Clinical History and Neurological Examination

3

Contents

Abstract

This chapter considers important aspects in the clinical history, including single item cognitive screening questions and family history, in the diagnosis of cognitive disorders, and also examines the diagnostic utility of various "non-canonical" neurological signs (attended alone, head turning, applause, *la maladie du petit papier*).

Keywords

Dementia · Diagnosis · History · Neurological signs

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3.1 History Taking

Guides to cognitive assessment which are accessible to, and designed for use by, all clinicians are available (e.g. Hodges 2007). History taking and physical examination are the touchstone of all neurological assessments and the first step in all diagnostic pathways (Larner et al. 2011). This is as true for individuals with cognitive complaints as for those with elemental neurological (sensory and/or motor) problems. History taking ("anamnesis") is by far the most important method of assessment.

A semi-structured approach to the history, sufficiently flexible to accommodate the variety of clinical presentation, is required. Application of Kipling's "six honest serving men" (what, why, when, how, where, who) may be useful (Fisher and Larner 2006; Larner 2007a; Box 3.1). This may also flesh out the social, occupational, and past medical history which will contextualise the current problems.

Box 3.1 One Suggested Approach to the History Taking in the Cognitive Clinic (Adapted from Larner 2007a)

What are the problems? Frequent repetition of questions or comments suggests organic amnesia. Impairment in instrumental activities of daily living, such as handling finances or medications, travelling by public or private transport, and using the telephone, should arouse concern since epidemiological studies show them to be predictive of dementia.

Why has the patient presented now? Have problems been worsening over some months? Or has some particular incident triggered patient decline? An acute episode of confusion (delirium) occurring during febrile illness or postoperatively may be the harbinger of progressive cognitive decline.

When did this happen? Many years of forgetfulness are less alarming than a history of 6–12 months of progressive decline. Also, when in the lifespan: pathological causes of memory complaint are much more common in later life, although around 5% of dementia cases occur before the age of 65 years (in the UK; Alzheimer's Society 2014).

How do the patient and family cope with the situation? Have there been work or domestic repercussions because of forgetfulness, e.g. complaints that work is not being done or even dismissal from work, others needing to take over the patient's usual household chores?

Where do the problems occur? Are they more noticeable in new or unusual situations? Does the patient prefer to be at home, to the extent that social withdrawal has occurred? Has occupational function been impaired?

Who makes the complaint of forgetfulness? Does it emanate primarily from the patient, or from relatives, friends and carers? If the latter, whilst the patient makes little of the difficulties, the clinical index of suspicion should be increased, likewise if patients are unable to give examples of memory lapses. Patients attending alone very seldom have dementia.

Some centres use a history proforma to ensure that all potentially relevant issues are addressed, including not only cognitive symptoms but also behavioural and psychiatric features. Key history points (Larner 2011a) will include:

- The specific complaint: if memory problems, ask for some examples of how the patient's memory lets her/him down.
- Age at onset (and hence duration) of the problem.
- Onset and course of the problem: sudden or gradual onset? Fluctuating or steadily progressive course?

In addition, the importance of obtaining collateral history from a knowledgeable informant cannot be overemphasized. In some centres a provisional diagnosis of Alzheimer's disease (AD) in pre-dementia stage is based largely on informant report (Burns and Morris 2008:7, 39–41).

Enquiries about the impact of cognitive problems on occupational and/or social functions should be made, since impairment in these domains is a *sine qua non* for a diagnosis of dementia in some criteria (e.g. DSM-IV; American Psychiatric Association 2000). Further insights may be gained by enquiring about the impact of symptoms on activities of daily living (ADL), both instrumental and basic activities (Box 3.2). Dedicated screening instruments for the assessment of ADLs are available (see Sect. 5.1).

Additional points worth enquiring about in the history include:

- Education and employment: extent of education and employment history may give some pointers to premorbid cognitive function, and hence expectations about appropriate performance on cognitive screening instruments.
- Appetite: may be poor, and associated with some weight loss, in the early stages of some dementias (e.g. Alzheimer's disease); change in dietary habit with a predilection for sweet foods may occur in behavioural variant frontotemporal dementia (bvFTD).

Box 3.2 History Taking in the Cognitive Clinic: Activities of Daily Living (ADLs)

Instrumental activities:

- Ability to use public and private transport
- Handling monetary transactions
- Using the telephone, e.g. recalling messages
- Managing medications

Basic activities:

- Feeding
- Dressing
- Toileting

- Mood: anxiety and depression can impact on memory function, and may be potentially reversible with appropriate medication (see Sect. 5.2).
- Sleep pattern: disturbed sleep may impair memory, for example in depression or specific sleep-related disorders such as obstructive sleep apnoea syndrome or restless legs syndrome (see Sect. 5.3).
- Drug use: both prescription and recreational drugs may impair cognition, for example due to anticholinergic or soporific effects.

Specific aspects of the history may have positive predictive value for specific dementia disorders (see Chap. 9). These include:

- Motor slowing, visual hallucinations, REM sleep behaviour disorder in dementia with Lewy bodies and Parkinson's disease dementia.
- Early speech production problems or impaired comprehension in the linguistic variants of frontotemporal lobar degeneration (FTLD).
- Personality change, either apathy or disinhibition; increased tendency to routines; development of sweet tooth; wandering without getting lost in bvFTD.
- Getting lost early; lack of confidence; early amnesia in Alzheimer's disease.
- Prior transient ischaemic attacks/strokes, emotional incontinence in vascular cognitive impairment and vascular dementia.

Analysis of conversational profile may also have diagnostic potential (Elsey et al. 2015).

History taking may be envisaged as a conversion of the patient (and collateral) episodic account into a semantic formulation. The key question which history taking should seek to answer is whether the account is one of self-reported lapses in memory retrieval in the absence of collateral verification, or an informant report of memory impairment with loss of self-appreciation by the patient, the latter being more in keeping with a neurodegenerative disorder (Burns and Morris 2008:53; Larner 2011a).

Pattern recognition and deductive skills, perhaps akin to the methodology used by the fictional detective Sherlock Holmes, who encountered various neurological disorders in his practice (Larner 2011b), and whose skills have been adduced to the service of interpretive (Hunter 1991) and evidence-based medicine (Nordenstrom 2007), are central to diagnostic formulation, supplemented where necessary by further investigations (discussed in Chaps. 4–7).

3.1.1 Single Item Cognitive Screening Questions

Do single specific questions have particular utility in either screening for or the diagnosis of dementia and cognitive disorders? The validity of this single question approach has been illustrated in other areas of neurology, for example by the finding that a single question ("When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by

walking or movement?") had very high sensitivity (1.00) and specificity (0.968) for the diagnosis of restless legs syndrome (Ferri et al. 2007). Clearly such single item screening questions may be subjected to pragmatic screening/diagnostic test accuracy studies (as outlined in Chap. 2).

In a prospective study, Creavin et al. (2015) found that three simple questions had high utility for dementia diagnosis: learning how to use new gadgets; problems handling personal finances; and problems with planning (commentary in Larner 2016a). A systematic review of single screening questions for cognitive impairment in older people found 11 eligible studies from 884 titles, with sensitivity range 26–96% and specificity range 45–100%, suggesting promise in informant-based single item screening questions for cognitive impairment, but insufficient evidence to support routine use (Hendry et al. 2015). Nevertheless, some have advocated the adoption of this approach.

3.1.1.1 Dementia CQUIN Question

The Dementia Commissioning for Quality and Innovation (Dementia CQUIN) policy document, a UK Government directive (Department of Health 2012), advocated a single screening question for cognitive impairment to be addressed to all individuals aged 75 years or over irrespective of the reason(s) for clinical presentation: "Have you been more forgetful in the past 12 months to the extent that it has significantly affected your life?". If answered in the affirmative, the CQUIN advised initiation of a "dementia risk assessment", exact nature unspecified (see Sect. 10.5.5).

No data on the sensitivity, specificity or other measures of discrimination for this screening question were presented in the Dementia CQUIN. Hence although it may have face validity, its ability to identify patients with and without dementia was unknown. Aji and Larner (2015) investigated this by asking the screening question to 100 consecutive patients attending a dedicated epilepsy outpatient clinic, on the grounds that subjective memory complaints are common in this patient population, variously related to underlying diagnosis, seizure frequency, medication effects, and comorbid affective disorder. They suspected that the sensitivity would be very high, with risk of identifying many false positives. In the event, nearly half of the patients questioned (48%) answered the screening question in the affirmative, although only one was aged greater than 75 years. None of these patients was judged to have dementia on clinical grounds.

3.1.1.2 Subjective Memory Complaints Likert Scale

Another single item cognitive screening question was described by Paradise et al. (2011), a five-point Likert scale for subjective memory complaints (SMC). Participants are asked "In general, how would you rate your memory?" with a choice of the following five responses: 1 = poor; 2 = fair; 3 = good; 4 = very good; or, 5 = excellent. The scale defined those rating their memory as either fair or poor (2 or 1) as experiencing SMC (SMC+). This Likert scale has been used as a screen for SMC in diagnostic test accuracy studies of cognitive screening instruments for mild cognitive impairment (O'Caoimh et al. 2016).

Aji and Larner (2017) administered the SMC Likert scale to 100 consecutive follow-up patients attending a dedicated epilepsy outpatient clinic. This study found a much lower self-rating of memory impairment using the Likert scale (20%) than the previous study (Sect. 3.1.1.1) which used a single yes/no screening question (48%). Using a Likert scale screening question may provide greater diagnostic discrimination than a simple yes/no question.

3.1.1.3 Metamemory

Metamemory may be defined as introspective knowledge or self-awareness of ones memory capabilities. Both the Dementia CQUIN screening question (Sect. 3.1.1.1) and the five-point SMC Likert scale (Sect. 3.1.1.2) may be judged to access the construct of metamemory, in that they address subjective memory judgements.

Both questions were administered (sequentially in counter-balanced order to avoid bias) to 50 consecutive new outpatients attending a dedicated cognitive disorders clinic (Larner 2018) along with a standard multidomain cognitive screening instrument, the mini-Addenbrooke's Cognitive Examination (MACE; see Sect. 4.1.5.5). Results (Table 3.1) showed that SMC Likert and MACE were highly sensitive for cognitive impairment (>0.95), but all the tests had low specificity (≤0.5). For the metamemory questions the accuracy, positive and negative predictive values were all around 0.5, with the exception of negative predictive value of 0.80 for SMC Likert, whereas MACE achieved better scores for all these parameters.

Since the standard patient assessment cognitive screening instrument, MACE, outperformed both the metamemory questions on all the measures of discrimination examined, this may cast doubt on the diagnostic utility of the metamemory construct, although further larger studies are required.

3.1.2 Family History of Dementia

Taking a family history is an integral part of the history taking process in all domains of medicine, not only neurology.

Many individuals attending cognitive disorders clinics with complaints of poor memory prove, following clinical and cognitive testing, to have no evidence for underlying cognitive impairment indicative of a neurodegenerative disorder, prompting diagnostic labels such as "worried well" and "subjective memory complainers" (see Sects. 1.4 and 8.3). What prompts these individuals to be sufficiently concerned about memory function to consult medical opinion is not entirely clear. Factors which may contribute to subjective memory complaint include affective disorders, such as anxiety and depression (Sect. 5.2.2; Hancock and Larner 2009a), sleep disturbance (Sect. 5.3.1; Hancock and Larner 2009b), and self-perception of impaired self-efficacy (Sect. 8.3).

Another possible factor is the presence of a family history of a dementing disorder (see Case Study 3.1). It has been reported that the occurrence of dementia in a close relative is a strong predictor of subjective forgetfulness (Commissaris

Table 3.1 Demographic and diagnostic parameters for single item cognitive screening (metamemory) questions (adapted from Larner 2018)

	Metamemory questions		
N	50		
F:M (% female)	26:24 (52)		
Age range (years)	26–84 (median 60.5)		
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.24		
Pre-test odds = prevalence/(1 − prevalence)	0.32		
Test	**CQUIN**	**SMC Likert**	**MACE**
Cut-off	**Yes/no**	**+/−**	**≤25/>25**
N	**30:20**	**45:5**	**37:13**
Accuracy	0.52 (0.38–0.66)	0.54 (0.40–0.68)	0.74 (0.62–0.86)
Net Reclassification Improvement (NRI)	0.28	0.30	0.50
Sensitivity (Se)	0.63 (0.43–0.82)	0.96 (0.88–1.00)	1.00
Specificity (Sp)	0.42 (0.23–0.61)	0.15 (0.02–0.29)	0.50 (0.31–0.69)
Y	0.05	0.11	0.50
PPV (= post-test probability)	0.50 (0.32–0.68)	0.51 (0.37–0.66)	0.65 (0.49–0.80)
NPV	0.55 (0.33–0.77)	0.80 (0.45–1.00)	1.00
PSI	0.05	0.31	0.65
LR+	1.08 (0.69–1.70) = unimportant	1.13 (0.94–1.36) = unimportant	2.0 = small
LR−	0.89 (0.56–1.39) = unimportant	0.27 (0.23–0.33) = small	∞
DOR	1.22 (0.78–1.92)	4.18 (3.48–5.03)	∞
Post-test odds (= pre-test odds × LR+)	0.35	0.36	0.64
CUI+	0.31 (very poor)	0.489 (poor)	0.65 (good)
CUI−	0.23 (very poor)	0.12 (very poor)	0.50 (adequate)

CQUIN Commissioning for Quality and Innovation, *SMC* subjective memory complaints, *MACE* mini-Addenbrooke's Cognitive Examination

et al. 1998). Concern based on the family history may be well justified in light of the increasing number of recognised genetically determined causes of dementia (Sect. 7.3). Although the family history may emerge or be volunteered during history taking, specific questions about this aspect may need to be addressed to the patient.

To investigate what effect positive family history of dementia might have on referrals to the Cognitive Function Clinic (CFC), a prospective observational study was undertaken, based on a clinical impression that a positive family history of

Case Study 3.1 Family History of Dementia

A 43 year-old lady was referred to the clinic by her general practitioner with memory complaints. She attended alone. Her specific complaints were of difficulty with peoples' names and forgetting ongoing tasks if distracted. There was a prior history of a seizure disorder, exact nature unspecified, but she was receiving neither antiepileptic nor any other medication. On direct questioning, she admitted to poor sleep, with sleep maintenance insomnia resulting in an estimated 4 h sleep per night, leaving her tired during the day. She was not working, and had lost interest in hobbies, but activities of daily living were preserved.

Her family history was positive for dementia. The patient (see Fig. 7.4, patient III.7) was one of seven siblings, all brothers, the three eldest of whom were affected, all with onset in their early 40s. Their mother was also affected. The brothers had been diagnosed with probable Alzheimer's disease (AD) on the basis of their clinical phenotype.

The patient's neurological examination was normal. Cognitive status was examined with the Mini-Mental State Examination (see Sect. 4.1.1) on which she scored 29/30 (1 point dropped out of 3 on delayed recall) and with the Montreal Cognitive Assessment (see Sect. 4.1.8) on which she scored 27/30 (normal ≥26/30; 1 point dropped out of 5 on delayed recall). Structural brain imaging was normal. In the absence of an objective measure of cognitive impairment, the patient was diagnosed with subjective memory complaint.

Following the death of one of her brothers, it became evident from post-mortem examination that he in fact had a tauopathy and not AD. Further investigation with neurogenetic testing showed that this was due to a splice site mutation in the gene encoding the microtubule associated protein tau on chromosome 17 (IVS10 + 16C > T), and hence his diagnosis was frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17; Doran et al. 2007). A cousin later presented with a clinical phenotype more typical of behavioural variant frontotemporal dementia but with the same tau gene mutation (Larner 2009a). In light of this information, the patient was offered referral to clinical genetics services for consideration of counselling prior to predictive genetic testing, but she declined this in light of her reassuring cognitive screening and neuroradiological findings.

dementia might be more common in clinic attenders without dementia (Larner 2013a). As part of clinical history taking, enquiry for a family history of dementia and/or AD was made in consecutive new patients attending the clinic over a 6-month period (April to September 2011 inclusive). The following definitions were used (after Cruts et al. 1998):

- "Autosomal dominant disease": ≥3 affected family members in at least two generations.
- "Familial disease": at least one first degree family relative affected.
- "Sporadic disease": no family history.

Of the 139 patients assessed (F:M = 73:66, 53% female; age range 18–88 years, median 61 years), 63 were judged to be either demented by DSM-IV criteria (American Psychiatric Association 2000) or to have mild cognitive impairment (MCI) by Petersen criteria (Petersen et al. 1999), hence the prevalence of cognitive impairment was 45%; 76 patients were not demented. Forty-three patients reported a positive family history of dementia. In only four instances were the criteria for "autosomal dominant disease" fulfilled, the remainder (39) having only "familial disease".

Of the 63 patients who received a diagnosis of dementia or MCI, 14 had a positive family history (all "familial disease"). Of the 76 patients who were judged to have neither dementia nor MCI, 29 had a positive family history (either "autosomal dominant disease", 4, or "familial disease", 25). Hence the frequencies of a positive family history in the two groups were 14/63 (=22.2%) and 29/76 (=38.2%) respectively. The relative risk or risk ratio of a patient with neither dementia nor MCI having a positive family history of dementia was 1.72 (95% confidence interval [CI] = 1.00–2.96). The null hypothesis that the proportion of patients with a positive family history of dementia was the same in the cognitively impaired and non-impaired groups was not rejected, although a trend was observed ($\chi^2 = 3.41$, df = 1; $0.1 > p > 0.05$). Using the Z test, the null hypothesis was rejected ($Z = 2.02$, $p < 0.05$).

As the data on family history of dementia in this study were based on patient report, with or without input from other family member, friend or carer, they are obviously subject to recall bias, which might be deemed a shortcoming. Nonetheless, since this reported family history is the one with which the patient operates, the data have ecological validity. (Note that this history may not be suitable for measuring heritability, where a metric such as the Goldman score may be required, from Goldman et al. 2005, modified by Rohrer et al. 2009; for an example of the use of the modified Goldman score, see Larner 2012a.) They suggest that a positive family history of dementia may be one stimulus for concerns about memory leading to consultation and onward referral.

A potential confounder of this result may be that patients with cognitive impairment might underreport a positive family history, for example as a consequence of an amnesic syndrome. However, since these individuals almost invariably attend the clinic with a relative, friend or carer (see Sect. 3.2.1), the risk of this confound may be minimised by the availability of collateral report.

It might be argued that using a more stringent definition of autosomal dominant disease (e.g. >3 affected family members in three generations, and/or disease age at onset <61 years) might alter the study conclusions (certainly this increases the chances of finding deterministic genetic mutations, e.g. Cruts et al. 1998; Campion

et al. 1999; Janssen et al. 2003). However, experience of eight families with deterministic genetic mutations for dementia seen in CFC (four with tau gene mutations, four with presenilin 1 gene mutations) found that in only three of these families was there a clear autosomal dominant pattern of disease transmission (using the same definition as used in this study); in four others there was familial disease, and one case was apparently sporadic, possibly due to *de novo* mutation. All but one of these families had early-onset (i.e. before 65 years of age) dementia (Doran and Larner 2009; see Sect. 7.3 for further details). All four of the patients in the family history study with a reported family history suggestive of autosomal dominant disease did not have cognitive impairment (Larner 2013a).

A study of first-degree relatives of patients with AD reported more subjective memory complaints than in the spouses of AD patients, especially in those with a prior history of depression (Tsai et al. 2006). Another study found this relationship only in the relatives of patients with early-onset AD, suggesting that increased monitoring of memory performance might occur when relatives enter the age range in which parents or siblings developed dementia (McPherson et al. 1995). It may be that these individuals are sensitized to the symptoms of memory impairment, or over-attend to apparent signs of cognitive loss, including memory lapses, as a consequence of their family history.

3.2 Neurological Examination

Neurological examination is guided by diagnostic hypotheses generated by history taking, which contextualise and give meaning (relevant, irrelevant) to the many signs which may be detected on neurological examination (Larner 2014a, 2016b). There are no neurological signs which are pathognomonic of dementia, in part because there is overlap with signs which may emerge with normal ageing (Larner 2006, 2012b, 2016b:6–7). In the appropriate setting certain features may be suggestive of the diagnosis, such as carphologia or floccillation (Larner 2007b).

A normal neurological examination may be anticipated in those with subjective memory complaint, but this is also the norm in neurodegenerative disorders such as Alzheimer's disease in its early stages. A number of neurological signs should be specifically looked for (Box 3.3; Larner 2011a, 2014a), since they may suggest specific disorders (also known as "secondary" dementias; Kurlan 2006) and/or broaden the differential diagnosis to the many neurological disorders which may have cognitive impairment as part of their phenotype (Larner 2013b). Measurement of blood pressure and auscultation for cardiac sounds and possible carotid bruits may be indicated if vascular dementia or vascular cognitive impairment is suspected.

The methodology used for assessing the diagnostic utility of neurological signs is similar to that used for cognitive and non-cognitive screening instruments (see Chap. 2).

Box 3.3 Neurological Signs to Look for in Patients Attending the Cognitive Clinic (Adapted from Larner 2011a, 2014a)

- Parkinsonism: Parkinson's disease dementia, dementia with Lewy bodies, progressive supranuclear palsy, corticobasal syndrome; may also be seen in Alzheimer's disease.
- Muscle wasting ± fasciculation; cachexia may be common to many dementias in their later stages, but concurrent fasciculation in the tongue or around the shoulder girdle suggests frontotemporal lobar degeneration with motor neurone disease (FTD/MND).
- Myoclonus: occurs early in sporadic Creutzfeldt-Jakob disease, late in Alzheimer's disease.
- Chorea: Huntington's disease.
- Sensory complaints: prion disease, especially variant CJD; multiple sclerosis.

3.2.1 "Attended Alone" Sign

The importance of collateral history from a knowledgeable informant when assessing individuals complaining of memory problems and in the diagnosis of dementia syndromes, particularly AD, has been emphasized in diagnostic guidelines (e.g. Knopman et al. 2001; Waldemar et al. 2007). Formalised input to the diagnostic process from a caregiver may be achieved through the use of structured interviews of informants, or informant scales (see Sect. 5.4).

Because of the importance of collateral history in the assessment of cognitive problems, all patients referred to CFC are sent written instructions, printed in bold type, requesting them to attend the clinic with someone who knows them well and can give information about them. These instructions are included with the letter giving the details of the clinic appointment (date, time, location).

Failure to attend CFC consultation with an informant, despite the prior provision of written instructions to do so, has been examined as a possible sign of absence of dementia in two consecutive studies over a 6-year period (September 2002 to August 2008) (Larner 2005a, b, 2009b). The results (Table 3.2) showed that the "attended alone" sign was a robust marker of the absence of dementia, with very high sensitivity, negative predictive value and negative likelihood ratio, but low specificity, positive predictive value and positive likelihood ratio, and clinical utility indices which were only adequate (rule in) or poor (rule out).

The utility of the attended alone sign may be dependent in part on the location in which patients are seen. In the study of the Instrumental Activities of Daily Living (IADL) Scale (see Sect. 5.1.1; Hancock and Larner 2007), of the patients completing the instrument without an informant present ($n = 63$), most did not have dementia (56, of whom 5 had mild cognitive impairment). Six of the seven patients adjudged to have dementia but attending the clinic alone lived close to the hospital,

Table 3.2 Demographic and diagnostic parameters of the "attended alone" sign for the absence of dementia (pooled data from Larner 2005a, 2009b, adapted)

	"Attended alone"
N	735
Prevalence of dementia (= pre-test probability)	0.45
Pre-test odds = prevalence/(1 − prevalence)	0.81
Accuracy	0.66 (0.61–0.72)
Net Reclassification Improvement (NRI)	0.21
Sensitivity (Se)	0.99 (0.91–1.07)
Specificity (Sp)	0.40 (0.37–0.43)
Y	0.39
PPV (= post-test probability)	0.57 (0.53–0.62)
NPV	0.98 (0.90–1.06)
PSI	0.55
LR+	1.65 (1.52–1.78) = unimportant
LR−	0.030 (0.027–0.033) = large
DOR	54.3 (50.1–58.9)
Post-test odds (= pre-test odds × LR+)	1.34
CUI+	0.56 (adequate)
CUI−	0.39 (poor)

the only medical institution in the town (Runcorn, Cheshire) where they were seen; the other patient travelled by ambulance arranged by his primary care practitioner.

A subsequent study of the "attended alone" sign in a large, independent outpatient cohort was undertaken to evaluate its utility as a simple screening test for the absence of dementia (Larner 2014b), as previously reported. Since "absence of dementia" may include individuals with MCI, the utility of the "attended alone" sign for identification of cognitively healthy individuals within the "absence of dementia" group was also examined, by excluding MCI patients. Over the 3-year study period (September 2008 to August 2011), a total of 726 new patients were assessed. The majority of referrals came from primary care physicians (500/726, =68.9%), the other major sources being psychiatry services (106/726, =14.6%) and other neurologists (88/726, =12.1%). Compared with the prior 6 year-period (September 2002 to August 2008), this suggested an increased (approximately doubled) referral rate (see Sect. 1.1).

Of the 726 patients, 480 (=66.1%) attended with an informant as requested, of whom 216 were diagnosed with either dementia or MCI, and 264 were diagnosed as cognitively healthy. In the attended alone group (n = 246), no patient was diagnosed as suffering from dementia but 16 patients were diagnosed with MCI and hence at possible risk of progressing to dementia, leaving 230 individuals diagnosed as cognitively healthy in this group. Prevalence of dementia/MCI (i.e. cognitive impairment) in the study population was therefore 31.9% (232/726). Dementia prevalence in previous studies (2002–2008) was 45.0% (331/735; MCI diagnoses not recorded). The null hypothesis that the proportion of patients with dementia/MCI in the study period versus the proportion with

dementia in the historical cohort was the same was rejected ($\chi^2 = 26.6$, df = 1; $p < 0.001$; see Sect. 1.4).

Diagnostic parameters for the "attended alone" sign for the absence of dementia (Table 3.3, left hand column) showed excellent sensitivity, negative predictive value, and negative likelihood ratio, as previously found (compare Table 3.2).

The sensitivity of the "attended alone" sign for identifying cognitively healthy individuals (i.e. excluding the MCI patients attending alone) was also examined (Table 3.3, right hand column). Again sensitivity, negative predictive value, and negative likelihood ratio were good. The relative risk or risk ratio of a patient with neither dementia nor MCI attending alone was 6.75 (95% confidence interval [CI] = 4.17–10.9). The null hypothesis that the proportion of patients attending alone was the same in the cognitively impaired and non-impaired groups was rejected ($\chi^2 = 112.1$, df = 1; $p < 0.001$).

Table 3.3 Demographic and diagnostic parameters of the "attended alone" sign for the absence of dementia or any cognitive impairment (adapted from Larner 2014b)

	"Attended alone"	
N	726	
F:M (% female)	343:383 (47.2)	
Age range	16–92 (median 61)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.32	
Pre-test odds = prevalence/(1 − prevalence)	0.47	
	Diagnosis of no dementia (i.e. presence of MCI or subjective memory complaint)	**Diagnosis of no dementia or MCI (i.e. presence of subjective memory complaint only)**
Accuracy	0.64 (0.60–0.67)	0.61 (0.58–0.65)
Net Reclassification Improvement (NRI)	0.32	0.29
Sensitivity (Se)	1.00	0.93 (0.90–0.97)
Specificity (Sp)	0.45 (0.41–0.49)	0.45 (0.41–0.49)
Y	0.45	0.38
PPV (= post-test probability)	0.48 (0.44–0.53)	0.47 (0.42–0.51)
NPV	1.00	0.93 (0.90–0.96)
PSI	0.48	0.40
LR+	1.82 (1.68–1.97) = unimportant	1.70 (1.56–1.86) = unimportant
LR−	0 = large	0.14 (0.13–0.16) = moderate
DOR	∞	11.8 (10.8–12.8)
Post-test odds (= pre-test odds × LR+)	0.86	0.80
CUI+	0.48 (poor)	0.44 (poor)
CUI−	0.45 (poor)	0.42 (poor)

Table 3.4 "Attended alone" sign, analysis by patient gender; cognitive impairment = dementia + MCI cases (adapted from Abernethy Holland and Larner 2013a)

	N	Cognitive impairment (% of N)	Attended alone (% of N)	Attended with (% of N)
Female	343	96 (28.0)	117 (34.1)	226 (65.9)
Male	383	136 (35.5)	129 (33.7)	254 (66.3)
Total	726	232 (32.0)	246 (33.9)	480 (66.1)

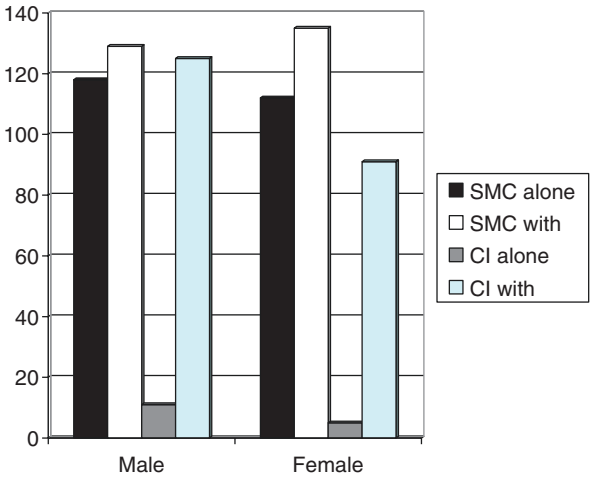

Fig. 3.1 "Attended alone" sign, analysis by patient gender; *SMC* subjective memory complaint, *CI* cognitively impaired (dementia + MCI) (adapted from Abernethy Holland and Larner 2013a)

Most neurological signs are evident in both men and women, but because there may be a behavioural component to the attended alone sign, analysis of the sign according to gender was undertaken (Table 3.4, Fig. 3.1; Abernethy Holland and Larner 2013a). The null hypothesis that the proportion of patients attending alone did not differ significantly by gender was not rejected ($\chi^2 = 0.02$, df = 1, $p > 0.5$). Looking at the diagnostic accuracy data by gender (Table 3.5) there was no obvious difference in the utility of the attended alone sign between the sexes.

Analysis of the attended alone sign by patient age was also performed (Table 3.6, Fig. 3.2), accepting that the age structure of the CFC population is unusual with a bias towards younger individuals (Sect. 1.3.1). The null hypothesis that the proportion of patients attending alone did not differ significantly by patient age was, unsurprisingly, rejected ($\chi^2 = 66.5$, df = 7, $p < 0.001$).

The attended alone sign is an easily observed and categorised clinical sign. As shown in these pragmatic studies of unselected new outpatient clinic cohorts it has good sensitivity for the absence of cognitive impairment. It may therefore be a useful screening observation, indicating in many cases that reassurance rather than intensive further investigation may be appropriate clinical management. Another

Table 3.5 Diagnostic parameters for "attended alone" sign analysed by patient gender (adapted from Abernethy Holland and Larner 2013a)

	Attended alone	
N	726	
F:M (% female)	343:383 (47.2)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.32	
Pre-test odds = prevalence/(1 − prevalence)	0.47	
	Female (*n* = 343)	**Male (*n* = 383)**
Accuracy	0.59 (0.54–0.64)	0.63 (0.59–0.68)
Net Reclassification Improvement (NRI)	0.27	0.31
Sensitivity (Se)	0.96 (0.92–0.99)	0.91 (0.87–0.96)
Specificity (Sp)	0.40 (0.34–0.47)	0.49 (0.43–0.55)
Y	0.36	0.40
PPV (= post-test probability)	0.45 (0.39–0.52)	0.48 (0.42–0.54)
NPV	0.95 (0.90–0.99)	0.92 (0.87–0.96)
PSI	0.40	0.40
LR+	1.60 (1.43–1.80) = unimportant	1.80 (1.58–2.06) = unimportant
LR−	0.11 (0.09–0.12) = moderate	0.17 (0.15–0.20) = moderate
DOR	15.1 (13.5–16.9)	10.4 (9.11–11.9)
Post-test odds (= pre-test odds × LR+)	0.75	0.85
CUI+	0.43 (poor)	0.47 (poor)
CUI−	0.38 (poor)	0.45 (poor)

Table 3.6 "Attended alone" sign, analysis by patient age; *SMC* subjective memory complaint, *CI* cognitive impairment (= dementia + MCI cases)

Age	N	SMC alone	SMC with	CI alone	CI with
16–20[a]	4	1	2	0	1
21–30	8	2	1	0	5
31–40	32	18	1	2	11
41–50	93	52	10	0	31
51–60	216	88	46	2	80
61–70	207	51	106	3	47
71–80	127	16	82	8	21
80+	39	2	16	1	20
Total	726	230	264	16	216

[a]Lower age limit of adult neurology outpatient clinics is 16 years

study has also reported that patients with functional memory disorders are less likely to be accompanied to the memory clinic than patients with dementia (40% vs 91%; Elsey et al. 2015).

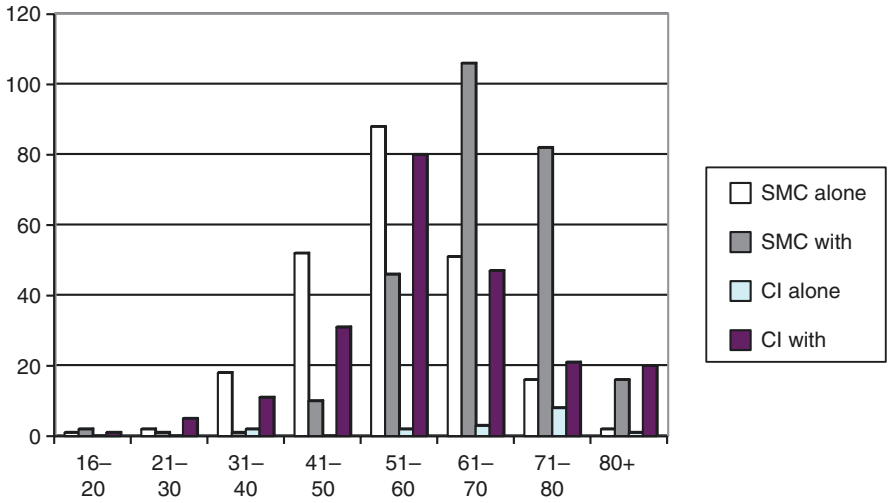

Fig. 3.2 "Attended alone" sign, analysis by patient age; *SMC* subjective memory complaint, *CI* cognitively impaired (dementia + MCI)

3.2.2 Head Turning Sign

Whilst taking the history from a patient with possible cognitive impairment.

> "the physician may observe that the patient exhibits the head turning sign (looking at his care-giver when asked a question), which is a common sign in A[lzheimer's] D[isease]" (Bouchard and Rossor 1996:37).

This phenomenon had probably been noted by earlier physicians, for example as a patient's tendency during case-taking to refer any questions to the person accompanying them (Allison 1962:14, 127). The phenomenon has also been described as a "positive head tilt" (Lipton and Marshall 2013:46), which might perhaps be confused with the head tilt observed in patients with some forms of diplopia or cervical dystonia (Larner 2016b:148). This clinically observed head turning sign is entirely different from the "head turn test" or head tracking test, a computerized measure of complex motor function requiring subjects to follow a moving object by moving their head, previously suggested to be of diagnostic use in Alzheimer's disease (Kluger et al. 1997).

Two prospective observational studies of day-to-day clinical practice have been undertaken to examine the utility of the head turning sign (HTS; Larner 2012c; Ghadiri-Sani and Larner 2013). HTS was operationalised thus: following introductions and initial pleasantries, HTS was adjudged to be present (HTS+) if the patient turned her/his head away from the interlocutor and towards the accompanying person(s) when first invited to describe symptoms (e.g. "Tell me about the problems you are having with your memory") or when specifically asked about them (e.g. "What problems are you having with your memory?" or "Can you give me an

example of how your memory lets you down?"). A verbal request for assistance from the patient to the caregiver was not required. Head turning later in the consultation, for example during administration of cognitive screening instruments, was not deemed HTS+ (cf. the operationalisation used by other authors: Fukui et al. 2011).

Over a 10-month period (January to October 2011), 207 consecutive new referrals were observed for the presence of HTS, of whom 82 (=39.6%) were judged to have cognitive impairment (Larner 2012c). This was a heterogeneous group, including cases of AD and mixed AD/cerebrovascular disease (26), amnestic MCI (28), frontotemporal lobar degenerations (FTLD; 8), dementia with Lewy bodies (DLB; 7), subcortical ischaemic vascular dementia (2), and miscellaneous others (11; see Case Study 7.2).

For the whole cohort, 52 (=25.1%) were HTS+ and 155 (=74.9%) were HTS−.

HTS+ was found to be very specific for the presence of cognitive impairment (0.98) but not very sensitive (0.60), with correspondingly excellent positive predictive value (0.94; Table 3.7, left hand column).

Of the HTS− group, 74 attended the clinic alone. Very few of those who attend memory disorders clinics alone have evidence of cognitive impairment (the

Table 3.7 Demographic and diagnostic parameters for head turning sign (adapted from Larner 2012c)

	HTS	
N	207	
F:M (% female)	109:98 (52.7)	
Age range (years)	18–91 (median 60)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.40	
Pre-test odds = prevalence/ (1 − prevalence)	0.67	
	Whole cohort (*N* = 207)	**Cohort minus "attended alone" (*n* = 133)**
Accuracy	0.83 (0.77–0.88)	0.76 (0.69–0.83)
Net Reclassification Improvement (NRI)	0.43	0.36
Sensitivity (Se)	0.60 (0.49–0.70)	0.63 (0.52–0.74)
Specificity (Sp)	0.98 (0.95–1.00)	0.95 (0.89–1.00)
Y	0.58	0.58
PPV (= post-test probability)	0.94 (0.88–1.00)	0.94 (0.88–1.00)
NPV	0.79 (0.72–0.85)	0.64 (0.54–0.75)
PSI	0.73	0.58
LR+	24.9 (8.0–77.2) = large	11.5 (3.78–35.1) = large
LR−	0.41 (0.13–1.28) = small	0.39 (0.13–1.20) = small
DOR	60.4 (19.5–187.3)	29.3 (9.62–89.2)
Post-test odds (= pre-test odds × LR+)	16.6	7.7
CUI+	0.56 (adequate)	0.59 (adequate)
CUI−	0.77 (good)	0.61 (adequate)

"attended alone" sign; see Sect. 3.2.1; Larner 2005a, b, 2009b, 2014b), and this was also the case in this cohort (four with MCI, none with dementia). The absence of an accompanying person to whom to turn their head might be deemed to disqualify these individuals from a study of HTS. Eliminating these patients, the diagnostic utility of HTS was recalculated ($n = 133$; Table 3.7, right hand column), again showing the sign to have good specificity (0.95) and positive predictive value (0.94). The null hypothesis that the proportion of HTS+ patients was the same in the cognitively impaired and non-impaired groups was rejected ($\chi^2 = 46.9$, df = 1; $p < 0.001$).

In a further, similar, study over a 10-month period (February to December 2012; Ghadiri-Sani and Larner 2013), 191 consecutive new outpatients were seen; 85 had cognitive impairment (55 with dementia by DSM-IV-TR criteria, 30 with MCI). Considering the whole cohort, HTS+ had sensitivity 0.61 and specificity 0.98 for the diagnosis of cognitive impairment (Table 3.8, left hand column). Considering only those patients who attended with an informant ($n = 113$), HTS+ had sensitivity 0.68 and specificity 0.94 for diagnosis of cognitive impairment, (Table 3.8, right hand column). All figures were comparable with the previous cohort (compare

Table 3.8 Demographic and diagnostic parameters for head turning sign (adapted from Ghadiri-Sani and Larner 2013)

	HTS	
N	191	
F:M (% female)	91:100 (47.6)	
Age range (years)	20–89 (median 60)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.45 (0.29 + 0.16)	
Pre-test odds = prevalence/(1 − prevalence)	0.82	
	Whole cohort (*N* = 191)	**Cohort minus "attended alone" (*n* = 113)**
Accuracy	0.82 (0.76–0.87)	0.76 (0.68–0.84)
Net Reclassification Improvement (NRI)	0.37	0.31
Sensitivity (Se)	0.61 (0.51–0.72)	0.68 (0.57–0.78)
Specificity (Sp)	0.98 (0.96–1.00)	0.94 (0.87–1.00)
Y	0.59	0.62
PPV (= post-test probability)	0.96 (0.91–1.00)	0.96 (0.91–1.00)
NPV	0.76 (0.69–0.83)	0.58 (0.45–0.70)
PSI	0.72	0.54
LR+	32.4 (8.13–129.3) = large	12.2 (3.13–47.2) = large
LR−	0.40 (0.10–1.58) = small	0.34 (0.09–1.33) = small
DOR	81.9 (20.5–326.7)	35.4 (9.11–137.2)
Post-test odds (= pre-test odds × LR+)	26.5	10.0
CUI+	0.59 (adequate)	0.65 (good)
CUI−	0.74 (good)	0.54 (adequate)

Table 3.9 Head turning sign, analysis by patient gender; cognitive impairment = dementia + MCI cases (adapted from Abernethy Holland and Larner 2013a)

	N	Cognitive impairment (% of N)	HTS+ (% of N)	HTS− (% of N)
Female	123	79 (64.2)	58 (47.2)	65 (52.8)
Male	123	76 (61.8)	48 (39.0)	75 (61.0)
Total	246	155 (63.0)	106 (43.1)	140 (56.9)

Tables 3.7 and 3.8), confirming that the head turning sign is very specific but not very sensitive for the diagnosis of cognitive impairment, with a high positive predictive value.

The relative risk or risk ratio of a patient with neither dementia nor MCI ($n = 113$) demonstrating HTS+ was 0.08 (95% confidence interval [CI] = 0.02–0.32). The null hypothesis that the proportion of HTS+ patients was the same in the cognitively impaired and non-impaired groups was rejected ($\chi^2 = 36.8$, df = 1; $p < 0.001$).

The exact neuropsychological correlates of HTS remain to be defined, although the impression gained from the CFC studies was that it might be a somatic marker of amnesia. Fukui et al. (2011) thought it might be the consequence of an imbalance between memory impairment and relatively preserved executive function, but it is of note that their cohort, unlike the CFC studies, did not include cases of FTLD. Patients with both behavioural and linguistic presentations of FTLD were observed to be HTS+ (Larner 2012c).

As with the attended alone sign (Sect. 3.2.1), there may be a behavioural component to the head turning sign. Analysis of HTS according to gender was undertaken by pooling the data from the two studies described above ($n = 398$, of whom 246, =62%, did not attend alone and hence could be assessed for HTS; Table 3.9; Abernethy Holland and Larner 2013a). In this selected subgroup, the null hypothesis that the proportion of patients with the head turning sign did not differ significantly by gender was not rejected although a trend was observed ($\chi^2 = 3.26$, df = 1, $0.1 > p > 0.05$). Looking at the diagnostic accuracy data by gender (Table 3.10) gave an impression that HTS may be of greater diagnostic utility in female patients.

HTS is an easily observed and categorised clinical sign. As shown in these pragmatic studies of unselected new outpatient clinic cohorts it has good specificity, i.e. is reliably absent in those without cognitive impairment. It may therefore be a useful screening observation, its presence indicating the need for further investigation of cognitive function, just as attending alone suggests that reassurance rather than further investigation is indicated.

The neurobiological correlates of HTS have been investigated, and correlation shown with CSF biomarkers of neurodegeneration (Tabuas-Pereira et al. 2016).

3.2.3 Applause Sign

The applause sign (*signe d'applause*, clapping test, three clap test) is elicited by asking a patient to clap their hands three times as quickly as possible, as

Table 3.10 Diagnostic parameters for head turning sign analysed by patient gender (adapted from Abernethy Holland and Larner 2013a)

	HTS	
N	246	
F:M (% female)	123:123 (50)	
Age range (years)	18–91	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.63	
Pre-test odds = prevalence/(1 − prevalence)	1.70	
	Female (*n* = 123)	**Male (*n* = 123)**
Accuracy	0.81 (0.74–0.88)	0.71 (0.63–0.79)
Net Reclassification Improvement (NRI)	0.18	0.08
Sensitivity (Se)	0.72 (0.62–0.82)	0.58 (0.47–0.69)
Specificity (Sp)	0.98 (0.93–1.00)	0.91 (0.84–0.99)
Y	0.70	0.49
PPV (= post-test probability)	0.98 (0.95–1.00)	0.92 (0.84–0.99)
NPV	0.66 (0.55–0.78)	0.57 (0.46–0.69)
PSI	0.64	0.49
LR+	31.7 (4.55–221.5) = large	6.80 (2.61–17.7) = large
LR−	0.28 (0.04–1.99) = small	0.46 (0.18–1.20) = small
DOR	111.4 (16.0–777.2)	14.8 (5.68–38.5)
Post-test odds (= pre-test odds × LR+)	54.0	11.6
CUI+	0.71 (good)	0.53 (adequate)
CUI−	0.65 (good)	0.52 (adequate)

demonstrated by the examiner (Larner 2016b:32). Clapping more than three times, deemed abnormal, was first demonstrated in progressive supranuclear palsy (PSP) but not in FTLD by Dubois et al. (2005). The applause sign was subsequently reported in other parkinsonian disorders such as Parkinson's disease, DLB, corticobasal degeneration, and multiple system atrophy (e.g. Abdo et al., 2007; Wu et al. 2008; Somme et al. 2013) suggesting that it reflected basal ganglia pathology. An experimental study by Luzzi et al. (2011) looked at the applause sign in cortical dementias, AD and FTLD, as well as in PSP, and found it to be present in all three conditions, with highest sensitivity in PSP (0.80), followed by FTLD (0.60) and AD (0.31), but with poor specificities (respectively 0.59, 0.56, 0.32) and low positive predictive values (respectively 0.31, 0.35, 0.35). It was concluded that the applause sign was a motor perseveration indicative of frontal lobe dysfunction. Isella et al. (2013) reported similar findings, with the sign more likely to be observed in corticobasal syndrome and DLB (prevalence around 40%) than in AD and posterior cortical atrophy (prevalence around 10%). In AD the applause sign may be independent of disease severity (reported prevalence in severe, moderate and mild AD of 0.60, 0.37, and 0.38 respectively) and does not correlate with cognitive functions other than frontal lobe dysfunction (Luzzi et al. 2013).

Two prospective observational studies of day-to-day clinical practice have been undertaken to examine the utility of the applause sign in CFC (Abernethy Holland and Larner 2013b; Bonello and Larner 2016). Patients were asked by the examiner to clap three times, and the number of claps was recorded. The results were categorized and scored according to the method of Luzzi et al. (2011):

- 3 claps = score 3 (normal)
- 4 claps = score 2 (abnormal)
- 5–10 claps = score 1 (abnormal)
- >10 claps = score 0 (abnormal)

Hence, applause sign score ranged from 0 to 3, impaired to normal (i.e. number of claps inversely related to applause sign score).

Of 100 consecutive new outpatients (F:M = 37:63; age range 20–88 years, median 59.5 years) seen over a 5-month period (September 2012 to January 2013), 37 were demented by DSM-IV criteria and 20 had MCI by Petersen criteria. Nineteen had the applause sign, of whom 9 had a dementia syndrome and 6 had MCI. Of patients with a synucleinopathy (PD-MCI, PDD, DLB; $n = 9$), 5 (=55%) had the applause sign, which was also seen in patients with AD, alcoholic dementia, and in 4 subjective memory complainers. Applause sign had poor sensitivity for the diagnosis of dementia (0.24) or cognitive impairment (0.26), but better specificity for these diagnoses (0.84 and 0.91 respectively; Table 3.11). Thus, unlike the situation in experimental studies of selected patient groups, in this pragmatic study of consecutive new outpatients the applause sign was specific (i.e. its absence effectively ruled out dementia or MCI) but not sensitive for a dementia or MCI diagnosis. As in previous studies, the applause sign was not found to be specific to a particular disease (Abernethy Holland and Larner 2013b).

Over a subsequent, non-overlapping, 12-month study period (January 2014 to January 2015), a total of 275 new patients was assessed with the applause sign (Bonello and Larner 2016). Final diagnoses were dementia (52), MCI (71), and subjective memory complaint only (SMC; 152). The null hypothesis that the proportion of patients with cognitive impairment did not differ significantly between applause sign score groups was rejected ($\chi^2 = 27.4$, df = 3, $p < 0.001$).

The results of this study (Table 3.12; Fig. 3.3) were very similar to those observed in the previous study, suggesting that the test is reproducible. The results showed an evident floor effect (211/272 assessable = 77.6% of the whole cohort scored at floor) and hence the applause sign lacks sensitivity (64% of patients with dementia or MCI had a normal applause sign score). Nevertheless, the applause sign was specific ($\geq$0.85) for each of the differentials assessed, meaning that the false positive rate was low in this high prevalence setting. An abnormal applause sign score is therefore supportive of a diagnosis of dementia or cognitive impairment, and may be useful as an indicator of the need for the administration of other screening tests to further investigate cognitive function when pre-test probability for cognitive dysfunction is high.

Table 3.11 Demographic and diagnostic parameters for applause sign (adapted from Abernethy Holland and Larner 2013b)

	Applause sign	
N	100	
F:M (% female)	37:63 (37)	
Age range (years)	20–88 (median 59.5)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.57 (0.37 + 0.20)	
Pre-test odds = prevalence/(1 − prevalence)	1.33	
	Dementia vs no dementia	**Any cognitive impairment (dementia + MCI) vs no cognitive impairment**
Accuracy	0.62 (0.52–0.72)	0.54 (0.44–0.64)
Net Reclassification Improvement (NRI)	0.25	−0.03
Sensitivity (Se)	0.24 (0.10–0.38)	0.26 (0.15–0.38)
Specificity (Sp)	0.84 (0.75–0.93)	0.91 (0.82–0.99)
Y	0.08	0.17
PPV (= post-test probability)	0.47 (0.25–0.70)	0.79 (0.61–0.97)
NPV	0.65 (0.55–0.76)	0.48 (0.37–0.59)
PSI	0.13	0.27
LR+	1.53 (0.69–3.42) = unimportant	2.82 (1.01–7.92) = small
LR−	0.90 (0.40–2.01) = unimportant	0.81 (0.29–2.27) = unimportant
DOR	1.70 (0.76–3.81)	3.48 (1.24–9.75)
Post-test odds (= pre-test odds × LR+)	2.03	3.74
CUI+	0.12 (very poor)	0.21 (very poor)
CUI−	0.55 (adequate)	0.44 (poor)

3.2.4 *La Maladie Du Petit Papier*

La maladie du petit papier is a name sometimes applied when patients present to consultations with a written list of their symptoms, sometimes extensive, a phenomenon encountered by every neurologist from time to time. However, the diagnostic significance of such notes is uncertain (Grover 2015).

Over a 6-month period (April to September 2015), *la maladie du petit papier* was observed in 17/508 (3.35%) consecutive new patient referrals (16 handwritten examples, 1 ipad). It was seen more often in referrals to cognitive disorders clinics (8/169 = 4.73%) than to general neurology clinics (9/339 = 2.65%) but there was no significant frequency difference ($\chi^2 = 1.07$, $p > 0.1$; Randall and Larner 2016).

Table 3.12 Demographic and diagnostic parameters for applause sign (adapted from Bonello and Larner 2016)

	Applause sign	
N	275 (272 assessable)	
F:M (% female)	138:137 (50.2)	
Age range (years)	18–91 (median 61)	
Prevalence of cognitive impairment (dementia + MCI) (= pre-test probability)	0.45 (0.19 + 0.26)	
Pre-test odds = prevalence/ (1 − prevalence)	0.81	
	Dementia vs no dementia	**Any cognitive impairment (dementia + MCI) vs no cognitive impairment**
Accuracy	0.79 (0.74–0.84)	0.65 (0.59–0.71)
Net Reclassification Improvement (NRI)	0.60	0.20
Sensitivity (Se)	0.54 (0.40–0.67)	0.36 (0.28–0.45)
Specificity (Sp)	0.85 (0.70–0.99)	0.89 (0.84–0.94)
Y	0.39	0.25
PPV (= post-test probability)	0.46 (0.33–0.58)	0.72 (0.61–0.83)
NPV	0.89 (0.84–0.93)	0.63 (0.57–0.70)
PSI	0.35	0.35
LR+	3.59 (2.40–5.37) = small	3.18 (1.92–5.28) = small
LR−	0.54 (0.36–0.81) = unimportant	0.72 (0.43–1.20) = unimportant
DOR	6.61 (4.42–9.89)	4.41 (2.66–7.32)
Post-test odds (= pre-test odds × LR+)	2.91	2.58
CUI+	0.25 (very poor)	0.26 (very poor)
CUI−	0.75 (good)	0.59 (adequate)

Final diagnoses in the cognitive clinic were functional cognitive disorder (6) and MCI (2), the latter secondary to either alcohol misuse or mild traumatic brain injury; none had dementia. *La maladie du petit papier* had high specificity (0.94) but low sensitivity (0.03), and hence very low false positive rate (0.06), for a diagnosis of cognitive impairment (Randall and Larner 2018).

La maladie du petit papier is a low frequency sign in both cognitive disorders and general neurology clinics. In cognitive clinics it was associated with subjective memory complaint; like the "attended alone" sign, its presence may therefore support a diagnosis of cognitive normality. It may assist in a positive diagnosis of functional cognitive disorder (Randall and Larner 2018).

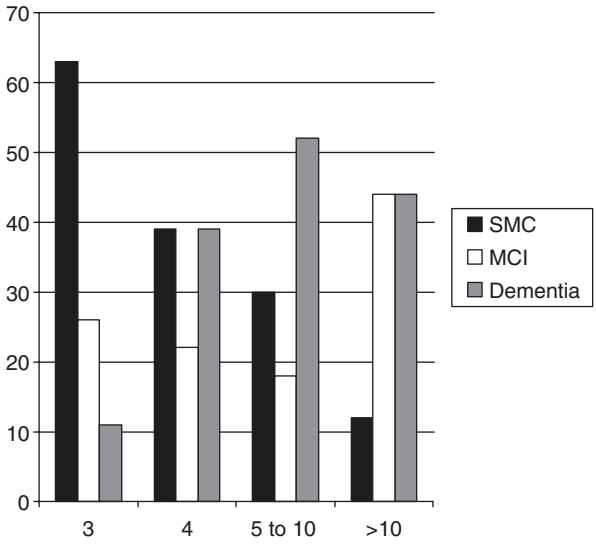

Fig. 3.3 Applause sign claps (abscissa) versus percentage of patients categorised by diagnosis (dementia/MCI/subjective memory complaint) (adapted from Bonello and Larner 2016) reprinted with permission

3.3 Summary and Recommendations

History taking is the cornerstone of any assessment for suspected dementia or cognitive impairment. It should encompass the history of the presenting complaint, past medical history, functional abilities, and family history. The importance of collateral history cannot be overemphasized. In certain circumstances, the history alone may be adequate for making a provisional diagnosis. If not diagnostic, it will guide the selection and contextualise the findings of subsequent neurological examination and investigations. Single item cognitive screening questions may have utility, but definitive evidence is awaited.

Although no signs are pathognomonic of dementia or cognitive impairment, nonetheless a number of neurological signs may be of use in assessment. In addition to signs elicited in the traditional, standard, textbook, canonical neurological examination, several other signs, which may be conveniently designated as "non-canonical" (Larner 2014a), may be of diagnostic value. In pragmatic diagnostic test accuracy studies the "attended alone" sign has been found to be very sensitive for absence of cognitive impairment; *la maladie du petit papier* may also support a diagnosis of cognitive normality. The head turning sign and the applause sign are both very specific (i.e. absent in the cognitively healthy). The head turning sign may be more useful in female patients. All these signs have the potential advantage of being easily observed and categorised, that is they all produce categorical data, which with the exception of the applause sign score, is dichotomous. The attended alone sign and the head turning sign have been noted to be of possible value in the differential diagnosis of functional cognitive disorders (Griem et al. 2016), and an independent study has claimed that "attended with" and head turning sign are simple, effective and sensitive (sic) methods of detecting cognitive impairment (Soysal et al. 2017; see also Williamson and Larner 2018).

References

Abdo WF, van Norden AG, de Laat KF, et al. Diagnostic accuracy of the clapping test in Parkinsonian disorders. J Neurol. 2007;254:1366–9.

Abernethy Holland AJ, Larner AJ. Effects of gender on two clinical signs (attended alone and head turning) of use in the diagnosis of cognitive complaints. J Neurol Sci. 2013a;333:e295–6.

Abernethy Holland AJ, Larner AJ. Applause sign: diagnostic utility in a cognitive function clinic. J Neurol Sci. 2013b;333:e292.

Aji BM, Larner AJ. Screening for dementia: is one simple question the answer? Clin Med. 2015;15:111–2.

Aji BM, Larner AJ. Screening for dementia: single yes/no question or Likert scale? Clin Med. 2017;17:93–4.

Allison RS. The senile brain. A clinical study. London: Edward Arnold; 1962.

Alzheimer's Society. Dementia UK update. 2nd ed. London: Alzheimer's Society; 2014.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR). 4th ed. Washington: American Psychiatric Association; 2000.

Bonello M, Larner AJ. Applause sign: screening utility for dementia and cognitive impairment. Postgrad Med. 2016;128:250–3.

Bouchard RW, Rossor MN. Typical clinical features. In: Gauthier S, editor. Clinical diagnosis and management of Alzheimer's disease. London: Martin Dunitz; 1996. p. 35–50.

Burns JM, Morris JC. Mild cognitive impairment and early Alzheimer's disease. Chichester: John Wiley; 2008.

Campion D, Dumanchin C, Hannequin D, et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am J Hum Genet. 1999;65:664–70.

Commissaris CJ, Ponds RW, Jolles J. Subjective forgetfulness in a normal Dutch population: possibilities for health education and other interventions. Patient Educ Couns. 1998;34:25–32.

Creavin S, Fish M, Gallacher J, Bayer A, Ben-Shlomo Y. Clinical history for diagnosis of dementia in men: Caerphilly prospective study. Br J Gen Pract. 2015;65:e489–99.

Cruts M, van Duijn CM, Backhovens H, et al. Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile Alzheimer disease. Hum Mol Genet. 1998;7:43–51.

Department of Health. Using the Commissioning for Quality and Innovation (CQUIN) payment framework. Guidance on the new national goals 2012–13. London: Department of Health, 2012.

Doran M, Larner AJ. Monogenic Mendelian causes of dementia: ten-year survey of a dementia clinic. Eur J Neurol. 2009;16(suppl3):291. (abstract P1731)

Doran M, du Plessis DG, Ghadiali EJ, Mann DMA, Pickering-Brown S, Larner AJ. Familial early-onset dementia with tau intron 10 +16 mutation with clinical features similar to those of Alzheimer disease. Arch Neurol. 2007;64:1535–9.

Dubois B, Slachevsky A, Pillon B, Beato R, Villalponda JM, Litvan I. "Applause sign" helps to discriminate PSP from FTD and PD. Neurology. 2005;64:2132–3.

Elsey C, Drew P, Jones D, et al. Towards diagnostic conversational profiles of patients presenting with dementia or functional memory disorders to memory clinics. Patient Educ Couns. 2015;98:1071–7.

Ferri R, Lanuzza B, Cosentino FI, et al. A single question for the rapid screening of restless legs syndrome in the neurological clinical practice. Eur J Neurol. 2007;14:1016–21.

Fisher CAH, Larner AJ. FAQs: memory loss. Practitioner. 2006;250(1683):14–6, 19, 21.

Fukui T, Yamazaki R, Kinno R. Can the "head-turning sign" be a clinical marker of Alzheimer's disease? Dement Geriatr Cogn Disord Extra. 2011;1:310–7.

Ghadiri-Sani M, Larner AJ. Head turning sign for diagnosis of dementia and mild cognitive impairment: a revalidation. J Neurol Neurosurg Psychiatry. 2013;84:e2.

Goldman JS, Farmer JM, Wood EM, et al. Comparison of family histories in FTLD subtypes and related tauopathies. Neurology. 2005;65:1817–9.

Griem J, Stone J, Carson A, Kopelman MD. Psychologic/functional forms of memory disorder. Handb Clin Neurol. 2016;139:407–17. [at 413]
Grover S. Don't dismiss the little notes that patients bring. BMJ. 2015;350:h20.
Hancock P, Larner AJ. The diagnosis of dementia: diagnostic accuracy of an instrument measuring activities of daily living in a clinic-based population. Dement Geriatr Cogn Disord. 2007;23:133–9.
Hancock P, Larner AJ. Clinical utility of Patient Health Questionnaire-9 (PHQ-9) in memory clinics. Int J Psychiatry Clin Pract. 2009a;13:188–91.
Hancock P, Larner AJ. Diagnostic utility of the Pittsburgh Sleep Quality Index in memory clinics. Int J Geriatr Psychiatry. 2009b;24:1237–41.
Hendry K, Hill E, Quinn TJ, Evans J, Stott DJ. Single screening questions for cognitive impairment in older people: a systematic review. Age Ageing. 2015;44:322–6.
Hodges JR. Cognitive assessment for clinicians. 2nd ed. Oxford: Oxford University Press; 2007.
Hunter KM. Doctors' stories. The narrative structure of medical knowledge. Princeton Univeristy Press: Princeton; 1991.
Isella V, Rucci F, Traficante D, Mapelli C, Ferri F, Appollonio IM. The applause sign in cortical and cortical-subcortical dementia. J Neurol. 2013;260:1099–103.
Janssen JC, Beck JA, Campbell TA, et al. Early onset familial Alzheimer's disease. Mutation frequency in 31 families. Neurology. 2003;60:235–9.
Kluger A, Gianutsos JG, Golomb J, et al. Patterns of motor impairment in normal aging, mild cognitive decline, and early Alzheimer's disease. J Gerontol B Psychol Sci Soc Sci. 1997;52:28–39.
Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001;56:1143–53.
Kurlan R, editor. Handbook of secondary dementias. New York: Taylor and Francis; 2006.
Larner AJ. "Who came with you?" a diagnostic observation in patients with memory problems? J Neurol Neurosurg Psychiatry. 2005a;76:1739.
Larner AJ. Two simple questions in the identification of dementia. J Neurol Neurosurg Psychiatry. 2005b;76:1317. (abstract 023)
Larner AJ. Neurological signs of aging. In: Pathy MSJ, Sinclair AJ, Morley JE, editors. Principles and practice of geriatric medicine. 4th ed. Chichester: Wiley; 2006. p. 743–50.
Larner A. Identify memory loss disorders. GP. 2007a;9(November):26–7.
Larner AJ. Carphologia or floccillation. Adv Clin Neurosci Rehabil. 2007b;7(4):25.
Larner AJ. Intrafamilial clinical phenotypic heterogeneity with *MAPT* gene splice site IVS10+16C>T mutation. J Neurol Sci. 2009a;287:253–6.
Larner AJ. "Attended alone" sign: validity and reliability for the exclusion of dementia. Age Ageing. 2009b;38:476–8.
Larner AJ. An approach to the cognitively-impaired adult. 2011a. http://learning.ebrain.net/course/view.php?id=37. Accessed 07 Nov 17.
Larner AJ. "Neurological literature": Sherlock Holmes and neurology. Adv Clin Neurosci Rehabil. 2011b;11(1):20. 22
Larner AJ. Intrafamilial clinical phenotypic heterogeneity with progranulin gene p.Glu498fs mutation. J Neurol Sci. 2012a;316:189–90.
Larner AJ. Neurological signs of ageing. In: Sinclair A, Morley JE, Vellas B, editors. Pathy's principles and practice of geriatric medicine. 5th ed. Chichester: Wiley; 2012b. p. 609–16.
Larner AJ. Head turning sign: pragmatic utility in clinical diagnosis of cognitive impairment. J Neurol Neurosurg Psychiatry. 2012c;83:852–3.
Larner AJ. Subjective memory complaints: is family history of dementia a risk factor? J Neurol Sci. 2013a;333:e295.
Larner AJ. Neuropsychological neurology: the neurocognitive impairments of neurological disorders. 2nd ed. Cambridge: Cambridge University Press; 2013b.
Larner AJ. Neurological signs of possible diagnostic value in the cognitive disorders clinic. Pract Neurol. 2014;14:332–5.

Larner AJ. Screening utility of the "attended alone" sign for subjective memory impairment. Alzheimer Dis Assoc Disord. 2014b;28:364–5.
Larner AJ. Three simple questions have high utility for diagnosing dementia in the primary care setting. Evid Based Ment Health. 2016a;19:e13.
Larner AJ. A dictionary of neurological signs. 4th ed. London: Springer; 2016b.
Larner AJ. Metamemory: a construct with diagnostic utility in a cognitive disorders clinic? Int J Geriatr Psychiatry. 2018;33:553–4.
Larner AJ, Coles AJ, Scolding NJ, Barker RA. A-Z of neurological practice. A guide to clinical neurology. 2nd ed. London: Springer; 2011.
Lipton AM, Marshall CD. The common sense guide to dementia for clinicians and caregivers. New York: Springer; 2013.
Luzzi S, Fabi K, Pesallaccia M, Silvestrini M, Provinciali L. Applause sign: is it really specific for Parkinsonian disorders? Evidence from cortical dementias. J Neurol Neurosurg Psychiatry. 2011;82:830–3.
Luzzi S, Fabi K, Pesallaccia M, Silvestrini M, Provinciali L. Applause sign in Alzheimer's disease: relationships to cognitive profile and severity of illness. J Neurol. 2013;260:172–5.
McPherson S, La Rue A, Fitz A, Matsuyama S, Jarvik LF. Self-reports of memory problems in relatives of patients with probable Alzheimer's disease. Int Psychogeriatr. 1995;7:367–76.
Nordenstrom J. Evidence-based medicine in Sherlock Holmes' footsteps. Oxford: Blackwell; 2007.
O'Caoimh R, Timmons S, Molloy DW. Screening for mild cognitive impairment: comparison of "MCI specific" screening instruments. J Alzheimers Dis. 2016;51:619–29.
Paradise MB, Glozier NS, Naismith SL, Davenport TA, Hickie IB. Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: a cross-sectional study. BMC Psychiatry. 2011;11:108.
Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56:303–8.
Randall A, Larner AJ. *La maladie du petit papier*: quantitative survey, clinical significance. J Neurol Neurosurg Psychiatry. 2016;87:e1.
Randall A, Larner AJ. *La maladie du petit papier*: a sign of functional cognitive disorder? Int J Geriatr Psychiatry. 2018;33:800.
Rohrer JD, Guerriero R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009;73:1451–6.
Somme J, Gomez-Esteban JC, Tijero B, Berganzo K, Lezcano E, Zarranz JJ. The applause sign and neuropsychological profile in progressive supranuclear palsy and Parkinson's disease. Clin Neurol Neurosurg. 2013;115:1230–3.
Soysal P, Usarel C, Ispirli G, Isik AT. Attended with and head-turning sign can be clinical markers of cognitive impairment in older adults. Int Psychogeriatr. 2017;29:1763–9.
Tabuas-Pereira M, Duraes J, Araujo R, et al. The head turning sign in Alzheimer's disease: its relationship with cognitive impairment and CSF biomarkers. Eur J Neurol. 2016;23(Suppl1):67. (O2110)
Tsai DH, Green RC, Benke KS, Silliman RA, Farrer LA. Predictors of subjective memory complaint in cognitively normal relatives of patients with Alzheimer's disease. J Neuropsychiatry Clin Neurosci. 2006;18:384–8.
Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia. Eur J Neurol. 2007;14:e1–26.
Williamson JC, Larner AJ. Attended with and head-turning sign can be clinical markers of cognitive impairment in older adults. Int Psychogeriatr. 2018;30:(in press).
Wu LJ, Sitburana O, Davidson A, Jankovic J. Applause sign in Parkinsonian disorders and Huntington's disease. Mov Disord. 2008;23:2307–11.