Familial Diffuse Lewy Body Disease, Eye Movement Abnormalities, and Distribution of Pathology

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Background: Familial diffuse Lewy body disease (DLBD) is rare and not yet associated with a defect in the synuclein gene. In the differential diagnosis of the parkinsonian syndromes, defects in vertical gaze tend to be identified with progressive supranuclear palsy. False-positive diagnosis of progressive supranuclear palsy can occur, and defects in vertical gaze have been reported in DLBD, although so far a pure vertical gaze palsy associated with pathological abnormalities in the substrate for vertical gaze has not been described.

Objectives: To report the clinical and pathological findings in 2 siblings with DLBD, and to relate the distribution of the pathological abnormalities in the brainstem to centers for vertical gaze.

Materials: For several years, 2 Irish siblings experienced a progressive parkinsonism-dementia complex associated in one with a defect in vertical gaze and in both with visual hallucinations.

Results: In both patients, results of pathological examination revealed (1) Lewy bodies positive for ubiquitin and α-synuclein together with cell loss and gliosis in the substantia nigra, locus ceruleus, and neocortex; and (2) similar findings in the rostral interstitial nucleus of the medial longitudinal fasciculus, the posterior commissure, and the interstitial nucleus of Cajal (substrates for vertical gaze).

Conclusions: Familial DLBD (not shown to be genetically as distinct from environmentally transmitted) has been shown to exist in an Irish family. Caution should be en-joined in the interpretation of defects in vertical gaze in the differential diagnosis of the parkinsonian syndromes.

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Parkinsonism is a feature of a number of disorders. The distinction of other conditions from Parkinson disease (PD) requires the presence of certain features atypical for PD. Diagnosis in elderly people and early PD cause additional problems. Autopsy studies suggest that accurate distinction is frequently not made, and many patients dying with a clinical diagnosis of PD may have parkinsonism due to another cause. Those syndromes that cause differential difficulty include progressive supranuclear palsy (PSP), diffuse Lewy body disease (DLBD), multiple system atrophy, and corticobasal ganglionic degeneration. The true relative frequency of these conditions is difficult to obtain. Prevalence studies are usually clinical, of necessity, whereas autopsy studies represent sampling. Thus, epidemiological conclusions based on clinicopathologic correlations prove difficult. Like PD, they are all degenerative disorders for which there is no reliable laboratory or imaging test.

Considerable overlap may exist in symptomatology, which is a function of topographic distribution. Autopsy demonstration of the appropriate pathological features remains the gold standard for accurate diagnosis. Here, the “specific” bodies seen in some of these conditions represent neurotubular and filamentous breakdown products and may not be responsible for either pathogenesis or clinical symptomatology. A recent review has suggested that the density distribution ratios of Lewy bodies is constant, independent of the clinical mode of presentation (eg, cortical vs subcortical). The diagnostic terminology, which may include clinical and pathological elements (eg, dementia with diffuse Lewy bodies, dementia of Alzheimer type with Lewy bodies), underlines a relative unspecificity.

Therefore, clinical diagnosis as a predictor of pathology is open to error. For instance, the clinical diagnosis of PSP, in which impairment of vertical eye movement receives particular significance, appears to be made more frequently than the
clinical diagnosis of DLBD, whereas, at a pathological level, dementia associated with Lewy bodies may be the second most common form of dementia after dementia of Alzheimer type. This finding implies a significant false-positive level of diagnosis of PSP.\textsuperscript{9,10} Clinically, vertical supranuclear palsy with postural instability, associated with mild dementia, is regarded as a reliable combination for predicting a diagnosis of PSP.\textsuperscript{11,12} but vertical gaze impairment may occur in DLBD\textsuperscript{13-15} and is a frequent accompaniment of aging.\textsuperscript{16-19}

In this report, we present clinical and pathological details of 2 siblings who had DLBD and who experienced a parkinsonism-dementia complex. One sibling manifested vertical (upward and downward) gaze palsy. Systematic examination of the brainstem revealed, in both patients, cell loss, gliosis, and Lewy bodies affecting the pathways for vertical gaze, in addition to the pathological features of DLBD.

### REPORT OF CASES

#### PATIENT 1

A 66-year-old man, previously healthy, began to experience deterioration in his golf game, largely due to impaired balance when swinging a club. This imbalance continued and progressed up to his death 14 years later. His memory had also become mildly impaired, and his bridge game had suffered. When seen 6 years after onset, he had a stiff gait with poor arm swinging. Bilateral cogwheeling and mild rigidity were present. He was treated with levodopa (300 mg/d) and carbidopa monohydrate (30 mg/d) with little response. He began to experience visual hallucinations, eg, he began to see numerous black balls scattered around him while playing golf. Other hallucinations were less clearly formed and could be articulated less clearly. Although the hallucinations persisted, they did not increase when the levodopa dosage was increased to 600 mg/d (to which he made some physical response). A defect in upward gaze gradually developed. This became accompanied by a defect in downward gaze of greater degree, of which he independently complained when he found that he could not reach when holding a book beneath eye level. He had brisk doll’s-eye movements. There were no upper motor signs. On the Wechsler Memory Scale–Revised, he achieved a verbal memory score of 81, a visual memory score below the basal level of 50, and a general memory score of 38. On the Warrington Recognition Memory Test, verbal and facial memory aspects were defective, the latter more severely. The one area of unaffected function was attentional memory, with a score of 112. His physical condition progressed to the point of incapacity. For the 2 years before his death, his intellectual deficit, which had been fluctuant, became more prominent.

#### PATIENT 2

A 73-year-old woman, a sister of patient 1, experienced a slow and steady decline in physical and mental function. She also had visual hallucinations, as reported by her family, although their time of onset could not be dated retrospectively. Her clinical signs included bradykinesia and rigidity, but not tremor. She had been treated with levodopa without effect. During the illness, which progressed for about 11 years, she also had intermittently high blood pressure, and Doppler ultrasonography revealed bilateral carotid bifurcation atherosclerosis. She underwent progressive severe physical and cognitive (not fluctuant) decline. When first seen by one of us (H.S.) 2 months before her death, she was permanently bed bound and not communicating. It proved impossible to test eye movements. All limbs were severely rigid, with cogwheeling. Arm reflexes were brisk, and due to the rigidity, could not be elicited in the legs. There was small-muscle wasting in the hands and feet.

Review of the family history revealed that the mother had died in the middle of her fourth decade of life, and the father had died in his ninth decade. Stepsiblings have not demonstrated any neurologic deficit. No previous record of a neurologic illness in either family was found.

### RESULTS

#### NEUROPATHOLOGIC EXAMINATION

Postmortem examination was limited in each case (by request) to examination of the brain. Macroscopic examination in both patients revealed no significant cerebral atrophy. Pallor was noted in the substantia nigra in both. Representative sections were taken from the midfrontal area; the superior and middle temporal, inferior parietal, and occipital cortices; anterior cingulate; amygdala; hippocampus; striatum; thalamus; midbrain (levels of the superior colliculus and pretectal regions); pons; medulla; and cerebellum. Midbrain regions related to vertical eye movement, including the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), posterior commissure, and interstitial nucleus of Cajal, were examined. Sections were stained with hematoxylin-eosin, and the following immunocytochemical markers were used: glial fibrillary acidic protein (1:1000; Dako, Cambridge, United Kingdom), BA4 (1:100; Dako), tau (1:90; Immunogenetics, Ghent, Belgium), ubiquitin (1:60; Novocastra, Newcastle, United Kingdom), and α-synuclein (1:3000; Chemicon, Harrow, United Kingdom).

Gliosis in the region of riMLF, interstitial nucleus of Cajal, and posterior commissure were graded semiquantitatively in conjunction with hematoxylin-eosin and glial fibrillary acidic protein staining, where 0 indicates absent; 1, mild; 2, moderate; and 3, severe.

#### NEUROPATHOLOGIC FINDINGS

Concentric hyaline intracytoplasmic eosinophilic inclusions (Lewy bodies) were found in the substantia nigra and locus ceruleus of both patients (Figure 1). In both locations, Lewy bodies were associated with cell loss, gliosis, and pigmentary incontinence of cells with extracellular melanin deposition. Occasional Lewy bodies were identified in the periaqueductal gray matter, oculomotor nucleus, riMLF, interstitial nucleus of Cajal, and dorsal vagal nucleus in both patients (Figure 2). In addi-
tion, both patients demonstrated cell loss and moderate gliosis in the posterior commissure and medial longitudinal fasciculus (Figure 3).

Less well-defined eosinophilic inclusions were identified in neurons of the neocortex in both patients (Figure 4). They were found in small neurones in the middle and lower cortical laminae of parahippocampal, insular, and occipital cortices and cingulate gyrus. These inclusions stained positively with ubiquitin and α-synuclein, but not with tau protein (Figure 5). Occasional tau-positive neurofibrillary tangles were identified in the hippocampus of patient 1, but numbers were insufficient for a diagnosis of dementia of Alzheimer type.

COMMENT

This report demonstrates, in 2 siblings, the presence of pathologic abnormalities specific for Lewy body disease, in addition to gliosis, in the areas that subserve vertical gaze. One of the patients, in addition to exhibiting parkinsonism, dementia, and visual hallucinations, demonstrated initially a defect in upward gaze followed by a more significant impairment in downward gaze. The other patient underwent assessment too late in the course of the disease for observations to be made about eye movement. Although the precise mechanism of symptom production in Lewy body diseases is not known, and the presence of α-synuclein and ubiquitin in Lewy body disease represents a secondary effect, such presence in the riMLF, the posterior commissure, and the interstitial nucleus of Cajal indicates some degree of clinicopathologic correlation. Vertical eye movement abnormalities have been previously described in DLBD, and a difficulty in separating the parkinsonian syndromes lies in the fact that the phenotype will be determined by the topographic distribution of the abnormality. In 3 previously described patients with DLBD and defects in vertical gaze,13-15 the eye signs were not pure, in that 2 had an associated defect in horizontal gaze,13,14 whereas 2 appeared to have little defect in downward gaze.13,15 Possibly in part for technical reasons, the pathological changes were found in the appropriate substrate for vertical gaze in only one of these
patients.13 No hallucinations were described in any of these patients, and a diagnosis of PSP was made. Although in the patients under current study, the presence of visual hallucinations suggested Lewy body disease, their absence, as can occur in Lewy body disease (they are not demanded as a sine qua non in the consensus guidelines),20 or their late appearance may lead to an erroneous diagnosis. Furthermore, medication-induced hallucinations are well recognized in PD.21

Marked concordance was found between two siblings in the appearance and distribution of the pathologic changes. It seems reasonable to assume that they both expressed the same synucleinopathy. In view of their mother’s early death, it is difficult to know if the synucleinopathies were genetic in origin, and, if so, what was the mode of inheritance. A limited number of familial DLBD cases have been reported.22-24 A dominant form of inheritance has been described in at least 2 families,25 whereas consanguinity appeared to play a part in one extended pedigree26 and in another smaller pedigree,24 although the pattern of inheritance did not appear typical in the latter. In view of the fact that most cases of DLBD are sporadic, taking into account the unspecific nature of Lewy bodies, and given the range and heterogeneity of the synucleinopathies,25 different genotypes may well exist.

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