Journal of Neuroimmunology 321 (2018) 29–35

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Prevalence of immunological diseases in a Finnish frontotemporal lobar degeneration cohort with the *C9orf72* repeat expansion carriers and non-carriers

Kasper Katisko[a], Eino Solje[a,b], Anne M. Koivisto[a,b], Johanna Krüger[c,d], Tuure Kinnunen[e], Päivi Hartikainen[a,b], Seppo Helisalmi[a], Ville Korhonen[f], Sanna-Kaisa Herukka[a,b], Annakaisa Haapasalo[b,g], Anne M. Remes[a,b,c,d,*]

[a] *Institute of Clinical Medicine – Neurology, University of Eastern Finland, FI-70211 Kuopio, Finland*
[b] *Neurocenter, Neurology, Kuopio University Hospital, FI-70029 Kuopio, Finland*
[c] *Medical Research Center, Oulu University Hospital, FI-90014 Oulu, Finland*
[d] *Unit of Clinical Neuroscience, Neurology, University of Oulu, FI-90014 Oulu, Finland*
[e] *Institute of Clinical Medicine – Clinical Microbiology, University of Eastern Finland, FI-70211 Kuopio, Finland*
[f] *Neurocenter, Neurosurgery, Kuopio University Hospital, FI-70029 Kuopio, Finland*
[g] *A.I. Virtanen Institute for Molecular Sciences, University of Eastern Finland, FI-70211 Kuopio, Finland*

ARTICLE INFO

Keywords:
Frontotemporal lobar degeneration
Frontotemporal dementia
Immunological disease
C9orf72
Comorbidity
Immunology

ABSTRACT

Recent studies have suggested a role for immune dysregulation behind the etiology of frontotemporal lobar degeneration (FTLD). Here, we have investigated the prevalence of immunological diseases in FTLD (N = 196) with and without the *C9orf72* repeat expansion, Alzheimer's disease (AD) (N = 193) and not cognitively impaired (NCI) subjects (N = 92). The prevalence was 16.3% in FTLD, 13.5% in AD and 15.2% in NCI. Although differences between the groups did not reach statistical significance, the frequency of immunological diseases was the highest in FTLD without the *C9orf72* expansion (22/117, 18.8%) and the lowest in FTLD with the expansion (6/56, 10.7%), suggesting that the *C9orf72* expansion possibly influences immunological pathways in FTLD.

1. Introduction

Frontotemporal lobar degeneration (FTLD) is a group of progressive neurodegenerative syndromes mainly affecting the frontal and temporal lobes of the brain. Clinically FTLD can be divided into two major clinical subgroups: 1) Behavioral variant frontotemporal dementia (bvFTD) characterized by personality changes (Rascovsky et al., 2011), and 2) primary progressive aphasias (PPA), a group of disorders that manifest as progressive loss of language functions (Gorno-Tempini et al., 2011). PPAs are further divided into three subgroups based on the clinical profile: non-fluent variant primary progressive aphasia (nfvPPA), semantic variant primary progressive aphasia (svPPA) and logopenic variant primary progressive aphasia (lvPPA), of which the last one is mainly associated with Alzheimer's disease (AD) (Gorno-Tempini et al., 2011).

FTLD is a neuropathologically and genetically heterogeneous group of diseases. The most common neuropathological subtypes are TDP-43- and Tau-positive FTLD (FTLD-TDP and FTLD-Tau, respectively) (Sieben et al., 2012). Familial forms of the disease are mainly associated with mutations in *C9orf72*, *MAPT* and *GRN* genes. Hexanucleotide repeat expansion in chromosome 9 open reading frame 72 -gene (*C9orf72*) is the most common genetic cause for familial FTLD and amyotrophic lateral sclerosis (ALS) (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The *C9orf72* repeat expansion and *GRN* mutations lead predominantly to TDP-43 neuropathology (DeJesus-Hernandez et al., 2011; Renton et al., 2011; Rohrer et al., 2009), while mutations in MAPT are associated with tau pathology (Rohrer et al., 2009). Notably, more than half of the FTLD cases are sporadic without any known genetic alterations (Rohrer et al., 2009), but show similar neuropathological features to familial FTLD cases (Cairns et al., 2007). Despite the recognized pathogenic mutations and different characteristic pathological features, the exact molecular pathogenic mechanisms of FTLD

* Corresponding author at: Unit of Clinical Neuroscience, Neurology, University of Oulu, P.O. Aapistie 7, FI 90014 Oulu, Finland.
E-mail addresses: kasperk@uef.fi (K. Katisko), eino.solje@uef.fi (E. Solje), anne.koivisto@kuh.fi (A.M. Koivisto), johanna.kruger@ppshp.fi (J. Krüger), tuure.kinnunen@uef.fi (T. Kinnunen), paivi.hartikainen@kuh.fi (P. Hartikainen), seppo.helisalmi@uef.fi (S. Helisalmi), villekor@student.uef.fi (V. Korhonen), sanna-kaisa.herukka@uef.fi (S.-K. Herukka), annakaisa.haapasalo@uef.fi (A. Haapasalo), anne.remes@oulu.fi (A.M. Remes).

https://doi.org/10.1016/j.jneuroim.2018.05.011
Received 25 February 2018; Received in revised form 21 May 2018; Accepted 21 May 2018

have remained unclear.

Recently, several preclinical and clinical studies have suggested a potential involvement of immune system dysfunction behind the etiology of FTLD (Atanasio et al., 2016; Burberry et al., 2016; Ferrari et al., 2014; Miller et al., 2016; Miller et al., 2013). Therefore, our aim here was to determine whether immunological diseases, and especially autoimmune diseases, are more common in FTLD patients when compared to patients with AD or not cognitively impaired (NCI) participants. We also investigated the prevalence of immunological diseases within the FTLD patient group in relation to the presence or absence of the *C9orf72* repeat expansion.

2. Materials and methods

2.1. Ethical considerations

The study was performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants. The study protocol was approved by the research ethics committees of Northern Savo hospital district and Northern Ostrobothnia hospital district.

2.2. Study cohort

Altogether 196 patients with FTLD were classified between the years 1999–2016 at the memory outpatient clinics of Kuopio University Hospital and Oulu University Hospital. An experienced neurologist, specialized in cognitive disorders, examined all of the patients and divided them into clinical subgroups. In total, 132 patients were diagnosed with bvFTD, 19 with FTLD-motoneuron disease (FTLD-MND), 37 with nfvPPA and eight with svPPA. The patients with bvFTD were diagnosed according to the latest diagnostic criteria by Rascovsky and colleagues (Rascovsky et al., 2011), and patients with PPAs were diagnosed according to the Gorno-Tempini diagnostic criteria (Gorno-Tempini et al., 2011). A retrospective review based on these same criteria was used for the patients that were originally diagnosed before the Rascovsky or Gorno-Tempini criteria were published. All patients with bvFTD, nfvPPA or svPPA fulfilled the criteria with either probable or definite diagnosis. Patients with FTLD-MND had at least probable diagnosis of bvFTD, nfvPPA or svPPA and also a lucid manifestation of motoneuron disease. None of the patients in our cohort were diagnosed with lvPPA.

In addition to the FTLD clinical subgroups, patients with FTLD were further divided into two subgroups based on whether they carry or not the *C9orf72* repeat expansion: the *C9orf72* repeat expansion carriers (N = 56) and the *C9orf72* repeat expansion non-carriers (N = 117). Within the clinical subgroups, 40 bvFTD, six nfvPPA, one svPPA and nine FTLD-MND patients carried the *C9orf72* repeat expansion. Genotyping data of the *C9orf72* repeat expansion was not available for 11.7% (23/196) FTLD patients (16 bvFTD, four nfvPPA, one svPPA and two FTLD-MND). Six patients without the *C9orf72* repeat expansion genotyping were neuropathologically confirmed as FTLD (5/6 FTLD-TDP and 1/6 FTLD-Tau), leading to a total of 62 patients with definite and 134 with probable FTLD according to the latest criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

For comparison, an age- and sex-matched group of patients (N = 193) with at least probable AD according to the McKhann criteria (McKhann et al., 1984) were identified during the years 1999–2017 at the memory outpatient clinics in Kuopio University Hospital and Oulu University Hospital. Patients were diagnosed by an experienced neurologist specialized in cognitive disorders and the diagnoses were based on clinical and neuropsychological examination, brain imaging and cerebrospinal fluid AD biomarkers.

Another control group was gathered from the memory outpatient clinic of Kuopio University Hospital, comprising of individuals who had undergone the same evaluations for cognitive disorders as the AD group, but who were eventually classified as not cognitively impaired (NCI) and without any diagnosed neurodegenerative disorder (N = 92).

2.3. Genetic analyses

The repeat-primed polymerase chain reaction assay (RP-PCR) (Renton et al., 2011) was used to indicate the presence or absence of the *C9orf72* repeat expansion in the FTLD patients. The results of PR-PCR were confirmed using Amplicon length analysis (van der Zee et al., 2013). Six patients in the *C9orf72* repeat expansion carrier group had an intermediate expansion (20–40 repeats) and the rest (N = 50) had a full expansion (> 40 repeats). All FTLD patients in the *C9orf72* repeat expansion non-carrier group had fewer than five repeats. Based on our previous reports showing that other known FTLD mutations (*GRN*, *MAPT*, *CHMP2B*) are extremely rare in Finnish population, these genes were not systematically sequenced (Kaivorinne et al., 2008, 2010; Krüger et al., 2009).

2.4. Clinical review

Medical histories were retrospectively reviewed for evidence of immunological diseases by using a modified classification from previous similar studies (Table 1) (Miller et al., 2016; Miller et al., 2013; Rugbjerg et al., 2009). Immunological diseases were further divided into different disease clusters (1. Cutaneous conditions, 2. Inflammatory arthritides, 3. Gastrointestinal disorders, 4. Connective

Table 1
Screened immunological diseases.

Addison's disease	Chorea minor	Hashimoto's thyroiditis	Pemphigus[2]	Sarcoidosis
Alopecia areata[b]	Chronic lymphocytic colitis	Henoch-Schönlein purpura[b]	Pernicious anemia	Sjögren's syndrome
Ankylosing spondylitis	Chronic rheumatic heart disease or rheumatic fever	Hypothyreosis[a,b]	Polyarteritis nodosa	Systemic lupus erythematosus (SLE)
Asthma[a,b]	Crohn's disease	Inclusion body myositis	Polymyalgia rheumatica	Systemic sclerosis
Autoimmune hemolytic anemia	Churg-Strauss vasculitis[b]	Immune thrombocytopenic purpura	Polymyositis	Temporal arteritis[2]
Autoimmune hepatitis	Dermatomyositis	Latent autoimmune diabetes in adults[b]	Primary biliary cirrhosis	Transverse myelitis
Autoimmune thyreoiditis[b]	Discoid lupus	Localized scleroderma	Primary sclerosing cholangitis[b]	Type 1 diabetes mellitus
Autoimmune urticaria[b]	Goodpasture's disease[b]	Lichen planus[b]	Psoriasis	Ulcerative colitis
Behçet's disease	Granulomatosis with polyangiitis	Lichen sclerosus	Psoriatic arthritis[b]	Uveitis (autoimmune)[2]
Bullous pemphigoid[b]	Graves's disease	Multiple sclerosis	Reactive arthritis	Vitiligo
Celiac disease	Guillan-Barré syndrome	Myasthenia gravis	Rheumatoid arthritis	

[a] Asthma and hypothyreosis were analyzed separately.
[b] Added to autoimmune disease collection (modified from Rugbjerg et al. (Rugbjerg et al., 2009)) that was used in previous studies (Miller et al., 2016; Miller et al., 2013).