RESEARCH ARTICLE

Rapidly Progressive Diffuse Lewy Body Disease

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ABSTRACT:

Background: Lewy body syndromes (mainly Parkinson's disease and dementia with Lewy bodies) share many clinical features and usually have a slowly progressive course. Some patients may show rapid symptoms progression.

Objective: To evaluate clinical and neuropathological features of patients with a rapidly progressive diffuse Lewy Body disease.

Methods: Review clinical records and pathological findings of 6 cases with diffuse Lewy Body disease and rapid disease progression (less than 18 months before death).

Results: Mean age at disease onset was 72.5 years, and mean disease duration was 9 months. Onset consisted of delirium in 3 patients and rapidly progressive dementia in the other three. All cases presented visual hallucinations and delusions; cognitive symptoms were fluctuating in two, parkinsonism occurred in four, and myoclonus in three. Brain MRI did not show cortical or basal ganglia hyperintensities. Periodic sharp waves were absent on EEG. 14.3.3 protein in CSF was negative. Myocardial ^{123}I-metaiodo-benzyl-guanidine SPECT showed marked reduction in tracer uptake in the 2 patients tested. Neuropathological studies did not identify any particular feature that could differentiate rapidly progressive diffuse Lewy body disease from classical diffuse Lewy body disease.

Conclusions: Diffuse Lewy body disease is a possible cause of rapidly progressive dementia and should be included in the differential diagnosis of confusional states of undetermined cause. In patients with rapidly progressive dementia, the presence of fluctuating cognition, parkinsonism, hallucinations, delusions, or severe dysautonomia, should raise the suspicion of diffuse Lewy body disease. Neuroimaging studies such as ^{123}I-metaiodo-benzyl-guanidine myocardial scintigraphy may support the clinical diagnosis of diffuse Lewy body disease.

Key Words: diffuse Lewy body disease; Lewy body syndromes; dementia with Lewy bodies; rapidly progressive dementia; Creutzfeldt-Jakob disease

Lewy bodies are the pathological hallmark of different disorders. These include Parkinson's disease (PD) that gives rise to a predominantly motor disorder, and dementia with Lewy bodies (DLB), which presents with fluctuating cognitive symptoms, visual hallucinations, and parkinsonism.[1] PD and DLB share many clinical features such as parkinsonism, delusions, hallucinations, depression, REM sleep behavior disorder (RBD) as well as dysautonomia, and share also many pathological features.[1–3] They are thought to represent different ends of the clinical spectrum of the same condition.[1]

DLB has a progressive course, with a mean survival after onset of symptoms of 5 to 8 years.[4,5] Some DLB patients, however, may show rapid symptoms progression to death within 1 to 2 years.[6,7] In these cases, the clinical diagnosis of DLB is usually difficult to establish and Creutzfeldt-Jakob disease (CJD) is often suspected.[7,8] We report 6 patients with pathologically proven diffuse Lewy body disease (DLBD) presenting clinically with rapidly evolving cognitive deterioration leading to death in an end-stage dementia with less than 18 months.

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Patients and Methods

Among patients with a neuropathological diagnosis of DLBD identified in the Neurological Tissue Bank Hospital Clínic-Universitat of Barcelona (UB-HC-NTB) during the time period 2003 to 2008, cases presenting with behavioral and cognitive symptoms and with disease duration from onset of symptoms to death in an end stage dementia within 18 months or less were studied. The clinical data of brain donors at the UB-HC-NTB was collected by flow chart review process, based on the information provided by treating physicians.

Pathological diagnosis of DLBD and other neurodegenerative disorders at the UB-HC NTB were made according to the current standard criteria.[2,9,10] Briefly, half brain is frozen and the other half is fixed in buffered formaldehyde solution for 4 weeks and cut in coronal slices of <1 cm thickness. Specimens from at least 25 brain areas, including those recommended by the BrainNet Europe II consortium (www.brainnet-europe.org) are embedded in paraffin and cut at 5- to 7-μm-thick sections that are stained with haematoxylin-eosin and luxol fast blue-Klüver Barrera. Immunohistochemistry was performed in selected brain areas according to suggested staining protocols[11,12] following the avidin-biotin-peroxidase method using specific antibodies that include those directed against βA4-amyloid (DAKO, clone 6F/3D, dilution 1:400), phosphorylated τ (Thermo Scientific, clone AT8, dilution 1:200), ubiquitin (DAKO, polyclonal, dilution 1:400), alpha-synuclein (Novocastra, clone KM51, dilution 1:500), TDP-43 (Abnova, clone 2E2-D3, dilution 1:500), neurofilaments (Novocastra, clone RT97, dilution 1:800), and Prion protein (Millipore, clone 3F4, dilution 1:300). PrP Western blot is performed at the Institute of Neuropathology, Hospital de Bellvitge, when CJD is clinically diagnosed or suspected.

Brain tissue of patients with rapidly progressive DLBD was screened for alpha-synuclein gene multiplications. In addition, progranulin mutations were also analyzed in those cases with TDP43-positive inclusion bodies on pathological examination. Genomic DNA was isolated from frontal cortex using standard methods in those cases with available frozen brain tissue. Alpha-synuclein gene multiplications were analyzed using the P051 and P052 Salsa MLPA Parkinson kit, following the Manufacturer instructions [MRC-Holland, Amsterdam, The Netherlands], and progranulin mutations as previously described.[13]

Results

Among 83 patients in whom the pathological substrate was DLBD (36 with a clinical diagnosis of PD with or without dementia, and 47 with a clinical picture of DLB), we identified 6 cases with rapidly evolving cognitive deterioration, with less than 18 months between symptoms onset and death in an end-stage dementia. In these 6 patients (4 men and 2 women), the mean age at disease onset was 72.5 years (range: 71–75), and mean disease duration was 9 months (range: 3–15). Clinical and pathological features of these cases are summarized in Tables 1 and 2. The mean age at onset of dementia for the remaining 41 patients with a clinical diagnosis of DLB and non-rapidly progressive course was 72.9 years (range: 56–89), and the mean disease duration was 6.5 years (range: 2–10). Among the 36 patients with a clinical diagnosis of PD, 25 developed dementia, which was non-rapidly progressive in all cases. In these 25 PD patients with dementia, the mean age at onset of dementia was 71.2 years (range: 61–79), and the mean duration of dementia was 4.9 years (range: 2–11).

In 3 patients (1, 3, and 4), the disease onset consisted of acute confusional state leading to consultation to a hospital emergency room. In two of them, slight cognitive and behavioral symptoms were present several months before the appearance of the acute confusional state. Medical events, drugs, or additional factors that could have triggered the acute confusional state in these 3 patients were not identified despite an adequate initial diagnostic workup. In one case, visual hallucinations, delusions, and unsteady gait were also present during the months before admission. In these 3 patients, neuropsychological testing was not possible due to severe attention deficits at onset or during disease course. The other 3 patients (cases 2, 5, and 6) had rapidly progressive cognitive decline and behavioral changes such as aggressiveness and disinhibition. They presented prominent deficits on attention, executive and visuospatial functions, and short-term memory, which developed within 3–6 months before seeking medical advice. In two of them, cognitive symptoms were fluctuating in nature, with periods of severe confusion alternating with others episodes of significant increased attention and lucidity within the same day.

During the course of the disease, all 6 patients presented well-formed visual hallucinations and structured delusions. Two patients had auditory hallucinations. Mild parkinsonism occurred in 4 patients and repeated falls in three. Action and spontaneous myoclonus were present in three. Cerebellar signs were absent in all patients. Severe dysautonomia occurred in 1 patient who developed orthostatic hypotension and syncopal episodes. Abnormal dream enacting behavior suggestive of RBD occurred in two and past history of depression in one. Significant worsening of cognitive symptoms occurred in 2 patients when treated with typical neuroleptic. None of the 6 patients was treated with levodopa. In one case, treatment with cholinesterase inhibitors did not improve mental status.

Brain MRI showed moderate whole brain atrophy but no cortical or basal ganglia abnormalities in any

TABLE 1. Clinical features of cases with rapidly progressive diffuse Lewy body disease

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at onset (sex)	72 (M)	72 (F)	71 (M)	72 (M)	73 (F)	75 (M)
Disease duration[a] (months)	3	6	7	5	15	15
Symptoms at onset	Acute onset (1 day) with confusion and disorientation	Insidious onset (3 months) with behavioral changes, cognitive decline, and visual hallucinations	Insidious onset (5 month) with memory loss and behavioral changes. Subacute worsening (2 weeks) with disorientation, agitation and falls	Insidious onset (4 months) with behavioral changes, memory loss, hallucinations, delusions, and unsteady gait with falls. Sub-acute worsening (2 weeks) with disorientation, confusion, and aggressiveness	Insidious onset (6 months) with memory loss, disorientation, gait slowness and falls	Insidious onset (6 months) with behavioral changes and cognitive decline
Fluctuating cognition	No	No	No	No	Yes	Yes
Visual hallucinations	Yes	Yes	Yes	Yes	Yes	Yes
Spontaneous parkinsonism	No	Mild symmetrical	No	Mild symmetrical	Moderate asymmetrical	Mild symmetrical
Delusions	Yes	Yes	Yes	Yes	Yes	Yes
Hallucinations in other modalities	No	Yes	MD	Yes	MD	MD
Neuroleptic sensitivity	Yes	No	No	No	No	Yes
Autonomic dysfunction	No	Yes	No	No	No	MD
Myoclonus	No	No	No	Limb action and reflex myoclonus	Right arm	Yes
Past history of depression	No	Yes	MD	No	No	MD
RBD	MD	Yes	MD	MD	Yes	MD
Consensus criteria for DLB[2]	Possible	Probable	Possible	Probable	Probable	Probable
WHO criteria for sporadic CJD[12]	Unlikely	Unlikely	Unlikely	Possible	Possible	Possible
Brain MRI	Mild whole brain atrophy	Mild whole brain atrophy. Leukoaraiosis	Mild brain atrophy	Mild whole brain atrophy	Bilateral parietal and temporal lobe atrophy. Leukoaraiosis	Marked whole brain atrophy. Leukoaraiosis
DAT SPECT	ND	Low striatal tracer uptake	ND	ND	ND	ND
MIBG myocardial scintigraphy	Low uptake	Low uptake	ND	ND	ND	ND
EEG	Symmetrical and generalized slowing	Slowness at 6–7 Hz, predominantly in the left temporal and occipital area	ND	Diffuse slowness at 5–6 Hz	Diffuse wave slowness	ND
14.3.3 in CSF	Negative	ND	Negative	Negative	Negative	ND
Clinical diagnosis by treating neurologist	LB syndrome	LB syndrome	CJD	CJD	CJD	LB syndrome

Disease duration from symptoms onset to death.
M, male; F, female; MD, unknown or missed data; ND, not done; LB, Lewy body; CJD, Creutzfeldt-Jakob disease.

patient. Small vessel vascular disease was detected in 3 patients. In 4 patients, EEG showed diffuse or asymmetrical temporal-occipital slowness, but periodic sharp wave complexes (PSWC) were not recorded. In all patients in whom it was tested, the 14.3.3 protein in CSF was negative (Table 1).

The clinical diagnosis before death or during the course of the illness was that of a Lewy Body disorder in 3 patients. In the remaining 3 patients, the clinical diagnosis during lifetime was CJD. Retrospectively, 4 of the 6 patients fulfilled the consensus criteria for the diagnosis of probable DLB and two for possible DLB.[2] The 3 patients presenting myoclonus and parkinsonism also fulfilled the WHO criteria for possible sporadic CJD; in the remaining 3 patients, the diagnosis of CJD was unlikely according to these criteria.[14]

According to the selection criteria of the cases presented, typical pathological changes of diffuse Lewy body pathology were present in all 6 cases (Table 2, Fig. 1): 4 cases had neocortical-diffuse and 2 had limbic (transitional) Lewy body type pathology.[2] No unusual or atypical findings in regards to the extension and severity of Lewy body pathology or the presence of concomitant pathology were detected. Five cases had additional Alzheimer's disease (AD) type pathology, which severity ranged from Braak and Braak stage II to VI (Table 2). Four of them had concomitant mild amyloid angiopathy, while another had small vessel pathology. Frequent TDP-43 immunoreactive cytoplasmic inclusions and neurites were present in one case mainly in temporo-mesial areas (Case 5), while other case showed TDP-43 cytoplasmic inclusions limited to amygdala and entorhinal region (Case 2). PrP immunochemistry and western blot were negative in all cases.

Alpha-synuclein gene multiplications were not found in any of the 4 cases with available frozen brain tissue (Cases 2, 3, 5, and 6). Proganulin gene mutations were not identified in the 2 cases with TDP43 positive inclusion bodies (Cases 2 and 5).

Two of the 6 patients were cared from onset to end of their illness at the Hospital Clinic of Barcelona, Neurology Service, and the final diagnosis of Lewy Body syndrome was strongly suspected while the patients were still alive. In the text that follows, we provide a detailed clinical description of these 2 cases.

Case 1

This 72-year-old man was found in the street with marked disorientation. There was no past-history of

TABLE 2. Pathological findings in cases with rapidly progressive diffuse Lewy body disease

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Brain weight (g)	1125	1240	1300	1320	1120	1300
Macroscopy	Mild generalized atrophy, mild nigral pallor	Mild nigral pallor	No marked signs of brain atrophy, small SAH left temporal pole, 1.5 cm	Moderate generalized atrophy, mild nigral pallor, mild atherosclerosis of basal arteries	Mild temporally accentuated atrophy, marked nigral pallor and mild pallor of LC, atherosclerosis of basal arteries	Mild generalized atrophy, mild nigral pallor
Spongiosis superficial cortical layers	Mild transentorhinal, temporal and amygdala	Mild cingulum, hippocampus	Absent	Absent	Mild, temporal	Mild, ento- and transentorhinal and temporal
Average alpha-synuclein LB/LN staging (1–4, according to DLB consortium 2005[2])						
Medulla obl/IX–X	3	4	4	3	3	2
Pons/LC	2	3	4	4	4	3
Midbrain/SN	2	3	4	3	3	3
Olfactory bulb	Some neurite and dots	4	1	NA	NA	NA
N. basalis Meynert	3	4	3	4	3	Few positive neurons
Amygdala	4	4	2	3	3	4
Transentorhinal cortex	4	4	2	3	2	4
Hippocampus CA2 plexus	Few neurites	Abundant neurites	Abundant neurites	Frequent neurites	Some neurites	Absent
Cingulate, anterior	4	3	2	3	2	4
Insula	2	3	1	4	1	3
Thalamus	3	2	2	3	1	3
Caudate nucleus	2	3	1	3	2	3
Putamen	2	3	2	3	2	2
Frontal cortex	3	3	1	3	2	2
Temporal cortex	3	4	1	4	2	3
Parietal cortex	2	4	1	3	Absent	2
Occipital cortex	3	3	Isolated	3	Absent	Absent
Spinal cord/IML column	Few dots	Isolated	Isolated	Isolated	Isolated	Isolated
Alpha-synuclein fine neurites	Yes, abundant in frontal	Yes, abundant in frontal and cigulum	Absent	Yes, abundant in frontal	Yes, few in temporal, absent in frontal	Yes, few in temporal
Lewy body type according to DLB consortium[a]	Diffuse neocortical	Diffuse neocortical	Limbic (transitional)	Diffuse neocortical	Limbic (transitional)	Diffuse neocortical
Concomitant pathology						
AD related pathology	Yes, mild-moderate	Yes, severe	No	Yes, moderate	Yes, moderate	Yes, severe
Abeta plaque score (mature plaques)	Moderate	Frequent, bilaminar distribution	Absent	Frequent, laminar distribution	Moderate, laminar distribution	Frequent
Neurofibrillary pathology	Stage III	Stage VI	Absent	Stage II	Stage III	Stage V
Tau-AT8 IR neuropil threads	Moderate	Abundant	Absent	Moderate	Absent	Abundant
CAA	Yes, mild	Yes, mild	Absent	Yes, moderate	Absent	Yes, mild
Capillary CAA	Absent	Focal cerebellum	Absent	Absent	Absent	Absent
TDP43 positive inclusion bodies	Absent	Yes, amygdala, entorhinal	Absent	Absent	Yes, amygdala, entorhinal, temporal, accumbens, inferior olive	Absent
Pathological PrP deposits	Not performed	Absent	Absent	Absent	Absent	Absent
Vascular pathology	Absent	Absent	Focal old temporal subarachnoidal hemorrhage	Absent	Small vessel disease white matter	Old infarction right putamen
Likelihood of DLB (considering LB and AD pathology, according to consensus DLB criteria)[2]	High	Intermediate	High	High	Intermediate	Intermediate

[a]LB scoring: 1 = mild; 2 = moderate; 3 = severe; 4 = very severe.
IX, 9th cranial nerve nucleus; X, 10th cranial nerve nucleus; LC, locus coeruleus; SN, substantia nigra; IML, intermediolateral column of the spinal cord; LB, Lewy bodies; LN, Lewy neurites; DLB, dementia with Lewy bodies; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; PrP, prion protein; SAH, subarachnoidal hemorrhage; NA, not available.

cognitive impairment and patient's relatives had not noticed any change in his mental state during the last weeks or days since he was able to perform correctly complex activities of daily living, such as managing his finances or doing his home duties until the day before. Other relevant medical events or familial history for neurological disorders were absent. Treatment with antidepressive or psychoactive drugs was absent.

At examination, the patient was drowsy, and the attention was reduced. He was disoriented and responses to questions were slow and inappropriate. He was unable to perform complex or sequential tasks. The rest of the neurological and physical examination was normal. Routine blood analyses were normal. Toxicological screening was negative. CT scan of the head showed only mild generalized brain atrophy. The CSF had normal cell count, protein and glucose values. Brain MRI disclosed mild diffuse brain atrophy, but no evidence of focal lesions. An EEG showed 5 to 6 Hz generalized slowing without epileptiform discharges or asymmetries. Microbiological cultures and PCR testing for herpes viruses in the CSF were negative. Screening for thyroid function, antithyroid antibodies, vitamins levels, and microbiological studies with serologies for HIV, syphilis and borreliosis, autoantibodies, plasma tumoral biomarkers, onconeural antibodies, and

porphyria disclosed no abnormalities. Thoracic and abdominal CT and whole-body 18F-glucose PET scan were normal. Duodenal biopsy ruled out Whipple's disease.

The ensuing days, the mental status of the patient progressively worsened, becoming more disoriented and confused, with disorganization of the speech and impossibility to perform simple tasks. There were daily oscillations in attention and alertness. Delusions of persecution and visual hallucinations (spiders and people) developed. At this moment, a lumbar puncture was repeated for 14.3.3 protein testing, but it was negative. A second EEG showed diffuse slow wave activity but no PSWC. A brain MRI did not show high signal in the striatum or in the cortex (T2, diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) sequences). Treatment with risperidone led to a paradoxical response with an increase in the intensity of these disturbances. Quetiapine (up to 200 mg/day) produced a slight improvement of agitation. Myocardial ^{123}I-meta-iodo-benzyl-guanidine SPECT (MIBG-SPECT) and dopamine transporter (DAT) SPECT were indicated. DAT SPECT could not be done because of agitation but MIBG-SPECT disclosed severe cardiac sympathetic denervation (heart-to-mediastinum ratio 1.35). In this context, a Lewy body syndrome was suspected. During the next weeks, the patient became progressively stuporous. He died in a nursing home as consequence of pneumonia, 3 months after disease onset.

Case 2

A 72-year-old woman presented at the Emergency Room with a 3 months history of personality and behavioral changes, aggressiveness, disorientation, and memory loss. She referred visual hallucinations (the presence of her dead brother); Her gait had slowed down during the month before the admission. Her relatives stated that they had not noticed any abnormality or change in the patient's cognitive state until the onset of symptoms 3 months earlier, although they mentioned that over the last 3 years she presented nightmares and talked or screamed while sleeping. She was a smoker and her past medical history was relevant for arterial hypertension, hypercholesterolemia, and episodes of mental depression within the previous 2 years. She was treated with pravastatin and valsartan, but antidepressive or other drugs had not been administered during the last months. Family history was negative for dementia or parkinsonism.

On neurological examination, the patient was disoriented and attention was diminished. Memory for recent events was severely impaired with confabulatory elements. She could not copy a simple figure nor perform simple calculations. Language was normal. Primitive reflexes such as grasping and sucking were present. We found mild symmetrical bradykinesia and rigidity. Rest or action tremor and myoclonus were absent. Her gait was slow with short steps. Cerebellar signs were absent. The rest of the neurological and physical examination was normal.

The same blood and CSF biochemical, microbiological, and serological screenings that have been described in Case 1 were done, disclosing no abnormalities. Brain CT and MRI showed mild generalized cortical brain atrophy with mild periventricular leukoaraiosis. EEG showed slow waves at 6 to 7 Hz, predominantly in the left temporal and occipital area.

During her hospital stay, the patient developed delusions of poisoning and visual hallucinations increased. She often displayed aggressive behavior. Quetiapine up to 400 mg daily was progressively introduced with slight improvement in delusional thinking and behavioral disturbances. In one occasion, the patient lost consciousness short after standing and orthostatic hypotension was detected. The diagnosis of a Lewy body syndrome was suspected, and consequently a DAT SPECT was performed. Reduced striatal tracer uptake, more marked on the right than in the left striatum, was observed. A MIBG-SPECT disclosed severe reduction of tracer uptake (heart-to-mediastinum ratio 1.21).

During the following weeks, her mental status rapidly declined. She was transferred to a nursing home, 2 months after admission. One month later, her speech was extremely reduced, and comprehension was preserved only for simple commands. The patient was wheelchaired and movements were slow in general. A week later, she died due to aspiration pneumonia.

Discussion

This study illustrates an atypical presentation of DLBD rapidly evolving to dementia and death, only several months after the onset of symptoms. There are few previous reports describing DLBD with rapidly progressive symptoms.[6–8,15–18] This fact suggests that, it is a rare condition but may also point to difficulties in the recognition of Lewy body syndromes beyond its usual disease course. In fact, such cases are often misdiagnosed as CJD. In series of patients with rapidly progressive dementia (RPD) in whom this prion diseases was clinically suspected, up to 3–8% of cases were pathologically diagnosed as DLBD.[7,8,16–18]

The diagnosis of Lewy body syndrome in patients with RPD can be difficult because many of the neurological symptoms are nonspecific and can be observed in other many causes of dementia including CJD.[19,20] The presence of myoclonus, a frequent sign of CJD, may add diagnostic confusion since it is not uncommon in Lewy body syndromes and seems to be particularly frequent in those cases with rapid symptom progression.[3,7,8,16] In our series, myoclonus was present, and prominent, in 3 patients. By contrast, any of

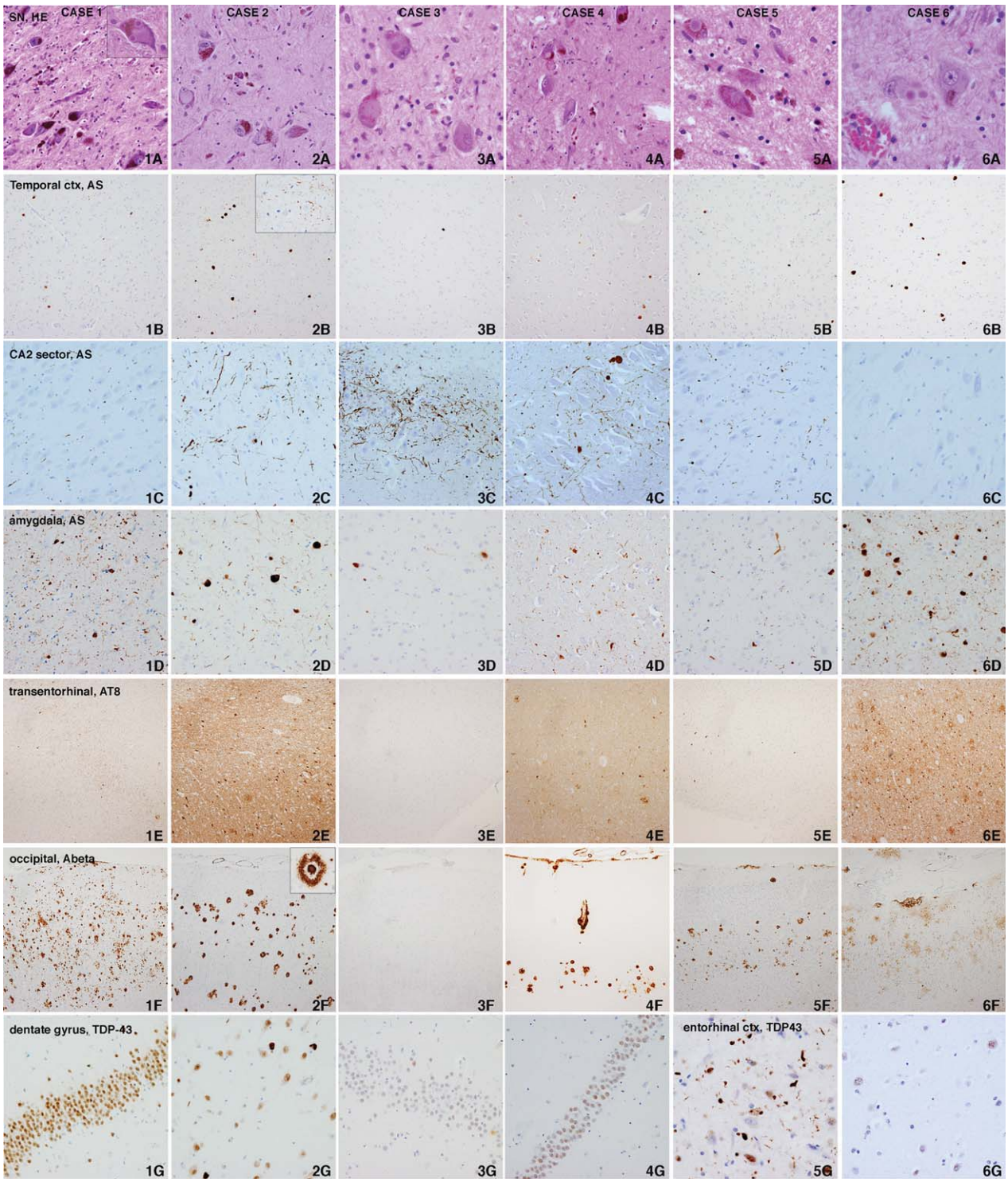

FIG. 1. Illustration of most relevant neuropathological findings in the 6 patients presented (Case 1 to Case 6, each case one column; see also Table 2 for details): First row (1A–6A) shows selected areas of substantia nigra of each patient with variable loss of pigmented neurons, extracellular pigment, and intraneuronal Lewy-bodies in haematoxylin & eosin stained sections. Second, third, and fourth row represent sections of temporal cortex (1B–6B), CA2 sector of hippocampus (1C–6C), and amygdala (1D–6D) of every patient stained with anti-alpha-synuclein antibodies showing in every case variable amounts of immunoreactive Lewy bodies and/or Lewy neurites. Rows five and six illustrate the range of Alzheimer-related co-pathology in transentorhinal cortex (1E–6E; anti-hyperphosphorylated tau antibody AT8) and in occipital cortex (1F–6F; anti-betaA4 antibody) in every individual. Last row shows results of TDP43-immunohistochemistry in dentate gyrus of hippocampus (1G, 3G, 4G) or entorhinal cortex (2G, 5G, 6G): physiological staining of neuronal nuclei and presence of neuronal intracytoplasmic inclusions in 2G and additional thin and thick neurites in 5G without cat-eye intranuclear inclusions. (Original magnifications: 1A, 2A, and 4A, ×200 (1A inset, ×600); 3A, 5A, and 6A, ×400; 1B–6B, ×100 (2B inset, ×400); 1C–5C, ×200; 6C, ×400; 1D–6D, ×200; 1E–6E, ×40; 1F–6F, ×40; (2F inset, ×400); 1G–4G, ×200; 5G–6G, ×400).

our patients presented cerebellar signs and visual disturbances, such as cortical blindness, visual field restriction, and disturbed perception of structures or colors. These cerebellar and visual signs are frequently present in CJD and are not usually found in Lewy body syndromes. Hence, their presence do not support the diagnosis of Lewy body syndrome in patients with RPD.[3,8,14] In addition, a recent study analyzing movement disorders in patients with suspected CJD, found that the presence of hypokinesia and the absence of ataxia made the diagnosis of CJD unlikely and suggested the presence of a degenerative dementia.[21]

In some patients presenting rapidly progressive DLBD, transient postoperative or illness-associated confusional states has been considered to precede the full development of dementia by several months.[22] This was not the case in our patients, although three of them presented with a prominent delirium. Episodes of confusion in Lewy body syndromes often occur during the course of the disease,[3] but delirium at disease onset in Lewy body syndromes could be a marker for particularly rapid progressive cases, since all the 3 patients in our series presenting this symptom had a very rapid course ranging from 3 to 7 months.

Once a Lewy body syndrome is clinically suspected in a patient with RPD, laboratory and neuroimaging tests may have a significant role in establish a clinical diagnosis: cortical and basal ganglia hyperintensities in DWI and FLAIR sequences are highly specific and sensitive for CJD and have not been reported in patients with DLBD.[23–25] Analysis for protein 14.3.3 protein in CSF is also helpful since it has a sensitivity of 94% and specificity of 84% for the clinical diagnosis of CJD.[26,27] 14.3.3 protein in CSF is usually negative in patients with rapidly progressive DLBD,[7,8] although occasionally some patients with Lewy body syndrome and rapid disease progression could have a positive result.[16] The presence of PSWC in EEG has a sensitivity of 66% and a specificity of 74% for the diagnosis of pathologically confirmed CJD.[27] However, PSWC are not pathognomonic for CJD and have been reported in other neurodegenerative diseases including DLBD.[28,29] Some studies suggest that EEG could not be efficient to discriminate between these two diseases,[7,16] but strict use of the criteria for PSWC proposed by Steinhoff et al. could be useful in differentiate those abnormal EEGs with periodic complexes observed in neurodegenerative diseases like DLBD from classical PSWC of CJD.[8,14,30,31]

DAT SPECT and myocardial scintigraphy with MIBG may prove helpful in supporting the diagnosis of a Lewy body syndrome. DAT imaging in Lewy body syndromes shows low striatal tracer uptake, which is not found in other dementias such as AD,[32] but abnormal DAT imaging has been reported in patients with CJD.[33] Abnormal myocardial scintigraphy with MIBG has been postulated as a marker for Lewy body syndromes,[34] and since the pathological process of CJD presumably does not involve the cardiac plexus, MIBG SPECT could be helpful in the differential diagnosis of DLBD and other causes of RPD.

We did not identify any particular pathological feature distinctive of rapidly progressive DLBD with respect to what is reported in the literature for DLBD.[35,36] We did not find multiplications or mutations in alpha-synuclein or proganulin genes in our patients with rapidly progressive DLBD. The biological substrate of the rapidly progressive course in some DLBD patients compared to others is still unknown. Whether some genetic variants and other factors like concomitant diseases such as AD or vascular pathology might play a role in disease evolution is still to be elucidated.

In summary, DLBD is a possible cause of RPD and should be included in the differential diagnosis of confusional states of undetermined cause after an adequate initial diagnostic workup. In patients with RPD, the presence of fluctuating cognition, spontaneous parkinsonism, hallucinations, delusions, severe dysautonomia, neuroleptic sensitivity or RBD symptoms, should raise the suspicion of DLBD. If diagnostic workup for CJD proves negative, the presence of an altered MIBG myocardial scintigraphy and an abnormal DAT SPECT may further support the clinical diagnosis of DLBD. ■

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