Diagnosis (1): Cognitive Syndromes, Comorbidities, No Diagnosis, and Wrong Diagnosis

8

Contents

Abstract

This chapter examines the various cognitive syndromes (e.g. amnesia, aphasia, agnosia) which may be defined by clinical assessment and investigation, as a prelude to establishing aetiological diagnosis. It also examines various comorbidities which may be encountered in dementia disorders, including behavioural and neuropsychiatric features, delirium, epilepsy and sleep-related disorders.

Keywords

Dementia · Diagnosis · Cognitive syndromes · Comorbidities

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8.1 Cognitive Syndromes

The diagnosis of specific disorders causing cognitive impairment or dementia (see Chap. 9) may be facilitated by the definition of cognitive syndromes. In other words, diagnosis of a clinical syndrome may inform the aetiological diagnosis, although the mapping is far from 1:1 because of the heterogeneity of pathological entities, with clinical phenotype depending on the exact topographic distribution of disease (Larner 2013a:1–22).

Cognitive neuropsychology often depends on unusual cases with highly circumscribed deficits for the development of ideas about brain structure/behaviour functional correlations (Shallice 1988). The messy contingencies of clinical practice seldom correspond to these archetypal cases, but nonetheless specific cognitive syndromes can often be delineated, which may facilitate differential diagnosis. The classical deficits, corresponding to the recognised domains of cognitive function examined by cognitive screening instruments (see Chap. 4), are amnesia, aphasia, agnosia, apraxia, and a dysexecutive syndrome. In turn, specific clinical diagnoses (see Chap. 9) may be arrived at based on these deficits and informed by investigation findings (see Chap. 7).

8.1.1 Memory: Amnesia

Amnesia is an acquired syndrome of impaired encoding of information resulting in impaired recall. Amnesic syndromes may be classified according to variables such as onset (acute, subacute, chronic), duration (transient, persistent), pattern (anterograde, retrograde), and course (fixed, progressive) (Fisher 2002; Papanicolaou 2006; Larner 2016:20–1). Many causes of amnesia are recognised (Box 8.1), some of which have been encountered in CFC.

Box 8.1: Causes of amnesia

Chronic/persistent:

Alzheimer's disease, amnestic mild cognitive impairment (aMCI)
Other neurodegenerative disorders: FTLD, DLB
Wernicke-Korsakoff syndrome, alcohol-related dementia
Limbic encephalitis (paraneoplastic or non-paraneoplastic)
Sequela of herpes simplex encephalitis
Hypoxic brain injury
Bilateral paramedian thalamic infarction/ posterior cerebral artery occlusion ("strategic infarct dementia")
Structural lesions: third ventricle tumour, colloid cyst; fornix damage; temporal lobectomy (bilateral; or unilateral with previous contralateral injury, usually birth asphyxia)

Inflammatory disorders, e.g. multiple sclerosis
Focal retrograde amnesia (rare)

Acute/transient:

Traumatic brain (closed head) injury
Adverse drug effect
Transient global amnesia (TGA)
Transient epileptic amnesia (TEA)
Migraine
Hypoglycaemia

8.1.1.1 Chronic/Persistent Amnesias

A chronic/persistent amnesic syndrome is the most common presentation of Alzheimer's disease (AD) often with evidence of mild dysfunction in other cognitive domains (e.g. perception, language, executive function), but sometimes occurring in isolation (Larner 2006a, 2008a), as enshrined in diagnostic criteria (Dubois et al. 2014; Boxes 7.1 and 7.2). A temporal gradient is often evident in the amnesia of AD, with more distant events being more easily remembered than recent happenings, often characterised by the patient's relatives as a defect in "short term memory" with preserved "long term memory". Verbal repetition ("repetitive questioning") regarding day to day matters, reflecting the anterograde amnesia, is one of the most common and, for relatives, most troubling symptoms of AD (Rockwood et al. 2007; Cook et al. 2009).

Mild cognitive impairment (MCI) was initially proposed as a term to describe cognitive impairment which did not amount to dementia, and in which activities of daily living were essentially preserved (Petersen 2003). For some this is a heterogeneous category (Sects. 2.2 and 9.1), whereas others, defining MCI by a score of 0.5 on the Clinical Dementia Rating scale, envisage MCI to be early-stage AD (Morris et al. 2001). However defined, MCI may be exclusively amnestic (single-domain amnestic MCI; aMCI) or show deficits in other domains (multi-domain amnestic MCI; Winblad et al. 2004).

All the multidomain cognitive screening instruments used in patient assessment (see Sect. 4.1) have memory testing paradigms, usually of the registration/recall type, sometimes with an added recognition paradigm, and specific (single domain) cognitive tests for memory are also available (e.g. Buschke et al. 1999). The hippocampal origin of the AD/amnestic MCI memory deficit may be examined by controlling for the encoding phase (e.g. the "5 words" test of Dubois et al. 2002). This may also help in the differentiation from physiological age-related memory complaints, the growing difficulty (lessening efficiency) in encoding new information which afflicts us all as we age.

Memory complaints may be evident in neurodegenerative disorders other than AD/aMCI, but are often accompanied by other more prominent symptoms which assist in differential diagnosis. Although a complaint of memory difficulties is not

infrequent from relatives of patients with frontotemporal lobar degeneration (FTLD) syndromes, this is more often related to behavioural and linguistic problems rather than amnesia per se, although amnesic presentations of pathologically confirmed FTLD have been described on occasion (e.g. Graham et al. 2005; Papageorgiou et al. 2016), and may be a particular feature in FTLD of late onset (Baborie et al. 2012, 2013). Diagnostic errors in which clinical overlap causes confusion between FTLD with AD may therefore occur (Davies and Larner 2009a), and some genetically-determined FTLD cases (Sect. 7.3.2) undoubtedly do present with an AD-like phenotype (Doran et al. 2007; Larner 2008b, 2009).

Dementia with Lewy bodies (DLB) may also be mistaken for AD, but typically there is more attentional disturbance and visuospatial dysfunction with relative preservation of memory (Sect. 9.3).

Alcohol-related memory problems, both Wernicke-Korsakoff syndrome (described before Korsakoff by Lawson in 1878; Larner and Gardner-Thorpe 2012) and alcohol-related dementia, have been seen only rarely in CFC, presumably because local services for alcohol problems absorb these patients, even though it is more prevalent amongst patients with early onset dementia. This situation may change in the future if binge drinking habits in youth translate into an epidemic of alcohol-related dementia in the future (Sachdeva et al. 2016; Cheng et al. 2017).

Autoimmune (also sometimes known as limbic) encephalitis is a syndrome of subacute or chronic amnesia, often accompanied by anxiety and depression, epileptic seizures, hypersomnia, and hallucinations, with active CSF (pleocytosis, raised protein). The syndrome may be viral, paraneoplastic, or non-paraneoplastic in origin (Schott 2006). Non-paraneoplastic limbic encephalitis may be associated with serum (and CSF) antibodies directed against neuronal antigens located either on the cell surface or intracellularly (Graus et al. 2016; Pollak et al. 2017).

First to be described were serum antibodies thought to be directed against voltage-gated potassium channels (VGKC-NPLE; Thieben et al. 2004; Vincent et al. 2004), but the underlying antigens in the VGKC complex were latterly shown to be leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) (Binks et al. 2018). A number of VGKC-NPLE patients have been reported from CFC (S Wong et al. 2008, 2010; Ahmad and Doran 2009; Ahmad et al. 2010). In a consecutive series, immunosuppressive therapy with plasma exchange, intravenous immunoglobulin, and intravenous followed by oral steroids was associated with prompt remission of epileptic seizures and correction of hyponatraemia (1 week), improvement in cognitive function as assessed with the Addenbrooke's Cognitive Examination and its revision (ACE and ACE-R; see Sects. 4.1.5.1 and 4.1.5.3) (3 months), and improvement in neuroradiological appearances (9 months) (S Wong et al. 2008, 2010). Some patients with VGKC-NPLE have been reported to develop a profound retrograde amnesia as a sequela of the acute disease (Chan et al. 2007), prompting speculation that some cases of "focal retrograde amnesia" (see below; Kapur 1993) may in fact be recovered episodes of VGKC-NPLE (Lozsadi et al. 2008). Hence, though rare, VGKC-NPLE must be considered in cases of subacute amnesia because of its potential reversibility.

An autoimmune encephalitis associated with antibodies directed against the NMDA receptor (anti-NMDAR encephalitis) was first described in young women with ovarian teratoma (Vitaliani et al. 2005), and subsequently in other patient groups. CFC experience has included a patient on long-term immunosuppression for a renal transplant who was unresponsive to standard treatment regimes (Titulaer et al. 2013) and who was eventually discovered to have an underlying lymphoma (Randall et al. 2018).

Autoimmune encephalitis associated with antibodies against glutamic acid decarboxylase (GAD) has also been seen in CFC (Bonello et al. 2014). Unlike VGKC-NPLE, this is a chronic non-remitting disorder, with antibody titres remaining high after immunosuppression, and patients often continue to have seizures despite intense anti-epileptic drug therapy (Malter et al. 2010). Sequential cognitive assessment of one patient with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al. 1998; see Sect. 4.1.11) showed no evidence for cognitive improvement over 30 months of follow-up (Bonello et al. 2014).

Structural damage to anatomical areas involved in memory function (Papez circuit) is an occasional cause of amnesia. Anterograde amnesia associated with damage to the fornix, a fibre bundle which connects the hippocampus to the mamillary bodies within the limbic system, has been described (Sweet et al. 1959), particularly following removal of third ventricle colloid cysts (Aggleton et al. 2000; Case Study 7.2). A patient with persistent anterograde amnesia with some additional executive dysfunction following removal of an isolated subependymal giant cell astrocytoma which invaded the left fornix has been seen in CFC (Ibrahim et al. 2009). Amnesia did show some improvement over a follow up period of 12 months, suggesting that tissue swelling secondary to traumatic surgical tissue dissection may have contributed to the clinical presentation and course.

Although cognitive impairment has been increasingly recognised as a clinical feature of multiple sclerosis (MS) in recent years (e.g. LaRocca 2011; Jongen et al. 2012), this is usually of subcortical type with impaired executive function and slowed processing speed as a consequence of progressive acquisition of white matter damage, whilst cortical cognitive syndromes such as amnesia are relatively rare: hence a typical "white matter dementia" (Filley 2012). An attempt to characterise isolated cognitive relapses has been made (Pardini et al. 2014). Prominent amnesia has been described in a cortical variant of MS, with or without aphasia, alexia and agraphia (Zarei et al. 2003). Acute presentation of MS with amnesia appears to be rare (Vighetto et al. 1991), particularly as a proven consequence of demyelination (Shanmugarajah et al. 2017). Other potential causes for this syndrome occurring in MS should always be considered. One patient with an acute onset of demyelinating disease, probably relapsing-remitting MS, and with the clinical phenotype of amnesia has been encountered in CFC (Larner and Young 2009). Cognitive impairment as a prominent early symptom of MS has also been encountered (Young et al. 2008). The rarity of amnesia in MS may perhaps explain the relatively lack of efficacy of cholinesterase inhibitors for cognitive impairment in MS (Larner 2010b:1701). Cognitive impairment may on occasion be encountered in other CNS inflammatory disorders, such as relapsing polychondritis (Ellis et al. 2017).

Focal retrograde amnesia is a rare syndrome in comparison with anterograde amnesia, in which recent events can be more easily recalled than distant ones, a reversal of the usual temporal gradient of amnesia (Kapur 1993). In one case of focal retrograde amnesia seen in CFC, the Autobiographical Memory Interview (Kopelman et al. 1989) showed autobiographical amnesia for childhood, teenage and adult life but the patient was able to give a reasonable account of current news events and auditory delayed recall was preserved. MR brain imaging showed some left temporal lobe atrophy (Larner et al. 2004a). The aetiology of focal retrograde amnesia is uncertain; in this case it may possibly have been related to prior alcohol misuse. Functional amnesias are typically retrograde in nature (Markowitsch and Staniloiu 2013).

8.1.1.2 Acute/Transient Amnesias

Probably the most commonly encountered acute/transient amnesia in CFC is transient global amnesia (TGA), although even this is rare (Fig. 8.1). TGA consists of an abrupt attack of impaired anterograde memory, often manifest as repeated and circular questioning, with a variably severe retrograde amnesia, but with intact working memory, semantic memory, and other cognitive domains (language, perception) and without clouding of consciousness or focal neurological signs (Bender 1956; Guyotat and Courjon 1956; Fisher and Adams 1958, 1964; Hodges 1991; Quinette et al. 2006; Bartsch and Deuschl 2010). Episodes are of brief duration (<24 h by definition, and usually 4–6 h), with no recollection of the amnesic period following resolution. Clinical diagnostic criteria have been formulated (Hodges and Warlow 1990). Recognised precipitating factors for TGA include emotional upset or physical exercise, including sexual activity (Larner 2008c). Predisposing factors include age (typically affects those in their 50s or 60s; Fig. 8.1), migraine (a population-based cohort study found that females with migraine aged 40–60 had a

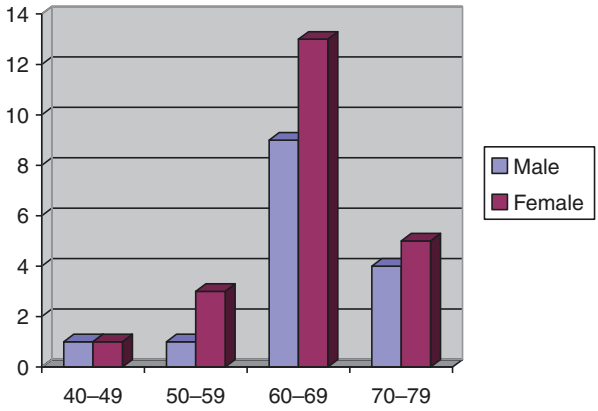

Fig. 8.1 Age and gender distribution of consecutive cases fulfilling diagnostic criteria for TGA (n = 37) seen in author's clinic over 16-year period (2002–2017) (adapted from Larner 2017b:98) reprinted with permission

greater risk of developing TGA: Lin et al. 2014) and possibly those with a familial history (Larner 2017a). Aetiology is uncertain but temporary deactivation or functional ablation of memory-related neuroanatomical substrates seems likely. The CFC experience of TGA has been described in detail elsewhere (Larner 2017b).

Transient epileptic amnesia (TEA) is a distinctive epilepsy syndrome, characterised by brief amnesic episodes, typically occurring on waking, and associated with accelerated long-term forgetting and autobiographical amnesia (Zeman et al. 2012). TEA enters the differential diagnosis of TGA (Ung and Larner 2014), but differs in a number of respects, including the timing and frequency of attacks. Only very occasional cases of TEA have been encountered in CFC (Larner 2017b:35–7). In one possible case, episodes initially diagnosed as parasomnias but typical of TEA had approximately the same age at onset as a more pervasive memory problem which evolved to AD (Krishnan and Larner 2009). Epileptic seizures in AD may take a number of forms, and may occur at onset of cognitive decline (although they become more frequent with disease duration; see Sect. 8.2.3), so this concurrence might possibly reflect shared pathogenic processes involving synaptic network pathology in the medial temporal lobes (Larner 2010a, 2011a). TEA has also been suggested as a cause of wandering behaviours observed in AD patients (Rabinowicz et al. 2000).

Other causes of acute/transient amnesia which have been seen on occasion in CFC, and which may need to be considered in the differential diagnosis of TGA and TEA (Larner 2017b:27–55), include profound hypoglycaemia (Cox and Larner 2016; Larner et al. 2003a) and migraine (Larner 2011b).

Amongst the many transient phenomena that may be encountered in the context of migraine attacks, amnesia is sometimes prominent. A patient who drove apparently safely for several miles, missing her turning, without awareness of her journey ("unconscious driving phenomenon") developed a headache typical of migraine, which she had suffered from since teenage years, at the end of her journey (Larner 2011b). A syndrome of acute confusional migraine is recognised in children (Pacheva and Ivanov 2013) which has some features akin to TGA (Sheth et al. 1995; Schipper et al. 2012); both may be examples of "cognitive migraine" (Larner 2013b).

Profound hypoglycaemia is a recognised cause of acute amnesia (Fisher 2002), but relatively few cases with longitudinal neuropsychological data have been reported. A patient seen in CFC (Case Study 8.1) illustrated a focal pattern of deficit, selective for anterograde memory and learning, probably reflecting hippocampal vulnerability to the effects of neuroglycopaenia, which gradually, though incompletely, reversed over a period of months (Larner et al. 2003a). However, at long-term follow up the patient had developed a dementia, with particular decline during a period of repeated profound hypoglycaemic episodes (Cox and Larner 2016).

Case Study 8.1: Acute amnesia due to hypoglycaemia, evolving to dementia
A 61-year old man with long-standing (ca. 50 years) insulin-dependent diabetes mellitus type 1 which was being treated with continuous subcutaneous insulin infusion was found collapsed with blood glucose of 1.0 mmol/L. After correction of hypoglycaemia, he noted difficulty remembering names of friends and content of recent conversations, necessitating use of external memory aids. Neuropsychological assessment showed normal attention, concentration, language and working memory function, but impaired verbal and visual immediate and delayed recall (WMS III, Camden Memory Tests). MR brain imaging was normal. There was gradual improvement in his memory function: at 4 months he continued to have impairments in short term verbal memory and learning but there was improvement in visual memory. Scores on MMSE at 1, 4 and 10 months were 27, 28, and 30/30, and on Addenbrooke's Cognitive Examination were 82, 93, and 93/100 respectively.

He was then lost to follow up, and not seen again until aged 75, by which time he was resident in a nursing home with a diagnosis of dementia (MoCA 12/30, MACE 11/30), presumed to be of vascular origin. Review of previous records showed repeated admissions for hypoglycaemia prior to nursing home placement, with MMSE 25/30 and 17/30 at age 65 and 67 (Fig. 8.2). Whether this decline was a consequence of repeated hypoglycaemic episodes was not clear: MR brain imaging at age 75 showed global brain atrophy but only minor ischaemic changes.

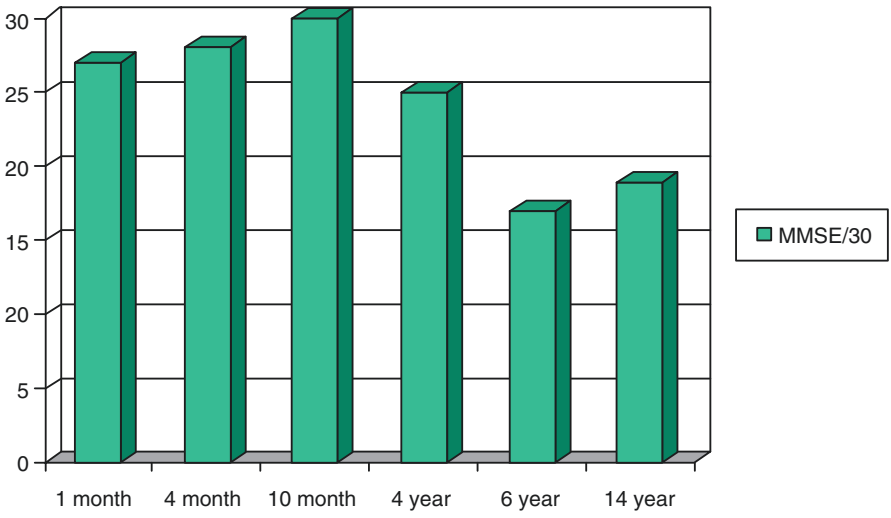

Fig. 8.2 Evolution of cognitive performance following recurrent episodes of profound hypoglycaemia: sequential MMSE scores plotted against period of follow up, to 14 years (adapted from Larner et al. 2003a; Cox and Larner 2016) reprinted with permission

8.1.2 Language: Aphasia, Alexia

Aphasia is an acquired syndrome of impaired language function affecting the spoken word. The symbolic code of language may also be impaired in the context of its written form, either in reading (alexia) or writing (agraphia), difficulties in which (e.g. fluency, comprehension) generally mirror those in the spoken form. Various causes of aphasia are recognised (Benson and Ardila 1996; Rohrer et al. 2008; Larner 2016:30–1). The possibility that linguistic structure may either determine or influence cognition is at the core of the so-called Sapir-Whorf hypothesis (linguistic relativity).

8.1.2.1 Aphasia

Various disorders may present with a primary complaint of aphasia in a cognitive disorders clinic.

Linguistic impairment is one of the commonly recognised presentations of FTLD (cf. behavioural presentation; Sect. 8.1.5). The aphasic phenotype may be either non-fluent or fluent, the syndromes of progressive non-fluent aphasia and semantic dementia, respectively (Neary et al. 1998; McKhann et al. 2001), now sometimes denoted as the agrammatic and semantic variants of primary progressive aphasia (Gorno-Tempini et al. 2011; see Sect. 9.2). Speech apraxia, the impaired articulation of speech sounds especially with increasing articulatory complexity, may be seen as a component of progressive non-fluent aphasia (Grossman 2012).

Aphasic presentations of Alzheimer's disease are well-recognised but rare (Caselli and Tariot 2010:91–9). Clinically these may sometimes have the phenotype of progressive non-fluent aphasia (PNFA) or, much less commonly, semantic dementia (Davies et al. 2005; Alladi et al. 2007). Gorno-Tempini et al. (2004) delineated a third type of progressive aphasia, logopenic progressive aphasia (LPA), characterized by slow speech with long pauses, impaired syntactic comprehension and anomia, in which AD pathology is the most common neuropathological substrate (Gorno-Tempini et al. 2008). LPA has been incorporated into modern clinicobiological AD diagnostic criteria (Dubois et al. 2014).

Aphasic presentations accounted for around 4.5% of new AD cases seen in CFC over a 6-year period (2000–2005) (Larner 2006a). Great care must be taken with this diagnosis, however, because of the possible confusion with linguistic presentations of FTLD; instances requiring diagnostic revision following the passage of time have been encountered (see Sect. 9.1; Davies and Larner 2009a).

Overlap between the linguistic features of PNFA and clinically diagnosed corticobasal degeneration (CBD) has been noted (Graham et al. 2003). However, the frequent occurrence of CBD phenocopies, the corticobasal syndrome (CBS; Doran et al. 2003), may possibly jeopardise this conclusion (Larner and Doran 2004).

Occasional unusual cases with linguistic presentations have been seen in CFC (Larner 2005a, 2006b, 2012a; Larner and Lecky 2007; Larner et al. 2004b). Acute aphasia is most often due to stroke in the middle cerebral artery territory of the dominant hemisphere. Occasional atypical, acute aphasic, presentations of

neurodegenerative disease, both FTLD and AD, have been seen in CFC following cardiac surgery, and initially mistaken for cerebrovascular disease (Larner 2005a). Presumably, an acute cerebral insult may render manifest a previously slowly progressing subclinical neurodegenerative disorder. Cerebrovascular disease is recognised to lower the threshold for the clinical manifestation of underlying AD pathology (Snowdon et al. 1997).

Aphasia is a rare presentation in multiple sclerosis (Lacour et al. 2004), in contrast to dysarthria which is common. The possibility of a second pathology should be considered when a patient with established MS develops acute aphasia, for example cases of partial seizures or non-convulsive status epilepticus causing aphasia ("status aphasicus") have been presented (e.g. Trinka et al. 2002). In a case of acute aphasia in a patient with long-standing MS seen in CFC, CT brain imaging showed a heterogeneous, partially calcified, lesion in the left lateral temporal lobe with an area of high density anterolaterally, suggesting an acute haemorrhage, confirmed on MR imaging, which also showed typical MS periventricular white matter changes. A second lesion returning heterogeneous signal was also observed in the left occipital lobe. These lesions were thought most likely to be cavernomas, hence entirely incidental to the MS (Larner and Lecky 2007).

8.1.2.2 Alexia

Various causes of alexia are recognised (Leff and Starrfelt 2014; Larner 2016:13–5). The classical disconnection syndrome of alexia without agraphia, also known as pure alexia or pure word blindness, is a form of peripheral alexia in which patients lose the ability to recognise written words quickly and easily. Although patients can write at normal speed, they are unable to read what they have just written. Some authorities classify this syndrome as a category-specific agnosia. Alexia without agraphia often coexists with a right homonymous hemianopia, a particular problem in a patient who passed through CFC (reported by Imtiaz et al. 2001) who sustained at least one accident because of his visual field defect.

Reading may be achieved through the tactile, as well as the visual, modality, as in Braille reading. The nineteenth century American physician Oliver Wendell Holmes (1809–1894) in his *Prelude to a volume printed in raised letters for the blind* (1885) noted Braille readers to be:

> … - you whose finger-tips
> a meaning in these ridgy leaves can find
> Where ours go stumbling, senseless, helpless, blind.

Alexia for Braille reading has rarely been reported (e.g. Birchmeier 1985; Signoret et al. 1987 [translated by Fisher and Larner 2008]; Hamilton et al. 2000), with an additional patient encountered in CFC (Larner 2007a; Case Study 8.2).

Case Study 8.2: Acute Braille alexia
A septuagenarian, blind from birth, a proficient Braille reader with her left index finger, found that she could not read following apparently uncomplicated coronary artery bypass graft surgery. On examination, her spoken language was fluent with no evidence of motor or sensory aphasia. There was no left-sided sensory neglect or extinction, and no finger agnosia. Testing stereognosis in the left hand, she was able to identify some objects (pen, ring, paper clip, watch) but was slow to identify a key, could not decide on the denomination of a coin (50 pence piece, heptagonal; or 10 pence piece, circular) and thought a £1 coin was a badge, although she identified this immediately with the right hand. Two-point discrimination was 3 mm on the pulp of the right index finger (minimum spacing possible between tines) but 5 mm on the pulp of the left index finger. MR imaging of the brain showed a few punctate high signal lesions on T_2-weighted and FLAIR sequences in subcortical white matter, thought to be ischaemic in origin, including one subjacent to the right motor cortex in the region of the internal watershed between anterior and middle cerebral artery territories.

Braille alexia may be viewed as the tactile homologue of pure alexia (alexia without agraphia), and may result from disruption of different, possibly overlapping, psychoperceptual mechanisms, some analogous to those postulated in pure alexia. It may reflect problems integrating tactile information over the temporal or spatial domains, hence an associative form of agnosia (Signoret et al. 1987; Fisher and Larner 2008). A frontal-parietal network may contribute to the integration of perception with action over time, and right hemisphere lesions may be associated with impaired integration of spatial information from multiple stimuli. Tactile agnosia (and astereognosis) may arise from lesions of the parietal area of the cerebral cortex (Luria 1980:168). Alternatively, Braille alexia may reflect a perceptual impairment, hence an apperceptive form of agnosia (Larner 2007a). Since Braille characters are close to the limits of normal perceptual resolution, impaired light touch perception following damage to primary sensorimotor cortex or its connections may result in degraded tactile identification and slowed Braille reading speed.

8.1.3 Perception: Agnosia

Agnosia is a syndrome, most usually acquired, of impaired higher sensory function leading to a failure of recognition, occurring most often in the visual modality but also in other sensory domains (Farah 1995; Ghadiali 2004; Larner 2016:8–9). As mentioned, Braille alexia may in fact be a form of tactile agnosia (see Sect. 8.1.2; Larner 2007a).

Agnosic presentations of Alzheimer's disease are well-recognised, sometimes described as posterior cortical atrophy (PCA; although this syndrome may on occasion have pathological substrates other than AD) or the visual variant of AD (Caselli and Tariot 2010:84–91; Dubois et al. 2014; Crutch et al. 2017). These accounted for around 3% of new AD cases seen in CFC over a 6-year period (2000–2005) (Larner 2006a). Although deficits in other cognitive domains, particularly memory, may be evident from the history or cognitive testing, sometimes the agnosic deficit is isolated, constituting an example of single domain non-amnestic MCI (Winblad et al. 2004); this has been encountered on occasion in CFC (Larner 2004a). Typically these individuals have already been seen by optometrists and/or ophthalmologists prior to referral with no cause for their visual complaint identified. Four patients with PCA were unable to differentiate between a normal and a backward clock (see Sect. 4.1.3.1; Larner 2007b).

Although FTLDs are classically associated with behavioural and linguistic problems with preserved visuoperceptual function, semantic dementia (SD; semantic variant of primary progressive aphasia) is recognised to encompass an associative agnosia, with impairment of object identification on both visual and tactile presentation, presumably a part of the semantic deficit in these patients. SD patients with predominantly non-dominant hemisphere degeneration may present with prosopagnosia (Thompson et al. 2003), a circumscribed form of visual agnosia characterised by an inability to recognise previously known human faces or equivalent stimuli (Larner 2016:261–2).

Agnosia for faces accompanying lesions of the right hemisphere was originally described by Charcot (Luria 1980:378). The term prosopagnosia was coined by Bodamer in 1947, although the phenomenon had been described toward the end of the nineteenth century by Quaglino in 1867 (Della Sala and Young 2003) and Hughlings Jackson in 1872 and 1876, as well as by Charcot in 1883. Brief accounts thought to be suggestive of prosopagnosia have been identified in writings from classical antiquity by Thucydides and Seneca (De Haan 1999). A developmental form of prosopagnosia is also described, which may cause significant social difficulties, as demonstrated by a patient seen in CFC (Larner et al. 2003b; Case Study 8.3).

Case Study 8.3: Developmental prosopagnosia

Assessed in his thirties, this man gave a history of lifelong difficulty identifying people by their faces, despite otherwise normal physical and cognitive development. Examples included failure to identify the faces of fellow pupils when a schoolboy, to identify familiar customers in the work environment, to recognize his wife in the street unless she was wearing familiar clothes, and to identify his children when collecting them from school. However, in his work as an optician, he was easily able to recognize different makes of spectacle frame. His neurological examination was unremarkable, with normal visual acuity, visual fields (confirmed by automated perimetry) and

fundoscopy, and there was no achromatopsia. His reading was fluent, and there were no obvious perceptual difficulties.

Neuropsychological assessment included: the WAIS-R (above average intelligence: Verbal IQ 128; Performance IQ 113, but impaired on Object Assembly subtest); Visual Object and Space Perception (VOSP) battery, on which all subtests (incomplete letters, silhouettes, object decision, progressive silhouettes) were above relevant 5% cut-off scores; the Birmingham Object Recognition Battery (BORB), on which all subtests were above relevant 5% cut-off scores; Warrington Recognition Memory Test, on which words were normal but faces impaired; the Graded Naming Test and the Boston Naming Test on both of which scores were in the normal range. On the Benton Facial Recognition Test (matching faces according to identity) he scored 40/54 (borderline impaired; excessively slow performance). On the Young and Flude Face Processing Tasks he was impaired on the identity matching task (39/48; >3 SD below control mean) and on gender identification (39/48; 2 SD below control mean), but normal on identification of emotional expression (47/48) and eye gaze direction (16/18). He had no subjective awareness that animals might have faces, a possible example of zooagnosia (Larner 2016:347).

Akinetopsia is the name given to a specific inability to see objects in motion whilst perception of other visual attributes remains intact, which may reflect lesions of area V5 of visual cortex (Zeki 1991; Larner 2016:13). Rarely described, a possible example of akinetopsia has been seen in CFC (Larner 2005b; Case Study 8.4). Neuropsychological deficits following carbon monoxide poisoning may be very focal, as for example in a renowned case of visual form agnosia (Goodale and Milner 2004).

Auditory agnosia is one of the clinical features of the semantic variant of primary progressive aphasia, manifesting with impaired word comprehension. As for visual agnosia, this auditory agnosia may be interpreted as a primary sensory abnormality, interlocutors suspecting a "hearing problem" when patients ask for auditory material to be repeated, sometimes prompting investigation with audiometry (McCormick and Larner 2018).

Macdonald Critchely described personification of paralysed limbs in hemiplegics following an initial anosognosia (unawareness of deficit), reporting patients who called their hemiplegic limbs "George", "Toby", "silly billy", "floppy Joe", "baby", "gammy", "the immovable one", "the curse", "lazy bones", and "the nuisance". Patients often showed a detached attitude towards their deficit which was treated with insouciance and cheerful acceptance. Most cases occurred in the context of left hemiplegia (Critchley 1955). A case of personification of a presumed functional neurological disability has been seen in CFC, although it was not apparent whether this was an anosognosic problem (Larner 2010c).

Case Study 8.4: Possible akinetopsia
A male patient in his twenties attempted suicide by deliberate carbon monoxide poisoning (acute carboxyhaemoglobin = 44.6%). On recovery from his acute illness, he complained of difficulty seeing, was unable to fixate or follow visual targets such as the examiner's face, but had normal voluntary saccadic eye movements in both amplitude and velocity. He had "leadpipe" rigidity in all four limbs but there was no tremor. He could walk only with assistance because of his visual difficulty. A diagnosis of delayed parkinsonism with visual agnosia secondary to carbon monoxide poisoning was made. Eventually he could ambulate without assistance but still found it difficult to perceive moving as opposed to stationary objects. Subsequent neuropsychological assessment confirmed an apperceptive visual agnosia. Magnetic resonance imaging of the brain showed bilateral high signal intensity in the caudate and putamen, accounting for his parkinsonism, as well as some subtle bilateral parieto-occipital cortical signal change more rostrally, perhaps accounting for his visual agnosia.

8.1.4 Praxis: Apraxia

Apraxia is an acquired syndrome of impaired voluntary movement despite an intact motor system with preservation of automatic/reflex actions (Larner 2016:32–3).

Of the neurodegenerative disorders, corticobasal degeneration (CBD) was typified in its early descriptions, emanating from movement disorders specialists, as showing unilateral limb apraxia, sometimes with the alien limb phenomenon (e.g. Gibb et al. 1989). However, it has become increasingly apparent that CBD phenocopies, labelled as corticobasal syndrome (CBS), are relatively common, with the underlying pathology often being Alzheimer's disease (e.g. Boeve et al. 1999, 2003; Alladi et al. 2007) and sometimes Pick's disease. Occasional cases of CBS with underlying AD or Pick-type pathology have been seen in CFC (Doran et al. 2003). Apraxic presentations of Alzheimer's disease are now well-recognised (Caselli and Tariot 2010:96–104), but rare: only one apraxic presentation was seen amongst new AD cases seen in CFC over a 6-year period (2000–2005) (Larner 2006a).

8.1.5 Executive Function: Dysexecutive Syndrome

Executive function is a broad umbrella term which may encompass a number of complex thought processes including functions such as problem solving, planning, goal-directed behaviour, and abstraction. In view of the heterogeneity of this construct, no one test can adequately probe "executive function", but a variety of neuropsychological tests may address elements of it, including the Wisconsin Card Sorting Test, word and design fluency tasks, proverb interpretation, cognitive estimates, Stroop task, and gambling tasks (Iowa, Cambridge). Dysexecutive syndrome

is an acquired syndrome of deficits or impairments in these various cognitive tasks which may be accompanied by (and indeed result from) behavioural dysfunction, ranging from disinhibition with loss of social mores to abulia, apathy and social withdrawal (Larner 2016:102). The variety of behavioural (or neuropsychiatric) features seen in this syndrome means that these patients may present initially to psychiatric services, with suspected manic or depressive disorders. Because of the overlap of neurologic and psychiatric symptomatology, these patients are often referred to the CFC by psychiatrists (see Sect. 1.2.2).

Executive dysfunction is typical of the behavioural variant of frontotemporal dementia (bvFTD; Rascovsky et al. 2011), and may emerge with time in the other, linguistic, FTLD phenotypes (Sect. 9.2). The executive impairments found may facilitate the differential diagnosis of bvFTD from AD (Bozeat et al. 2000), and their assessment is incorporated into certain screening instruments such as the Cambridge Behavioural Inventory (see Sect. 5.2.1). In contrast to the impulsiveness which compromises the performance of bvFTD patients on gambling tasks, a patient with semantic dementia has been seen who was still able to bet regularly on horse racing with moderate success despite being essentially mute (Larner 2007c).

The question as to whether a frontal variant of AD (fvAD) exists has been approached in two different ways. Some have defined such a variant based on neuropsychological assessments suggesting a disproportionate impairment of tests sensitive to frontal lobe function. For example, Johnson et al. (1999) reported a group of 63 patients with pathologically confirmed AD, of whom 19 were identified with greater neurofibrillary pathology in frontal as compared to entorhinal cortex, of whom three had disproportionately severe impairment on two neuropsychological tests of frontal lobe function (Trail Making Test A, FAS letter fluency test) at the group level. No details of the clinical, as opposed to the neuropathological and neuropsychological, phenotype of these patients were given, for example whether they presented with behavioural dysfunction akin to that seen in bvFTD. Woodward et al. (2010) defined cases of fvAD as AD subjects scoring in the lowest quartile of scores on the Frontal Assessment Battery (Dubois et al. 2000; see Sect. 4.2.1). Using other assessment scales, these fvAD patients appeared to be simply more severely affected AD patients. In contrast to this approach based on neuropsychological test performance, others have defined a frontal AD variant based on a clinical picture suggestive of bvFTD but with additional investigation evidence suggestive of AD (Larner 2006c; Caselli and Tariot 2010:104–8), although neuropathological confirmation of such cases is rare (e.g. Alladi et al. 2007; Taylor et al. 2008). Clinico-biological diagnostic criteria recognise the fvAD variant (Dubois et al. 2014). Some AD patients with presenilin 1 gene mutations (Sect. 7.3.1) may have a phenotype suggestive of bvFTD (Larner and Doran 2006, 2009; Larner 2013c). One PSEN1 mutation (G183V) has been reported in which there was not only the clinical but also the neuropathological phenotype of bvFTD (Dermaut et al. 2004). One family with the R269G PSEN1 mutation with prominent behavioural and psychiatric symptoms has been seen in CFC (Doran and Larner 2004).

Marked executive dysfunction producing a frontal type of dementia has also been encountered in a patient with X-linked adrenoleukodystrophy (X-ALD),

confirmed on clinical, biochemical and neurogenetic grounds, who was inadequately compliant with his treatment regime (Larner 2003a). Cases of X-ALD presenting with adult onset dementia have only rarely been reported, some with prominent frontal lobe dysfunction (e.g. Powers et al. 1980) and some with behavioural features ("manic-depressive psychosis") which might possibly have been indicative of frontal lobe involvement (Angus et al. 1994).

Behavioural disturbance sufficient to prompt legal redress (antisocial behaviour order, or ASBO, issued by a court) may result from brain disease; this has been seen in a possible case of neuroacanthocytosis (Doran et al. 2006; Larner 2007d).

8.2 Comorbidites

The comorbidities of cognitive disorders, both psychiatric and physical, have attracted greater attention in recent times (Kurrle et al. 2012). Their presence may be apparent on history taking (see Chap. 3) but may require the use of dedicated screening instruments for their identification (see Chap. 5).

8.2.1 Behavioural and Neuropsychiatric Features

The ubiquity of behavioural and psychological symptoms of dementia (BPSD; Finkel et al. 1996) has been increasingly recognised, not least because they, rather than cognitive impairments, are the most common antecedents of nursing home placement, the most costly aspect of dementia care. Since the assessment and treatment of BPSD lies outwith the training and expertise of most neurologists, and because of the close links between CFC and local old age psychiatry facilities, patients developing BSPD have typically been referred on rather than managed in house. Moreover, because some antipsychotic medications used to treat BPSD have been associated with an excess mortality secondary to cerebrovascular disease, behavioural rather than pharmacological therapeutic approaches are now recommended (Cerejeira et al. 2012; Kales et al. 2015).

The FTLDs are often accompanied by non-cognitive neuropsychiatric manifestations such as apathy, disinhibition, loss of insight, transgression of social norms, emotional blunting, and repetitive and stereotyped behaviours (Mendez et al. 2008a; Box 10.3). In a series of FTD/MND patients reported from CFC, over two-thirds were under the care of a psychiatrist at time of diagnosis, some with provisional diagnoses of hypomania or depression, and all of whom were receiving either antidepressant or neuroleptic medications, sometimes in addition to anti-dementia drugs, suggesting that neuropsychiatric symptoms are not uncommon in this condition (Sathasivam et al. 2008). Psychotic symptoms including delusions and hallucinations are, however, rarely seen in FTLDs (Mendez et al. 2008b). FTD/MND may be an exception to this generalisation, sometimes manifesting an early psychotic phase characterised by hallucinations and delusions which may be dramatic and bizarre but transient. This may be related to presence of the C9orf72 hexanucleotide

repeat expansion (Sect. 7.3.2) which has been associated with a number of neuropsychiatric features. For example, in a patient cohort from the United Kingdom it was noted that 38% of mutation carriers presented with florid psychotic symptoms, for which initial psychiatric diagnoses of delusional psychosis, somatoform psychosis, and paranoid schizophrenia had been made. An additional 28% had paranoid, delusional and irrational thinking. Delusions were much more common than hallucinations (Snowden et al. 2012). However, in a large series of FTD patients, Le Ber et al. (2013) reported that hallucinations were indicative of GRN rather than C9orf72 mutations.

A patient with delusion of pregnancy related to the C9orf72 hexanucleotide repeat expansion has been seen in CFC (Larner 2008d, 2013d; Case Study 5.1). This mutation has also been associated with presentations as obsessive-compulsive disorder (Calvo et al. 2012) and bipolar disorder (Floris et al. 2013). A schizophrenia-like psychosis has been reported on occasion as the presenting feature of early-onset FTLD (Velakoulis et al. 2009) but there does not seem to be an association between C9orf72 repeat expansions and schizophrenia (Huey et al. 2013). A patient with a provisional diagnostic label of "undifferentiated schizophrenia" who eventually developed neurological signs and proved to have this mutation has been seen in CFC (Ziso et al. 2014). A bvFTD patient with Cotard syndrome (delusion of negation), a phenomenon previously reported in SD (Mendez and Ramirez-Bermudez 2011), has also been seen in CFC (Larner 2016:83).

Visual hallucinations are included amongst the core criteria in the diagnostic criteria for dementia with Lewy bodies (McKeith et al. 1996, 1999, 2005, 2017). These are usually complex images of people or animals, although the sensation of a presence, someone standing beside the patient (*anwesenheit*; Larner 2016:28–9), is also relatively common in parkinsonian syndromes (Fénélon et al. 2000). A pathologically confirmed case of sporadic Creutzfeldt-Jakob disease (CJD) was initially mistaken for DLB because of the presence of visual hallucinations as well as motor features of parkinsonism and orthostatic hypotension, but the very rapid progression prompted diagnostic re-evaluation. Of note, the visual hallucinations in this case took the form of simple colours rather than complex shapes. Post mortem neuropathology was consistent with the MV1 subtype of CJD (Parchi et al. 1999; Du Plessis and Larner 2008). The Heidenhain variant of sporadic CJD, accounting for perhaps 20% of cases, is characterized by visual disorders throughout the disease course which may include blurred vision, diplopia, visual field restriction, metamorphopsia, cortical blindness, and visual hallucinations (Kropp et al. 1999; Armstrong 2006).

Progressive psychiatric disturbances are one of the typical and often early features of variant CJD (vCJD; Spencer et al. 2002) but these may also occur on occasion in sporadic CJD. Psychiatric features are the presenting feature in around 20% of sCJD patients (Wall et al. 2005; Rabinovici et al. 2006), although not mentioned in current diagnostic criteria. We have experience of a patient with a psychiatric prodrome diagnosed as depression for many months before progressive cognitive decline and investigation features typical of sCJD became apparent (Ali et al. 2013), likewise in a young patient suspected to have vCJD but which proved to be a rare phenotype of sCJD (Williamson and Larner 2016).

8.2.2 Delirium

Delirium is a clinically heterogeneous syndrome characterised by cognitive and behavioural features, diagnostic criteria for which require disturbance of consciousness (which may take the form of subtle attentional deficits only), change in cognition, and onset over a short period of time with fluctuation during the course of the day (Larner 2004b). It is a richly varied syndrome ranging from hypoactive to hyperactive states, with a number of recognised precipitating factors (infection, metabolic derangement, various medications) and predisposing factors (age, medical comoribidty, visual and hearing impairment). Dementia is one of the recognised predisposing factors for delirium (Davis et al. 2012), and the differential diagnosis may be difficult, since the two may coexist ("delirium superimposed on dementia"; Morandi et al. 2012).

It is exceptionally unusual for delirium per se to present in an outpatient setting, such as CFC, rather than acutely, although a history of previous episodes of unexplained confusion may be obtained in patients presenting to the clinic with cognitive impairments or dementia. Use of the Confusion Assessment Method may assist with the diagnosis of delirium (CL Wong et al. 2010), but it may sometimes be necessary to institute empirical therapy for presumed delirium (i.e. review medications, treat underlying infection, correct metabolic abnormalities, reduce sensory impairments).

8.2.3 Epilepsy

The concurrence of epileptic seizures and cognitive decline has a broad differential diagnosis (Lozsadi et al. 2008; Larner 2010a, 2011d). Epileptic seizures may either be a cause of cognitive dysfunction (generalised and complex partial seizures are usually characterised by amnesia for the event) or be associated with cognitive disorders. In the former category, occasional cases of repeated seizures producing a phenotype akin to AD have been reported (e.g. Høgh et al. 2002; Tombini et al. 2005). More commonly, however, AD may be accompanied by epileptic seizures.

Alzheimer did not mention seizures in his original reports. Allison (1962:118) claimed that Solomon Carter Fuller (1912) noted, in what is probably the first paper on Alzheimer's disease to be published in English, convulsive fits in a pathologically confirmed case in the later stages. However, a reading of Fuller's lengthy case report leads to the assumption that Allison was referring to the "short periods of unconsciousness or dream-like states" which occurred in the two years before the patient's "final breakdown" (Fuller 1912:441), but no account of convulsion was found (Larner 2013e). However, Fuller noted in his summary of previously published cases that "In a few of the cases motor disturbances have been noted as residua of epileptiform convulsions. Convulsions with loss of consciousness, however, have not been observed, save in the terminal stage, epileptiform attacks and muscular twitchings being recorded" (Fuller 1912:554). An early, definite, report of epileptic seizures in pathologically confirmed AD is that of Hannah (1936).

Epileptic seizures in AD have become a subject of increasing interest in recent times (Larner 2010a, 2011a; Irizarry et al. 2012; Pandis and Scarmeas 2012; Chin and Scharfman 2013; Vossel et al. 2017). This has been prompted, at least in part, by laboratory observations of transgenic animals harbouring pathogenic AD mutations. Such animals have been shown not only to have high brain levels of amyloid beta-peptides and to develop AD pathological changes and cognitive deficits, but also to have spontaneous non-convulsive seizure activity in cortical and hippocampal networks (Palop et al. 2007). GABAergic sprouting, with enhanced synaptic inhibition and deficits in synaptic plasticity, was observed in the dentate gyrus in these mouse models. It has also been shown in experimental animals that amyloid beta-peptides may induce neuronal hyperexcitability and trigger progressive epilepsy (Minkeviciene et al. 2009). These animal models have been used to investigate possible treatments with anti-epileptic drugs (Ziyatdinova et al. 2011).

These animal studies have raised the possibility that epileptiform activity, with or without clinical seizures, is an integral part of the AD phenotype, rather than being merely an epiphenomenon. High rates of subclinical epileptiform activity have been reported in early-onset AD patients (Vossel et al. 2016) and epidemiological studies have reported clinical seizures particularly in early-onset disease (e.g. Mendez et al. 1994; Amatniek et al. 2006; Bernardi et al. 2010). Epileptic seizures have been reported in around 20% of reported presenilin-1 mutations causing early-onset AD, prompting the suggestion that this may be a genetic epilepsy syndrome (Larner 2011c).

It has been repeatedly observed that seizure prevalence increases with disease duration in AD (Larner 2010a) although a study in CFC showed that a small percentage of newly diagnosed AD patients (6.8%) had seizures at the time of AD diagnosis and that in half of these (3.4% of the whole cohort) no explanation for seizures other than AD could be identified (Lozsadi and Larner 2006). The NINCDS-ADRDA clinical diagnostic criteria for AD stated that epileptic seizures in advanced disease are consistent with a diagnosis of probable AD, whereas epileptic seizures at onset or early in the course of the illness make the diagnosis of probable AD uncertain or unlikely (McKhann et al. 1984); early occurrence of seizures remains an exclusion criterion for typical AD in modern criteria (Dubois et al. 2014). However, this study (Lozsadi and Larner 2006) clearly indicated that early seizures should not entirely rule out the diagnosis of AD. Seizures may occasionally precede cognitive symptoms (Picco et al. 2011).

Treatment of seizures in AD remains largely empirical (e.g. Belcastro et al. 2007; Cumbo and Ligori 2010; Jenssen and Schere 2010; Lippa et al. 2010; Vossel et al. 2013); the need for controlled clinical trials is evident (Larner and Marson 2011). Clearly drugs with potential for adverse cognitive effects (e.g phenobarbitone, primidone, phenytoin, topiramate) are best avoided. With their better adverse effect profile, newer anti-epileptic medications such as lamotrigine and levetiracetam may be preferred (Belcastro et al. 2007; Cumbo and Ligori 2010; Lippa et al. 2010; Vossel et al. 2013). Interestingly, there is some evidence that levetiracetam may decrease neuropathological burden and reverse spatial memory deficits in a transgenic animal model of AD (Shi et al. 2013).

Epileptic seizures have long been recognised as part of the phenotype of Down syndrome (DS), particularly with increasing age (e.g. Veall 1974; Puri et al. 2001). A syndrome of senile myoclonic epilepsy in Down syndrome (De Simone et al. 2010) or late-onset myoclonic epilepsy in Down syndrome (LOMEDS) has been delineated and seems to be common (Li et al. 1995; Möller et al. 2001). This has been observed in the small numbers of patients with DS seen in CFC (Larner 2007e, 2011d). Aetiopathogenesis is uncertain, but may be related to constitutive overexpression of amyloid beta-peptides derived from the APP gene, present in an extra copy in trisomy 21. Epileptic seizures also appear to be frequent in rare families with AD due to APP locus duplication (Cabrejo et al. 2006).

Epileptic seizures may be seen in a number of other neurodegenerative disorders (Larner 2007f, 2010d). In prion disease, seizures have been reported in sporadic CJD, sometimes as the presenting feature, with focal motor seizures, nonconvulsive status epilepticus, and generalised status epilepticus all reported. Localization-related seizures have been reported as the first presentation of variant CJD (Silverdale et al. 2000) but this would seem to be a rare or even exceptional event (Spencer et al. 2002). Epileptic seizures are rarely encountered in FTLDs, and if present should probably give pause as to the correctness of the diagnosis, likewise in synucleinopathies (DLB, PDD) and late-onset Huntington's Disease, although seizures are said to be more common in the juvenile onset (Westphal variant) form of HD. It would be anticipated that seizures are common in vascular and mixed dementia, since cerebrovascular disease is a recognised risk factor for late-onset seizures. Patients with stroke who have epileptic seizures may be at increased risk of dementia. In a cohort of stroke patients without pre-existing dementia, the occurrence of epileptic seizures was an independent predictor of new-onset dementia within 3 years of stroke (Cordonnier et al. 2007).

8.2.4 Sleep-Related Disorders

The importance of sleep for cognitive function, particularly for memory consolidation, has become increasingly apparent (Yang et al. 2014). The link between amyloid pathology and impaired hippocampal-dependent memory consolidation in AD may be mediated through non-REM sleep disruption (Mander et al. 2015).

Sleep-related disorders may be a signature of neurodegenerative disease, as for example REM sleep behaviour disorder (see Case Study 5.2) and synucleinopathies such as DLB. Sleep disturbance is a feature of AD which worsens with advancing disease. Insomnia may be a characteristic feature of some prion diseases, familial and sporadic fatal insomnia (Max 2007). Aspects of sleep may be assessed with screening instruments such as PSQI and SDI (see Sect. 5.3).

Even in the absence of neurodegenerative disease, sleep disturbance may be relevant to complaints reported in the cognitive clinic. Poor sleep quality correlates with subjective memory complaint (see Sect. 5.3.1; Hancock and Larner 2009a). This may reflect an underlying affective disorder such as depression, but other

Case Study 8.5: Obstructive sleep apnoea-hypopnoea syndrome
Following a stroke of undetermined aetiology affecting his right side, a male patient in his late twenties developed tiredness, weight gain and excessive daytime somnolence. By the time of his referral to CFC, one year poststroke, he had still not returned to work and was described as hard to motivate. His sleep was described as restless, with loud snoring and witnessed apnoeas. He was obese (weight 140 kg; BMI 40 kg/m^2). On the Epworth Sleepiness Scale his score was abnormally high (18/24). Neuropsychological assessment showed mild impairment of cognitive function, with slight reductions in verbal reasoning and verbal comprehension performance, poor performance on tests of short term memory and learning, reduced verbal fluency and mild attentional problems. Non-verbal reasoning, language, visuospatial and constructional functions were intact. The pattern of deficits was thought typical of a subcortical process. Overnight home oximetry showed severe cyclic fluctuations in oxygen saturation with a desaturation index (i.e. decrease in oxygen saturation by ≥4% per hour of sleep) of >60, indicative of severe obstructive sleep apnoea-hypopnoea syndrome (Larner 2003b:151 [Case 2], 2008e:198).

sleep-related disorders should be borne in mind since they may have specific treatments. Sleep-related disorders presenting with cognitive complaints which have been seen on occasion in CFC include obstructive sleep apnoea (Larner 2003b; Lim and Larner 2008; Case Study 8.5), central sleep apnoea (Larner and Ghadiali 2008), restless legs syndrome (Davies and Larner 2009b), and shift-work sleep disorder (Larner 2010e). With regard to the latter, poor sleep quality is commonplace in shift workers (Akerstedt 2003) and sleep deprivation is recognised to have adverse consequences on cognitive function (Durmer and Dinges 2005). Poor sleep quality is associated with amnestic and non-amnestic function in older patients (Miller et al. 2014).

8.2.5 Diabetes Mellitus

The relationship between diabetes mellitus (DM) and cognitive function has attracted significant research attention, not least because of the increasing prevalence of type 2 DM in the population. Cognitive dysfunction in general, and Alzheimer's disease with or without cerebrovascular disease in particular, may be chronic complications of DM, but the pathophysiology is uncertain. Possible mediating and modulating factors may include the effects of glycaemic control: hyperglycaemia, hyperinsulinaemia (with subsequent insulin resistance), and failure of insulin degrading enzyme (protease) activity (Cheng et al. 2012; McCrimmon et al. 2012; Koekkoek et al. 2015; Schilling 2016). Treatment-induced hypoglycaemia might also be a factor (Larner 2013a:177–8; Case Study 8.1).

A survey of 235 consecutive new outpatients attending CFC over a 10-month period (September 2012–April 2013; F:M = 107:128; age range 18–89 years, median 59 years) found 18 with type 2 DM (= 7.7%; F:M = 4:14; age range 38–84 years, median 62 years). Of those with DM, only 5 had dementia, but 10 of the 13 non-demented DM patients were adjudged to have MCI, giving a prevalence of cognitive impairment of 0.83 in this group, as compared to 0.49 in the whole group (dementia 71, MCI 43). The relative risk or risk ratio for cognitive impairment in patients with DM compared to non-diabetics (n = 217) was 1.83 (95% CI = 1.57–2.08). Of the whole group with cognitive impairment, 15 out of 114 had DM, whilst only 3 of the 121 cognitive healthy individuals had DM. The relative risk or risk ratio for DM in patients with cognitive impairment compared to cognitive healthy individuals was 5.31 (95% CI = 4.09–6.52). These data prompt the question as to whether screening of cognitive function in patients with DM should be considered (Price and Larner 2013).

8.3 No Diagnosis; Functional Cognitive Disorders

Many patients attending CFC are found, following clinical, neuropsychological, and neuroimaging assessment, to have no evidence for the presence of an underlying cognitive disorder to account for their symptoms. Indeed, longitudinal evidence from 2002 to the present suggests that the proportion of demented patients seen in CFC has gradually decreased over the years (see Sect. 1.4; Fig. 1.8), although the proportions of all patients referred to CFC with either dementia or cognitive impairment over the period 2009–2016 have not changed significantly. The proportion of patients with no evidence of cognitive impairment or cognitive disorder has remained between 50 and 60% (Table 8.1; Fig. 8.3). These changes may possibly be a consequence of national directives, such as the National Dementia Strategy of 2009 in England (Department of Health 2009), which has raised awareness of the diagnosis of dementia amongst both primary care practitioners and the general public, causing more patients with memory symptoms to present.

Table 8.1 Referral numbers and diagnoses, CFC 2009–2016 (compare with Table 1.3; see Fig. 8.3)

Year	N	Any cognitive disorder/cognitive impairment (% of N)	No cognitive disorder/cognitive impairment (% of N)
2009	249	106 (42.6)	143 (57.4)
2010	233	96 (41.2)	137 (58.8)
2011	227	92 (40.5)	135 (59.5)
2012	245	107 (43.7)	138 (56.3)
2013	323	154 (47.7)	169 (52.3)
2014	323	153 (47.4)	170 (52.6)
2015	328	139 (42.4)	189 (57.6)
2016	340	145 (42.6)	195 (57.4)
Total (%)	2268	992 (43.7)	1276 (56.3)

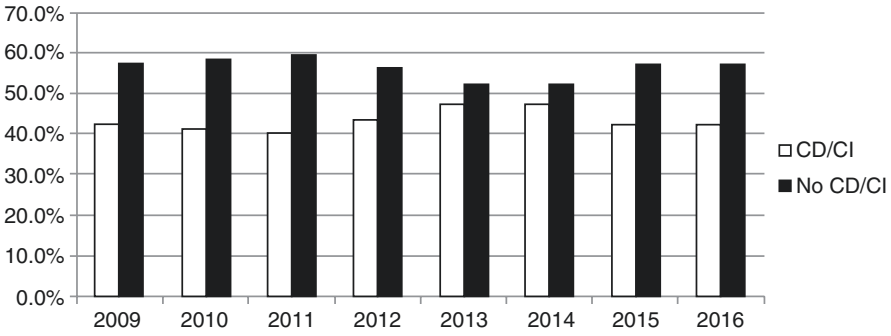

Fig. 8.3 Proportion of patients with or without cognitive disorder (CD) or cognitive impairment (CI) presenting to CFC, 2009–2016 (courtesy of Dr. V Bharambe)

The UK National Institute for Health and Clinical Excellence (NICE) suggested a memory clinic base rate for dementia of 54% (2010). However, a report from 30 Alzheimer's Centers in the USA reported 50% of patients seen were diagnosed as having normal cognition (Steenland et al. 2010). These figures may greatly overestimate current CFC experience, where over the past decade rates between around 20–30% have been seen (Table 1.3). This predominance of subjective memory complaint should not surprise us: in the seventeenth century La Rochefoucauld (1613–1680) noted that "Everybody complains of his memory, but nobody of his judgement" (*Maxims*, 89). Identification and reassurance of those individuals with purely subjective memory complaint is an important function of cognitive and memory clinics, a task which may also be facilitated by use of cognitive screening instruments (Larner 2017c).

The exact nature of this non-demented non-diagnostic group remains unclear, but it is probably heterogeneous, as reflected in the various diagnostic labels which have been applied, including "memory complainers", "worried well", subjective memory impairment, mild cognitive dysfunction, and functional memory disorder (Schmidtke et al. 2008; Blackburn et al. 2014). Stone et al. (2015) have proposed that a positive diagnosis of "functional cognitive disorder", analogous to other functional (e.g. movement, epilepsy) disorders, may be made based on inconsistency or incongruence of symptoms. The typology of functional cognitive disorders may be broad, encompassing mood disorder (depression/anxiety), normal cognitive experience, dementia health anxiety (e.g. in the context of a positive family history), other functional disorders (e.g. fibromyalgia, chronic fatigue syndrome), dissociative amnesia, medication effects, and malingering (Stone et al. 2015). In this context, it should be noted that memory complaints and cognitive impairment feature among the functional neurological symptoms seen in clinics dedicated to these disorders (e.g. Fig. 1 in Reuber et al. 2007:628). Memory complaints may be as common following non-head injury as in mild traumatic brain injury (Lees-Haley et al. 2001), as one feature of the post-trauma syndrome.

Some non-demented individuals attending the clinic have the kind of simple memory lapses which are common to many (Jónsdóttir et al. 2007), such as going

into a room and not recalling why, particularly if distracted by another task, suggesting an attentional rather than a mnemonic dysfunction. Difficulty in naming individuals (as opposed to objects) is a particularly common complaint (Kapur and Pearson 1983) but in isolation this is seldom cause for concern: naming is a challenging test from the neuropsychological perspective, being an example of cross-modal non-contextual paired associate learning. A lack of correlation between subjective and objective memory impairment is often found in such cases (Kapur and Pearson 1983). Memory lapses which are recalled in great detail during clinical consultation are seldom pathological, reflecting as they do an absence of source amnesia. Cognitive anosognosia, as manifested by many AD patients, is far more worrying. The importance of the clinical history in trying to differentiate between these possibilities cannot be overemphasized (Larner 2011e).

Some memory complainers may simply be intuiting the decline in cognitive efficiency which comes to us all as a feature of the physiological change in memory function with age (Larner 2006d, 2012b): physiological cognitive decline may be evident in early middle age, between 45–49 years (Singh-Manoux et al. 2012). Hypervigilance to physiological memory lapses may be one cause of subjective memory complaints. It may also be pertinent to point out that forgetting may sometimes be physiological rather than pathological (e.g. the quote attributed to Friedrich Nietzsche [1844–1900] that "Many a man fails as an original thinker simply because his memory is too good"). Many other neurological disorders may also be accompanied with cognitive impairment (Larner 2008e, 2013a; Larner et al. 2011), so evidence of a neurological disorder other than a dementia syndrome may be evident.

Some memory complainers may harbour brain disease insufficient to mandate a diagnosis of dementia (i.e. MCI). It is recognised that older people with subjective memory complaints (SMC; see Sects. 3.1.1.2 and 3.1.1.3) are more likely than those without SMC to progress to dementia (Mitchell et al. 2014); absence of SMC may be a marker excluding dementia and MCI (Mitchell 2008).

The factors which contribute to subjective memory complaints prompting attendance for clinical consultation are complex (i.e. many factors interacting which cannot be reliably predicted with mathematical analysis). Differentiating worried well patients from those with amnestic mild cognitive impairment may be difficult, even using screening instruments for memory complaints (Ahmed et al. 2008). However, some clues may be gleaned from empirical analysis of clinical cohorts and calculation of relative risks or risk ratios (Table 8.2). The presence of a positive family history of dementia may sensitize individuals to physiological memory lapses and/or exacerbate anxieties sufficient to prompt referral (Sect. 3.1.2; Larner 2013f). Sleep-related disorders (Sect. 5.3) which may or may not be part of an affective disorder (anxiety, depression; Sect. 5.2), may also contribute to memory difficulties. Simple screening instruments such as the Pittsburgh Sleep Quality Index (PSQI; Sect. 5.3.1; Hancock and Larner 2009a) and the Patient Health Questionnaire-9 (PHQ-9; Sect. 5.2.2; Hancock and Larner 2009b) may identify those individuals who might benefit from interventions to tackle poor

Table 8.2 Summary of relative risks or risk ratios from CFC studies (>1 = increased risk; with 95% confidence intervals)

(a) Risk of no dementia vs. dementia:		
	Relative risk or risk ratio	Reference
Impaired ADL (IADL Scale score ≤13/14)	0.57 (0.48–0.68)	Hancock and Larner (2007)
Depression (PHQ-9 score >9/27)	3.32 (1.48–7.43)	Hancock and Larner (2009b)
Poor sleep quality (PSQI score ≤5/21)	1.79 (1.38–2.31)	Hancock and Larner (2009a)
(b) Risk of no cognitive impairment vs. any cognitive impairment (dementia + MCI)		
	Relative risk or risk ratio	Reference
+ve family history of dementia	1.72 (1.00–2.96)	Larner (2013f)
Attended alone sign	6.75 (4.17–10.9)	Larner (2014)
Head turning sign (HTS+)	0.08 (0.02–0.32)	Ghadiri-Sani and Larner (2013)
(c) Risk of dementia vs. no dementia:		
	Relative risk or risk ratio	Reference
Any referral from primary care	0.55 (0.40–0.74) and 0.66 (0.49–0.89)	Fearn and Larner (2009)
Patient age ≤ 65 years	0.22 (−0.12–0.56),	Price and Larner (2013)
(d) Risk of any cognitive impairment (dementia + MCI) vs. no cognitive impairment:		
	Relative risk or risk ratio	Reference
Patient age ≤ 65 years	0.38 (0.17–0.59)	Price and Larner (2013)
Diabetes mellitus as comorbidity	1.83 (1.57–2.08)	Price and Larner (2013)

sleep and/or affective disorder. Conversely, attending CFC alone (Sect. 3.2.1; Larner 2014), absence of the head turning sign (Sect. 3.2.2; Ghadiri-Sani and Larner 2013), *la maladie du petit papier* (Sect. 3.2.4; Randall and Larner 2018), and preservation of activities of daily living (Sect. 5.1.1; Hancock and Larner 2007) may all point towards preserved cognitive health. Referrals from primary care have a lower risk of dementia diagnosis than those from secondary care (Sect. 1.2.1).

Management in the absence of evidence of any neurological disorder is based on reassurance. Sometimes this may be all that is required, but scheduled longitudinal assessment to see what, if any, change has occurred may be necessary, for example the prognosis of functional cognitive disorders is not well defined. To avoid practice effects on cognitive testing, reassessment should be no more frequent than 6 monthly and preferably longer (Heilbronner et al. 2010). Longitudinal volumetric neuroimaging techniques may also be useful to detect advancing brain atrophy. There is no compelling evidence yet available to suggest that "brain training" games or puzzles such as Sudoku have any utility in these circumstances to improve memory function.

8.4 Wrong Diagnosis

It is debatable which is the greater clinical evil, making no diagnosis or making a wrong diagnosis; making a possible error of omission or an error of commission. In terms of the matrix of confusion (Fig. 2.1), this may be characterised in terms of false negative or false positive diagnosis, the (relative) costs associated with which are difficult to determine (see Sect. 6.1.1).

As previously mentioned (Chap. 7), diagnostic errors based on over-reliance on investigations, particularly structural imaging reported to show brain atrophy, have been encountered (Larner 2004c; Davies and Larner 2009a). Contextualising all investigation results in terms of the clinical history and neurological examination is paramount in all neurological diagnosis (Larner et al. 2011), and hence the optimal (though not infallible) way to avoid diagnostic error.

When (not if!) diagnostic errors occur, the clinician should reflect on their potential salutary heuristic value, as cogently described by Sir William Gowers (1894):

> It is always pleasant to be right, but it is generally a much more useful thing to be wrong … if you are wrong you generally gain in knowledge and gain perception of the way in which your method of diagnosis needs improvement.

8.5 Summary and Recommendations

The differential diagnosis of cognitive syndromes is very broad, and hence potentially daunting to the uninitiated. However, the number of syndromes commonly encountered in CFC is relatively circumscribed, with amnesia accounting for the majority of cases. Definition of specific cognitive syndromes (e.g. amnesia, aphasia, dysexecutive syndrome) may guide differential diagnosis of specific dementia syndromes (see Chap. 9). The presence of defined comorbidities may assist in differential diagnosis, as well as having implications for management.

Failure to establish a specific syndrome or diagnosis in those attending a neurological cognitive clinic is not uncommon (as in other spheres of neurological practice), and does not seem to be simply a consequence of clinician incompetence. The uncertainty attendant upon "no diagnosis" may be the most difficult thing for patients and other clinicians, in both primary and secondary care, to deal with, and potentially risks exacerbating the situation through increased anxiety. Therefore, putting in place some sort of management plan (e.g. interval assessment, or onward referral to other services as appropriate) is essential to try to assuage these concerns.

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