THE GENETIC BASIS OF FRONTOTEMPORAL DEMENTIA, AMYOTROPHIC LATERAL SCLEROSIS AND CYSTIC FIBROSIS

G. Andrade¹, A. Ferreira¹, P. Câmara Pestana¹, B. Côrte-Real¹, Frederico Simões do Couto^{1,2}

¹Serviço de Psiquiatria e Saúde Mental, Hospital Santa Maria – Centro Hospitalar Universitário Lisboa Norte

²Invited Professor of Psychiatry & Pharmacology, Faculdade de Medicina de Lisboa

INTRODUCTION

The genetic basis between frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) is established. Up to 40% patients with FTD¹ and 10% with ALS² have a positive family history.

FTD and ALS are on a continuum of broad neurodegenerative disorders, sharing common genetic basis^{2,3,4}.

Cystic fibrosis (CF) is an autosomal recessive disorder. Some studies suggest an association with ALS through TARDBP mutations⁵. To the best of our knowledge, this may be the first clinical case with a hypothetical genetic relation between FTD, ALS and CF.

METHODS

Non-systematic literature review on the eventual relationship between FTD, ALS and CF. Clinical data were collected during the inpatient admission. Informed consent was obtained. Genetic tests were performed in Institute for Molecular And Cell Biology – IBMC (Oporto University, Portugal).

DISCUSSION

The most common genetic finding in patients with FTD and ALS is the expanded hexanucleotide repetition in C9ORF72 gene, and less frequent mutations in the TARDBP and FUS/TLS genes.

Although the relationship between FTD with ALS and CF is not described, some authors suggest a common pathway between ALS and CF. Interestingly, the genetic study performed did not reveal any genetic alteration on the studied genes, including the TARDBP one.

Although his mother has dementia of Alzheimer's type, the patient clinical assessment and investigation were not suggestive of it, with biomarkers having a helpful role in that distinction.

Not all mutations involved in FTD, ALS and CF are identified and the relation between those entities should be clarified. Since CF is an autosomal disease it means that both parents are carriers. This means that probably we may be in the presence of a new common and unknown genetic cause of FTD, ALS and CF.

CASE REPORT

We report a 59 year-old male who had been unemployed and divorced for 7 years. There is a positive family history of dementia of Alzheimer's type in his mother. Also, his 15-years-old daughter died with respiratory complications of CF ($\Delta 508$ and A561 E mutations).

GENOGRAM

TIMELINE

In June of 2018, the patient was brought to the emergency room by the police and he was admitted to the psychiatric inpatient unit, under the Portuguese Mental Health Law.

DIAGNOSTIC EVALUATION

- Clinical manifestations associated with neuropsychological evaluation and brain MRI were compatible with **probable behavior variant FTD**.
- Muscular atrophy, spasticity, fasciculations and progressive dysphagia and dyspnea were detected. The performed eletromyography showed the presence of **definitive criteria for bulbar ALS**.
- Genetic test did not reveal expanded hexanucleotide repetition in C9ORF72 gene (alleles with 2 and 8 GGGGCC).
- Multi-gene panel by Next Generation Sequencing (NGS) did not reveal any mutations of the following genes: CHCHD10, CHMP2B, CSF1R, DCTN1, FUS, GRN, MAPT, OPTN, PRKAR1B, SIGMAR, SQSTM1, TARDBP, TBK1, TREM2, TUBA4A, UBQLN2, VCP, hnRNPA1 and hnRNPA2B1.

REFERENCES

- [1] Bang, J., Spina, S., & Miller, B. L. (2015). Non-Alzheimer's dementia 1 Frontotemporal dementia. *The Lancet*, 386(10004), 1672–1682.
- [2] Verma, A. (2014). Tale of two diseases: Amyotrophic lateral sclerosis and frontotemporal dementia. *62*(4).
- [3] Ji, A., Zhang, X., Chen, W., & Huang, W. (2017). Genetics insight into the amyotrophic lateral sclerosis / frontotemporal dementia spectrum. 145–154.
- [4] Lee, S., & Huang, E. J. (2017). Modeling ALS and FTD with iPSC-derived neurons. *Brain Research*, 1656, 88–97.
- [5] Lo, C., Cooper-knock, J., Garrard, K., Martindale, J., Williams, T., & Shaw, P. (2013). Concurrent amyotrophic lateral sclerosis and cystic fibrosis supports common pathways of pathogenesis.

ACKNOWLEDGEMENT

Dra Sara Vacas, Psychiatrist, Hospital Beatriz Ângelo.
Dra Isabel Conceição, Neurology Service, CHULN.
Dra Ana Rebelo, Neuropsychologist, Psychiatry and Mental Health Service, CHULN.
Dra Patrícia Arinto, Dra Ana Lopes, Dra Isabel Alonso, Molecular Geneticists of IBMC.