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Motor neuron diseases

ALS and frontotemporal dementia belong to a common disease spectrum

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ABSTRACT

ALS is now understood to be a complex multisystem neurodegenerative disease because areas other than the motor cortices of the brain undergo degeneration. Frontotemporal dementia (FTD) may be associated with motor neuron disease, and the transactive response DNA-binding protein 43 (TDP-43) is a major pathological substrate underlying both diseases. The recent discovery of a gene that can cause both FTD, ALS and FTD-ALS, C9ORF72, has modified the way for considering these two pathologies. These findings would allow the development of potential biomarkers and therapeutic targets for these devastating diseases. This review summarizes the key points leading up to our current understanding of the genetic, clinical and neuropathological overlap between FTD and ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is the most common form of adult onset motor neuron degeneration that affects the upper and the lower motor neurons (UMNs and LMNs) and the corticospinal tract. ALS is now understood to be a complex multisystem neurodegenerative disease because areas other than the motor cortices of the brain undergo degeneration. Frontotemporal dementia (FTD) is characterised by selective involvement of the frontal and temporal lobes, that is associated with changes in behaviour, personality, frontal executive deficits and language dysfunction. Three FTD subtypes are described including behavioral variant FTD (bvFTD) which manifests with disinhibition, compulsive or perseverative behaviour, overeating, apathy and emotional blunting associated with a most severe cortical atrophy in the frontal and anterior temporal lobes, often worse on the right than on the left side and two language variants – semantic variant primary progressive aphasia (svPPA) which exhibits loss of conceptual knowledge for words (left-sided degeneration) or faces and people (right-sided degeneration) due to selective involvement of the anterior temporal lobes and non-fluent variant PPA (nfvPPA) characterized by agrammatic, nonfluent language output and apraxia of speech.

The modern age of a possible association between motorneuron disease (MND) and FTD began in 1990 when

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Mitsuyama reported 71 patients with a presenile dementia and motor neuron disease [1]. Around the same time, Neary et al. described four patients with rapidly progressive dementia marked by a frontal lobe dysfunction in association with clinical features of MND [2]. The realization that FTD-MND had distinctive neuropathology began in the 1980s with the first reports of ubiquitin-positive immunoreactive inclusions in the cytoplasm of motor neurons [3,4]. Additionally, evidence of ubiquitin-positive inclusions in the extra-motor cortex was shown in both pure ALS patients [5] and ALS patients with dementia [6]. These ubiquitin-positive inclusions became the pathological hallmark of the FTD-MND syndrome. A key finding determining the link between FTD and MND was the identification of the transactive response DNA-binding protein 43 (TDP-43) in 2006 as the major inclusion protein associated with ubiquitinated inclusions in the vast majority of ALS patients, and in the most common pathological subtype of FTD, now referred to as frontotemporal lobar degeneration with TDP-43 pathology (FTLD-TDP) [7,8]. The recent discovery of a gene that can cause both FTD and ALS, C9ORF72, has modified the way for considering these two pathologies. In this review, we describe the clinical, pathological and genetic features in favor of a continuum between ALS and FTD.

2. Epidemiology

European studies estimated the prevalence of FTD at 15–22 per 100,000 inhabitants aged 45–64 years, similar to the prevalence of early-onset Alzheimer disease in this age group. Two studies reported incidence of FTD at 3.5–4.1 cases per 100,000 person-years in the age group 45–64 years [9,10], with no obvious gender differences [11,12]. The mean age of onset of FTD is typically in the fifth to seventh decades of life [13] with approximately 10% having an onset over 70 years [14]. Median survival in FTD has been estimated at 6–11 years from symptom onset and 3–4 years from diagnosis [15,16]. Hodges et al. reported the longest survival in nfvPPA (mean: 10.6 years from onset) followed by bvFTD (8.2 years) and SD (6.9 years) which could reflect the wide differences in underlying pathology [15]. Survival appears to be shorter and decline more rapid when associated with MND (2.4–4.9 years from onset and 1.2–1.4 years from diagnosis) [16,17].

The frequency of FTD in ALS patients varies in the literature. Studies done in the past 10 years [18,19] have suggested that roughly 50% of patients with ALS have some cognitive impairment, and 10–15% reach criteria for diagnosis of FTD. Bulbar onset of symptoms and lower educational attainment have been associated with cognitive involvement [20], and cognitive impairment in ALS has been associated with shorter survival. Similarly, approximately 15% of FTD patients develop clinical symptoms of motor neuron dysfunction. In some instances, FTD precedes ALS by many years; in others, ALS precedes FTD.

3. Pathological hallmarks underlying the link between frontotemporal dementia and ALS

Frontotemporal lobar degeneration can be divided into two major subtypes: FTLD with tau-positive inclusions (FTLD-tau); and FTLD with ubiquitin-positive and TDP-43-positive but tau-negative inclusions (FTLD-TDP) [21]. FTLDTDP appears to be the primary pathology underlying the overlap between FTD and motor neuron disease.

3.1. *FTLD-TDP*

Neumann et al. led to the identification of the transactive response DNA-binding protein with MW 43 kD (TDP-43) as the ubiquitinated pathological protein in most cases of FTLD-U as well as the majority of sporadic ALS and some familial ALS cases [7]. TDP-43 pathology is present in 90% of ubiquitin-positive FTLD cases and non-SOD1 ALS cases with FUS-positive inclusions accounting for the majority of remaining ubiquitin-positive TDP-43 negative inclusions [22,23]. Another subtype with TDP-43 pathology was described, associated with the familial syndrome of inclusion body myopathy with Paget's disease of bone and FTD caused by mutations in the VCP gene [24]. As a result, cases of FTLD with TDP-43 pathology are now designated as FTLD-TDP and the term FTLD-U is no longer recommended.

3.2. *FTLD-FUS, FTLD-UPS and FTLD-ni*

Approximately 6–20% of FTLD disorders are not associated with TDP-43 or tau pathology, but are characterized by ubiquitin-positive, TDP-43/tau negative inclusions. Many such cases have shown immunoreactivity with the fused-in-sarcoma (FUS) antibody [25] but none of the FTLD-FUS cases had FUS gene mutations [26]. The FUS protein is involved in DNA repair and regulation of RNA splicing [27]. The morphology of the intranuclear inclusions appear to be pathognomic of this subtype [28]. FTLD-FUS cases are characterized by a young age at onset, behavioural variant of FTD, negative family history and caudate atrophy on MRI. FUS-positive inclusions are also found in patients with neuronal filament inclusion disease (NIFID), who mainly present with a behavioural variant of FTD, and a rapid clinical course [29]. Finally, cases of ubiquitin-positive, TDP-43 and FUS-negative inclusions have been termed FTLD-UPS cases. Most of these cases carry a CHMP2B mutation [30].

4. Genetics underlying the link between frontotemporal dementias and MND

The majority of families with autosomal dominant FTD have a mutation in one of three genes; the microtubule-associated-protein-tau gene (MAPT), the progranulin gene (GRN) and the C9ORF72 gene. The most important discovery remains that of the C9ORF72 locus on chromosome 9p, responsible for a majority of the hereditary cases of FTD, ALS and FTD-ALS. Before the identification of C9ORF72, only 20–30% of familial ALS cases were explained by mutations in the superoxide dismutase-1 gene (SOD1), and the genes encoding TDP-43 (TARDBP) and fused in sarcoma (FUS). Mutations in TARDBP are responsible for 4–6% of familial ALS and 1% of sporadic ALS [31]. Mutations in TARDBP cause rarely FTD or corticobasal syndrome [32]. Mutations in FUS are causative of approximately 1 and 4% of apparent sALS and fALS respectively. About