Table 1 continued

Present criteria	McKhann et al. criteria
6. Frontotemporal neuronal loss and gliosis with ubiquitin-positive/P62-positive, TDP-43- and tau-negative inclusions, the most likely diagnoses are:	
FTLD-U with *CHMP2B* mutation	
Basophilic inclusion body disease (BIBD)	
Other as yet unidentified FTLD-U, non-TDP-43 proteinopathies	
7. Frontotemporal neuronal loss and gliosis with ubiquitin/P62 and -internexin-positive inclusions, the most likely diagnosis is:	
Neuronal intermediate filament inclusion disease (NIFID)	

CHMP2B charged multivesicular body protein 2B gene, *FTLD* frontotemporal lobar degeneration, *FTLD-U* FTLD with ubiquitin-positive, tau-, -synuclein-, TDP-43-, and neuronal intermediate filament protein-negative inclusions, *MAPT* microtubule-associated protein tau gene, *MND* motor neuron disease, neurofibrillary tangle dementia, also called tangle predominant form of senile dementia, *PGRN* progranulin gene, *TDP-43* TAR DNA-binding protein 43, *VCP* valosin-containing protein gene

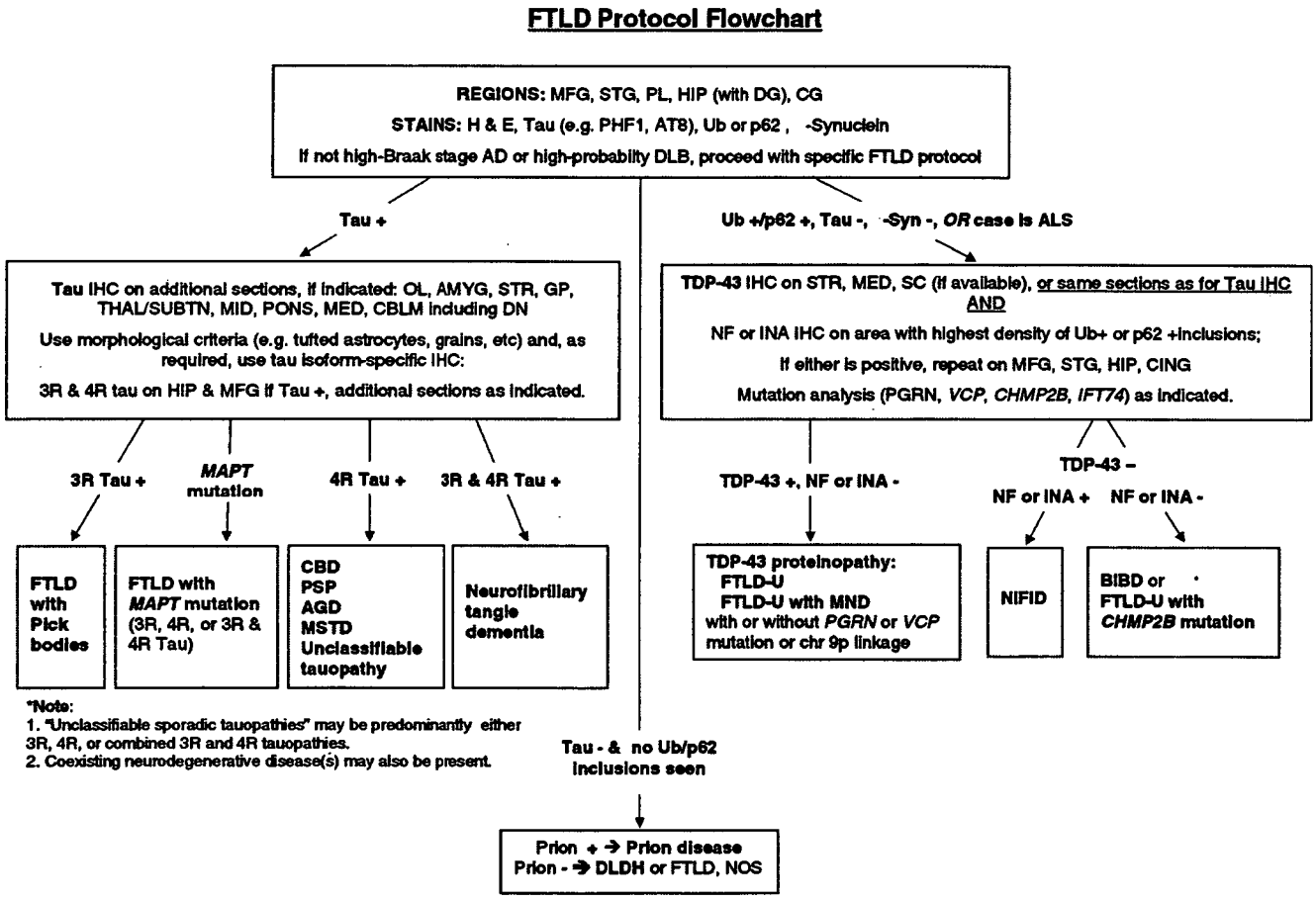

Fig. 1 Frontotemporal lobar degeneration neuropathology algorithm flow chart. *AD* Alzheimer's disease, *AGD* argyrophilic grain disease, *AMYG* amygdala, *BIBD* basophilic inclusion body disease, *CBD* corticobasal degeneration, *CBLM* cerebellum including the dentate nucleus (*DN*), *CHMP2B* charged multivesicular body protein 2B gene, *CG* cingulate gyrus, *DLB* dementia with Lewy bodies, *DLDH* dementia lacking distinctive histologic features, also called FTLD according to McKhann et al. [4] criteria, *FTLD* frontotemporal lobar degeneration, *FTLD-U* FTLD with ubiquitin-positive, tau-negative inclusions, *GP* globus pallidus, *H&E* hematoxylin and eosin, *HIP* hippocampus, *IHC* immunohistochemistry, *INA* -internexin, *MAPT* microtubule-associated protein tau gene, *MED* medulla oblongata, *MFG* middle frontal gyrus, *MID* midbrain including the substantia nigra, *MND* motor neuron disease, *MSTD* sporadic multiple system tauopathy with dementia, *NIFID* neuronal intermediate filament inclusion disease, *NF* neurofilament; neurofibrillary tangle dementia, also called tangle predominant form of senile dementia, *NOS* not otherwise specified, *OL* occipital lobe, *PGRN* progranulin gene, *FL* frontal lobe, *PL* parietal lobe, *PSP* progressive supranuclear palsy, *SC* spinal cord, *STG* superior temporal gyrus, *STR* striatum, *TDP-43* TAR DNA-binding protein 43, *THAL/SUBTN* thalamus and subthalamic nucleus, *Ub* ubiquitin, *VCP* valosin-containing protein gene, *3R, 4R, or 3R and 4R* tau isoforms containing 3, 4, or 3 and 4 microtubule-binding repeats

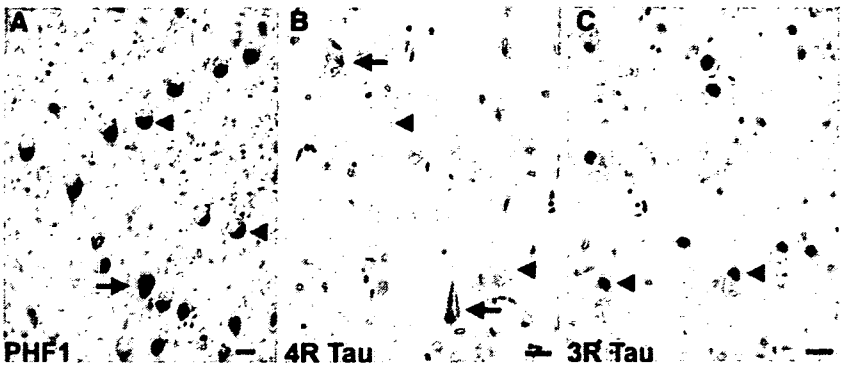

Fig. 2 Frontotemporal lobar degeneration with Pick bodies. Pick bodies (*arrowheads*) and a neurofibrillary tangle (*arrow*) in the subiculum (**a**) are immunolabeled by anti-phosphorylated tau antibodies (*PHF1* immunohistochemistry). Pick bodies are not immunolabeled with anti-4R tau antibodies (*arrowheads*), while neurofibrillary tangles are immunolabeled (*arrows*) (**b**). Anti-3R tau antibodies clearly label Pick bodies (*arrowheads*) (**c**). **b** 4R tau (ET3) and **c** 3R tau (RD3) immunohistochemistry. *Bars* 10 m

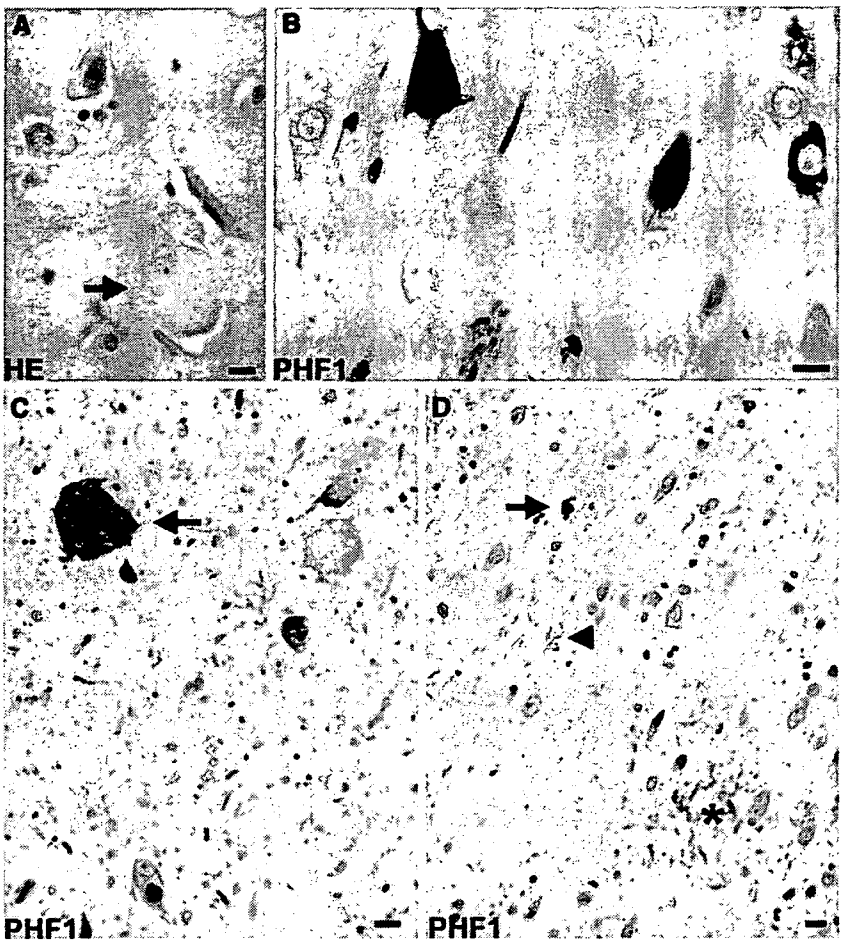

Fig. 3 Corticobasal degeneration. **a** A swollen achromatic neuron (*arrow*) in the middle frontal gyrus. Hematoxylin and eosin (*HE*). **b** Tau-positive neurofibrillary tangles in the pyramidal neurons of the CA1 hippocampal subfield. **c** A globose neurofibrillary tangle (*arrow*) in the locus coeruleus. **d** An astrocytic plaque (*asterisk*), coiled body (*arrow*), and threads (*arrowhead*) in the deep cortical laminae and white matter of the parietal lobe. **b, c, d** Anti-phosphorylated tau (*PHF1*) immunohistochemistry. *Bars* 10 m

arrive at the neuropathologic diagnosis of one of the disease entities causing FTLD. It is appreciated that it may not be practical, possible, or even necessary, to undertake sophisticated neuroanatomical investigations of neuron and synapse density, biochemistry or molecular genetics in every case. For these reasons, the following neuropathologic algorithm has been developed, which should be feasible at most dementia research centers. It is envisaged that this algorithm, with its inbuilt criteria for diagnosis, will supersede existing neuropathologic criteria [3], and become the standard operational protocol for the working neuropathologic diagnosis of FTLD (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14).

Recently, staging schemes have been developed that no longer rely on capricious silver impregnation methods, but employ instead sensitive monoclonal and polyclonal

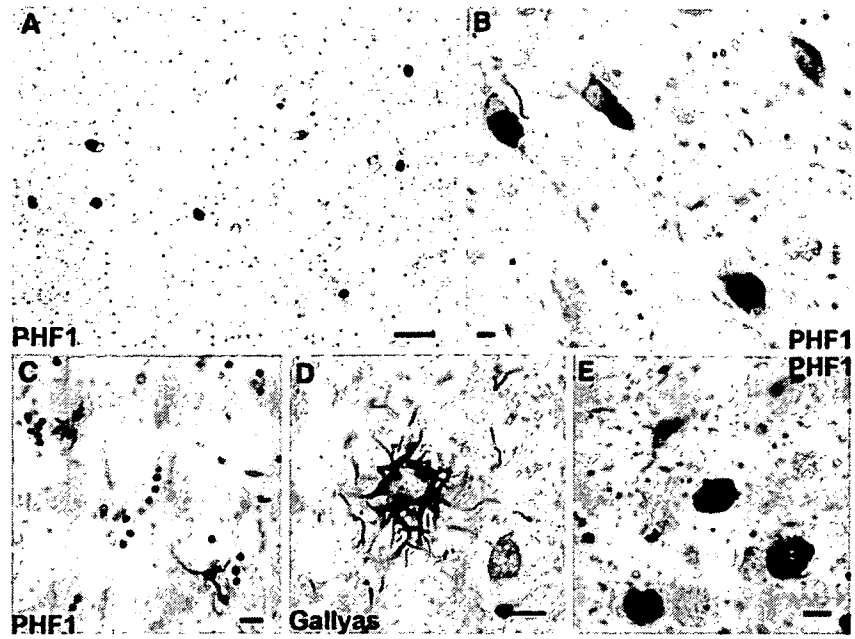

Fig. 4 Progressive supranuclear palsy. Neurofibrillary tangles in the subthalamic nucleus (**a**), occulomotor nucleus (**b**), and locus coeruleus (**e**). Tufted astrocytes in the putamen (**c** and **d**). **a**, **b**, **c**, **e** Anti-phosphorylated tau (*PHF1*) immunohistochemistry. **d** *Gallyas* silver impregnation. *Scale bars* **a** 50 m, **b**, **c**, **d**, **e** 10 m

antibodies that detect, by IHC, the pathologic proteins of the major neurodegenerative diseases [9, 10, 52]. Multicenter studies have confirmed the reproducibility and reliability of IHC over traditional staining methods, and IHC is recommended for the detection of the signature lesions of FTLD [1, 53], when appropriate. Thus, neurodegenerative diseases with -synuclein pathology, with or without A plaques and tau-positive neurofibrillary tangle (AD) pathology (i.e., DLB, Parkinson's disease, and multiple system atrophy), or those with plaque and tangle pathology (i.e. Alzheimer disease) are excluded using established sampling schemes and diagnostic criteria for these diseases [18, 52].

Tau-positive inclusions

Where neurofibrillary tangles alone are present, in the absence of A plaques, in the context of neuronal loss and gliosis, NTD, also called tangle predominant form of senile dementia, which, like AD tangles, contain tau composed of all six isoforms, is a diagnostic possibility. Where the distribution of neuronal and glial tau pathology is more widespread and includes frontal, temporal, and parietal neocortex, basal ganglia, and brainstem nuclei, then sporadic MSTD may be indicated [6]. Neurofibrillary tangles in more subcortical regions including the basal ganglia, subthalamic nucleus, midbrain, and pontine nuclei indicate progressive supranuclear palsy [31, 72]. Distinguishing lesions in PSP are tau-positive tufted astrocytes and are found in affected neocortical and subcortical regions. Corticobasal degeneration is characterized by frontal and temporal atrophy that is not infrequently asymmetric, neuronal loss, gliosis, swollen achromatic neurons that are faintly tau-positive, and tau-positive neurofibrillary tangles in the neocortex, basal ganglia, and brainstem nuclei [24, 27]. Distinguishing lesions in CBD are tau-positive astrocytic plaques and threads found in the affected neocortex and subcortical white matter and in the basal ganglia. In both PSP and CBD, tau-positive oligodendroglial inclusions called coiled bodies are seen, but these are generally at a lower density than inclusions in astrocytes. Tau-positive ovoid structures (glial processes), astrocytes, and oligodendroglial inclusions (coiled bodies), when confined to the medial temporal lobe and limbic structures, indicate another tauopathy, AGD [7]. If globose tau-positive NCIs, called Pick bodies, are present in the non-pyramidal (dentate gyrus granule cells) and pyramidal neurons of area CA1 of the hippocampus, and pyramidal neurons of the temporal and frontal lobes, then FTLD with Pick bodies may be present [80]. Pick bodies are largely or wholly composed of 3R tau, which can be demonstrated by IHC or immunoblotting, while the tau-positive inclusions of PSP, CBD, MSTD, and AGD all contain 4R tau indicating that these latter disorders may represent a spectrum of 4R tauopathies [13, 74]. Finally, FTLD with *MAPT* mutation, also called FTD with parkinsonism linked to chromosome 17 (FTDP-17), is not only clinically and genetically heterogeneous (more than 40 mutations have been reported in the *MAPT* gene), but is also neuropathologically heterogeneous. The spectrum of neuronal and glial pathology seen in 3R, 4R, and combined 3R and 4R tauopathies is also found in such cases of familial tauopathy [15, 44, 70]. For the practicing neuropathologist, the presence of this spectrum of pathology in a case warrants further genetic investigation particularly if there is an autosomal dominant pattern of

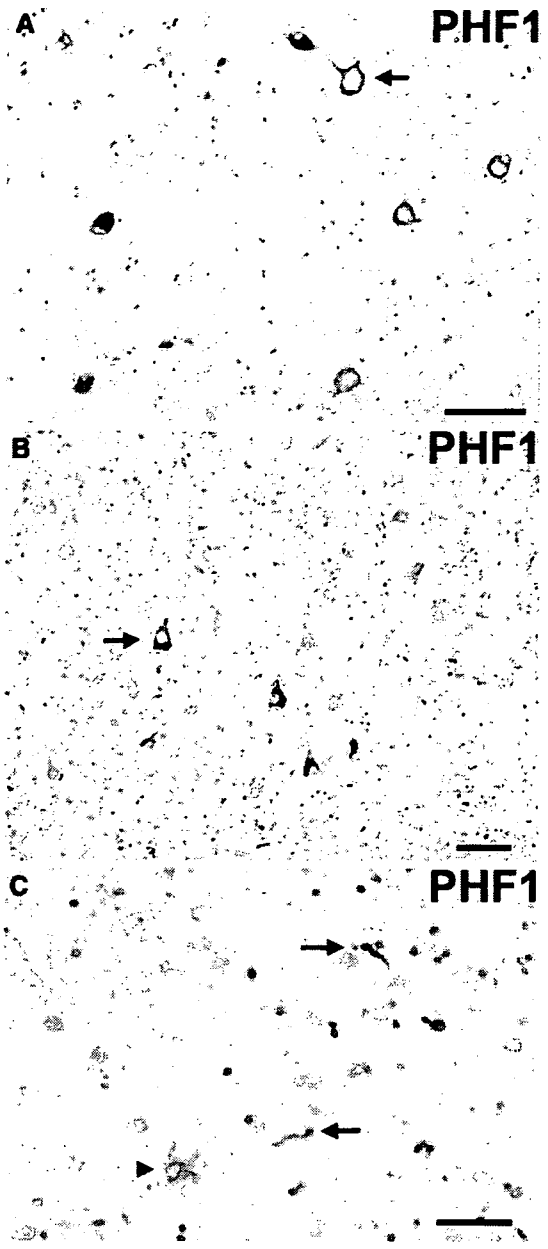

Fig. 5 Argyrophilic grain disease. A swollen achromatic neuron (*arrow*) with pale center and more intense tau-immunoreactive periphery in the subiculum. Tau-immunoreactive grains in the neuropil and diffusely stained pyramidal neurons (*arrow*) indicating a pre-neurofibrillary tangle stage in the pyramidal layer of the hippocampus (**b**). A tau-immunoreactive astrocytic inclusion (*arrowhead*) and oligodendroglial cytoplasmic inclusions called coiled bodies (*arrows*) in the CA1 subfield of the hippocampus. (**a, b, c**) Anti-phosphorylated tau (*PHF1*) immunohistochemistry. *Scale bars* (**a**) 100 m and (**b** and **c**) 50 m

inheritance. Similar 3R and 4R tau heterogeneity is seen in some tauopathies that cannot be categorized as FTLD with Pick bodies, PSP, CBD, or AGD, and in individuals without *MAPT* mutations. Such a case may have tau pathology in the distribution described in sporadic MSTD, or may have to be categorized as "unclassifiable sporadic tauopathy."

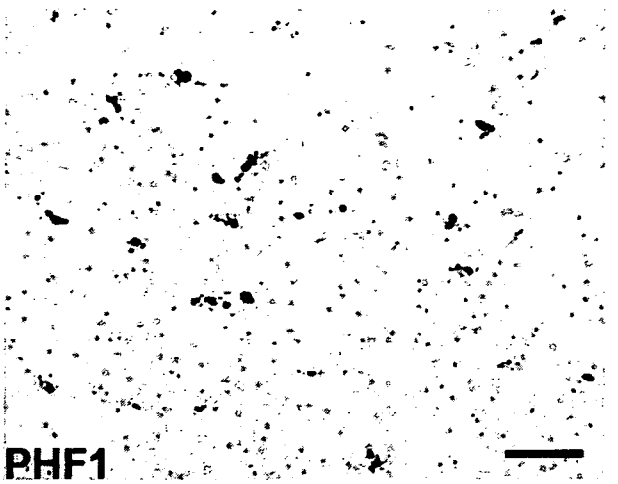

Fig. 6 Sporadic multiple system tauopathy with dementia. Neuronal and glial globular inclusions at the gray/white junction. Anti-phosphorylated tau (*PHF1*) immunohistochemistry. *Scale bar* 100 m

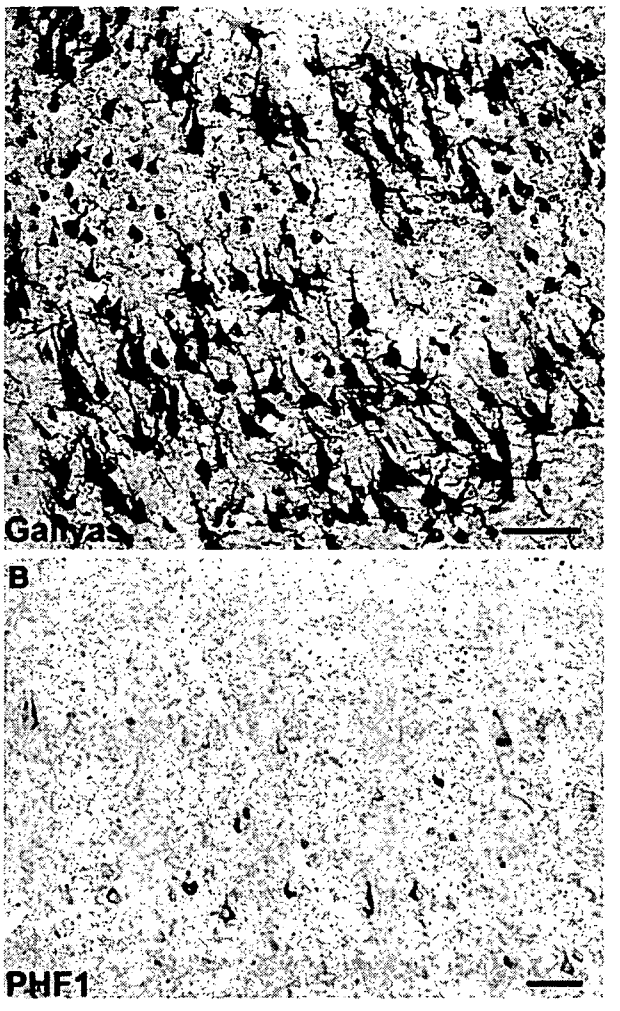

Fig. 7 Neurofibrillary tangle dementia. **a, b** Numerous neurofibrillary tangles in the upper and lower pyramidal neurons of the occipitotemporal cortex; no neuritic plaques or amyloid deposits are present. **a** *Gallyas* silver impregnation. **b** Anti-phosphorylated tau (*PHF1*) immunohistochemistry. *Scale bars* 50 m

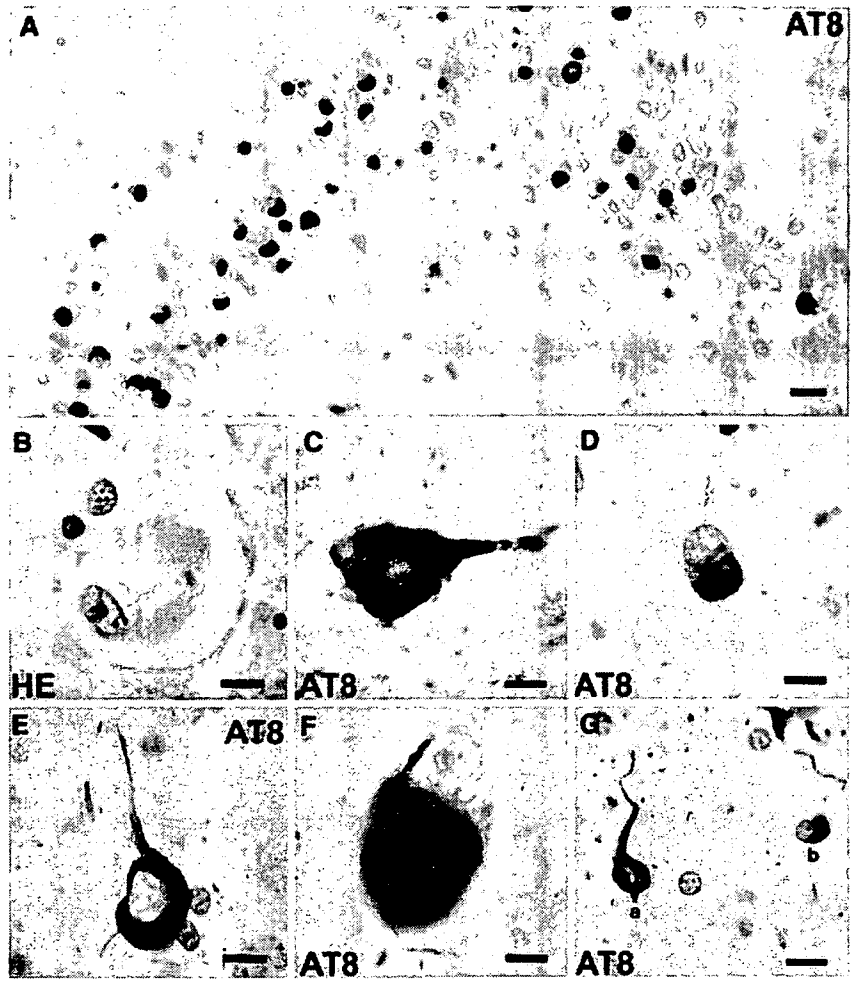

Fig. 8 Frontotemporal lobar degeneration (FTLD) with *MAPT* mutation. Inclusions in FTLD with *MAPT* G389R mutation (**a**) and FTLD with *MAPT* intron 10 + 16 mutation (**b–g**). **a** Numerous tau-immunoreactive Pick body-like inclusions in the granule neurons of the dentate fascia. **b** A swollen achromatic neuron in the superior temporal gyrus. **c** A swollen neuron with a central area of pale anti-tau immunoreactivity surrounded by more intense staining. Fibrillary material surrounds the nucleus and extends into the apical dendrite. **d** An intraneuronal inclusion resembling a Pick body in the superior frontal gyrus. **e** A neurofibrillary tangle-like inclusion in layer V of the superior frontal gyrus. **f** A globose neurofibrillary tangle-like inclusion in the dorsal raphé nucleus. **g** An astrocytic fibrillary inclusion (**a**) and a coiled body (**b**) in an oligodendrocyte in the white matter of the frontal lobe. **b** Hematoxylin and eosin (*HE*); (**a**, **c–g**) anti-phosphorylated tau (*AT8*) immunohistochemistry. *Scale bars* 10 m. (Adapted from Ref. [44]; reproduced with permission)

Tau-negative, ubiquitin-positive inclusions

TDP-43 proteinopathy

Immunohistochemistry for ubiquitin, P62, and TDP-43 in cases with FTLD generally reveals similar pathology that includes a spectrum of neuronal (NCIs, DNs, and NIIs) and glial, predominantly oligodendroglial, cytoplasmic inclusions (GCIs) [62, 61]. However, there are significant differences in the immunohistochemical findings with ubiquitin, P62, and TDP-43. Ubiquitin immunoreactivity is present in extensive age-related pathology in gray and white matter, e.g., dot-like bodies and granular degeneration of myelin, which can mask subtle neuronal and glial pathology and can be difficult to interpret. P62 immunostaining detects the same range of pathological structures as anti-ubiquitin, but highlights less age-related pathology, making interpretation somewhat less demanding. TDP-43 immunoreactivity is present in nuclei of most cells types and changes in distribution within affected neurons in disease. Screening cases using TDP-43 immunostaining as a primary diagnostic tool, as might be used for tau and -synuclein accumulations, is more demanding. Four histologic subtypes of FTLD-U have been proposed, based on the predominant type of inclusion present as detected using anti-ubiquitin, its distribution in the cortex, and density [16, 63, 66]. Other types have been proposed as well and take into account involvement of other brain regions (e.g., hippocampus or corpus striatum) and the morphology of the lesions [2, 38]. Patterns of FTLD-U histology based solely on cortical pathology include a system proposed by Sampathu et al. [66], and Neumann et al. [63]; while Mackenzie et al. [49]

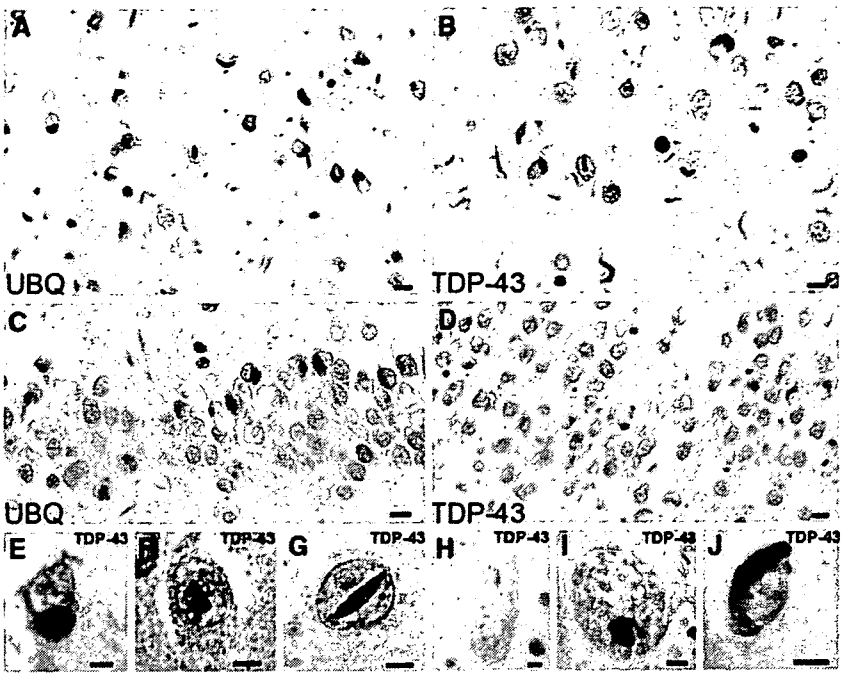

Fig. 9 Frontotemporal lobar degeneration (FTLD)-U with or without MND: spectrum of *TDP-43* pathology. Adjacent sections of superficial frontal neocortex showing neuronal cytoplasmic inclusions (NCIs), dystrophic neurites (DNs), and isolated neuronal intranuclear inclusions (NIIs) stain for both ubiquitin (**a**) and *TDP-43* (**b**). NCI in the dentate granule cells stain for ubiquitin (**c**) and *TDP-43* (**d**). Neuronal and glial inclusions include NCI (**e**), round and lentiform NIIs (**f, g**); skein-like (**h**), and compact round (**i**) NCI in the lower motor neurons; and glial cytoplasmic inclusion (GCI) (**j**). (**a** and **c**) ubiquitin immunohistochemisty (**b, d, e–j** *TDP-43* immunohistochemistry). *Scale bars* 10 m (**a–d**); 5 m (**e–j**) (Adapted from Ref. [16]; reproduced with permission)

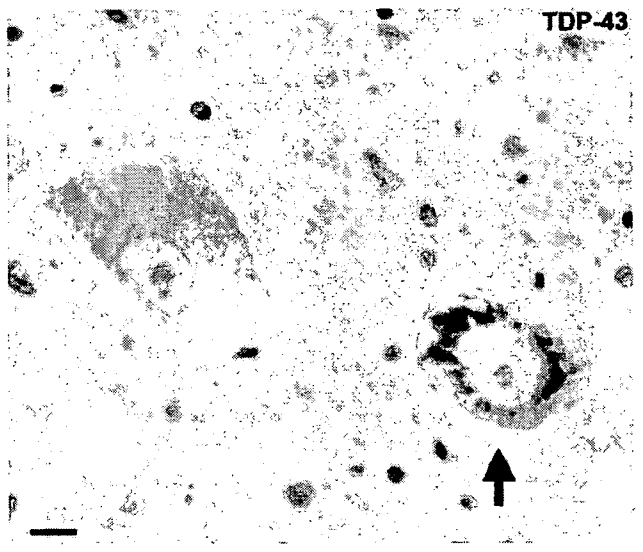

Fig. 10 Frontotemporal lobar degeneration-U with MND. Diffuse perinuclear staining in a motor neuron (*arrow*). *TDP-43* immunohistochemistry. *Scale bar* 10 m

have proposed a system that includes cortical and dentate fascia inclusions. In all these schemes the same descriptors were employed to differentiate subtypes, though the numbering of each subtype differed among schemes. In the present composite scheme, type 1 cases (as in [66], but known as type 2 in Mackenzie et al. [49]) are characterized by an abundance of long DNs, predominantly in the superficial cortical laminae, with few or no NCIs or NIIs. Type 2 cases (as in [66], but known as type 3 in Mackenzie et al. [49]) are characterized by numerous NCIs in both superficial and deep cortical laminae as well as infrequent DNs and sparse or no NIIs. Type 3 cases (as in [66], but known as type 1 in Mackenzie et al. [49]) are characterized by pathology predominantly in the superficial cortical layers with numerous NCIs, DNs, and variable numbers of NIIs. Type 4 cases [16, 63] are distinguished by numerous NIIs and infrequent NCIs and DNs in the neocortical areas with relative sparing of the hippocampus, consistent with the pathology described in cases of FTLD with *VCP* mutations (but see ref. [30]). Consensus on the validity, reliability, and reproducibility of the various proposed typing schemes, as well as their clinical significance, remain to be determined.

If TDP-43- and ubiquitin- or P62-positive, tau- and -synuclein-negative inclusions are found in the superficial laminae of the frontal and temporal neocortex and neurons of the dentate gyrus, the most likely diagnosis is FTLD-U [21, 36, 45]. If in addition, there is TDP-43 proteinopathy and ubiquitin-positive inclusions in the lower motor neurons and evidence of motor neuron loss, gliosis, Bunina bodies, and corticospinal tract degeneration, FTLD with MND is the most likely diagnosis [53, 64, 79].

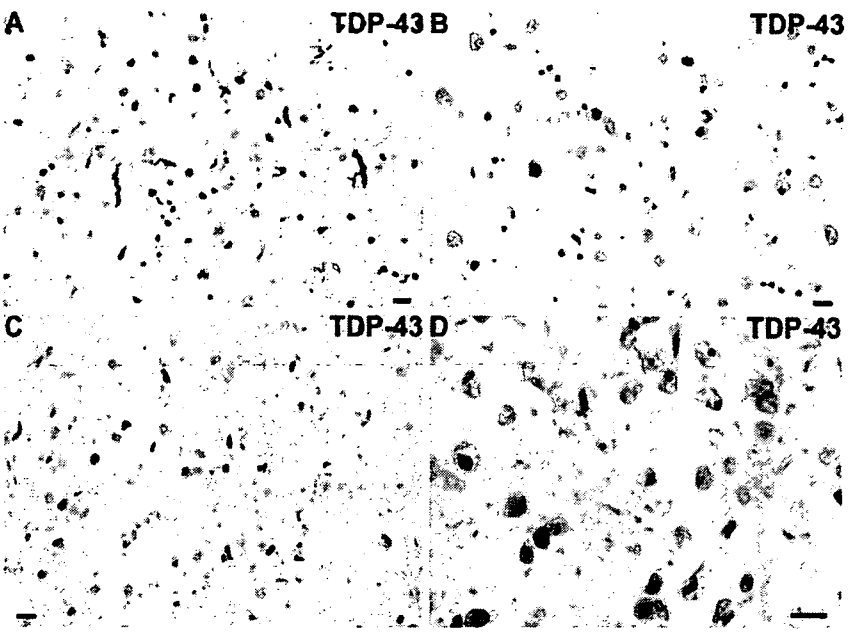

Fig. 11 Frontotemporal lobar degeneration-U, subtypes 1–4. **a–d** Type 1 is characterized by long and tortuous dystrophic neurites (DNs) in lamiae II/III with relatively few neuronal cytoplasmic inclusions (NCIs) and no neuronal intranuclear inclusion (NII). **b** Type 2 has numerous NCIs, relatively few DNs, and no NII is present. **c** Type 3 has numerous NCIs and DNs and an occasional NII in lamina II. **d** Type 4 pathology in a case of FTD with *VCP* mutation is characterized by numerous NII and DN, but few NCI. *TDP-43* immunohistochemistry. *Scale bar* 10 m (**a–d**). (Adapted from Ref. [14]; reproduced with permission)

There is heuristic value in the sub-classification of FTLD-U beyond pathologic description alone, with clinical and genetic correlates of histologic patterns emerging. Cases with type 1 histology are associated with SD, whereas cases of FTLD with MND frequently show type 2 histology [49]. In genetic terms, cases with *PGRN* or *VCP* gene mutations, and in cases linked to chromosome 9, distinct patterns of ubiquitin- and TDP-43-positive inclusions are also seen. FTLD with *PGRN* mutation cases often display a PNFA clinical phenotype and exclusively show type 3 histology [16], whereas those with *VCP* mutations have type 4 histology. Cases linked to chromosome 9 have type 2 histology [16] and the majority of such cases also have ubiquitin- and TDP-positive inclusions in the upper and lower motor neurons, identical to those encountered in sporadic MND [16] or sporadic FTLD with MND where a similar type 2 histology is often present [49]. These latter data indicate that the pathology of FTLD linked to chromosome 9p is a specific subtype of FTLD-U (type 2) and that TDP-43 is the disease-associated protein. Biochemistry of sporadic cases of FTLD with and without MND, cases of sporadic ALS, and familial cases of FTLD-U with *PGRN* and *VCP* mutations, and those linked to chromosome 9p, all have a characteristic biochemical signature: TDP-43 is detected in the detergent-insoluble urea fractions from affected regions and is abnormally phosphorylated, with additional protein bands of ~25 and 45 kDa, as well as a high molecular smear, and is ubiquitinated [16, 61, 62, 63]. The quantity of these modified TDP-43 species detected by biochemistry [62, 63] may be variable, but correlates with the amount of pathology detected by IHC. Additionally, the 45 kDa species collapse into a 43 kDa band upon dephosphorylation with alkaline phosphatase, indicating that TDP-43 is abnormally phosphorylated, with features paralleling the biochemical changes seen in the tauopathies. Hippocampal sclerosis (HS) may be found as a coexisting pathology in FTLD-U with or without MND, and small numbers of ubiquitin- and TDP-43-positive inclusions may be seen exclusively in the dentate granule cells. Preliminary data indicate that some, or perhaps most, cases of HS are TDP-43 proteinopathies [2], but further studies on larger samples of "pure HS" and biochemical studies are required to determine the nosologic status of HS.

TDP-43-negative inclusions

In those cases that have ubiquitin- or P62-positive, TDP-43-, tau-, and -internexin-negative NCIs in the frontal and temporal lobes and dentate gyrus, the most likely diagnosis is FTLD with *CHMP2B* mutation [16]. Mutations in the *CHMP2B* gene are the cause of FTD-linked to chromosome 3 in a large Danish pedigree [68]. Human CHMP2B is a component of the endosomal secretory complex, which becomes dysregulated by the gene defect. However, the absence of DN and the presence of granular, ubiquitin-positive structures within the neocortex of these cases distinguish this FTLD-U subtype from the types 1–4 described above. Thus, based on the small number of cases studied to date, familial FTLD with *CHMP2B* mutation appears to be a distinctive pathologic subtype of FTLD-U and is not a TDP-43 proteinopathy on the basis of IHC.

In cases of FTLD where there is frontotemporal neuron loss and gliosis, -internexin- or neurofilament-positive, TDP-43-, -synuclein-, and tau-negative, and variably ubiquitinated but P62-positive neuronal inclusions, the most likely diagnosis is neuronal intermediate filament inclusion disease [14]. Where there is FTLD and P62-positive,

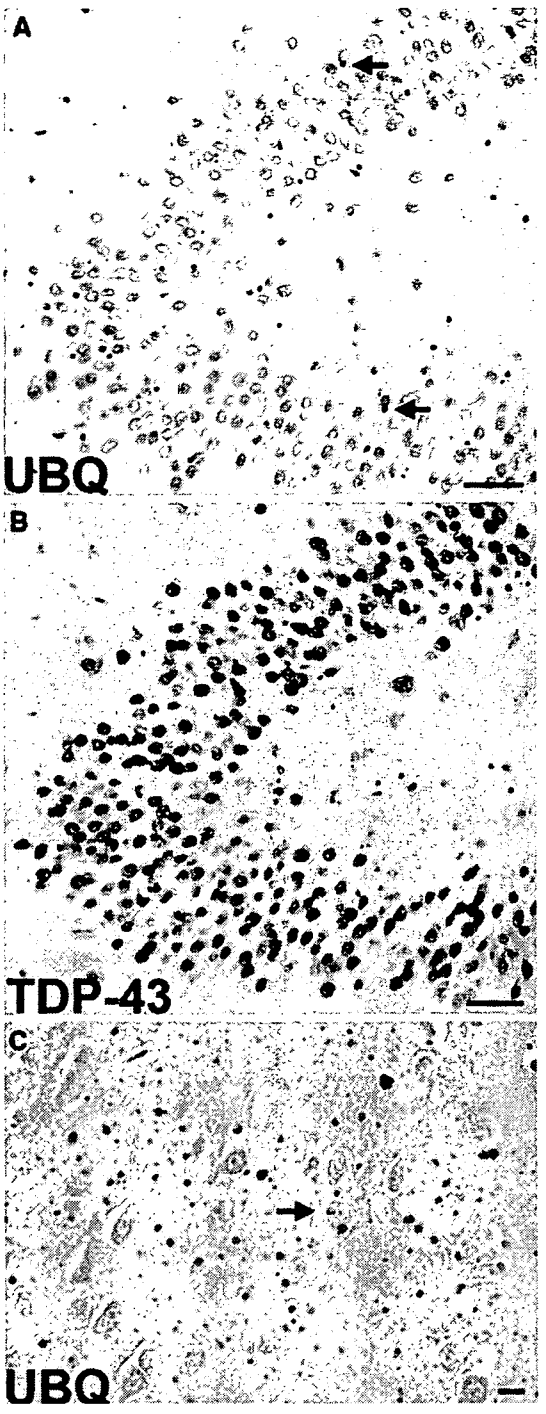

Fig. 12 Frontotemporal lobar degeneration with *CHMP2B* mutation. **a** Sparse ubiquitin-immunoreactive NCIs (*arrows*) in the granule neurons of the dentate fascia. The NCIs are not labeled with anti-*TDP-43* antibodies (**b**). Ubiquitin-positive neuropil aggregates and a sparse NCI (*arrow*) in the frontal lobe of an affected 61-year-old female (**c**). *Scale bars* **a**, **b** 50 m, **c** 10 m

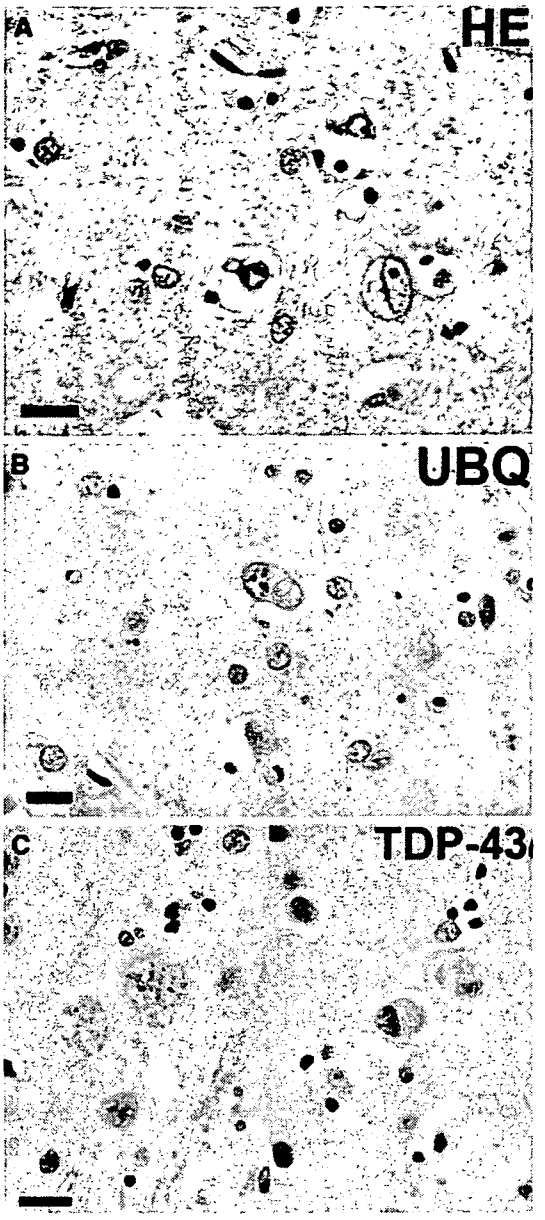

Fig. 13 Basophilic inclusion body disease. **a** A basophilic inclusion (BI) in the precentral gyrus (motor cortex), with a similar, weakly ubiquitin-immunoreactive inclusion in (**b**). **c** Neurons with basophilic inclusions showing fine granular perikaryal *TDP-43* positivity in neurons with BIs on the left and negative in neurons with BIs on the right. **a** Hematoxylin and eosin; **b** ubiquitin, and **c** *TDP-43* immunohistochemistry. *Scale bars* 20 m

variably ubiquitin-positive, TDP-43-, -internexin-, -synuclein-, and tau-negative basophilic inclusions, the most likely neuropathologic diagnosis is basophilic inclusion body disease (BIBD) [58]. If all of the antibodies listed above and routine histological stains such as hematoxylin and eosin fail to reveal signature lesions, and if prion disease has been excluded by IHC or molecular genetics, the remaining FTLD diagnosis is dementia lacking distinctive histologic features (DLDH) [42]. However, it should be borne in mind that in many of the earlier histopathologic surveys, a relatively high proportion of cases of DLDH were encountered [32, 67]. Re-evaluation of such cases using either more sensitive ubiquitin IHC methodologies

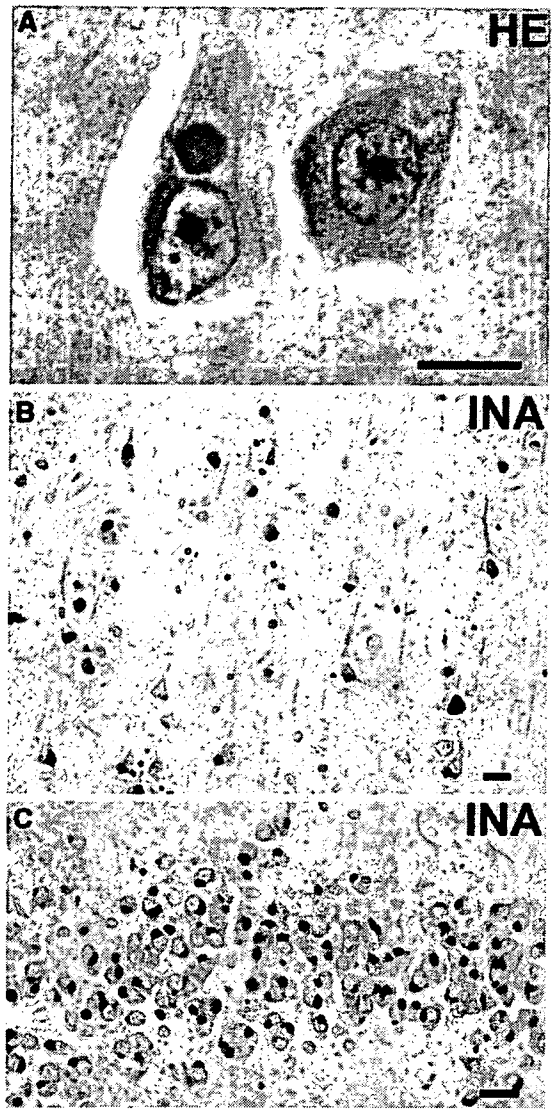

Fig. 14 Neuronal intermediate filament inclusion disease. **a** Eosinophilic Lewy body-like NCI in a pyramidal neuron of the CA1 subfield of the hippocampus. **b** -Internexin immunoreactive NCIs in layer III of the superior temporal gyrus. **c** Numerous -internexin immunoreactive NCIs in the granule neurons of the dentate fascia. **a** Hematoxylin and eosin; **b**, **c** -internexin immunohistochemistry. *Scale bars* 10 m

[25, 45, 51] or TDP-43 IHC [21] shows DLDH to be an uncommon cause of FTLD and, indeed, it still remains to be proven as a discrete entity with diagnostic criteria other than default characteristics being employed when all IHC and other methods have failed to reveal signature lesions.

Conclusions

The proposed criteria for the neuropathologic diagnosis of FTLD described here are an evolution of the previous criteria described by McKhann et al. [53]. When formulating these proposed criteria, we acknowledged revised staging schemes for other disorders (e.g., AD and DLB), which recommend the use of IHC for the diagnosis of neurodegenerative diseases, replacing silver impregnation methods and averting the lack of reproducibility between centers when these stains are used. We have incorporated the recent identification of new entities into the nosology of FTLD. Most significantly, the discovery of TDP-43 as the major pathologic protein of most forms of FTLD identifies a novel molecular pathology, TDP-43 proteinopathy, and this is now included in the revised criteria. We have also considered the great progress in determining the molecular genetics of FTLD. In addition to FTLD with *MAPT* mutation, other familial subtypes are now recognized on the basis of the neuropathology of ubiquitin and/or TDP-43 IHC, biochemistry, and molecular genetics (FTLD with *PGRN*, *CHMP2B*, and *VCP* mutations, and cases linked to chromosome 9p), which reveal a strong correlation between genotype and neuropathologic phenotype. To facilitate neuropathologic diagnoses of FTLD at research and other centers, commercially available antibodies are now readily available for the identification of the underlying molecular pathologies (e.g., TDP-43 proteinopathy and tauopathy) and the rational diagnosis and nosology of a case of FLTD that comes to autopsy. The neuropathologic diagnostic algorithm described here is based on the current level of knowledge, but the consortium members appreciate that further study of TDP-43 proteinopathy may reveal new subtypes and that other FTLD entities may yet be identified. The proposed neuropathologic algorithm will facilitate efforts to improve the diagnosis of FTLD and encourage multi-center clinico-pathologic studies. Together, these efforts should improve the early and reliable neuropathologic diagnosis of the FTLD, raise the awareness of possible coexisting pathologies, and facilitate research efforts into pathogenesis and potential treatments where none currently exists.

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Original article

Serum levels of cytokines and EEG findings in children with influenza associated with mild neurological complications

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Abstract

We studied the relation among serum cytokine levels, EEG changes, and mild neurological complications (delirium and febrile seizure) in children with influenza. The serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and soluble tumor necrosis factor receptor-1 (sTNFR-1) were measured in 27 children with proven influenza infection with mild neurological complications (10 patients with delirium and 17 with febrile seizures) and seven control children. EEG was recorded in 14 children with neurological complications. EEG showed focal slowing in four of nine patients with delirium and in four of five with febrile seizures. Generalized slowing was observed in one patient with delirium. The median serum IL-6 level was 31.2 ± 15.1 pg/ml (range, 7.5–64.5 pg/ml) in the delirium group, 42.3 ± 44.0 pg/ml (range, 8.0–196.0 pg/ml) in the febrile seizure group, and 15.4 ± 7.0 pg/ml (range, 7.2–28.0 pg/ml) in the control group. Serum TNF-α and sTNFR-1 levels were not different among three groups. Mild neurological complications associated with influenza were related to the mildly abnormal serum IL-6 levels and EEG findings. The combination of these parameters will be useful for early diagnosis and differentiation of neurological complications in children with influenza. Further studies will be necessary for investigating that IL-6 has the diagnostic value for differentiation between severe encephalopathy and mild neurological complications in children with influenza.

Keywords: Interleukin-6; Influenza; Electroencephalography

1. Introduction

Influenza-associated encephalopathy often results in death or neurological sequelae. Early recognition of influenza-associated encephalopathy is desirable in order to improve the outcome of the patients. Delirium is sometimes seen during the early stage of influenza-associated encephalopathy, before consciousness is markedly reduced. It can be an alarming sign and a clue to an early diagnosis. However, febrile delirium is often observed in children without encephalopathy [1–5]. It would be helpful if we could distinguish patients with delirium evolving into encephalopathy from those without encephalopathy.

The mechanism of delirium is poorly understood. Several reports have examined the relationship between influenza-associated encephalopathy and cytokines [6–11]. However, few studies have examined the relationship between cytokines and mild neurological complications such as delirium and febrile seizure. Therefore, we

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studied the relation among serum cytokine levels, electroencephalogram (EEG) changes, and neurological complications in children with influenza.

2. Patients and methods

The study subjects were 27 children with proven influenza infection with mild neurological complications who consecutively visited Okazaki City Hospital during the winters of 2002–2004. The control patients were seven patients with proven influenza without neurological complications who agreed to participate in the study. Influenza antigen was detected from pharyngeal swabs in all patients. Blood was sampled for measuring cytokines as soon as possible after the influenza infection was confirmed.

The serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and soluble tumor necrosis factor receptor-1 (sTNFR-1) were measured within 48 h after the onset of fever in all but two children. When the children had neurological complications, cytokines were measured within 24 h after their occurrence. The concentrations of serum IL-6 were measured using a two-step sandwich-type chemiluminescent enzyme immunoassay; serum TNF-α and sTNFR-1 were measured using a quantitative sandwich-type enzyme-linked immunosorbent assay.

The children with mild neurological complications were divided into two patient groups. The delirium group (group De) contained the patients with delirious behavior, such as fear, hallucinations, and disorientation, and recovering consciousness within 24 h. Some of these patients also had seizures. The febrile seizure group (group FS) was defined as patients with febrile seizures without delirium or impaired consciousness. The control group consisted of seven patients without neurological complications.

In addition, EEG and measurement of serum cytokines were performed in two patients with influenza-associated encephalopathy during the same period. Encephalopathy was defined as impaired consciousness lasting for more than 24 h with or without other neurological symptoms such as seizures. Those with vascular, metabolic, endocrine, or toxic disorders were not included into encephalopathy. Because the number of patients with encephalopathy was small, we excluded these patients from statistical analyses.

EEGs were recorded 4–72 h after the appearance of neurological complications. EEG findings during wakefulness were classified into three categories (Fig. 1): normal, focal slowing defined as the insertion of high-voltage slow waves mainly in the occipital regions with preserved rhythmic alpha activities, and generalized slowing defined as generalized high-voltage slow waves without rhythmic alpha activity. In all of the patients with generalized slowing, EEG findings were not altered by opening and closing the eyes.

This study was approved by the Ethics Committee of Okazaki City Hospital. Written informed consent was obtained from the parents of each child.

Statistical analysis was performed using StatView software. With regard to the patient characteristics, the Kruskal–Wallis test was used for numerical variables and the χ-square test was used for categorical variables. The Kruskal–Wallis test was also used to analyze the serum cytokine concentration among three groups. If significant differences were found, Tukey's test was performed as a post hoc test. A p value below 0.05 was considered statistically significant.

3. Results

The characteristics of the patients are summarized in Table 1. Ten patients were categorized in group De and 17 in group FS. In group De, four of them also had a febrile seizure. Although there was no significant difference, the majority of the children in group De was male and used antipyretics before they developed a neurological complication. The manifestations of febrile delirium included meaningless speech, periodic crying without an apparent trigger, blank eyes, and hallucinations, such as "My mother has grown a beard", "My sister is running around", and "These are not human hands".

EEGs were obtained in nine patients in group De and five in group FS (Table 1). In 11 cases, the EEG was recorded within 36 h after the neurological complication appeared. In four patients with both delirium and a seizure, EEGs were recorded 10–33 h after the appearance of a seizure. Focal slowing was seen in four patients each in groups De and FS. Generalized slowing was observed one patient in group De. A 2-year-old boy in group De whose EEG showed generalized slowing had a seizure after he developed delirious behavior. Impaired consciousness lasted for 5 h. EEG was recorded 36 h or more after the onset of neurological complications in three of five patients with normal EEG.

The relation between neurological complication and the serum cytokine levels is shown in Fig. 2. The median serum IL-6 level was 31.2 ± 15.1 pg/ml (range, 7.5–64.5 pg/ml) in group De, 42.3 ± 44.0 pg/ml (range, 8.0–196.0 pg/ml) in group FS, and 15.4 ± 7.0 pg/ml (range, 7.2–28.0 pg/ml) in the control group. The serum IL-6 level differed significantly between group De and the control group and between group FS and the control group (each $p < 0.05$). The serum IL-6 level reached 196 pg/ml in one child in group FS. His seizure was a generalized one lasting 5 min, and no other neurological abnormalities were observed.

Serum TNF-α level was less than 5 pg/ml in most patients in the De, FS, and control groups. A remark-

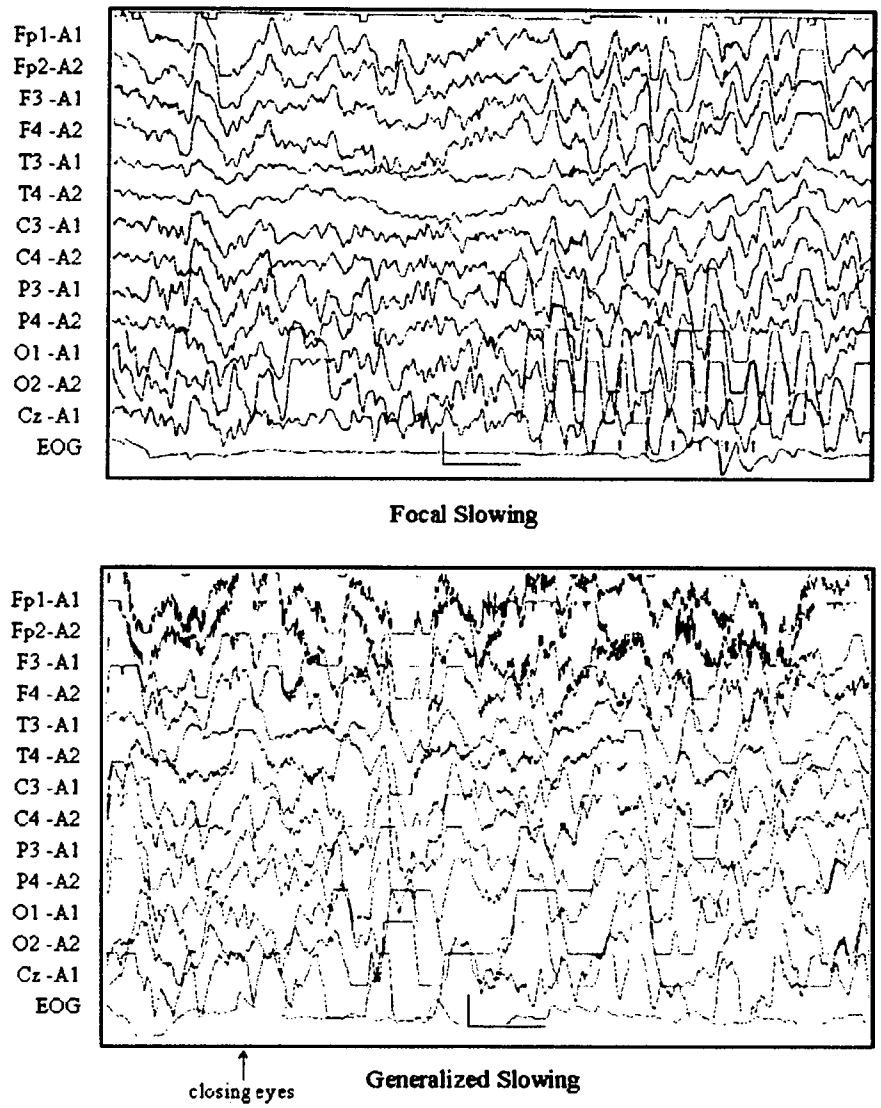

Fig. 1. EEG findings. (Upper) Focal slowing. Insertion of slow waves in the occipital regions with preserved rhythmic alpha activities was observed. (Lower) Generalized slowing. Generalized high-voltage slow waves without rhythmic alpha activities were recognized.

Table 1
The clinical characteristics, EEG findings, and serum IL-6 levels of the patients

	Delirium ($n = 10$)	Febrile seizure ($n = 17$)	Control ($n = 7$)
Age (years)	2–6 (4.3)	0.75–7 (2.7)	0.25–10 (3.2)
Sex (M:F)	9:1	11:6	2:5
Body temperature (°C)	38.4–41.0 (40.0)	38.9–41.0 (40.0)	37.8–40.0 (39.1)
Interval from the onset of fever (h)	0–36 (20.6)	0–25 (11.7)	
Seizure	4 (40%)	17 (100%)	0
Use of antipyretics	7 (70%)	4 (24%)	2 (29%)
Use of antiviral drug	5 (50%)	6 (35%)	1 (14%)
EEG findings			
Generalized slowing	1	0	
Focal slowing	4	4	
Normal	4	1	

The values were presented as range (median).

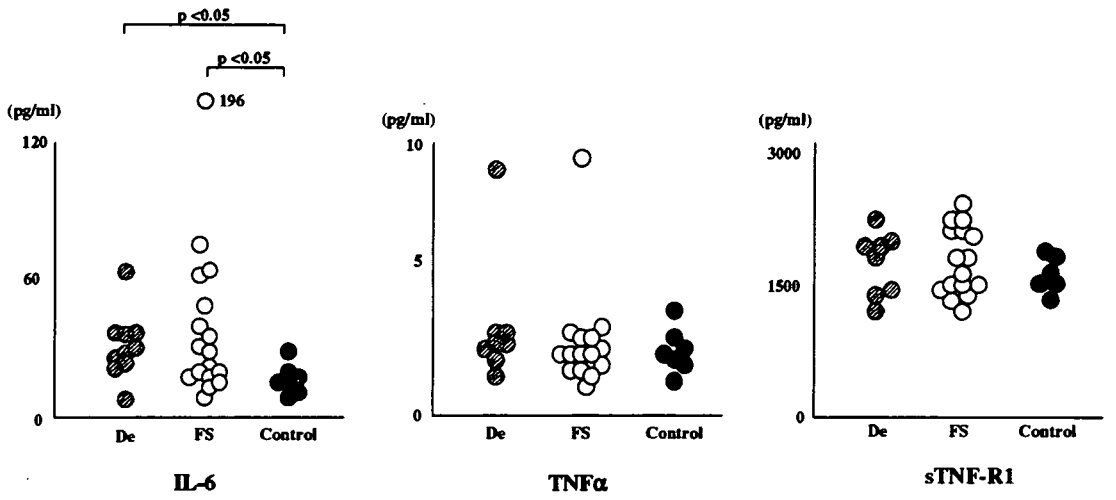

Fig. 2. Neurological complications and serum cytokines levels. The serum IL-6 level differed significantly between group De and the control group and between group FS and the control group (each $p < 0.05$). De, patients with delirium; FS, patients with febrile seizures.

able elevation of serum sTNFR-1 levels was not observed in any patients. There were no significant differences in the serum TNF-α and sTNF-R1 levels among these groups.

As to patients with encephalopathy, one of them was a 1-year-old boy with clustered seizures followed by delirium and impaired consciousness. EEG showed generalized slowing and serum IL-6 level was high (117 pg/ml). TNF-α and sTNF-R1 were not measured. The other was a 4-year-old boy who had a prolonged seizure as the first neurological manifestation. EEG revealed generalized slowing. He developed deep coma and severe brain edema within 5 days after admission, and died 3 weeks later. His serum IL-6 level was markedly elevated to 262 pg/ml, whereas sTNF-R1 was not increased (2570 pg/ml). TNF-α was not measured.

The relation among the severity of the EEG abnormality, the serum IL-6 concentration, and neurological complications is shown in Fig. 3. Although there was no statistical difference among the three groups, serum IL-6 level was the highest in infants with generalized slowing (median 117 pg/ml, range 38.4–262 pg/ml) and was the lowest in those with normal EEG (median 28.3 pg/ml, range 7.5–38.4 pg/ml). Serum IL-6 level was in-between in infants with focal slowing (median 32 pg/ml, range 14.8–75.4 pg/ml).

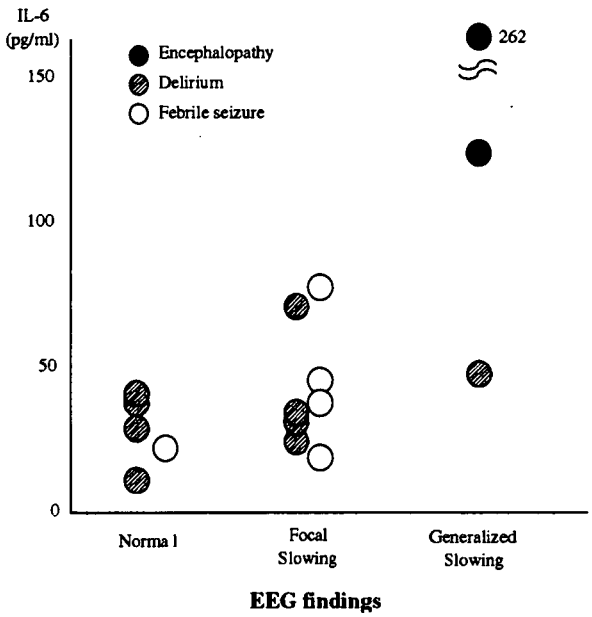

Fig. 3. The relation among the serum IL-6 levels, EEG findings, and neurological complications.

4. Discussion

The pathophysiology of hypercytokinemia in influenza-associated encephalopathy is poorly understood. It has been postulated that mucosal influenza infection triggers hypercytokinemia, followed by the activation of brain astrocytes and microglia. This may result in increased production of cytokines in the brain [14,15]. IL-6 is thought to be an indicator of the severity of influenza-associated encephalopathy [6–9]. TNF-α is a potent tissue-damaging cytokine and is elevated in patients with influenza-associated encephalopathy with poor prognosis [6,8,9]. TNF-α can be underestimated because it is unstable. On the other hand, the concentration of sTNF-R1, an inhibitor of TNF-α, reflects the bioactivity of TNF-α [16,17]. We chose to study these cytokines because they are thought to participate in the pathogenesis of neurological complications associated with influenza.

Our study revealed that IL-6 was mildly elevated in some children with delirium and febrile seizures. There have been a few reports that serum IL-6 is increased slightly in febrile seizures [18–20], whereas there have been no reports of the cytokine levels in febrile delirium. This suggests that IL-6 participates in the development of febrile delirium, as well as in influenza-associated encephalopathy. Delirium usually appears when patients have a high fever. Therefore, one can postulate that it results from intrinsic neuronal responses to elevated body temperature or immune responses to influenza. However, our previous study showed that some patients had delirium even after fever subsided with the use of antipyretics [4,21]. Therefore, we consider that humoral changes involving cytokines are more closely related to delirium than to high body temperature itself, although little is known of the pathophysiology of delirium during febrile illness. A mild elevation of cytokines might cause relatively mild neurological symptoms, such as convulsions and delirium.

Delirium can be observed during the very early phase of influenza-associated encephalopathy and can be an alarming sign. However, delirium is observed in some febrile children without encephalopathy. We previously demonstrated that the EEG was useful for distinguishing between children with encephalopathy and those with delirium without encephalopathy [4]. Unfortunately, an EEG is not always available, and its interpretation is not always easy. Therefore, the serum IL-6 level can be helpful for the diagnostic evaluation of patients with neurological complications.

In this study, some children with febrile delirium exhibited mild EEG changes, in agreement with previous reports [3,4]. We reported that the EEG showed slow waves in the occipital regions in 13 of 15 children with febrile delirium [4]. Similar EEG findings have been reported in children [3] and even in adults with febrile delirium [12,13]. It is interesting that similar EEG changes were also observed in some children with a febrile seizure. We observed focal slowing in four of five children with a febrile seizure. This implies that mild EEG changes, such as focal slowing, are common and non-specific in febrile children with mild neurological complications. Conversely, generalized slowing was observed in only three patients, two of whom were diagnosed with encephalopathy. Therefore, generalized slowing on EEG is a clue to the early diagnosis of encephalopathy in children with influenza or other febrile illness. On the other hand, four children with delirium had normal EEG. EEG was recorded 72 h after the appearance of delirium in two of them. EEG abnormalities in these patients may have been mild, if present, and have disappeared before EEG was undertaken. This indirectly suggests that an elevation of serum IL-6 levels was mild in patients with mild EEG abnormalities. However, EEG immediately after an appearance of delirium will be desirable in order to obtain its optimal diagnostic value.

The results of our study suggest that the combination of EEG and serum IL-6 level may enhance a diagnostic value. Patients with delirium or febrile seizure had mild EEG abnormalities and a mild increase in the serum IL-6. Patients with encephalopathy showed severe EEG abnormalities and markedly elevated serum IL-6. We might be able to predict a poor outcome, when a patient shows both severe EEG abnormalities and a markedly elevated serum IL-6 level.

In this study, patients with delirium were grouped together whether they had had a febrile seizure or not. This is because the differentiation between delirium with and without encephalopathy will be quite important apart from the presence or absence of a febrile seizure. In addition, our previous study suggested that clinical features and EEG findings in patients with delirious behavior were not different between those with and without a febrile seizure [4]. EEGs in our patients were recorded at least 4 h after a febrile seizure. Therefore, EEGs were not likely to be affected by a seizure.

The major shortcoming of this study is the insufficient statistical analysis of the serum cytokine levels, EEG findings, and neurological complications, although there were significant differences in the serum IL-6 level between the control group and groups De and FS. The number of patients was small and interval from the onset of symptom to EEG or blood sampling was not uniform. Our study is the first to suggest a correlation involving the serum cytokine levels, EEG findings, and mild neurological complications. Further studies with more patients with encephalopathy are necessary to clarify this relationship.

In conclusion, mild neurological complications associated with influenza were related to the mildly abnormal serum IL-6 levels and EEG findings. The combination of these parameters will be useful for the early diagnosis and differentiation of neurological complications in children with influenza. Further studies will be necessary for investigating that IL-6 has the diagnostic value for differentiation between severe encephalopathy and mild neurological complications in children with influenza.

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Vocal cord paralysis in myasthenia gravis with anti-MuSK antibodies

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About 20% of patients with generalized myasthenia gravis (MG) have undetectable serum antibodies to the nicotinic acetylcholine receptor (AChR). These patients are referred to as having seronegative MG. Recently, it has been demonstrated that about 50% of patients with generalized seronegative MG have antibodies to the surface membrane enzyme muscle-specific tyrosine kinase (MuSK) in Caucasian populations and a high frequency of respiratory crises.[1] Here, we report a case of MG with anti-MuSK antibodies presenting with vocal cord paralysis, facial muscle weakness, and bulbar palsy.

Case report. A 56-year-old man showed mild upper limb muscle weakness and fatigue on swallowing and chewing that worsened at the end of days in April 2000. He was admitted to our hospital in February 2001. Neurologic examination revealed mild muscle weakness and atrophy of his proximal muscles in the neck, shoulder, upper arm, and thigh. Nasal voice and dysphagia and facial muscle weakness were also observed, There was no ptosis or diplopia. Although repetitive nerve stimulation (RNS) showed a decrementing response in abductor digiti minimi and orbicularis oculi muscles, anti-AChR antibodies were not detected and the edrophonium (anticholinesterase) test was negative. CT scan of his thorax showed no thymoma. As we observed obvious muscle atrophy in his proximal muscles without fluctuation of muscle weakness, we thought a myopathy with myasthenic features[2] was likely present. The thyroid profile demonstrated elevated levels of anti-thyroglobulin antibodies (676.0 U/mL; normal range <0.3 U/mL), anti-thyroid peroxidase antibodies (812 U/mL; normal range <0.3 U/mL), and thyroid-stimulating hormone (43.74 μIU/mL; normal range 0.6 to 4.1 μIU/mL) with a low level of free thyroxine (0.5 ng/dL; normal range 0.9 to 1.6 ng/dL). Thyroid anti-microsomal antibodies showed an elevated titer of 1:6,400 (normal range <60). Thus, a diagnosis of hypothyroid myopathy caused by autoimmune chronic thyroiditis was made, and thyroid hormone replacement therapy resulted in improvement in proximal muscle weakness, whereas bulbar palsy and facial muscle weakness did not improve satisfactorily.

On June 9, 2005, the patient presented with a 3-month history of exertional dyspnea and stridor, which worsened at the end of days. Arterial blood gas analysis showed normal results in room air: pH, 7.406; P_aO_2, 92.7 mm Hg; and P_aCO_2, 43.8 mm Hg. However, the pulmonary function test showed a substantial reduction in ventilatory muscle strength; vital capacity (VC) was 2.5 L, and %VC was 71.2%. Fiberoptic laryngoscopy revealed that his vocal cords were located in the paramedian position and the abduction of the vocal cords in inspiration was limited (figure, A). Vocal cord movement did not change after an IV injection of edrophonium. Tracheostomy was performed on June 15, 2005, although the etiology of his vocal cord paralysis remained unknown. We considered the fluctuation of stridor and the decrementing response on RNS as clues to the etiology. We investigated anti-MuSK antibodies and detected an elevated anti-MuSK antibody (6.25 nmol/L; normal range <0.05 nmol/L). Oral prednisolone therapy was initiated on October 27, 2005, leading to improvement of bulbar palsy and facial weakness. Fiberoptic laryngoscopy performed on December 20, 2005, also revealed an opening in the airway and improvement of vocal cord paralysis (figure, B). After more than 6 months of follow-up and continued treatment for MG, the patient continues to require tracheostomy, because his vocal cord paralysis persists.

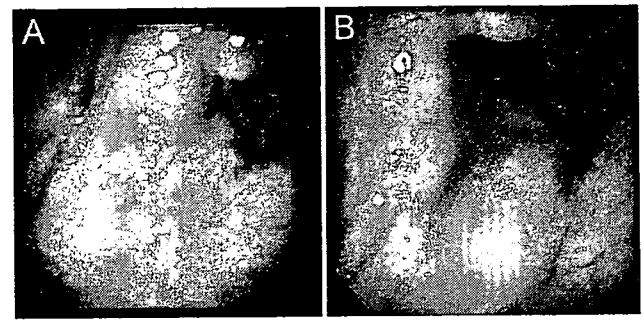

Figure. Fiberoptic laryngoscopic findings of maximal abducent position of vocal cords. (A) There was a limitation of abduction of the vocal cords before prednisolone treatment. (B) An opening in the airway and improvement of vocal cord paralysis were observed after treatment.

Discussion. Vocal cord paralysis associated with MG has been reported including cases with anti-AChR antibodies[3-5] and seronegative MG.[6,7] However, it is interesting that this patient with MG, presenting with vocal cord paralysis after a 5-year history of fatigue on swallowing and chewing, had anti-MuSK antibodies. Thus, vocal cord paralysis is considered a new clinical presentation of MG with anti-MuSK antibodies. Furthermore, MG can show respiratory crisis due to vocal cord paralysis without severe respiratory muscle paralysis in previously reported patients[3-7] and this patient. Although the edrophonium test was positive in all of those reported patients with MG with vocal cord paralysis, it was negative in our patient, which delayed the diagnosis of MG. As the effect of edrophonium is negative in 30% of MG with anti-MuSK antibodies,[1] there is the possibility of MG with anti-MuSK antibodies, even if the edrophonium test is negative.

Because it is difficult to make a diagnosis of MG in seronegative MG with only stridor as a initial symptom,[6,7] it might be useful to investigate the anti-MuSK antibodies in those patients, particularly in patients with bulbar palsy and facial weakness.

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Steroid dementia: A follow-up

Oliver Sacks, MD, FRCP; and Melanie Shulman, MD

We offer a follow-up report on the patient described in our brief communication, "Steroid dementia: an overlooked diagnosis."[1]

We described how Mr. K originally developed a mixed picture of psychosis and an Alzheimer-like dementia in the summer of 2001, apparently in consequence of the steroids he was taking. His psychosis promptly cleared when the steroids were stopped, and his intellectual status improved greatly, although some evidence of intellectual and executive compromise remained. It was still unclear, when we last saw Mr. K. (in September 2003), whether there might have been a core of neurodegenerative disease in addition to the seemingly reversible steroid dementia.

We have recently (June 2006) re-examined Mr. K. He continues, at age 76, to travel extensively and to work fulltime as an international businessman. He is able to manage all of his financial dealings independently. He scored 30 of 30 on a Mini-Mental State Examination and had a digit span of 8 digits forward and 6 backward. He scored 56 of 60 on the Boston Naming Test.[2] He was able to name 21 animals in 60 seconds (albeit with two perseverations) and did alphanumeric sequencing rapidly (40 seconds) and without error. Immediate and delayed recall, language comprehension of syntax–complex material, visual constructions, etc., were equally intact.

This robust performance on all cognitive fronts, 5 years after he was considered to have Alzheimer disease, is inconsistent with such a diagnosis and seems to confirm our impression that his months-long dementia in 2001 was solely a consequence of the steroids he was taking.

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