FRONTOTEMPORAL DEMENTIAS: UPDATE ON RECENT DEVELOPMENTS IN MOLECULAR GENETICS AND NEUROPATHOLOGY

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Frontotemporal dementias (FTD) are the second most common type of presenile dementias, considered to be clinically and pathologically different from Alzheimer’s dementia (AD). FTD differs clinically from AD because memory loss is rarely an early symptom. Instead, FTD is usually denoted by behavioural and language difficulties, and may co-occur with motor neuron disease (MND). Frontotemporal lobar degeneration (FTLD) with ubiquitin-positive, tau-negative inclusions (FTLD-U) is the most common underlying pathology with and without MND. TAR DNA-binding protein 43 (TDP-43), encoded by the TARDBP gene, has been identified as the major pathological protein of FTLD-U with or without MND, demonstrating that abnormal TDP-43 alone is sufficient to cause neurodegeneration. FTLD is a genetically complex disorder. A proportion of cases of FTLD-U have various pathogenic mutations in the progranulin (GRN) gene. Other FTLD-U entities with TDP-43 proteinopathy include FTLD-U with valosin-containing protein (VCP) gene mutation and FTLD with MND linked to chromosome 9p. In contrast, chromosome 3-linked dementia, a FTLD-U with chromatic modifying protein 2B (CHMP2B) mutation, has TDP-43 negative inclusions. Thus, TDP-43 defines a novel class of neurodegenerative diseases called TDP-43 proteinopathies. These recent discoveries will contribute to an accurate diagnosis, and facilitate the development of diagnosis and therapy.

KEY WORDS: frontotemporal lobar degeneration, granulin, motor neuron disease, mutation, TARDBP, TDP-43 protein
aggregates of phosphorylated and ubiquitinated TDP-43 defines a novel class of neurodegenerative diseases called TDP-43 proteinopathies that includes FTLD-U, FTLD, MND, and ALS. The increasing life expectancy will result in increased prevalence of neurodegenerative diseases. This review focuses on exciting findings providing a number of important advances in our understanding of the neuropathology, molecular genetics, and biochemistry of FTD, as one of neurodegenerative diseases that have occurred recently in this rapidly developing field of dementia research.

NEUROPATHOLOGY OF FTLD

FTLD comprises a neuropathologically heterogeneous group of neurodegenerative diseases which share the common feature of predominant degeneration of the frontal and temporal lobes (13-15). FTLD can broadly be divided into two main classes, based on abnormal accumulation of hyperphosphorylated tau protein: those with tau-positive and with tau-negative inclusions. Whereas, in the past, most attention focused on FTLD associated with tau-based pathology and microtubule-associated protein tau gene (MAPT) mutations (tauopathies), there has recently been greater attention paid to non-tau or tau-negative FTLD (non-tauopathies) (14). FTLD-U accounts for 5% to 15% of all dementia disorders (16).

GENETIC STUDIES

FTLD is a genetically complex disorder, with multiple genetic factors contributing to the disease. A positive family history with an autosomal dominant pattern of inheritance and high penetrance is usually found in one quarter to one half of patients (17, 18).

Figure 1 Spectrum of FTLD (14, 15) in a cohort of 48 cases published elsewhere (2). The FTLD-U (or FTLD-MND-type) is the most common pathology associated with clinical FTD

Abbreviations:
CBD = corticobasal degeneration
FTDP17 = frontotemporal dementia with parkinsonism linked to chromosome 17
PiD = Pick’s disease
PSP = progressive supranuclear palsy
AGD = argyrophilic grain disease
TOD = tangle only dementia
FTLD-MND-type = frontotemporal dementia with motor neuron disease type inclusions
IBMPFD = inclusion body myopathy with Paget’s disease of bone and frontotemporal dementia
DLDH = dementia lacking distinctive histopathology
Various pathogenic mutations in the progranulin (GRN) gene were recently reported in individuals with FTLD-U linked to chromosome 17q21 (19, 20). The GRN gene is mutated in 5% to 10% of patients with FTD and in about 20% of patients with familial FTD (21), similar to that of FTD with MAPT mutations (22). For the current list of pathogenic mutations in FTLD please refer to: http://www.molgen.ua.ac.be/FTDMutations/. It is now recognised that FTLD-U is the most common pathology associated with clinical FTLD (5). Also, several genes and a locus on chromosome 9 have been linked to familial FTLD-U. Genetic defects include mutations in the chromatin modifying protein 2B (CHMP2B gene), the cause of chromosome 3-linked FTLD, and mutations in the valosin-containing protein (VCP) gene associated with inclusion body myopathy, with Paget’s disease, and with frontotemporal dementia, which is the cause of chromatin 9-linked FTLD (18, 23). Locus heterogeneity for FTLD and MND is indicated by the presence of other genetic loci at 9p. The ubiquitinated pathological protein in FTLD-U has been identified as TAR DNA-binding protein 43 (TDP-43) (9-11). As more entities are investigated, the pathological TDP-43 protein is found to be a component of the inclusions of an increasing number of neurodegenerative diseases.

CLINICAL PHENOTYPE OF FTD

Recently, we retrospectively examined charts of 48 FTD individuals in order to find clinical differences between FTD and AD. All cases of FTD met pathological criteria for FTLD (14, 15). Clinically, behavioural and language features, including impulsivity, disinhibition, and social withdrawal were significantly different between FTD and AD, as reported previously (24). The most distinctive feature of FTD, on psychometric tests, was a significant impairment of frontal lobe functioning, as reported earlier (25). The identification of different mutations in the GRN gene in hereditary dysphasic disinhibition dementia families 1 and 2 (HDDD 1 and HDDD 2) (26, 27) links these families to other FTLD-U families with GRN mutation (28, 29). A complicating feature in both HDDD families is the presence of AD-type early memory loss which correlated with coexisting AD pathology in almost half of the cases, which distinguishes them from other families with no or little coexisting neurodegenerative disease (26, 27).

Interestingly, another family with the same GRN A9D mutation has been reported in an individual with corticobasal syndrome (30), indicating, again, clinical heterogeneity associated with the same mutation.

CONCLUSION

For practicing clinicians, the knowledge that changes in behaviour and language difficulties distinguish those with FTD from AD is important, although clinical and cognitive features may overlap between the two. Typically, patients with FTD do not have an amnestic syndrome, at least in the early stage of the disease, which distinguishes them from AD.

Major discoveries have been made in the recent past in the genetics, biochemistry, and neuropathology of FTD. TDP-43, encoded by the TARDBP gene, is the major pathological protein of FTLD-U with or without MND. Thus, TDP-43 defines a novel class of neurodegenerative diseases called TDP-43 proteinopathies. FTLD-U is now recognised as the most common pathology associated with clinical FTLD. New developments such as the discovery of TDP-43 as disease protein have opened new view on FTD, as well as its relation to motor neuron disease.

In summary, the new genetic and pathological information now opens the way for a novel diagnostic approach. The diagnostic responsibility will increase with the development of new diagnostic tests. It is anticipated that these discoveries will contribute to an accurate diagnosis, and facilitate the development of specific therapy.

Acknowledgements

The author thanks Professor Nigel J Cairns, PhD, FRCPath, Director, Alzheimer’s Disease Research Center Neuropathology Core, Washington University, St. Louis, MO, USA for his valuable comments of the manuscript. Dr. Liščić has been supported by a Fulbright grant (68428174) at the Alzheimer’s Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA.

This work was supported by the Ministry of Science, Education and Sports, Republic of Croatia (grant no. 022-1340036-2083 “Frontotemporal Dementia”).

REFERENCES


Sažetak

FRONTOTEMPORALNE DEMENCIJE - PRIKAZ NOVIH DOSTIGNUĆA IZ PODRUČJA MOLEKULARNE GENETIKE I NEUROPATOLOGIJE


KLJUČNE RIJEČI: bolest motornog neurona, frontotemporalna lobarna degeneracija, granulin (GRN) mutacije, TARDBP, TDP-43 protein

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