The hypothalamus in Parkinson Disease

Sandyk R.*, Iacono R.P.**, Bamford C.R.*
** Department of Neurology
** Department of Surgery (Neurosurgery) University of Arizona Tucson, Arizona

It is currently believed that Parkinson disease (PD) is due to a degenerative process that independently damages multiple areas of the central and peripheral nervous system. Loss of nigrostriatal dopamine is now widely recognized as being directly related to the motor symptoms in Parkinson's disease. Parkinsonian patients also exhibit symptoms and signs suggestive of hypothalamic dysfunction (e.g. dysautonomia, impaired heat tolerance). The latter clinical features are supported by pathological, biochemical and endocrinological findings. Lewy body formation has been demonstrated in every nucleus of the hypothalamus, specifically the tuberomamillary and posterior hypothalamic. Preferential involvement of the hypothalamus was also noted in patients after post-encephalitic parkinsonism. Loss of dopamine (30-40%) in the hypothalamus of affected patients has been shown in recent studies, and is compatible with the reported abnormalities of growth hormone release in response to L-dopa administration, elevated plasma levels of MSH, and reduced CSF levels of somatostatin and beta-endorphins in these patients. Deranged immunological mechanisms have been found in PD patients including the presence of autoantibodies against sympathetic ganglia neurons, adrenal medulla and caudate nucleus. On the evidence of on pathological studies demonstrating the early vulnerability of the hypothalamus in aging and PD, and the known role of the hypothalamus in immune modulation, we expect that it will be shown that primary damage to the hypothalamus leads to subsequent secondary degeneration of structures receiving direct projections from the hypothalamus. Within this framework, the dopaminergic systems may be damaged, since striatal dopamine synthesis and receptor sensitivity have been shown to be regulated by ACTH and alpha-MSH through direct arcuate nucleus-striatal projections. We also demonstrate that virtually all other areas well known to be impacted upon in Parkinson disease receive significant hypothalamic peptidergic projections.

Key-Words: Parkinson disease

Introduction

While the motor manifestations of Parkinson disease (PD) have been attributed to degeneration of nigrostriatal dopaminergic neurons, other features of the disease including depression, dementia and autonomic symptoms suggest a more widespread CNS involvement in the disease [1]. Indeed, cell loss and the formation of Lewy bodies have been demonstrated in other pigmented neurons such as the locus coeruleus (LC), dorsal motor nuclei of the vagus, sympathetic ganglia and the hypothalamus [2,3]. In addition, biochemical data have demonstrated decline in the activity of other neurotransmitters in PD including noradrenaline [4], serotonin (5-HT) [5], histamine [84],
GABA [6] and a variety of neuropeptides [1,7,8,9,10,11], supporting Barbeau's concept that PD is a systemic rather than a focal degenerative disorder [9].

In his essay on the "shaking palsy", James Parkinson indicated that PD patients were likely to lose control of bladder and bowel functions in the later stages of the disease [10]. Subsequent studies have indeed documented autonomic insufficiency as an integral part of the PD symptomatology [11,13]. More recent studies have suggested that the degenerative process underlying the autonomic dysfunction in PD is either diffuse [8] or bilaterally symmetric involving the hypothalamus and perhaps also the sympathetic ganglia [14]. The recent study by Uhle et al [19] demonstrating changes in peptidergic receptors in the substantia nigra of Parkinsonian patients suggests to us that the dysfunction attributed to the substantia nigra may in fact be a secondary phenomenon due to a hypothalamic lesion, the hypothalami being the major source of peptidergic projection to the substantia nigra.

Autonomic symptoms in Parkinson disease

Autonomic dysfunction in PD was first reported by James Parkinson himself in 1870 [10]. Abnormalities of salivation, sweating, bladder and bowel functions are common features of the disease he described, and orthostatic hypotension, although less common, in perhaps the most common form of dysautonomia. Other features of the parkinsonian autonomic deficit include sialorrhea, seborrhea, dysphagia, heat and cold intolerance and impotence [15,82].

Severe orthostatic hypotension in idiopathic PD has been reported by Vanderheaghen et al [16] and Bassett and Oppenheimer [17]. In most untreated PD cases and those treated with anticholinergics, the postural drop in blood pressure (BP) is asymptomatic. Gross et al [18] found that postural drop in BP in the upright position was significantly greater even in mild cases of the disease indicating that evaluation of autonomic functions may serve as a reasonably good guide to the assessment of autonomic functions in Parkinson disease.

In addition to postural hypotension, Barbeau et al [19] found that PD patients had a lower mean BP than age-matched controls. The differences, particularly evident when standing, were thought to contribute a "chronic state of fatigue and to occasional episodes of postural dizziness". Similarly, McDowell and Lee [20] reported a lower mean BP in PD patients, often leading to significant orthostatic fall. In an extensive study of BP levels including 411 patients by Aminoff et al [21], systolic and diastolic levels were similar in the mild and moderate groups, but significantly higher in those with tremor than in patients with predominant bradykinesia.

Although it was initially suggested that anticholinergic drug therapy was a possible cause of hypotension in PD patients [23], later studies [23,24] failed to demonstrate any effect on BP of these drugs. McDowell and Lee [20] reported a fall of systolic BP by greater than 30 mm Hg in 25% of patients treated with L-dopa. Similarly, Calne et al [25] reported a significant increase in postural fall in BP in L-dopa treated patients. In a more recent study, Goetz et al [26] studied autonomic functions before and after medication (levodopa, amantadine or dopamine receptor agonists) when motor disability was maximal ("Off"), patients had higher resting pulse rate, greater orthostatic fall in BP and decreased responses to Valsalva and cold pressure stimuli than their spouse-controls. After treatment, when function was optimal ("On"), the cardiovascular reflex abnormalities remained, but were no worse. These findings indicated that continued use of dopaminergic drugs was entirely safe in PD patients, as the drugs did not appear to exacerbate a preexisting orthostatic BP drop.

The pathological basis of the orthostatic hypotension in PD patients is not clear. In cases where parkinsonian features occur as a part of multisystem atrophy (MSA), postural hypotension is believed to result from cell loss in the intermediolateral column of the spinal cord [27]. However, the site of the lesion responsible for postural hypotension in idiopathic PD is not yet established with certainty. Appenzeller and Gross [22] postulated that hypothalamic lesions were the basis of dysautonomia of PD, while Vanderheaghen et al [16] postulated that lesions in the sympathetic ganglia may play an important role in the pathoetiology of the orthostatic hypotension in PD patients.

Abnormalities in sweating and temperature regulation are common among PD patients [15,97]. In 1888, Gowers [28] described a hemiparkinsonian patient with excessive head sweating involving only the parkinsonian side. Patchy impairment of sweating has also been reported by Aminoff and Wilcox [21] in 50% of patients, and confirmed subsequently by other researchers [12,21,22]. Appenzeller and Gross [22] documented abnormal thermoregulatory sweating response in 10 out of 25 PD patients, an effect attributed to degenerative changes in the hypothalamus and paravertebral sympathetic ganglia. In a more recent study, Goetz et al [26] demonstrated increased sweating in the head and neck to heat stimulation in 31 chronically treated PD patients. Sweating abnormalities resolved with anti-PD medication, suggesting that dopamine (DA) may play a role in the mechanisms underlying impaired thermoregulation in PD patients. Abnormal temperature control regul-