Diffuse Lewy Body Disease Presenting as Multiple System Atrophy

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ABSTRACT: ***Objectives:*** The majority of patients with diffuse Lewy body disease have cognitive or psychiatric manifestations as part of their initial presentation. A sizable minority present with parkinsonian features alone. Autonomic features may also occur, typically after the development of cognitive changes. We aim to demonstrate that diffuse Lewy body disease may rarely also present with parkinsonism accompanied by marked autonomic dysfunction in the absence of significant cognitive or psychiatric abnormalities. ***Methods:*** Case report based on a retrospective chart review and neuropathological examination. ***Results:*** We report on a patient in whom a clinical diagnosis of multiple system atrophy was made based on a presentation of parkinsonism with prominent and early autonomic involvement. The former included postural tremor, rigidity and bradykinesia, while the latter consisted of repeated falls due to orthostasis and the subsequent development of urinary incontinence midway through the course of her illness. She was poorly tolerant of dopaminergic therapy due to accentuated orthostasis. Benefit from levodopa was limited and only evident when attempted withdrawal resulted in increased rigidity. There was no history of spontaneous or drug-induced hallucinations, delusions or fluctuating cognition, and in contrast to the prominence and progression of her parkinsonian and autonomic features over the first several years, cognitive impairment did not occur until the final stages of her illness, seven years after the onset of initial symptoms. Neuropathological examination revealed numerous Lewy bodies in both neocortical as well as subcortical structures consistent with a diagnosis of diffuse Lewy body disease. There was marked neuronal loss in the substantia nigra as well as the autonomic nuclei of the brainstem and spinal cord. ***Conclusions:*** In addition to cognitive, psychiatric, and parkinsonian presentations, diffuse Lewy body disease may present with parkinsonism and prominent autonomic dysfunction, fulfilling proposed criteria for the striatonigral form of MSA.

RÉSUMÉ: Maladie à corps de Lewy diffuse se présentant comme une atrophie multisystémique. ***Buts:*** La majorité des patients atteints de la maladie à corps de Lewy diffuse ont des manifestations cognitives ou psychiatriques qui font partie du tableau initial. Une forte minorité consulte pour des manifestations exclusivement parkinsoniennes. Une dysautonomie peut également faire partie du tableau, typiquement après l'apparition des changements cognitifs. Notre but est de démontrer que la maladie à corps de Lewy diffuse peut aussi donner un tableau de parkinsonisme accompagné d'une dysautonomie sévère en l'absence d'anomalies cognitives ou psychiatriques importantes. ***Méthode:*** Nous présentons une revue rétrospective du dossier et de l'examen neuropathologique d'un cas. ***Résultats:*** Nous rapportons le cas d'une patiente chez qui un diagnostic clinique d'atrophie multisystémique a été posé parce qu'elle présentait un parkinsonisme associé à une dysautonomie sévère et précoce. Le parkinsonisme était caractérisé par un tremblement postural, de la rigidité et de la bradykinésie, alors que les manifestations de la dysautonomie étaient des chutes répétées dues à l'orthostatisme et l'apparition éventuelle d'incontinence urinaire pendant l'évolution de sa maladie. Elle tolérait mal la thérapie dopaminergique à cause de l'exagération de l'orthostatisme. La lévodopa était peu efficace et le bénéfice devenait évident seulement parce qu'elle présentait une augmentation de la rigidité quand on tentait de la cesser. Il n'y avait pas d'histoire d'hallucinations spontanées ou induites par la médication, de délire ou de fluctuations cognitives et, contrairement à l'importance et à la progression de ses manifestations parkinsoniennes et dysautonomiques pendant les premières années d'évolution de sa maladie, la détérioration cognitive n'est apparue que dans la phase finale de sa maladie, sept ans après le début des symptômes. L'examen neuropathologique a montré de nombreux corps de Lewy dans le néocortex ainsi que dans les structures sous-corticales, ce qui est compatible avec un diagnostic de maladie à corps de Lewy diffuse. Il y avait une perte neuronale marquée dans la substance noire ainsi que dans les noyaux du système nerveux autonome du tronc cérébral et de la moelle épinière. ***Conclusions:*** Le tableau initial de la maladie à corps de Lewy diffuse peut être soit des manifestations cognitives, psychiatriques ou parkinsoniennes mais aussi un parkinsonisme accompagné d'une dysautonomie importante, ce qui remplit les critères qu'on a récemment proposés pour l'AMS-P probable.

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Diffuse Lewy body disease (DLBD) may have a broad range of clinical presentations.[1-6] Common features include parkinsonism and cognitive disturbances, often with a fluctuating cognitive status and the presence of hallucinations which may be spontaneous or drug-induced. Parkinsonism with various combinations of rigidity, tremor, bradykinesia, gait impairment and postural abnormalities may be the sole presenting feature in 20-25% of cases.[6] Supportive, but not essential for the diagnosis, are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions and hallucinations in modalities other than the more common visual domain. Although autonomic dysfunction is a recognized feature,[7] a presentation with prominent dysautonomia combined with parkinsonism in the

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absence of cognitive dysfunction as in the case described below has not been previously reported.

Case Report

An 87-year-old woman first presented to our clinic in 1991. Her symptoms began with impaired right hand coordination four years earlier followed by similar symptoms in her left hand shortly thereafter. Starting around this time she experienced posturally related episodes of lightheadedness. These progressed over the next two years causing repeated falls which resulted in bilateral wrist fractures. She had no bowel or bladder symptomatology at the time of her first visit. She never developed an overt tremor, but had reported an intermittently occurring whole body "internal tremor", first noted in 1989. At the same time she had developed burning sensations in the legs at night which were improved by moving her legs around or by getting up and walking. In 1990, well after orthostatic symptoms had begun, she was first treated with a levodopa/carbidopa preparation. She had some improvement in her tremor sensation, incoordination and restless legs symptoms, but experienced an increase in orthostatic faintness. She was treated with a maximum dose of levodopa/benserazide 100/25 mg five times per day which was decreased to t.i.d. because of markedly excacerbated orthostasis. Her only other treatment was with selegiline for six weeks, which was discontinued due to worsened orthostasis. Clonazepam 0.5 mg at night was used early in the management of her restless legs syndrome. Her mental status examination was reported as normal on neurologic evaluation in 1990. She denied any impairment of intellectual or language function. Past medical history was non-contributory and there was no history of neurologic illness in the family.

On initial assessment in 1991, her Unified Parkinson's Disease Rating Scale mentation score was 1 indicating mild, consistent forgetfulness but without disorientation or definite impairment of functioning at home and was not felt to be excessive for her age. There was no history of hallucinations. Supine blood pressure was 180/80 mm Hg with a postural drop to 145/70 mm Hg. General examination was otherwise unremarkable. Fundoscopic and cranial nerve examinations were normal. Facial expressivity was mildly decreased. There was no tremor at rest, but a postural tremor of the outstretched hands was present and was accentuated with action on the left. There was moderate rigidity in the neck and right arm and mild rigidity in the other extremities. Rapid alternate motion rate was mildly to moderately slowed in all four extremities. Reflexes were normal except for absent ankle jerks and her plantar responses were flexor. Vibratory sense was diminished distally but all other modalites were intact. She had to push off to arise from a chair. Posture was moderately stooped with decreased armswing but with reasonably good stride and performance on turns. She was able to execute a tandem gait. Her postural reflexes were markedly impaired with a demonstrated tendency to fall upon posterior displacement.

Over the next three years she developed urinary incontinence and leg swelling as well as fluctuating blood pressures with continued orthostatic hypotension and supine hypertension. When seen in follow-up in 1992, no onset of benefit or wearing off effect of her levodopa was present. However, at her last visit in 1994, it was reported that she would become more rigid without her medication which at that time included bromocriptine 2.5 mg b.i.d. as well as levodopa/benserazide 100/25 mg t.i.d. She did not develop dyskinesias on any of her treatments. At the time of this last visit she was ambulatory only with the aid of a walker and living in a nursing home. There was no history of hallucinations or fluctuating cognitive disturbances. A brain MRI in 4/92 showed generalized atrophy compatible with her age and non-specific bilateral white matter lesions. Notes from the nursing home indicated that she remained cognitively intact until 7/94 at which time she was described as becoming forgetful. She fractured her left hip in 1/95 after falling and was subsequently wheelchair-bound. By 10/95 disorientation to time and place was noted although she continued to recognize family and primary caregivers. In the last nine months of life she became completely bed-bound and was unable to follow commands. She passed away in 3/97 at the age of ninety-three.

Neuropathological examination

Post-mortem examination was confined to the brain and spinal cord. The brain was bisected in the fresh state and the left half was frozen. The right half of the brain and the spinal cord were fixed in formalin. The weight of the right half of the brain was 590 grams after fixation. There was mild diffuse cortical atrophy (Figure 1). The basal ganglia were unremarkable and the ventricles were not enlarged. There was severe loss of pigment in the substantia nigra (Figure 2) and the locus coeruleus. The brainstem, cerebellum and spinal cord were otherwise unremarkable.

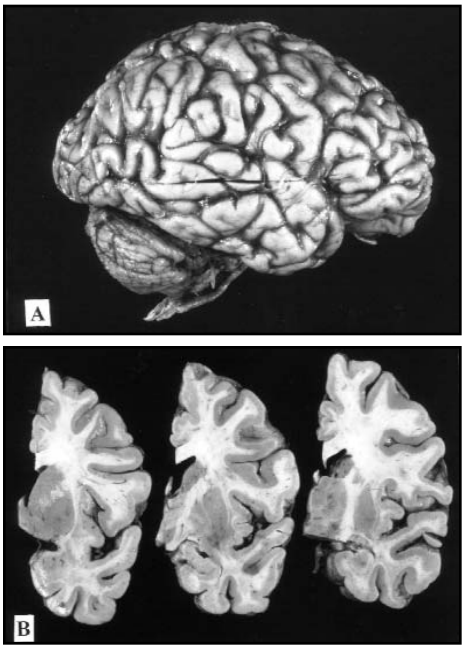

Figure 1: *External examination of the right cerebral convexity (A) and coronal sections through the right cerebral hemisphere show a mild degree of diffuse cortical atrophy (B).*

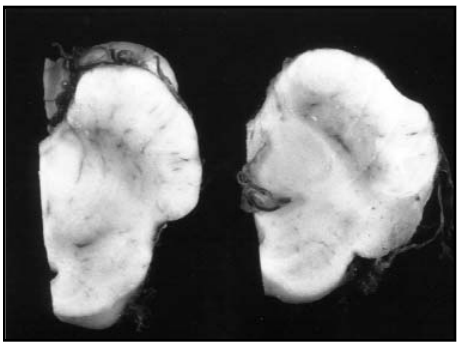

Figure 2: *The substantia nigra reveals a marked loss of pigmentation.*

Multiple tissue blocks were sampled from the cerebral hemisphere, brainstem, cerebellum and spinal cord. The blocks were embedded in paraffin and five micron thick sections were obtained and stained with the Bielschowsky silver stain or immunostained for ubiquitin (Dako, 1:400 for 1 hour).

Microscopic examination revealed severe neuronal loss and gliosis in the nucleus basalis of Meynert, substantia nigra, locus coeruleus, dorsal motor nucleus of the vagus, intermediolateral nucleus of the spinal cord and sacral autonomic nuclei. Pale neurons and Lewy bodies were abundant in the nucleus basalis, substantia nigra (Figure 3a) and locus coeruleus. They were also

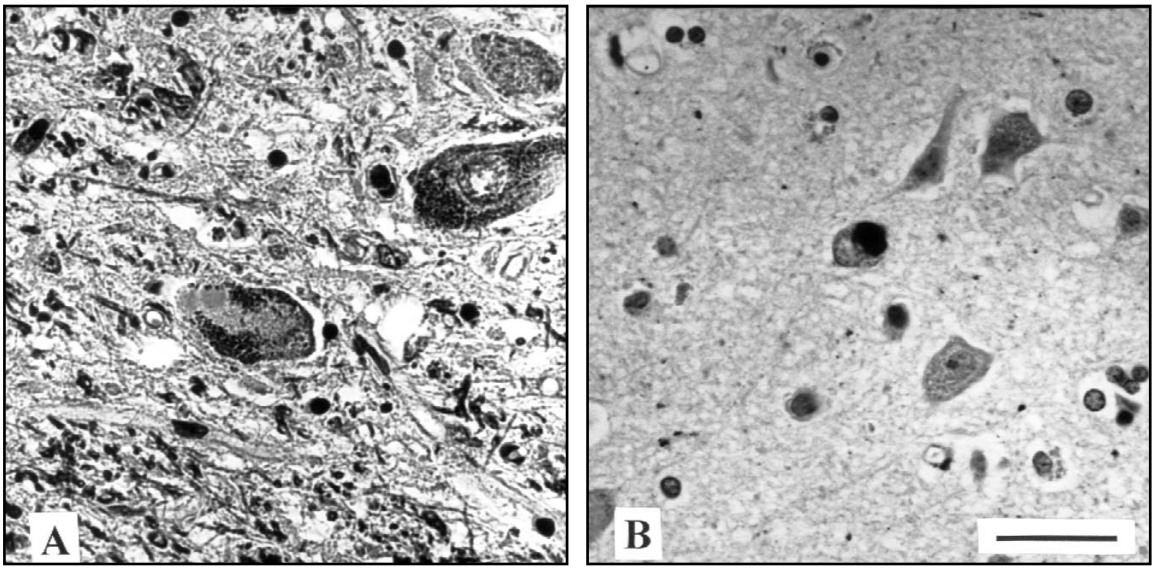

Figure 3: *The substantia nigra shows extensive neuronal loss and abundant Lewy bodies (A). Lewy bodies are also present diffusely in the neocortex (B). Hematoxylin-eosin/Luxol fast blue (A) and ubiquitin immunostain (B).*

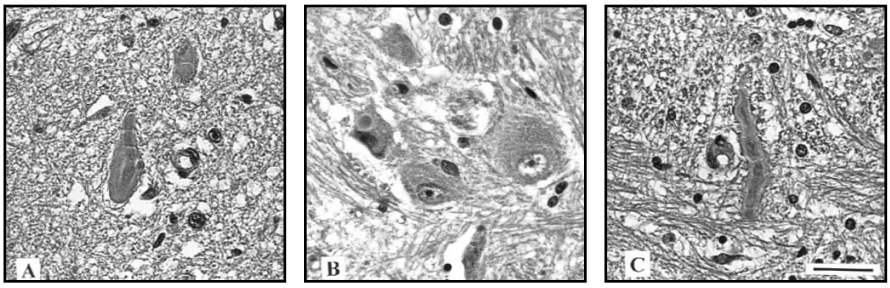

Figure 4: *The dorsal motor nucleus of the vagus displays severe neuronal loss and frequent Lewy bodies, often intraneuritic (A); Lewy bodies are also present in the rostral lateral medulla, both intracytoplasmic (B) and intraneuritic (C). Hematoxylin-eosin/Luxol fast blue.*

abundant and chiefly intraneuritic in the dorsal motor nucleus of the vagus (Figure 4a). Significant neuronal loss was not observed in the hypothalamus or the rostral lateral medulla, but Lewy bodies were easily found in both locations (Figure 4b and c). Lewy bodies were rarely found in the autonomic nuclei of the spinal cord (Figure 5a and b). Examination of the cerebral cortex revealed the presence of Lewy bodies diffusely (Figure 3b). The cortical blocks were originally sampled in accordance with the proposed guidelines for the diagnosis of dementia with Lewy bodies.[6] They were immunostained for ubiquitin and evaluated semi-quantitatively as suggested in the above guidelines. All regions examined (cingulate, frontal, temporal, parietal, entorhinal) showed well in excess of five Lewy bodies for a total Lewy body score of 10/10, corresponding to Lewy body disease of the diffuse type. A few ubiquitin positive Lewy body neurites were also observed in the CA2 sector of the hippocampus (Figure 6). Alzheimer-type changes were modest and consisted of a few tangles in the parahippocampal gyrus, a moderate number of neuritic and diffuse plaques as well as a few tangles in the amygdala, and a few diffuse plaques in the striatum. The cerebral cortex showed a maximum density of sparse neuritic plaques, moderate diffuse plaques and no tangles when scored according to the CERAD scale.[8] The striatum was unremarkable except for the presence of a marked degree of arteriolosclerosis. No oligodendroglial inclusions were present.

Discussion

Cognitive impairment is the central feature required by consensus criteria for a diagnosis of DLBD.[6] The majority of DLBD cases initially present with cognitive or psychiatric changes[9] and many experience prominent hallucinations, delusions, or fluctuations in cognitive status. Others may present with parkinsonism, only later developing dementia. This was the course of our patient, however, in contrast to most patients with this course, at onset she had prominent autonomic symptoms accompanying the parkinsonism. Although orthostatic hypotension is not uncommon in Lewy body Parkinson's disease (PD), the presence of severe orthostatis resulting in falls as a presenting symptom is most unusual in this disorder and encouraged a diagnosis of multiple system atrophy (MSA). The lack of a classical resting tremor is compatible with this diagnosis[10] although it may also be absent in DLBD.[6,7,9] Other clinical features which might have suggested a diagnosis of the striatonigral form of MSA,[10] such as facial myoclonus and pronounced anterocollis were absent. Although these features may be more specific for MSA than PD,

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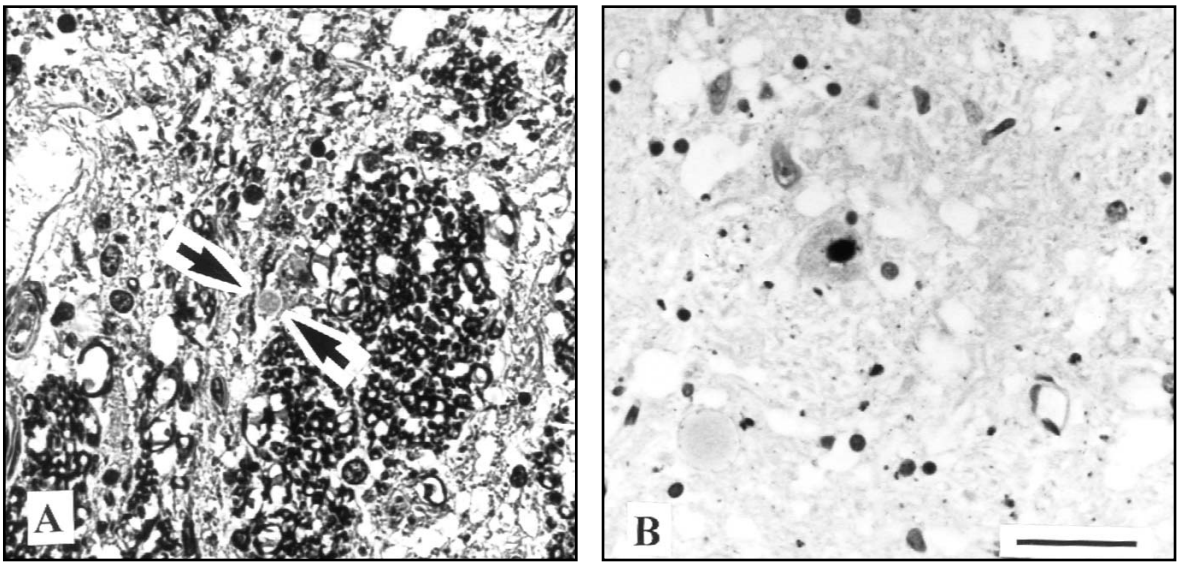

Figure 5: *The intermediolateral nucleous of the thoracic cord (A) and the sacral autonomic nuclei (B) both show severe neuronal loss and rare Lewy bodies. Hematoxylineosin/Luxol fast blue (A) and ubiquitin immunostain (B).*

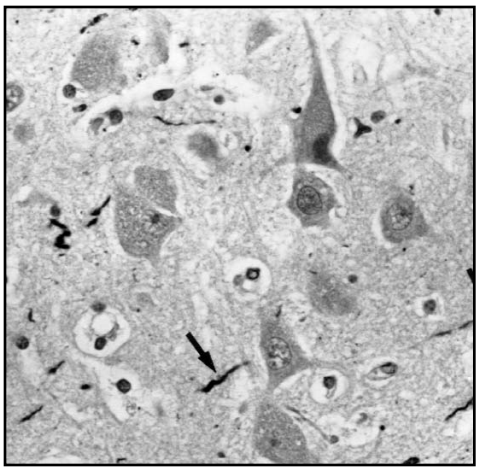

Figure 6: *Few ubiquitin positive neurites are seen in the CA2 sector of the hippocampus. Ubiquitin immunostain.*

the sensitivity of these criteria for a diagnosis of MSA is rather low. Similarly, although MRI changes supportive of a diagnosis of MSA were not present, these too have high specificity but low sensitivity.[11] The initial limited beneficial response to levodopa treatment and the absence of a sustained response is compatible with either MSA[10] or DLBD.[9] Levodopa may induce prominent cranial dystonia in patients with MSA.[12] Although this was not seen in our patient, it is probably an uncommon side effect and its absence is unhelpful in diagnosis. As is typical in MSA, our patient also had sensitivity to dopaminergic therapy which exacerbated her orthostasis. In DLBD, dose-limiting side effects are often psychiatric.[5] Neuropathological examination disclosed the presence of Lewy body disease of the diffuse type with extensive involvement of autonomic nuclei and no evidence of MSA.

In addition to the typical neuropsychiatric or parkinsonian presentations, uncommon or rare manifestations of Lewy body disease have included familial cases[13] and a clinical presentation of progressive supranuclear palsy.[14,15] Also included within the spectrum of Lewy body disease, although without neocortical involvement, are segmental cranial dystonia,[16] dysphagia associated with Lewy bodies and severe neuronal loss in the dorsal vagal nuclei,[17] achalasia with Lewy bodies in degenerating ganglion cells within the esophageal myenteric plexus,[18] and finally, most relevant to our case, pure autonomic failure with Lewy bodies in the sympathetic ganglia and distal autonomic axons as well as in the substantia nigra, locus coeruleus and substantia innominata.[19] Lewy bodies may also be present incidentally, especially in the brains of those over 60 years of age.[20]

Autonomic features have been noted in other cases of DLBD; however, when present, they generally become evident later in the course. In the series of nine patients with pathologically proven DLBD without coexisting Alzheimer's disease reported by Hely et al.[21] four developed urinary symptoms one to five years after onset and two became symptomatic with orthostatic hypotension nine and five years after onset. These patients all had prominent neuropsychiatric manifestations and other features commonly associated with DLBD. A single case with the "common form" of DLBD (with coexisting Alzheimer-type pathology) reported in an autopsy series had a clinical diagnosis of Shy-Drager syndrome (SDS).[7] This patient was among three out of 28 cases with the common form of DLBD and a progressive cortical dementia who had "dizziness" at their initial presentation. In contrast, none of their nine patients with the pathologically pure form of DLBD presented with autonomic symptomatology or carried a clinical diagnosis of SDS.

The prominence and early onset of autonomic symptoms in our patient's case and the lack of prominent cognitive features until much later in her course were unusual for DLBD and more typical of MSA. This case further underscores the broad clinical spectrum within which DLBD may present. In addition to the commonly occurring cognitive, psychiatric and parkinsonian presentations, DLBD may present with parkinsonism

accompanied by both early and prominent autonomic dysfunction, fulfilling criteria for a diagnosis of the striatonigral form of MSA.[10]

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