PSYCHIATRIC ASPECTS OF BASAL GANGLIA DISEASES

Mirela Vlastelica

Private psychiatric practice, Medical University School, University of Split, Split, Croatia

SUMMARY

   This review clarifies the fact that basal ganglia diseases are psychiatric as much as neurological diseases. It illustrates psychiatric aspects in Parkinson's disease and other hereditary basal ganglia diseases such as Wilson's disease, Huntington's chorea and others. In these diseases, psychological disorders can be difficult to diagnose, whether they are concomitant with the primary (neurological) disease, they are its consequence, or they are the result of a specific pharmacotherapy prescribed for these disease, etc. Thus, the choice of appropriate psychopharmacotherapy for these disorders represents a very subtle problem.

Key words: *basal ganglia - psychiatric aspects - comorbidity*

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INTRODUCTION

Basal ganglia diseases, like many other neurological diseases, manifest different psychiatric disorders as clinical features. It is therefore justified to consider them neuropsychiatric and not only neurological disorders. Psychiatric issues can be an integral part of neurological disease, but they may also occur in the comorbidity.

Having been recognized to have a leading role in the control of motor functions, basal ganglia also have a role in integration of emotions with cognitive and motor behavior.

Thus, psychiatric symptoms should not be observed as secondary or additional phenomena in these disorders.

Psychological disorders in basal ganglia diseases can be difficult to diagnose, whether they are concomitant with a neurological disease, they are its consequence, or they are the result of a specific pharmacotherapy prescribed for the primary (neurological) disease.

On the other hand, patients can be as sensitive to side effects of the medication prescribed for the primary disease as to the associated psychopharmaceutical, which further complicates clinical features.

Therefore, the choice of appropriate psycho-pharmacotherapy for these disorders represents a very subtle problem.

This paper presents psychiatric aspects of Parkinson's disease and aspects of hereditary basal ganglia diseases such as Wilson disease, Huntington's chorea and other diseases.

DEPRESSION IN PARKINSON'S DISEASE (PD)

Psychiatric symptoms often coexist with Parkinson's disease, while depression and anxiety are the most common conditions accompanying this disease.

Diagnosing is not easy since clinical symptoms of depression often overlap with the symptoms of PD (e.g. unmodified affect, work disability, lack of drive, loss of libido, etc.). However, depression in PD is qualitatively different from primary depression in that the sense of guilt, self-destructive thoughts and suicide are much less frequent (Allain et al. 2000).

However, there are three major issues related to treatment of depression in PD:

1. Do antidepressants induce parkinsonian symptoms?

Tricyclic antidepressants can improve motor symptoms of PD (anticholinergic effect), while SSRIs are mentioned as antidepressants that can induce parkinsonian symptoms (serotonergic effect). There is not enough data yet about venlafaxine (serotonin and noradrenalin reuptake inhibitor, dual effect), for instance.

2. The safety of antidepressants is questionable in PD – tricyclic antidepressants can cause delusions, cognitive disturbances, or orthostatic hypotension (while blocking alpha-adrenergic receptors), and in this sense, SSRIs are safer.

3. What are the interactions between antidepressants and antiparkinsonian medications?

SSRIs are known for their ability to cause serotonergic syndrome (changes in mental status, delusions, myoclonus, prespiration, hyperreflexia, tremor, diarrhea, fever; this syndrome can even be fatal). However, it is also known that SSRIs are safer than tricyclic antidepressants when cardiovascular side effects are concerned. On the other hand, antiparkinsonian drugs themselves can cause important changes in mental status so that the interaction between antidepressants and antiparkinsonian drugs is always a topical issue.

Other researches on depression in PD, for instance the one of Slaughter and associates (http://neuro.psychiatryonline.org/cgi/content) who studied MEDLINE, focused their analysis on 45 case studies of PD depression covering the period from 1922 to 1998. The

research showed that the prevalence of depression was 31%, while clinical manifestations included: apathy, psychomotor retardation, memory disfunction, pessimism, irrationality, and suicidal thoughts and behavior. Depression was treated with SSRIs, most commonly with sertraline.

Again, some other studies mention a 40-50% prevalence of depression in PD; they also discuss the efficiency of antidepressants in PD depression treatment. Even though case studies indicate that SSRIs may potentially worsen motor symptoms of PD, they are still chosen as the first choice medication for treatment of PD depression.

Hoogendijk and associates (http://neuro. psychiatryonline.org/cgi/content) have established that the prevalence of the depression concomitant with PD varies greatly in literature. This can be explained by certain symptoms that overlap, so that the newly established category in DSM-IV „mood disorder due to a general medical condition" is justified.

OTHER PSYCHIATRIC DISORDERS IN PARKINSON'S DISEASE

Parkinson disease is often followed by both emotional and cognitive disorders. As already said, depression is frequent, then anxiety, phobia and apathy. Hallucinations, delusions, sleep disorders, etc. are also possible.

In psychiatric practice there are frequent examples that increasingly point to the existence of psychological disturbances, most commonly depression that can be an integral part of Parkinson's disease. Very often depression is the early symptom because of which a patient is brought to his doctor, most commonly a psychiatrist, and only after a thorough observation is performed is an early stage of Parkinson's disease diagnosed.

Likewise, there are many examples of older patients who develop an emergency due to sudden attacks of choking, dyspnea, and tachycardia. After a cardiac observation is made, cardiac etiology of disorders is ruled out and most commonly a panic attack is diagnosed. However, resting tremor of the hands, slowness of movement, or rigidity of the limbs etc. is subsequently identified. In these cases SSRIs may reduce symptoms, but can not eliminate them. Only after L-dopa therapy is applied, will neurological symptoms improve and panic attacks are reduced as well.

However, there are psychiatric and cognitive side effects that are induced by antidepressants themselves (Starkstein & Merello 2007), which certainly has to be taken into account. Panic attacks in PD can also be a long term complication resulting from L-dopa therapy. This is because a decrease of dopaminergic activity of the striatal receptors can induce disinhibition in locus ceruleans, hence the increase of the central noradrenergic activity can hypothetically cause a panic attack.

Nevertheless, panic attacks are rarely described in the context of the newly discovered PD. While it is safe to assume that PD medications can cause hallucinations, those patients who do not take the medication can also be susceptible to hallucinations and are therefore representative of de novo PD (Matsui et al. 2006). From this we can conclude that the pathogenesis of panic attacks in PD is practically unknown. It probably has to do with the dopaminergic noradrenergic system. Furthermore, since degeneration of the raphe is considered a disorder of the serotonergic system, the serotonergic system plays a role in PD as well.

Still, the source of greater distress for both the patients and those who look after them is the occurrence of psychosis in PD. Although the availability of atypical antipsychotics to some extent solves the clinical dilemma of how to preserve motor functions while psychosis is treated, our understanding of psychosis in PD is still in its infancy.

Depression, panic attacks and psychosis can be predecessors as well as part of PD. However, the clearest cases are those caused by antiparkinsonian drugs.

Two thirds of patients with PD experience mood swings and fluctuation of motor functions. Many researchers indicate that mood swings are related to motor fluctuation in that patients experience decline in their mood during immobility („off"), and improvement when they are „on" (mobile). However, motor and emotional conditions are not in consistent correlation. When they are correlated, the most common pattern is common occurrence of poor mood, increased level of anxiety, and reduced motor functions (http://neuro. psychiatryonline.org/cgi/content).

Maia et al. (http://neuro.psychiatryonline.org/cgi/ content) have evaluated the frequency of OCD (obsessive-compulsive disorder), OCS (symptoms), and related conditions – such as tics, trichotillomania, and body dysmorphic disorder in 100 patients with PD and 100 control respondents. In comparison to the control group, OCD, OCS and related disorders have not been more frequent in PD. Nevertheless, studies have detected the correlation between some OCSs and the left-sided predominance of motor symptoms in PD. This suggests that the expression of obsessive compulsive symptoms can be referred to right side hemisphere activity.

DYSTONIA AND PARKINSON'S DISEASE

According to studies available at http://neuro. psychiatryonline.org/cgi/content, patients with dystonia show a prevalence of the following: major depressive disorder 25%, bipolar disorder 7.1%, atypical bipolar disorder 7.1%, social phobia 17.9% and generalized anxiety disorder (GAD) 25%. This is significant in comparison to the control group (p<0.005). Of these,

social phobia and GAD preceded dystonia, while bipolar disorder developed secondarily, after the appearance of dystonia.

In these studies, simple phobia was significantly important with PD patients (35.7%, p<0.0001), as much as atypical depression (21.4%). Additionally, PD was associated with primary phobia and secondary atypical depression.

These results are considered in light of the pallidothalamic physiology in dystonia and in PD.

PROGRESSIVE SUPRANUCLEAR PARALYSIS AND PARKINSON'S DISEASE

Patients with progressive supranuclear paralysis (PSP) show significantly more apathy and disinhibition, while patients with PD show more hallucinations, delusions and depression.

Studies show that patients with PSP have symptoms compatible with a lesion of the orbitofrontal and medial frontal cortex, such as disinhibition and apathy. On the other hand, PD patients show symptoms related to monoaminergic disorder, such as psychosis and depression.

BASAL GANGLIA CALCIFICATION

In the study of Edward Lauterbacha et al. (1994) two cases of basal ganglia calcification including globus pallidus are shown. Both patients had cognitive dysfunctions, symptoms similar to temporal lobe syndrome (amnesia, perceptual disfunction, and visual hallucinations in particular) and myoclonus. The first patient manifested depression, auditory hallucinations, anxiety, paranoia and postural tremor. The second patient manifested multifocal dystonia with dystonic tremor.

These cases complement reports on psychotic phenomena and dementia related to the pathology of the pallidum. They open a new pathophysiological insight into the possible role of the globus pallidus in neuropsychiatric conditions. The cases point at a specific pattern of hallucination, paranoia, depression, myoclonus and dystonia. This can further indicate its role in the genesis of schizophrenia, mood disorders, and anxiety disorder.

HEREDITARY BASAL GANGLIA DISEASES AND GERIATRIC PSYCHIATRY

Basal ganglia diseases are common in older people. Even though motor disorders are the leading symptoms, neuropsychiatric symptoms are common and have significant clinical consequences. Studies show that dementia appears with the majority of PD patients and it is difficult to differentiate this dementia from Lewy-body dementia (www.medscape.com/viewarticle). The prevalence of PD, the most common basal ganglia disease, is approximately 1 per thousand, and in persons of 65 years of age up to 1%.

Visual hallucinations in PD are correlated with (visual) agnosia, memory disorder, disorder in reality testing, and REM sleep behavior disorder.

Basal ganglia have been recognized as having a leading role in the control of motor functions as well as in integration of emotion with cognitive and motor behavior.

Therefore, psychiatric symptoms should be observed as secondary or additional phenomena linked with these disorders.

HEREDITARY BASAL GANGLIA DISEASES

Hereditary diseases of basal ganglia such as Huntington's disease, Wilson's disease and Fahr's disease rarely present with an initial psychotic syndrome, which is hard to differentiate from the prodrome of schizophrenia (www.medscape.com/viewarticle).

HUNTINGTON'S DISEASE (autosomal dominant disease) is typically followed by chorea and progressive dementia. Affective psychiatric symptoms and psychosis are very common. Psychosis may be the first sign of the disease, especially if the disease appeared early.

WILSON'S DISEASE (lenticular degeneration) damages liver and brain in general, and very rarely appears in the form of isolated psychosis. Wilson's disease is the most significant of these three diseases because it can be effectively treated. The pathognomic Kayser-Fleischer's ring (which may not always be present), low serum ceruloplasmin levels and high 24hour urine copper levels are sufficient for diagnosing the disease. Liver biopsy with the quantitative measurement of copper is the gold standard for definite diagnosis. Genetic testing is impractical as there are over 100 identified mutations and symptomatic and asymptomatic mix of heterozygotes.

FAHR'S DISEASE (familial idiopathic basal ganglia calcification) remains controversial with regard to psychiatric symptoms and psychosis. Basal ganglia calcifications are typically detected on CT scans by accident because they also exist in families with asymptomatic heritage. On the other hand, the correlation between psychosis and idiopathic basal ganglia calcification is evident in certain families.

Huntington's disease in particular can be considered a paradigm of neuropsychiatric disease as it has all three components, „Triad syndrome 3D": dyskinesia, dementia, depression (http://psy.psychiatryonline.org/cgi/content).

Degenerative diseases such as Huntington's, Parkinson's and Wilson's disease are traditionally classified as movement disorders. However, cognitive

and psychiatric manifestations are equally important. This group of diseases also include progressive supranuclear paralysis (PSP), idiopathic basal ganglia calcification, familial calcification of basal ganglia (or Fahr's disease), neuroakanthocytosis, Sydenham's chorea and postencephalitic parkinsonism.

In his original description of the disease that bears his name (HD), George Huntington established that there exists "a tendency to insanity and suicide". It has been found that in HD the prevalence of lifelong mood disorder is 38%, while 22% of patients meet the major unipolar depression criteria. The suicide rate in HD is 4-6 times higher than in general population, and especially so with people older than 50.

The neuropathological basis of depression in HD could be related to early neuronal lesions in the caudatum medialis, which is correlated with limbic structures. Subcortical structures that are damaged in basal ganglia diseases, such as the caudatum in HD, are connected with the orbitofrontal and prefrontal cortex by complex frontal-sub cortical pathways. PET shows reduced metabolism of the prefrontal cortex in depressive patients without primary neurological disease.

In Wilson's disease (lenticular degeneration) the prevalence of depression is 20%. Depression may also occur in progressive supranuclear paralysis (PSP), the disease that degenerates basal ganglia, medulla oblongata and cerebral cortex. Personality changes and labile affects occur side by side with the depression.

Usually, depression is underdiagnosed in patients with a basal ganglia disease. Communication with patients may be damaged; irritability, agitation or social withdrawal may also occur. Furthermore, because of such a situation, patients may get demoralized, loose self-confidence and crave for death. Nevertheless, an opinion that depression in these circumstances (these diseases) is "understandable", sometimes misleads doctors to accept the reactive origin of patient's symptoms prematurely, thus failing to apply an appropriate and more aggressive treatment. In deciding between "reactive" and "organic" etiology of depression, a clinician must examine previous history of depressive episodes, presence of depression among relatives, specific losses in his/her life, life changes, everything that preceded the episode.

Also, there is a risk of diagnosing wrongly (overdiagnosed). Physical changes such as weight loss, sleeping disorder, bradykinesia, weaker facial expression, apathy etc. can be mistaken for a major depressive episode, which may lead to unnecessary pharmacotherapy of the patient who is particularly sensitive to CNS side effects of antidepressants.

As long as there is no antidepressant that will be uniquely effective in these diseases, patients suffering from basal ganglia diseases are particularly sensitive to harmful side effects such as sedation and anticholinergic causes of cognitive disorders. Therefore, tricyclics are not considered first choice medicine, but SSRIs are better tolerated, as well as more recent antidepressants such as venlafaxine.

If depression is followed by delusions, hallucinations, and significant agitation, (anxiety) it is necessary to include antipsychotics in the treatment. If there is no choice, one should know that depressive patients with HD usually tolerate ECT perfectly well. The treatment of the primary disease may be sufficient if depression is a secondary occurrence in a disease (e.g. hypothyroidism). So, in Wilson's disease treatment with penicillin is often used and it improves the psychiatric as well as the neurologic symptoms.

Even though depression in HD is the most common psychiatric disease, a small number of patients may become manic with euphoric or irritable mood; may get impulsive and hyperactive; they may get sleeplessness and delusions of grandiosity. Some may even have a classic bipolar disorder. Mania and hypomania in HD patients occur with prevalence of 4-10%. They need to be treated with mood stabilizers. However, in cases of basal ganglia disease it should not be lithium, as patients react to lithium less and are more susceptible to intoxication. Antipsychotics and ECT may also be included in the treatment.

PSYCHOSIS AND BASAL GANGLIA DISEASES

A hypothetical correlation between basal ganglia pathology and primary psychotic disorder has been established. For instance, many of the Parkinson's disease (PD) symptoms including poverty of speech, flat affect, and psychomotor retardation constitute the negative symptoms of schizophrenia. Likewise, it is known that schizophrenic patients who are on antipsychotics can develop extra pyramidal syndrome like PD.

Recent studies show a greater frequency of psychosis in patients with Huntington's disease (HD), between 3-12%. There is also a higher risk of psychosis in earlier stages of HD.

The neuropathology of psychosis in HD has not been understood yet. It is possible that a relative hyper dopaminergic condition, which results in selective degeneration of neurons that contain other neurotransmitters (so that dopamine is relatively higher), influences subcortical pathways leading to psychotic symptoms. In psychosis with HD, PET shows a drop of metabolism in the anterior of both hemispheres, which is similar to the relative hypo frontality seen in PET of schizophrenic patients.

In Wilson's disease, psychosis is rarer; it occurs in less than 2% cases.

Postencephalitic parkinsonism (microscopic focal inflammations of substantia nigra and basal ganglia) can also manifest in the form of psychosis. The manifestation is more of a delirium than a psychotic condition. Chronic sequelae cause personality disorder and a full scale of symptoms similar to schizophrenia.

According to some studies (Davison and Bagely, 2007), 15%-30% of these patients have paranoid-hallucinatory psychosis, and 10 % of them have a condition similar to the once described "dementia praecox" (http://psy. psychiatryonline.org/cgi/content).

Finally, Fahr's disease (or familial idiopathic basal ganglia calcification), a disorder characterized by parkinsonism or choreoathetosis, subcortical dementia, focal cortical deficit such as dysphasia, can be manifested in psychosis.

A new episode of psychotic symptoms, even with patients with basal ganglia disease, requires a search for precipitating factors. They can often be induced by antiparkinsonian medication, because a hyper-dopaminergic condition or anticholinergic delirium occurs at that point.

The use of antipsychotics in basal ganglia diseases is complex because of the risk of deterioration of the primal disease (basal ganglia). To that effect it is better to avoid higher doses of high potent antipsychotics (classic) and switch to atypical antipsychotics (olanzapine, risperidone, quetiapine) as they are better tolerated. Attention should be paid to the development of tardive dyskinesia caused by medication, because it may then be considered a prime disorder.

CONCLUSION

Basal ganglia, recognized to have the leading role in the control of motor functions, also have a role in integration of emotions with cognitive and motor behavior. Therefore, psychiatric symptoms should not be observed as secondary or additional phenomena in these disorders. Basal ganglia disorders are neuro-psychiatric disorders indeed, not simply a neurological condition.

Psychological disorders affecting the basal ganglia can be difficult to diagnose, whether they are con-comitant with the neurological disease, they part of a comorbidity or its consequence. They can often be the result of a specific pharmacotherapy prescribed to these patients.

Patients can be sensitive to the side effects of medication, be it the medication prescribed for the primary disease or a psychopharmacological medica-tion. This may create difficulties when selecting an adequate psycho-pharmacotherapy in patients suffering from basal ganglia disease.

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Correspondence:

PhD. Mirela Vlastelica, Ass.Professor
Vukasovićeva 10, 21000 Split, Croatia
E-mail: mirelavlastelica@yahoo.com