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NEUROLOGICAL UPDATE

# Neurological update: dementia

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**Abstract** Dementia continues to enjoy a high public and political profile, the latter exemplified by the recent G8 summit meeting declaration to develop a cure or treatment by 2025. This is only likely to be achieved by a deeper understanding of the clinical and pathophysiological phenomena of dementia disorders, many examples of which have appeared in the *Journal of Neurology* in 2013 and which are reviewed here.

**Keywords** Alzheimer's disease · Dementia · Frontotemporal dementias · Parkinsonism · Prion diseases

## Introduction

Dementia is a major global health issue that is likely to impose significant and increasing burdens on individuals and nations in the coming decades [39]. Academic interest in dementia, perhaps at least in part stimulated by increased research funding, continues to escalate with the ultimate hope of discovering treatments to address these clinical and societal burdens. There also appears to be a political will to support this undertaking, as exemplified by a G8 summit meeting in December 2013, which made a commitment to develop a cure or treatment for dementia by 2025.

In this review, recent findings from papers published in the *Journal of Neurology* over the year January-December 2013 are discussed, supplemented as appropriate with publications from elsewhere. To ensure manageability, the focus has been restricted to primary neurodegenerative dementing disorders and the material has been organized according to clinical diagnosis, eschewing matters already discussed in previous reviews that have examined dementia and neuroimaging [3], and Alzheimer's disease [14] and its epidemiology [35].

Cognitive impairment is not, of course, restricted to these canonical "cognitive disorders", but may be seen in many neurological disorders, including those with vascular, inflammatory, metabolic, structural, and infective etiologies [24]. Many papers examining cognitive impairment in such examples of "secondary" dementia have appeared in the *Journal* in 2013, most particularly related to stroke [17, 18, 28], including cortical venous sinus thrombosis [7] and multiple sclerosis [5, 9, 42, 43].

## Alzheimer's disease (AD)

Although typically presenting as an amnesic syndrome, clinical variants of AD are well recognized. These atypical cases may present serious diagnostic challenges, with significant risk of delayed diagnosis if AD is not considered in the differential. Posterior cortical atrophy is one such variant, presenting with visuospatial problems. It may also be associated with a syndrome of logopenia, characterized by anomia, impaired fluency, and word length-dependent deficit [31]. Another possible AD variant is corticobasal syndrome (CBS): it is generally recognized that CBS may be the consequence not only of corticobasal degeneration (CBD) but also of various other underlying pathologies, including AD. A case of CBS with progressive apraxic agraphia with micrographia due to AD has been reported, with AD diagnosis based on brain imaging with Pittsburgh B compound showing evidence for the accumulation of amyloid beta-peptide [44].

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Although first described in progressive supranuclear palsy (PSP), the applause sign (clapping more than three times in response to an instruction to clap three times) may also be observed in AD, although its sensitivity for cognitive impairment is low [1, 19]. The neuropsychological correlates of the applause sign were examined in a study of 105 AD patients with disease of variable severity. The only significant predictive variable was the Stroop test, suggesting that the applause sign correlated with frontal lobe dysfunction [29], as has also been postulated in PSP.

In addition to cognitive symptoms, behavioral features are commonly encountered in AD. One of the most frustrating behavioral symptoms for carers is patient apathy. A voxel-based morphometry study has suggested that apathy in AD patients may be related to atrophy in the ventromedial orbitofrontal cortex and left insula; a similar finding was observed in apathetic patients with PSP [45]. Whether behavioral features of AD are associated with worsening of cognitive function was examined in the ICTUS study, which reported that no cluster based on items in the Neuropsychiatric Inventory (psychotic, affective, behavioral) was found to influence the cognitive course of AD [8].

A variety of investigations may be used to try to confirm or refute a clinical diagnosis of AD. Changes in CSF biomarkers typically seen in AD (reduced amyloid-beta peptide, increased tau) have also be seen in certain CNS infective disorders [22], although these are unlikely to be confused with AD on clinical grounds. Sophisticated imaging of cortical thickness has been reported to differentiate AD and dementia with Lewy bodies [26]. AD biomarkers may also support the diagnosis of mild cognitive impairment due to AD [15], permitting the early diagnosis of AD before dementia intervenes and at a time that therapeutic intervention might be most meaningful.

The genetics of AD has been a subject of immense interest and research endeavor over the past 20 years. AD due to deterministic autosomal dominant mutations is rare, but the discovery of the responsible genes (APP, presenilin 1 and presenilin 2) has given many insights into disease pathogenesis, as well as indicating possible treatment options. Mutations of presenilin 1 (*PSEN1*) are the most commonly identified cause of autosomal dominant AD, the clinical phenotype of which may include features not typically seen in late-onset AD [25]. For example, a clinical phenotype resembling autosomal dominant spinocerebellar ataxia but associated with the *PSEN1* S169L mutation has been reported [6]. Multiple genetic risk factors for AD have been described, of which apolipoprotein E (*APOE*) remains the most significant, possibly acting through an effect on cholesterol metabolism. A meta-analysis examining the association between a single nucleotide T/C polymorphism in intron 2 of the cholesterol-24S-hydroxylase gene (*CYP46A1*) has concluded that this does increase AD risk, an effect strengthened in carriers of the APOE epsilon-4 allele [27].

Although various therapeutic targets have been explored in animal models [40], this has yet to translate into clinically effective treatment for AD, the latest casualty at the phase 3 trial stage being the secretase inhibitor semagacestat [11].

## Parkinson's disease dementia, dementia with Lewy bodies, and other parkinsonian disorders associated with cognitive impairment

The recognition that Parkinson's disease is associated with an increasing prevalence of cognitive impairment over time, contrary to the first impressions of James Parkinson, has been one of the most significant stimuli to research in PD in recent times. Criteria for Parkinson's disease dementia (PDD) formulated under the auspices of the Movement Disorders Society have been examined for their usefulness and limitations in a cohort of 40 PD patients. A preliminary simplified checklist based on the criteria was (unsurprisingly) less sensitive than exhaustive examination for diagnosis of PDD, but specificity was high. The study also noted the utility of the Mattis Dementia Rating Scale for diagnosis of PDD [20].

Cognitive deficits may be apparent in incident PD patients. A 1-year follow-up study of 91 patients noted the change in bradykinesia to be associated with the change in working memory and mental flexibility, while postural instability and gait disturbances were associated with change in visuospatial memory. A fall in phonemic fluency with pramipexole treatment was also noted [10]. Serum epidermal growth factor levels have been proposed as a biomarker for early cognitive impairment in PD, based on a study which found correlations with semantic fluency [36]. An association has also been reported between the presence of orthostatic hypotension and cognitive performance in PD, with worse sustained attention, visuospatial and verbal memory in those with OH, changes that were not related to concurrent cerebrovascular disease [38].

Normal pressure hydrocephalus (NPH) is often categorized with parkinsonian disorders with associated cognitive impairment. Caution about the diagnosis of NPH was suggested by a report of four patients with antemortem diagnosis of NPH who were found at postmortem to have either PD (1) or PSP (3) [30]; another report noted three such cases with ultimate diagnoses of PSP, CBD, and an atypical parkinsonism type unknown [13].

## Frontotemporal lobar degenerations (FTLDs)

Frontotemporal lobar degenerations constitute a group of neurodegenerative disorders that are heterogeneous at the clinical, neuropathological, and genetic levels of analysis. Diagnosis of FTLD may be delayed, in part because of this heterogeneity.

Clinical signs suggestive of FTLD would be therefore welcome. Environmental dependency behaviors such as imitation behavior and utilization behavior have been reported to occur much more frequently in behavioral variant frontotemporal dementia (bvFTD) than in AD, particularly when information is gathered not only from observation of the patient in the clinic but also from caregiver history. Imitation behavior may be exclusive to bvFTD [16]. Environmental dependency behaviors, which may also occur in PSP, may result from dysfunction within a frontoparietal network [23]. Ideomotor apraxia may be more common in the agrammatic variant of primary progressive aphasia (PPA), which is generally categorized with FTLD, than in the logopenic variant of PPA, which is more usually considered to be a variant of AD [2].

The spectrum of presentations of FTLD associated with the C9orf72 hexanucleotide repeat expansion, now recognized to be the most common genetic cause of FTLD, continues to expand, including psychiatric presentations [49]. A patient presenting with bipolar affective disorder has been reported [12]. Mimics of bvFTD include not only psychiatric disorders but also, on rare occasions, structural brain lesions: a case of giant serpentine aneurysm of the anterior cerebral artery presenting as bvFTD has been reported [21].

## Prion diseases

Prion diseases are noteworthy not only for their intriguing pathogenetic mechanisms and variable etiology (sporadic, inherited, iatrogenic) but also for their clinical heterogeneity, which may render diagnosis difficult.

Cases of sporadic Creutzfeldt–Jakob disease (sCJD) may resemble PSP (early falls, vertical supranuclear gaze palsy), particularly those with the MM2 subtype [37]. The PSP phenotype has also been reported in inherited prion disease as a consequence of mutations in the prion protein gene (*PRNP*), specifically R208H [47], this in contrast to a previous report of this mutation, which was characterized clinically by ataxia. A novel *PRNP* mutation, I215V, in a Spanish family was associated with pathological findings of CJD in two cases but of AD in a third [34]. A case of sCJD with isolated spastic monoparesis mimicking motor neurone disease has also been reported [32].

A study of diagnostic investigations in a group of 30 patients with rapidly progressive dementia, including 17 cases eventually found to have sCJD, showed that the latter group had cerebellar dysfunction, higher CSF tau levels, positive CSF 14-3-3 protein, and diffusion-weighted imaging (DWI) hyperintensities, while EEG changes were similar for the two groups. DWI was therefore suggested to be of particular help in identifying CJD cases [48]; this may also be true for atypical presentations [4]. Functional imaging with FDG-PET may also have a role in diagnosis of sCJD despite overlapping features with other rapidly progressive dementias [41].

The differential diagnosis of rapidly progressive dementia resembling prion disease includes lithium toxicity [33]. A disorder with pathological findings of spongiform encephalopathy, typical of prion disease yet without staining for the prion protein or evidence of *PRNP* mutation, has also been reported [46].

## Conclusions

The panoply of techniques now available for the investigation of dementia disorders is very evident in the papers reviewed here. Regrettably, this increased understanding of disease phenomenology has yet to be translated into meaningful treatment modalities. It is to be hoped that any similar review of publications in subsequent years will be able to focus on the efficacy of novel therapies as well as disease phenotype and pathogenesis.

**Conflicts of interest** None.

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