detailed analysis of CAM and DSI (Table 1) shows that, as expected, disorientation and memory problems are not useful for diagnosis of delirium given the low positive predictive value. On the other hand, inattention and disturbance of consciousness seem to be more reliable symptoms for diagnosis of delirium, having the advantage of not requiring prolonged assessment.

Our study was conducted on a real group of acutely admitted older people being assessed by junior medical doctors. We confirmed that CAM, which is based on DSM-III-R, is a good screening instrument for delirium in this subset of patients because of its simplicity, suitability for non-communicating patients and psychometric proprieties. We should highlight the need for specific training to apply this scale, as recommended by Inouye [5], since it requires determining the level of consciousness and attention which are often difficult to assess. Although we also found the DSI usefulness in routine clinical practice, it can easily lead to over-diagnosing delirium when the DSM-IV criteria are used as the gold standard. Our study revealed that MMSE could not be used in a quarter of patients. Similarly, AMT (suggested in the BGS guidelines), although less complex as it is purely verbal, may be difficult to use in clinical practice in this context. Other assessment approaches, dependent more on clinical observation (e.g. of inattention and disturbance of consciousness), may therefore be more appropriate to screen for delirium without the necessity for cognitive assessment, as demonstrated in our study.

Our study represents a practical clinical implementation of the BGS guidelines for delirium. Diagnosis of delirium should be done by skilled professionals, with good knowledge of this clinical syndrome and confidence in applying reliable tools as part of routine clinical practice. Teaching these skills needs to be an essential part of the medical curriculum, so that junior clinicians are empowered to think about delirium and how to recognise it early. This in turn will contribute to earlier diagnosis and treatment of this syndrome.

Key points

- Recognition of delirium should be done by skilled professionals.
- We confirm that CAM is a good screening instrument for delirium in elderly with dementia. However, there is a further need for specific training to apply CAM, since it requires assessment of level of consciousness and attention.
- The usefulness of MMSE in elderly with delirium is limited, with one-quarter of the elderly not able to be assessed because of altered level of consciousness, inability to communicate or rapidly deteriorating medical condition.
- Delirium symptom instrument (DSI), although useful in diagnosing delirium, can easily lead to over-diagnosing delirium when DSM-IV criteria are used as a golden standard.

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C-reactive protein and memory function suggest antagonistic pleiotropy in very old nondemented subjects

SIR—A possible role of inflammation in the development of dementia [1] has led to investigations examining whether C-reactive protein (CRP), a systemic marker of inflammation, is associated with worse cognitive function and decline in old age. Elevated CRP has been associated with worse global and specific cognitive functioning [2–7], although other studies have found no relationship between CRP and cognition [8–10]. Most studies have examined samples averaging <75 years

[3–6, 9, 10]. We hypothesised that elevated CRP would be related to worse cognitive function in very old cognitively healthy subjects.

Methods

Subjects

Cognitively healthy subjects with no other preconditions beyond their age being 75 years or more were recruited from the Bronx Veterans Affairs Medical Center (BxVAMC) and senior centres in New York metropolitan area for a project investigating cardiovascular risk factors and cognition. The Mount Sinai School of Medicine and the BxVAMC both provided IRB approval and all subjects gave written informed consent.

Cognitive assessment

We evaluated overall cognitive functioning by direct assessments and informant interviews using the Clinical Dementia Rating scale (CDR) [11] and included only subjects with CDR = 0 (not demented). In addition, subjects with a history of a neurological, medical or psychiatric disorder potentially affecting cognition (e.g. stroke, schizophrenia)—by self-report, informant report or medical charts—were excluded.

The subjects received a neuropsychological test battery, described previously [12]: the Mini Mental State Exam (MMSE), tests of memory (sum of immediate recall trials 1, 2 and 3), delayed recall, recognition and savings (100∗delayed recall/immediate recall trial 3), executive functions (Trail making A, Trail making B), intelligence (Shipley) and language (word fluency).

Blood samples

The subjects' blood samples were sent to the BxVAMC haematology laboratory and wide-range CRP, possessing near-perfect correlation with high-sensitivity CRP [13], was measured from plasma using the ADVIA 1650 Chemistry System with a CRP latex reagent. Also, apolipoprotein E (APOE) genotyping and other values relevant to cardiovascular risk factors (e.g. cholesterol, haemoglobin A1C) were measured.

Statistical procedures

Subjects were first categorised into conventionally identified 'low' (≤1.0 mg/l), 'normal' (>1.0 mg/l and ≤3.0 mg/l) and 'high' (>3.0 mg/l) CRP groups [14]. Logarithmic transformation of the non-normally distributed CRP was applied for all other statistical analyses. The MMSE was used to examine global cognitive function. To summarise the other neuropsychological tests, we conducted a factor analysis using varimax rotation. Stepwise regression assessed the linear and quadratic associations of CRP with each factor and MMSE, controlling for age, sex and education, for the entire sample, and divided by sex, or by the presence of an APOE-e4 allele. Two-sided tests were employed.

Table 1. Demographics and partial correlations for total sample and APOE-e4 non-carriers and carriers

Variable	Total sample[a]	Non-APOE-e4 carriers	APOE-e4 carriers
Demographics			
n	176	123	50
Mean age (SD)	85 (6)	85 (6)	85 (6)
Male/female	112/64	79/44	31/19
Mean years of education (SD)	15 (3)	15 (3)	14 (4)
Partial correlations (linear effect) with log(CRP)[b]			
Memory	0.26***	0.26**	−0.06
Executive/language	−0.18*	−0.15	−0.19
MMSE	−0.11	−0.06	−0.21

[a]Includes three subjects not genotyped for APOE.
[b]Controlling for age, sex and years of education in multiple regression analysis.
*$P < 0.05$, **$P < 0.005$, ***$P < 0.001$

Results

Of the 189 nondemented subjects with CRP measurements, 13 subjects did not have neuropsychological test data allowing for the factor analysis, and were excluded. This left 176 subjects (112 men, 64 women) with full neuropsychological test data [mean age: 85 ± 6 years; mean years of education: 15 (±3)]. The preponderance of males reflects the many subjects recruited through the BxVAMC. There were 123 subjects with no APOE-e4 allele (3/3: $n = 92$; 2/3: $n = 31$), 50 subjects with an e4 allele (3/4: $n = 35$; 2/4: $n = 10$; 4/4: $n = 5$) and three missing DNA. The factor analysis produced a model with two factors, one primarily including memory functions (high weights from delayed recall, savings and recognition) and one primarily including executive/language functions (high weights from Trail making B, word fluency, Trail making A, immediate recall and Shipley).

Untransformed mean CRP level was 2.5 mg/l ± 5.2 mg/l (ranging from 0.00 to 41.50) with 97 having 'low', 40 'normal' and 39 'high' CRP levels. Memory scores were significantly different [$F(2, 170) = 4.34$, $P = 0.01$] across groups, where the low-CRP group had worse memory scores than the other two groups. The groups did not differ in executive/language score or MMSE. As indicated in Table 1, we found that higher CRP values were significantly associated with lower (worse) executive/language function scores and also with higher (better) memory scores. The CRP relationship with MMSE was not significant. No quadratic associations were significant.

There were no differences in CRP, memory, executive/language or MMSE scores in subjects divided by the presence of an APOE-e4 allele. CRP was significantly positively related to memory in those subjects with no

APOE-e4 allele, but not in those with an e4 allele. We divided the sample by sex and found a similar pattern of associations in both sexes (memory: males, $r = 0.21$, $P < 0.05$; females, $r = 0.26$, $P < 0.05$; executive/language: males, $r = -0.20$, $P < 0.05$; females, $r = -0.26$, $P < 0.05$; MMSE: males, $r = -0.14$, n.s.; females, $r = -0.17$, n.s.). We also divided the sample by whether subjects were ascertained from the BxVAMC ($n = 48$, all males) or from the community at large ($n = 128$, 64 males and 64 females), and observed similar significant patterns in each group. Finally, the results were not affected by the inclusion of cholesterol level (total, LDL or HDL), haemoglobin A1C or smoking history as covariates.

Discussion

Contrary to our prediction, elevated CRP was *positively* associated with good memory. This relationship was specific to subjects without an APOE-e4 allele. The unexpected direction of this relationship might be due to the age characteristics of our sample. Evidence implicating elevated CRP as a correlate of impaired cognition comes primarily from samples of younger old [2–6, 15], and the few studies that included the very old have not generally found such a relationship [3, 8]. As studies begin to focus on risk factors for cognitive impairment, decline, dementia and AD in the oldest old, the effects of risk factors previously identified for relatively younger cohorts appear to vary considerably. For example, the increased risk attributable to a positive family history for AD or carrying the APOE-e4 allele is substantially lower for an 85 year old than for a 65 year old [16, 17]. Interestingly, other factors associated with cardiovascular risk and disease have shown similar apparently age-related discrepant effects. The metabolic syndrome is associated with cardiovascular disease and diabetes and has been found to be a risk factor for cognitive impairment and dementia in younger old [18]. However, the metabolic syndrome was associated with a decelerated cognitive decline in a very old sample in a recent longitudinal study [19]. Also, we recently observed an unexpected relationship between both total and LDL cholesterol with good memory function [20]. Similarly, evidence for other factors (e.g. low blood pressure, weight loss) associated with reduced risk for cardiovascular disease and sometimes also for dementia may, in the very old, be associated with an increased risk of dementia [21, 22].

We found no association between CRP and MMSE but, consistent with our initial prediction, elevated CRP was associated with lower levels of executive/language functioning. Previous studies of younger samples have also observed that elevated CRP is related to worse performance in cognitive functions including tests of executive function [3], and also of memory [2, 6] and global cognitive functioning [3, 4]. In our study, relationships were observed between CRP with both memory and executive/language factors, calculated through factor analysis as independent of each other, but those relationships ran in opposite directions. Thus, our study suggests that the relationship between CRP and cognitive function is not a simple one but varies depending on the specific type of cognitive function examined. In this context, we note that impairments in these two areas of cognitive function may have different implications for subsequent overall cognitive health; reduced executive/language functions may be a normal characteristic of aging, while age-associated memory impairments may indicate a degenerative process [23]. If so, then in a very old population, elevated CRP may be associated with more normal age-related impairments in executive/language function, whereas it also is associated with individuals who, by virtue of their better memory function, are less liable to dementia.

A limitation of any cross sectional study is the bias introduced by studying only those eligible subjects who survive long enough to be ascertained. It is possible that, like CRP [24], a relatively weak memory even in cognitively normal individuals may increase mortality [25]. An interaction between them would be an additional possible selection bias. A more fundamental limitation of a cross sectional study is that it does not distinguish between differences in stable memory level and differences in change in memory over time. We plan to follow our sample longitudinally to see whether the association of high CRP with good memory is observed for changes in memory over time. Our sample was clearly biased in favour of male subjects, due primarily to recruiting from the BxVAMC, and this reduces the representativeness of the sample. We note, however, that the patterns observed remain both when we examine each sex separately and when we examined BxVAMC and other community subjects separately.

While the association of elevated CRP with worse executive/language functioning is consistent with findings in younger samples, the association of elevated CRP with good memory runs in the opposite direction. An age-related variable effect of CRP on memory function may reflect antagonistic pleiotropy, which refers to gene and other effects that may be favourable at one point in life and unfavourable at another [26]. This has been associated with genes that improve early fitness but lead to diminished functioning later, but the opposite age effect has also been described [27]. An individual who survives to a late age may develop processes that adapt to the challenges that these risk factors pose at an earlier age. Such an adaptation might fall under the maxim of 'what doesn't kill you makes you stronger'. Alternatively, it is possible that rare individuals possess inherited protection from factors which to most other people pose a threat throughout life. At earlier ages, such protected individuals would be greatly outnumbered by those who face increased risk of disease in the presence of these factors. At these ages, elevated levels in a given risk factor would be associated with less successful cognitive ageing. At very late ages, however, mortality will have disproportionately diminished the ranks of the less protected individuals and survivors from this frailer group will tend to have a lower risk factor profile. The initially small protected group would tend to disproportionately survive to late ages and include those with 'high risk' factor profiles. Collectively examining these very old people would

lead to associations between those high levels of 'risk factors' and successful cognitive ageing. Thus, a dynamic reapportionment of those with liability versus resistance may occur at the extremes of old age and this may help explain a variable effect of risk factors with age.

Key points

- Reports that increased CRP is associated with cognitive functioning deficits in the elderly have not looked at very old populations.
- We examined, cross-sectionally, CRP and memory and executive function in a very old, nondemented population.
- We found that higher CRP was modestly associated with weaker executive functioning, as predicted, but unexpectedly it was also associated with a better memory function.
- The latter may be an example of antagonistic pleiotropy, i.e. effects that may be unfavourable at one point in life and favourable at another.
- Alternatively, the high-functioning survivors at these very old ages may disproportionately include genetically protected individuals who at earlier ages were rare in their age cohort.

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Conflicts of interest

None.

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Inter-rater reliability of the DRS-R-98 in detecting delirium in frail elderly patients

SIR—Delirium is a common, but often under-recognised problem in elderly people. Simple instruments to detect and grade delirium have been proposed as a remedy to under-recognition. Such instruments need to be reliable across different raters, as they are likely to be used by clinicians with differing clinical specialisations and levels of experience. Inter-rater reliability (IRR) has not been rigorously studied for most delirium rating scales, and even then typically by developers of the scales [1]. These studies commonly report different IRR statistics, and use IRR and inter-rater agreement interchangeably, even though they are not exactly the same [1]. Pearson's correlation (r) is a measure of consistency between raters which may be high even when agreement is low. An intraclass correlation coefficient (ICC) is a measure of variance, and hence measures IRR. Cohen's kappa (κ) is a measure of chance-corrected absolute agreement between raters. Its variation, the weighted κ, weights agreement by degree (agreement is higher if there is only a one-point difference and progressively lower as the difference increases) [1, 2].

Here, we assessed the IRR of DRS-R-98 [3]. This instrument is a revised version of the Delirium Rating Scale (DRS) [4] and allows for assessment of both delirium diagnosis and severity. It has been validated for use by psychiatrists with experience in delirium [3]. We also sought to further explore the construct validity of the DRS-R-98 by investigating whether IRR systematically varies by cognitive diagnosis and level of frailty.

Methods

Sample

We used a convenience sample of geriatric medicine patients at a 1000-bed tertiary care teaching hospital in Halifax, Canada, between November 2003 and November 2006. Using a standard formula [5] and accepting that an intraclass correlation of 0.7 would be the minimum acceptable, we aimed for at least 36 per diagnostic group of no cognitive impairment (NCI), delirium and dementia.

IRR was assessed for pairs of raters, from a pool of three staff geriatricians and six residents in internal, family or geriatric medicine. Each pair included a staff geriatrician with experience in delirium. The raters did not have extensive training in the instrument, except that it had been demonstrated by someone familiar with its use (KR) and they referred to the standard DRS-R-98 instructions at the time of assessment [3]. Each patient was independently and blindly assessed by two raters within 1 h.

Instruments

All patients had a Comprehensive Geriatric Assessment (CGA) [6] and Mini-Mental State Examination (MMSE) [7] as part of usual care prior to administration of the DRS-R-98. These were done during the same clinical encounter (e.g. outpatient visit or hospital admission) but for inpatients, not necessarily on the same day. Dementia and delirium were diagnosed using DSM-IV diagnostic criteria. We used standard criteria for 'cognitive impairment, no dementia' (CIND) [8]. The cognitive diagnoses were NCI, CIND, dementia, delirium, delirium superimposed on CIND and delirium superimposed on dementia.

The DRS-R-98 is a clinician-rated instrument. It includes 13 severity 'symptoms' [sleep–wake cycle disturbance, perceptual disturbances and hallucinations, delusions, liability of affect, language, thought process abnormalities, motor agitation or retardation, orientation, attention, memory (short- and long-term) and visuospatial ability] and 3 'diagnostic items' (temporal onset, fluctuation and physical disorder) [3]. The ICC between two raters for the DRS-R-98 total score was first reported as 0.98 [3].

We rated frailty using a Frailty Index derived from the patient's CGA at admission [6, 9, 10]. Impairments were counted in 10 domains: cognition, emotion, communication, mobility, balance, bowel and bladder function, nutrition, activities of daily living and social resources. Each item was scored 0 = no problem, 0.5 = minor problem and 1.0 = major problem. Based on prior distributions of scores, [9, 10] we made two modifications to the FI-CGA to better characterise co-morbidities and medications. First, instead of the original scoring, the co-morbidities were simply counted and the medications were scored as 0 = no medications, 0.5 for each of the first five medications and 1.0 for each medication $\geq$6. The deficit count was divided by 80, the highest possible score if all problems were present and given a maximum of 40 illnesses and medications, to yield an index ranging from 0 to 1.