THE UNKNOWN ROAD FROM MANIA TO MORIA: A CASE REPORT WITH A NEW ASSOCIATED GENE HETEROZYGOTY

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INTRODUCTION:

- Recent evidence on Bipolar Disease (BD) suggests it is a progressive condition with cognitive decline. Kraepelin description of chronic mania reminds us of the hallmark symptoms of the behavioral variant of Frontotemporal Dementia (FTD). It is well known that some FTD cases start with mania-like symptoms. Some authours have hypothetized a Frontal Lobe Syndrome (FLS) as a result of end-stage BD. Some other authors speculate that our perception of the natural course and outcome of chronic BD is altered by the use of medication.
- DCTN1 codes for the largest dynactin subunit, playing an essential role in retrograde axonal transport and in neuronal autophagy. DCTN1 pathogenic mutations are rare, and may play a role in frontotemporal lobar degeneration; mutations in DCTN1-Exon 2, were found to cause Perry syndrome (PS), a rare inherited neurodegenerative disorder characterized by rapidly progressive early-onset parkinsonism, central hypoventilation, weight loss, insomnia and depression. In 2018 a novel co-segregating splice site variant in the DCTN1 gene was discovered in a family with a history of BD and major depressive disorder.
- MAPT is a gene well known for its association with FTD.

OBJECTIVES AND METHODS To present a clinical case linking FTD with BD. An unsystematic bibliographic review was conducted using the search engine Pubmed® and the keywords: “Bipolar Disease and Frontotemporal Dementia” and “DCTN1 and Frontotemporal Dementia” and “DCTN1 and Bipolar Disease”.

RESULTS

Clinical Case:

Man with a previous BD type 1 diagnosed in his early twenties, characterized by desinhibition and impulsivity, alongside excessive consumption of alchool and benzodiazepines, plus compulsive shopping. At the age of 44 he started behavioural changes with lack of insight, culminating over the years in a severe executive dysfunction, apathy, lack of self-care, hiperorality and hipersexuality, weight loss, parkinsonism and severe lack of musculoskelitical postural tonus at the current age of 58, wich deserved him the diagnosis of FTD; concomitantly, he developed severe sleep aphnea with need of mechanical ventilation. He has both family history of BD and undiagnosed *dementia*.

Complementary Exams:

- A wide range of blood, neurological and neurophysiological exams were performed but resulted normal or unspecific
- Cranial – CT: “(...) Moderate supratentorial ventricular enlargement as well as (...) corticosubcortical atrophy(...)”
- A genetic battery test for FTD scored heterozigoty for both the MAPT and DCTN1 genes; both these variants have unknown clinical meaning:

- *DCTNM1 (NM_004082,4)-c.3146G>A(p.(Arg1049Gln)) – Exon 26, rare variant rs72659383*

- *MAPT (NM_001123066.3) – c.1535C>A (p.(Pro512His)) – Exon 10, rare variant rs 192236920*

Differential Diagnosis:

- **1st Hypothesis – FTD:** lack of inhibition, apathy, emotional withdraw, irritability and even parkinsonism, are well known symptoms of FTD; this patient condition progressed over time, with a crescendo of cognitive impairments, and with positive cerebral atrophy and positive MAPT heterozygosity

- **2nd Hypothesis – Frontal Lobe Syndrome associated with BD:** although there is behavioural and functional impairments, such condition would not *progress* over time and should cause almost no frontal/temporal atrophy or hypoperfusion

- **3rd Hypothesis – Perry Syndrome:** mood/personality change, parkinsonism and age of onset are similar in PS and FTD; however, this clinical case has a disease course of 14 years, while the prognosis of PS is usually a 5 year life-expectancy; PS is caused by known mutations on exon 2, not exon 26

CONCLUSIONS Is there a specific kind of frontal dementia/frontal dysfunction following BD, or is there a link between BD and FTD? Does this case illustrate two different time frames of the same disease, or two (maybe three?) different / competing diseases? Can this be an atypical case of Perry Syndrome? Does the use of current medication impairs our perception of the evolution of chronic mania? Will our current classification of mental disorders continue to make sense in the era of genetic medicine?

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