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REVIEW

Depressive symptoms in neurodegenerative diseases

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Abstract

Depressive symptoms are very common in chronic conditions. This is true so for neurodegenerative diseases. A number of patients with cognitive decline and dementia due to Alzheimer's disease and related conditions like Parkinson's disease, Lewy body disease, vascular dementia, frontotemporal degeneration amongst other entities, experience depressive symptoms in greater or lesser grade at some point during the course of the illness. Depressive symptoms have a particular significance in neurological disorders, specially in neurodegenerative diseases, because brain, mind, behavior and mood relationship. A number of patients may develop depressive symptoms in early stages of the neurologic disease, occurring without clear presence of cognitive decline with only mild cognitive deterioration. Classically, depression constitutes a reliable diagnostic challenge in this setting. However, actually we can recognize and evaluate depressive, cognitive or motor symptoms of neurodegenerative disease in order to establish their clinical significance and to plan some therapeutic strategies. Depressive symptoms can appear also lately, when the neurodegenerative disease is fully developed. The presence of depression and other neuropsychiatric symptoms have a negative impact on the quality-of-life of patients and caregivers. Besides, patients with depressive symptoms also tend to further decrease function and reduce cognitive abilities and also uses to present more affected clinical status, compared with patients without depression. Depressive symptoms are treatable. Early detection of depressive symptoms is very important in patients with neurodegenerative disorders, in order to initiate the most adequate treatment. We review in this paper the main neurodegenerative diseases, focusing in depressive symptoms of each other entities and current recommendations of management and treatment.

Key words: Neurodegenerative diseases; Alzheimer; Depressive symptoms; Frontotemporal degeneration; Vascular dementia; Lewy body disease; Depression; Dementia

Core tip: Neurodegenerative diseases commonly associate depressive symptoms. Depressive symptoms of neurodegeneration occur both in the beginning and in the main course of neurodegenerative diseases. They can dominate the clinical picture mostly in the first stage of disease. Besides, depressive symptoms decrease quality of life of patient and relatives in every

stage of disease. This is certainly an usual condition in Alzheimer's disease, by far the main cause of dementia worldwide. Such a situation often happens in neurodegenerative diseases. Depressive symptoms are treatable and its treatment can improve perceived health status and welfare of patients and relatives.

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INTRODUCTION

Depressive symptoms are very common in general medical practice and its frequency is remarkable in neurological diseases. Really, depressive symptoms are usual in chronic diseases; every kind of chronic or limiting condition is frequently associated with mood disorders[1]. However, from the very first glance it is apparent that the association between mood disorders and brain disorders is clearly more complex than the association between depressive symptoms and other group of diseases. The mean reason of this complexity is simple: the diseases of the brain have the potential to modify the mood of the affected person as brain is the ultimate controller of the behavior.

In the present paper, we review the relation between depressive symptoms and neurodegenerative disorders from a clinical point of view, focusing on the depressive symptoms described in main neurodegenerative diseases. Specially in neurodegenerative disease, depression may appear as an early symptom and depression may be the main manifestation, more often but no only in the early stages of degenerative brain processes. These depressive symptoms are relevant in medical practice as they can be the more important demand noted by patient or caregivers. Besides, they have an impact on the quality-of-life of patients and have been associated with increased caregiver burden, more rapid progression of disability and functional decline and earlier institutionalization and mortality[2]. However, although the importance of depressive symptoms, they have little or no interest regarding on diagnosis of neurological diseases; so, the features that clearly define the neurodegenerative disease are cognitive or motor symptoms, and not mood disturbances.

DEPRESSION, DEPRESSIVE SYMPTOMS AND COGNITION

Following the DSM-V classification[3] (Table 1) depression is defined as a mood disorder which expresses itself as a combination of symptoms with predominance of affective ones (sadness, desperation, apathy, anhedonia and subjective sensation of discomfort), also associating cognitive and physic phenomenology, causing a marked decreased interest in daily life activities.

In presence of any neurodegenerative disease, the depression diagnosis may be difficult. Frequently, depressive symptoms are masked by cognitive decline. Often cognitive symptoms and mood disorders mix in such a way that it's difficult to determine what group of symptoms are the most relevant to the patient. Neurological patients have difficulty to express typical feelings of sadness and hopelessness. Instead of sadness, prominent symptoms in neurodegenerative diseases may be anhedonia, anxiety, panic, motor disturbances and also lack of concentration. Lack of concentration or indecisiveness is a symptom that can be characteristic of cognitive decline caused by neurodegenerative diseases[4,5] but its specificity is not elevated. Weight loss and sleep disorders, often valuable symptoms of depression, can appear in neurological diseases with or without any associated mood disturbance. On the other hand, patients with neurodegenerative diseases use to manifest apathy[6]. This mood symptom is easily mistaken as anhedonia, that marked decrease in interest or pleasure with different activities to be considered as a main symptom of depression. Also, some particular neurological symptoms complicate the diagnosis because different reasons; as an example, the existence of a language disorder provokes difficulty of patient to express feelings. Another condition like pseudobulbar palsy may be misdiagnosed of depression as result of misunderstanding the significance of pathological crying or emotional lability.

From the clinical point of view, often depression and dementia are combined and their clinical phenomenology can be coincident and considered as strongly linked. From the epidemiological point of view, late-onset depression itself may be considered a risk factor or an early symptom of develop dementia[7]. So, certainly, this risk factor relation as explanation about the epidemiologic link between late-onset depression and dementia is not the only possibility, and other ones will be mentioned soon. It has been proposed that neurodegenerative disease may express as depressive symptoms in the early stages. That explanation is supported amongst other data by neuropathological evidences[8]. Thus, there would be common neuropathological hallmarks found in cognitive impairment that also are associated to depressive symptoms. So, depressive symptoms may be an early manifestation of diseases that later will cause dementia, not really a "risk factor" for dementia. On the other hand, psychopathology experts have argued that the depressive symptoms may be a consequence of self-perception of cognitive deterioration by patient[9].

From the opposite point of view, patients with depression commonly present cognitive disturbances. Cognitive disturbances, specially attention, short term memory, psychomotor speed, and executive function are often reported by depressive patients[10,11]. In fact, it has been observed that functional impairment in depression is closely related to severity of depression and cognitive

Table 1 Criteria for major depressive episode: DSM 5

Five (or more) of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood; or (2) loss of interest or pleasure
Depressed mood most of the day, nearly every day, as indicated by either subjective report (*e.g.*, feels sad or empty) or observation made by others (*e.g.*, appears tearful)
Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
Significant weight loss when not dieting or weight gain (*e.g.*, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
Insomnia or hypersomnia nearly every day
Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
Fatigue or loss of energy nearly every day
Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
The symptoms are not due to the direct physiological effects of a substance (*e.g.*, a drug of abuse, a medication) or a general medical condition (*e.g.*, hypothyroidism)

disturbance[12]. Interestingly, attentional deficits are part of the current diagnostic criteria of major depression and are commonly found in clinical practice[13]. In addition, several studies have shown the improvement of cognitive functions in patients with major depression treated with selective serotonin reuptake inhibitors[14] (SSRI) or dual serotonergic-noradrenergic reuptake inhibitors.

However, cognitive impairment in depression may produce some added difficulties. On one hand assessment of cognitive impairment may be difficult because of severity of depression. On the other hand, cognitive impairment can remain after antidepressant treatment despite of remission of depressive symptoms[15-17]. Thus, it may be recommended to continue the pharmacological and non-pharmacological treatment in presence of cognitive deficits[18], even though neurotransmission and other biological pathways and mechanisms involved in the association of cognitive deficits and major depression remain not clearly understood.

Several risk factors to develop dementia after a depressive episode have been described: mainly, high cultural level, depression severity and failure of treatment with antidepressive drugs[19]. The role of other risk factors, such as stress, depression severity and/or treatment with psychotropic drugs itself continues unclear[20].

So, it is essential to distinguish between depressive symptoms that can be the very first symptom of a neurodegenerative process and those ones what are not linked to this group of brain diseases.

DEPRESSIVE SYMPTOMS IN THE DIFFERENT NEURODEGENERATIVES DISEASES

Alzheimer's disease

Alzheimer's disease is the paradigmatic dementia's cause. As it is, provokes progressive memory and other cognitive functions impairment and causes marked decline in activities of daily living and variable behavioral changes. Neuropathologically it is characterized by neuronal loss with associated accumulation of neurofibrillary tangles and amyloid plaques. Currently, Alzheimer's disease is the most frequent cause of dementia all over the world as a whole and in most, if not all, population subgroups.

Most of the patients suffering from Alzheimer's associate behavioral and psychological symptoms, so called "non cognitive" symptoms, at some point of the evolution of the disease[21,22]. The prevalence of these symptoms is found to oscillate between 60% to 90% of cases, depending on both defined population and methodology of the study[23-26]. These neuropsychiatric symptoms are not included within the diagnostic criteria; in contrast, they contribute to develop a great disability and mortality and represent the main reason for patient institutionalization[27].

Early detection of neuropsychiatric symptoms is very important because they are the main cause of caregiver burden and also they cause acceleration of cognitive decline. In fact, when this symptomatology is observed and correctly identified, it may be treated with pharmacological and non-pharmacological treatment with improvement of the quality of life of patients and caregivers[28]. When these neuropsychiatric symptoms are identified, they can be prevented to recur too. Frequently, neuropsychiatric symptoms may fluctuate during the course of the disease and they disappear when cognition is severely impaired[29,30]. Depressive symptoms are included within this category of neuropsychiatric symptoms and are specially common in early stages of disease when lack of concentration and inattention are commonly found[31].

Depressive symptoms are usual in Alzheimer's disease patients according to different studies[32]. Based on descriptive population studies, about 80% of Alzheimer's patients can develop depressive symptoms to a greater or lesser degree in the whole course of the disease[33]. Depressive symptoms may vary and disappear, in contrast to cognitive symptoms that remain steady and invariably progress with the course of disease. In most cases, depression may be less intense than the depression found in neurologically healthy people or depression in another subtypes of brain diseases like cognitive impairment due to brain vascular disease, so

Table 2 The cornell scale for depression in dementia

Mood-related signs
Anxiety: Anxious expression, rumination, worrying
Sadness: Sad expression, sad voice, tearfulness
Lack of reaction to present events
Irritability: Annoyed, short tempered
Behavioral disturbance
Agitation: Restlessness, hand writing, hair pulling
Retardation: Slow movements, slow speech, slow reactions
Multiple physical complaints (score 0 if gastrointestinal symptoms only)
Loss of interest: Less involved in usual activities (score only if change occurred acutely, *i.e.*, in less than one months)
Physical signs
Appetite loss: Eating less than usual
Weight loss: (score 2 if greater than 5 pounds in one month)
Lack of energy: Fatigues easily, unable to sustain activities
Cyclic function
Diurnal variation of mood: Symptoms worse in the morning
Difficulty falling asleep: Later than usual for this individual
Multiple awakening during sleep
Early morning awakening: Earlier than usual for this individual
Ideational disturbance
Suicidal: Feels like is not worthy living
Poor self-steem: Self-blame, self-depreciation, feelings of failure
Pessimism: Anticipation of the worst
Mood congruent delusions: Delusions of poverty, illness or loss
Scoring system
A= Unable to evaluate; 0 = Absent; 1 = Mild to intermittent; 2 = Severe score greater than; 12 = Probable depression

Table 3 Provisional diagnostic criteria for depression in Alzheimer's disease

Three or more of the following criteria over the same 2-wk period, representing a change from previous functioning:
Depressed mood (sad, hopeless, discouraged, tearful)
Decreased positive affect or pleasure in response to social contacts and activities
Social isolation or withdrawal
Disruption in appetite
Disruption in sleep
Psychomotor agitation or retardation
Irritability
Fatigue or loss of energy
Worthlessness, hopelessness or excessive guilt
Recurrent thoughts of death or suicidal ideation
All criteria are met for dementia of the Alzheimer's type
Symptoms cause distress or disruption in functioning
Symptoms do not occur exclusively during delirium
Symptoms are not due to substances (medications or drugs of abuse)

called, when intense, vascular dementia[34,35].

The recognition of depression in Alzheimer's patients may be a challenge for different reasons: first of all, the absence of a validated questionnaire to detect and quantify the disorder. Second, dementia symptoms themselves like apathy can be confounded with typical features of depression such as sadness or anhedonia, masking the depressive disorder. Finally, the cognitive impairment of these patients supposes difficulties in the expression of sadness, hopelessness and other common affective feelings.

Numerous instruments have been proposed for assessing mood disorders and other neuropsychiatric symptoms in patients suffering from dementia. In 1994 the group of Cummings published the Neuropsychiatric Inventory[36] (NPI). The NPI has been used to characterize neuropsychiatric symptoms in several neurological diseases and is currently the most used scale for this purpose. NPI largely correlates with increasing disability in activities of daily living and increasing cognitive impairment. It has shown to be able to demonstrate the improvement on behavioral symptoms in Alzheimer's disease and other dementias after appropriate treatment[37]. In the initial version of the NPI, this scale evalued ten neuropsychiatric symptoms[38]: delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, apathy, irritability, disinhibition and aberrant motor behaviour. Later, two more items, sleep and eating disorders, were added.

NPI is passed as a structured interview driven by the professional and answered by the caregiver, focusing on the presence or absence of neuropsychiatric symptoms and their intensity. A form to be self-administered by the caregiver[39] (NPI-Q) and another one to be used in nurse home settings[40] (NPI-NH) have been developed later. Different translations of the NPI in its distinct forms are validated in a great number of languages[41-43].

Another more specific instruments to describe and quantify mood disorders in patients with dementia also has been developed: The Dementia Mood Assessment Scale[44] and the Cornell Scale for Depression in Dementia (CSDD)[45]. Particularly, the CSDD is widely used and it allows to differentiate between cognitive and mood symptoms (Table 2). It also may be useful to measure response to treatment and it's commonly used in clinical trials on this purpose.

Finally, specific provisional diagnostic criteria for depression in Alzheimer's disease (PDC-dAD) were proposed in 2002[46] (Table 3). PDC-dAD have shown to provide higher prevalence rates of depression than generic diagnostic criteria[47] such as ICD-10, CAMDEX or DSM-IV. The PDC-dAD are similar to standard depression diagnosis but reduces the importance on verbal expression and in contrast includes irritability and social isolation. Patients must have a diagnosis of Alzheimer's disease and three or more listed symptoms during two weeks. The symptoms must include low mood or decreased pleasure in daily living activities.

Together with depression, apathy is the most common symptom in Alzheimer's disease[48]. Both depression and apathy have a negative impact on evolution of the disease. Frequently, apathy is difficult to separate from depression. In fact, it's often a symptom observed in depression[49]. However, apathy can exist isolated without depression and it is not rare to find isolated apathy. Some paper have addressed the situation that both apathy and depression occur simultaneously in Alzheimer's disease and when both apathy and depression occur it has been shown that they are clinically and anatomically independent[50,51]. In fact, several neurophysiological studies focus on prevalence and clinical features of apathy have been

able to characterize this symptom and formulate some differences in relation to depression[52-54].

Certainly, the significance of depression or the significance of apathy in patients with neurodegenerative disease are different. First, apathy increases the risk of being diagnosed of dementia in patients with mild cognitive impairment and apathy do it more frequently that isolated depression in mild cognitive impairment[55]. Also, apathy tends to be more prevalent as cognitive function declines, in contrast to prevalence of depression that it's reduced in advanced stages of dementia[56]. On the other hand, apathy do not respond to antidepressive treatment, actually, antidepressive treatment have been reported even to increase the intensity of apathy in some cases[57].

As stated, depressive symptoms are important in patients with mild cognitive impairment. Mild cognitive impairment is characterized by cognitive symptoms and demonstrated impairment in neuropsychological testing but no significant functional decline, so patients with MCI do not fulfill dementia diagnostic criteria[58]. Its most common etiology is Alzheimer's disease and constitutes a high risk group to develop dementia at an annual rate of 10% to 15%[59-61].

Behavioral abnormalities are reported in 35%-75% of mild cognitive impairment patients[62]. As in Alzheimer's disease, neuropsychiatric symptoms in mild cognitive impairment are associated with cognitive decline and disability[63]. The most common behavioral symptoms are apathy, anxiety, depression, irritability and agitation[64,65]. Less common symptoms are euphoria, hallucinations, disinhibition and aberrant motor behavior. As previously commented, coexistence of depression and apathy or the presence of isolated apathy have shown to increase the risk of later conversion to Alzheimer's disease[66].

Depressive symptoms have been described up to 30% of the patients with mild cognitive impairment and in most studies depression was the most common neuropsychiatric symptom followed by apathy and irritability[67-69].

Frontotemporal degeneration

Frontotemporal degeneration or frontotemporal dementia (FTD) is clinically characterized by progressive behavioural changes such as disinhibition, compulsion, hyperorality or dietary changes. Patients also show social interpersonal dysfunction. Involvement of memory and other cognitive functions[70,71] is later than behavioural alterations. All these symptoms are due to degeneration of frontal and temporal lobes.

Nowadays, it's commonly accepted that frontotemporal degeneration is expressed with any of three main clinical variants: the more common behavioural variant FTD that have been forementioned and the language variants semantic dementia and progressive non-fluent aphasia[72]. There is also an overlap of FTD with motor neuron disease (FTD-MND or FTD-ALS), as well as another overlap exists with the parkinsonian syndromes progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS)[73]. Characteristicly, a certain grade of parkinsonism tends to be present in all syndromes.

Depression is quite common in FTD (40% of cases in the study by Levy *et al*[74]), although generally with mild or moderate intensity. When depressive symptoms are present, they usually do not manifest as typical features of major depression. Indeed, patients experience mainly apathy and decreased energy, hyperphagia and inappropriately preserved self-esteem, feature that it's extremely uncommon in usual depression.

The diagnostic challenge of FTD is the predominance of clashing behavioral symptoms. Consequently, it's difficult to make an adequate diagnose in initial stages of the process. Often patients may be misdiagnosed with psychiatric disorders conditioning a delay in the diagnosis of neurodegenerative disease. Psychopharmacological treatment with antipsychotics can cause more prominent motor symptoms and thus another confounding factor may contribute to misdiagnosis and failure to provide appropriate treatment.

Lewy body disease

Lewy body disease is another of the most frequent primary causes of degenerative dementia behind Alzheimer's disease. Both Lewy body disease and Parkinson's disease with or without dementia have been proposed to constitute a group of disorders called α-synucleinopathies. This proposal takes the fact that both entities' neuropathological handmark is the presence of Lewy bodies in different regions of the brain, mainly limbic, paralimbic and neocortical regions, and Lewy bodies are constituted mainly by the protein α-synuclein. Lewy body disease is clinically expressed with the presence of dementia associated with visual hallucinations, parkinsonism and a remarkable fluctuation of symptoms. Severe neuroleptic sensitivity is also typical of this disease[75]. Although these evident clinical features would seem to easily distinguish Lewy body dementia from Alzheimer's disease, in the common practice such a distinction is difficult to be made, specially in the early stages. The presence of visual hallucinations becomes relevant in differential diagnosis to Alzheimer's disease[76,77].

Depression in Dementia with Lewy bodies is similar to depression in Alzheimer's disease. Several studies have found higher rate of depression specially in early stages. Also depressive symptoms seems to be more severe[78]. First guidelines for diagnosis of Body Lewy's disease were described in 1996 and laterly in 1999. Current reviewed diagnostic criteria since 2005[75] includes depression as supportive feature of the disease (Table 4).

Corticobasal degeneration

Corticobasal degeneration (CBD) is histopathologically characterized by focal cortical neuronal loss and gliosis. It has been included into the spectrum of frontotemporal lobar degeneration as well as PSP and Pick's disease. All of these entities are biologically included into the group of tauopathies because tau protein is the main

Table 4 Diagnostic criteria for Lewy bodies disease

Central feature
Progressive dementia-deficits in attention and executive function are typical
Prominent memory impairment may not be evident in the early stages
Core features
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent complex visual hallucinations
Spontaneous features of parkinsonism
Suggestive features
REM sleep behavior disorder which can appear years before the onset of dementia and parkinsonism
Severe intensity to neuroleptics occurs in up to 50% of LBD patients who take them
Low dopamine transporter uptake in the brain's basal ganglia as seen on SPECT an PET imaging scans
Supportive features
Repeated falls and syncope (fainting)
Transient, unexplained loss of consciousness
Autonomic dysfunction
Hallucinations of other modalities
Visuospatial abnormalities like depth perception, object orientation, directional sense and illusions
Other psychiatric disturbances like systematized delusions, aggression and depression
A probable LBD diagnosis require either
Dementia plus two or more core features, or
Dementia plus one core features and one or more suggestive features

LBD: Lewy body dementia; PET: Positron emission tomography; SPECT: Single photon emission computed tomography.

component of different microscopic alterations to be found in these diseases. CBD presents in a sporadic pattern without familial aggregation. The common clinical presentation of CBD is the CBS associated to progressive asymmetric rigidity, limb apraxia, alien limb phenomenon, cortical sensory loss, myoclonus and dystonia. However, neither CBS patients have always CBD neuropathology when their brain is studied, nor corticobasal histopathology itself produces always CBS.

In fact, CBS is associated commonly with Alzheimer's disease histopathology. On the other hand, corticobasal histopathology has been associated to different clinical presentations like PSP, FTD or nonfluent/agrammatic primary progressive aphasia.

Depression is common in CBD and it has been described in up to 70% of these patients[79]. Conversely to the findings of similar studies in other neurodegenerative disease, Litvan *et al*[80] found in CBD patients a high prevalence of depression (73%) superior to the prevalence of apathy (40%). As it occurs specially in patients with FTD and another neurodegenerative diseases with prominent neuropsychiatric symptoms, the clinical predominance of depressive symptoms may explain that this entity can be misdiagnosed as a primary psychiatric disorder[81].

Huntington's disease

Huntington's disease is a highly penetrant autosomal dominant disease caused by a mutant protein - huntingtin - that results from an expanded CAG repetition. The progressive neurodegenerative disorder caused by Huntington's disease typically includes chorea and dystonia, incoordination, cognitive decline, and behavioural disturbances.

Classical and recent studies have shown that apathy, aggression and disinhibition are common. Suicide rates in Huntington's disease patients are over four times those of the general population[82,83]. Depression is diagnosed up to 40% of cases[84,85].

Parkinson's disease

Parkinson's disease manifests mainly with motor disturbances. Typically it causes asymmetric bradykinesia, resting tremor, rigidity and in later stages postural instability. Pathologically is characterized by depigmentation of substantia nigra due to loss of melanin-laden dopaminergic neurons containing eosinophilic cytoplasmic inclusions called Lewy bodies and mainly composed of α-synuclein, as previously mentioned.

Apart from motor symptoms that constitute the main clinical features, a wide range of nonmotor symptoms exists since early stages of the disease. These nonmotor symptoms are olfactive disturbances, depression, dementia, sleep disorders, fatigue, apathy and autonomic symptoms. Such a symptoms and other ones like dementia, a late complication of typical Parkinson's disease, are recognized as a major cause of disability and decline of quality of life in patients suffering from Parkinson's disease, especially in the more advanced stages[86]. Characteristically, depressive symptoms may experience fluctuation in the same way as motor symptoms, being often severe in off-periods[87,88]. They may appear in all stages of Parkinson's disease, and also precede motor symptoms[89]. Although sometimes is difficult to identify depressive symptoms in this patients, several risk factors have been described for developing depression: severity of cognitive impairment, female sex, onset of parkinsonian symptoms before age 40 and history of depression prior to diagnosis of Parkinson's disease[90].

Prevalence of depressive symptomatology varies from 20% to 50% in Parkinson's disease. Depressive symptoms are frequently associated with greater disability, rapid progression of motor symptoms and cognitive impairment[91-93]. In fact, depression is the main negative factor that impacts quality of life in Parkinson's disease and it may precede motor symptoms for years[94].

Depression in Parkinson's disease is different in some aspects from major depression: on one hand, guilty or worthlessness and suicidal ideation are not common[95]. Furthermore, only a small percentage of patients have major depression (2%-7%) and most of cases experience minor depression or mild depressive symptoms.

However, despite of frequency and importance of depression in Parkinson's disease, there are not any defined diagnostic criteria for depressive disorder in Parkinson's disease. The current gold standard

for establishing the diagnosis of depression in these patients remains the DSM criteria[96,97].

PSP

PSP is a rare neurodegenerative disorder clinically characterized by symmetrical parkinsonism, postural instability and falls, slowing of vertical saccades and frontal lobe symptoms. It's no so rare degeneration. Although classically grouped into the so-called Parkinson-plus syndromes, nowadays PSP is considered into the Frontotemporal Degeneration Complex. Histopathologically PSP presents cellular inclusions composed by aggregated tau protein that accumulate in prefrontal cortex, globus pallidus, substantia nigra and subthalamic nucleus.

Behavioral abnormalities are often observed in PSP patients, more than half experiencing apathy, depression, and sleeping problems[98]. In fact, the most common feature of mood disorder is apathy, found in more than 90% of PSP patients[99].

Vascular dementia

Cerebrovascular disease is the second most common cause of acquired cognitive impairment. Vascular cognitive impairment and vascular dementia are within the spectrum of cognitive impairment occurring as a result of cerebrovascular disease. The current definition of vascular dementia includes the hereditary vascular dementias, multi-infarct dementia, post-stroke dementia, subcortical ischemic vascular disease and atherosclerotic dementia dementia[100].

Referring to behavioural and psychological symptoms of vascular cognitive impairment, depression and apathy are the commonest symptoms found in most of studies[101-103]. Emotional lability is frequently reported as a classic feature of pseudobulbar palsy[104].

In comparison to Alzheimer's disease, prevalence of depressive symptoms in several studies has shown different results. Some studies showed higher prevalence and severity of depression in vascular dementia[105-107], but other publications has not been found significant differences in the prevalence of neuropsychiatric symptoms between Alzheimer's disease and vascular dementia patients[108-111].

In relation to the affected lobe, patients with posterior circulation lesions have shown a significantly lower rate of depression than patients with middle cerebral artery lesions. Moreover, depression following posterior circulation infarcts was of significantly shorter duration than depression following carotid strokes. Patients develop more severe depressive symptoms according to severity of stroke[112]. In addition, depression may be commoner in subcortical strokes[113] (lacunar state).

THERAPEUTIC APPROACH AND RECOMMENDATIONS

A wide variety of treatments have been used to improve neuropsychiatric symptoms in neurologic diseases including antipsychotics, antidepressive drugs or anti-convulsant ones. Non-pharmacological interventions like supportive psychotherapy or psychological counseling are recommended either complimentary or alternative to drug treatment.

Regarding primary dementias, cholinesterase inhibitors have shown a mild but consistent effect on behavioral symptoms in Alzheimer's disease[114]. They reduce behavioral changes and delay cognitive and functional decline and should be initiated earlier than others pharmacological treatments.

Neuropsychiatric symptoms like apathy, depression, and aberrant motor behavior are the most likely to improve[115,116]. Memantine tends to improve specially agitation and irritability more than mood symptoms, apathy, and aberrant motor behavior. Combination therapy with cholinesterase inhibitors may have advantages in patients with multiple neuropsychiatric symptoms[117]. Current evidence also recommends to use cholinesterase inhibitors in patients with Parkinson's disease with a positive effect on cognitive function and behavioral disturbances. The effect on body Lewy disease remains unclear but usually it's similar at the effect on Alzheimer's disease. Neither cholinesterase inhibitors nor memantine have shown effectiveness in frontotemporal dementias.

Besides cholinesterase inhibitors and memantine, other psychopharmacological treatments should be used individually considering the presence of comorbidities and associated medications. In most of patients, useful treatments are SSRIS, specially sertraline and citalopram[118-123]. Paroxetine has been proposed specifically to fontotemporal dementia[124,125] and Parkinson's disease[126]. However, paroxetine has been associated to further impairment of motor symptoms in some patients[127].

In case of Parkinson's disease patients, is important to determine if depressive symptoms appear in off-periods. In this case, adjustment of antiparkinsonian medication usually allows to obtain an improvement of depression.

Generally, classical drugs as tricyclic antidepressants are poorly tolerated; worsening of mental status is a common secondary effect of its use in this group of patients. By its anticholinergic effect, tricyclic antidepressants tend to worse cognition and also generate orthostatic hypotension, specially in patients with advanced disease[128]. Fluoxetine and fluvoxamine are less used because of potential interactions. Other antidepressive drugs, such as mirtazapine, trazodone, duloxetine and venlafaxine may be used but possibly their use may be restricted to cases of very limited or no response to initial treatment with SSRI[117]. Atypical antipsychotics should be used with extreme caution: their side effects are frequent in dementia patients and easily overcome the possible therapeutic effect. An increase of death rates have been found with the use

of every antipsychotic drug, more marked with typical ones but also present with atypical ones; so these drugs are commonly restricted to old age patients by administrative normatives in most of countries.

The commonly proposed therapeutic strategy to establish the effective dosage of antidepressive and antipsychotic drugs is that of "start low and go slow". That means to start with low doses and progressively increase dosage with caution to minimize side effects. Clinical evolution should be closely observed and clinician must evaluate the possibility of modifying or stopping the pharmacological treatment according to the intensity of symptoms and the potential harm of drug treatment.

Specially in elderly, depressive symptoms may be first manifestation of a neurodegenerative disease. Although clinical patterns of neurodegenerative diseases are different, the presence of depression may be insufficient to distinguish between them. Thus, in most cases it is required to observe closely the clinical evolution to lead the accurate diagnosis. Specific complementary test like neuroimaging or lumbar punction may be useful and can provide data to ascertain a correct diagnosis.

In conclusion, neuropsychiatric symptoms and specially depression are frequent in dementia stages and in most of neurodegenerative diseases. Depressive symptoms contribute significantly to increase disability, morbidity, caregiver burden and illness costs. To limit their extent, adequate identification and evaluation of these symptoms is essential to initiate appropriate early non-pharmacological and pharmacological treatment.

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