Diagnosis (2): Disorders Causing Dementia and Cognitive Impairment

9

Contents

Abstract

This chapter examines the various cognitive disorders (e.g. Alzheimer's disease, frontotemporal lobar degenerations, parkinsonian disorders, cerebrovascular disorders) which may be defined by clinical assessment and investigation, emphasizing their clinical heterogeneity.

Keywords

Dementia · Diagnosis · Cognitive disorders · Alzheimer's disease · Frontotemporal lobar degeneration · Parkinsonian disorders · Vascular dementia

The delineation of cognitive syndromes (see Chap. 8) may narrow differential diagnostic considerations for specific dementia disorders. There are many causes of the dementia syndrome and of cognitive impairment (e.g. see Mendez and Cummings 2003; Kurlan 2006; Larner 2008a, 2010a, 2013a, 2014; Filley 2012; Dickerson and Atri 2014). Only those most often encountered in practice at the Cognitive Function

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Clinic (CFC) at the Walton Centre for Neurology and Neurosurgery (WCNN) in Liverpool are discussed here; evolving diagnostic criteria are listed in Chap. 2 (Box 2.2). Other disorders, such as delirium (Sect. 8.2.2) and depression (Sects. 5.2.2 and 5.2.4), may need to be considered in the initial differential diagnosis, as independent or superimposed causes of cognitive impairment.

9.1 Alzheimer's Disease and Mild Cognitive Impairment

Alzheimer's disease (AD) is by far the most common neurodegenerative disorder seen in CFC, the relatively young age of the casemix notwithstanding. Around 95% of these AD cases have presented with the typical amnesic syndrome, the remainder comprising the focal cortical variants presenting with agnosia, aphasia, apraxia, or dysexecutive syndrome (Larner 2006a, 2008b). These variant presentations (Caselli and Tariot 2010) are acknowledged in updated AD diagnostic criteria (McKhann et al. 2011; Dubois et al. 2014).

Errors in the diagnosis of AD sometimes occur, even in the best centres. Patients diagnosed with AD in other clinics but who have proved not to have dementia on longitudinal follow up at CFC have been encountered on occasion. Over-reliance on structural brain imaging reported to show "atrophy" may have been instrumental in the misdiagnosis of these cases (see Sect. 7.2.1; Larner 2004).

An examination of the CFC database of patients in whom either an initial diagnosis of AD was made and/or cholinesterase inhibitors were prescribed, covering the period January 2000 to end June 2008 (8½ years), was interrogated to identify those in whom diagnostic revision was required, based on disease progression with emergence of new features during follow-up (Davies and Larner 2009). Of 300 patients on the database, 289 (= 96.3%) were initially clinically diagnosed with probable AD using NINCDS-ADRDA criteria (McKhann et al. 1984). From this group, 8 patients initially diagnosed with AD in whom subsequent diagnostic revision was required were identified (= 2.8%; F:M = 1:7, age range at diagnosis 52–63 years, median 58 years). In all cases, diagnosis was revised from AD to FTLD due to the emergence, in isolation or combination, of behavioural (7), linguistic (2), and motor (1) features more typical of the FTLD phenotypes (Sect. 9.2). Onset of these changes was noted between 12 months and 5 years (median 18 months to 2 years) after initial diagnosis. Two patients were eventually shown to harbour tau gene mutations (Larner 2008c, 2009a); both had a family history of early-onset dementia (parent or siblings affected), but in neither case did the available details permit the conclusion of autosomal dominant inheritance of disease (i.e. ≥3 affected in individuals in 2 generations; Cruts et al. 1998). One of these patients developed prototypical FTLD behavioural features, the other a phenotype of progressive supranuclear palsy, 3 and 4 years after initial diagnosis respectively. Of the six other patients, all with early-onset disease (i.e. onset ≤65 years of age), none had a family history of dementia and hence all were initially diagnosed with sporadic probable AD. Two were initially thought to have aphasic presentations of AD, since they had apparent amnesia in addition to aphasia, but both gradually developed behavioural

features requiring their reclassification as FTLD. A further two patients also evolved behavioural features after amnesic presentations. The two remaining patients with amnesic presentations developed progressive impoverishment of language function suggestive of the progressive non-fluent aphasia phenotype, as well as behavioural features. In one of these cases, English was not the patient's first language, thereby confounding initial assessment. That FTLD may on occasion have been misdiagnosed as AD is perhaps not surprising, as symptom overlap between AD and FTLD was evident in definitions then used in widely accepted clinical diagnostic criteria (Varma et al. 1999). In clinical practice initial assessment is essentially cross-sectional, whilst longitudinal assessment may reveal new features mandating diagnostic revision. The adoption of more modern diagnostic criteria for AD (Dubois et al. 2007, 2014; McKhann et al. 2011) and FTLDs (Gorno-Tempini et al. 2011; Rascovsky et al. 2011) may obviate the problem of symptom overlap.

Genetically determined AD has been rarely encountered (see Sect. 7.3.1), all those detected harbouring presenilin 1 gene mutations (Larner and du Plessis 2003; Doran and Larner 2004a, 2006; Larner et al. 2007), and none with either APP or presenilin 2 mutations. Patients with Down syndrome invariably harbour AD pathology after the age of 50 years (Mrak and Griffin 2004), presumably because of the extra copy of the APP gene in trisomy 21. The neuropathological features may have the clinical correlate of cognitive decline and dementia, but such cases have rarely been seen in CFC (see Sect. 9.6; Larner 2007, 2011a; Case Study 7.4).

Mild cognitive impairment (MCI) was initially proposed as a term to describe cognitive impairment which did not amount to dementia, which might purely affect the domain of memory (amnestic MCI) or multiple domains of cognition (Petersen 2003). This may represent prodromal AD, and some authors have used these terms almost interchangeably (Burns and Morris 2008), whereas others have used the term "MCI" to denote a more heterogeneous concept encompassing cognitive impairment associated with other brain disorders which can progress to dementia, including Parkinson's disease (Litvan et al. 2012) and cerebrovascular disease (vascular cognitive impairment; Gorelick et al. 2011), and possibly also frontotemporal dementia (De Mendonca et al. 2004). This may explain the varying estimates of rate of MCI progression to dementia (Mitchell and Shiri-Feshki 2009). Dubois et al. (2007) eschewed the category of mild cognitive impairment altogether, whereas the 2011 National Institute on Aging-Alzheimer's Association criteria have retained MCI, four categories of which are described (Albert et al. 2011). Whatever terminology may be used, the early symptomatic phases of dementing disorders might represent a significant opportunity for treatment, particularly if disease-modifying therapies can be discovered and brought to the clinical arena.

9.2 Frontotemporal Lobar Degenerations

Frontotemporal lobar degenerations (FTLD) are less common than AD overall but in the presenile age group they may be as prevalent as AD (Ratnavalli et al. 2002), although other population based studies find AD to be more prevalent in this age

group (Harvey et al. 2003). Hence FTLDs make up a significant component of CFC work, in part because of the relatively young age at onset of patients seen in this setting (see Sect. 1.3.1). In addition, patients referred to CFC from psychiatrists (see Sect. 1.2.2) have an increased frequency of FTLD, mostly the behavioural variant. FTLD in the elderly may be underreported, and may differ in clinical and pathological phenotype from early-onset disease (Baborie et al. 2012, 2013).

FTLDs are heterogeneous at the clinical, neuropsychological, neuropathological and genetic level (Snowden et al. 1996; Hodges 2007; Warren et al. 2013; Dickerson 2016). Of the various clinical phenotypes encompassed by the FTLD rubric (Neary et al. 1998), behavioural variant (bvFTD; Rascovsky et al. 2011) and the agrammatic variant of primary progressive aphasia (avPPA; formerly known as progressive non-fluent aphasia) are more common than the semantic variant of primary progressive aphasia (svPPA; also known as semantic dementia; Gorno-Tempini et al. 2011). This has been the experience in CFC (Larner et al. 2005a; Davies and Larner 2010; Larner 2012a, b; Case Studies 4.2, 4.3, 5.1, 7.3, 7.5 and 7.6), consistent with reports from other centres seeing larger numbers of FTLD cases.

Cases of FTLD with motor neurone disease (FTD/MND) have also been seen (see Sect. 1.2.2; Doran et al. 2005; Hancock and Larner 2008; Larner 2008d, 2013b; Sathasivam et al. 2008; Larner and Gardner-Thorpe 2012; Ziso et al. 2014; Case Study 7.6). Many of the cases have been referred from psychiatry clinics or are under concurrent care of psychiatrists, but it is of note that FTD/MND is not mentioned in DSM-IV-TR (American Psychiatric Association 2000), either as a specific cause of dementia or in the catch-all category of "Dementia due to other general medical conditions". This omission is surprising in light of the fact that FTD/MND may present with neuropsychiatric symptoms (Sect. 8.2.1), leading to referral to psychiatrists rather than neurologists in the first instance. These neuropsychiatric symptoms include disinhibition, which may be mistaken for hypomania, and self-neglect and poverty of speech which may be mistaken for depression (Sathasivam et al. 2008), as well as florid delusions (Larner 2008d, 2013b; Ziso et al. 2014). Disinhibition was presumed to be the substrate for the "animal-like behaviour" seen in one patient with bvFTD who, according to his wife, used to bark like a dog, a behaviour which may fall under the rubric of lycanthropy (Larner 2010b).

As far as genetically determined cases of FTLD are concerned (Sect. 7.3.2), it was formerly the case that large centres reported either a preponderance of tau compared to progranulin mutations (Seelaar et al. 2008) or roughly equal numbers (Rohrer et al. 2009). However, following the discovery of the C9orf72 hexanucleotide repeat expansion (DeJesus-Hernandez et al. 2011; Renton et al. 2011), this has superseded both tau and progranulin mutations in frequency (Boeve et al. 2012; Dobson-Stone et al. 2012; Hsiung et al. 2012; Mahoney et al. 2012; Majounie et al. 2012; Simon-Sanchez et al. 2012; Snowden et al. 2012).

Families with tau gene mutations (FTDP-17) have been seen on occasion in CFC (see Sect. 7.3.2). In some of these cases the proband received an initial diagnosis of probable AD, with features more typical of FTLD only emerging at a later

stage of disease. This clinical heterogeneity has also been observed with some of the other tau gene mutations (Larner and Doran 2009a), such as R406W (Lindquist et al. 2008). This diagnostic error, FTLD confused with AD, has also been noted in sporadic FTLD patients (Davies and Larner 2009), perhaps related to the overlap of older diagnostic criteria (Varma et al. 1999). Occasional FTLD cases with progranulin and C9orf72 mutations have also been seen in CFC (Sect. 7.3.2; Larner 2012b, 2013b, 2017 Cases 2 and 3 [Table 4.32]; Ziso et al. 2014; McCormick and Larner 2018).

Unusual forms of FTLD have also been seen, defined on neuropathological grounds. Neuronal intermediate filament inclusion disease (NIFID) was initially defined by intraneuronal cytoplasmic inclusions of variable morphology which immunostained for all class IV intermediate filament (IF) proteins, namely NF-H, NF-M, NF-L, and alpha-internexin (Cairns et al. 2004). More recently it has been shown that a much larger proportion of the inclusions in NIFID are immunoreactive with the *fused in sarcoma* (FUS) protein than with IF (Neumann et al. 2009), leading to changes in the suggested nomenclature to FTLD-FUS (Mackenzie et al. 2010). These cases have a broad phenotype which may overlap with both corticobasal degeneration and motor neurone disease, and the pathological diagnosis may be unsuspected ante mortem (Menon et al. 2011).

Late diagnosis of FTLD is a common problem, even following contact with medical services, with an average delay of nearly 3 years in a Scandinavian series in which nearly three-quarters of patients initially received a non-dementia diagnosis (Rosness et al. 2008). Such delays are of particular frustration to caregivers who are often sure something is wrong. An integrated care pathway (ICP) has been developed in the hope of hastening FTLD diagnosis (see Sect. 10.6; Davies and Larner 2010).

9.3 Dementia with Lewy Bodies, Parkinson's Disease Dementia, REM Sleep Behaviour Disorder, and Other Parkinsonian Disorders (PSP, CBD)

Dementia with Lewy bodies (DLB) is claimed by some authors to be the second most common of the neurodegenerative dementias, but has been encountered relatively rarely in CFC, in contrast to other centres, although this low prevalence does appear to fall within the range of prevalence estimates for the general population (Zaccai et al. 2005).

Based on the greater impairment of attentional and visuospatial function, and the relative preservation of orientation and memory function, in DLB as compared to AD (e.g. Salmon et al. 1996; Downes et al. 1998; Ballard et al. 1999; Calderon et al. 2001), Ala et al. (2002) derived a weighted subscore from the Mini-Mental State Examination (MMSE) for DLB diagnosis. Prospective use of the Ala subscore (and its modifications derived from the ACE and MoCA) has not proved of particular use in CFC for prospective diagnosis (see Sects. 4.1.1.1, 4.1.5.2, and 4.1.8.1).

DLB may sometimes be mistaken for CJD (e.g. Haïk et al. 2000; Tschampa et al. 2001; Van Everbroeck et al. 2004; Larner 2006b; Du Plessis and Larner 2008), not least because rapidly progressive instances of DLB have been described (Momjian-Mayor et al. 2006; Gaig et al. 2011). One differential diagnostic clue is that the visual hallucinations of DLB are generally well formed (animals, people) compared with the rather elemental visual hallucinations (colours, shapes) which may occur in CJD (Du Plessis and Larner 2008). EEG findings of periodic sharp wave complexes may sometimes be found in DLB, adding to the phenotypic overlap (see Sect. 7.4.1; Doran and Larner 2004b). Orthostatic hypotension may be a feature of DLB, sometimes occurring initially in isolation and prompting a diagnosis of pure autonomic failure (Larner et al. 2000). Orthostatic hypotension may predispose to repeated syncope, one of the supporting features in DLB diagnostic criteria (McKeith et al. 2005, 2017). A case of fragile X-associated tremor/ataxia syndrome (FXTAS) which was mistaken for DLB (parkinsonian signs, possible REM sleep behaviour disorder, and frontal executive type cognitive impairments) has also been seen (Connon and Larner 2017, Case 2).

Parkinson's disease dementia (PDD) is likely to become an increasing problem, since most patients with PD followed longitudinally develop some evidence of cognitive decline over time (Reid et al. 2011; Williams-Gray et al. 2013). Few patients with PDD have been seen in CFC presumably because they are managed in either dedicated movement disorder clinics or, because of the neuropsychiatric problems, psychiatry clinics. Instruments such as the MMP and MoCA (see Sects. 4.1.2 and 4.1.8) may be useful for the detection of cognitive impairments in PDD.

REM sleep behaviour disorder (REMBD) occasionally presents to the cognitive clinic (Case Study 5.2). Presence of REMBD, sometimes referred to as "dream enactment", may be a useful clue to the diagnosis of synucleinopathies such as DLB, PDD, and multiple system atrophy (MSA), often preceding by years the diagnosis of the underlying neurological disorder (Boeve et al. 2007). REMBD has now been incorporated amongst the core clinical features in diagnostic criteria for DLB (McKeith et al. 2017). A diagnosis of REMBD should always prompt clinical and cognitive assessment for an underlying condition. REMBD is often amenable to treatment with clonazepam (Larner et al. 2005b).

DLB and PDD are sometimes referred to as "Lewy body dementias" (Walker et al. 2015), in distinction from other parkinsonian syndromes which may be accompanied by neuropsychological impairment as well as movement disorder (Larner 2013a:48–51), but which are characterised pathologically as tauopathies, rather than synucleinopathies, in particular progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Occasional cases of PSP have been seen in CFC; the phenotype has also been seen in association with tau gene mutations (Larner 2009a, 2012c; Larner and Doran 2009a) and in a case of Perry syndrome (Aji et al. 2013a, b), as well as being mistaken for normal pressure hydrocephalus (Schott et al. 2007). PSP has also been reported in patients with the C9orf72 hexanucleotide repeat expansion (Le Ber et al. 2013). Cases of suspected CBD but with other pathological substrates, so called corticobasal syndrome (CBS; Boeve et al. 2003; Doran et al. 2003), are well-recognised (e.g. Menon et al. 2011).

9.4 Vascular Dementia, Vascular Cognitive Impairment

Vascular dementia (VaD) and vascular cognitive impairment (VCI) are recognised to be heterogeneous entities with respect to both pathology and pathogenesis (Wahlund et al. 2009; Gorelick et al. 2011), including vasculopathic and thrombotic disorders. Mixed dementia, defined as the coexistence of AD and VaD (Langa et al. 2004), may be the most common neuropathological substrate of dementia (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study 2001; Schneider et al. 2009). Cerebrovascular disease may modulate the clinical expression of AD pathology (Snowdon et al. 1997). The old dichotomy of AD and VaD is now superseded by an integrative approach to aetiology with a continuum or spectrum running from pure boundary cases through entities such as "AD with vascular lesions" and "VaD with AD changes". VCI is analogous to MCI, representing a syndrome of cognitive impairment short of dementia as a consequence of vascular brain injury (Bowler and Hachinski 2003). A category of mild cognitive dysfunction, MCD, has also been proposed for cognitive impairment short of dementia in white matter disorders such as SLE (Kozora and Filley 2011; Filley 2012:391–2).

Cases of pure vascular dementia, such as subcortical ischaemic vascular dementia (Román et al. 2002), have rarely been encountered in CFC. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) has been seen on occasion (see Sect. 7.3.3; Case Study 7.7; Doran and Larner 2009).

Though unusual, intracranial dural arteriovenous fistula (dAVF) must also be considered amongst reversible causes of vascular cognitive impairment and dementia. Experience with intracranial dAVF seen at CFC (Wilson et al. 2010; Randall et al. 2015) has shown impairments in attention, memory and executive functioning. One common clinical feature which was not fully captured by the standard neuropsychological and cognitive tests administered was the impairment in cognitive processing speed, suggestive of subcortical involvement. This may be a reflection of the marked prolongation of cerebral transit time seen with radiological contrast studies, late angiographic views indicating that venous drainage of brain parenchyma may be considerably delayed. Of note, despite marked cognitive improvement after endovascular fistula embolisation, residual deficits were evident in some cognitive domains even up to 2 years after treatment, presumably related to irreversible structural changes in the brain, such as complete or partial venous infarction of tissues subjected to chronic venous hypertension.

9.5 Prion Disease (Prionoses)

Prion diseases have attracted much attention in recent years, not least because of their novel biology as sporadic, inherited, and iatrogenic conditions (Collinge 2001), and despite their clinical rarity. Variant Creutzfeldt-Jakob disease (CJD) has been viewed as a major public health issue.

Case Study 9.1: Clinical diagnosis: sporadic CJD
A 75 year-old lady was brought to CFC by ward staff from another hospital; she was unable to give any history. Previously very fit and active, she had apparently developed cognitive problems over a 5-month period. A month or so after symptom onset her MMSE was 21/30 and a CT brain scan was reported to be normal. However her decline was relentless, requiring hospital admission because of failure to cope at home. Aside from some myoclonic jerks her neurological examination was normal. A diagnosis of sporadic CJD was suspected on the basis of the rapid decline and the myoclonic jerks. Subsequent EEG was abnormal with a non-specific slow background but no triphasic waves were seen. CSF analysis was positive for 14–3-3 protein.

In addition to the classical presentation of rapidly progressive cognitive decline with myoclonus (Case Study 9.1), prion disorders can present with multifocal symptoms including cerebellar, visual cortical, extrapyramidal, pyramidal, and psychiatric symptoms (Nakatani et al. 2016), some examples of which have been seen in CFC, including visual hallucinations (Du Plessis and Larner 2008), psychiatric presentations (Ali et al. 2013; Williamson and Larner 2016), stroke-like symptoms (Ghadiri-Sani et al. 2015), and myelopathy (Ziso et al. 2017).

An audit of prion disease cases seen at CFC over a 12-year period (1990–2001 inclusive) (Larner and Doran 2004) found that 82 patients with suspected CJD were referred from the Mersey Region to the National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU) in Edinburgh; 65 referrals were made after 1995 when the UK epidemic of variant CJD (vCJD) began (Will et al. 1996). Sixty-six patients (80%) presented initially to non-neurologists. Forty-four referrals were of in-patients at WCNN, usually transferred from district general hospitals by visiting neurologists. Thirty-eight cases were referred to NCJDSU directly from district general hospitals or from Alder Hey Children's Hospital, Liverpool. Prion disease was confirmed pathologically in 43 of 82 referrals, giving an overall diagnostic accuracy of 0.52. Of the confirmed prion disease cases, 33 had sporadic CJD, 8 had vCJD (e.g. Silverdale et al. 2000; Lorains et al. 2001), and 2 had iatrogenic disease; there were no familial cases. Of the non-prion cases (39), eight were found to have alternative diagnoses only at postmortem, principally AD and DLB (see Sects. 9.1 and 9.3). Autoimmune encephalitides may also mimic CJD (Schott et al. 2003; Geschwind et al. 2008).

Although diagnosis of prion disease may be straightforward (e.g. Case Study 9.1), there may be difficulties if the phenotype is unusual, for example with prominent parkinsonism and orthostatic hypotension (Du Plessis and Larner 2008), or there is a long prodrome of psychiatric symptoms (Ali et al. 2013; Williamson and Larner 2016). Neuropsychiatric features, once claimed to be a distinguishing feature of vCJD, are in fact quite common in sCJD, even early in the disease course (Wall et al. 2005; Rabinovici et al. 2006). They were also prominent in another patient seen in CFC whose non-identical twin was discordant for the disease. Patient

age may also confuse diagnostic thinking: although sporadic CJD is usually a disorder of older people some variants may occur in young people (e.g. Williamson and Larner 2016), and although variant CJD typically occurs in younger patients it may also affect older individuals (Lorains et al. 2001; el Tawil et al. 2015). Rapidly progressive cognitive decline from causes other than CJD may sometimes lead to diagnostic confusion, including on occasion brain tumour (Case Study 7.1), dural AV fistula (Randall et al. 2015), and rapidly progressive DLB (Sect. 9.3) or AD (Jayaratnam et al. 2008; Schmidt et al. 2010). Some forms of CJD may progress slowly (Ali et al. 2013).

Whether subclinical vCJD, which may be more common than previously thought (Gill et al. 2013), might manifest with different clinical features, particularly in patients valine homozygous at PRNP gene codon 129, remains to be seen.

9.6 Learning Disability; Down Syndrome

The assessment of individuals with learning disability remains problematic for most neurologists, since generally they have received little or no training in this area, far less developed any claims to expertise. Most patients with learning disability are referred to neurology services because of episodes of loss of or impaired consciousness which may reflect epileptic seizures (see Sect. 8.2.3) (Adab and Larner 2006; Larner 2007, 2009b, 2011a; Sells and Larner 2011; Milburn-McNulty and Larner 2018), although occasional patients are sent to CFC with possible progression of cognitive dysfunction. Cases of learning disability in the context of neurofibromatosis-1 (NF1), fragile X syndrome, infantile Refsum disease, and Sotos syndrome have sometimes been seen (Larner 2008e; Milburn-McNulty and Larner 2018).

Many forms of learning disability are inadequately understood at the pathological or aetiological level, but some are better characterised. For example, in those with Down syndrome (trisomy 21), cognitive decline often reflects the inevitable development of Alzheimer type pathology, first reported by Struwe in 1929 (see also Mrak and Griffin 2004; Prasher 2005). Down syndrome patients have on occasion been seen in CFC (Larner 2007; Case Study 7.4). A syndrome of myoclonic epilepsy may be typical of Down syndrome (De Simone et al. 2010), and examples have been seen in CFC (Larner 2011a). The exact place of cholinesterase inhibitors in the management of cognitive decline in Down syndrome remains to be defined, but it would seem likely that their greatest benefit, if any, might be in the early stages of cognitive decline (Larner 2010c).

9.7 Other Causes of Dementia and Cognitive Impairment

Although some form of cognitive impairment is thought to be common in multiple sclerosis (MS), few patients have been seen in CFC other than with an unusual phenotype (Case Study 9.2: Young et al. 2008), presumably because most MS patients with cognitive issues are managed within dedicated clinics (as for cognitive

Case Study 9.2: Clinical diagnosis: Multiple sclerosis

A patient presented in his early 30s with poor visual acuity, eye movement disorder, spastic quadriparesis and cognitive impairment characterised by poor memory and lack of insight. MR brain imaging showed typical periventricular white matter changes of multiple sclerosis but CSF oligoclonal bands were absent. Over a 10-year period of follow-up, cognitive impairment progressed with a subcortical pattern of dementia; MR showed brain atrophy as well as white matter changes. Secondary generalised tonic-clonic seizures developed at age 40, requiring escalating doses of antiepileptic drugs. Interictal EEG showed generalised slow wave activity but no focal changes.

Three of the patients four siblings were also diagnosed with MS (age range at diagnosis 28–35 years), all complicated with cognitive impairment progressing to dementia; one also had epilepsy from childhood. All siblings died (age at death 35–42 years); one had a post-mortem examination of the brain which showed definite MS and no other pathological changes.

The proband was negative for PTPRC (CD45) mutation reported in familial MS (Nicholas et al. 2003) and also for presenilin-1 (PSEN1) mutations which are associated with early-onset Alzheimer's disease, sometimes complicated with spastic paraparesis, white matter changes and epilepsy (Larner and Doran 2006, 2009b; Larner 2011b, 2013c).

impairment in the context of cerebrovascular disease and movement disorders). Currently there seems to be no compelling evidence for cognitive benefit in MS for cognitive rehabilitation, symptomatic drugs, or disease modifying treatments (Amato et al. 2013).

As previously mentioned (see Sect. 8.1.1.1), alcohol-related cognitive problems have rarely been seen in CFC. Likewise, cognitive disorders associated with HIV infection have rarely been referred. Presumably this reflects local availability of dedicated services for these conditions. There has been a dramatic decline in HIV dementia incidence since the advent of highly active antiretroviral therapy (HAART) with nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, but prevalence of HIV-associated neurocognitive disorders has increased because of improved life expectancy. In addition to viral burden, persistent neuroinflammation and AD-like neurodegenerative changes may contribute to HIV-associated cognitive problems, requiring additional therapeutic approaches (Clifford 2017).

Structural brain lesions causing potentially reversible dementia or cognitive decline have rarely been seen (Larner 2013d; Case Study 7.1). There have been occasional cases of brain tumour (though not always relevant to cognitive decline: Abernethy Holland and Larner, 2008) and dural arteriovenous fistula (see Sect. 9.4), but no instances of subdural haematoma or normal pressure hydrocephalus (see Case Study 7.2). Indeed, two patients diagnosed elsewhere with, and shunted for,

"normal pressure hydrocephalus" eventually proved to have frontotemporal lobar degeneration (Davies and Larner 2010).

Other causes of dementia and cognitive impairment have occasionally been encountered in CFC. Because of the relatively young age of the patients referred (see Sect. 1.3.1), genetic and metabolic causes of dementia may be seen, since these are much more common in younger cohorts (Doran 1997; Rossor et al. 2010; Davies et al. 2011). Huntington's disease (HD) has very rarely been seen in CFC, most cases presenting to general neurology or movement disorders clinics (Larner 2008e; Ziso et al. 2015). Other conditions seen on occasion in CFC include X-linked adrenoleukodystrophy (X-ALD) (Larner 2003), Perry syndrome (Aji et al. 2013a, b), and relapsing polychondritis (Ellis et al. 2017).

9.8 Summary and Recommendations

The differential diagnosis of disorders causing cognitive symptoms is potentially very broad (Larner 2013a), as with cognitive syndromes (Chap. 8), and hence potentially daunting. However, the number of commonly encountered conditions is relatively circumscribed, with AD accounting for the majority of cases (many more will have subjective memory complaints or functional cognitive disorder; Sect. 8.3). Definition of specific cognitive syndromes (e.g. amnesia, aphasia, dysexecutive syndrome) may guide differential diagnosis of specific dementia syndromes. This is preferable to the old binary, probabilistic diagnostic strategy (e.g. McKhann et al. 1984), which was dependent on the presence of dementia before a diagnosis of AD could be made. Newer criteria (e.g. Dubois et al. 2007, 2014; Albert et al. 2011; Sperling et al. 2011) seek to establish AD diagnosis earlier in the disease course at a time when intervention with disease-modifying treatment might stand a greater chance of success (Aisen et al. 2011). As robust biomarkers of disease are defined, a biological or pathogenetic definition of disease may be possible, as is already the case for those few families harbouring deterministic genetic mutations. Specific diagnosis is the first step to specific therapy, although currently available treatment modalities have limited efficacy (see Chap. 10).

References

Abernethy Holland AJ, Larner AJ. Central nervous system/brain tumour 2-week referral guidelines: prospective 3-year audit. Clin Oncol. 2008;20:201–2.

Adab N, Larner AJ. Adult-onset seizure disorder in 18q deletion syndrome. J Neurol. 2006;253:527–8.

Aisen PS, Andrieu S, Sampaio C, et al. Report of the task force on designing clinical trials in early (predementia) AD. Neurology. 2011;76:280–6.

Aji BM, Medley G, O'Driscoll K, Larner AJ, Alusi SH. Perry syndrome: a disorder to consider in the differential diagnosis of parkinsonism. J Neurol Sci. 2013a;330:117–8.

Aji BM, Fratalia L, Alusi SH, Larner AJ. Perry syndrome: more common than previously thought and associated with early cognitive impairment. Abstract Book. Integration by Translation. XX

World Congress on Parkinson's Disease and Related Disorders, Geneva, Switzerland, 8–11 December; 2013b. p. 106–7 (abstract 393).
Ala T, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ. The Mini-Mental State exam may help in the differentiation of dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry. 2002;17:503–9.
Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270–9.
Ali R, Barborie A, Larner AJ, White RP. Psychiatric presentation of sporadic Creutzfeldt-Jakob disease: a challenge to current diagnostic criteria. J Neuropsychiatry Clin Neurosci. 2013;25:335–8.
Amato MP, Langdon D, Montalban X, et al. Treatment of cognitive impairment in multiple sclerosis: position paper. J Neurol. 2013;260:1452–68.
American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed., text revison (DSM-IV-TR). Washington: American Psychiatric Association; 2000.
Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG, Burn DJ, Keir G, Larner AJ, Mann DM, Perry R. Frontotemporal dementia in elderly individuals. Arch Neurol. 2012;69:1052–60.
Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG, Burn DJ, Keir G, Larner AJ, Mann DM, Perry R. Elderly individuals with FTLD. JAMA Neurol. 2013;70:412–3.
Ballard CG, Ayre G, O'Brien J, et al. Simple standardised neuropsychological assessments aid in the differential diagnosis of dementia with Lewy bodies from Alzheimer's disease and vascular dementia. Dementia Geriatr Cogn Disord. 1999;10:104–8.
Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol. 2003;54(Suppl5):S15–9.
Boeve BF, Silber MH, Saper CB, et al. Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain. 2007;130:2770–88.
Boeve BF, Bovlan KB, Graff-Radford NR, et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. Brain. 2012;135:765–83.
Bowler JV, Hachinski V, editors. Vascular cognitive impairment: preventable dementia. Oxford: Oxford University Press; 2003.
Burns JM, Morris JC. Mild cognitive impairment and early Alzheimer's disease. Detection and diagnosis. Chichester: Wiley; 2008.
Cairns NJ, Grossman M, Arnold SE, et al. Clinical and neuropathologic variation in neuronal intermediate filament inclusion disease. Neurology. 2004;63:1376–84.
Calderon J, Perry R, Erzinclioglu S, Berrios GE, Dening T, Hodges JR. Perception, attention and working memory are disproportionately impaired in dementia with Lewy bodies compared with Alzheimer's disease (AD). J Neurol Neurosurg Psychiatry. 2001;70:157–64.
Caselli RJ, Tariot PN. Alzheimer's disease and its variants: a diagnostic and therapeutic guide. Oxford: Oxford University Press; 2010.
Clifford DB. HIV-associated neurocognitive disorder. Curr Opin Infect Dis. 2017;30:117–22.
Collinge J. Prion diseases of humans and animals: their causes and molecular basis. Annu Rev Neurosci. 2001;24:519–50.
Connon P, Larner AJ. Fragile X-associated tremor/ataxia syndrome: cognitive presentations. Br J Hosp Med. 2017;78:230–1.
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.
Davies M, Larner AJ. Clinical misdiagnosis of Alzheimer's disease: getting it wrong again. Eur J Neurol. 2009;16(Suppl3):351. (abstract 2036).
Davies M, Larner AJ. Frontotemporal dementias: development of an integrated care pathway through an experiential survey of patients and carers. Int J Care Pathways. 2010;14:65–9.
Davies RR, Doran M, Larner AJ. Early-onset dementia. Prog Neurol Psychiatry. 2011;15(4):12–6.

De Mendonca A, Ribeiro F, Guerreiro M, Garcia C. Frontotemporal mild cognitive impairment. J Alzheimers Dis. 2004;6:1–9.
De Simone R, Puig XS, Gélisse P, Crespel A, Genton P. Senile myoclonic epilepsy: delineation of a common condition associated with Alzheimer's disease in Down syndrome. Seizure. 2010;19:383–9.
DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucelotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72:245–56.
Dickerson BC, editor. Hodges' frontotemporal dementia. 2nd ed. Cambridge: Cambridge University Press; 2016.
Dickerson B, Atri A, editors. Dementia. Comprehensive principles and practice. Oxford: Oxford University Press; 2014.
Dobson-Stone C, Hallupp M, Bartley L, et al. C9ORF72 repeat expansion in clinical and neuropathologic frontotemporal dementia cohorts. Neurology. 2012;79:995–1001.
Doran M. Diagnosis of presenile dementia. Br J Hosp Med. 1997;58:105–10.
Doran M, Larner AJ. Prominent behavioural and psychiatric symptoms in early-onset Alzheimer's disease in a sib pair with the presenilin-1 gene R269G mutation. Eur Arch Psychiatry Clin Neurosci. 2004a;254:187–9.
Doran M, Larner AJ. EEG findings in dementia with Lewy bodies causing diagnostic confusion with sporadic Creutzfeldt-Jakob disease. Eur J Neurol. 2004b;11:838–41.
Doran M, Larner AJ. Familial Alzheimer's disease due to presenilin-1 Y115C mutation. J Neurol. 2006;253(Suppl 2):II91. (Poster P359).
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, Enevoldson TP, Fletcher NA, Ghadiali E, Larner AJ. Pathological heterogeneity of clinically diagnosed corticobasal degeneration. J Neurol Sci. 2003;216:127–34.
Doran M, Enevoldson TP, Ghadiali EJ, Larner AJ. Mills syndrome with dementia: broadening the phenotype of FTD/MND. J Neurol. 2005;252:846–7.
Downes JJ, Priestley NM, Doran M, Ferran J, Ghadiali E, Cooper P. Intellectual, mnemonic and frontal functions in dementia with Lewy bodies: a comparison with early and advanced Parkinson's disease. Behav Neurol. 1998;11:173–83.
Du Plessis DG, Larner AJ. Phenotypic similarities causing clinical misdiagnosis of pathologically-confirmed sporadic Creutzfeldt-Jakob disease as dementia with Lewy bodies. Clin Neurol Neurosurg. 2008;110:194–7.
Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007;6:734–46.
Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014;13:614–29. [Erratum Lancet Neurol. 2014;13:757].
el Tawil S, Mackay G, Davidson L, Summers D, Knight R. Will R. Variant Creutzfeldt-Jakob disease in older patients. J Neurol Neurosurg Psychiatry. 2015;86:1279–80.
Ellis RJ, Mbizvo GK, Jacob A, Doran M, Larner AJ. Relapsing polychondritis complicated by cognitive dysfunction: two distinct clinical phenotypes? Int J Neurosci. 2017;127:124–34.
Filley CM. The behavioral neurology of white matter. 2nd ed. Oxford: Oxford University Press; 2012.
Gaig C, Valledeoriola F, Gelpi E, et al. Rapidly progressive diffuse Lewy body disease. Mov Disord. 2011;26:1316–23.
Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking Creutzfeldt-Jakob disease. Arch Neurol. 2008;65:1341–6.
Ghadiri-Sani M, Sekhar A, Larner AJ. A stroke of ill-fortune: an unexpected diagnosis following a stroke-like event. Br J Hosp Med. 2015;76:54–5.
Gill ON, Spencer Y, Richard-Loendt A, et al. Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. BMJ. 2013;347:f5675.

Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:2672–713.
Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76:1006–14.
Haïk S, Brandel J-P, Sazdovitch V, et al. Dementia with Lewy bodies in a neuropathologic series of suspected Creutzfeldt-Jakob disease. Neurology. 2000;55:1401–4.
Hancock P, Larner AJ. A case of frontotemporal lobar degeneration with MND. Prog Neurol Psychiatry. 2008;12(3):15–8.
Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry. 2003;74:1206–9.
Hodges JR, editor. Frontotemporal dementia syndromes. Cambridge: Cambridge University Press; 2007.
Hsiung GY, DeJesus-Hernandez M, Feldman HH, et al. Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Brain. 2012;135:709–22.
Jayaratnam S, Khoo AK, Basic D. Rapidly progressive Alzheimer's disease and elevated 14-3-3 proteins in cerebrospinal fluid. Age Ageing. 2008;37:467–9.
Kozora E, Filley CM. Cognitive dysfunction and white matter abnormalities in systemic lupus erythematosus. J Int Neuropsychol Soc. 2011;17:385–92.
Kurlan R, editor. Handbook of secondary dementias. New York: Taylor and Francis; 2006.
Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA. 2004;292:2901–8.
Larner AJ. Adult-onset dementia with prominent frontal lobe dysfunction in X-linked adrenoleukodystrophy with R152C mutation in ABCD1 gene. J Neurol. 2003;250:1253–4.
Larner AJ. Getting it wrong: the clinical misdiagnosis of Alzheimer's disease. Int J Clin Pract. 2004;58:1092–4.
Larner AJ. Frequency of agnosic, apraxic and aphasic presentations of Alzheimer's disease. Eur J Neurol. 2006a;13(Suppl 2):193. (abstract P2098).
Larner AJ. Creutzfeldt-Jakob disease misdiagnosed as dementia with Lewy bodies: response to the paper by Kraemer et al. (J Neurol 2005;252:861-2). J Neurol. 2006b;253:960.
Larner AJ. Down syndrome in the neurology clinic: Too much? Too little? Too late? Down Syndr Res Pract. 2007;12:69–71.
Larner AJ. Neuropsychological neurology: the neurocognitive impairments of neurological disorders. Cambridge: Cambridge University Press; 2008a.
Larner AJ. Alzheimer's disease. In: Cappa SF, Abutalebi J, Démonet JF, Fletcher PC, Garrard P, editors. Cognitive neurology: a clinical textbook. Oxford: Oxford University Press; 2008b. p. 199–227.
Larner AJ. Mutation negative early-onset familial Alzheimer disease: consider screening for tau gene mutations. Alzheimer Dis Assoc Disord. 2008c;22:194–5.
Larner AJ. Delusion of pregnancy in frontotemporal lobar degeneration with motor neurone disease (FTLD/MND). Behav Neurol. 2008d;19:199–200.
Larner AJ. Monogenic Mendelian disorders in general neurological practice. Int J Clin Pract. 2008e;62:744–6.
Larner AJ. A 50-year old man with deteriorating cognitive function and impaired movement. PLoS Med. 2009a;6(1):e1000019.
Larner AJ. Deletion of 18q. In: Lang F, editor. Encyclopedia of molecular mechanisms of disease (3 volumes). Berlin: Springer; 2009b. p. 503–4.
Larner AJ. What's new in dementia? Clin Med. 2010a;10:391–4.
Larner AJ. Neurological signs: lycanthropy. Adv Clin Neurosci Rehabil. 2010b;10(4):50.
Larner AJ. Cholinesterase inhibitors—beyond Alzheimer's disease. Exp Rev Neurotherapeutics. 2010c;10:1699–705.
Larner AJ. Senile myoclonic epilepsy in Down syndrome. Seizure. 2011a;20:512.
Larner AJ. Presenilin 1 mutation Alzheimer's disease: a genetic epilepsy syndrome? Epilepsy Behav. 2011b;21:20–2.

Larner AJ. Progressive nonfluent aphasia in a bilingual subject: relative preservation of mother tongue. J Neuropsychiatry Clin Neurosci. 2012a;24:E9–10.
Larner AJ. Intrafamilial clinical phenotypic heterogeneity with progranulin gene p.Glu498fs mutation. J Neurol Sci. 2012b;316:189–90.
Larner AJ. FTDP-17: two-year follow-up of motor and cognitive features following autologous stem cell transplantation. J Neuropsychiatry Clin Neurosci. 2012c;24:E1–2.
Larner AJ. Neuropsychological neurology: the neurocognitive impairments of neurological disorders. 2nd ed. Cambridge: Cambridge University Press; 2013a.
Larner AJ. Delusion of pregnancy: a case revisited. Behav Neurol. 2013b;27:293–4.
Larner AJ. Presenilin-1 mutations in Alzheimer's disease: an update on genotype-phenotype relationships. J Alzheimers Dis. 2013c;37:653–9.
Larner AJ. Cerebral mass lesions presenting in a cognitive disorders clinic. Br J Hosp Med. 2013d;74:694–5.
Larner AJ. Neurological update: dementia. J Neurol. 2014;261:635–9.
Larner AJ. FRONTIER Executive Screen (FES). Poster P0034, Association of British Neurologists Annual Meeting, Liverpool, 3–5 May, 2017.
Larner AJ, Doran M. Prion disease at a regional neuroscience centre: retrospective audit. J Neurol Neurosurg Psychiatry. 2004;75:1789–90.
Larner AJ, Doran M. Clinical phenotypic heterogeneity of Alzheimer's disease associated with mutations of the presenilin-1 gene. J Neurol. 2006;253:139–58.
Larner AJ, Doran M. Clinical heterogeneity associated with tau gene mutations. Eur Neurol Rev. 2009a;3(2):31–2.
Larner AJ, Doran M. Genotype-phenotype relationships of presenilin-1 mutations in Alzheimer's disease: an update. J Alzheimers Dis. 2009b;17:259–65.
Larner AJ, du Plessis DG. Early-onset Alzheimer's disease with presenilin-1 M139V mutation: clinical, neuropsychological and neuropathological study. Eur J Neurol. 2003;10: 319–23.
Larner AJ, Gardner-Thorpe C. Mills syndrome with dementia. Eur Neurol J. 2012;4(2):29–32.
Larner AJ, Mathias CJ, Rossor MN. Autonomic failure preceding dementia with Lewy bodies. J Neurol. 2000;247:229–31.
Larner AJ, Brookfield K, Flynn A, Ghadiali EJ, Smith ETS, Doran M. The cerebral metabolic topography of semantic dementia. J Neurol. 2005a;252(Suppl 2):II106. (abstract P399).
Larner AJ, Hart IK, Cresswell P, Doran M. REM sleep behaviour disorder in the cognitive function clinic. Eur J Neurol. 2005b;12(Suppl2):218. (abstract 2211).
Larner AJ, Ray PS, Doran M. The R269H mutation in presenilin-1 presenting as late-onset autosomal dominant Alzheimer's disease. J Neurol Sci. 2007;252:173–6.
Le Ber I, Camuzat A, Guillot-Noel L, et al. C9ORF72 repeat expansions in the frontotemporal dementias spectrum of diseases: a flow-chart for genetic testing. J Alzheimers Dis. 2013;34:485–99.
Lindquist SG, Holm IE, Schwartz M, et al. Alzheimer disease-like clinical phenotype in a family with FTDP-17 caused by a MAPT R406W mutation. Eur J Neurol. 2008;15:377–85.
Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012;27:349–56.
Lorains JW, Henry C, Agbamu DA, Rossi M, Bishop M, Will RG, Ironside JW. Variant Creutzfeldt-Jakob disease in an elderly patient. Lancet. 2001;357:1339–40.
Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta Neuropathol. 2010; 119:1–4.
Mahoney CJ, Beck J, Rohrer JD, et al. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. Brain. 2012;135:736–50.
Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucelotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012;11:323–30.

McCormick LJ, Larner AJ. "Could you repeat that?": not always a hearing problem! Br J Hosp Med. 2018;79. (in press)
McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology. 2005;65:1863–72.
McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. Neurology. 2017;89:88–100.
McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Service Task forces on Alzheimer's disease. Neurology. 1984;34:939–44.
McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–9.
Mendez MF, Cummings JL. Dementia: a clinical approach. 3rd ed. Philadelphia: Butterworth-Heinemann; 2003.
Menon R, Barborie A, Jaros E, Mann DMA, Ray PS, Larner AJ. What's in a name? Neuronal intermediate filament inclusion disease (NIFID), frontotemporal lobar degeneration-intermediate filament (FTLD-IF) or frontotemporal lobar degeneration-fused in sarcoma (FTLD-FUS)? J Neurol Neurosurg Psychiatry. 2011;82:1412–4.
Milburn-McNulty P, Larner AJ. Episodic loss of consciousness: when targeted genetic testing contributes to diagnosis. Prog Neurol Psychiatry. 2018;22. (in press)
Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia—meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009;119:252–65.
Momjian-Mayor I, Pizzolato GP, Burkhardt K, et al. Fulminant Lewy body disease. Mov Disord. 2006;21:1748–51.
Mrak RE, Griffin WS. Trisomy 21 and the brain. J Neuropathol Exp Neurol. 2004;63:679–85.
Nakatani E, Kanatani Y, Kaneda H, et al. Specific clinical signs and symptoms are predictive of clinical course in sporadic Creutzfeldt-Jakob disease. Eur J Neurol. 2016;23:1455–62.
Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998;51:1546–54.
Neumann M, Roeber S, Kretzschmar HA, Rademakers R, Baker M, Mackenzie IRA. Abundant FUS pathology in neuronal intermediate filament inclusion disease. Acta Neuropathol. 2009;118:605–16.
Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study. Lancet. 2001;357:169–75.
Nicholas RS, Partridge J, Donn RP, Hawkins C, Boggild MD. The role of the PTPRC (CD45) mutation in the development of multiple sclerosis in the North West region of the United Kingdom. J Neurol Neurosurg Psychiatry. 2003;74:944–5.
Petersen RC, editor. Mild cognitive impairment. Aging to Alzheimer's disease. Oxford: Oxford University Press; 2003.
Prasher VP. Alzheimer's disease and dementia in Down syndrome and intellectual disabilities. Oxford: Radcliffe Publishing; 2005.
Rabinovici GD, Wang PN, Levin CM, et al. First symptom in sporadic Creutzfeldt-Jakob disease. Neurology. 2006;66:286–7.
Randall A, Ellis R, Hywel B, Davies RR, Alusi SH, Larner AJ. Rapid cognitive decline: not always Creutzfeldt-Jakob disease. J R Coll Phys Edinb. 2015;45:209–12.
Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456–77.
Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. Neurology. 2002;58:1615–21.
Reid WG, Hely MA, Morris JG, Loy C, Halliday GM. Dementia in Parkinson's disease: a 20-year neuropsychological study (Sydney Multicentre Study). J Neurol Neurosurg Psychiatry. 2011;82:1033–7.

Renton AE, Majounie E, Waite A, et al. A hexanucelotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011;72:257–68.
Rohrer JD, Guerriero R, Vandrovcova J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology. 2009;73:1451–6.
Román GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol. 2002;1:426–36.
Rosness TA, Haugen PK, Passant U, Engedal K. Frontotemporal dementia—a clinically complex diagnosis. Int J Geriatr Psychiatry. 2008;23:837–42.
Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. Lancet Neurol. 2010;9:793–806.
Salmon DP, Galasko D, Hansen LA, et al. Neuropsychological deficits associated with diffuse Lewy body disease. Brain Cogn. 1996;31:148–65.
Sathasivam S, Doran M, Larner AJ. Frontotemporal lobar degeneration with motor neurone disease (FTLD/MND): presentations in psychiatric practice. Int J Psychiatry Clin Pract. 2008;12:138–41.
Schmidt C, Redyk K, Meissner B, et al. Clinical features of rapidly progressive Alzheimer's disease. Dement Geriatr Cogn Disord. 2010;29:371–8.
Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. J Alzheimers Dis. 2009;18:691–701.
Schott JM, Warren JD, Rossor MN. The uncertain nosology of Hashimoto encephalopathy. Arch Neurol. 2003;60:1812.
Schott JM, Williams DR, Butterworth RJ, Janssen JC, Larner AJ, Holton JL, Rossor MN. Shunt responsive progressive supranuclear palsy? Mov Disord. 2007;22:902–3.
Seelaar H, Kamphorst W, Rosso SM, et al. Distinct genetic forms of frontotemporal dementia. Neurology. 2008;71:1220–6.
Sells RA, Larner AJ. Genetic causes of learning disability with epilepsy in the general neurology clinic. Eur J Neurol. 2011;18(Suppl2):184. (abstract P1315).
Silverdale M, Leach JP, Chadwick DW. New variant Creutzfeldt-Jakob disease presenting as localization-related epilepsy. Neurology. 2000;54:2188.
Simon-Sanchez J, Dopper EG, Cohn-Hokke PE, et al. The clinical and pathological phenotype of C9ORF72 hexanucleotide repeat expansions. Brain. 2012;135:723–35.
Snowden JS, Neary D, Mann DMA. Fronto-temporal lobar degeneration. Fronto-temporal dementia, progressive aphasia, semantic dementia. New York: Churchill Livingstone; 1996.
Snowden JS, Rollinson S, Thompson JC, et al. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Brain. 2012;135:693–708.
Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer's disease. The Nun Study. JAMA. 1997;277:813–7.
Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:280–92.
Struwe F. Histopathologische Untersuchungen über entstehung und wesen der senile Plaques. Zeitschrift für die gesamte Neurologie und Psychiatrie. 1929;122:291–307.
Tschampa HJ, Neumann M, Zerr I, et al. Patients with Alzheimer's disease and dementia with Lewy bodies mistaken for Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry. 2001;71:33–9.
Van Everbroeck B, Dobbeleir I, De Waele M, De Deyn P, Martin J-J, Cras P. Differential diagnosis of 201 possible Creutzfeldt-Jakob disease patients. J Neurol. 2004;251:298–304.
Varma AR, Snowden JS, Lloyd JJ, et al. Evaluation of the NINCDS-ADRDA criteria in the differentiation of Alzheimer's disease and frontotemporal dementia. J Neurol Neurosurg Psychiatry. 1999;66:184–8.
Wahlund L-O, Erkinjuntti T, Gauthier S, editors. Vascular cognitive impairment in clinical practice. Cambridge: Cambridge University Press; 2009.
Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. Lancet. 2015;386:1683–97.

Wall CA, Rummans TA, Aksamit AJ, Krah LE, Pankratz VS. Psychiatric manifestations of Creutzfeldt-Jakob disease: a 25-year analysis. J Neuropsychiatry Clin Neurosci. 2005;17:489–95.

Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. BMJ. 2013;347:f4827.

Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet. 1996;347:921–5.

Williams-Gray CH, Mason SL, Evans JR, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. J Neurol Neurosurg Psychiatry. 2013;84:1258–64.

Williamson J, Larner AJ. Young-onset cognitive decline: not always variant Creutzfeldt-Jakob disease. Eur J Neurol. 2016;23(Suppl 1):368. (abstract P21049).

Wilson M, Doran M, Enevoldson TP, Larner AJ. Cognitive profiles associated with intracranial dural arteriovenous fistula. Age Ageing. 2010;39:389–92.

Young CA, Boggild M, Larner AJ. A familial syndrome of multiple sclerosis, early-onset dementia and epilepsy. Eur J Neurol. 2008;15(Suppl3):142. (abstract P1428).

Zaccai J, McCracken C, Brayne C. A systematic study of prevalence and incidence studies of dementia with Lewy bodies. Age Ageing. 2005;34:561–6.

Ziso B, Marsden D, Alusi S, Larner AJ. "Undifferentiated schizophrenia" revisited. J Neuropsychiatry Clin Neurosci. 2014;26:E62–3.

Ziso B, Larner AJ, Alusi SH. Stuck in the middle: Huntington's disease or not Huntington's disease? J Neuropsychiatry Clin Neurosci. 2015;27:e85–6.

Ziso B, Larner AJ, Aji BM. Suspected cervical myelopathy: an unexpected diagnosis. Br J Hosp Med. 2017;78:50–1.