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FRONTO-TEMPORAL DEMENTIA: THE ROLE OF INFLAMMATION AND IMMUNITY

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Summary

Frontotemporal Dementia (FTD) is a neurodegenerative disorder which is characterized by behavioural abnormalities, language impairment, and deficits of executive functions. Behavioural variant FTD (bvFTD) and Primary Progressive Aphasias (PPAs) represent the most common phenotypes. The identification of mutations responsible for autosomal dominant inherited disorder, namely *Microtubule Associated Protein Tau (MAPT)*, *Granulin (GRN)* and *chromosome 9 open reading frame 72 (C9orf72)* mutations, contributed to elucidate the molecular pathways involved in brain depositions of either Tau or TAR DNA-binding protein 43 (TDP43) inclusions. In FTD cases associated with pathogenic *MAPT* mutations, Tau accumulation in neurons and glia has been explained in terms of abnormal phosphorylation of the protein, or an altered proportion in the ratio of the 4R and 3R Tau isoforms; conversely, *GRN* mutation haploinsufficiency and *C9orf72* ex- pansion lead to TDP43 aggregation, with a less clear mechanism. However, in the majority of sporadic FTD patients, the molecular pathways triggering Tau or TDP43 protein deposition are still to be uncovered. No risk factors other than genetic background have been recognised in FTD. An immuno-mediated inflammatory hypothesis to neurodegenerative processes has been claimed on the basis of epidemiological studies and genome-wide association analysis (GWAS). Moreover, for some cases of FTD language variants, an autoimmune condition has been suggested. In this review, a brief evaluation of literature data on immune homeostasis in FTD is presented, in order to provide potentially evidence-based approaches for a disease still orphan of any treatment.

Key words: Dementia, Fronto-Temporal Lobar Degeneration, Glutamate Receptors, autoimmunity

Introduction

Frontotemporal Dementia (FTD) is one of the most common neurodegenerative conditions after Alzheimer Disease (AD). Most FTD patients are affected by progressive behavioral abnormalities, language impairment, and deficits of executive functions [1, 2]. The two main pathological hallmarks in FTD are represented by brain depositions of either Tau or TAR DNA-binding protein 43 (TDP43) [3] selectively affecting the frontal and temporal regions. Pathogenic mutations in Microtubule Associated Protein Tau (MAPT), Granulin (GRN) and expansion on chromosome 9 open reading frame 72 (C9orf72) are the main causative genetic factors and the identification of these genes contributed to a major understanding of the disease. Nevertheless it is still unknown whether Tau and TDP43 deposits represent the initial mechanism or simply the result of other unknown environmental, genetic or inflammatory factors [4-9]. At present, though genetic background is still considered the major determinant of the disease [10, 11], evidences from different sources highlighted the role of inflammation in agreement with several discoveries in Autoimmune Encephalitis (AIE) which contributed to modify the paradigm of the Central Nervous System (CNS) as an immune privileged-site [12].

The contribution of GluR3 autoantibodies to FTD etiology

In FTD, different observations argued for an immune system involvement and significant prevalence of autoimmune disorders has been observed [13, 14, 15]. Genome-wide association analysis (GWAS) in FTD found a significant enrichment for elements of the immune system involved in antigen presentation, including the HLA-DR5 locus [16] and granulin has been associated with inflammatory and wound response [17]. Again, in TREM2 T66M knock-in mouse models there is a dysfunction in microglia and aberrant glucose metabolism in the frontal lobes [18]. Recently, our group reported anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) antibodies in a significant proportion of patients fulfilling clinical diagnostic criteria for FTD [19, 20, 21]. On the other hand, emerging evidence of frontotemporal areas involvement in autoimmune CNS disorders has been increasingly reported in the past years. More generally, antibody-associated neuronal autoimmune diseases has become a heterogeneous group of syndromes mainly divided into two groups: classic paraneoplastic syndromes (PNS), linked to the presence of a specific systemic cancer, and autoimmune encephalitis (AIE), with antibodies directed towards the extracellular domain of surfaced neuronal proteins, causing direct neuronal

injury [22, 23, 24]. In the absence of neoplasia, the etiopathogenic mechanism underlying autoimmune activity has been less understood. The first auto-antibody to be identified, against GluR3, was in Rasmussen's encephalitis, in 1950s [25, 26]. Moreover, in the autoimmunity CNS disorders spectrum, limbic encephalitis is a well-recognized condition, defined as a subacute onset of short term memory loss, behavioral changes and seizures, mainly involving the temporo-medial lobes and the amygdalae, with variable evidence of CSF inflammation [27]. Different types of neuronal antibodies have been recently identified and, specifically, antibodies directed against voltage-gated potassium channels (VGKC-Abs) are often associated with limbic encephalitis, presenting with seizures, amnesia and medial temporal lobe inflammation [28-29]. Predominantly in young women, another type of auto-antibody, directed against the N-methyl- D-aspartate subtype of ionotropic glutamate receptors (NMDAR) has been identified, which seems to be commonly associated with a prominent movement disorder [30-32]. Dysfunction of glutamatergic signaling can also result in limbic encephalitis when the immune system attacks the AMPA glutamate receptors, which mediate the majority of fast excitatory synaptic transmission in the CNS [33]. Patients affected are usually women older than 50 years old, who present with subacute memory loss, confusion, agitated behavior, and seizures. Remarkably, in the last decade new autoimmune synaptic antibodies have been discovered, namely anti-Leucine-rich glioma inactivated 1 (anti-LGI1), anti-contactin-associated protein-like 2 (anti-Caspr2), and anti- γ-aminobutyric acid class B (anti-GABAB) receptors [29] thus underlining the role of antibody-mediated attack to neuronal structures [33].

Toward an alternative GluR3 autoantibodies dependent etiologic mechanism for FTD

The etiopathogenic mechanisms underlying CNS autoimmunity are still unknown, although an infective trigger has been proposed. Notably, 20% of patients with Herpes simplex virus encephalitis have relapsing symptoms, especially in children, without viral reactivation or response to acyclovir but, in some cases, they show anti-NMDAR antibodies [34] supporting the view that the infectious prodrome, whenever it occurs, represents an inflammatory event associated with CSF lymphocytosis. In fact, it has been proposed that the inflammatory reaction might be responsible for a temporary and/or localized disruption of the BBB, allowing antibodies to gain entry into the CNS [35-35]. Still it is unclear what drives regional vulnerability, but it has been claimed that serum antibodies might find facilitated conditions to penetrate into the brain

of patients through the heavily vascularized nasal mucosa and the olfactory sensory axons, as well as via the trigeminal nerve into the brainstem [37] though there is evidence that the expression of neuronal antigens is region-specific [38]. More importantly, serum IgA/IgM anti-NMDAR occurs in a significant number of patients with undefined dementia, characterized by higher frequency of CSF abnormalities, sub-acute or fluctuating disease progression and immunotherapy response [39]. Besides those reversible syndromes, clearly linked to a monophasic inflammatory immune-mediated reaction, increasing data seem to emphasize the link between inflammation and neurodegenerative processes. In fact, a robust demonstration of an autoimmunity process linked to neuro-degeneration, has been provided by the identification of IgLON5-antibody in patients with sleep disorders, abnormal behavior, movements and brainstem symptoms with a chronic progressive disease course; Tau protein aggregation has been observed in the hypothalamus, thalamus and brainstem in brain autopsy [40-43]. Furthermore, an inflammatory contribution to neurodegenerative disorders pathogenesis has been hypothesized both in AD [12] both in the senile and presenile populations [44]. With regard to FTD, though a substantial genetic component has been reported in around 10-20% of genetic FTD cases [45-47], no substantial risk factors responsible for sporadic dementia have been identified yet. Notably, a genome-wide association study (GWAS) conducted on a large cohort of mainly clinically diagnosed FTD, has identified a significant association with the HLA locus, supporting the claim that neuro-degeneration might be triggered by the immune system [16]. Furthermore, Miller and colleagues have shown a higher prevalence of systemic autoimmune disease in semantic variant PPA (svPPA) patients [13] consistent with similar subsequent findings in FTD patients with C9orf72 expansion [48]. Another recent and substantial evidence of autoimmunity co-existence in neurodegenerative disorders has been proved by the detection of anti-AMPA GluA3 antibody in serum and cerebrospinal fluid (CSF) of a single FTD patient; the extension of the study to a large clinical series of FTD demonstrated a significant proportion positive for anti-GluA3 antibodies in serum as well as in cerebrospinal fluid [19-20]. As a matter of fact, the incubation of rat hippocampal neuronal primary cultures with CSF with anti-GluA3 antibodies led to a decrease of GluA3 subunit synaptic localization of the AMPA receptor (AMPAR) and loss of dendritic spines. The significant reduction of the GluA3 subunit seems to correlate with increased levels of neuronal tau protein [20]. Altogether these findings argue for a potential role exerted by the dysregulation of the immune homeostasis in FTD, even though it has to establish at what stage autoimmunity plays an active role in neurodegenerative process.

Several neuroimaging studies including different autoimmune disease have shed some lights on the multifaced impact of immunomediated neuroinflammation [49-54]. Despite normal findings in NMDAR encephalitis, longitudinal imaging studies showed that severe disease courses can result in hippocampal or mild global atrophy, with functional, volumetric and white matter changes in the hippocampus correlating with memory performance, disease severity and duration [48, 55]. Similarly, AMPAR and LGI1R encephalitis lead to hippocampal atrophy later in their course [56-58]. Among others, the perisylvian region and the insula are the predominant site for signal abnormality and atrophy [31, 59, 60], with evidence of asymmetrical insular and frontal atrophy correlating with epilepsy duration [61]. Similarly, FTD presents with a focal atrophic pattern affecting primarily the frontotemporo- insular structures [62, 63], even though different patterns may be identified, according to the presenting clinical syndrome [64-70]. Interestingly, in addition to white matter hyperintensities [71, 72], several studies have highlighted a common limbic involvement in FTD, even in the very early disease phases [73-76]. In the last years, microglial activation has become a novel target of PET tracers, such as radio-labeled PK11195, which binds to the translocator protein (TSPO). TSPO is localized on the mitochondrial membrane and it is only minimally expressed in the healthy brain, whereas overexpressed in neuroinflammatory disorders [77]. The application of TSPO imaging to neurodegenerative disorders has confirmed the concurrent presence of inflammation in many conditions, usually reflecting the regional distribution of the pathology [78]. With regard to FTLD, microglial activation has been demonstrated both in tauopathies [79, 80], and in TDP43 proteinopathies [81]. Interestingly, microglial activation has been described before the occurrence of overt anatomical changes in MAPT presymptomatic carriers [82] as well as in the less atrophic hemisphere of FTD patients [83]. These data in addition to open a new avenue have the potential of offering a therapeutic strategy for sporadic cases. Indeed, while patients with autoimmune encephalitis (i.e. anti-NMDA or anti-AMPA receptor encephalitis) are often seriously affected, these disorders have been shown to be responsive to immunomodulatory therapies [35, 84-87]. In the context of FTD, few case reports of antibody–associated encephalopathies (i.e. anti-VGKC, anti-NMDA and anti-AMPA-mGluR3) presenting as frontotemporal dementia–like syndromes have also shown initial beneficial responses after intravenous immunoglobulins, steroid infusions, or rituximab treatment [88-90]. Overall these findings contribute to expand the notion of possible therapeutic perspectives in the treatment of autoimmune related neurodegeneration, in which immunomodulating treatments could potentially reduce or revert the

intracellular accumulation of pathological protein aggregates. It has to acknowledge that the very few available data may anticipate a new pathogenesis and treatment in FTLD for selected cases in whom an early diagnosis "autoimmune FTD" and a prompt treatment could be critical to prevent irreversible neuronal damage and reduce possible neurological sequelae.

References

[1] Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology 76(11): 1006-14 (2011).

[2] Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134(Pt 9): 2456- 77(2011).

[3] Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol 114(1): 5-22 (2007).

[4] Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature 393(6686): 702-5 (1998).

[5] Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature 442(7105): 920-4 (2006).

[6] Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 442(7105): 916-9 (2006).

[7] DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron 72(2): 245-56 (2011).

[8] Hernandez I, Fernandez MV, Tarraga L, Boada M, Ruiz A. Frontotemporal Lobar Degeneration. Review and update for clinical neurologists. Curr Alzheimer Res (2017).

[9] Che XQ, Zhao QH, Huang Y, Li X, Ren RJ, Chen SD, et al. Genetic Features of MAPT, GRN, C9orf72 and CHCHD10 Gene Mutations in Chinese Patients with Frontotemporal Dementia. Curr Alzheimer Res 14(10): 1102-08 (2017).

[10] Premi E, Gazzina S, Bozzali M, Archetti S, Alberici A, Cercignani M, et al. Cognitive reserve in granulin-related frontotemporal dementia: from preclinical to clinical stages. PLoS One 8(9): e74762 (2013).

[11] Rohrer JD, Warren JD, Fox NC, Rossor MN. Presymptomatic studies in genetic frontotemporal dementia. Rev Neurol (Paris) 169(10): 820-4 (2013).

[12] McGeer PL, McGeer EG. NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. Neurobiol Aging 28(5): 639-47.(2007).

[13] Miller ZA, Rankin KP, Graff-Radford NR, Takada LT, Sturm VE, Cleveland CM, et al. TDP-43 frontotemporal lobar degeneration and autoimmune disease. J Neurol Neurosurg Psychiatry 84(9): 956-62 (2013).

[14] Rogalski E, Weintraub S, Mesulam MM. Are there susceptibility factors for primary progressive aphasia? Brain Lang 127(2): 135-8 (2013).

[15] Weintraub S, Fahey C, Johnson N, Mesulam MM, Gitelman DR, Weitner BB, et al. Vasectomy in men with primary progressive aphasia. Cogn Behav Neurol 19(4): 190-3 (2006).

[16] Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A, Kwok JB, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. Lancet Neurol 13(7): 686-99 (2014).

[17] He Z, Ong CH, Halper J, Bateman A. Progranulin is a mediator of the wound response. Nat Med 9(2): 225-9 (2003).

[18] Kleinberger G, Brendel M, Mracsko E, Wefers B, Groeneweg L, Xiang X, et al. The FTD-like syndrome causing TREM2 T66M mutation impairs microglia function, brain perfusion, and glucose metabolism. EMBO J 36(13): 1837-53 (2017).

[19] Borroni B, Manes MA, Alberici A, Cosseddu M, Bernasconi P, Archetti S, et al. Autoimmune frontotemporal dementia: a new nosological entity? Alzheimer Dis Assoc Disord 31(3): 259-262 (2017).

[20] Borroni B, Stanic J, Verpelli C, Mellone M, Bonomi E, Alberici A, et al. Anti-AMPA GluA3 antibodies in Frontotemporal dementia: a new molecular target. Sci Rep 7(1): 6723 (2017).

[21] Selmi C, Barin JG, Rose NR. Current trends in autoimmunity and the nervous system. J Autoimmun 75: 20-29 (2016).

[22] Kayser MS, Dalmau J. The emerging link between autoimmune disorders and neuropsychiatric disease. J Neuropsychiatry Clin Neurosci 23(1): 90-7 (2011).

[23] Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 77(2): 179-89 (2011).

[24] Rasmussen T, Olszewski J, Lloydsmith D. Focal seizures due to chronic localized encephalitis. Neurology 8(6): 435-45 (1958).

[25] Varadkar S, Bien CG, Kruse CA, Jensen FE, Bauer J, Pardo CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. Lancet Neurol 13(2): 195-205 (2014).

[26] Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain 123 (Pt 7): 1481-94 (2000).

[27] Buckley C, Oger J, Clover L, Tuzun E, Carpenter K, Jackson M, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol 50(1): 73-8 (2001).

[28] Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 127(Pt 3): 701-12 (2004).

[29] Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61(1): 25-36 (2007). Autoimmunity and Frontotemporal Dementia Current Alzheimer Research, 2018, Vol. 15, No. 00 7

[30] Dale RC, Irani SR, Brilot F, Pillai S, Webster R, Gill D, et al. Nmethyl- D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. Ann Neurol 66(5): 704-9 (2009).

[31] Florance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 66(1): 11-8 (2009).

[32] Kessels HW, Malinow R. Synaptic AMPA receptor plasticity and behavior. Neuron 61(3): 340-50 (2009).

[33] Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B. Autoimmune Encephalitis: Pathophysiology and Imaging Review of an Overlooked Diagnosis. AJNR Am J Neuroradiol 38(6): 1070-78 (2017).

[34] Armangue T, Moris G, Cantarin-Extremera V, Conde CE, Rostasy K, Erro ME, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. Neurology 85(20): 1736-43 (2015).

[35] Graus F, Saiz A, Lai M, Bruna J, Lopez F, Sabater L, et al. Neuronal surface antigen antibodies in limbic encephalitis: clinical-immunologic associations. Neurology 71(12): 930-6.(2008).

[36] Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. Nmethyl- D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly nonparaneoplastic disorder of both sexes. Brain 133(Pt 6): 1655-67 (2010).

[37] Cutforth T, DeMille MM, Agalliu I, Agalliu D. CNS autoimmune disease after Streptococcus pyogenes infections: animal models, cellular mechanisms and genetic factors. Future Neurol 11(1): 63-76 (2016).

[38] Pruss H, Holtje M, Maier N, Gomez A, Buchert R, Harms L, et al. IgA NMDA receptor antibodies are markers of synaptic immunity in slow cognitive impairment. Neurology 78(22): 1743-53 (2012).

[39] Doss S, Wandinger KP, Hyman BT, Panzer JA, Synofzik M, Dickerson B, et al. High prevalence of NMDA receptor IgA/IgM antibodies in different dementia types. Ann Clin Transl Neurol 1(10): 822-32 (2014).

[40] Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, et al. A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 13(6): 575-86 (2014).

[41] Simabukuro MM, Sabater L, Adoni T, Cury RG, Haddad MS, Moreira CH, et al. Sleep disorder, chorea, and dementia associated with IgLON5 antibodies. Neurol Neuroimmunol Neuroinflamm 2(4): e136 (2015).

[42] Cagnin A, Mariotto S, Fiorini M, Gaule M, Bonetto N, Tagliapietra M,et al. Microglial and Neuronal TDP-43 Pathology in Anti-IgLON5- Related Tauopathy. J Alzheimers Dis 59(1): 13-20 (2017).

[43] Gelpi E, Hoftberger R, Graus F, Ling H, Holton JL, Dawson T, et al. Neuropathological criteria of anti-IgLON5-related tauopathy. Acta Neuropathol 132(4): 531-43 (2016).

[44] Neary D, Snowden J. Fronto-temporal dementia: nosology, neuropsychology, and neuropathology. Brain Cogn 31(2): 176-87 (1996).

[45] Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, et al. The heritability and genetics of frontotemporal lobar degeneration. Neurology 73(18): 1451-6 (2009).

[46] Mesulam MM. Primary progressive aphasia. Ann Neurol 49(4): 425-32 (2001).

[47] Premi E, Pilotto A, Alberici A, Papetti A, Archetti S, Seripa D, et al. FOXP2, APOE, and PRNP: new modulators in primary progressive aphasia. J Alzheimers Dis 28(4): 941-50 (2012).

[48] Miller ZA, Sturm VE, Camsari GB, Karydas A, Yokoyama JS, Grinberg LT, et al. Increased prevalence of autoimmune disease within C9 and FTD/MND cohorts: completing the picture. Neurol Neuroimmunol Neuroinflamm 3(6): e301 (2016).

[49] Appenzeller S, Rondina JM, Li LM, Costallat LT, Cendes F. Cerebral and corpus callosum atrophy in systemic lupus erythematosus. Arthritis Rheum 52(9): 2783-9 (2005).

[50] Muscal E, Traipe E, de Guzman MM, Myones BL, Brey RL, Hunter JV. Cerebral and cerebellar volume loss in children and adolescents with systemic lupus erythematosus: a review of clinically acquired brain magnetic resonance imaging. J Rheumatol 37(8): 1768-75 (2010).

[51] Ainiala H, Dastidar P, Loukkola J, Lehtimaki T, Korpela M, Peltola J, et al. Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: a population-based study. Scand J Rheumatol 34(5): 376-82 (2005).

[52] Tamagno G, Celik Y, Simo R, Dihne M, Kimura K, Gelosa G, et al. Encephalopathy associated with autoimmune thyroid disease in patients with Graves' disease: clinical manifestations, follow-up, and outcomes. BMC Neurol 10: 27 (2010).

[53] Morgen K, McFarland HF, Pillemer SR. Central nervous system disease in primary Sjogrens syndrome: the role of magnetic resonance imaging. Semin Arthritis Rheum 34(3): 623-30 (2004).

[54] Kleffner I, Dorr J, Ringelstein M, Gross CC, Bockenfeld Y, Schwindt W, et al. Diagnostic criteria for Susac syndrome. J Neurol Neurosurg Psychiatry 87(12): 1287-95 (2016).

[55] Kalra S, Silman A, Akman-Demir G, Bohlega S, Borhani-Haghighi A, Constantinescu CS, et al. Diagnosis and management of Neuro-Behcet's disease: international consensus recommendations. J Neurol 261(9): 1662-76 (2014).

[56] Heine J, Pruss H, Bartsch T, Ploner CJ, Paul F, Finke C. Imaging of autoimmune encephalitis--Relevance for clinical practice and hippocampal function. Neuroscience 309: 68-83 (2015).

[57] Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol 13(3): 276-86 (2014).

[58] Wei YC, Liu CH, Lin JJ, Lin KJ, Huang KL, Lee TH, et al. Rapid progression and brain atrophy in anti-AMPA receptor encephalitis. J Neuroimmunol 261(1-2): 129-33 (2013).

[59] Bien CG, Granata T, Antozzi C, Cross JH, Dulac O, Kurthen M, et al. Pathogenesis, diagnosis and treatment of Rasmussen encephalitis: a European consensus statement. Brain 128(Pt 3): 454-71 (2005).

[60] Wang ZI, Krishnan B, Shattuck DW, Leahy RM, Moosa AN, Wyllie E,et al. Automated MRI volumetric analysis in patients with Rasmussen syndrome. AJNR Am J Neuroradiol 37(12): 2348-55 (2016).

[61] Wagner J, Schoene-Bake JC, Bien CG, Urbach H, Elger CE, Weber B. Automated 3D MRI volumetry reveals regional atrophy differences in Rasmussen encephalitis. Epilepsia 53(4): 613-21 (2012).

[62] Gordon E, Rohrer JD, Fox NC. Advances in neuroimaging in frontotemporal dementia. J Neurochem 138 Suppl 1: 193-210 (2016).

[63] Moller C, Hafkemeijer A, Pijnenburg YAL, Rombouts S, van der Grond J, Dopper E, et al. Different patterns of cortical gray matter loss over time in behavioral variant frontotemporal dementia andAlzheimer's disease. Neurobiol Aging 38: 21-31 (2016).

[64] Borroni B, Cosseddu M, Pilotto A, Premi E, Archetti S, Gasparotti R, et al. Early stage of behavioral variant frontotemporal dementia: clinical and neuroimaging correlates. Neurobiol Aging 36(11): 3108-15 (2015).

[65] Jastorff J, De Winter FL, Van den Stock J, Vandenberghe R, Giese MA, Vandenbulcke M. Functional dissociation between anterior temporal lobe and inferior frontal gyrus in the processing of dynamic body expressions: Insights from behavioral variant frontotemporal dementia. Hum Brain Mapp 37(12): 4472-86 (2016).

[66] Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, et al. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. Arch Neurol 65(2): 249-55 (2008).

[67] Mandelli ML, Vitali P, Santos M, Henry M, Gola K, Rosenberg L, et al. Two insular regions are differentially involved in behavioral variant FTD and nonfluent/agrammatic variant PPA. Cortex 74: 149-57 (2016).

[68] Collins JA, Montal V, Hochberg D, Quimby M, Mandelli ML, Makris N, et al. Focal temporal pole atrophy and network degeneration in semantic variant primary progressive aphasia. Brain 140(Pt 2): 457-71 (2017).

[69] Shoamanesh A, Preis SR, Beiser AS, Vasan RS, Benjamin EJ, Kase CS, et al. Inflammatory biomarkers, cerebral microbleeds, and small vessel disease: framingham heart study. Neurology 84(8): 825-32 (2015).

[70] Tu S, Leyton CE, Hodges JR, Piguet O, Hornberger M. Divergent longitudinal propagation of white matter degradation in logopenic and semantic variants of primary progressive aphasia. J Alzheimers Dis 49(3): 853-61 (2016).

[71] Paternico D, Premi E, Gazzina S, Cosseddu M, Alberici A, Archetti S, et al. White matter hyperintensities characterize monogenic frontotemporal dementia with granulin mutations. Neurobiol Aging 38: 176-80 (2016).

[72] Sudre CH, Bocchetta M, Cash D, Thomas DL, Woollacott I, Dick KM, et al. White matter hyperintensities are seen only in GRN mutation carriers in the GENFI cohort. Neuroimage Clin 15: 171-80 (2017).

[73] Kim EJ, Sidhu M, Gaus SE, Huang EJ, Hof PR, Miller BL, et al. Selective frontoinsular von Economo neuron and fork cell loss in early behavioral variant frontotemporal dementia. Cereb Cortex 22(2): 251-9 (2012).

[74] Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. Lancet Neurol 14(3): 253-62 (2015).

[75] Allman JM, Tetreault NA, Hakeem AY, Manaye KF, Semendeferi K, Erwin JM, et al. The von Economo neurons in the frontoinsular and anterior cingulate cortex. Ann NY Acad Sci 1225: 59-71 (2011).

[76] Santillo AF, Englund E. Greater loss of von Economo neurons than loss of layer II and III neurons in behavioral variant frontotemporal dementia. Am J Neurodegener Dis 3(2): 64-71 (2014).

[77] Wu C, Li F, Niu G, Chen X. PET imaging of inflammation biomarkers. Theranostics 3(7): 448-66 (2013).

[78] Dupont AC, Largeau B, Santiago Ribeiro MJ, Guilloteau D, Tronel C, Arlicot N. Translocator protein-18 kda (tspo) positron emission tomography (pet) imaging and its clinical impact in neurodegenerative diseases. Int J Mol Sci 18(4): pii: E785 (2017).

[79] Gerhard A, Trender-Gerhard I, Turkheimer F, Quinn NP, Bhatia KP, Brooks DJ. In vivo imaging of microglial activation with [11C](R)-PK11195 PET in progressive supranuclear palsy. Mov Disord 21(1): 89-93 (2006).

[80] Lant SB, Robinson AC, Thompson JC, Rollinson S, Pickering-Brown S, Snowden JS, et al. Patterns of microglial cell activation in frontotemporal lobar degeneration. Neuropathol Appl Neurobiol 40(6): 686-96 (2014).

[81] Cagnin A, Mariotto S, Fiorini M, Gaule M, Bonetto N, Tagliapietra M, et al. Microglial and neuronal tdp-43 pathology in anti-iglon5-related tauopathy. J Alzheimers Dis 59(1): 13-20 (2017).

[82] Miyoshi M, Shinotoh H, Wszolek ZK, Strongosky AJ, Shimada H, Arakawa R, et al. In vivo detection of neuropathologic changes in presymptomatic MAPT mutation carriers: a PET and MRI study. Parkinsonism Relat Disord 16(6): 404-8 (2010).

[83] Cagnin A, Rossor M, Sampson EL, Mackinnon T, Banati RB. In vivo detection of microglial activation in frontotemporal dementia. Ann Neurol 56(6): 894-7 (2004).

[84] Seki M, Suzuki S, Iizuka T, Shimizu T, Nihei Y, Suzuki N, et al. Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 79(3): 324-6 (2008).

[85] Smith JH, Dhamija R, Moseley BD, Sandroni P, Lucchinetti CF, Lennon VA, et al. N-methyl-D-aspartate receptor autoimmune encephalitis presenting with opsoclonus-myoclonus: treatment response to plasmapheresis. Arch Neurol 68(8): 1069-72 (2011).

[86] Wingfield T, McHugh C, Vas A, Richardson A, Wilkins E, Bonington A, et al. Autoimmune encephalitis: a case series and comprehensive review of the literature. QJM 104(11): 921-31 (2011).

[87] Raha S, Gadgil P, Sankhla C, Udani V. Nonparaneoplastic anti-Nmethyl- D-aspartate receptor encephalitis: a case series of four children. Pediatr Neurol 46(4): 246-9 (2012).

[88] Titulaer MJ, McCracken L, Gabilondo I, Armangue T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol 12(2): 157-65 (2013).

[89] Suppiej A, Nosadini M, Zuliani L, Pelizza MF, Toldo I, Bertossi C, et al. Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review. Brain Dev 38(7): 613-22 (2016).

[90] Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 83(2): 142-50 (2014).

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