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Psychosis as an Isolated Manifestation of COVID-19 in Non-Demented Patients with Parkinson's Disease: Clinical Cases and Literature Review

G. Lokominaitė*
R. Kaladytė Lokominienė**

**Faculty of Medicine, Vilnius University, Lithuania*

***Centre of Neurology, Vilnius University, Lithuania*

Summary. Psychotic disorders in patients with Parkinson's disease are usually associated with poor cognitive performance, comorbidities, and changes in treatment regime. Despite the recognition of cognitive deficit as a major risk factor for psychosis in Parkinson's disease, psychotic events have been reported in patients without dementia. SARS-CoV-2 is now recognized as a harmful invader of the nervous system, and defining its consequences still requires multidirectional research. Patients with Parkinson's disease may develop psychosis during COVID-19 infection. According to our observation, psychotic disorder seems to be an isolated manifestation of SARS-CoV-2 infection in Parkinson's disease. In this article, we present two clinical cases of non-demented patients with Parkinson's disease who underwent full vaccination against SARS-CoV-2. The patients were on stable antiparkinsonian medication, had no previous psychiatric disturbances, and developed psychosis as a consequence of COVID-19 without any other clinical signs of infection; no recurrent psychotic disorders were registered during the one-year follow-up. The discussion on diagnostic difficulties and treatment options includes a review of the literature. We recommend to perform reverse transcription polymerase chain reaction (RT-PCR) swab testing for SARS-CoV-2 in patients with Parkinson's disease who develop acute psychosis.

Keywords: Parkinson's disease, COVID-19, SARS-CoV-2, psychosis.

INTRODUCTION

In the last three years since the first human SARS-CoV-2 infection, clinical and observational studies have demonstrated a clear association between COVID-19 and neuropsychiatric disorders; the incidence of these complications was higher in patients requiring hospitalization and intensive care during the COVID-19 pandemic through the acute phase and even during the post-COVID period [1–3]. Psychotic disorders were observed in 1.4% of patients, the first psychotic episode in 0.42% of patients, with its incidence in the course of COVID-19 being statistically significantly higher compared to both influenza and other respiratory infections (p<0.0001) [1]. An analysis of 2-year retrospective cohort studies including 1 284 437 patients by Taquet M et al. [1], using data from health-care records of approximately 89 million patients (collected from hospital, primary care, and specialist providers), demonstrated different dynamic courses of psychiatric disorders. According to Taquet M et al., the increased incidence of mood and anxiety disorders was transient, with no overall excess of these diagnoses compared with other respiratory infections, but the increased risk of psychotic disorder (HR 1.27 [1.18-1.37], p<0.0001), cognitive deficit (HR 1.36 [1.33-1.39], p<0.0001), dementia (HR 1.33 [1.26-1.41], p<0.0001), and epilepsy or seizures (HR 1.14 [1.09-1.19], p<0.0001) persisted throughout and were similar during the delta and omicron waves. Children appeared to have a more benign overall profile of psychiatric risk than adults and especially the elderly, but their sustained higher risk of cognitive deficit, insomnia,

Address:
Rūta Kaladytė Lokominienė
Centre of Neurology, Vilnius University
Santariškių Str. 2, LT-08661 Vilnius, Lithuania
E-mail: ruta.lokominiene@mf.vu.lt

intracranial haemorrhage, ischaemic stroke, nerve, nerve root, and plexus disorders, psychotic disorders, and epilepsy or seizures in 6 months was also significant, with HRs ranging from 1.20 [1.09-1.33] to 2.16 [1.46-3.19] [1].

Undoubtedly, patients with COVID-19 may experience psychiatric symptoms, including psychosis [1–3], but to date there is a lack of specific evidence from clinical trials. Chaudhary AMD et al. recently published a systematic review to evaluate the occurrence of new-onset psychosis or exacerbation of clinically stable psychosis during COVID-19; as the authors could not find any specific clinical trials, they included 57 unique case reports and case series [3]. The mean age of the patients at onset of psychotic symptoms was 43.4 years for men and 40.3 years for women; it is important to note that 69% of these patients had no prior history of psychiatric disorders [3]. The clinical picture was typical: most patients had mild COVID-19-related symptoms and the most commonly reported psychotic symptoms were delusions and hallucinations; the course of psychosis in COVID-19 was consistent with the clinical severity of COVID-19 and mostly favorable as psychotic symptoms improved significantly or resolved completely in 72% of patients [3].

Patients with neurodegenerative disorders such as Parkinson's disease (PD) appear to be more vulnerable to mental health disorders such as stress, depression, anxiety, or worsening quality of life during COVID-19 lockdown. Nabizadeh F et al. published a systematic review of 21 studies with a total of 5236 PD cases on psychological outcomes of COVID-19 [2]: most of the studies demonstrated the increase of the severity or the prevalence of psychiatric disturbance due to the COVID-19 pandemic in PD patients (the prevalence of anxiety was 14.0-66.5%, depression 0-50%, apathy 0-50%, impulse control disorders 44%, sleep problems 35.4-68.9%), but they did not cover psychotic events. There is still a lack of studies on the prevalence of psychotic events in PD patients with COVID-19. Psychotic disorders in patients with PD are usually associated with poor cognitive performance, comorbidities, and changes in treatment regime. Despite the acknowledgement of cognitive deficit as a main risk factor for psychosis in PD, it has been reported that minor (illusions) and even major (hallucinations and delusions) psychotic events can be experienced by non-demented PD patients. Each case of psychotic disorder in PD patients is always a diagnostic and therapeutic challenge for clinicians as it requires specific management decisions to stop the psychosis, to prevent its recurrence and at the same time to avoid deterioration of the patient's motor and non-motor functioning.

In this article, we present two clinical cases of non-demented patients with PD who developed psychosis as a consequence of COVID-19 without any other clinical signs of infection. The patients were on stable antiparkinsonian medication, had no significant previous psychiatric disturbances, and were fully vaccinated against SARS-CoV-2. No recurrent psychotic disorders were registered in the patients during the available one-year follow-up period.

REPORT ON CLINICAL CASES

Both patients were treated in the outpatient department of Vilnius University Hospital Santaros Klinikos (VUHSK). Signed consent for the use of medical data for the clinical report was obtained from the patients.

CASE 1

A 70-year-old man was diagnosed with PD 10 years ago when he reported kinetic tremor and mild slowness of the right hand. At the initial examination in 2012, there were no complaints of smell, taste, bowel movements, REM behavior or impulse control. Family history was negative. Brain magnetic resonance imaging (MRI) was normal. The diagnosis of PD, stage 1 according to the Hoehn-Yahr scale, was confirmed by a positive single-photon emission computed tomography (SPECT) scan with ioflupane [I-123], which revealed reduced radiotracer uptake in the putaminal areas, with the left side more affected; the putamen/nucleus caudatus ratio was 0.74. The patient was prescribed ropinirole, which was gradually titrated up to 16 mg/day for symptomatic effect and was well tolerated. Propranolol 80 mg/day was added to control kinetic tremor. The concomitant diseases were primary arterial hypertension (treated with ramipril 10 mg/day) and chronic lumbar radiculopathy in the right (treated with physiotherapy and non-steroid anti-inflammatory medications during exacerbations). The patient was consulted at the VUH SK regularly, not less than twice a year. As motor symptoms generalized over two years, rasagiline 1 mg/day was added, followed by amantadine 200 mg/day. Over the next 2 years, the dose of amantadine was increased to 400 mg/day. The patient was monitored for impulse control, sleep quality and daytime alertness, cognitive, motor and psychiatric symptoms. He reported no impulse control disorder (ICD), sudden sleep attacks or daytime somnolence, no psychotic events or mood disorders. The patient worked full-time job as a technical supervisor and reported episodic insomnia and anxiety at several consultations, which were relieved by low doses of bromasepam. Amantadine was discontinued and reintroduced several times because of progression of motor symptoms. As tremor, rigidity and bradykinesia progressed, levodopa/carbidopa 100/25 mg×3 times/day was introduced in 2017 and increased to 400 mg/day in 2020 (levodopa equivalent daily dose, LEDD=1170 mg/day). The patient was vaccinated against SARS-Cov-2 in May 2021, June 2021 and November 2021. During a routine contact consultation at the VUHSK on 20 July 2021, the patient reported that tremor and stiffness of the right extremities increased only during stress and slightly interfered with activity, sometimes it was difficult to fall asleep in the evening, but there were no sudden sleep attacks and somnolence during the day, no ICD according to subjective report, no history of COVID-19; episodic exacerba-

tion of lumbar pain required oral analgesia (lornoxicam 8 mg×1-2 times/day). Objective status was without negative dynamics: normal consciousness and cognition, slight hypomimia, mild bradykinesia and rigidity in the right arm and leg (1 point on the Unified Parkinson's Disease Rating Scale, UPDRS), mild postural tremor of the hands (2 UPDRS points in the left and 1 UPDRS point in the right), minimal postural instability (correction in one step during the postural test), hypestesia in right S1 dermatome, Lasegue's sign negative, blood pressure 140/90 mmHg, heart rate 75 beats/min. The diagnosis was Parkinson's disease, stage 2.5 according to the Hoehn-Yahr scale; episodic insomnia; chronic right S1 radiculopathy; osteochondrosis. The dose of propranolol was increased from 80 mg/day to 120 mg/day; there were no other corrections in the treatment scheme (rasagiline 1 mg/day, ropinirol 16 mg/day, amantadine 200 mg × 2 times/day, levodopa/benserazide 100/25 mg × 4 times/day). The next consultation was scheduled for January 2022. In December 2021, the patient suddenly became agitated, reported delusions and hallucinations (unknown people at home, doing harm) and started to behave inadequately (fought with unreal invaders), so he was urgently admitted to a psychiatric hospital. The patient had no fever, cough or gastrointestinal distress. There were no abnormalities in laboratory analyses, chest X-ray and brain CT; the test for COVID-19 on addmission was negative. The next day, the real-time PCR test for SARS-Cov-2 RNA was positive. The patient was treated in the psychiatric department of another hospital with olanzapine 15 mg/day, lorazepam 2.5 mg/day; rasagiline and ropinirol were discontinued, but amantadine, propranolol and levodopa remained unchanged. The psychotic condition resolved in 4 weeks and the patient was discharged with olanzapine 10 mg/day, which was changed to quetiapine 100 mg/day and zopiclone 7.5 mg/day in March 2022 by the consultant psychiatrist. During the neurological examination at the VUHSK in April 2022, the patient and his wife reported about the disappearance of hallucinations, delusions and sleep disturbances, but complained of significantly worsened motor condition (severe retardation, rigidity and rest tremor) and of a wearing-off phenomenon. On objective examination, the patient's general and local bradykinesia and hypokinesia were rated 3 points, rest tremor 2 points in the right and 1 point in the left extremities on the UPDRS, postural instability was present, able to change positions independently with difficulty; cognitive condition was normal (29 points on the Mini-Mental State Examination, MMSE). PD was stage 3 according to the Hoehn-Yahr scale. The medication scheme was adjusted: amantadine was discontinued, the dose of standard-release levodopa/benserazide increased to 200/50 mg×4 times/day and controlled-release levodopa 200 mg was added at night, rasagiline 1 mg/day was reintroduced (LEDD=1050 mg/day); quetiapinum 25 mg-25 mg-50 mg and propranolol 40 mg×3 times/day were continued. In July 2022, the motor condition improved and no major or minor psychotic events were reported by the patient and family. The last visit of the patient to the VUHSK was in March 2023. There was a deterioration of the motor condition during the last 8 months, but no signs of psychosis during the last year. On objective examination, his general and local bradykinesia and hypokinesia were rated 2-3 UPDRS points, rest tremor was 1 UPDRS point in the right side, postural instability was present, able to change the positions independently with difficulty; cognitive condition was normal (30 points on the Mini-Mental State Examination, MMSE). The dose of standard-release levodopa was gradually increased from 800 mg/day to 1200 mg/day, quetiapine was reduced to 25 mg at night, rasagiline, propranolol and controlled-release levodopa remained unchanged (LEDD=1550 mg/day). At follow-up in April 2023, the patient and his wife reported his condition to be stable, with motor improvement and without psychiatric abnormalities.

CASE 2

A 61-year-old man began to feel loss of smell 20 years ago, constipation and insomnia 15 years ago, episodic vocalisations and motor reactions during nightmares, slowness of the left leg and gait disturbance 10 years ago. He was diagnosed with PD at a regional hospital 9 years ago and prescribed levodopa. Family history was positive: the patient's father was diagnosed with PD. The initial brain MRI showed microangiopatic foci. Concomitant diseases were arterial hypertension (nebivolol 5 mg/day) and hypercholesterolemia (rosuvastatin 10 mg/day). The patient had a full-time shift job. In February 2017, during the patient's first consultation at the VUHSK, he reported using prolonged levodopa 200 mg×4 times/day (LEDD=600 mg/day). Objective examination revealed hypophonia, bradilalia, fragmented smooth pursuit, moderate general and local bradykinesia (2 UPDRS points), continuous rest tremor in the right (leg 3 UPDRS points, arm 2 UPDRS points), tendence to propulsion, stable on postural test, no synkinesia in the left, short steps, no signs of dementia. PD was stage 2.5 according to the Hoehn-Yahr scale, and the treatment scheme was changed: levodopa regime was adjusted (standard release 200 mg×3 times/day and controlled release 200 mg at bedtime), rasagiline 1 mg/day was introduced and gradually amantadine 100 mg×2 times/day was added (LEDD=1050 mg/day), melatonin 3 mg in the evening for REM parasomnias. The effect was positive but partial, and in March 2017, ropinirol 2 mg/day was added and titrated to 12 mg/day (LEDD=1250 mg/day) in 6 months. No side effects were reported during follow-ups, and questionnaires on ICD and daytime somnolence were negative. In 2018, the patient reported a wearing-off phenomenon and was prescribed entacapone 200 mg×3 times/day with standard-release levodopa (1400 mg/day). After relief of fluctuations in 2019, the patient reported fatigue and episodic somnolence in the second half of the day, without sudden

sleep attacks. His score on the Epworth Sleepiness Scale (ESS) was 8 points. Ropinirol was divided into 8 mg in the morning and 4 mg in the evening and the dose of amantadine was increased to 400 mg/day (LEDD=1600 mg/day), and the ESS score became 4 points, there were no sudden sleep attacks. Gradually, the patient began to experience choreatic dyskinesia which he did not considered troublesome. He missed his visit in 2020 during the lockdown and arrived at the VUHSK PD consultiation room in September 2021. He was vaccinated against SARS-Cov-2 three times (January, January, September 2021). The patient complained of gradual worsening of his condition in the last years: increased dyskinesia, slurred speech, insomnia, nightmares and arousal during night sleep; he denied ICD and sudden sleep attacks, his ESS score was 10 points, he was driving and working. He reported that a regional neurologist had increased combined levodopa to 4 intakes per day and ropinirol to 16 mg/day (LEDD=1916.8 mg/day). Objective examination during ON period with troublesome dyskinesia revealed normal cognition (MMSE score 30), generalized moderate chorea, hyperkinetic dysarthria with improvement on fixation of attention, rigidity 1 UPDRS point, more prominent in the left, no tremor, able to stand up with arms crossed on chest without assistance, gait unstable but independent, blood pressure 140/90 mmHg, heart rate 78 beats/min. The patient's PD was stage 3, and he was recommended to stop entacapone and to decrease ropinirol to 12 mg/day (LEDD=1675 mg/day). At the follow-up visit in December 2021, his condition remained complicated with the same complaints; he reintroduced entacapone because his motor symptoms worsened after excluding entacapone and decreasing ropinirol (LEDD=1875 mg/day). The patient was scheduled for hospitalization at the VUHSK Department of Neurology for further examination (polysomnography, multi-team evaluation for deep brain stimulation). The patient was admitted to the Department of Neurology in January 2021. His PCR for SARS-Cov-2 RNA 24 hours before admission was negative. Blood and urine analysis showed no abnormalities, therapeutic condition and ECG were normal, videofluoroscopy for dysphagia revealed no abnormalities. Neurological condition was similar to previously described, MMSE score was 30. The patient started filling the PD diary, but was not thorough. The patient was consulted by a rehabilitologist and started to attend kinesitherapy and speech therapy. He refused a planned consultation with a psychiatrist for revealing underlying psychiatric pathology and insomnia. On the fourth day of hospitalization, in the morning, the patient became confused and reported some visual hallucinations (relatives in the ward, unknown objects) with insight preserved; there were no changes in general condition, no fever, no signs of trauma, no abnormalities of urination and bowel movements; the day before repetitive PCR for SARS-Cov-2 RNA was negative. The patient repeatedly refused to consult a psychiatrist, so he was under constant observation after treatment adjustments were made (amantadine and entacapone was discontinued and quetiapine 25 mg at bedtime was prescribed). Within a few hours the patient became agitated, aggressive towards clinicians and was transferred to the department of psychiatry. Treatment recommendations for PD at transfer were: to discontinue amantadine, taper ropinirole to 4 mg/day (and discontinue in case of persisting psychosis), continue standard release levodopa 200 mg×4 times/day (or increase to 5 times/day), controlled release levodopa 200 mg at bedtime, rasagiline 1 mg in the morning. PCR for SARS-Cov-2 RNA on admission to the emergency room of the psychiatric department was positive. The patient was treated in the department of psychiatry for 10 days until complete resolution of symptoms; chest X-ray and brain CT scan revealed no abnormalities. He was discharged to out-patient regime in a stable condition without psychotic activity with the recommendation to continue quetiapine 50 mg at bedtime. There are no data on the patient's objective neurological status and further psychiatric condition during the last year as he did not attend a contact consultation after the psychosis.

DISCUSSION AND LITERATURE REVIEW

The management of psychosis in PD is a challenge for clinicians, caregivers and/or family members of patients. It begins with recognition of the psychotic event, includes causative diagnosis, adjustment of PD treatment and antipsychotic treatment if needed, and leads to preventive measures.

In 2007, the joint National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Mental Health (NIMH) work group defined the landscape of psychosis in PD and, despite further deeper insights into pathogenesis over the past 16 years, these criteria are presented in the Table 1 and remain the gold standard for diagnosing psychosis in PD (PPD) to date [4].

Table 1. **Diagnostic criteria for psychosis in Parkinson's disease according to NINDS and NIMH work group, 2007** [4]

1. Characteristic symptoms	At least one symptom of illusions, false sense of presence, hallucinations, or delusions
2. Primary diagnosis	Per United Kingdom Brain Bank Criteria for PD
3. Chronology of symptoms	Psychosis symptoms occur after PD onset
4. Associated features	Note symptoms as occurring with or without insight, dementia, or PD treatment
5. Exclusion of other causes	Symptoms are not better accounted for by another cause of parkinsonism
6. Duration of symptoms	Symptoms recur or are continuous for 1 month

Table 2. **Screening tool and treatment algorithm for the diagnosis and management of psychosis in Parkinson's disease, 2022** [13]

I. Pre-visit screener	1. Does the patient see, hear or otherwise sense the things that others do not? (e.g., seeing people or animals that are not, hearing music, misidentifying objects)	
	2. Does the patient believe things that others do not believe to be true? (e.g., that other people are cheating, conceiving, harming, conspiring against them)	
II. Clinician's assessment	Does the patient have hallucinations or delusions that affect or disrupt any of his/her behaviors or activities or cause distress including caregiver?	
	IF YES -	IF NO -
	Psychosis in Parkinson's disease with or without dementia	Reassess at the next visit
III. Treatment guidance	1. Assess and treat secondary medical and comorbid psychiatric conditions, adjust medications (anticholinergics, opioids, miorelaxants, tricyclic antidepressants) and initiate behavioral intervention	
	2. Optimize medications for Parkinson's disease (e.g., amantadine, dopamine agonists)	
	3. Initiate treatment: Clozapine and pimavanserine – clinically useful; Quetiapine – possibly useful; Avoid other atypicals if possible.	
	4. Re-evaluate in 4-6 weeks	
	5. If symptoms persist, adjust and add other medications	

In the typical clinical case-scenarios, the minor phenomena gradually evolve to formed visual hallucinations with insight initially preserved but lost in later stages; delusions and non-visual (auditory, tactile, olfactory) hallucinations may also develop over time. This spectrum of positive symptoms occurs after the onset of Parkinson's disease, with or without insight, dementia, or PD treatment, other causes of parkinsonism have been excluded [4]. PPD is diagnosed when symptoms recur or are continuous for at least one month. Our patients did not have such progressive history of evolution of psychotic symptoms and this fact favors for secondary cause of psychosis. Obviously, the reporting of illusions, false sense of presence, hallucinations, or delusions in outpatients may be not comprehensive or even absent in routine clinical practice, especially in case of cognitive decline, loss of insight, lack of support, caregivering or comprehension [5].

Screening for psychosis in PD should be active, especially after the introduction of new medications, in all cases of advanced disease, or in patients with pre-existing cognitive deficits. Up to 70% of PD patients experience hallucinations and/or delusions at some point during the course of the disease, but they (and/or their caregivers) often do not report these debilitating non-motor symptoms to physicians unless specifically questioned.

The most common movement disorder-focused screening tools used in clinical research are the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [6], the MDS-Non-Motor Rating Scale [7], MDS Non-Motor Symptoms Scale (NMSS) [8], the Non-Motor Symptoms Questionnaire (NMSQ) [9], and the Scale for Assessment of Positive Symptoms Adapted for Parkinson's Disease (SAPS-PD) [10, 11]. Such screening tools and rating scales for PPD that were developed for clinical trials are too complicated for routine clinical use or do not define psychotic symptoms clearly enough to inform treatment decisions, as described in a recently published review article by Sabbagh M et al. [12]. The lack of simplified and standardized screening limits the identification of patients suffering from PPD and reduces the early probability and effectiveness of specific intervention. Therefore, in 2022, a US expert panel reviewed the literature for existing guidelines on the diagnosis and management of psychosis in PD and developed an elegant screening tool and treatment guidance for practical clinical approach to PPD [13]. This algorithm consists of two parts: (1) a brief pre-visit screening part to be completed by the patient and caregiver, and (2) a clinician part to be completed via clinical interview with the patient and caregiver [13], as shown in Table 2.

We looked at the possible causes of psychosis in both previously described clinical cases. Patient-related risk factors usually include dementia, sensory deprivation, sleep disturbances, severe or even end-stage comorbidities. In patients with PD, underlying cognitive impairment or preceding psychiatric disorders increase the risk of psychotic events during acute concomitant diseases. Neither of our patients had been diagnosed with any serious internal insufficiencies, cognitive deficits, significant anxiety or depression, impulse control disorders, minor or major psychotic events prior to the manifestation this psychotic episode. Both of them had a history of episodic insomnia due to job-related peculiarities (stress, shifts), but there was no report of any change in the burden of distress prior to the onset of the psychotic event.

Excluding any cause other than positive SARS-CoV-2 antigen, we searched for explanations for the absence of typical symptoms of infection, such as fever, pain, rhinitis, cough, pulmonary complications, or gastrointestinal disturbances. In a systematic review of COVID-19-related new-onset psychosis by Chaudhary AMD et al., 25% of patients presented with classic COVID-19 symptoms (fever, cough, malaise, headache, loss of taste and smell, myalgia, shortness of breath, diarrhea), and others had clinical variations; most patients had mild COVID-19-re-

lated symptoms and 26.3% of patients had moderate to severe COVID-19-related disease; 8.8% of patients had a complicated course, with the death of one patient due to COVID-19 complications [3]. Anosmia and ageusia are admitted to be specific to the clinical presentation of COVID-19, but in PD patients this rule is not reliable as decreased sense of smell (and sometimes taste) is one of the most frequent and earliest non-motor symptoms of PD.

Vaccination against SARS-Cov-2 helps prevent or alleviate clinical symptoms of the infection, and both of our patients were fully vaccinated in accordance with legislative requirements. Breakthrough infection is associated with a lower number of symptoms, a shorter duration of symptoms, a lower likelihood of persistent symptoms for >28 days (i.e., a lower rate of "long COVID-19"), and a higher likelihood of asymptomatic infection compared with infection in unvaccinated individuals [14–16]. Although the preventive effect wanes over time, vaccination may explain (to some extent) the lack of other clinical symptoms of coronavirus infection in the cases described.

We evaluated the list of prescribed medications in the cases presented according to the national electronic health registry. The treatment regime has not changed in the last 6 months: there have been no dose escalations or new prescriptions. There were no signs of overdose or aberrant behavior in our cases. Both our patients were treated with amantadine 200 mg × 2 times/day. Since the beginning of the pandemic, there have been suggestions that amantadine may have some protective effect against COVID-19. However, the latest evidence from clinical studies have not demonstrated any preventive benefits of this medication. F. Przytuła et al. recently published the results of an observational, retrospective, multicenter cohort study of five hundred and fifty-two (n=552) idiopathic PD patients and concluded that amantadine does not affect either the severity or the risk of developing COVID-19 [17].

It is important to differentiate psychotic events from focal neurological symptoms, such as hemianopsia and other visual disturbances, aphasia, apraxia, and REM-behavior disorder. Although the search for causes in PPD includes a variety of therapeutic conditions and a detailed pharmacological history, it is important to remember that some underlying diseases may be oligosymptomatic like COVID-19 in vaccinated patients. In a systematic review of COVID-19-related new-onset psychosis in the general population by Chaudhary AMD et al., reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 was positive in 66.7% of patients, reactive COVID-19 IgM/IgG antibodies were reported in 8.7% of patients, and the diagnostic test used was not reported in the rest of cases [3]. These data confirm that SARS-Cov-2 is a potent provocative factor for psychotic events. Therefore, when facing PPD, clinicians should not be misled by the fact that Parkinson's disease is a main cause or a single underlying condition of psychotic symptoms. Thorough etiological investigations in PPD should include RT-PCR for COVID-19 even in the absence of other clinical signs of infection.

Practical recommendations

Untreated symptoms of PPD are associated with worse outcomes, poor quality of life, and significant distress to the caregiver and patient. The management of psychosis in PD is a challenge for clinicians, caregivers and/or the patient's immediate environment. An appropriate treatment plan for PPD is developed according to the results of assessment (Table 2). Assessment and management of secondary causes (therapeutic, medical) should be carried out without delay, e.g., diagnosis and management of anemia, pain, sleep disturbances, urinary tract infection, sensory deprivation, hyponatremia, hypothyrosis, aberrant drug behavior, overuse of over-the-counter (OTC) medications. When optimizing antiparkinsonian medications, the rule should be to stop first the one which was introduced the last; if the treatment regime has been stable, it is recommended to stop first those with the strongest propsychotic activity and then continue with the others if psychosis persists: STEP 1 – anticholinergics; STEP 2 – amantadine; STEP 3 – dopamine agonists; STEP 4 – COMT inhibitors; STEP 5 – MAOB inhibitors. Levodopa is considered the safest medication in terms of psychotic activity in PD. As the decrease in LEDD leads to a worsening of the PD condition, the LEDD should be compensated with levodopa and maintained at a safe rational level. Antipsychotic treatment is introduced when necessary. Only a few medications are considered to have sufficient safety profile: clozapine and pimavanserine are considered to be clinically useful according to MDS and NICE guidelines; quetiapine – possibly useful; it is recommended to avoid other atypicals (all other antipsychotics) if possible [5, 12, 13].

We did not find any specific recommendations for the treatment of PPD in COVID-19. Future studies will provide a more precise analysis of the prevalence, severity, associated pathology of psychological manifestations and outcomes of COVID-19 in PD patients, and possibly will lead to some specific treatment guidelines for PPD.

CONCLUSIONS

Psychotic disorders in patients with PD are usually associated with poor cognitive performance, comorbidities and changes in treatment regime. Despite the acknowledgement of cognitive deficit as a major risk factor for psychosis in PD, psychotic events have been reported to occur in patients without dementia. SARS-CoV-2 so far is recognized as a harmful invader of the nervous system, and defining its consequences still requires multidirectional research. Patients with PD may develop psychosis during COVID-19 infection. According to our observation, psychotic disorder may be an isolated manifestation of SARS-CoV-2 infection in PD, as in the presented two clinical cases of non-demented patients who were on stable antiparkinsonian medication, did not previously express

any psychiatric disturbance and who developed psychosis as a consequence of COVID-19, without any other clinical signs of infection; they had been fully vaccinated against SARS-CoV-2; no recurrent psychotic disorders were registered during available one-year follow-up. We recommend that patients with PD who develop acute psychosis should have a reverse transcription polymerase chain reaction (RT-PCR) swab test for SARS-CoV-2.

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G. Lokominaitė, R. Kaladytė Lokominienė

PSICHOZĖ KAIP IZOLIUOTAS COVID-19 KLINIKINIS SINDROMAS, SERGANT PARKINSONO LIGA BE DEMENCIJOS: ATVEJŲ PRISTATYMAS IR LITERATŪROS APŽVALGA

Santrauka

Psichoziniai sutrikimai, sergant Parkinsono liga, dažniausiai siejami su kognityviniu deficitu, lydinčiomis ligomis ir medikamentinio gydymo režimo pasikeitimais. Nors kognityvinis sutrikimas laikomas svarbiausiu Parkinsono ligos metu ištinkančios psichozės rizikos veiksniu, psichoziniai sutrikimai gali vystytis ir demencijos neturintiems pacientams. Šiuo metu žinoma, kad SARS-Cov-2 virusas pažeidžia nervų sistemą, tačiau atokių įvairialypių šios invazijos pasekmių tyrimai vis dar tęsiami. Parkinsono liga sergantiems pacientams psichozė gali vystytis COVID-19 infekcijos metu. Remiantis mūsų pastebėjimais, panašu, kad psichozinis sutrikimas gali būti izoliuotu SARS-Cov-2 infekcijos klinikiniu sindromu pacientui, sergančiam Parkinsono liga. Šiame straipsnyje pateikiami dviejų pacientų, kurie sirgo Parkinsono liga be demencijos ir buvo pilnai vakcinuoti nuo SARS-Cov-2, klinikiniai atvejai. Pacientai laikėsi stabilaus Parkinsono ligos gydymo režimo, neturėjo ankstesnių psichikos sutrikimų ir patyrė ūminę psichozę, susijusią su COVID-19, nesant kitų klinikinių šios infekcijos požymių. Vėlesnės stebėsenos metu per 12 mėnesių jokių rekurentinių psichozinių sutrikimų nestebėta. Straipsnyje aptariami pacientą, sergantį Parkinsono liga, ištikusios psichozės etiologinės diagnostikos sunkumai ir gydymo galimybės. Rekomenduojame pacientus, sergančius Parkinsono liga, kuriems išsivysto ūminė psichozė, tirti dėl SARS-Cov-2 infekcijos.

Raktažodžiai: Parkinsono liga, COVID-19, SARS-Cov-2, psichozė.

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