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DIFFICULTIES IN DIAGNOSING PARKINSON'S DISEASE WITH DEMENTIA AND DEMENTIA WITH LEWY BODIES IN CLINICAL PRACTICE

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Dementia is a chronic cognitive decline affecting all domains of cognition with an unfavorable outcome, observed in both dementia with Lewy bodies (DLB) and Parkinson's disease (PD). These two conditions belong to the group of alpha-synucleinopathies. In DLB and PD, attention, goal-directed activity, visual-spatial orientation, visual-constructive ability, and memory are affected. The similarity of the profile of cognitive impairment in PD with dementia and DTL leads to some difficulties in the diagnosing of these two diseases. Using their own observations, the authors have demonstrated that an important aspect in making the correct diagnosis is objective information from relatives and analysis of the available medical records.

Keywords: dementia, dementia with Lewy bodies (DLB), Parkinson's disease (PD), cognitive impairment, visual hallucinations.

Introduction. Parkinson's disease (PD) and dementia with Lewy bodies (DLB), or diffuse Lewy bodies disease, are associated neurodegenerative diseases that belong to the group of alpha-synucleinopathies and have similar cognitive, behavioral, and autonomic disturbances [1, 2]. Alpha-synuclein is a protein consisting of 140 amino acids, which can aggregate under pathological conditions to form intracellular inclusions - Lewy bodies [7].

According to the Braak theory, the neurodegenerative process in PD undergoes 6 stages and starts from the nuclei of the vagus nerve and the olfactory bulb. Classical motor symptoms appear at stage 3 of the degenerative process, when the Lewy bodies are found in the neurons of the substantia nigra of the midbrain. Starting from stage 4, the process involves the cortex neurons, which causes the development of cognitive disorders and their progression up to the dementia level [8]. In DLB, the neurodegenerative process is multifocal, and Lewy bodies are found in the cerebral cortex from the very early stages, which may explain the early onset of cognitive impairment. However, in DLB brainstem lesions may be less severe than in PD, resulting in a less prominent presentation of parkinsonism in patients [9].

In 2017, McKeith and colleagues published updated criteria for the diagnosis of DLB, in which dementia is a core symptom of the disease. Additionally, cognitive fluctuations, visual hallucinations, REM sleep disorder, and signs of parkinsonism are considered to be main features. Symptoms such as hypersensitivity to neuroleptics, falls, severe autonomic dysfunction, hyposmia, anxiety, and apathy are attributed to supportive (but not obligatory) criteria [5]. Thus, dementia is an obligatory feature of DLB.

Regarding PD, at the early stages 20% of patients have mild to moderate cognitive impairment [3]. After 3.5 years, 57% of patients have moderate cognitive impairment, and in 10% of cases, cognitive impairment already reaches the degree of dementia; after 17 years of the disease, dementia develops in almost 80% of patients with PD. Risk factors for the development of dementia in PD includes: age, akinetic-rigid form of the disease, reduced semantic speech, genetic factors, low level of education, and postural instability [10]. Thus, dementia in PD develops later, while in DLB it is already present from the disease onset. In this regard, it is useful to apply the "first-year rule" in clinical practice: if dementia presents in the background of PD after at least 1 year from the onset of motor symptoms, it is regarded as PD with dementia; if dementia develops within the first year from the onset of parkinsonism or even precedes or occurs simultaneously with the development of motor symptoms, these cases are classified as DLB [11].

Table 1 lists the overlapping features and distinguishing features of dementia in PD and DLB [6].

Hence, the cognitive impairment profile in PD with dementia and DLB is nearly identical. When patients are approached without obtaining objective information from relatives or medical records, there may be difficulties in establishing a correct diagnosis.

Further, we present two clinical cases of PD with dementia and DLB.

Clinical case №1. Patient E., 60 years old, was referred to the neurology department with complaints of slowness and depletion of movements, unsteadiness and freezes when walking, acceleration during forward movement, urinary incontinence, persistent constipation, loss of sense of smell, change of handwriting, feelings of sadness, anxiety, sleep disorders, non-intimidating visual hallucinations.

Patient had been ill during 7 years. First symptoms of disease in the form of slowness of movements were noticed by her colleagues. Slowness of movements and shuffling when walking appeared next year. Neurologist diagnosed Parkinson's disease and prescribed 50 mg of piribedil 3 times a day. During treatment, the patient began to show positive dynamics. On the third year of the disease, she had mild urinary incontinence, worsened motor symptoms such as difficulties with standing up from the chair, tremor and increased slowness of movements. At the fourth year of the disease the patient started therapy with levodopa (levodopa/carbidopa 250/25 mg 3 times a day) with a slight effect in the form of reduction of stiffness. From the fifth year of illness, when she lived alone at home, she began to invite strangers home from the street,

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Similarities and differences of PD with dementia and DLB (according to Jellinger K. и Korczyn A., 2018; modified by authors)

Sign	PD with dementia	Lewy bodies dementia
Паркинсонизм	Obligatory	Less pronounced than in PD May absent in 25% of patients Tremor less frequent
Cognitive impairment	Dysregulation	Dysregulation with greater impairment of memory and attention than in PD
Visual-spatial impairment	Typical	Typical
Visual hallucinations	Frequently caused by dopaminergic therapy, but can also occur spontaneously	More frequent, spontaneous, not associated with visual-spatial and gnosis impairment
Anxiety, depression	Typical	Typical
Rapid eye movement phase sleep disorder	Yes, can precede motor symptoms	Yes, can precede dementia
Sensitivity to neuroleptics	+	+++
Autonomic failure	+	++

called them her close friends and offered them food. At the same time, relatives began to notice that the patient periodically began to babble, talking to non-existent people, saw them in the room and in the window. Sometimes she was critical of her own visions, mood swings with pronounced anxiety and restlessness were noted.

At the admission, the patient was taking levodopa/carbidopa 250/25 mg 3 times daily, pramipexole 1 mg once daily and levodopa/benserazide 200/50 mg 3 times daily. The duration of this medication combination is unknown, due to cognitive impairment and lack of discharge.

In the neurologic status: anosmia, hypomimia, bradylalia, positive oral automatism reflexes. Muscle tone in the arms was elevated by the "cogwheel" type, predominantly on the left; in the legs, elevated by the "lead tube" type, more on the left. Tremor of the jaw. Severe oligobradykinesia. Pull-test is positive. Shuffling gait. Bending posture. Drug-induced dyskinesias in the trunk and limbs. She scored 73 on part 3 of the UPDRS scale.

The patient was awake and appeared untidy. While examining her, keeps quietly singing along to the motive of the song, says she "spins in her head", so she feels better. She interacts, self-criticism was reduced. She follows instructions, easily exhausted.

Attention is unfocused, easily distracting. Mnestic impairments such as difficulty with the delayed reproduction, cannot remember with the help of cues. Reduced volume of auditory verbal memory. Reduced phonetic speech activity (7 words per minute, while normal is 11 words). Difficulties in assimilation of motor series in the dynamic praxis test, substitutions for stereotypies were noted. She failed the clock drawing test (Fig. 1A). Serial counting impairment also was noted. Therefore, taking into account the findings of the examination, we can suggest the presence of cognitive disorders of a dysregulatory neurodynamic character associated with cortical frontal dysfunction.

The MoCA test was performed - 13/30 points, the Hospital Anxiety and Depression Rating Scale (HADS) scored 15 points for anxiety and 11 points for depression.

Brain MRI revealed moderate atrophic changes of the cerebral hemispheres, cerebellum, slight atrophy of midbrain.

Based on the medical history (she has been observed with PD for 7 years, symptoms of cognitive decline have been present since the 5th year of the disease) and clinical presentation (parkinsonism, dementia, visual-spatial disturbances, visual hallucinations, autonomic dysfunction, drug-induced dyskinesias) the patient was diagnosed with PD with dementia.

Treatment correction was carried out: one drug of levodopa was withdrawn, leaving only levodopa/carbidopa in a dose of 250/25 mg 3 times a day, pramipexole was withdrawn, and memantine was added with titration up to 20 mg/day and atypical neuroleptic quetiapine 12.5 mg before bedtime. After 3 weeks, as a result of treatment correction, drug-induced dyskinesias had resolved, the severity of hypokinesia and muscle rigidity had decreased, walking became better (scored 41 points on Part 3 of the UPDRS), visual hallucinations had resolved, and her clock drawing test score had improved (Figure 1B), with a score of 20/30 points on the MoCA.

Clinical case №2. Patient K., 69 years old, came to the consultation with her daughter, with complaints of recurrent visual hallucinations, memory loss, forgetfulness, general weakness, trembling of the right limbs, muscle stiffness, more in the right limbs, slowness of movement, walking freezes.

The patient has been observed since

a b

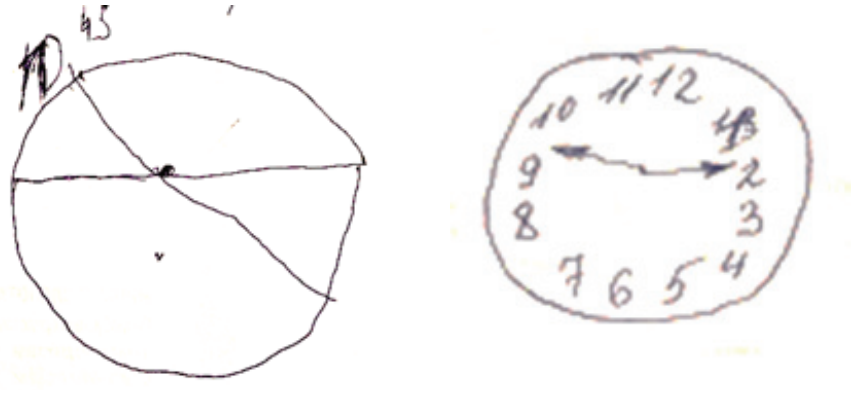

Fig. 1. Result of patient E's clock drawing test: A - at admission: the face and arrows are missing, sectoral pattern determined; B - during therapy correction: slight displacement of digits on the face, equal size of the arrows.

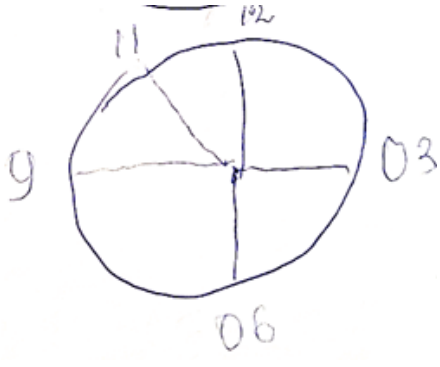

Fig. 2. K.'s clock drawing test results.

the onset of the disease. At the age of 65 years, right leg trembling and shuffling when walking appeared. Initially, the patient did not notice the symptoms, because they were explained as a result of a food poisoning. Over the next six months, however, her right hand began to tremble and her memory started to decline. At the same year the patient came to us for treatment. Examination revealed hemiparkinsonism in the right side, rest tremor in the right extremities, with a score of 38 on UPDRS Part 3. In addition, extracampine hallucinations in the form of false presence were revealed, she was not able to perform the clock drawing test (Fig. 2), her verbal activity was reduced (phonetically associated words - 4, semantically associated words - 2), visual memory was reduced (spontaneous reproduction of 2 pictures out of 12), but recognition was preserved (she named 11 pictures out of 12 with hints). An MRI scan of the brain detected moderate convexital atrophy of the frontal regions. On account of the equal severity and simultaneous development of parkinsonism and cognitive impairment, the diagnosis of diffuse Lewy bodies disease was established. She was prescribed levodopa/benserazide titrated up to 100 mg/25 mg 3 times daily, acetylcholinesterase inhibitor donepezil titrated up to 10 mg daily (however, she took only 5 mg daily because of fear of adverse effects). During therapy, however, motor activity improved and extracampine phenomena were eliminated.

The year following, visual hallucinations commenced, she began to see her children. During examination there was no deterioration of motor symptoms, she was not able to perform the clock drawing test, she drew sectors, there was a deterioration of visual memory: she was able to reproduce only 4 pictures with hints, 5 false memories were detected. For relieving hallucinations, the atypical neuroleptic drug quetiapine in a dose of 12.5 mg at night was recommended, and the dose of donezepil was increased up to 10 mg. There was significant improvement during treatment: hallucinations were eliminated, the patient became able to take care of herself better, and could do her own domestic routine work.

After 6 months, the patient continued to worsen: she began to speak to herself, and the slowness of her movements became more pronounced. Examination revealed a significant increase in parkinsonian symptoms (she scored 62 on UPDRS Part 3). Due to increase of motor symptoms the dose of levodopa/benserazide was increased up to 150/37.5 mg 3 times a day with positive effect. Relatives began to notice fluctuations in severity of cognitive impairment: at evening hours, the patient became clearer, more adequate.

For the next two years (2020-2021), the patient was at home due to COVID-19 restrictive measures. During this time, the cognitive status significantly worsened, visual hallucinations became more frequent, but there was no rapid increase in the symptoms of parkinsonism.

Neurological examination showed: hyposmia, hypomimia, oral automatism reflexes, muscle tone of extremities moderately increased by lead tube type, S>>D; strength in extremities sufficient, without any paresis; a resting tremor in left arm, right leg; moderate hypokinesia, D<S; pull-test is positive; shuffling, achyrokinesis on right side (she scored 37 on UPDRS scale, part 3).

She was unable to complete the clock drawing test, cube copying test; verbal activity decreased (phonetic - 1 word per min, semantic - 2 words per min). She scored 9/30 on the MoCA scale.

Discussion. In summary, the cognitive profile of both patients was nearly identical at the time of examination. The only thing that cardinally distinguished the patients was time of cognitive impairment onset. Patient E.'s dementia developed along with the long-lasting PD. It is highly likely that her visual hallucinations were associated with excessively high doses of levodopa medications (she was taking 1350 mg/day) and intake of dopamine receptor agonist pramipexole, a group of drugs which more frequently than levodopa cause development of hallucinations. We abstained from prescribing acetylcholinesterase inhibitors due to bradycardia. When the hallucinations steadily resolved, the atypical neuroleptic can be completely withdrawn. In contrast, in patient K., the onset of cognitive impairment was almost simultaneous with the development of parkinsonian symptoms. We also observe visual-spatial impairment and visual hallucinations. Additionally, fluctuations of the cognitive status were detected. All these factors combined made the diagnosis of DLB possible.

Conclusion. PD and DLB are clinically and pathomorphologically similar diseases; both relate to disorders with accumulation of Lewy bodies. The difference is in the more widespread neurodegenerative process in DLB and, consequently, in the early development of cognitive impairment. Treatment of DLB and PD with dementia has similarities: to reduce the severity of parkinsonism there is a preference for levodopa drugs, regardless of the age of the patient; to treat cognitive impairment, acetylcholinesterase inhibitors and the NMDA-receptor antagonist memantine are prescribed; to relieve hallucinations, atypical neuroleptics are cautiously prescribed.

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