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BIPOLAR DISORDER PROGRESSION TO DEMENTIA WITH FRONTAL FEATURES. A SCOPING REVIEW PROTOCOL

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Abstract

Background: A subset of patients with bipolar disorder (BD) develop a midlife cognitive/behavioral decline that overlaps with the clinical features of behavioral variant Frontotemporal Dementia (bvFTD). Several case reports and case series have described different clinical features and outcomes of a frontal cognitive/behavioral decline in patients with history of BD. Given that this presentation is scarcely reported, a first step to better characterize this specific condition is to perform an evidence synthesis report. **Objective**: This scoping review protocol aims to describe whether patients with history of BD who later develop a dementia syndrome with frontal cognitive/behavioral decline exhibit different clinical features and patterns of progression. **Information sources**: Studies will be retrieved from MEDLINE (PubMed), PsychINFO, EMBASE and Google Scholar, no other sources will be considered. **Inclusion criteria**: Studies describing patients with an established diagnosis of BD preceding a later development of dementia with frontal cognitive/behavioral decline. **Exclusion criteria**: Studies written in languages different than Spanish or English or French that could not be appropriately translated, or whose full text files could not be retrieved, and studies describing manic or BD symptoms, but not an antecedent history consistent with bipolar disorder, as a clear prodrome of bvFTD diagnosis. Data will be extracted by two researchers and verified by agreement. This protocol complies with the PRISMA-P, PRISMA ScR and JBI manual for evidence synthesis scoping review guidelines.

Keywords: *frontotemporal, bipolar disorder, frontal dementia, cognitive decline, behavioral decline, late onset bipolar disorder*

Introduction

Bipolar Disorder (BD) is an affective disorder with a variable course and elevated risk of later dementia.[1,2] A subset of patients with BD develop a progressive pattern of cognitive decline that may include dysfunction referable to the frontal or temporal lobes, some of whom meet criteria for behavioral variant Frontotemporal Dementia (bvFTD). [3–5]

The cognitive impairment in young adult BD population is well known. Classically BD impairs multiple cognitive domains, including verbal memory, executive function, attention, processing speed and theory of mind even during euthymia. [3,6] Despite the current evidence suggesting that cognitive decline in BD is not progressive [7,8] a steeper cognitive decline has been recognized in Older Adults with Bipolar Disorder (OABD), a term used to describe people ≥ 50 to 60 years old with an established diagnosis of BD either with early/classic onset BD (henceforth referred as EOBD) or late onset BD (henceforth referred as LOBD). OABD cognitive decline is manifested by deficits of verbal learning and verbal and visual memory, and milder deficits in processing speed, working memory, cognitive flexibility, verbal fluency, psychomotor function, executive functions, attention, inhibition, and recognition compared with healthy controls.[9] Despite this cognitive profile, which has been replicated in different studies including in OABD[10], a small subset of patients develop a decline characterized by severe frontal cognitive and/or behavioral symptoms that often is hard to distinguish from bvFTD and is not currently categorized with current diagnostic criteria.[4]

Lebert and colleagues described a particular presentation with frontal features including executive and behavioral dysfunction and slow progression after 6 years of follow up in 13 OABD patients with EOBD. Further, this group of patients did not fulfill clinical diagnostic criteria for any specific neurodegenerative disease, suggesting a dementia phenotype that may represent a "post-bipolar dementia syndrome".[5]

Subsequently, case reports described two OABD patients with EOBD and mutations in the progranulin gene (GRN), associated with familial FTD, one of whom qualified for a formal diagnosis of definite bvFTD and the other for non-fluent primary progressive aphasia (nfPPA). [11] Following these reports, associations between FTD and OABD were proposed, and additional descriptions were published of patients with EOBD or LOBD progressing over years to different subtypes of dementia with frontal clinical features, including reports of bvFTD[12,13], a non-progressive bvFTD state known as bvFTD phenocopy[14] or a particular type of dementia with frontal features and slow progression not fulfilling the clinical diagnostic criteria for bvFTD or other neurodegenerative disease [14,15].

Study Rationale

Some systematic reviews[1,2,16] addressing topics of BD and FTD are currently available. However, these are focused on the analysis of differences between BD and FTD, or BD progression to "unspecified dementia". There is one non-systematic narrative review describing BD features among patients with an established diagnosis of FTD [4] that is limited to FTD diagnosis. Furthermore, the "frontal variants" of Alzheimer Disease (AD) could be easily misclassified as FTD, we will extend our search looking for behavioral and dysexecutive AD variants. Given that reports of patients with a history of BD developing a "frontal dementia phenotype" or the progression to an established FTD diagnosis are scarce; we consider that a scoping review design to be suitable for our objectives.

The clinical categorization of patients with OABD either with EOBD or LOBD onset history, who develop frontal cognitive/behavioral dysfunction is challenging. The progression and association of cognitive decline with frontal symptoms in patients with BD is not completely understood. The characterization of patients that start with EOBD or LOBD and show a progression to some form of dementia with frontal symptoms is an important next step to facilitate identification of mechanisms, modifiable risk factors and treatment development.

Methods

Research questions

Table 1. Research questions are described as follows according to PCC, PFO and PICo frameworks

Question type	Framework	Description
Main research question	PCC (**P**opulation, **C**oncept, **C**ontext)	In patients with a prior diagnosis of BD(P), which are the clinical features and patterns of progression (C) of frontal cognitive/behavioral decline (C)?
Secondary research question 1	PFO [**P**opulation, **P**rognostic **F**actors (or models of interest), Outcome]	In patients with a prior history of BD (P), is dementia with frontal cognitive/behavioral decline (F) a syndrome with different clinical features and patterns of progression) (O)?
Secondary research question 2	PICo (**P**opulation, **P**henomenon of **I**nterest, **C**ontext)	In patients with EOBD or LOBD (P), are patterns of progression different (I) when dementia with frontal cognitive/behavioral decline is present (Co)?
Secondary research question 3	PICo (**P**opulation, **P**henomenon of **I**nterest, **C**ontext)	In patients with BD (P), do the quantity or quality of affective clinical features vary (I) among the different types of patterns of progression to dementia(s) with frontal cognitive/behavioral decline (Co)?

Objectives

- The primary objective is to describe if a dementia syndrome with frontal cognitive/behavioral decline has different clinical features and patterns of progression in patients with a prior diagnosis of BD.

Secondary objectives are:

- To explore if documented cases of patients with history of EOBD or LOBD who later develop dementia with frontal cognitive/behavioral decline exhibit different patterns of progression (e.g. neurodegenerative, unknown etiology, etc).
- o describe and compare the clinical features of BD among those who exhibit a progression to a known neurodegenerative disease with frontal cognitive/behavioral impairment (bvFTD, bvAD, nfPPA, svPPA, others) or to another not yet categorized dementia with frontal-temporal cognitive/behavioral decline.

Protocol development

Determination of review type was performed according to the research questions and objectives using an online tool and results indicated a scoping review which is available at https://rightreview.knowledgetranslation.net/map/results?id=15127&code=J5Oe1xPMqp.

The consultation of the International Prospective Register of Systematic Reviews (PROSPERO) and the Open Science Framework (OSF)searching for ongoing protocols of systematic or scoping reviews related to our research questions did not retrieve relevant records (November 17th, 2022).

The protocol for this scoping review complies with the JBI Manual for Evidence Synthesis as well as the Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA 2020), and the PRISMA extensions for protocols (PRISMA-P), and scoping reviews (PRISMA-Scr).

Search strategy

A trained researcher elaborated our search strategy. This strategy was not adapted from any previous protocol and is reported according PRISMA-ScR. Published studies will be retrieved from MEDLINE (PubMed), Embase and PsycINFO.

Search algorithms were elaborated using an online tool and are publicly available (https://app.2dsearch.com/new-query/638d28eed8e8fd000491a015). The algorithms will be adjusted using the same tool described above for each of the different databases. Additionally, we will perform a search in Google Scholar including the first 100 results using Publish or Perish software.

Articles written in languages different from Spanish, English and French will be included if they can appropriately be translated using Google translate and/or Deepl or if appropriate translations are available. No additional filters will be applied for the search (e.g. time range, full text, etc.). For those studies whose full-text files could not be retrieved we will contact the author(s). No additional search sources will be considered.

Duplicates will be identified using Covidence and Zotero. Followed by a manual revision only the earliest publication will be included.

The screening process (title/abstract stage) will be performed using Covidence and will be pilot-tested with a random sample of 25 studies. Screening steps will include title/abstract and full text. The later will be used for those studies selected for inclusion after the first screening stage. Eligibility will be assessed by two independent researchers using Covidence and discrepancies in selected articles will be resolved in agreement according to the inclusion and exclusion criteria. After six months of initial search and before final analysis a new search will be run to identify new published studies for potential inclusion. Search results will be displayed in a PRISMA flow diagram.

Table 2. Definitions of variables according to CoCoPop framework.

Condition	bvFTD case: Definition of possible, probable, or definite bvFTD according to specific clinical diagnostic criteria.[19] Possible, probable or definite cases of Behavioral variant Alzheimer Disease (bvAD), defined according specific clinical research criteria.[20] Possible or definite cases of Dysexecutive variant Alzheimer Disease (dAD), defined according specific clinical research criteria. [21] Primary progressive aphasia case: Definition of possible, probable, or definite nfPPA, svPPA or lvPPA according to specific clinical diagnostic criteria [22] Other type of frontal cognitive/behavioral decline will be defined as: A case with
Context	Clinical detailed descriptions including features of symptoms, clinical batteries, structural brain imaging, functional brain imaging (SPECT/PET), pathology reports, gene mutations reports, and other biomarkers) Progression of dementia will be defined as a decline in clinical features on follow up either with evidence of a detailed clinical description (cognitive symptoms and neurological examination) and/or objective measures with cognitive/behavioral batteries and/or positive biomarkers for a known neurodegenerative disease.
Population	Bipolar Disorder: Case definition according to DSM 5 criteria (at least one episode of mania). [17] LOBD: Definition of BD with an onset equal or later than 40 years age according to definition from The International Society of Bipolar Disorders Task Force.[18]

Eligibility criteria

Inclusion Criteria

Studies describing patients with an established diagnosis of BD according to DSM 5 diagnostic criteria who later develop a dementia with cognitive frontal/behavioral decline. Studies should include details of progression; this means, a follow up of the case(s) at least at two different times. Studies methods may include original reports, original case reports/case series, other observational study designs (cohort, case-control), clinical trials (either randomized or non-randomized), systematic reviews, meta-analysis, and we also are planning to include narrative reviews, letter(s) to the editor, conference proceedings, or other type of article describing BD and progression to frontal cognitive/behavioral decline. Only studies analyzing clinical data in humans will be considered.

Exclusion criteria

Articles in languages other than English, Spanish or French that cannot be appropriately translated.
Duplicated references.
Studies whose full text cannot be retrieved
Studies describing manic or depressive BD symptoms as a clear prodrome or clinical manifestations of bvFTD diagnosis or other neurodegenerative disease, without an antecedent history consistent with BD. Studies describing patients with BD who later develop mild cognitive impairment. Descriptions of manic or depressive symptoms as the cause of dementia syndrome.

Data charting

Data will be collected by one searcher and verified by another using predefined criteria and Covidence. Discrepancies will be solved with an agreement between the main two searchers. An extraction format will be pilot tested with a random sample of 25 studies and the format may be adjusted as necessary. Studies with original data (case reports, case series, cohorts, systematic reviews etc.) and without original data (narrative reviews, letter(s) to the editor, etc.) will be analyzed separately. Results will be displayed in tables.

The main outcomes of interest are the following:
Studies with original data: 1) Clinical features of BD (age at onset, treatment(s), family history of psychiatric disorders and/or neurodegenerative diseases, number of manic episodes, number of depression episodes, definition of treatment resistant BD, number of years of evolution prior to frontal cognitive/behavioral decline, history of psychosis). 2)Clinical features of frontal cognitive/behavioral decline. Including each symptom described, either cognitive (executive dysfunction, working memory, etc.), behavioral (disinhibition, apathy, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, etc.) and/or neurological (motor neuron disease, aphasia, movement disorders, etc.), and inclusion of cognitive/behavioral clinical batteries, if any. 3)Biomarkers of neurodegeneration/progression (structural brain imaging, functional brain imaging, genes, plasma or CSF Nfl, tau protein, amyloid protein, other proteins. Detailed descriptions of progression including a clear decline in cognitive and/or neurological symptoms in at least 2 different evaluations, describing the mean time between first and second cognitive/behavioral evaluation).

Studies without original data: we will register the same variables described above if they are available.

Data synthesis

Data summaries from original data will be displayed in table(s) figures or graphs. Other types of review articles without original data will be presented as a narrative synthesis. Results will be presented as originally reported, no conversions will be applied if different measurement units are involved.

Registration

This scoping review protocol has been registered at the Open Science Framework https://doi.org/10.17605/OSF.IO/GP25A

Conclusions

This protocol has some strengths and limitations. The main objective is to clarify the dementia with frontal symptoms phenotype(s)in patients with a prior history of BD. Additionally, to describe the BD phenotype(s) of patients developing dementia with frontal symptoms.
There are few prior reports with a systematic search strategy describing patients with BD and their outcomes related to frontal cognitive/behavioral decline. We will take cautiously the history record of manic and depressive cases as it has been demonstrated that patients with BD rarely report the number of prior episodes accurately. [23] The results of this protocol will be valuable for the understanding of frontal cognitive and behavioral decline in patients with a previous history of BD.

Author's contributions

R.R.G. provided original idea, protocol development, topic expertise, drafted the manuscript and coordination of coauthors.
S.Y. contributed to the protocol methodology, review of manuscript.

E.F. provided original idea, topic expertise, review of manuscript and coordination of coauthors.
I.P.N. provided methodological expertise, contributed supervising the protocol methodology, review of manuscript.

References

1. Diniz BS, Teixeira AL, Cao F, Gildengers A, Soares JC, Butters MA, et al. History of Bipolar Disorder and the Risk of Dementia: A Systematic Review and Meta-Analysis. Vol. 25, American Journal of Geriatric Psychiatry. Elsevier B.V.; 2017. p. 357–62.
2. Azevedo de, Velosa J, Delgado A, Finger E, Berk M, Kapczinski F, et al. Systematic Review Or Meta-Analysis Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses ACTA PSYCHIATRICA SCANDINAVICA. Acta Psychiatr Scand. 2020;2020:510–21.
3. Bora E, Bora E. Neuropsychological functioning and neuroimaging in bipolar disorder: Evidence of neuroprogression. In: Neuroprogression in Psychiatry. Oxford University Press; 2019. p. 161–74.
4. Mendez MF, Parand L, Akhlaghipour G. Bipolar disorder among patients diagnosed with frontotemporal dementia. J Neuropsychiatry Clin Neurosci. 2020;32(4):376–84.
5. Lebert F, Lys H, Haëm E, Pasquier F. Dementia following bipolar disorder. Encephale. 2008; 34(6):606–10.
6. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: A systematic review of cross-sectional evidence. Bipolar Disord. 2006; 8(2):103–16.
7. Samamé C, Martino DJ, Strejilevich SA. Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. J Affect Disord [Internet]. 2014;164:130–8. Available from: https://pubmed.ncbi.nlm.nih.gov/24856566/
8. Samamé C, Cattaneo BL, Richaud MC, Strejilevich S, Aprahamian I. The long-term course of cognition in bipolar disorder: a systematic review and meta-analysis of patient-control differences in test-score changes. Psychol Med [Internet]. 2022; 52(2):217–28. Available from: https://pubmed-ncbi-nlm-nih-gov.proxy1.lib.uwo.ca/34763735/
9. Montejo L, Solé B, Jiménez E, Borràs R, Clougher D, Reinares M, et al. Aging in bipolar disorder: Cognitive performance and clinical factors based on an adulthood-lifespan perspective. J Affect Disord. 2022; 312:292–302.
10. Montejo L, Torrent C, Jiménez E, Martínez-Arán A, Blumberg HP, Burdick KE, et al. Cognition in older adults with bipolar disorder: An ISBD task force systematic review and meta-analysis based on a comprehensive neuropsychological assessment. Bipolar Disord [Internet]. 2022; 24(2):115–36. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bdi.13175
11. Cerami C, Marcone A, Galimberti D, Villa C, Scarpini E, Cappa SF. From genotype to phenotype: Two cases of genetic frontotemporal lobar degeneration with premorbid bipolar disorder. J Alzheimer's Dis. 2011;27(4):791–7.
12. Meisler MH, Grant AE, Jones JM, Lenk GM, He F, Todd PK, et al. C9ORF72 expansion in a family with bipolar disorder. Bipolar Disord. 2013;15(3):326–32.
13. Papazacharias A, Lozupone M, Barulli MR, Capozzo R, Imbimbo BP, Veneziani F, et al. Bipolar disorder and frontotemporal dementia: An intriguing association. J Alzheimer's Dis [Internet]. 2017;55(3):973–9. Available from: https://pubmed.ncbi.nlm.nih.gov/27802240/
14. Dols A, Krudop W, Möller C, Shulman K, Sajatovic M, Pijnenburg YAL. Late life bipolar disorder evolving into frontotemporal dementia mimic. Neuropsychiatr Dis Treat [Internet]. 2016 Sep 7;12:2207–12. Available from: https://pubmed.ncbi.nlm.nih.gov/27660450/
15. A M, G C, P V, E M, L R, D S, et al. Bipolar disorder and dementia: where is the link? Psychogeriatrics [Internet]. 2011;11(1):60–7. Available from: https://pubmed.ncbi.nlm.nih.gov/21447111/
16. MR M, S P, D D, F K, TA C. Bipolar Disorder and Frontotemporal Dementia: a Systematic Review. Acta Psychiatr Scand [Internet]. 2021; Available from: https://pubmed.ncbi.nlm.nih.gov/34390495/
17. Severus E, Bauer M. Diagnosing bipolar disorders in DSM-5 [Internet]. Vol. 1, International Journal of Bipolar Disorders. SpringerOpen; 2013. p. 1–3. Available from:https://journalbipolardisorders.springeropen.com/articles/10.1186/2194-7511-1-14
18. Sajatovic M, Strejilevich SA, Gildengers AG, Dols A, Al Jurdi RK, Forester BP, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force [Internet]. Vol. 17, Bipolar Disorders. Blackwell Publishing Inc.; 2015. p. 689–704. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bdi.12331
19. 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. 2011;134(9):2456–77.
20. Neuroscience A, Universiteit V, Memory C, Neuroscience A, Francisco S, Imaging B, et al. 1,2* ,. 2021;1–31.
21. Townley RA, Graff-Radford J, Mantyh WG, Botha H, Polsinelli AJ, Przybelski SA, et al. Progressive dysexecutive syndrome due to Alzheimer's disease: a description of 55 cases and comparison to other phenotypes. Brain Commun. 2020;2(1):1–19
22. Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76(11):1006–14.
23. Martino DJ, Marengo E, Igoa A, Scápola M, Urtueta-Baamonde M, Strejilevich SA. Accuracy of the number of previous episodes reported by patients with bipolar disorder. Compr Psychiatry. 2016 Feb;65:122-7. doi: 10.1016/j.comppsych.2015.11.005. Epub 2015 Nov 24. PMID: 26774000.