Are People with Subjective but no Objective Memory Complaints at Increased Risk of Dementia?

Case

A 55-year-old teacher who lives alone seeks help for memory complaints. She reports forgetting the names of students and losing items around the house but has minimal evidence of functional impairment, no difficulty driving and no history of mental or physical illness. She has a history of hypertension but is otherwise well. She is worried about the risk of future dementia.

Should this patient be concerned about the risk of dementia? For younger people with minimal risk factors is the MMSE sufficient as a screening test? At this stage are further investigations indicated and in the absence of a formal diagnosis can anything be done to help?

Subjective memory complaints (SMCs) are everyday memory and related cognitive concerns expressed by people who may or may not have deficits on objective testing. SMC are of course common in people with mild cognitive impairment (MCI) and dementia and depending of how they are defined may occur in up to 50% of the healthy elderly population although after exclusion of depression a rate of around 20-30% is more typical. The rate of complaints in those under 55 years is very poorly studied but Commissaris and colleagues (1998) found that 39% of people with a mean age of 33.9 answered positively to the question “Do you consider yourself forgetful?”, suggesting perceived deficits are probably more common than thought.

One important issue when trying to elicit SMC is that awareness of deficits generally decreases as severity of cognitive impairment increases (particularly in the most severe stages). Moreover many people who suspect cognitive problems may be reticent about disclosing them and in many cases are reluctant to undergo formal testing. For this reason informant report is strongly recommended where available, and is independently predictive of diagnosis and decline. Although definitions of SMC have not been operationalised numerous several self-report questionnaires have been developed and can be used simply in clinical practice. Examples of validated tools are the Everyday Memory Questionnaire – Revised (EMQ-R) and the Short Memory Questionnaire (SMQ). It is now recognised that the presence of SMC is associated with distress and reduced quality of life. Causes of SMC without objective complaints are diverse but conceptually it may be helpful to try and separate those with no evidence of cognitive impairment from those with subclinical cognitive change and those with mild cognitive impairment. A simple classification based on these three domains is illustrated (Figure 1 above).

Indeed psychological factors such as depression influence expression of memory complaints. Therefore perceived forgetfulness is not always a sinister irreversible finding and even when examined cross-sectionally most purely subjective memory complaints do not interfere with daily function. Practically anyone with memory complaints should also be asked about symptoms of depression, and ideally screened with a severity questionnaire such as the Patient Health Questionnaire (PHQ9). The prognostic significance of SMC is important but until recently poorly studied. A review identified only seven studies published up to 2000 that considered dementia longitudinally and of these five studies found an association between baseline SMC and dementia after two years or more. However these
studies were all in the elderly population and also did not account for baseline MCI and/or objective neuropsychological impairment. Two recent studies have been informative. Wang et al (2004) examined 1,883 subjects without dementia or objective cognitive impairment (they scored 91 or higher on the 100-point Cognitive Ability Screening Instrument).11,12 Developed dementia during five years of follow-up. For subjects who reported SMCs at baseline ages of 70, 75 and 80 years, the hazard ratios of developing dementia were 6.0, 3.2 and 1.6 respectively. That risk was modest for the younger groups. Additionally, a subset of people with baseline normal cognition who reported a high level of subjective deterioration had a higher risk for developing dementia (OR = 2.7; CI 95%, 1.45–4.98). In a small study Galassi et al (2010) followed 92 SMC patients for four years stratified into those with SMC alone and those with MCI. During the follow-up, 45.5% of SMC remained unchanged, 13.0% were diagnosed as MCI and only one progressed to dementia. Of the MCI patients, 32.3% remained stable, 18.4% developed dementia and 4% reverted to SMC alone. Visual attention, behavioral memory, frontal/executive function and caregivers’ distress were independent predictors of progression to dementia.13 This preliminary data suggests a modest but significant risk of decline in older people with purely subjective complaints but no data has been forthcoming in younger adults. Our group recently conducted a meta-analysis of conversion studies. Compared to those without SMC, MCI and those with MCI. The relative risk of progression (SMC vs healthy elderly) from these studies was 2.18 (1.48 – 3.29). More informative perhaps the annual conversion rate for those with SMC was 2.7% (95% CI 2.0% to 3.6%). A major modifying variable in determining risk in those with subjective but those with MCI and SMC is function (activities of daily living). Unfortunately this is one area that is often inadequately tested in routine clinical care, leading to the assumption that function was always normal in MCI and SMC. Whilst gross function impairment is uncommon, new research suggests an important subset are subtly impaired. Data from the Spanish Neurological Diseases in Central Spain study (NEDICES) cohort involving 1,073 participants reported SMC questions this assumption.14 Of 730 individuals with pure SMC, 18.1% had significantly impaired function and 3.5% had severely impaired function measured by the Pfeffer scale.15 It is likely that those with SMC and impaired function are at increased risk of dementia even when symp- toms present under 65 years. Clinically this means that everyone reporting SMC should also be tested for impaired function and whilst this can be done clinically it can also be useful to use an objective scale.

The clinical approach to people with possible early dementia or MCI has been exten- sively described elsewhere.16,17 I would recom- mend putting clinically worrying SMC in that category. Clinically worrying SMC would include SMC with evidence of objective cognitive or functional decline, informant concern, evidence for early progression as well individuals with concomitant risk factors for dementia (such as co-existent vascular disease). A reasonable work up would include physical and neurological examination, neuropsychological testing and neuroimaging focusing on a standardized tests for dementia and MCI. Focal atrophy on magnetic resonance imaging (MRI) of the medial temporal region and decreased metabolism in this area as well as parietal lobes on 18F-fluorodeoxyglucose-poiton-emission tomography (FDG-PET) has been shown to predict the conversion from mild cognitive impairment to Alzheimer’s disease. However, imaging in particular, PET is not widely available and CSF biomarkers may offer an alterna- tive.18 However no method has has excellent accu- racy in the earliest stages. In this case the preliminary MMSE of 29/30 is probably insufficient if there is any clinical reason for concern. The MMSE, although popular, has been found to have insufficient accuracy in the diagnosis of MCI (sensitivity 62.7%; specificity 63.3%).19 The accuracy of other cognitive tools is under active investigation but the reported 30th percentile score on the ACE certainly seems to rule out appreciable cognitive impairment.20 Nevertheless a remaining question in this case is whether any formal intervention can be recommended. Although there is extensive data on the treat- ment of early dementia and modest data on treatment of MCI, there is paucity of RCT evidence for those with memory complaints alone.21 Work involving the asymptomatic elderly and observation of cohorts is currently ongoing.22 It is likely that pure SMC is not an entirely benign condition, the risk of dementia in working age adults remains to be clarified23 and no good preventative strategies other than correcting obvious risk factors and sensible lifestyle advice currently exist. Clearly there are many areas of uncertainty when it comes to subjective without objective complaints and it is difficult indeed potentially misleading to give too rigid a forecast at base- line. Nevertheless in the absence of functional decline although the risk is elevated in absolute terms it is still modest (about 3% per year). This risk can not be assumed to be constant but should be reassessed after serial examina- tions. For younger people under 55 years without functional decline or cognitive impair- ment on neuropsychological tests (not simply the MMSE alone which is insufficient) then neuroradiology and CSF testing can be consid- ering useful but not yet essential. A careful psychiatric history is certainly essential While we await strong evidence for preventive strate- gies monitoring in the form of serial bi-annual testing with a convenient battery such as the CAMCOG is recommended along with robust treatment of vascular risk factors such as hyper- tension.