Following previous guidelines,[22] low serum CRP was defined as <1.0 μg/mL at all 4 timepoints; moderate/high levels were defined as above 1.0 μg/mL at any timepoint. Serum TNFα and IL-6 levels were simplified by the use of quartile ranges, based on subject numbers found at baseline assessment. Low serum TNFα was defined as that found in the lowest quartile for TNFα (<2.4 pg/mL) at all 4 timepoints and high serum levels as above 2.4 pg/mL at any timepoint. Low serum IL-6 was defined as that found in the lowest quartile for IL-6 (<2.8 pg/mL) at all 4 timepoints and high serum levels as above 2.8 pg/mL at any timepoint. The average NPI score for each individual over the 6-month follow-up period was determined by taking the mean of the 3 NPI scores (product of the frequency and severity) at the 3 timepoints at 2, 4, and 6 months and was not normally distributed. Impairment of an individual NPI symptom was based on its presence (i.e., frequency of ≥1) at any time during the 6-month follow-up period. Allowing for a 10% dropout rate, 300 subjects gave 90% power to detect a significant difference ($\alpha = 0.017$) of 15% between the total NPI score in subjects in the lowest quartile compared to subjects in the top 3 quartiles. Relationships between variables was assessed using a mixture of Student *t* test, Fisher exact test, χ^2, Mann Whitney *U*, and Spearman correlations. Data interaction was assessed using logistic regression analysis.

RESULTS

A total of 366 subjects were approached for inclusion. A total of 51 subjects or their carers declined participation; 15 subjects did not fulfill NINCDS-ADRDA criteria. The 51 nonparticipating subjects did not differ with respect to age (nonparticipants age 82.6 [SE 0.9] years vs participants 82.8 [SE 0.4]; mean difference 0.2 [95% confidence interval (CI) −2.1 to 2.3 years], *t* test $p = 0.9$) or gender (female nonparticipants 38/51 [75%] vs female participants 198/300 [67%], χ^2 1.4, $p = 0.2$). A total of 25 subjects were clinically unresponsive at baseline with severe end-stage dementia, i.e., ADAS-Cog scores greater than 60 points, and were excluded from further analysis due to the difficulty in assessing the development of a delirium over the follow-up period.

Baseline data. Of the 275 subjects, 161 (59%) fulfilled NINCDS-ADRDA criteria for probable AD and 114 (41%) possible AD. The mean age of the cohort at baseline was 82.7 (SD 7.4) years. A total of

Table 1 Baseline serum systemic inflammatory markers and demographics

Systemic levels of inflammatory marker (n)	Age (SE), y	Sex, n (%) women	Baseline ADAS-Cog score (SE), patients
CRP			
Low <1 μg/mL (83)	81.0 (0.8)[a]	50 (60.2)[d]	28.0 (1.5)[g]
High ≥1 μg/mL (186)	83.5 (0.6)	124 (66.7)	30.7 (0.9)
TNFα			
Low <2.4 pg/mL (65)	79.5 (1.0)[b]	43 (66.2)[e]	25.6 (1.6)[h]
High ≥2.4 pg/mL (204)	83.9 (0.5)	131 (64.2)	31.0 (0.9)
IL-6			
Low <2.8 pg/mL (66)	81.1 (0.9)[c]	43 (65.2)[f]	30.0 (1.5)[i]
High ≥2.8 pg/mL (203)	83.3 (0.5)	131 (64.5)	29.3 (0.9)

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive subscale; CI = confidence interval; CRP = C-reactive protein; IL-6 = interleukin-6; TNFα = tumor necrosis factor α.
[a] Mean difference 2.5 (95% CI 0.6 to 4.5) years; *t* test $p = 0.01$.
[b] Mean difference 4.4 (95% CI 2.4 to 6.4) years; *t* test $p < 0.0001$.
[c] Mean difference 2.2 (95% CI 0.2 to 4.3) years; *t* test $p = 0.03$.
[d] χ^2 1.0, $p = 0.3$.
[e] χ^2 0.08, $p = 0.8$.
[f] χ^2 0.01, $p = 0.9$.
[g] Mean difference 2.7 (95% CI −6.1 to 0.7) patients; *t* test $p = 0.1$.
[h] Mean difference 5.4 (95% CI 1.9 to 9.0) patients; *t* test $p = 0.003$.
[i] Mean difference −0.7 (95% CI −2.9 to 4.3) patients; *t* test $p = 0.7$.

99 (36%) subjects were men. At baseline, subjects had a mean ADAS-Cog score of 29.6 (SD 13.0) points. Blood sampling was obtained in 269/275 (98%) subjects at baseline. Median serum CRP was 2.5 (interquartile range [IQR] 0–5.8) μg/mL and was moderate/high (serum level ≥1 μg/mL) in 186 (70%) subjects. Serum TNFα and IL-6 was detectable in all subjects (TNFα median 3.3 pg/mL [IQR 2.4 pg/mL–4.2 pg/mL]; IL-6 median 4.5 pg/mL [IQR 2.8 pg/mL–8.0 pg/mL]).

Low levels of all systemic inflammatory markers at baseline were associated with a younger age, but not gender. Low baseline levels of TNFα, but not CRP or IL-6, were associated with lower ADAS-Cog scores at baseline (table 1).

Six-month follow-up period. A total of 222 (81%) subjects had complete clinical and systemic inflammatory marker follow-up at 2, 4, and 6 months. Of the 53 subjects who did not complete the study, 15 subjects died before study completion and 38 subjects refused phlebotomy or further cognitive assessment at some point during the study. There was no significant difference between those subjects who completed the study in terms of age (completers 82.4 [SE 0.5] years vs noncompleters 83.9 [SE 1.0] years; mean difference 1.5 [95% CI −0.7 to 3.7] years, *t* test $p = 0.2$), gender (female completers 142 [64%] vs female noncompleters 34 [64%], χ^2 0.001, $p = 1.0$), or baseline ADAS-Cog score (completers 28.9 [SE 0.8] patients vs noncompleters 32.2 [SE 2.0] patients; mean difference 3.3 [95% CI −0.6 to 7.2] patients, *t* test $p = 0.1$).

Of the 222 subjects who completed the study, 110 (45.5%) had a total of 150 systemic inflammatory events; 90 (41%) were taking a cholinesterase inhibitor (CheI) and 88 (40%) an antidepressant. Sixty-six subjects (30%) had a history of hypertension, 35 (16%) hypercholesterolemia, and 16 (7%) type 2 diabetes. The use of CheI or antidepressants was not related to the presence of the 3 core features of sickness behavior (symptoms present in 78 [87%] subjects taking a CheI vs 105 [80%] subjects not taking a CheI, χ^2 1.9, $p = 0.2$; symptoms present in 70 [80%] subjects taking an antidepressant vs 113 [84%] subjects not taking an antidepressant, χ^2 0.8, $p = 0.4$).

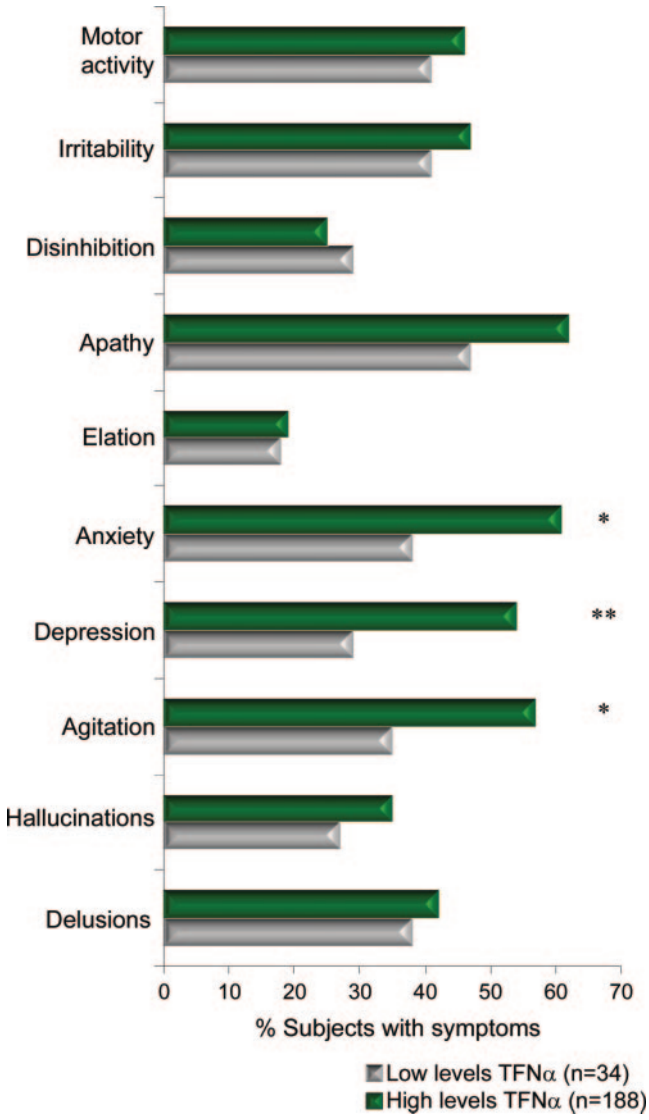
Neuropsychiatric features and delirium. The median NPI score over the 6-month period was 8.2 (IQR 3.3–13.7) patients and was significantly correlated with age at baseline (Spearman correlation −0.18, $p = 0.007$). Delirium was identified in 25 (11.2%) subjects during the 6-month follow-up period. No relationship was found with age and development of delirium (delirium absent age 83.0 [SE 0.5] years vs delirium present 81.0 [SE 1.6] years; mean difference 1.6 years [95% CI −1.5 to 4.7], $p = 0.3$).

Subjects with delirium had a higher median NPI score over the 6-month follow-up period than those without identified delirium (delirium absent NPI score 6.7 [IQR 2.7–12.7] patients vs delirium present 11.0 [IQR 15.7–22.7] patients, MWU $p < 0.0001$). The frequency of individual symptoms in subjects with or without delirium is shown in table 2 and figure e-1. All symptoms were numerically more frequent in subjects with delirium compared to those without delirium and this was

Table 2 Frequency of neuropsychiatric features in subjects with or without presence of delirium

Neuropsychiatric feature	Delirium absent (n = 197), n (%)	Delirium present (n = 25), n (%)	
Delusions	77 (39)	15 (60)	χ^2 4.0, $p = 0.046$
Hallucinations	62 (32)	13 (52)	χ^2 4.2, $p = 0.04$
Agitation	98 (50)	21 (84)	χ^2 10.5, $p = 0.001$
Depression	94 (48)	18 (72)	χ^2 5.2, $p = 0.02$
Anxiety	108 (55)	20 (80)	χ^2 5.8, $p = 0.02$
Elation	35 (18)	6 (24)	χ^2 0.6, $p = 0.5$
Apathy	116 (59)	16 (64)	χ^2 0.2, $p = 0.6$
Disinhibition	44 (22)	13 (52)	χ^2 10.2, $p = 0.001$
Irritability	86 (44)	17 (68)	χ^2 5.3, $p = 0.02$
Motor activity	81 (41)	19 (76)	χ^2 10.9, $p = 0.001$

Figure 1 Frequency distribution of neuropsychiatric features in subjects with Alzheimer disease over the 6-month follow-up period by low or high levels of tumor necrosis factor-α (TNFα)



*$p \leq 0.05$, ** $p \leq 0.01$, adjusted for baseline age, gender, Alzheimer's Disease Assessment Scale Cognitive subscale score, and presence of delirium during follow-up.

statistically significant for all symptoms except for elation and apathy. The 3 core features of sickness behavior were more common in subjects with an identified delirium over the 6-month follow-up period than those without an identified delirium (sickness behavior symptoms present in 24 [96%] subjects with identified delirium compared to 159 [81%] subjects without an identified delirium; Fisher exact test $p = 0.04$). There was a significant relationship between baseline ADAS-Cog score and NPI score during the 6-month follow-up period (Spearman correlation 0.24, $p < 0.0001$) and between baseline ADAS-Cog score and the development of a delirium (delirium present baseline ADAS-Cog score 36.4 patients vs delirium absent 28.0 patients [mean difference 8.4 points (3.3 to 13.6)], $p = 0.001$).

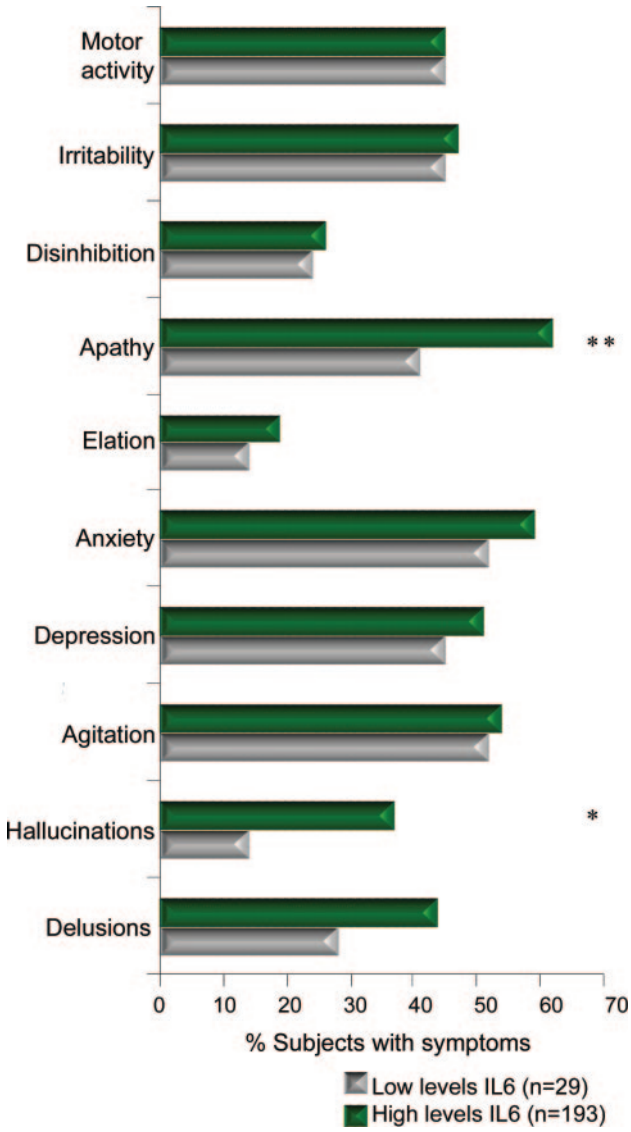
Systemic inflammatory markers. During the 6-month follow-up period, 27 subjects with low serum CRP levels at baseline had serum CRP levels that remained at less than 1.0 μg/mL, 34 subjects with low serum TNFα levels at baseline had serum TNFα levels that remained at less than 2.4 pg/mL, and 29 subjects with low serum IL-6 levels at baseline had serum IL-6 levels that remained at less than 2.8 pg/mL.

Systemic inflammatory markers and delirium. Subjects with low CRP throughout the study were not less likely to experience an episode of delirium than subjects with high CRP (low CRP 3.7% vs high CRP 12.6%, χ^2 1.8, $p = 0.20$). Likewise, subjects with low IL-6 throughout the study were not less likely to experience an episode of delirium than subjects with high IL-6 (low IL-6 3.4% vs high IL-6 12.4%, χ^2 2.0, $p = 0.15$). There was a trend to suggest that subjects with low TNFα throughout the study were less likely to experience an episode of delirium than subjects with high TNFα (low TNFα 2.9% vs high TNFα12.8%, χ^2 2.8, $p = 0.09$).

Systemic inflammatory markers and neuropsychiatric features. There was no statistical difference in the NPI score in subjects with low CRP levels throughout the 6-month follow-up period compared to subjects with high CRP levels (low CRP 6.0 [IQR 2.0–14.0] vs high CRP 8.3 [IQR 3.3–13.7], MWU $p = 0.5$).

Subjects with low TNFα levels throughout the 6-month follow-up period had a lower NPI score over this same time period (low TNFα 4.8 [IQR 1.1–9.4] vs high TNFα 8.8 [IQR 3.7–14.0], MWU $p = 0.01$). The frequency of individual symptoms in subjects with low compared to high levels of TNFα is shown in figure 1. With the exception of disinhibition, all other symptoms were numerically more frequent in subjects with high levels of TNFα compared to those with low levels and this was statistically significant for the presence of agitation (χ^2 5.4, $p = 0.02$), depression/dysphoria (χ^2 7.1, $p = 0.008$), and anxiety (χ^2 6.2, $p = 0.01$) with a trend for apathy (χ^2 2.6, $p = 0.1$). The relationships between the presence of these symptoms and high TNFα levels was largely unchanged following adjustment for baseline ADAS-Cog score, age, gender, and the presence of delirium during the 6-month follow-up period: agitation (odds ratio [OR] 2.6 [95% CI 1.1 to 5.8], $p = 0.02$), depression/dysphoria (OR 3.1 [95% CI 1.3 to 7.0], $p = 0.008$), anxiety (OR 3.0 [95% CI 1.3 to 6.9], $p = 0.007$), and apathy (OR 2.1 [95% CI 1.0 to 4.6], $p = 0.06$).

Figure 2 Frequency distribution of neuropsychiatric features in subjects with Alzheimer disease over the 6-month follow-up period by low or high levels of interleukin-6 (IL-6)



*$p \leq 0.05$, **$p \leq 0.01$, adjusted for baseline age and gender.

Subjects with low IL-6 levels throughout the 6-month follow-up period also had a lower NPI score over this same time period (low IL-6 4.3 [IQR 0.7–9.2] vs high IL-6 8.7 [IQR 3.7–13.8], MWU $p = 0.02$). The frequency of individual symptoms in subjects with low compared to high levels of IL-6 is shown in figure 2. All symptoms, with the exception of motor activity, were numerically more frequent in subjects with high levels of IL-6 compared to those with low levels, and this was statistically significant for the presence of hallucinations (χ^2 6.0, $p = 0.015$) and apathy (χ^2 4.5, $p = 0.03$) with a trend for delusions (χ^2 2.6, $p = 0.1$). The relationships between the presence of these symptoms and high IL-6 levels were largely unchanged following adjustment for baseline age and gender (hallucinations, OR 4.0 [95% CI 1.3 to 12.1], $p = 0.015$; apathy, OR 2.9 [95% CI 1.3 to 6.6], $p = 0.01$) and delusions (OR 2.2 [95% CI 0.9 to 5.4], $p = 0.08$).

Table 3 Period prevalence of systemic inflammatory events during the 6-month follow-up period and number (%) of subjects with this event experiencing one or more of the 3 core features of sickness behavior

Systemic inflammatory event (no. of subjects identified with event)	No. (% of subjects identified with event) of subjects with one or more core features of sickness behavior
No event (112)	87 (78)
Respiratory infection (51)	44 (86)
Genitourinary infection (27)	22 (82)
Accidental trauma (32)	27 (84)
Gastrointestinal infection (14)	14 (100)
Other infections (13)	13 (100)
Surgical intervention (11)	10 (91)
Myocardial infarction (2)	1 (50)
History of hypertension (66)	54 (82)
History of hypercholesterolemia (35)	30 (86)
History of type II diabetes (16)	15 (94)

The period prevalence of the 3 core features of sickness behavior for subjects experiencing specific SIEs is shown in table 3.

DISCUSSION The history of cytokine-induced sickness behavior has been extensively reviewed elsewhere.[4,23] We have argued that these symptoms are likely to be exaggerated and prolonged in subjects with AD due to prior microglial activation in AD[24] and to the effects of SIEs and chronic comorbid conditions associated with raised systemic inflammation, e.g., diabetes.[25] We have previously shown that raised serum TNFα, but not CRP, is associated with increased cognitive decline in AD, independent of delirium[8]; elsewhere there is evidence that raised serum TNFα and IL-6, but not CRP, is associated with cognitive impairment in diabetes.[26] Here we show that raised serum TNFα and IL-6, but not CRP, is associated with an approximately 2-fold increase of NPI scores and an increased frequency of neuropsychiatric symptoms characteristic of sickness behavior, independent of delirium. The lack of relationship between raised CRP as an indicator of systemic inflammation and behavioral symptoms may reflect findings in the elderly that CRP is neither a good predictor of systemic inflammation[27,28] or involved in peripheral to brain communication of sickness behavior.

While every effort was made to identify episodes of delirium in this prospective study using well-validated tools, it is possible that some episodes of delirium may have been missed. However, the frequency of delirium found in this study is in keeping with other community studies of AD,[29,30] and it is notable that the core features of sickness behavior symptoms (apathy, anxiety, and depression) were also common (occurring in around 80%) in those subjects without detectable delirium.

As hypothesized, we found that the 3 core symptoms of sickness behavior were more frequent in subjects with AD with a raised proinflammatory cytokine profile. There appears to be some variability in the effects of different inflammatory events on the development of sickness behavior but small numbers preclude any meaningful comparisons. However, high levels of TNFα and IL-6 were also associated with a general increased frequency of a wide range of symptoms which are not commonly identified as characteristic of sickness behavior (figure 2). These symptoms are common in AD, even in the absence of delirium, and may reflect an exaggerated cytokine response in the brain due to priming of the microglia and enhanced sensitivity to modest systemic inflammatory signals.[5,25] The higher co-occurrence of sickness behavior in subjects with delirium raises the possibility that delirium may represent an extreme nonadaptive presentation of sickness behavior. Thus, there may be a continuum of behavioral changes: in healthy young individuals systemic inflammation inducing benign and transient changes in the CNS while similar systemic changes induce more severe symptoms in a population with dementia. Likewise, delirium may require a more severe systemic inflammation in healthy young individuals but only a mild event in individuals with dementia.[31] It is notable that the symptom profile shown by raised TNFα and IL-6 while both exhibiting apathy also differ. Thus, raised TNFα is associated with symptoms more characteristic of depressive symptomatology while raised IL-6 is more characteristic of a psychotic profile (figures 1 and 2) and is consistent with cluster analyses of the NPI in subjects with AD.[32] In addition, subjects with mild cognitive impairment show a NPI profile that is remarkably similar to that associated with sickness behavior,[33] suggesting that the early presentation of these symptoms might represent the neurochemical consequences of microglial activation and consequently explain their poor cognitive outcome.[34]

AUTHOR CONTRIBUTIONS

Prof. Holmes: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding. Dr. Cunningham: drafting/revising the manuscript, study concept or design, contribution of vital reagents/tools/patients. E. Zotova: analysis or interpretation of data, acquisition of data. D. Culliford: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Prof. Perry: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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DISCLOSURE

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