PROGRESSIVE SUPRANUCLEAR PALSY-PURE AKINESIA WITH GAIT FREEZING

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S u m m a r y. Main diseases in the spectrum of atypical parkinsonism include progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and multiple system atrophy (MSA). We present a case of PSP. A 66-year-old female was admitted to the Department of Neurology for the progression of generalized motor slowing, muscular rigidity, tremor and postural instability. Levodopa was the first-line treatment introduced, and it reduced a number of freezing episodes, and improved her movements. Nevertheless, PSP as one of severe neurodegenerative diseases progresses relentlessly, and is fatal after a few years.
K e y w o r d s: progressive supranuclear palsy, atypical parkinsonism, tau protein.

INTRODUCTION

Progressive supranuclear palsy (PSP) is an uncommon neurodegenerative disorder considered one of atypical parkinsonisms. Other members of this group are dementia with Lewy bodies (DLB), corticobasal degeneration (CBD) and multiple system atrophy (MSA) [1]. MSA is dominated by autonomous and cerebellar disorders. In the CBD there is dystonia and upper limb apraxia. DLB includes early dementia, hallucinations, and fluctuating character of the symptoms. PSP is linked genetically and biochemically to tau protein abnormalities with a mean age of onset around the age of 65 [2, 3]. Incidence of the disease is 5.8- 6.4 per 100,000 [4, 5]. It increases greatly after the age of 65, and it may be more than two times higher than in people aged 40 to 64 [6].

This syndrome was described for the first time in 1964 by Steele, Richardson, and Olszewski as an unusual constellation of progressive axial dystonic rigidity, dysarthria, supranuclear gaze palsy, pseudobulbar palsy, and mild dementia [7,8]. In 1972, Steele noted that the disease tends to locate in different parts of the brain, is of different degree, and occurs at a different time. Considering those facts, he predicted clinical variants of PSP are likely to occur [9]. After a couple of years, it turned out that he was right. Since the time when PSP was characterized for the first time, numerous phenotypes have been described and correlated with the accumulation of faulty tau proteins in various regions of the brain [10]. Despite many trials, no effective treatment has been proposed so far. There are practically no cases of autopsy-confirmed PSP in patients under the age of 40 years [11]. PSP affects cognition, movement, balance, gait, behavior, swallowing, eye movements, speech, and mood [8]. At an early stage, slowed vertical saccades are often the only manifestations detected in the eyes. Other typical symptoms are pseudobulbar palsy, axial rigidity, positive pyramidal signs, retrocollis, and sometimes mild tremor.

MATERIALS, METHODS AND AIM

The article reviews the literature on PSP, and presents a case of a 66-year-old female with PSP who was admitted to the Department of Neurology. She was diagnosed with the subtype of PSP referred to as “pure akinesia with gait freezing”.

CASE REPORT

A 66-year-old female was admitted to the Department of Neurology for a progression of generalized motor slowing, muscular rigidity, tremor, and postural instability, which she had for 4 years. Moreover, she suffered from ongoing memory impairment.

On admission, neurological examination revealed affected upgaze ocular movement, extrapyramidal syndrome with progressive axial rigidity, positive applause sign, and bradykinesia. Numerous episodes of freezing were observed. The patient was confined to a wheelchair.

During hospitalization in the Department of Neurology the patient undergone multiple diagnostics tests. Mini-Mental State Examination (MMSE) test did not find any significant cognitive decline. The patient scored 29 out of 30 maximum. However, the patient reported memory problems. Psychological examination was performed. She was co-operative, and auto- and allo-psychically oriented. Mild dysarthria was observed, however its severity, according to the patient, it varied over the time. MRI scan of the head revealed minor disseminated white matter lesions located in the frontal and parietal lobes, probably of angiogenic origin, cortico-subcortical atrophy of the frontal, parietal and temporal lobes was observed together with degeneration of the frontal cerebellar lobes. No lesions were found in the midbrain. The ventricular system was symmetrical, not dilated and not displaced.

Based on anamnesis, physical examination, and diagnostic tests, the diagnosis of progressive supranuclear palsy subtype pure akinesia with gait freezing (PSP-PAGF) was made.

DISCUSSION

Neurodegeneration in PSP is strongly linked to pathological tau proteins. In this disease loss of regular tau function or toxic enhancement of tau function is observed [12]. Tau is a microtubule-associated protein that is present predominantly in the neurons of the central nervous system. Tau is active primarily in the distal regions of the axons. It is responsible for proper structural functions such as stabilization and flexibility [13]. Moreover, it takes part in the axonal transport, regulation of mitosis and apoptosis. In all tauopathies, tau becomes hyperphosphorylated, and this leads to microtubules disengagement [14, 15]. It causes attenuation of the bonds between microtubules and aggregation. Resultant dysfunction of neurons and their degeneration is observed. In tauopathies, there is a strong correlation between the extent of tau pathology and the degree of clinical symptoms [16]. In PSP intracerebral tau tangle-like accumulations of faulty tau protein are predominantly located in the basal ganglia, diencephalon, cerebellum, and brainstem [17].

To diagnose PSP four criteria must be met: sporadic occurrence, age ≥ 40 at the onset of first PSP-related symptoms, and a gradual progression of the disease. These are mandatory inclusion criteria. Old criteria based on either vertical supranuclear gaze palsy (ocular motor dysfunction) alone, or together with prominent postural instability with falls in the first year of the onset (postural instability) [18]. Recently, two new functional domains were added, i.e. akinesia and cognitive dysfunction [11]. The patient presented all 4 cardinal clinical symptoms. Revised criteria, besides main clinical features, included different types of PSP which resulted in improved diagnostic sensitivity in comparison to the old criteria.

PSP belongs to the group of atypical parkinsonisms (or Parkinson-plus disorders). This group is characterized by the presence of additional symptoms beside typical of the Parkinson disease. Main disorders observed in patients with Parkinson disease are slowed movement, rigidity, tremor, and impaired balance and coordination. Therefore patients with atypical parkinsonism, beside the symptoms observed in parkinsonism, present additional symptoms and signs, such as vertical gaze palsy, and early postural instability leading to frequent backward falls. In the reported case, there was ongoing slowness of movement, tremor, rigidity, postural instability and frequent backward falls. There are several clinical subtypes of PSP. The clinical heterogeneity of the disease is associated with variability of quantitative regional distribution of abnormal tau protein, its accumulation, aggregation, and loss of the neurons [19].

These subtypes are determined basing on the combination of early stage clinical features. The subtypes of PSP include classic progressive supranuclear palsy-Richardson syndrome (PSP-RS), progressive supranuclear palsy-parkinsonism (PSP-P), progressive supranuclear palsy-corticobasal syndrome (PSP-CBS), progressive supranuclear palsy-behavioral variant of frontotemporal dementia (PSP-bvFTD), progressive supranu-

clear palsy-progressive non-fluent aphasia (PSP-PNFA), and progressive supranuclear palsy-pure akinesia with gait freezing (PSP-PAGF) [10, 19]. The main differences between these few subtypes of PSP are presented in Table 1. In PSP-P there is asymmetric bradykinesia and limb rigidity without supranuclear vertical gaze palsy at the beginning. Patients with PSP-RS present early postural instability, subtle eye movement abnormalities, and frontal-subcortical deficits. PSP-PAGF is characterized by freezing gait, postural instability with falls, axial rigidity, and absence of limb rigidity. The symptoms of PSP-CBS are apraxia of the limbs, bradykinesia, levodopa-unresponsive rigidity, pyramidal and Babinski's signs. Patients with PSP-PNFA present disfluent speech, agrammatism, and phonemic errors. Characteristic features of PSP-bvFTD are personality changes, unrestrained and compulsive behaviors, distractibility, emotional dementia [19].

The onset of PSP-R usually occurs in the mid-60s. First symptoms are non-specific, such as blurred vision, dry eyes, photophobia, dizziness, fatigue, and dizziness leading to falls [19]. Then the disease gradually progresses. The reported case was diagnosed as PSP subtype, PSP-PAGF as the patient had numerous episodes of gait freezing. Correct diagnosis is commonly delayed up to 4 years after the onset of symptoms. The main symptom, and the greatest hazard in this subtype is postural instability with falls that appear early on. Furthermore, she presented apparent speech disturbance (dysarthria), the stiffness of the limbs and trunk together with impaired balance and coordination. Freezing episodes are observed during walking, talking and writing [20,21]. Freezing of gait is not specific only for PSP, therefore several other conditions should be taken into consideration. Differential diagnosis should also consider advanced Parkinson disease, MSA, CBD, DLB, and advanced gait disorders. This symptom predominates in the clinical picture of PSP, MSA, and DLB [22].

Table 1. Main differences between clinical features of PSP-RS, PSPS-P, PSP-PAGF, PSP-CBS, PSP-PNFA, PSP-bvFTD [3, 19, 31, own elaboration].

Subtypes of PSP	PSP-RS	PSP-P	PSP-CBS	PSP-PNFA	PSP-bvFTD	PSP-PAGF
Rigidity	mainly axial	mainly rigidity of limb	mainly rigidity of limb	+	+	axial
Postural instability	+	-	-/+	-	-	+
Falls	+					+
Early cognitive disorders	+	-	+	+	+	-
Non-fluent aphasia	+	-	+	+ (mainly)	+	-
Pyramidal and Babinski's signs	+	+	+	+	+	+
Levodopa response	-	+	-	-	-	-

Neuropsychometry testing is adjusted to the performance of different cognitive domains [19]. Besides the mentioned conditions, the neuropsychiatric changes are relevant in PSP. Depression, apathy, or agitation may be present during the early stages of the disease, however, they are often mild and as a result are frequently overlooked. Frontal lobe dysfunction is the most consistent deficit in PSP [23]. The symptoms include behavioral changes, apathy, emotional lability with uncontrollable laughter or crying, obsessive-compulsive behavior, and aggressive outbursts [19]. Nevertheless, these findings should be differentiated with primary psychiatric disorders. Misdiagnosis and prescription of antipsychotics may intensify extrapyramidal symptoms [24].

Atrophy of the midbrain and superior cerebellar peduncle and dilatation of the third ventricle are the characteristic findings of PSP on MRI scans of the head [19]. The MRI scan of the reported case revealed cortico-subcortical atrophy of the frontal, parietal and temporal lobes.

Levodopa is used during the first stage of the disease. There is no causal treatment as yet. In our patient, levodopa was used together with benserazide. The therapy resulted in reduced number of freezing episodes, and improved her movements. Levodopa is known to cause moderate, yet transient relief of symptoms in more than half of patients. Administration of levodopa together with a decarboxylase inhibitor restrains its peripheral

conversion to dopamine [25]. It mostly eases Parkinson symptoms like akinesia and rigidity. The same study also proved amantadine, 300 mg daily, improved bradykinesia, rigidity, and range of impaired eye movements [26]. Other drugs used in PSP therapy are dopaminergic agents, antipsychotics, acetylcholinesterase inhibitors, selective serotonin reuptake inhibitors, and Botulinum toxin [25].

During the therapy, it is important to apply a multidisciplinary approach including neurology, physiotherapy, occupational therapy, speech pathology, nutrition, neuropsychology, psychiatry, and palliative care [19]. Multidisciplinary aerobic, intense motor-cognitive rehabilitation may have beneficial effects on patients suffering from PSP. Exercises improve balance, gait, and sight control [27].

CONCLUSIONS

Majority of patients with atypical parkinsonism present symptoms of typical parkinsonism, including resting tremors, slowed movement, stiffness, gait difficulty, and postural instability. In addition, they present other symptoms and signs that are not typically observed in parkinsonism, such as vertical gaze palsy and early postural instability leading to frequent backward falls. Patients with PSP often have 'worried' facial expression. The symptoms are caused not only by the loss of cells in the substantia nigra, but also by additional degeneration of cells in certain parts of the nervous system. Each type of PSP is heterogenic, has its own clinical picture and prognosis. Progressive supranuclear palsy usually develops fairly rapidly and iminently [28]. Median of survival age from diagnosis is 7 years [29, 30]. Currently, there is no effective treatment for PSP, however, the growing interest in new tau-directed therapies may result in finding causative treatment in the future.

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