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GUEST EDITORIAL

The neuropsychiatric burden of neurological diseases in the elderly

Psychogeriatrics began as an extension of psychiatry, with an emphasis on the unique manifestation of psychiatric disorders in the elderly. Early in the history of psychogeriatrics there was an emphasis on late-onset or late-enduring depression; paraphrenia and late-onset psychotic disorders; the late-life phases of schizophrenia; and anxiety and substance abuse disorders in the elderly. Growing recognition of the increasing frequency of Alzheimer's disease (AD) in the course of aging and the high prevalence of behavioral disturbances in patients with AD led psychogeriatricians to study the diagnosis and management of this disorder.

Increasing recognition that brain dysfunction is manifested by behavioral as well as cognitive and functional decline, and the evolution of appropriate instrumentation for detecting behavioral changes in patients with neurological disorders has produced an enhanced awareness of the neuropsychiatric burden of other neurologic diseases in the elderly. The high rate of behavioral changes and neuropsychiatric symptoms across a range of neurological disorders in aged individuals requires engagement of the psychogeriatric community in the management of these conditions. The behavioral and psychological symptoms of neurological disorders are under-recognized and under-treated. These symptoms cause marked patient and caregiver distress, contribute to institutionalization of affected individuals, and are detrimental to quality of life (Shin *et al.*, 2005; Cummings, 2003). Behavioral symptoms in neurological disorders may respond to treatment with psychotropic agents or anti-dementia compounds and recognition of the behavioral symptoms may assist in diagnosis and differential diagnosis of dementia. The behavioral phenotype may eventually assist in choosing and guiding disease-modifying therapies.

Neuropsychiatric manifestations of late-onset neurological disorders

Alzheimer's disease

Alzheimer's disease is the most well-studied late-onset neurological disorder with neuropsychiatric manifestations. Dementia of the Alzheimer type is characterized by memory impairment, decline in at least one other cognitive domain, deterioration from a previously higher level of function, impairment of activities of daily living, gradual deterioration, and absence of an alternative explanation, including delirium.

Pathologically, AD is characterized by the accumulation of amyloid beta protein in the form of neuritic plaques, formation of intracellular neurofibrillary tangles, and neuronal death. There is evidence of inflammation, excitotoxicity, and apoptosis as mediators of neuronal demise (Cummings, 2004). AD features a wide range of behavioral manifestations reflecting its widespread and diverse neuropathology. Apathy, agitation, depression, anxiety and irritability, are common, occurring in a majority of patients (Mega *et al.*, 1996). Delusions, hallucinations, disinhibition, and euphoria are less common but occur in a substantial minority. Neuropsychiatric symptoms become more common in patients with more advanced disease. The occurrence of multiple behavioral changes simultaneously presents a clinical management challenge more complicated than that encountered with management of more mono-symptomatic psychiatric conditions.

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is often a prodromal state presaging the appearance of AD or other dementing disorder (Petersen *et al.,* 2001). Not all patients with MCI progress to AD, but patients with an amnestic type of memory disorder fully evaluated for other causes of cognitive impairment and showing memory deterioration over time progress to AD at a rate of approximately 15% per year (Petersen *et al.*, 1999). Patients with MCI commonly manifest behavioral changes. Forty-four per cent of patients with MCI in community studies (Lyketsos *et al.*, 2002; Lopez *et al.*, 2003) and nearly 90% of patients in clinical samples (Hwang *et al.*, 2004) manifest behavioral alterations. Depression, anxiety, irritability, and apathy are the most common neuropsychiatric symptoms exhibited by patients with MCI. Moreover, patients with behavioral symptoms are most likely to progress to AD within a defined observation period (Copeland *et al.*, 2003). These studies suggest that MCI shares the behavioral phenotype of early AD and that the occurrence of this phenotype may assist in predicting early progression to diagnosable Alzheimer-type dementia.

Vascular dementia

Vascular dementia (VaD) is a product of multiple strokes and ischemic brain injury, and is most commonly associated with subcortical lacunar infarctions and ischemic injury to hemispheric white matter. Vascular dementia is manifested by a dementia syndrome, focal neurological signs, abnormal brain imaging, and a temporal link between the occurrence of cerebrovascular events and onset and evolution of the dementia syndrome. Patients with VaD exhibit behavioral disturbances similar to those of patients with AD. However, depression and psychosis are more common in patients with ischemic brain injury (Lyketsos *et al.*, 2000).

Patients with VaD commonly have mixed cerebrovascular disease and Alzheimer type pathology at autopsy and recognition of patients with this mixed clinical syndrome is currently problematic.

Frontotemporal lobar degeneration

Frontotemporal lobar degeneration (FTLD) includes three clinical syndromes: 1) semantic dementia featuring semantic aphasia and visual agnosia; 2) primary progressive aphasia characterized by a progressive non-fluent language disorder; and 3) frontotemporal dementia (FTD) with prominent behavioral changes (Neary *et al.*, 1998). Patients with FTLD have abnormalities of tau and ubiquitin metabolism affecting primarily frontal and temporal structures Patients with FTD exhibit marked behavioral symptoms including apathy, disinhibition, and elevated mood (Levy *et al.*, 1996). In addition, patients with FTD may exhibit behavioral changes unusual in other dementing disorders, including stereotyped and repetitive behaviors reminiscent of obsessive compulsive disorder (Ames *et al.*, 1994; Nyatsanza *et al.*, 2003), hyperorality and alterations in eating behaviors (Miller *et al.*, 1997) and the emergence of artistic talent in individuals not previously evidencing such ability (Miller *et al.*, 1998). These disorders constitute behavioral features uniquely linked to FTD.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is a dementia syndrome in which neuropsychiatric symptoms constitute a diagnostic criterion. DLB is characterized by the presence of dementia and at least two of the following three symptoms: visual hallucinations, fluctuating cognition, and parkinsonism (McKeith *et al.*, 1996). Pathologically, patients with DLB have Lewy-type pathology in brainstem, limbic/transitional cortex, and neocortex. Patients with DLB commonly exhibit delusions, depression, and rapid eye movement sleep behavior disorder (Ballard *et al.*, 2001b; 2004; Weiner *et al.*, 1996; Boeve *et al.*, 1998; 2004). DLB can be diagnosed only following a comprehensive neuropsychiatric assessment, and distinguishing DLB from other dementing disorders similarly requires the evaluation of neuropsychiatric phenomena in patients presenting with a dementing disorder.

Parkinson's disease

Parkinson's disease (PD) features a syndrome composed of rest tremor, rigidity, and akinesia with no detectable cause, a therapeutic response to dopaminomimetics, the absence of cerebellar deficits, absence of pyramidal features, absence of lower motor neuron disease, absence of a vertical gaze palsy, and limited autonomic dysfunction (Pal *et al.*, 2002). Pathologically, PD is characterized by the accumulation of alpha-synuclein-positive Lewy bodies in

cells of substantia nigra and, to a lesser extent, in the cerebral cortex. There is a marked loss of pigmented neurons in the brainstem. Depressive symptoms are present in approximately half of patients with PD (Tandberg *et al.*, 1996; McDonald *et al.*, 2003), although major depression is much less frequent. Depression is more common in patients with the akinetic-rigid form of PD (McDonald *et al.*, 2003) and in patients with cognitive impairment (Tandberg *et al.*, 1996). Depression may precede the occurrence of PD, and the presence of late-onset depression is highly correlated with the emergence of PD. Anxiety is also common in PD and may occur with or without associated depression (Starkstein *et al.*, 1993; Menza *et al.*, 1993). Visual hallucinations are a frequent feature of PD occurring in approximately 30% of patients (Sanchez-Ramos *et al.*, 1996; Fenelon *et al.*, 2000). Hallucinations typically follow therapy with dopaminomimetic agents (Goetz *et al.*, 2001) but specific host factors, particularly the presence of cognitive impairment, increase the probability of their occurrence (Sanchez-Ramos *et al.*, 1996; Fenelon *et al.*, 2000). Fifteen to thirty per cent of patients with PD meet criteria for rapid-eye-movement sleep behavior disorder (Comella *et al.*, 1998; Gagnon *et al.*, 2002). More rare neuropsychiatric phenomena observed in some PD patients include obsessive-compulsive symptoms (Alegret *et al.*, 2001), punding, pathological gambling, and a levodopa addiction syndrome known as hedonistic homeostatic dysregulation (Giovannoni *et al.*, 2000). PD is a common neurological syndrome in the elderly, is associated with a wide repertoire of behavioral changes, and represents a significant management challenge to optimal psychogeriatric care.

Parkinson's disease with dementia

Dementia associated with Parkinson's disease (PDD) is characterized by a dementia syndrome whose onset follows the appearance of diagnosable PD. Dementia is six times more common in patients with PD than in the general elderly population (Emre, 2003; Aarsland *et al.*, 2001a). The presence of a dementia syndrome represents a risk factor for the occurrence of neuropsychiatric phenomena in patients with PD. Delusions, visual hallucinations, and depression are all more common in patients with PDD than in PD patients without dementia (Cummings, 2003). Approximately 30% of patients with PDD exhibit delusions and 50% manifest visual hallucinations (Aarsland *et al.*, 2001b). Among individuals studied at autopsy, there is a more marked correlation between cortical Lewy bodies and the presence of a dementia syndrome than between Alzheimer type pathology and cognitive impairment (Hurtig *et al.*, 2000; Mattila *et al.*, 2000). This suggests that PDD is a form of DLB although neuropsychiatric symptoms are more common in the latter (Aarsland *et al.*, 2001c).

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is diagnosed in patients with a vertical gaze palsy, postural instability, falls within the first year of onset of symptoms, presence of a progressive neurological disorder with onset after age forty, and absence of evidence of another neurological disease that could explain the clinical features (Litvan *et al.*, 1996a). Progressive supranuclear palsy is a tauopathy that shares clinical and pathological features with FTD. Patients manifest marked apathy and may exhibit disinhibition (Litvan *et al.*, 1996b). Mild depression, anxiety, and pseudobulbar affect are common in patients with PSP (Menza *et al.*, 1995) but delusions and hallucinations are rare (Aarsland *et al.*, 2001b), assisting in the differentiation of Parkinsonian syndromes associated with PSP from those of PD.

Corticobasal degeneration

Corticobasal degeneration (CBD) presents with one of two clinical syndromes: 1) rigidity and at least one of the following cortical signs – apraxia, corticosensory loss, or alien limb phenomenon; or 2) asymmetric rigidity, dystonia, and focal reflex myoclonus (Mahapatra *et al.*, 2004). Like PSP and FTD, CBD is a tauopathy with tau-positive inclusions in both basal ganglia and cortical structures. Patients with CBD manifest depression at high rates; approximately half exhibit apathy; and fewer patients feature irritability and agitation. Delusions, hallucinations, disinhibition, and anxiety are less common (Litvan *et al.*, 1998).

Comment

Late-onset neurological disorders are associated with prominent neuropsychiatric phenomena. Most affected patients will exhibit behavioral and psychological symptoms as a manifestation of their disease. Neuropsychiatric symptoms may appear early in the course and are a common harbinger of the emergence of dementias in patients with MCI. Prodromal states of DLB and FTD are likely to exhibit neuropsychiatric symptoms, but the AD-MCI equivalent syndromes for these dementias remain to be established. Psychiatric symptoms are a major component of the burden presented by late-onset neurological diseases and present a challenge to psychogeriatrics to develop appropriate management strategies. Diminished quality of life is an inevitable consequence of the presence of behavioral disturbances in patients with late-onset neurological conditions. Depression has frequently been associated with diminished quality of life across neurological disorders. In patients with stroke, depression is associated with poor quality of life and poor recovery (Astrom *et al.*, 1992; Jonkman *et al.*, 1998). Similarly, depression has been associated with impaired quality of life

measures in patients with PD (Kuopio *et al.*, 2000), and in patients with dementia (Gonzalez-Salvador *et al.*, 2000; Shin *et al.*, 2005). Several studies have identified a relationship between treatment with psychotropic medications and diminished quality of life, suggesting that patients with more severe behavioral problems requiring pharmacotherapy have diminished quality of life or that side-effects associated with treatment for behavioral disturbances adversely affect quality of life (Gonzalez-Salvador *et al.*, 2000; Albert *et al.*, 1996; Ballard *et al.*, 2001). The presence of behavioral disturbances in patients has consistently been linked with lower quality of life in caregivers (Shin *et al.*, 2005; Coen *et al.*, 2002; Markowitz *et al.*, 2003). Effective management of neuropsychiatric symptoms, particularly those related to mood abnormalities, may improve both patient and caregiver quality of life.

There is urgent need for the development of effective therapies for neuropsychiatric symptoms in aged patients with neurological disorders. There have been few randomized placebo-controlled trials of psychotropic agents in patients with neurological disease. Few agents have been approved by regulatory agencies specifically for treatment of behavioral symptoms in patients with neurologic conditions. Preliminary studies suggest that atypical antipsychotics reduce psychosis and agitation in patients with AD (Katz *et al.*, 1999; Brodaty *et al.*, 2003; De Deyn *et al.*, 1999; Street *et al.*, 2000) Likewise, neuroleptic drugs decrease psychosis and agitation in patients with AD (Devanand *et al.*, 1998; Sultzer *et al.*, 1997). Recent concern about increased stroke and deaths associated with atypical antipsychotics has resulted in a reassessment of the use of these medications. Mood-stabilizing agents such as carbamazepine and valproate ameliorate agitation in patients with dementia (Porsteinsson *et al.*, 2001; Tariot *et al.*, 1998); and selective serotonin reuptake inhibitors may reduce symptoms of depression in patients with AD (Lyketsos *et al.*, 2003). Preliminary studies suggest that antidepressants or electroconvulsive therapy may reduce mood symptoms in patients with PD (Ceravolo *et al.*, 2000; Hauser and Zesiewicz, 1997; Douyon *et al.*, 1989). Atypical antipsychotics reduce symptoms of psychosis and agitation in patients with PD (Parkinson Study Group, 1999; Wolters *et al.*, 1996; Workman *et al.*, 1997; Fernandez *et al.*, 1999), although exacerbation of parkinsonism may be observed. Reports of psychopharmacologic agents in other neurological disorders with neuropsychiatric manifestations are anecdotal or derived from open-label studies. Dopamine agonists may reduce depression in PD (Baronti *et al.*, 1992; Cummings, 1999). Controlled clinical trials are necessary to establish the dosage ranges and side-effect profiles that may be unique to each neurological condition.

Another avenue of investigation relevant to reducing the neuropsychiatric burden of neurological disease is to assess the impact of anti-dementia and disease-specific therapies on neuropsychiatric symptoms. Preliminary

observations suggest that cholinesterase inhibitors and memantine reduce behavioral symptoms in patients with AD (Cummings, 2000; Trinh *et al.*, 2003; Tariot *et al.*, 2004). Initial studies also suggest that cholinesterase inhibitors reduce behavioral symptoms in VaD (Erkinjuntti *et al.*, 2002), DLB (McKeith *et al.*, 2000), and DAPD (Emre *et al.*, 2004). In most of these studies, behavioral measures have been included as secondary outcomes, and it is important to conduct studies of symptomatic and disease-modifying anti-dementia agents where behavioral changes are included as primarily outcomes, in order to more confidently asses the neuropsychiatric impact of these therapies.

Development of pharmacologic and non-pharmacological interventions successful in reducing the neuropsychiatric burden of neurological disease promises to have a marked impact on patient caregiver distress, patient and caregiver quality of life, and behavior-associated disabilities.

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