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Progressive Supranuclear Palsy

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Progressive Supranuclear Palsy

DESCRIPTION

Progressive supranuclear palsy (PSP) is one of the most common parkinsonism-plus syndromes. Acknowledging the seminal contributions of the three physicians who first described the condition (Steele, Richardson, & Olszweski, 1964), PSP is also referred to as Steele–Richardson–Olszweski syndrome. PSP is a rapidly progressive degenerative disease. The characteristic syndrome consists of supranuclear ophthalmoplegia, pseudobulbar palsy, and axial dystonia, although it may take over a year for these features to develop fully (Ropper & Brown, 2005). Early prominent features include postural instability, falls, executive dysfunction, and slowed information processing. The hallmark symptom is a vertical gaze palsy that is often downward but can sometimes occur only upward. Typical age of onset is in the 60s (range 45–75 years) with a median survival time of approximately 6 years from the initial onset of symptoms (Litvan, Agid, et al., 1996; Litvan, Mangone, et al., 1996). There are conflicting reports whether males or females are more likely to develop PSP (Bower, Maraganore, McDonnell, & Roca, 1997; Golbe, 1996). Overall prevalence is estimated between 1.4 and 6.4 per 100,000 (Golbe, Davis, Schoenberg, & Duvoisin, 1988; Schrag, Ben-Shlomo, & Quinn, 1999).

NEUROPATHOLOGY/PATHOPHYSIOLOGY

The pathophysiology of PSP involves severe neuronal degeneration of subcortical structures and minimal cortical lesions. Lesion sites are somewhat variable and typically occur between the upper brainstem and basal ganglia. Broadly, there is evidence of neuronal loss in the striatum and substantia nigra, and degeneration of structures in the basal ganglia, upper brainstem, and cerebellum (Agid, Ruberg, DuBois, & Pillon, 1987). Lesions may compromise the nigrostriatal pathway, basal forebrain, pedunculopontine nucleus, subnucleus compactus, mesencephalopontine tegmental nuclei, and locus ceruleus (Grafman, Litvan, & Stark, 1995). Dopamine levels drop drastically during the course of the illness leading to parkinsonian-type symptoms.

Degeneration impacts ascending pathways from subcortical structures to the prefrontal cortex. Grafman et al. (1995) hypothesized that pathology in the dorsolateral frontal, lateral-orbitofrontal, and anterior cingulate circuits contributes to specific cognitive dysfunctions (executive functioning, social-cognitive, and attention).

Although frontal lobe pathology is not prominent, multiple positron emission tomography (PET) studies have revealed frontal hypometabolism (Bhatt, Snow, Martin, Peppard, & Calne, 1991; Blin et al., 1990; Blin et al., 1992), and some imaging studies have reported significant frontal cortical atrophy (Cordato, Halliday, Harding, Hely, & Morris, 2000; Cordato et al., 2002; Gröschel et al., 2004). MRI studies have found atrophy of midbrain structures most pronounced in the superior colliculi and pons (Masucci, Borts, Smirniotopoulos, Kurtzke, & Schellinger, 1985; Schonfeld, Globe, Sage, Safer, & Duvoisin, 1987).

NEUROPSYCHOLOGICAL/CLINICAL PRESENTATION

Consistent with subcortical dysfunction, common manifestations of PSP reflect executive dysfunction, including cognitive slowing, impaired set-shifting, and decreased verbal fluency (Grafman et al., 1995; Jacobs, Levy, & Marder, 2003). It is generally believed that these deficits are related to frontal deafferentation secondary to subclinical lesions, although some researchers have hypothesized a more direct relationship between frontal lobe pathology and behavioral deficits (Cordato et al., 2002). Immediate and delayed recall of information can vary from normal to impaired, whereas recognition memory is improved or intact (Jacobs et al., 2003). Primary language abilities are typically preserved, though word-finding problems may develop years following formal diagnosis (Lezak, Howieson, & Loring, 2004). Not surprisingly given ocular involvement, visuospatial skills are often impaired. Visual attention impairment is typically related to duration of PSP (Kertzman, Robinson, & Litvan, 1990).

The course of physical symptoms consists of postural instability and falls several years prior to formal diagnosis. The hallmark physical symptom of PSP is a vertical gaze palsy that typically occurs relatively late in the disease process. Compensation for visual limitations can frequently lead to falls. Bradykinesia, rigidity, impaired control of mouth/neck are also relatively common later in the course. It is notable that the development of core symptoms may present late, or never develop, during the course of the disease (Litvan et al., 2003). For example, histological confirmed cases of PSP have been reported without ophthalmoplegia (Santacruz, Uttl, Litvan, & Grafman, 1998). Respiratory arrest may occur due to a degenerative process involving the brainstem respiratory centers, or be secondary to pneumonia. Unlike Parkinson's disease, patients with PSP tend to have more of an erect rather than a stooped posture and lack tremor (Ropper & Brown, 2005).

Consistent with executive dysfunction, two of the most common behavioral manifestations of PSP are apathy and disinhibition. One study administered the Neuropsychiatric Inventory to 22 patients with PSP and found apathy to be the most prevalent neuropsychiatric feature, present in 91% of patients (Litvan, Mega, Cummings, & Fairbanks, 1996). Disinhibition was exhibited by one-third of patients, followed by dysphoria (18%) and anxiety (18%). Impaired metacognitive awareness has also been observed and is attributed to the disruption of frontostriatal feedback loops (O'Keeffe et al., 2007). Obsessive behaviors, euphoria, and depressive symptoms are also possible (Destee et al., 1990). Sleep abnormalities are prevalent as well and are most often characterized by shortened total sleep time, frequent awakenings, and decreased REM sleep (Cummings, 2003).

DIAGNOSIS

Although multiple diagnostic criteria have been proposed (e.g., Collins, Ahlskog, Parisi, & Maraganore, 1995; Tolosa, Valldeoriola, & Marti, 1994), those set forth by Litvan et al. (1996) are the most frequently cited in the literature and form the basis for the National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy (NINDS-SPSP; Litvan et al., 2003) clinical criteria. Diagnosis of "possible PSP" requires either vertical supranuclear palsy *or* both slowing of vertical saccades and postural instability with falls during the 1st year of disease onset. "Probable" diagnosis of PSP requires vertical supranuclear palsy *and* prominent postural instability with falls within the 1st year of disease onset. Diagnosis of possible or probable PSP requires symptom onset at or after age 40, and it is necessary that there be a gradual progression of symptoms. "Definite" diagnosis of possible or probable PSP requires histopathologic confirmation at autopsy.

NINDS-SPSP clinical criteria provide a number of supportive criteria to assist in differential diagnosis. Supportive motor features include symmetric akinesia or rigidity (proximal greater than distal) and neck dystonia. An early onset of two or more of the following cognitive symptoms is also supportive of PSP diagnosis: impaired abstraction, decreased verbal fluency, "utilization or imitation behavior," "frontal release" signs, and apathy. In addition, PSP may be considered if motor symptoms do not respond, or minimally respond, to levodopa therapy and if there are early symptoms of dysphagia or dysarthria.

PSP is often misdiagnosed early in the course of the disease as Parkinson's disease or confused with other parkinsonian disorders. Severity and pattern of executive deficits characterized by slowed information processing, impaired accuracy in carrying out plans, and difficulty in set shifting tends to differentiate PSP patients from others with basal ganglia lesions (Robbins et al., 1994). The combination of postural instability leading to falls early in the course of the disease and vertical gaze palsy are also key symptoms in differentiating PSP from other disorders with parkinsonism and dementia.

Neuroimaging techniques can be useful in differential diagnosis. Diffusion-weighted imaging has shown promise in differentiating PSP from Parkinson's disease early in disease onset based on increased regional apparent diffusion coefficients in the putamen, globus pallidus, and caudate nucleus (Seppi et al., 2003). An additional reliable manner to differentiate PSP from Parkinson's disease is significantly lower anteroposterior diameter of the midbrain on axial T2-weighted magnetic resonance images (Warmuth-Metz, Naumann, Csoti, & Solymosi, 2001).

Differential diagnosis between PSP and corticobasal degenerative syndrome (CBDS) is challenging. These conditions have numerous factors in common including similar neuropsychological profiles (Pillon et al., 1995), pathological features (Feany, Mattiace, & Dickson, 1996), and the finding that both conditions are considered to be predominantly 4-repeat tauopathies (Kertesz & Munoz, 2004). Further complicating the differential diagnosis, individuals with CBDS may exhibit vertical gaze palsy, falls, and symmetrical extrapyramidal syndrome (Litvan, Goetz, & Lang, 2000). One possible distinguishing feature between these syndromes is greater atrophy of the midbrain, pons, thalamus, and striatum in PSP relative to CBDS (Boxer et al., 2006).

TREATMENT

Unfortunately, PSP is a treatment-resistant and degenerative condition. Although dopaminergic agents can improve the parkinsonian features, they can also induce adverse side effects, such as orthostatic hypotension, hallucinations/delusions, and gastrointestinal complaints (Kompoliti, Goetz, Litvan, Jellinger, & Verny, 1998). It is recommended that anticholinergic agents be avoided (Cummings, 2003). There is no significant improvement with levodopa therapy.

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Pseudotumor Cerebri

DESCRIPTION

Pseudotumor cerebri represents a syndrome that is characterized by persisting headache and papilledema (unilateral or bilateral) in the absence of focal neurologic signs, abnormal CSF composition, and enlarged ventricles or an intracranial mass. The presentation is associated with increased intracranial hypertension, most commonly idiopathic in nature.

Pseudotumor cerebri is most frequently observed in overweight young women with a relative