50 Years of Progressive Supranuclear Palsy

Richardson's Syndrome

Carlo Colosimo
Department of Neurology and Psychiatry, Sapienza University, Rome, Italy

Fifty years ago, Richardson, Steele and Olszewski presented at the American Neurological Association meeting the clinical and neuropathological features of eight patients, representing the first description of progressive supranuclear palsy (PSP). Their classical paper, remarkably accurate, insightful and complete, still forms the basis for recognizing this disease [1,2]. The post-mortem examination of their cases showed prominent nerve cell loss and gliosis in the pallidum, red nucleus and subthalamic nuclei, and in the reticular formation [2]. Similar changes were noted in substantia nigra, locus coeruleus, superior colliculi, vestibular and dentate nuclei. Neurofibrillary tangles and granuovacuolar changes were also noted with the same distribution. No cortical pathology was described in the original report. The biochemical underpinnings of PSP became clearer in 1986, when it was first reported that the filamentous aggregates found brain autopsies from patients with PSP shared antigenic determinants with microtubule-associated protein tau [3]. The advances in neurosciences of PSP during the last decades have led to the discovery that abnormal 4-repeat tau deposition in brainstem, basal ganglia and neocortical areas is the main event in the pathogenesis of the disorder.

The most frequently reported symptoms at onset in the classic form of this disease are impaired balance, movement slowness, subtle personality changes (apathy, disinhibition), bulbar symptoms and impaired oculomotion [4]. In the early stage of the classic PSP phenotype, the motor symptoms already respond poorly to dopaminergic drugs [5]. In the more advanced stages, patients manifesting classic PSP generally have a motor disorder characterized by bilateral bradykinesia, axial rigidity, and imbalance with severe gait unsteadiness. The prominent axial rigidity influences the posture, which may be characteristically erect like the cases reported by Richardson and collaborators (who depicted it as 'nuchal dystonia'), or more closely resemble the stooped posture seen in Parkinson's disease (PD). Progressive imbalance leads to repeated and frequent falls (usually backward). Some patients may have postural tremor and less commonly tremor at rest resembling PD. Patients with PSP often develop dysphagia and a characteristic growling high-pitched severe dysarthria, with mixed spastic and parkinsonian features. The diagnostic feature that best distinguishes PSP is a vertical gaze limitation with preserved oculocephalic reflexes: however, vertical gaze problems may be absent in up to 50% of the cases, and are rarely the presenting symptom of PSP. Because upgaze limitations can be present also in healthy persons (owing to anatomical changes within the orbit during aging), downgaze limitations are a far more specific finding suggesting PSP. An important point in the differential diagnosis is that several neurological conditions other than PSP can manifest with apparently similar oculomotor dysfunction (Table 1).

Already Steele and Richardson noted that the disease they described extended beyond the motor system to include “mental symptoms”, “personality changes”, and “dementia” [2]. The prominent bradykinesia characterizing PSP is paralleled by cognitive slowing, difficulty in generating words, and severe apathy [6]. In contrast, other cognitive functions such as language comprehension, recognition memory and visuospatial functions remain relatively well preserved.

The clinical spectrum of PSP has been recently expanded in several clinical syndromes with distinctive features from the classical description of Richardson and co-workers. All these clinical PSP variants reflect varying anatomical tau pathology distributions, but they share histopathologic, biochemical and genetic features with classic PSP. In 2005 Williams and colleagues renamed the classic PSP form as Richardson’s syndrome (RS), also proposing other terms for the different phenotypes of this disease [7]. RS probably represents only a minority of all cases of definite PSP.

The estimated prevalence of PSP (per 100.000 in the population) in the various studies ranges from 1.3 to 4.9, but is possibly underestimated, whereas the analytical epidemiology of PSP is even more uncertain. [8]. The clinical symptoms of PSP commonly begin in the seventh decade, although occasionally as early as the fifth decade. The median onset age is of 63 years, and the disease affects both sexes despite a slight male predominance [4]. PSP is a disease characterized by a progressive worsening of neurological symptoms and increasing motor disability. Cognitive and behavioural symptoms also progress, but tend to remain selective until the late stages of the disease; in particular, the behavioural picture remains dominated by the pronounced apathy. The prognosis of PSP remains poor, and the disease leads to death within a few years after symptom onset. Mean survival ranges from 5.9 to 9.7 years according to the different series. These data come from series including mainly patients with the RS phenotype: other clinical variants differ in disease progression rates and disease duration, usually having a longer disease course than RS.

References

1. Richardson JC, Steele JC, Olszewski J. Supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia. Transactions of the American Neurological Association 8, 25-29 (1963).
2. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. Arch Neurol 10, 333-359 (1964).
3. Pollock NJ, Mirra SS, Binder LI, Hansen LA, Wood JG. Filamentous aggregates in Pick's disease, progressive supranuclear palsy, and Alzheimer's disease share antigenic determinants with microtubule-associated protein, tau. Lancet Nov 22;2[8517],1211 (1986)
4. Colosimo C, Bak TH, Bologna M, Berardelli A. Fifty years of progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 85:938-944 (2014)
5. Colosimo C, Albanese A, Hughes AJ, de Bruin VM, Lees AJ. Some specific clinical features differentiate multiple system atrophy (striatonigral variety) from Parkinson’s disease.

Arch Neurol 52, 294-298 (1995).
6. Bak T.H., Crawford L.M., Berrios G., Hodges J.R. Behavioural symptoms in progressive supranuclear palsy and frontotemporal dementia. J Neurol Neurosurg Psychiatry 81, 1057-1059 (2010).
7. Williams DR, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. Brain 128, 1247–1258 (2005)
8. Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet 354, 1771-1775 (1999)

Table 1. Other causes of vertical ophthalmoplegia

Parkinson's disease
Multiple system atrophy parkinsonian variant
Corticobasal degeneration
Dementia with Lewy bodies
Motor neuron disease
Frontotemporal dementia and parkinsonism linked to chromosome 17
Huntington's disease
AD cerebellar ataxias (SCA 1, 2, 3, 7, 17)
Kufor-Rakeb disease (PARK 9)
Hereditary spastic paraplegia
Postencephalitic parkinsonism
Prion diseases
Progressive external ophthalmoplegia
Multi-infarct state
Tumors compressing the brainstem (pinealoma, glioma)
CNS lymphoma
Myasthenia gravis
Niemann-Pick type C disease
Drug-induced disorder
Wernicke's encephalopathy
Whipple's disease