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Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations

Ian R. A. Mackenzie,
Department of Pathology and Laboratory Medicine, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada

Manuela Neumann,
Institute of Neuropathology, University Hospital of Zurich, Zurich, Switzerland

Eileen H. Bigio,
Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Nigel J. Cairns,
Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO, USA

Irina Alafuzoff,
Section of Neuropathology, Kuopio University, Kuopio, Finland

Jillian Kril,
Department of Pathology, The University of Sydney, Sydney, NSW, Australia

Gabor G. Kovacs,
Institute of Neurology, Medical University of Vienna, Vienna, Austria

Bernardino Ghetti,
Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Glenda Halliday,
Prince of Wales Medical Research Institute, University of New South Wales, Sydney, NSW, Australia

Ida E. Holm,
Department of Pathology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark

Paul G. Ince,
Neuropathology Group, University of SheYeld Medical School, SheYeld, UK

Wouter Kamphorst,
Department of Pathology, Vrije University Medical Centre, Amsterdam, The Netherlands

Tamas Revesz,
Department of Molecular Neuroscience, Queen Square, London, UK

Annemieke J. M. Rozemuller,
Department of Pathology, Vrije University Medical Centre, Amsterdam, The Netherlands

Samir Kumar-Singh,

I. R. A. Mackenzie Department of Pathology, Vancouver General Hospital, 855 West 12th Ave, Vancouver, BC V5Z 1M9, Canada e-mail: E-mail: ian.mackenzie@vch.ca.

Department of Molecular Genetics, University of Antwerp, Antwerp, Belgium

Haruhiko Akiyama,
Tokyo Institute of Psychiatry, Tokyo, Japan

Atik Baborie,
Neuropathology, The Walton Centre for Neurology and Neurosurgery, Liverpool, UK

Salvatore Spina,
Department of Pathology and Laboratory Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

Dennis W. Dickson,
Neuropathology Laboratory, Mayo Clinic College of Medicine, Jacksonville, FL, USA

John Q. Trojanowski, and
Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

David M. A. Mann
Clinical Neuroscience Research Group, Greater Manchester Neurosciences Centre, University of Manchester, Salford, UK

Introduction

The neuropathology associated with the clinical entities frontotemporal dementia (FTD, behavioral variant FTD), progressive non-Xuent aphasia (PNFA) and semantic dementia (SD), is heterogeneous with the common feature being a relatively selective degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration, FTLD). As in other neurodegenerative conditions, most pathological subtypes of FTLD are characterized by specific kinds of intracellular protein inclusions. In the past few decades, the biochemical composition of many of these inclusion bodies has been determined. There is a growing trend to classify FTLD based on the presumed molecular defect, in the belief that this most closely reflects the underlying pathogenic process and because many of the eponymous and descriptively named syndromes of the past are now known to have imperfect clinicopathological correlation.

A comprehensive consensus paper on the neuropathologic diagnostic and nosologic criteria for FTLD was recently published in this journal [3]. These criteria incorporate several important recent advances in our understanding of the molecular genetics and pathology of FTLD; specifically, the discovery of several new FTLD-associated gene abnormalities and the identification of TDP-43 as the pathological protein in most tau-negative FTLD. The criteria employ a protein-based approach for the neuropathologic diagnosis and classification of FTLD; however, the nomenclature for individual conditions has not been revised to reXect this.

Specific problems with current nomenclature

Further advances in our understanding of the disease specificity and sensitivity of TDP-43 pathology have resulted in confusion around the use of the term “frontotemporal lobar degeneration with ubiquitinated inclusions” (FTLD-U). “FTLD-U” was originally developed for cases in which the characteristic inclusions are only visible with ubiquitin immunohistochemistry. It was anticipated that the ubiquitinated protein (or proteins) would eventually be identified and that this would allow more specific nomenclature and reclassification. Accordingly, when a small subset of cases was discovered to have inclusions that were also immunoreactive for class IV intermediate filaments, these were given a new

designation (neuronal intermediate filament inclusion disease, NIFID) and removed from the FTLD-U category. However, when TDP-43 was recently identified as the pathological protein in most of the remaining cases of FTLD-U [2,9], this convention was not immediately followed. FTLD-U has continued to be used with the assumption that all the remaining genetic and pathologic subtypes of FTLD-U are TDP-43 proteinopathies. However, recent studies have demonstrated that this is not the case; at least one familial subtype [the Danish kindred with autosomal dominant FTD linked to chromosome 3 (FTD-3), caused by a *CHMP2B* mutation] and a significant proportion of sporadic FTLD-U cases, do not have signatory pathological TDP-43 [4,5,7,10]. Therefore, the group currently designated as FTLD-U appears to include several distinct entities, the largest of which (TDP-43-positive) no longer satisfies the original definition of the term.

A second area of uncertainty relates to the disease specificity of TDP-43 pathology. Although the initial reports suggested that pathological TDP-43 was specific for FTLD-U and ALS, several recent studies have found TDP-43-positive inclusions in a significant proportion of cases with other neurodegenerative conditions, such as Alzheimer's disease (AD), Lewy body disease and some primary tauopathies [1,8,12]. This TDP-43 pathology had not been recognized previously because ubiquitin immunohistochemistry does not distinguish it from the other coexisting (tau or α-synuclein) pathology. Although the concomitant TDP-43 pathology is usually restricted to limbic structures of the mesial temporal lobe, it sometimes extends into the neocortex and can closely resemble FTLD-U. It is currently not known if this represents a coincidental primary pathological process, which contributes to the clinical phenotype, or a secondary change of little pathogenic significance, occurring in susceptible neuronal populations. Furthermore, there are currently no neuropathologic criteria for FTLD-U that define the extent and anatomic distribution of pathology needed for the diagnosis. Therefore, pending further clinicopathological correlative studies, it is uncertain whether or not a diagnosis of FTLD-U should be made when TDP-43 pathology is found in conjunction with other neurodegenerative processes.

The following recommendations are meant to serve two purposes. First, to introduce a protein-based nomenclature for FTLD that is simple, consistent and transparent, and one that can easily accommodate future discoveries. Second, to modify existing terminology to address the specific issues related to FTLD-U and TDP-43 pathology, described above.

Recommendations

1. FTLD should be retained as the general terminology for pathological conditions that are commonly associated with the clinical entities of FTD, PNFA and/or SD, and in which degeneration of the frontal and temporal lobes is a characteristic feature. It is recognized, however, that other anatomical regions (especially the parietal lobes and striatonigral system) may also be involved in some of these cases.
2. Major subdivisions should be designated by the protein abnormality that is presumed to be pathogenic or most characteristic of the condition (i.e. FTLD-protein) (Table 1).
3. When a new entity is discovered or when the molecular identity of the major pathological factor in an existing group is clarified, the appropriate term will be FTLD-pathological molecule.
4. Whenever possible, cases should be further sub-classified, using current terminology, to define the specific pattern of pathology [i.e. FTLD-tau (CBD) or FTLD-TDP (type 2)] (Table 1).

5. Cases with inclusions that can only be demonstrated with immunohistochemistry against proteins of the ubiquitin proteosome system (UPS), should be designated FTLD-UPS. This would include FTD-3 and the recently described cases of FTLD with ubiquitin-positive, TDP-43-negative inclusions [4,5,7,10]. This designation recognizes that the TDP-43-negative inclusions may immunostain for UPS proteins other than ubiquitin, such as p62. This change should also avoid confusion with the previous terminology of FTLD-U.

6. Existing terms should be retained for rare causes of FTLD that have characteristic pathological features of unknown biochemistry, such as basophilic inclusion body disease (BIBD).

7. Cases of FTLD with no inclusions visible with special histochemical stains or the relevant immunohistochemistry should be designated FTLD-ni (no inclusions). This provides consistency in nomenclature and replaces the term “dementia lacking distinctive histopathology (DLDH), which many feel to be unsatisfactory because it suggests that pathologic changes are completely absent.

8. A diagnosis of FTLD—TDP should only be made in the presence of another (non-TDP-43) pathological process when the other pathology is considered too minor to have caused dementia (i.e., senile plaques or neurofibrillary tangles at densities below that required for the diagnosis of AD). When TDP-43 pathology is encountered in a case that fulfills neuropathologic criteria for some other neurodegenerative condition (such as AD), the presence and anatomical distribution of TDP-43 pathology should be indicated in a descriptive fashion [i.e. AD with limbic (or diffuse) TDP-43 pathology].

Summary

These recommendations provide a simple system of nomenclature that reflects our current understanding of the molecular pathology of FTLD and that can easily accommodate future discoveries. The terminology will allow neuropathologists to communicate their findings in a concise and unambiguous fashion. Terms that have become obsolete (i.e., FTLD-U) have been eliminated, while other traditional names for specific patterns of pathology within these broad protein-based categories can still be used without contradiction. This also provides a neuropathologic nosology that can be correlated with molecular genetic and clinical features. The next logical step will be to convene a meeting of international experts to update the clinical and pathological diagnostic criteria for FTLD and to develop an integrated classification scheme that reflects the many recent advances in the field.

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Table 1

Recommended nomenclature for frontotemporal lobar degenerations

Current terminology	Recommended new terminology	Major pathological subtypes[a]
tau-positive FTLD	FTLD-tau	PiD
		CBD
		PSP
		AGD
		MSTD
		Unclassifiable
tau-negative FTLD		
FTLD-U		
TDP-43-positive	FTLD-TDP	Type 1-4[b]
		Unclassifiable
TDP-43-negative	FTLD-UPS	aFTLD-U
		FTD-3
NIFID	FTLD-IF	
DLDH	FTLD-ni	
Other		
BIBD	BIBD	

aFTLD-U atypical frontotemporal lobar degeneration with ubiquitinated inclusions, *AGD* argyrophilic grain disease, *BIBD* basophilic inclusion body disease, *CBD* corticobasal degeneration, *DLDH* dementia lacking distinctive histopathology, *FTD-3* frontotemporal dementia linked to chromosome 3, *FTLD* frontotemporal lobar degeneration, *FTLD-U* FTLD with ubiquitinated inclusions, *IF* intermediate filament, *MSTD* multiple system tauopathy with dementia, *ni* no inclusions, *NIFID* neuronal intermediate filament inclusion disease, *PiD* Pick's disease, *PSP* progressive supranuclear palsy, *TDP* TDP-43, *UPS* ubiquitin proteosome system

[a] Indicates the characteristic pattern of pathology, not the clinical syndrome. Note that FTDP-17 is not listed as a pathological subtype because cases with different *MAPT* mutations do not have a consistent pattern of pathology. These cases would all be FTLD-tau, but further subtyping would vary

[b] Must specify which classification system is being used [6,11]