Chapter 9

Progressive Supranuclear Palsy (PSP)

Objective

To describe the history, core symptoms, pathology, and etiology of progressive supranuclear palsy (PSP).

Disease Overview

PSP is a group of diseases that exhibit parkinsonism and is a neurodegenerative disease that develops after middle age. The prevalence was 5.3-5.8 per 100,000 population according to most reports in the world. but recently a prevalence of 17-20 per 100,000 has been reported with ageing of the population. The main symptoms are supranuclear ocular motor dysfunction, dorsiflexion of the neck (cervical dystonia), akinesia, subcortical dementia, and impulsive behavioral disorder. In recent years, pathological studies have identified various disease types. Biochemical studies have shown that PSP is one of the diseases belonging to 4-repeat tauopathy (4RT), but the mechanism of tau accumulation and the pathogenesis of neuronal loss remain unclear. Many cases are sporadic, but hereditary PSP is also found. Most hereditary PSP cases are autosomal dominant. There are no obvious risk factors for disease development, but education history is the only weak risk factor. Tau haplotype analysis has indicated that PSP is associated with the H1 haplotype, while the frequency of H2 haplotype is low. However, from the studies of tau haplotypes in Japan, the Japanese population has exclusively H1 haplotype. According to Williams et al.[1], Richardson syndrome (PSP-RS) tends to be more common in men, but there is no gender difference in PSP-parkinsonism (PSP-P). The disease duration is 5.9 years for Richardson syndrome and 9.1 years for PSP-P. The most frequent causes of death are aspiration pneumonia, asphyxia, malnutrition, and trauma. Falls within 1 year of onset, dysphagia in early stage, and urinary incontinence are poor prognostic factors. There is no effective curative therapy, and only symptomatic therapies are available.

History and Classification

In 1964, Steele et al.[2] reported PSP as a disease entity with main clinical symptoms of axial rigidity, akinesia, tendency to fall, cognitive impairment, and supranuclear ocular motor dysfunction in the vertical direction; as well as pathological findings of neurogenic changes in the globus pallidus, substantia nigra, subthalamic nucleus, eye movement-related nucleus, tegentum, dentate nucleus, and inferior olivary nucleus. The first diagnostic criteria for PSP were conducted by Litvan et al.[3] in 1996. Then in 2007 and 2009, Williams et al.[1] classified PSP cases into Richardson syndrome (54%) that exhibits classical PSP; PSP-parkinsonism (PSP-P; 32%) which shows a clinical picture resembling Parkinson's disease with left-right asymmetric symptoms partially responsive to L-dopa; and atypical PSP (14%) that includes pure akinesia with gait freezing (PAGF), PSP with corticobasal syndrome (PSP-CBS), and PSP with progressive non-fluent aphasia (PSP-PNFA) (2009). Researchers in Japan and overseas have also reported a cerebellar variant of PSP (PSP-C)[4]. New diagnostic criteria have been proposed by the International Movement Disorder Society[5]. At present, the disease concept of PSP tends to be expanding, and elucidation of the pathogenesis is expected to control the etiology of PSP.

References

1) Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol 2009; 8: 270-279.
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3) Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996; 47: 1-9.
4) Koga S, Aoki N, Uitti RJ, et al. When DLB, PD, and PSP masquerade as MSA: an autopsy study of 134 patients. Neurology 2015; 85: 404-412.
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CQ 9-1

What are the features of dementia symptoms in progressive supranuclear palsy (PSP)?

Answer

- The characteristic dementia symptoms of classical PSP (also termed Richardson syndrome; PSP-RS) are generally referred to as subcortical dementia. The symptoms include slowed thinking, impulsiveness, stubbornness, and perseveration.
- One-third of the patients with PSP-RS present dementia, personality change, emotional disorder, and memory impairment as onset symptoms.

Comments and evidence

PSP-RS accounts for approximately one-half of the PSP cases. The clinical features of the cognitive symptoms are described below.

- Initial symptoms of PSP:

Two-thirds of the cases present motor symptoms and ocular motor-related symptoms as onset symptoms. One-third of the cases present dementia symptoms or psychiatric symptoms at onset. These symptoms include depression, irritability, aggression, emotional lability, apathy, slowed thinking, and memory impairment. Approximately one-half of them manifest behavioral disorders as onset symptoms.

- Features of behavioral disorders and cognitive impairment in PSP:

The basic symptoms are attention deficit, indifference, and reduced level of interest to the surrounding. These symptoms were called subcortical dementia in the past, and they show features of frontotemporal dementia including slowed thinking, attention deficit, executive impairment, amnesia, apathy, reduced vocabulary, and depression. The speed of response becomes marked reduced due to slowed thinking. Initially it seems that the patient has no response to a question, but after a while he/she would give an accurate response. The behavioral disorders are mainly impulsive behavioral disorders and socially inappropriate behaviors such as compulsive eating, addiction to gambling, and impulse buying. Some of the behaviors are considered to be drug-induced, but there is no consensus. Tendency to fall and "applause sign" are manifestations of behavioral disorder and cognitive impairment. In the study of Yatabe et al. using Neuropsychiatric Inventory (NPI) and Stereotypy Rating Inventory (SRI), there were no differences between frontotemporal lobar degeneration (FTD) and PSP.

■ Further reading

1) Respondek G Stamelou M, Kurz C et al: The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. Mov Disord. 2014; 29: 1758-1766.
2) Williams DR, Lees AJ: Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. Lancet Neurol 2009; 8: 270-279.
3) O'Sullivn SS, Djamshidian A et al: Impulsive-compulsive spectrum behaviors in pathologically comfirmed progressive supranuclear palsy. Mov Disord. 2010; 25: 638-642.
4) Yatabe Y, Hashimoto M, et al: Neuropsychiatric symptoms of progressive supranuclear palsy in a dementia clinic. Psychogeriatrics. 2011; 11: 54-59.
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CQ 9-2

Are there useful therapies for cognitive impairment in progressive supranuclear palsy (PSP)?

Recommendation

Although no therapies for PSP have been developed, there are symptomatic treatments for individual symptoms but no treatment specific for cognitive symptoms. 2C

Comments and evidence

No curative therapies and no therapies for symptom relief and prevention specifically for PSP have been developed. At present, symptoms are treated individually. Although drugs that are useful for other diseases are being used for the treatment of PSP, the efficacy of most of these drug for PSP has not been proven [1, 2].

Pharmacotherapy for psychiatric symptoms of PSP

According to the report of Liepelt et al. [3] in 2010, among the cholinesterase inhibitors, only rivastigmine has been found to improve cognitive function, but the trial was a small observational study. Clinical trials of drugs for PSP reported since the last guideline failed to show good results [2, 3]. Recently, trial of mesenchymal stem cell transplantation has been started, and experimental therapeutic methods are being developed [4].

References

1) Sorbi S, Hort J et al. EFNS-ENS guidelines on the diagnosis and management of disorders associated with dementia. Eur J Neurology. 2012; 19: 1159-1179.
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3) Liepelt I, Gaenslen A, Godau J, et al: Rivastigmine for the treatment of dementia in patients with progressive supranuclear palsy: clinical observations as a basis for power calculations and safety analysis. Alzheimers Dement. 2010; 6: 70-74.
4) Giardano R, Canesi M, Isalberti M et al: Autologous mesenchymal stem cell therapy for progressive supranuclear palsy: translation into a phase 1 controlled, randomized clinical study. J Translat Med. 2014; 12: 14.