Clinical and Pathological Heterogeneity of Neuronal Intermediate Filament Inclusion Disease

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Objective: To report new cases of neuronal intermediate filament inclusion disease (NIFID).

Design: Case report.

Patients: Pathologically proved NIFID was found in 2 patients from the Universitat de Barcelona–Hospital Clínic Brain Bank. The findings of a neuropathological examination in both patients revealed intracellular inclusions that were detected with hematoxylin-eosin and stained positive for antineurofilament and α-internexin antibodies, variably for ubiquitin, and negatively for τ, α-synuclein, and TAR-DNA binding protein 43.

Interventions: Medical records were retrospectively reviewed.

Results: The first patient developed progressive behavioral changes characterized by apathy and indifference at the age of 37 years, and frontotemporal dementia was diagnosed. The second patient developed progressive tremor and mild speech disturbances at the age of 70 years. Her neurological examination results showed mild dysarthria, hyponimia, a mild rigid-akinetic left-predominant parkinsonism, and bilateral rest and postural tremor. The clinical impression was atypical parkinsonism. No response was obtained with levodopa, and the disease progressed rapidly, with falls and frontal-subcortical cognitive impairment.

Conclusions: Late-onset presentation may be the clinical debut of NIFID. These 2 cases confirm the clinical and pathological heterogeneity of NIFID and suggest its inclusion in the differential diagnosis of several neurodegenerative disorders, including frontotemporal dementia and atypical parkinsonism.

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NEURONAL INTERMEDIATE filament inclusion disease (NIFID) is a distinct neurological disorder that is pathologically characterized by gliosis and neuronal loss and deposition of intermediate neurofilaments containing α-internexin. The term NIFID was first used by Cairns et al. The first case reported was a frontotemporal dementia (FTD), and this is the most frequent clinical presentation. Neuronal intermediate filament inclusion disease may also include pyramidal and extrapyramidal signs. We report 2 new cases that confirm the considerable heterogeneity of the clinical and pathological phenotypes of this disease.

CASE 1

A right-handed 37-year-old man developed progressive behavioral changes characterized by apathy and indifference. Three years later, his family noticed language and memory disturbances. He also presented inappropriate laughing and frequent falls. On hospital admission, 4 years after disease onset, the neurological examination disclosed generalized hyperreflexia, hypertonia in the right upper limb, and elicitation of primitive reflexes. The results of a neuropsychological examination displayed lack of insight, disinhibition, severe attentional deficits, altered verbal retention, executive dysfunction, nonfluent...
aphasia, and visuospatial and dressing apraxia. Medical and family histories were nonsignificant. Cerebral perfusion single-photon emission computed tomography revealed left frontotemporal hypoperfusion, while cranial computed tomography revealed frontotemporal atrophy. The clinical diagnosis was FTD. During follow-up, the patient’s condition continued to decline and he fell into a state of akinetic mutism. He died at the age of 44 years from aspiration pneumonia, and a neuropathological examination was performed.

NEUROPATHOLOGICAL STUDY

The brain weighed 1200 g and macroscopically showed severe bilateral frontal and temporal atrophy. The microscopic examination revealed severe neuronal loss with gliosis and spongiosis in superficial layers of frontal, temporal, and anterior parietal cortices. There was also significant gliosis and moderate neuronal loss in the caudate and putamen. Less severe changes were present in the hippocampus, with severe neuronal loss in CA1. Pale, round or ovoid, intracytoplasmic inclusions were observed in the neocortex in sections stained with hematoxylin-eosin (Figure, A). In addition to the frontal, temporal, and cingular cortex, similar neuronal cytoplasmic inclusions were seen in the hippocampus, amygdala, striatal nuclei, thalami, and brainstem. These inclusions were strongly immunoreactive, best seen with antibodies to α-internexin (Figure, B) and phosphorylated neurofilament epitopes, and moderately immunoreactive to ubiquitin. Inclusions did not stain for antibodies to τ, α-synuclein, and TDP-43; the result of α-amyloid immunostaining was also negative. Some torpedoes in Purkinje cells were also found.

CASE 2

A 70-year-old woman with diabetes mellitus and hypertension developed progressive tremor and mild speech disturbances and experienced multiple falls. The initial neurological examination showed mild dysarthria, hypomimia, mild rigid-akinetic left-predominant parkinsonism, and bilateral rest and postural tremor. The results of oculomotor testing were normal. No dysautonomia

Figure. In case 1, pyramidal neurons of the frontal cortex show pale neuronal intracytoplasmic inclusions in hematoxylin-eosin–stained sections (arrows) (A); these inclusions are strongly immunoreactive to α-internexin (B). In case 2, intracytoplasmic neuronal inclusions in hematoxylin-eosin–stained sections (arrows) (C) are stained with antibodies to phosphorylated neurofilament epitopes (clone RT97) (D) and to α-internexin (E and F, respectively). C is the frontal cortex; D, thalamus; E, cingular cortex; and F, pons. In A and B, the bar indicates 50 µm; in C through F, the bar indicates 25 µm.
was present. Her grandmother reportedly had had similar symptoms, but medical records were not available. Cranial computed tomography disclosed mild cortical-subcortical atrophy. The clinical impression was atypical parkinsonism. Levodopa therapy was started, but no response was obtained with 450 mg/d. The disease progressed rapidly, and the patient developed significant gait disturbances, experienced falls, and developed frontal-subcortical cognitive impairment. She was institutionalized 2 years after disease onset. She died at the age of 75 years, and a neuropathological study was performed.

**NEUROPATHOLOGICAL STUDY**

The brain weighed 1040 g and showed moderate global atrophy predominantly in the parietal lobes. The substantia nigra was mildly pale. The microscopic study revealed pale neuronal intracytoplasmic inclusions, demonstrated by hematoxylin-eosin staining (Figure, C) in the neocortex, striatal nuclei, thalami, and several nuclei of the brainstem, including the pons. These inclusions were identical to those observed in the former patient. They were also immunoreactive to α-internexin and stained variably for phosphorylated neurofilament epitopes and ubiquitin (Figure, D-F). The results of immunostaining to τ, α-synuclein, and TDP-43 were negative. Axonal degeneration was detected in the cerebellar cortex. The substantia nigra exhibited a selective loss of pigmented cells. There were moderate senile plaques in the frontal and cingular cortex and striate nuclei and sparse plaques in the remaining neocortical areas.

**COMMENT**

We report 2 news cases of NIFID with different clinical presentations: FTD and atypical parkinsonism. To our knowledge, only 16 cases of NIFID have been reported in the literature. All of them have an early age at onset (mean age, 38 years; range, 25-56 years), but our second patient extends the range of age at onset to 70 years. Clinically, frontal cognitive impairment, as in patient 1, is present in most previously described patients with NIFID and leads to the diagnosis of FTD (Table). Movement disorders are also frequent, but rarely appear as the first or predominant manifestation of the disease, as described in patient 2. Parkinsonian symptoms in this patient failed to respond to levodopa, as has also been reported in other patients with NIFID who have parkinsonism, although the levodopa dose administered to our patient was relatively low. Both patients described herein experienced falls at an early stage of the disease, and pyramidal signs and akinesia also occurred in the advanced stage. These clinical features are also present in most previously described patients (Table).

A family history of NIFID is not common in these patients, suggesting that it is typically a sporadic disease. Furthermore, no mutations or duplications were found in the α-internexin gene in 4 patients with sporadic NIFID studied, although an animal model resembling NIFID has been developed through genetic duplication and triplication of the α-internexin gene. Patient 2 had a grandmother with similar symptoms, although limited clinical information on this patient does not allow us to make an accurate diagnosis.

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**Table. Clinical Features of the 2 Presented Cases and 16 Previously Described Patients With NIFID**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Previous Dataa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>8 men and 8 women</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>37</td>
<td>70</td>
<td>38 (25-56)b,c</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>7</td>
<td>5</td>
<td>4.74 (2.5-13.0)c</td>
</tr>
<tr>
<td>Family history</td>
<td>N</td>
<td>Yd</td>
<td>1/16</td>
</tr>
<tr>
<td>Language deficit (mutism)</td>
<td>Y</td>
<td>Y</td>
<td>15/16</td>
</tr>
<tr>
<td>Memory loss</td>
<td>Y</td>
<td>Y</td>
<td>13/15</td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>Y</td>
<td>Y</td>
<td>12/13</td>
</tr>
<tr>
<td>Behavior changes</td>
<td>Y</td>
<td>Y</td>
<td>10/16</td>
</tr>
<tr>
<td>Frontal lobe signs</td>
<td>Y</td>
<td>Y</td>
<td>15/16</td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>Y</td>
<td>Y</td>
<td>14/16</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>Y</td>
<td>Y</td>
<td>13/15</td>
</tr>
<tr>
<td>Oculomotor abnormality</td>
<td>N</td>
<td>N</td>
<td>9/15</td>
</tr>
<tr>
<td>Early falls</td>
<td>Y</td>
<td>Y</td>
<td>6/7</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>FTD</td>
<td>Atypical parkinsonism</td>
<td>7 FTD, 1 FTD plus MND, 1 FTD plus parkinsonism, 2 CBD, 1 CBD plus PLS, 1 PLS, 1 MSA, 1 atypical dementia, and 1 atypical MND</td>
</tr>
</tbody>
</table>

Abbreviations: CBD, corticobasal degeneration; FTD, frontotemporal dementia; MND, motor neuron disease; MSA, multiple system atrophy; N, no; NIFID, neuronal intermediate filament inclusion disease; PLS, primary lateral sclerosis; Y, yes.

aData are given as number of patients affected/total number of patients described for this sign or symptom.

b A patient started at the age of 3 years with dysarthria, but at the age of 26 years, she experienced a sudden decline of motor and cognitive functions.

c Data are given as mean (range).

dThis patient had a grandmother with similar symptoms, although limited clinical information on this patient does not allow us to make any definitive statement on the familial distribution of the disease.

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From a pathological standpoint, the most common pattern of cerebral atrophy in patients with NIFID is frontotemporal and caudate atrophy and, to a lesser extent, atrophy of the parietal lobes. The commonly described pattern is similar to that of patient 1. In contrast, parietal atrophy was more remarkable in patient 2. The neuropathological hallmark of NIFID is intracellular inclusions that stain positively for antineurofilament and anti-α-internexin antibodies, variably for ubiquitin, and negatively for α, α-synuclein, and TDP-43 antibodies. We found these inclusions located in the neocortex, hippocampus (in patient 1 only), subcortical nuclei, and brainstem. The cerebellum was also affected in both patients, with Purkinje cell loss and frequent torpedoes in patient 1. Intraneuronal inclusions have been described in NIFID, but we did not observe any in these 2 patients. Previous reports conclude that neuronal intermediate filament inclusions are more abundant in younger patients. However, we found more in the older patient, suggesting that the pathological features of the disease may be more heterogeneous than previously described.

In conclusion, the present report extends the clinical and pathological spectrum of NIFID to include a possible late clinical debut of the disease. Neuronal intermediate filament inclusions should be included in the differential diagnosis of neurodegenerative disorders, such as FTD and atypical parkinsonism, although neuropathological study is essential for its diagnosis.

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