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Cognitive Function and Psychiatric Symptoms in Early- and Late-Onset Frontotemporal Dementia

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Key Words
Cognitive function/psychiatric symptoms, frontotemporal dementia · Early-onset frontotemporal dementia · Late-onset frontotemporal dementia

Abstract
Background/Aim: Some recent studies mentioned that late-onset frontotemporal dementia (FTD) is more common than previously assumed. Although much research has been done in the field, there are no systematic studies which have compared clinical characteristics of early- and late-onset FTD. The aim of this study was to compare cognitive function and psychiatric symptoms in patients with early- and late-onset FTD. ***Methods:*** Study participants were consecutive outpatients. There were 35 FTD patients; their mean age at onset was 63.0 years. We studied sex, education, duration from onset to consultation, Clinical Dementia Rating (CDR) scores, Mini-Mental State Examination (MMSE) scores, Raven's Coloured Progressive Matrices (RCPM) scores, and Neuropsychiatric Inventory (NPI) scores at first consultation of early- and late-onset FTD patients. ***Results:*** There were no significant differences in sex ratio, education, CDR scores, and duration from onset to consultation. There were significant differences in the total MMSE scores, 'three-word recall task', 'construction task', and RCPM scores; late-onset groups scored significantly lower than early-onset groups. There were significant differences in the apathy domain of NPI and total NPI scores; late-onset groups scored significantly higher than early-onset groups. ***Conclusion:*** Late-onset FTD patients may have memory and visuospatial deficits in addition to their behavioural changes, even if they are clinically diagnosed according to consensus diagnostic criteria. They also present more apathy, and they may have a different histolopathological background.

Introduction

Frontotemporal lobar degeneration (FTLD) is the term for primary cerebral degeneration involving the frontal and/or anterior temporal lobes associated with a spectrum of non-Alzheimer-type cortical pathology [1, 2]. Because it gives rise to three different clinical syndromes determined by the distribution of atrophy, FTLD is comprised of three subgroups called frontotemporal dementia (FTD), semantic dementia, and progressive non-fluent aphasia [2]. FTD is the most common clinical phenotype of FTLD, accounting for approximately half of all

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Table 1. Demographic variables of the patient groups (mean ± SD)

	Early-onset FTD	Late-onset FTD	p
Number of patients	21	14	
Age at onset, years	58.0 ± 5.6	70.7 ± 5.0	0.000
Male/female ratio	11/10	7/7	1.000
CDR score (0.5/1/2/3)	8/6/5/2	1/5/6/2	0.211
Education, years	11.0 ± 3.7	10.2 ± 3.2	0.536
Duration from onset to consultation, years	4.5 ± 2.9	3.7 ± 2.1	0.394

FTLD cases [3, 4]. As patients with FTD may present characteristic behavioural changes, including loss of insight, disinhibition, apathy, mood changes, stereotypic behaviour, and abnormal eating behaviour, it is associated with a high degree of caregiver burden [1, 5–8].

It was generally reported that FTD occurs mainly among individuals aged 50–65 years, and FTD is the common cause of primary dementia in the presenium, accounting for up to 20% of all presenile dementia cases [9–11]. However, some recent hospital-based studies reported that late-onset FTD patients were more common than previously assumed [4, 12]. As far as we know, there are only few studies about late-onset FTD [13], and there are no systematic studies comparing clinical characteristics of early- and late-onset FTD.

The aim of this study was to compare cognitive function and psychiatric symptoms in consecutive patients with early- and late-onset FTD attending a memory clinic in Japan.

Patients and Methods

Study participants were 35 consecutive outpatients of the Higher Brain Function Clinic of the Department of Neuropsychiatry, Ehime University Hospital, with a diagnosis of FTD between January 1997 and September 2005. All the patients were evaluated by senior neuropsychiatrists, underwent both physical and neurological examinations, as well as standard psychiatric evaluation to exclude major functional psychiatric disorders such as schizophrenia or mood disorders. We also used the usual battery of screening blood tests including vitamin B_{12} and thyroid function assessment to exclude treatable causes of dementia. FTLD patients, including FTD, semantic dementia, and progressive non-fluent aphasia, were diagnosed according to the international consensus criteria [2].

All patients with FTD underwent MRI or CT, and almost all patients underwent HMPAO-SPECT. All patients with FTD showed either frontal atrophy on structured imaging and/or frontal lobe hypoperfusion on HMPAO-SPECT [14, 15]. Patients were assessed by means of a comprehensive neuropsychological test battery, including the Mini-Mental State Examination (MMSE) [16], Clinical Dementia Rating (CDR) [17], Raven's Coloured Progressive Matrices (RCPM) [18], digit span tasks, word fluency tasks, clock drawing test, and ADAS-Jcog (Alzheimer's Disease Assessment Scale – cognitive component; Japanese version). The presence of psychiatric symptoms was assessed during a structured caregiver interview using the Neuropsychiatric Inventory (NPI) [19]. The NPI evaluates ten neuropsychiatric disturbances common in dementia: delusion, hallucination, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, and aberrant motor behaviour. The validity and reliability of the NPI have been proven both in Western countries and Japan [20].

We routinely and systematically gathered information to determine the onset of the illness according to caregivers with a standard interview; the 'onset' was the time when the caregiver initially noticed any changes in the patient which reflected a substantial change from the patient's premorbid state, rather than a long-standing character trait.

Early-onset dementia was defined as dementia with age at onset <65 years, and late-onset dementia was defined as dementia with age at onset ≥65 years. We examined differences in sex, education, duration from onset to consultation, and CDR, MMSE, RCPM, and NPI scores at first consultation between early- and late-onset FTD groups.

All examinations were conducted after obtaining informed consent from all subjects or their caregivers.

Statistical Analysis

Data analyses were carried out using SPSS. Statistical differences between the two groups were assessed by the t test for age, education, and duration from onset to consultation. The Mann-Whitney U test was conducted for the comparison of MMSE total score, MMSE recall domain, RCPM score, NPI total score, and NPI subscores. The χ^2 test with post hoc Fisher's exact test was conducted for comparison of CDR grade and MMSE construction domain.

Results

There were a total of 35 FTD patients, the mean age at onset was 63.0 ± 8.3 years, and 40% of them were over 65 years old at onset. Demographic variables of the two patient groups are summarized in table 1. There were no significant differences between the two groups with re-

gard to sex, education, CDR, and duration from disease onset to consultation. As an initial symptom, 19 out of 21 early-onset and 11 out of 14 late-onset patients showed behavioural changes.

Table 2 shows the cognitive function between the two patient groups. There were significant differences in the total MMSE score, 'recall of three words' domain, 'construction' domain, and RCPM scores between the two groups; patients in the late-onset FTD group scored significantly lower than those in the early-onset FTD group. We did not compare other neuropsychological results because some FTD patients did not manage to complete these tasks because of their behavioural symptoms (7 out of the 21 early-onset patients and 4 out of the 14 late-onset patients).

Table 3 shows the comparison of psychiatric symptoms between the two groups according to NPI score. There were significant differences in the apathy domain of the NPI and in the total NPI score between the two groups; late-onset FTD patients scored significantly higher than early-onset FTD patients.

Table 2. Comparison of cognitive function between the two groups (mean ± SD)

	Early-onset FTD	Late-onset FTD	p
MMSE total score	21.3 ± 7.6	14.1 ± 9.9	0.023
MMSE recall domain	1.6 ± 1.2	0.8 ± 1.1	0.048
MMSE construction domain (0/1)	4/17	10/4	0.002
RCPM score	23.1 ± 5.4	14.3 ± 9.5	0.006

Table 3. Comparison of psychiatric symptoms (total NPI score) between the two groups (mean ± SD)

	Early-onset FTD	Late-onset FTD	p
Delusion	0.6 ± 1.3	1.3 ± 3.5	0.778
Hallucination	0.2 ± 0.9	1.1 ± 3.3	0.630
Agitation	1.9 ± 2.6	3.9 ± 3.7	0.103
Dysphoria	0.8 ± 1.5	0.8 ± 1.8	0.881
Anxiety	1.6 ± 3.1	1.2 ± 1.9	0.934
Euphoria	0.8 ± 1.9	1.6 ± 2.6	0.377
Apathy	4.5 ± 3.8	7.1 ± 3.0	0.040
Disinhibition	2.6 ± 3.8	4.5 ± 4.3	0.278
Irritability	0.9 ± 1.6	3.0 ± 4.1	0.342
Aberrant motor behaviour	5.6 ± 5.1	7.3 ± 4.1	0.293
Total NPI score	19.5 ± 11.1	31.9 ± 17.3	0.012

Discussion

This study is the first to compare the cognitive function and psychiatric symptoms in patients with early- and late-onset FTD using standardized test batteries. It was generally reported that FTD occurs mainly among individuals aged 50–65 years; the average onset age was reported to be around 57 years in European and North American patients [21]. However, the mean onset age of our series of FTD patients was 63.0 ± 8.3 years, which is older than that reported in European and North American studies [1, 9, 10, 22]. Forty-percent of all FTD patients were in the late-onset group, i.e., age at onset ≥65 years.

The reason for this difference may be based on the role of heredity; namely, most Japanese cases of FTLD are sporadic [23], while the FTLD cases in European and North American countries were accompanied by an extensive family history. In a community-based study in the UK [9], almost one third of the cases (29%) with FTLD had a positive family history. In a nationwide survey in The Netherlands, 38% of the FTD patients had 1 or more first-degree relatives with dementia before the age of 80 years [24]. Among our 35 patients, there were none with a family history of FTLD, and only 5 patients with a family history of any kind of dementia. Onset age of sporadic FTD patients may be later than that of familial FTD patients, although a study done in the UK [25] reported that there were no significant differences in onset age between those with tau mutation-positive, familial tau mutation-negative, and sporadic patients. We need further studies on the relationship between onset age and genetics.

In our research, late-onset FTD patients showed significantly lower values than early-onset FTD patients in the total score of MMSE, 'recall of three words' domain and 'construction' domain of MMSE, and in the RCPM score, although the severity of dementia according to the CDR score did not differ between the two groups. This result suggests that late-onset FTD patients might present different cognitive impairment compared to early-onset FTD patients. FTD patients were known to have better memory abilities and visuospatial abilities than Alzheimer's disease (AD) patients [2, 26, 27]. The 'recall of three words' domain of the MMSE reflects memory function of the subject, and those who have memory disturbance such as AD patients did not score well in this domain [28, 29]. The RCPM score reflects visuoconstructive or visuo-

spatial functions of a subject, and those who have visuospatial dysfunction such as AD or Lewy body dementia did not score well on this item [30]. Late-onset FTD patients tend to have some memory and visuospatial deficits at least on neuropsychological test batteries. In fact, 4 out of the 14 caregivers of late-onset FTD patients noticed forgetfulness, while 2 out of 21 caregivers of early-onset FTD patients noticed it during the course of the disease. They may have cortical pathology of temporal/parietal lobes or vascular disease behind the primal atrophy in frontal lobes [31]. For this reason, we compared the differences on MRI scans between early- and late-onset FTD patients with three senior neuropsychiatrists separately and blinded to the patients and found no difference in the presence of parietal atrophy or ischemic changes between the two groups. However, as we did not conduct volumetry or other statistical analysis of MRI, there is a possibility of effects from other pathologies.

Apathy was one of the most predominant psychiatric symptoms following aberrant motor behaviour in both early- and late-onset FTD patients. Late-onset FTD patients presented more apathy compared to early-onset FTD patients according to NPI scores, although the severity of dementia according to CDR scores did not differ between the two groups. Apathy is known to be a very common change that occurs in FTD patients [7, 32], and is aggravated with the progression of dementia. Apathetic FTD patients have atrophy extending into the dorsolateral frontal cortex or into the anterior cingulate cortex [7, 33]. Previous studies demonstrated an association between anterior cingulate hypoperfusion and the severity of apathy in AD patients [34, 35]. These results suggest that apathy of late-onset FTD patients may be associated with the pathology of the frontal cingulate or dorsolateral frontal area. Late-onset FTD patients may have different pathological and genetic backgrounds compared to early-onset FTD patients, even though we still need to accumulate data.

Turning to the comparison of early-onset AD and late-onset AD, early-onset AD patients were reported to have rapid deterioration, as well as language problems and visuospatial dysfunction [36–38]. Our previous research comparing behavioural and cognitive functions in early-onset AD and late-onset AD using the same methodology [39] showed that in both groups there was no difference in the prevalence of apathy and cognitive functions. The results of our FTD patients differed from these findings in AD patients. Late-onset FTD patients had deficits in memory and visuospatial function and tended to be more apathetic. Characteristics of early-onset AD patients may not be generally applicable to all early-onset neurodegenerative diseases.

There are a few methodological issues that should be taken into consideration to appreciate our results fully. Firstly, to determine the age at onset of degenerative dementia is difficult, especially in FTD. In this study, the onset of dementia was defined as the time when the caregiver initially noticed the patient's changes; however, there is a possibility that the estimated time of onset is a subjective estimate given by the caregivers. Initial symptoms of FTD patients are variable as we reported previously [40], which may make it difficult for caregivers to estimate the time of onset.

Secondly, as this study is based on hospital-based data of the neuropsychiatry department rather than community-based data, it can be claimed that selection bias affects our results. General physicians may refer patients without behavioural symptoms or patients with distinct neurological signs to other departments. Nevertheless, epidemiologic data of non-AD dementias are insufficient because pure cross-sectional or population studies are impractical for diseases with a low prevalence. Furthermore, epidemiologic studies of dementia typically survey people aged 65 years and older, so they may exclude a considerable number of cases of FTD. Therefore, data from hospital-based studies are more realistic.

Thirdly, in this study, we clinically diagnosed FTD patients according to consensus criteria for FTLD [2]. We did not perform lumbar puncture or pathological examination and we could not discuss abnormal tau deposits or pathological background in this study. Recent research revealed that FTD patients consist of pathological heterogeneous groups, including Pick's disease with or without Pick bodies, FTDP-17 (FTD with parkinsonism linked to chromosome 17), dementia lacking distinctive histology, corticobasal degeneration, and motor neuron disease [31, 41, 42]. There is a possibility that early- and late-onset FTD patients had different pathological backgrounds as we described above, although antemortem consensus diagnosis of FTLD was moderately sensitive and very specific [43].

Fourthly, although there was no significant difference between the two groups in the severity of dementia according to the CDR score, the CDR was designed to assess the severity of dementia mainly in AD patients and was not specifically designed to assess the severity of FTD accurately. The severity of dementia in FTD patients could not be assessed with complete accuracy in this study; however, so far this is the only standardized assessment scale of FTD severity available. This is the common lim-

itation of clinical research of FTD as in other previous clinical studies. Although we found no difference between the two groups regarding the duration from onset to consultation, there is also a possibility that in both groups disease proceeds at a different speed.

In conclusion, FTD is a common cause of early-onset dementia; as previously reported, late-onset FTD patients should not be overlooked especially in spontaneous cases. Late-onset FTD patients may have memory and visuospatial impairments to some extent and tend to be more apathetic than early-onset FTD patients, in addition to other symptoms which are the same as in early-onset FTD. Further clinicopathological studies are required.

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ORIGINAL PAPER

Basophilic inclusion body disease and neuronal intermediate filament inclusion disease: a comparative clinicopathological study

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Abstract While both neuronal intermediate filament inclusion disease (NIFID) and basophilic inclusion body disease (BIBD) show frontotemporal lobar degeneration and/or motor neuron disease, it remains unclear whether, and how, these diseases differ from each other. Here, we compared the clinicopathological characteristics of four BIBD and two NIFID cases. Atypical initial symptoms included weakness, dysarthria, and memory impairment in BIBD, and dysarthria in NIFID. Dementia developed more than 1 year after the onset in some BIBD and NIFID cases. Upper and lower motor neuron signs, parkinsonism, and parietal symptoms were noted in both diseases, and involuntary movements in BIBD. Pathologically, severe caudate atrophy was consistently found in both diseases. Cerebral atrophy was distributed in the convexity of the fronto-parietal region in NIFID cases. In both BIBD and NIFID, the frontotemporal cortex including the precentral gyrus, caudate nucleus, putamen, globus pallidus, thalamus, amygdala, hippocampus including the dentate gyrus, substantia nigra, and pyramidal tract were severely affected, whereas lower motor neuron degeneration was minimal. While α-internexin-positive inclusions without cores were found in both NIFID cases, one NIFID case also had α-internexin- and neurofilament-negative, but p62-positive, cytoplasmic spherical inclusions with eosinophilic p62-negative cores. These two types of inclusions frequently coexisted in the same neuron. In three BIBD cases, inclusions were tau-, α-synuclein-, α-internexin-, and neurofilament-negative, but

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occasionally p62-positive. These findings suggest that: (1) the clinical features and distribution of neuronal loss are similar in BIBD and NIFID, and (2) an unknown protein besides α-internexin and neurofilament may play a pivotal pathogenetic role in at least some NIFID cases.

Keywords α-Internexin · Caudate nucleus · Frontotemporal dementia · TDP-43 · Motor neuron disease

Introduction

Basophilic inclusion body disease (BIBD) is a rare disease entity, whose clinical phenotype includes dementia and motor neuron disease (MND) [25]. Cases of dementia having basophilic inclusions were originally called "generalized variant of Pick's disease" [24]. The clinical and pathological features of BIBD were reported to be young onset, remarkable degeneration in the frontotemporal cortex, caudate nucleus, and substantia nigra, and the occurrence of round cytoplasmic basophilic inclusions immunonegative for tau or neurofilament. As far as we know, only seven autopsy cases of generalized variant of Pick's disease have been reported [11, 14, 24, 36]. Like the generalized variant of Pick's disease, the onset age in MND cases with basophilic inclusions reported previously is very young, often under 40 years. MND with basophilic inclusions is also very rare, and only about ten cases of this subtype have been reported [1, 13, 18, 19, 22, 23, 28, 30, 33, 34, 37, 41].

Recently, a new disease entity of frontotemporal lobar degeneration (FTLD) called neuronal intermediate filament inclusion disease (NIFID), neurofilament inclusion body disease (NIBD), or neurofilament inclusion disease (NFID) was proposed [5, 6, 16]. A pathological hallmark of NIFID is the occurrence of neurofilament-positive intraneuronal inclusions. More recently, it was reported that α-internexin immunohistochemistry reveals the inclusions more sensitively and specifically [6, 39].

The morphological features of the inclusions in NIFID on conventional stains are quite similar to those of inclusions in BIBD. Further, the BIBD cases previously reported were not always fully examined immunohistochemically. Therefore, the clinical and pathological characteristics in BIBD have not been fully established, and whether the clinicopathological features of BIBD are different from those of NIFID remains unclear. In the present study, we first used α-internexin and neurofilament immunohistochemistry to differentiate NIFID cases from our series of cases that were previously diagnosed as BIBD, based on conventional stains. Then, we compared the clinical features, distribution of neuronal loss, and immunohistochemical characteristics of BIBD and NIFID cases.

Materials and methods

Subjects

Six cases previously diagnosed as BIBD were selected from our autopsy series. A diagnosis of BIBD had been made based on the conventional histopathological features of basophilic inclusion bodies reported previously: (1) round or oval intraneuronal inclusions that are detected by hematoxylin-eosin (H&E), Klüver-Barrera, and Bodian stains according to previous reports [24] and (2) that are not immunolabeled with antibodies against tau, α-synuclein, or ubiquitin. The six cases were immunohistochemically reexamined.

Neuropathological examination

Brain tissue samples from all subjects were fixed postmortem with 10% formalin and embedded in paraffin. Sections (10 μm thick) from the frontal, temporal, parietal, occipital, insular, and cingulate cortices, hippocampus, amygdala, basal ganglia, midbrain, pons, medulla oblongata, cerebellum, and spinal cord were prepared. These sections were stained by the hematoxylin-eosin (H&E), Klüver-Barrera, Holzer, methenamine silver, Bodian, and Gallyas-Braak methods.

Sections from representative regions of the cerebrum, brainstem, and spinal cord were examined immunohistochemically using antibodies to ubiquitin (Z0458, rabbit, polyclonal, 1:5,000, Dako, Glostrup, Denmark), ubiquitin (MAB1510, mouse, monoclonal, 1:500, Chemicon, Burlingame, CA, USA), phosphorylated tau (AT8, mouse, monoclonal, 1:3,000, Innogenetics, Ghent, Belgium), phosphorylated neurofilament (SMI31, mouse, monoclonal, 1:1,000, Sternberger, Lutherville, MD, USA), phosphorylation-independent neurofilament (SMI32: mouse, monoclonal, 1:100, Sternberger Monoclonals, Baltimore, MD, USA), α-internexin (ab32306, rabbit, polyclonal, 1:100, Abcam Plc., Cambridge, UK), phosphorylated α-synuclein (psyn#64, mouse, monoclonal, 1:1,000, Wako, Osaka, Japan), TDP-43 (10782-1-AP, rabbit, polyclonal, 1:500, ProteinTech Group Inc., Chicago, IL, USA), N-terminus of p62 protein (p62-N, guinea pig, polyclonal, 1:500, Progen Biotechnik GmbH, Heidelberg, Germany), C-terminus of p62 protein (p62-C, guinea pig, polyclonal, 1:500, Progen Biotechnik GmbH), polyglutamine (1C2, mouse, monoclonal, 1:10,000, Chemicon, Burlingame, CA, USA), and glial fibrillary acidic protein (GFAP, rabbit, polyclonal, 1:5,000, Dako). Deparaffinized sections were incubated with 1% H_2O_2 in methanol for 20 min to eliminate endogenous peroxidase activity in the tissue. Sections were treated with 0.2% TritonX-100 for 5 min and washed in phosphate-buffered saline (PBS, pH 7.4). When using anti-ubiquitin, anti-neurofilament,

anti-N-terminus p62, anti-C-terminus p62, and anti-α-internexin antibodies, the sections were pretreated by autoclaving for 10 min in 10 mM sodium citrate buffer at 120°C. After blocking with 10% normal serum, the sections were incubated for 72 h at 4°C with one of the primary antibodies in 0.05 M *Tris*–HCl buffer, pH 7.2, containing 0.1% Tween and 15 mM NaN_3. After three 10-min washes in PBS, the sections were incubated in biotinylated anti-rabbit, anti-mouse, or anti-guinea pig secondary antibody for 1 h, and then in avidin-biotinylated horseradish peroxidase complex (ABC Elite kit, Vector, Burlingame, CA, USA) for 1 h. The peroxidase labeling was visualized with 0.2% 3,3′-diaminobenzidine (DAB) as the chromogen. The sections were counterstained with hematoxylin. For double staining with N-terminal-specific p62 antibody (p62-N) and anti-α-internexin antibody (ab32306), primary antibody labeling in the first cycle (p62-N) was detected in the same way as single staining except that the DAB reaction was intensified with nickel ammonium sulfate to yield a dark purple precipitate. Then, primary antibody labeling in the second cycle (ab32306) was detected in the same way as single staining. The sections were counterstained with nuclear fast red for double immunostaining.

Semiquantitative assessment of histopathological lesions

Neuronal loss and gliosis in representative regions were semiquantitatively evaluated. The degree of degeneration in the cerebral cortex was assessed on H&E-, KB-, and GFAP-stained sections according to the following grading system employed in our previous study [43]: −, no histopathological alteration; +, slight neuronal loss and gliosis are observed only in the superficial layers; ++, obvious neuronal loss and gliosis are found in cortical layers II and III, and status spongiosis and relative preservation of neurons in layers V and VI are often present; and +++, pronounced neuronal loss with gliosis is found in all cortical layers, and the adjacent subcortical white matter exhibits prominent fibrous gliosis. In the basal ganglia and brainstem nuclei, the degree of neuronal loss and gliosis was assessed on H&E-, KB-, and GFAP-stained sections according to the following grading system: -, neither neuronal loss nor gliosis is observed; ±, mild gliosis is observed on H&E- or GFAP-immunostained sections, but neurons are not reduced in number; +, mild gliosis and mild neuronal loss are present; ++, neuronal loss and gliosis are moderate, but tissue rarefaction is absent; and +++, severe neuronal loss, severe fibrous gliosis, and tissue rarefaction are observed. Degeneration of the corticospinal tract at the level of the cerebral peduncle and medulla oblongata and of the frontopontine tract in the cerebral peduncle was assessed by loss of myelin, glial proliferation, and presence of macrophages, and indicated as + (present) or − (absent).

Results

Among six cases previously diagnosed as BIBD, neurofilament-positive inclusions were disclosed in two cases, and the inclusions also showed intense immunoreactivity to α-internexin; thus, the diagnosis of these cases was changed to NIFID. The other four cases were again diagnosed as BIBD. Limited clinical and pathological data in cases 1 [9], 2 [15], 3 [20], 5 [32, 36], and 6 [42] have been reported in Japanese.

Case reports

Case 1 (BIBD)

This man was 40 years old at the time of death. He initially complained of difficulty working in high places at age 34. Subsequently, weakness in the left hand and dysarthria developed. Neurological examination at age 35 revealed muscle weakness, fasciculation, and cerebellar ataxia including lack of coordination of the left side extremities. Apathy and oral dyskinesia also developed. Subsequently, involuntary movements such as an alien-hand sign to grasp something with the left hand, deviation of the tongue to the right side, and spastic paralysis in the left extremities also emerged. He obtained an IQ score of 89 on the Wechsler Adult Intelligence Scale (WAIS). At age 36, he could not walk without support. Reduction of utterance, impaired comprehension of speech, disorientation, bradykinesia, swallowing disturbance, ideomotor apraxia, and dressing apraxia were found. Weakness of the left facial muscles and four extremities, muscle atrophy of the tongue, left sternocleidomastoid muscle, and hands, and fasciculation of the legs were also observed. Deep tendon reflexes were hyperactive, and the Babinski sign was positive on the right side. Examinations of blood and cerebrospinal fluid were unremarkable. Electromyography and nerve conduction velocity testing were within normal limits, and neurogenic patterns were observed on muscle biopsy specimens. He died of pneumonia, with a clinical course of 6 years and 4 months. The final neurological diagnosis was amyotrophic lateral sclerosis (ALS) with dementia or Creutzfeldt-Jakob disease.

Case 2 (BIBD)

The patient was a man who was 63 years old at the time of death. He initially developed obsessive ideas and behaviors at the age of 57 years. Subsequently, stereotypic behaviors occurred. He had no relevant past medical or family history. Neurological examination at age 57 disclosed obsessive behaviors, impaired facial recognition, euphoria, and emotional incontinence. Baseline blood examinations were

within normal limits. He was tested using the WAIS and obtained an IQ score of 99. At age 58, apathy, restlessness, oral tendency, disorientation in time and place, impaired memory function, and disturbance of calculation ability were observed. No motor neuron signs, parkinsonism, or cerebellar symptoms were noted, and his gait was normal. He obtained an IQ score of 77 on the WAIS. Parkinsonism first developed at age 59 and primitive reflexes at age 63. He died about 6 years after the onset. The final neurological diagnosis was Pick's disease.

Case 3 (BIBD)

This was a housewife who was 67 years at the time of death. She presented initially with an obsession with collecting things at the age of 56. Subsequently, memory disturbance occurred. She neglected her housework and began to eat only rice and pickled vegetables. At age 58, she was inflexible, drinking too much, and had pica. She had no relevant past medical or family history. Neurological examination at age 58 revealed memory disturbance, impairment of calculation ability, disorientation, emotional unconcern, verbal perseveration, and lack of insight. Blood, urine, and cerebrospinal fluid examinations were within normal limits. Thereafter, double incontinence, verbal stereotypy, echolalia, and reduction of spontaneous speech output were found. She became bedridden at age 60. At age 65, involuntary movements like chorea of the head, four extremities, and trunk occurred. This was a quick, small movement, and she shook her head to the right or left side. In addition, athetosis-like movements of the left arm developed. She died of cardiac failure with a clinical course of 12 years. Her neurological diagnosis was Pick's disease.

Case 4 (BIBD)

This was a 47-year-old man at the time of death. His initial symptom was self-centered behavior at the age of 40; subsequently, disinhibition, irritability, and stereotypic behaviors also occurred. He had no relevant past medical or family history. Neurological examination at age 42 disclosed indifference and lack of insight. The snout reflex was positive. Memory disturbance, aphasia, and constructional impairment were not found. A verbal fluency test revealed poor generation of words (animals = 10, letters = 4). He scored 27/30 on the MMSE (cut off: 24/25) and 25/36 on Raven's Colored Progressive Matrices (cut-off: 24/25). On the WAIS-Revised (WAIS-R), he obtained a verbal IQ score of 77, performance IQ score of 68, and full-scale IQ score of 70. On the Wechsler Memory Scale-Revised (WMS-R, mean ± standard deviation in all subscales = 100 ± 15), he obtained scores on verbal memory of 64, visual memory of 57, general memory of 50, attention/concentration of 80, and delayed recall <50. Restlessness, irritability, and social breakdown became increasingly remarkable. Thereafter, bilateral forced grasping, rigidity in the four extremities, retrocollis, reduction of utterance, aspontaneity, and sexual disinhibition developed. He died of pneumonia with a clinical course of about 7 years. His neurological diagnosis was the frontal-predominant type of Pick's disease.

Case 5 (NIFID)

This was a 73-year-old woman at the time of death. She presented initially with difficulty speaking clearly at the age of 67 years. Thereafter, she was aware of writing incomprehensible sentences. She had no relevant past medical or family history. Neurological examination at age 68 disclosed dysarthria, forced laughing, and effortful and monotonous speech output. Palatal reflex and pharyngeal reflex were decreased. Muscle weakness, atrophy, fasciculation, or pathological reflex was not found. Deep tendon reflex was slightly increased in the four extremities. Upward gaze was slightly restricted. Buccofacial apraxia was found. Baseline blood, urine, and cerebrospinal fluid examinations were unremarkable. An electromyogram was within normal limits. Verbal IQ and performance IQ scores tested by the WAIS-R were 100 and 87, respectively, and a full-scale IQ score was 94. She scored 161/165 on the Token test. She showed poor results on the Wisconsin Card Sorting test, presumably because of an inability to shift attention and frontal dysfunction, attaining only one category with frequent perseverative errors. On the Western Aphasia Battery (WAB), she scored 8/10 for information content, 9.2/10 for auditory word recognition, 4.2/10 for repetition, 8.6/10 for object naming, 6/10 for word fluency, 9.8/10 for reading aloud, and 10/10 for spontaneous writing. Abilities of naming, aural comprehension, and reading were preserved. On the WMS-R, she scored 128 for verbal memory, 68 for visual memory, 84 for general memory, 80 for attention/concentration, and 74 for delayed memory. At age 69, swallowing disturbance, repetitive motor actions, and gait instability occurred, and her utterance was limited to moans. Thereafter, vertical supranuclear gaze palsy, bradykinesia, rigidity, anterocollis, forced grasping, bilateral Babinski signs, dressing apraxia, fasciculation of the tongue, and myoclonus in the left arm developed. She died of pneumonia with a clinical course of 5 years and 8 months. The neurological diagnosis was slowly progressive aphasia.

Case 6 (NIFID)

A 29-year-old forwarding agent became aware of his disinhibited and self-centered behaviors. He started borrowing

money, used illegal stimulants, and repeatedly caused traffic accidents. Stereotypic behaviors also occurred. He was admitted to a psychiatric hospital at age 33. He had no relevant past medical or family history. Neurological examination revealed reduction of speech output, indifference, repetitive behaviors, emotional incontinence, sucking reflex, and urinary and fecal incontinence. Baseline blood, urine, and cerebrospinal examinations were unremarkable. Electromyography was within normal limits. Although he was initially suspected to have schizophrenia, the diagnosis was changed to early onset Pick's disease. Thereafter, forced grasping, sucking reflex, snout reflex, palmomental reflex, Babinski reflex, pica, utilizing behavior, and hypersexuality also developed. No muscle weakness, muscle atrophy, or impairment of spatial function was found. Electromyography and nerve conduction velocity testing were within normal limits. At age 36, flexion in all four extremities, swallowing difficulty, and bilateral ankle clonus developed. Rigidity and tremor were not observed during the course. He died of pneumonia at age 37 about 8 years after the onset.

Summary of clinical features of BIBD and NIFID

The clinical features in all BIBD and NIFID cases are summarized in Table 1. The mean age at onset was 46.8 ± 11.6 years in BIBD cases and 48.0 ± 26.9 years in NIFID cases. The mean disease duration was 7.8 ± 2.8 years in BIBD cases and 6.9 ± 1.6 years in NIFID cases. BIBD and NIFID cases shared several clinical features besides frontal symptoms. The onset symptoms were frontal syndrome in three BIBD and one NIFID cases. Other onset symptoms included muscle weakness (one BIBD case), dysarthria (one BIBD and one NIFID cases), and memory impairment (one BIBD case). Dementia developed more than 1 year after the onset in one BIBD and one NIFID cases, but did not exhibit frontal syndrome at onset. Dysarthria, dysphasia, upper and lower motor neuron signs, gait disturbance, parkinsonism, and parietal symptoms were noted in both diseases during the course. Memory impairment and involuntary movements like alien-hand sign, athetosis, and chorea were found only in BIBD cases in our series.

Radiological findings in BIBD and NIFID

The BIBD (case 4) and NIFID cases (cases 5 and 6) that were examined radiologically consistently showed rapidly progressive severe atrophy in the frontotemporal lobe and caudate nucleus. A flattened caudate nucleus was observed by 1–5 years after the onset (Figs. 1, 2). In both NIFID cases, the frontal atrophy was accentuated in the convexity, and the temporal base was relatively preserved in the early course. Positron emission tomography (PET) of a NIFID case (case 5) disclosed left side-predominant hypometabolism in the perisylvian region as well as frontal lobes, being compatible with the findings of corticobasal degeneration (CBD; data not shown).

Neuronal loss in BIBD and NIFID

The distribution of cerebral atrophy in BIBD and NIFID cases is shown in Table 2. The distribution of frontotemporal atrophy in our BIBD cases varied from case to case (Fig. 3a, b). However, in the NIFID cases, the frontal convexity was prominently affected, and the temporal base was relatively preserved (Fig. 3d, e, f). Atrophy of the frontal convexity was accentuated in the posterior portion rather than the anterior portion in one NIFID case (case 5; Fig. 3d). Evident atrophy in the precentral gyrus was found in two BIBD (cases 3 and 4) and both NIFID cases (Fig. 3a, b, d, e). All BIBD and NIFID cases showed severe caudate atrophy with a concavity of the ventricular surface (Fig. 3c, f).

Microscopically, BIBD and NIFID cases had similar topographical distributions and severities of neuronal loss (Table 2). Severe neuronal loss in the frontal and/or temporal cortex was frequently found in both diseases, and subcortical gliosis with loss of the myelin in the frontal lobes was evident in all BIBD and NIFID cases. No ischemic change was noted in the white matter in the frontotemporal lobe in any BIBD and NIFID case. Astrocytosis in the primary motor cortex was found in one NIFID and all BIBD cases, and severe neuronal loss was encountered in one BIBD case and one NIFID case. The corticospinal tract was degenerated in three BIBD and both NIFID cases (Fig. 4a, c). Various degrees of frontopontine tract degeneration were also noted in all BIBD and NIFID cases in which the cerebral peduncle was examined (Fig. 4e, f). Neurons in the hypoglossal nuclei were spared in number in all BIBD and one NIFID cases, although astrocyte proliferation in this site was frequently noted in both diseases. In two cases, one BIBD and one NIFID, which clinically exhibited lower motor neuron signs and for which spinal cord tissues were available, evident gliosis was found in the anterior horns; however, the anterior horn cells in these cases were spared in number (Fig. 4b, d). In the basal ganglia in both diseases, the caudate nucleus was consistently affected by severe neuronal loss (Fig. 5a). Severe degeneration was frequently found in the putamen also (Fig. 5b). Further, some of the BIBD and NIFID cases showed severe degeneration in the thalamus and globus pallidus. In both BIBD and NIFID, the neurons in the nucleus basalis of Meynert were relatively spared in number despite the presence of evident glial proliferation. The substantia nigra was affected by severe neuronal loss in all of our subjects, except for one

Table 1 Clinical features of BIBD and NIFID

	BIBD			NIFID		
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Male	Male	Female	Male	Female	Male
Age at onset (years)	34	57	56	40	67	29
Duration (years)	6.3	6	12	7	5.7	8
Initial symptoms	Weakness in the left hand, dysarthria	Obsessive behaviors	Behavioral change memory impairment, altered eating habits	Disinhibition	Dysarthria	Disinhibition
Prominent features	Motor neuron disease	Dementia	Dementia	Dementia	Dysarthria, aphasia	Dementia
Clinical diagnosis	ALS with dementia	Pick's disease	Pick's disease	Pick's disease	Slowly progressive aphasia	Early-onset Pick's disease
Oculomotor abnormalities					+	
Dysarthria	+				+	
Dysphasia	+			+	+	
Primitive reflex[a]		+		+	+	+
Gait disturbance	+	+	+	+	+	+
Upper motor neuron signs	+				+	+
Lower motor neuron signs	+				+	
Parkinsonism	+	+		+	+	
Disinhibition				+		+
Apathy, indifference	+	+	+	+	+	+
Economy of effort[b]		+		+		+
Reduction of utterance	+	+		+		+
Stereotypy		+	+	+	+	+
Oral tendency		+				+
Hypersexuality				+		+
Altered dietary habits			+			+
Apraxia and other parietal signs	+	+			+	
Buccofacial apraxia					+	
Memory impairment		+	+			
Face recognition impairment		+	+			
Involuntary movements[c]	+		+			
Cerebellar signs	+					

[a] Palmomental reflex, grasp reflex, sucking reflex, and/or snout reflex

[b] Denkfaulheit

[c] Alien-hand sign (case 1), athetosis (case 3), or chorea (case 3)

BIBD case in which the degeneration was moderate (Fig. 5c). Moderate to severe neuronal loss in the insular and cingulate cortices, amygdala, ambient gyrus, subiculum, and parahippocampal gyrus was consistently found in both diseases. The hippocampal pyramidal neurons were strikingly reduced in number in three BIBD cases for which tissue was available, and one NIFID case also (Fig. 6a, b). Furthermore, marked reduction of the hippocampal granular cells was encountered in two of the three BIBD cases for which tissue was available, and in one NIFID case (Fig. 6a, b).

Inclusion bodies in BIBD and NIFID

All BIBD and NIFID cases had a varying number of round or oval intraneuronal cytoplasmic inclusions (Fig. 7a, b, c). The two diseases could not be distinguished by the morphological features of the inclusions as revealed by conven-

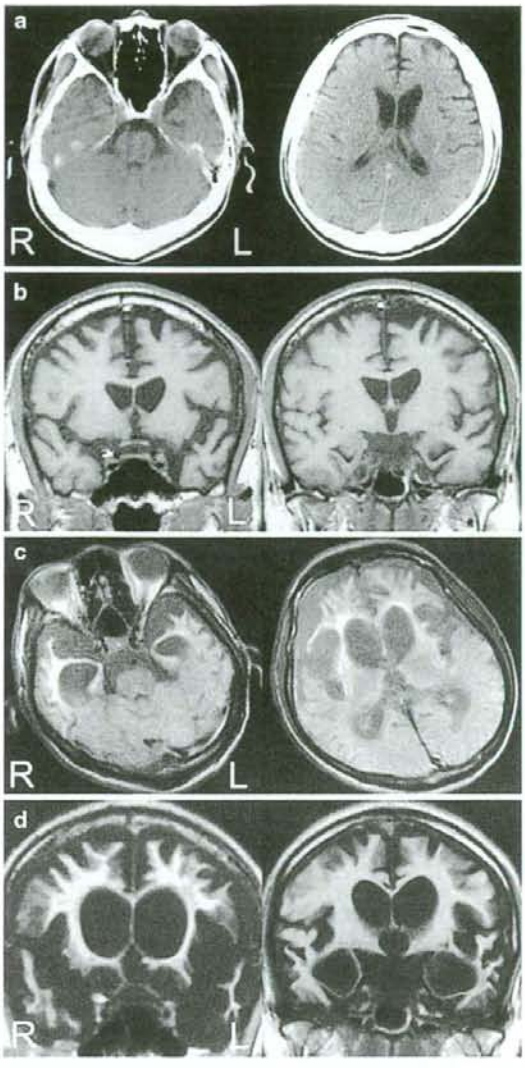

Fig. 1 Serial structural radiographic images of BIBD (case 4). Mild, but not negligible, atrophy in the frontal and temporal lobes and caudate nucleus is seen 2 years after the onset (**a**, **b**). The cortical atrophy is prominent in the frontal convexity and left superior temporal gyrus, and the temporal base is well spared at this time (**b**). Fluid attenuated inversion recovery (FLAIR) images 4 years after onset show severe atrophy in the basal ganglia including the caudate nucleus, frontal convexity, and temporal lobes (**c**, **d**)

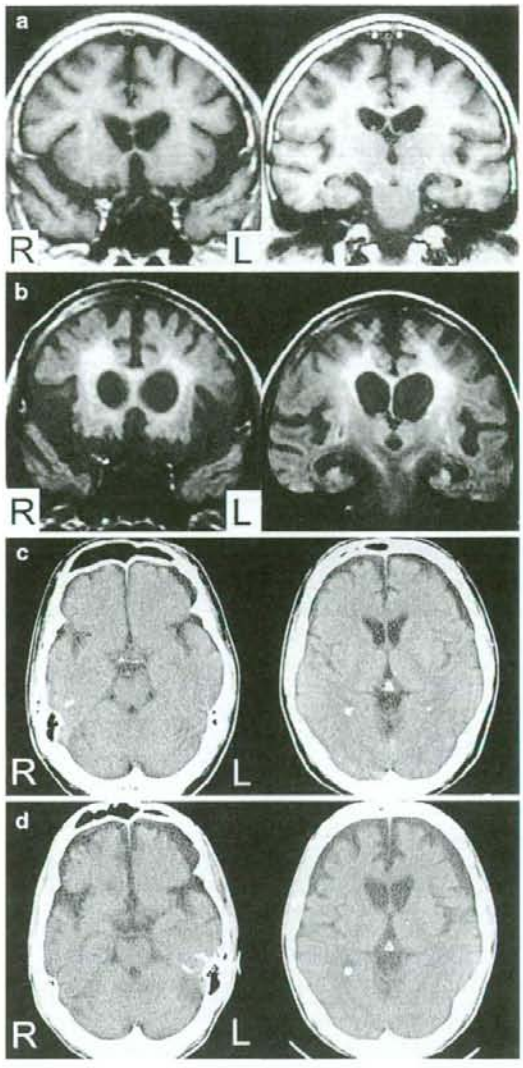

Fig. 2 Serial structural images of NIFID (cases 5 and 6). Coronal T1 images 16 months after the onset in case 5 clearly show the atrophy in the caudate nucleus (**a**). Five years after the onset, the severity of the frontal convexity in case 5 was more prominent in the posterior than in the anterior portion, and the temporal base appears to be spared (**b**). Serial CT images of NIFID in case 6 show mild atrophy in the frontal lobes and caudate nucleus 4 years after onset (**c**). The caudate nucleus is already flattened 5 years after onset, but the temporal lobes are relatively spared (**d**)

tional stains; however, intraneuronal cytoplasmic inclusions having distinct eosinophilic cores were noted only in one NIFID case (case 5, Fig. 7d).

In both NIFID cases, neurofilament-positive inclusions and α-internexin-positive inclusions were encountered in the affected cortex (Fig. 7e). Accumulations of neurofilaments as well as of α-internexin were seen in the hippocampal pyramidal neurons. These accumulations usually had a round or cap-like appearance. In contrast to these aggregates, the spherical inclusions with distinct eosinophilic cores observed in one NIFID case (case 5) were α-internexin-negative and neurofilament-negative (Fig. 7f, g, i, j). Inclusions with cores were frequently encountered in the CA3-4 of the hippocampus and pontine nucleus,

Table 2 Distribution of pathological changes in BIBD and NIFID

	BIBD				NIFID	
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Brain weight (g)	1,230	1,140	880	940	940	940
Cerebral atrophy	Ttip	Ftip, Fbase, Tbase	Ftip, Fbase, Tbase	F, Tbase	Fconv	Fconv, Ttip
Neuronal loss and astrocytosis						
Superior frontal gyrus	+++	+++	++	+++	+++	++
Medial frontal gyrus	+++	+	++	+++	++	+
Inferior frontal gyrus	+++	++	++	+++	++	+
Orbital gyrus	+++	+++	+	+++	+	++
Primary motor cortex	+++	+	+	+[a]	+++[a]	−[a]
Superior temporal gyrus	+++	+	++	+++	+	++
Medial temporal gyrus	+++	++	+++	+++	++	+
Inferior temporal gyrus	+++	+++	+++	+++	++	−
Parietal cortex	+	na	na	+	++	−
Insular cortex	+++	++	+++	+++	+++	++
Cingulate gyrus	+++	+++	+++	+++	++	++
Amygdala	+++	+++	na	+++	+++	++
Ambient gyrus	+++	++	+++	+++	+++	++
CA1 of hippocampus	+++	+++	+++	na	+++	−
Hippocampal dentate gyrus	+++	++	+++	na	++	−
Subiculum	+++	+++	+++	na	+++	+++
Entorhinal cortex	+++	+++	na	na	++	++
Parahippocampal gyrus	+++	++	+++	+++	++	++
Caudate nucleus	+++	+++	+++	+++	+++	+++
Putamen	+++	++	+++	+++	+++	+++
Globus pallidus	++	++	++	++	+++	++
Thalamus	+	++	±	+++	+++	+
Subthalamic nucleus	±	±	na	±	na	±
Nucleus basalis of Meynert	+	±	±	±	±	±
Dentate nucleus of	+	±	±	±	±	−
Cerebellum						
Trochlear nucleus	na	±	na	±	±	±
Oculomotor nucleus	na	na	na	na	±	±
Substantia nigra	+++	++	+++	+++	+++	+++
Red nucleus	±	na	±	na	±	±
Locus ceruleus	++	±	±	++	±	+
Pontine nucleus	±	±	±	±	±	±
Dorsal vagal nucleus	±	na	±	±	±	−
Hypoglossal nucleus	±	±	±	±	+	±
Inferior olivary nucleus	+	±	±	+	++	±
Frontopontine tract	na	+[b]	+[b]	+[b]	+	+
Corticospinal tract						
Cerebral peduncle	na	−	+	+	+[c]	+
Medulla oblongata	+	−	+	+	+	+
Anterior horn	±	na	na	na	±	na

F frontal, *Ftip* Frontal tip, *Fbase* frontal base, *Fconv* frontal convexity, *Ttip* temporal tip, *Tbase* temporal base. The severity of degeneration in the cerebral cortex, basal ganglia, and brainstem nuclei: -, no histopathological alteration; ±, no neuronal loss but gliosis; +, slight neuronal loss and gliosis; ++, moderate neuronal loss and gliosis; +++, severe neuronal loss and gliosis. Degeneration in the pyramidal tract and that in the frontopontine tract: +, present; −, absent. See details in the text. *na* not available

[a] Moderate astrocytosis was found in the deep cortical layer and adjacent white matter

[b] Degeneration was more evident in the frontopontine tract than in the corticospinal tract at the level of the cerebral peduncle

[c] Degeneration was more evident in the corticospinal tract than in the frontopontine tract at the level of the cerebral peduncle

Because the inclusions with cores were hematoxylin-positive, they were readily distinguished from α-internexin and neurofilament aggregates even in the single immunohistochemistry. Some of the inclusions with cores were surrounded by various amounts of α-internexin and neurofilament aggregates, ranging from a small accumulation (Fig. 7g) to

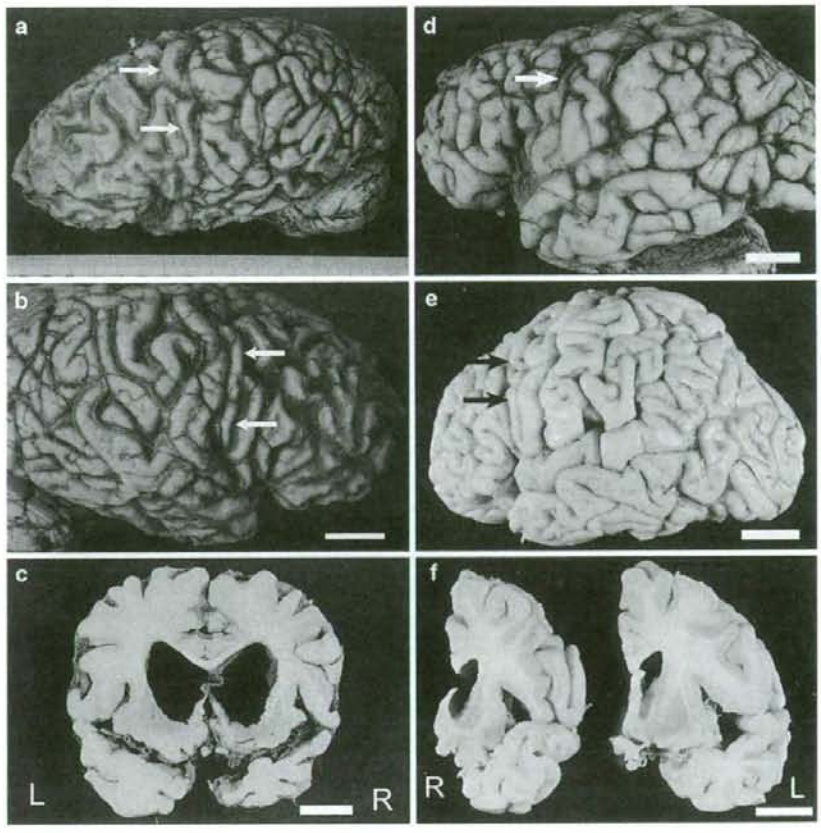

Fig. 3 Macroscopic findings in BIBD and NIFID. **a**, **b** Marked atrophy of the frontal and temporal lobes in BIBD (case 3). The bilateral precentral gyri are atrophic (*arrows*). **c** Severe atrophy in the basal ganglia as well as the right temporal lobe in BIBD (case 2). Severe dilation of the lateral ventricles with concavities of the ventricular surface is seen. **d** Severe atrophy in the frontal convexity in NIFID (case 5). The most severely affected region appears to be the precentral gyrus (*arrow*). The temporal cortices appear to be spared. **e** Severe atrophy in the frontal cortices including the precentral gyrus (*arrows*) in NIFID (case 6). **f** Although caudate atrophy is prominent, the frontotemporal cortices appear to be relatively spared in NIFID (case 6). All scale bars = 2 cm

a dense and diffuse cytoplasmic pattern (Fig. 7h). In a few of the inclusions with cores that were surrounded by dense aggregates of α-internexin or neurofilament, weak to intense immunoreactivity of α-internexin or neurofilament, respectively, was noted. The inclusions with cores usually contained the epitope of p62 (Fig. 7k). Some of the inclusions with cores also showed weak ubiquitin immunoreactivity. In both NIFID cases, there were no lesions immunostained by anti-C-terminal-specific p62, TDP-43, or polyglutamine antibody. Double immunohistochemistry demonstrated that p62-positive spherical inclusions with cores frequently coexisted with α-internexin-positive inclusions in the cytoplasm of the hippocampal pyramidal neurons (Fig. 7l, m, n, o, p, q). The cores of the inclusions showed absent or only weak p62 immunoreactivity (Fig. 7l, m, n, o, p). α-Internexin aggregates often showed spicules or a tangle-like appearance (Fig. 7p, q). Both p62 and α-internexin aggregates were also found in the cytoplasm of the dentate granular cells, which were often intermingled (Fig. 7r). Although no inclusions with cores were seen in the other NIFID case, a small number of p62-positive inclusions were found in the hippocampus and pontine nucleus. No intranuclear inclusions immunopositive for neurofilament, α-internexin, or p62 were found in our NIFID cases.

In the BIBD cases, no immunoreactivity of tau, α-synuclein, ubiquitin, neurofilament, α-internexin, TDP-43, polyglutamine, or p62-C was seen in inclusions. However, some inclusions in the pontine nucleus in cases 1, 2, and 4 were labeled with anti-N-terminus of p62 antibody (Fig. 7s).

The distribution of basophilic inclusion bodies in BIBD cases was consistent with that reported previously [24]: the inclusions were most frequently found in the basal ganglia and brainstem nuclei. The inclusions were also found in the motor neurons in the hypoglossal nuclei in three BIBD cases (cases 1, 3, and 4) and in the spinal anterior horn cells in one BIBD case (case 1), who presented clinically with lower motor neuron signs. Although scant, the inclusions were noted in the hippocampus, subiculum, parahippocampal gyrus, amygdala, and cerebellar dentate nucleus. In NIFID cases, α-internexin-positive inclusions were frequently observed in the frontotemporal cortex, hippocampal pyramidal neurons, and dentate granular cells. Many inclusions were also encountered in the pontine nucleus (cases 5 and 6) and inferior olivary nucleus (case 5), and to

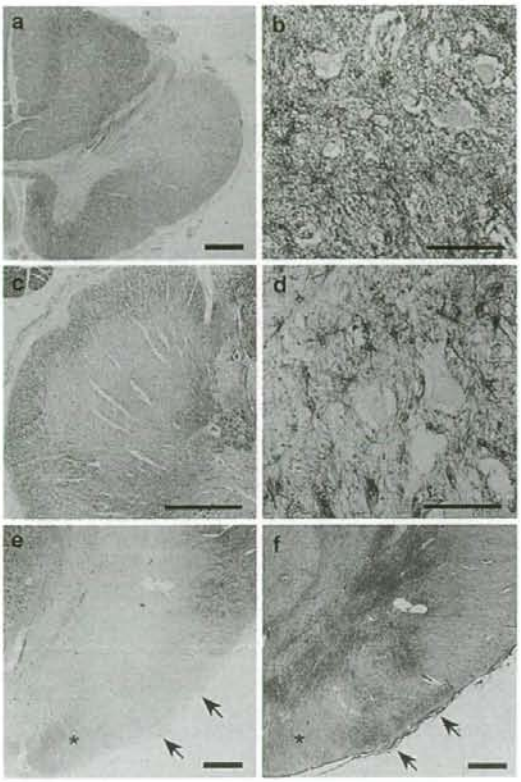

Fig. 4 Motor system involvement in BIBD and NIFID. **a** The cervical cord in BIBD (case 1). Evident loss of myelin in the corticospinal tract is seen. **b** The cervical cord in BIBD (case 1). Severe gliosis in the anterior horn is noted, although the anterior horn cells appear to be spared in number. **c** The cervical cord in NIFID (case 5). Severe loss of myelin in the corticospinal tract is observed. **d** The lumbar cord in NIFID (case 5). Evident gliosis in the anterior horn is seen, but neurons are spared. **e**, **f** Evident loss of myelin with gliosis in the corticospinal tract in the cerebral peduncle (*arrows*) in an NIFID case (case 5). The corticobulbar fibers appear to be involved also, but the degeneration in the frontopontine tract is relatively mild in this case (*asterisks*). **a**, **c**, **e** KB stain; **b**, **d**, **f** Holzer stain. Scale bars = (**a**, **c**, **e**, **f**) 1 mm, (**b**, **d**) 100 μm

a lesser frequency, in the dentate nucleus in the cerebellum (case 5).

None of the cases showed neurofibrillary changes, argyrophilic grains, senile plaques, Lewy bodies, or Pick bodies on silver-stained or immunostained sections. No immunoreactivity of TDP-43 was noted in the spinal cord, hypoglossal nuclei, hippocampus, or frontotemporal cortices in BIBD and NIFID cases.

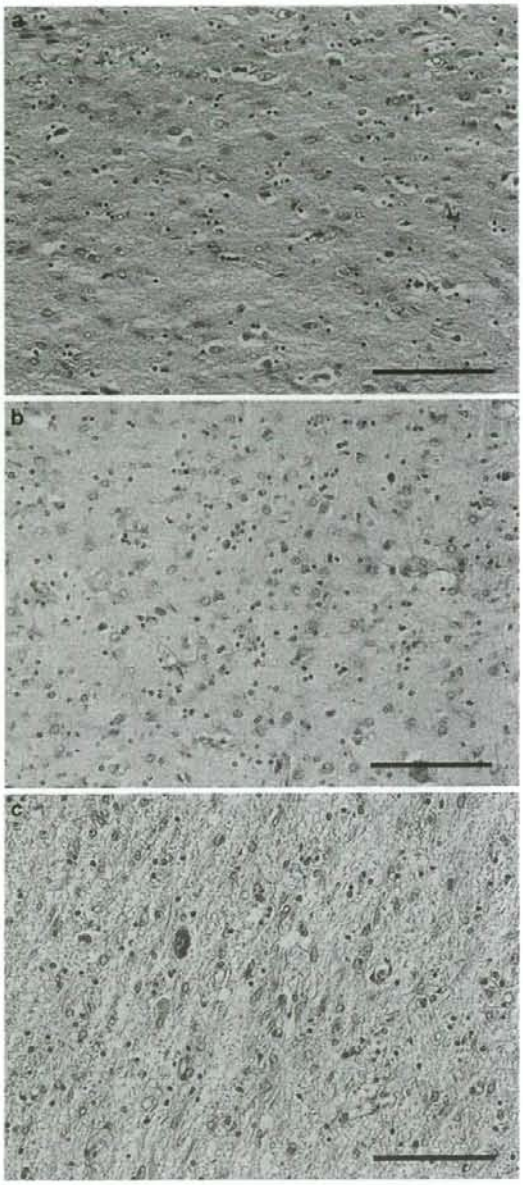

Fig. 5 The basal ganglia and substantia nigra in BIBD and NIFID. **a** Marked neuronal loss and astrocytosis with tissue rarefaction in the caudate nucleus in a BIBD case (case 2). **b** Severe neuronal loss with astrocytosis in the putamen in a BIBD case (case 3). **c** Severe neruonal loss and astrocytosis in the substantia nigra in a NIFID case (case 6). Free melanin was also scattered. **a**, **b**, **c** H&E stain. All scale bars = 100 μm

Discussion

Among six cases previously diagnosed as having basophilic inclusions using conventional stains, the diagnosis of two cases (33%) was changed to NIFID. The clinical features of our NIFID cases were consistent with those reported previously. NIFID cases and BIBD cases shared several clinical

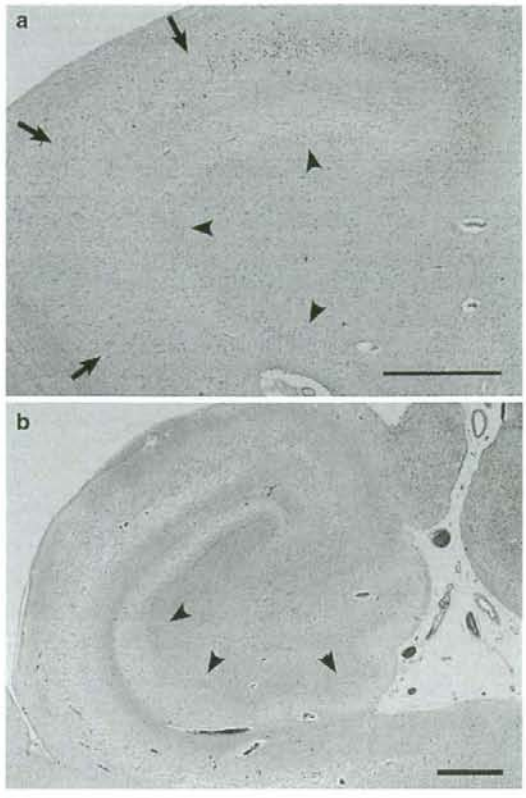

Fig. 6 Severe degeneration of the hippocampus in BIBD and NIFID. **a** BIBD (case 2). *Arrows* indicate severe loss of pyramidal neurons from the CA1 to the subiculum. In addition, the dentate granular cells have almost completely disappeared (*arrowheads*). **b** NIFID (case 5). The pyramidal neurons from the subiculum to CA4 have almost completely disappeared. The dentate granular cells are evidently reduced in number (*arrowheads*). **a**, **b** H&E stain. Scale bars = (**a**, **b**) 1 mm

features besides frontal symptoms, including dysarthria, motor neuron signs, parkinsonism, memory impairment, and parietal symptoms. Given these findings, it seemed to be difficult to clinically differentiate NIFID from BIBD. The distribution and severity of neuronal loss in BIBD cases also resembled those in NIFID cases: severe degeneration was frequently found in the caudate nucleus, putamen, substantia nigra, and pyramidal tract, as well as the frontotemporal cortex. Severe neuronal loss in the hippocampal pyramidal neurons was noted in all three BIBD cases for which the tissues were available and one NIFID case. Further, all of these cases had moderate to severe loss of the granular cells in the hippocampal dentate gyrus. The distribution corresponded to the clinical manifestations of both diseases.

In our BIBD and NIFID cases, the precentral gyrus and pyramidal tract were frequently affected, while the lower motor neurons tended to be spared in number. In previous BIBD cases, especially in MND cases with basophilic inclusions, clinical and pathological evidence of both upper and lower motor neuron involvement was often described. In previous NIFID cases also, the pyramidal tract degeneration was frequently noted, while the lower motor neuron degeneration in NIFID was frequently minimal [7, 17]. Although it is unusual, some of our BIBD and NIFID cases presented clinically with lower motor neuron signs, but did not have significant neuronal loss in the spinal anterior horn cells. The development of lower motor neuron signs in these cases may be explained by the formation of neuronal inclusions with evident astrocytosis in the corresponding sites. Although weakness was noted in some of the previous NIFID cases [7, 17], as far as we know, other lower motor neuron signs including fasciculation and muscle atrophy are rare in NIFID [4, 17, 21, 31]. These clinical findings also appear to support the view that the motor system involvement in NIFID tends to be restricted to the precentral gyrus and pyramidal tract. Further pathological findings need to be accumulated to clarify the histopathological profiles of motor system involvement in BIBD and NIFID.

TDP-43 accumulation is observed in several diseases with motor system involvement, including amyotrophic lateral sclerosis (ALS), FTLD with ubiquitin pathology (FTLD-U) [3, 29], Guamanian parkinsonism–dementia complex (PDC) [12], and Guamanian ALS [10], and to a lesser degree, in some diseases without motor neuron degeneration [2, 26]. In our BIBD and NIFID cases, TDP-43 immunoreactivity was not found in any inclusions, motor neurons, the hippocampal dentate gyrus, or the frontotemporal cortex, which are the preferred sites of TDP-43 accumulation in ALS and FTLD-U. In the consensus criteria recently reported by the Consortium for FTLD also [8], it was accepted that BIBD cases usually lack TDP-43 accumulation, although some of the neurons bearing basophilic inclusions in BIBD cases can show fine granular perikaryal immunoreactivity of TDP-43. Our results also support the view that TDP-43 is not a major pathogenic protein in BIBD and NIFID.

It is noteworthy that the cerebral atrophy in the NIFID cases was accentuated in the frontal convexity rather than the temporal base. Further, in one NIFID case, the frontal atrophy was more prominent in the posterior portion and extended to the parietal region. These findings are in accordance with the previous view that the parietal cortex in NIFID is often affected [7, 17], and that NIFID cases can exhibit CBD-like symptoms including apraxia [16, 17]. On the other hand, alien-hand sign and apraxia were also observed in our BIBD cases, suggesting that BIBD as well as NIFID should be included in the differential diagnosis of a patient presenting with CBD-like symptoms.

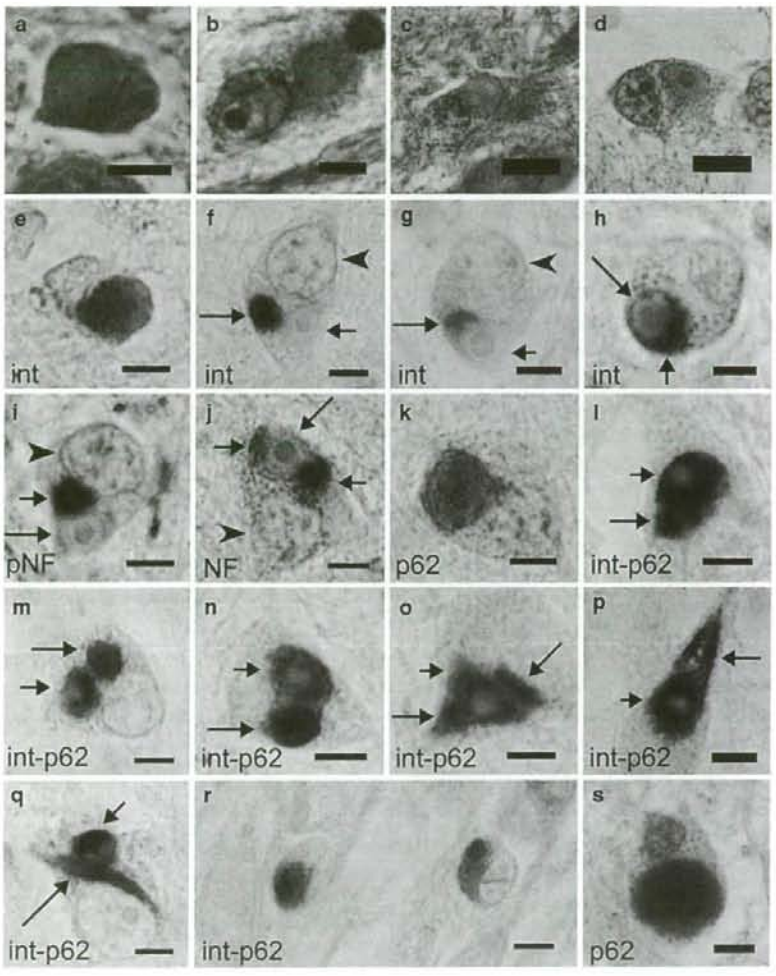

Fig. 7 Intraneuronal inclusions in BIBD (**a**, **b**, **s**) and NIFID (**c**, **d**, **e**, **f**, **g**, **h**, **i**, **j**, **k**, **l**, **m**, **n**, **o**, **p**, **q**, **r**). **a** An inclusion in the pontine nucleus in BIBD. **b** An inclusion in the nucleus basalis of Meynert in BIBD. **c** An inclusion without an eosinophilic core in the pontine nucleus in NIFID. **d** An inclusion with a distinct eosinophilic core (so-called cherry spot) in the CA4 in NIFID. **e** An α-internexin-positive inclusion in the frontal cortex in NIFID. **f** An α-internexin-positive inclusion in a hippocampal pyramidal neuron in NIFID (*long arrow*). The neuron also has an α-internexin-negative inclusion with a distinct core, which appears to correspond to the so-called cherry spot (*short arrow*). An *arrowhead* indicates a nucleus. **g** α-Internexin-negative inclusions with cores in NIFID (*short arrow*) were often accompanied by various amounts of α-internexin accumulation (*long arrow*). An *arrowhead* indicates a nucleus. The CA4. **h** Inclusions with cores in NIFID (*long arrow*) were often surrounded by a dense and diffuse cytoplasmic accumulation of α-internexin (*short arrow*). The pontine nucleus. **i**, **j** Most of the inclusions with cores in NIFID (*long arrows*) were hardly recognized by anti-neurofilament antibodies. *Short arrows* indicate neurofilament aggregates that contact the inclusions with cores. *Arrowheads* indicate nuclei. The CA4. **k** Inclusions with cores in NIFID usually show intense p62immunoreactivity. The CA4. **l**, **m**, **n**, **o** Inclusions with cores in NIFID were p62-positive, but the cores themselves were p62-negative (*black, short arrows*). α-Internexin aggregates frequently coexisted with the p62-positive inclusions with cores in the same neuron (*brown, long arrows*). The hippocampal CA4. **p** Two spicule-shaped neurofilament-positive inclusions (*brown, long arrow*) and a p62-positive spherical inclusion (*black, short arrow*) in a hippocampal neuron in NIFID. The core of the latter inclusion is p62-negative. **q** An α-internexin-positive inclusion showing a spicule-like appearance in NIFID (*brown, long arrow*). A p62-positive round inclusion with a hollow appearance is also present in the same neuron (*black, short arrow*). The CA3. **r** (α-Internexin (*brown*) and p62 (*black*) aggregates in the hippocampal dentate gyrus in NIFID. They were often intermingled. **s** Some inclusions in the pontine nucleus in BIBD cases are p62-positive. **a**, **c**, **d** H&E stain; **b** Klüver-Barrera stain; **e**, **f**, **g**, **h** (α-internexin immunohistochemistry. **i** SMI31 immunohistochemistry; **j** SMI32 immunohistochemistry; **k**, **s** p62-N immunohistochemistry; **l**, **m**, **n**, **o**, **p**, **q**, **r** double immunohistochemistry using anti-α-internexin antibody (*brown*) and anti-N-terminal specific p62 antibody (*black*). **a** Case 3; **e** case 6; **c**, **d**, **f**, **g**, **h**, **i**, **j**, **k**, **l**, **m**, **n**, **o**, **p**, **q**, **r** case 5; **b**, **s** case 2. Scale bar = (**a**, **b**, **c**, **d**) 10 μm, (**e**, **f**, **g**, **h**, **i**, **j**, **k**, **l**, **m**, **n**, **o**, **p**, **q**, **r**, **s**) 5 μm

The degeneration of the basal ganglia in the BIBD and NIFID cases, which did not differ between the two diseases, was more severe and extensive than that in CBD. In our previous semiquantitative study, the globus pallidus and substantia nigra in CBD cases usually showed severe degeneration with fibrous gliosis, but unlike BIBD and NIFID, the putamen and caudate nucleus did not [38]. The development of involuntary movements observed in our BIBD cases might be associated with the severe alteration in the striatum.

All of our BIBD cases for which the tissue was available had severe neuronal loss with gliosis in the hippocampus, although this site was originally reported to be spared in BIBD [24]. Further, all these cases also showed evident loss of dentate granular cells with severe astrocytosis. Loss of neurons in the hippocampus including the dentate gyrus was also observed in one NIFID case. As far as we know, although a varying degree of neuronal loss in the hippocampal pyramidal neurons in NIFID has been described, a reduction in the number of dentate granular cells has not been noted in any previous NIFID case [4, 7, 16, 21, 27]. Whether the severity of the hippocampal lesion differs in NIFID and BIBD remains to be elucidated.

The NIFID cases examined in this study had two types of intraneuronal cytoplasmic inclusions that were differentiated immunohistochemically: (1) neurofilament- and α-internexin-positive round, cap-like, or spicule-shaped inclusions lacking cores and (2) p62-positive but neurofilament- or α-internexin-negative spherical inclusions bearing distinct eosinophilic cores. The morphological features of the latter inclusions were quite similar to those of the "compound intraneuronal inclusion bodies" described by Schochet and Earle in 1970 [35]. At least three cases with compound intraneuronal inclusion bodies have been reported, and interestingly, they were young-onset dementia or MND, and often showed remarkable frontotemporal and caudate atrophy and pyramidal tract degeneration [11, 33, 35]. More recently, Josephs et al. [16] called the eosinophilic core a "cherry spot". Several previous studies demonstrated the morphological and immunohistochemical heterogeneity of inclusions in NIFID. Bigio et al. [4] noted three different morphologic types of intracytoplasmic inclusions in a NIFID case: Pick-like bodies, pleomorphic inclusions, and hyaline conglomerate-like inclusions. They noted that a small number of Pick-like bodies were faintly neurofilament-positive, but the latter two inclusions showed intense neurofilament immunoreactivity. Mackenzie and Feldman [21] described two types of inclusions in an NIFID case: Pick body-like inclusions and hyaline conglomerate inclusions. They described Pick body-like inclusions as round or oval, consistently ubiquitin-positive, rarely neurofilament-positive, and often surrounded by diffuse cytoplasmic immunoreactivity of the neurofilament. They also noted that the center of some hyaline conglomerate inclusions had small, round or elongated eosinophilic masses, but the inclusions appeared to be irregular, sometimes multilobulated, and neurofilament-positive. Thus, the characteristics of the inclusions were not in accordance with those of the inclusions with eosinophilic cores that we observed. Uchikado et al. [40] also noted the presence of α-internexin-negative inclusions in NIFID. Like our results, they observed p62-positive and α-internexin-positive inclusions within the same neuron. However, they noted that round, p62-positive inclusions often occupied a central core of larger α-internexin inclusions, being inconsistent with our results that inclusions with eosinophilic cores were α-internexin-negative. Uchikado et al. further demonstrated electron microscopically that inclusions in NIFID contain two types of components. Based on the presence of neurofilament-negative inclusions, Mackenzie and Feldman [21] speculated that whether NIFID is a single disease entity remains to be elucidated. Indeed, our results led us to speculate that an unknown protein besides neurofilament and α-internexin may play a pivotal pathogenic role at least in some NIFID cases, and possibly, neurofilaments and α-internexin accumulate secondarily in NIFID cases having inclusions with eosinophilic cores. To understand the histopathological heterogeneity in NIFID, further immunohistochemical and biochemical findings need to be accumulated.

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