frontiers | Research Topics

Case reports in aging psychiatry

Edited by
Vincenza Frisardi, Yoo Hyun Um, Ram J. Bishnoi, Shaheen E. Lakhan and Takuma Inagawa

Published in
Frontiers in Psychiatry

FRONTIERS EBOOK COPYRIGHT STATEMENT

The copyright in the text of individual articles in this ebook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this ebook is the property of Frontiers.

Each article within this ebook, and the ebook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this ebook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or ebook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714
ISBN 978-2-8325-4386-3
DOI 10.3389/978-2-8325-4386-3

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Case reports in aging psychiatry

Topic editors

Vincenza Frisardi — Geriatric Unit, Department of Continuous Care and Integration, IRCCS AOUBO Policlinico Sant'Orsola, Italy

Yoo Hyun Um — Catholic University of Korea, Republic of Korea

Ram J. Bishnoi — University of South Florida, United States

Shaheen E. Lakhan — Click Therapeutics, Inc., United States

Takuma Inagawa — National Center of Neurology and Psychiatry, Japan

Citation

Frisardi, V., Um, Y. H., Bishnoi, R. J., Lakhan, S. E., Inagawa, T., eds. (2024). *Case reports in aging psychiatry*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-4386-3

Table of contents

04 Editorial: Case reports in aging psychiatry
Vincenza Frisardi

07 Editorial: Case reports in aging psychiatry
Ram J. Bishnoi

09 Case report: Delusional infestation in dementia with Lewy bodies
Daiki Taomoto, Hideki Kanemoto, Yuto Satake, Kenji Yoshiyama, Masao Iwase, Mamoru Hashimoto and Manabu Ikeda

16 Case Report: Depression × dementia with Lewy bodies in the elderly: The importance of differential diagnosis
Alexandre M. Valença, Cláudia Cristina Studart Leal, Gustavo C. Oliveira, Talvane M. de Moraes, Antonio E. Nardi and Mauro V. Mendlowicz

22 Case report: Amnestic mild cognitive impairment in multiple domains associated with neurofascin 186 autoantibodies: Case series with follow-up and review
Niels Hansen, Anne Sagebiel, Kristin Rentzsch, Sina Hirschel, Jens Wiltfang, Björn H. Schott and Bartels Claudia

28 Case report: Anti-CARPVIII autoantibody-associated mixed dementia
Niels Hansen, Bianca Teegen, Sina Hirschel, Jens Wiltfang, Björn H. Schott, Berend Malchow and Bartels Claudia

32 Anti-leucine-rich glioma-inactivated 1 encephalitis revealed by a manic episode: insights from frontal lobe dysfunction in neuropsychiatry through neuropsychology and metabolic imaging. A case report
Federica Porpiglia, Maxime Guillaume, Evangeline Bliaux, Dimitri Psimaras, Pierre Decazes, Olivier Guillin, Maud Rothärmel and Alexandre Morin

38 Case report: Mixed dementia associated with autoantibodies targeting the vesicular glutamate transporter 2
Niels Hansen, Bianca Teegen, Sina Hirschel, Jens Wiltfang, Björn H. Schott, Claudia Bartels and Caroline Bouter

43 A case with burning mouth syndrome followed by dementia with Lewy bodies: a case report
Motoko Watanabe, Wataru Araki, Chihiro Takao, Chizuko Maeda, Risa Tominaga, Yasuyuki Kimura, Gayatri Nayanar, Trang Thi Huyen Tu, Takashi Asada and Akira Toyofuku

48 Lithium management of periodic mood fluctuations in behavioural frontotemporal dementia: a case report
Vicent Llorca-Bofí, Iolanda Batalla, Maria Ruiz-Julián, Marina Adrados-Pérez, Esther Buil-Reiné, Gerard Piñol-Ripoll, Xavier Gallart-Palau and Aurora Torrent

frontiers | Frontiers in Psychiatry

TYPE Editorial
PUBLISHED 01 November 2023
DOI 10.3389/fpsyt.2023.1305521

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Federica Piras,
Santa Lucia Foundation (IRCCS), Italy

*CORRESPONDENCE
Vincenza Frisardi
✉ vincenza.frisardi@aosp.bo.it

RECEIVED 01 October 2023
ACCEPTED 11 October 2023
PUBLISHED 01 November 2023

CITATION
Frisardi V (2023) Editorial: Case reports in aging psychiatry. *Front. Psychiatry* 14:1305521. doi: 10.3389/fpsyt.2023.1305521

COPYRIGHT
© 2023 Frisardi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Case reports in aging psychiatry

Vincenza Frisardi*

Geriatric Acute Care, Orthogeriatric Unit and Center for Diagnosis of Cognitive Disorders and Dementia, Istituto di RicerCa a Carattere Scientifico (IRCCS), Azienda Ospedaliera Universitaria Bologna (AOUBO), Bologna, Italy

KEYWORDS

aging, psychiatric, neurodegenerative disease, dementia, ageism, mood disorders, depression, late-onset

Editorial on the Research Topic
Case reports in aging psychiatry

According to the World Health Organization (WHO)'s projected demographic trends, it is expected that by 2050 about 20% of the population will be over 65 years of age, and 15% of this age group will have psychiatric disorders (1). Neuropsychiatric symptoms, such as depression, anxiety, agitation, and dysphoria, are among the most common psychiatric disorders in old age. Improvements in patient outcomes and the ability to hypothesize alternative diagnoses can result from advances in clinical practice that have been conducted as a result of significant information and new ideas being presented in case reports. The importance of having access to case reports in the emerging, demanding, and challenging field of aging psychiatry has increased. Sharing such valuable and trustworthy information helps us to understand pathogenesis, target new molecular pathways, and improve the quality of care and treatment. Another important aspect of publishing case reports is to produce knowledge that will help the medical community understand more about individualized medicine.

In recent decades, the field of geriatric psychiatry has developed into an independent discipline, incorporating elements of psychiatry, neurology, and geriatric medicine. In this perspective shift, a life-span orientation could be helpful for the recognition of all processes relevant to late-life disorders that often begin in midlife and could be most therapeutically tractable in their early phases. Therefore, the term geriatric psychiatry could be obsolete soon (2). This Research Topic aims to highlight unique cases of patients presenting with an unexpected/unusual diagnosis, treatment outcome, or clinical course. Case reports in this Research Topic provide insight into the differential diagnosis, decision-making, and clinical management of unusual cases and are a valuable educational tool for practitioners and investigators.

Mood disorders, psychosis, and dementia

In light of a paradigm shift, mood disorders and psychosis in older adults are considered a heterogenous later-life neuropsychiatric syndrome caused by pathophysiologically distinct brain disorders such as Alzheimer's disease (AD), vascular dementia, mixed-dementia, Lewy body dementia (LBD), or frontotemporal dementia, with differences in neuropathology and initial clinical presentation (3). Early diagnosis of LBD can be challenging, particularly in the context of differentiation with the spectrum of mood disorders. Valença et al. show a case

of LBD diagnosed as a refractory depression rather than dementia, highlighting how this missed diagnosis could have serious negative consequences (including legal repercussions).

Clinical cases are also crucial to increase knowledge of clinical presentations of psychiatric symptoms in the context of the neurodegenerative process, contributing to a more agile decision-making process. Taomoto et al. report two cases of LBD presenting with delusional infestation and responding better to AChEI than antipsychotics. When delusional infestation (or Ekbom syndrome) occurs, patients are generally diagnosed with delusional disorders, schizophrenia, depression, and dementia and mistaken treatments prescribed.

Aging and mental health: new frontiers

Late-life neuropsychiatric disorders result from a complex interaction between psychopathology and aging processes affecting brain structure and function (4). To study these interactions, researchers of geriatric mental health have embraced an interdisciplinary approach spanning genetics, molecular biology, cellular physiology, and immunology in addition to maintaining traditional collaborations with geriatric medicine and neurology. Furthermore, new attention has been given to early markers of the preclinical stage of dementia and new underlying biological mechanisms. Neurofascin 186 autoantibodies are known to occur in peripheral nervous system disorders. Recently, additional central nervous system involvement has been reported in conjunction with neurofascin 186 autoantibodies. Hansen et al. (a) suggest a relationship between the neurofascin 186 antibody-associated autoimmunity and the amnestic mild cognitive impairment that occurs in multiple domains, but the lack of immunotherapy interventions in the presented cases requires further studies to confirm and clarify its role. Immune system and blood–brain barrier dysfunction are implicated in the development of dementia syndrome, but their causal role remains not completely understood. Based on some extensive *in silico*, *in vitro*, and *in vivo* studies, a new mechanistic model of AD as a brain-centric autoimmune disorder has been proposed in response to various initiating stimuli, leading to an interdependent immune- and proteinopathic process (5). Autoimmune-based psychiatric syndromes have emerged as a novel category of disorders. Lessons from autoimmune encephalitis and psychosis have revealed specific immunotherapeutic agents termed first- and second-line immunotherapies also applied in patients presenting autoantibody-associated psychiatric syndromes. Furthermore, randomized, placebo-controlled trials are needed to evaluate immunotherapies in patients with autoimmune-based psychiatric syndromes and to prove their efficacy, inferiority, or superiority over other immunotherapies.

Cancer and neuropsychiatric disorders could share some intriguing etiological commonalities (6). Hansen et al. (b) report an interesting case of dementia syndrome associated with anti-carbonic anhydrase-related protein VIII (CARPVIII) autoantibodies. CARPVIII is reported to be associated with colorectal and breast cancer as well as to paraneoplastic cerebellar degeneration. In addition to dementia's possible autoimmune origin, these authors found circumstantial evidence of a vascular component. Due to anatomical fiber projections, it is conceivable that cognition may be chronically impaired in patients with persistent CARPVIII autoantibodies due to dysfunctional connectivity between the cerebellum, cortex, and hippocampus. Another possibility is that preexisting vascular dementia characterized by severe cerebral microangiopathy is exacerbated by an inflammatory process detected by CARPVIII antibodies [Hansen et al. (b)].

Finally, because of the symptoms overlapping between late-life depressive syndromes and Alzheimer's like dementia, some common underlying mechanisms have been proposed, such as glutamatergic pathway signaling (4). Vesicular glutamate transporter 2 (VGlut2), as a part of the glutamatergic systems, seems to play a specific role. Antibodies against the VGlut2 transporter could cause synaptic dysfunction, and for the first time in the context of cognitive impairment, Hansen et al. (c) describe the diagnosis of clinically and cerebrospinal fluid (CSF)-based AD associated with VGlut2 autoantibodies. However, a pathophysiological basis as the cause of the symptoms remains speculative and cannot be proven at present, requiring further investigation in larger cohorts to be conclusive.

Due to double stigmatization (age and mental illness), insufficiently qualified personnel, and lack of care structures for behavioral and psychological disorders in dementia BPSD in acute setting, the management of BPSD is still challenging for healthcare professionals and affects the quality of care of older adults suffering from these conditions (7). The diagnosis and treatment of older patients with psychiatric illnesses require specific abilities, skills, and attitudes to adequately classify psychiatric symptoms (e.g., major depression in old age vs. late-onset bipolar disorders), manage behavioral disturbances (e.g., due to neurocognitive disorders), identify overlapping symptoms to reach the appropriate diagnosis and treatment, manage the complex clinical situations, involve multimorbidity and polypharmacy, as well as master communication and specific tasks and conflicts in the geriatric population. Moreover, some late-onset disorders are unrecognized and very often are attributed to the neurodegenerative process increasing the burden of diagnostic flow without a clear benefit for patients and their caregivers. This prejudice could delay diagnosis, exposing the patient to a risk of being labeled as suffering from another disorder or leading to chronic symptoms and lack of subsequent therapeutic success. Porpiglia et al. report the case of a patient affected by limbic encephalitis (also known as antibody-mediated encephalitis) with neuropsychiatric features at the onset. In this case report, psychiatric-onset LE clouded the clinician's judgment, leading to a misdiagnosis, delayed treatment, and poor prognosis. This attitude to attributing neuropsychiatric symptoms to aging-related neurodegenerative diseases causes patients to be diagnosed as being affected by dementia with all the negative consequences for patients and society that this entails.

Perspective

In conclusion, this Research Topic provided significant clinical cases in the field of aging psychiatry. Further research is needed in aging psychiatry because older adults are more likely to experience mental health problems, and they may face unique challenges in accessing and receiving appropriate treatment. There is a need for a better understanding of the complex interplay between

mental health and aging, the psychological substrate of late-onset behavioral disorders, as well as the specific mechanisms underlying these relationships. Fighting agism and stigma toward mental health in old age is a priority. Despite limitations in drawing clear conclusions from the series of case reports, this Research Topic expands the spectrum of mechanisms underlying neurodegenerative disorders for which there is yet no available effective treatment on a large scale. Moreover it shed light on the importance of carefully analyzing each case where neuropsychiatric manifestations are the prevailing symptoms. This will prevent misdiagnosis and deleterious results and increase knowledge in this very fascinating and demanding field. Even if more resources are available for detecting, monitoring, and treating the most common pathologies in the elderly, more efforts are needed in research and clinical practice to make aging psychiatry more acknowledged. This Research Topic of articles is moving in this direction.

Author contributions

VF: Writing—original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

I thank the authors who submitted their findings and readers who will appreciate the aim of this Research Topic.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author declared that she was an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. World Health Organization. *Fact Sheet 381*. Geneva: World Health Organization. (2015). Available online at: http://www.who.int/mediacentre/factsheets/fs381/en/ (accessed September 30, 2023).

2. Rutherford BR, Taylor WD, Brown PJ, Sneed JR, Roose SP. Biological aging and the future of geriatric psychiatry. *J Gerontol A Biol Sci Med Sci*. (2017) 72:343–52. doi: 10.1093/gerona/glw241

3. Ismail Z, Creese B, Aarsland D, Kales HC, Lyketsos CG, Sweet RA, et al. Psychosis in Alzheimer disease — mechanisms, genetics and therapeutic opportunities. *Nat Rev Neurol*. (2022) 18:131–144. doi: 10.1038/s41582-021-00597-3

4. Frisardi V, Panza F, Farooqui AA. Late-life depression and Alzheimer's disease: the glutamatergic system inside of this mirror relationship. *Brain Res Rev*. (2011) 67:344–55. doi: 10.1016/j.brainresrev.2011.04.003

5. Meier-Stephenson FS, Meier-Stephenson VC, Carter MD, Meek AR, Wang Y, Pan L, et al. Alzheimer's disease as an autoimmune disorder of innate immunity endogenously modulated by tryptophan metabolites. *Alzheimers Dement (NY)*. (2022) 8:e12283. doi: 10.1002/trc2.12283

6. Frisardi V, Pollorsi C, Sambati L, Macchiarulo M, Fabbo A, Neviani F, et al. The Italian framework of bipolar disorders in the elderly: old and current issues and new suggestions for the geriatric psycho-oncology research. *Biomedicines*. (2023) 11:1418. doi: 10.3390/biomedicines11051418

7. Frisardi V, Davoli ML. The role of neurocognitive disorders in sustaining "ageism as a key factor for noninvasive ventilation failure". In: Esquinas AM, Fabbo A, Koc F, Prymus A, Farnik M, editors. *Noninvasive Mechanical Ventilation and Neuropsychiatric Disorders*. Cham: Springer. (2023).

frontiers | Frontiers in Psychiatry

TYPE Editorial
PUBLISHED 28 November 2023
DOI 10.3389/fpsyt.2023.1306422

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Federica Piras,
Santa Lucia Foundation (IRCCS), Italy

*CORRESPONDENCE
Ram J. Bishnoi
bishnoi@usf.edu

RECEIVED 03 October 2023
ACCEPTED 14 November 2023
PUBLISHED 28 November 2023

CITATION
Bishnoi RJ (2023) Editorial: Case reports in aging psychiatry. *Front. Psychiatry* 14:1306422. doi: 10.3389/fpsyt.2023.1306422

COPYRIGHT
© 2023 Bishnoi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Editorial: Case reports in aging psychiatry

Ram J. Bishnoi*

Department of Psychiatry and Behavioral Neurosciences, University of South Florida, Tampa, FL, United States

KEYWORDS

case reports (publication type), aging, dementia, neurocognitive disorder, atypical presentation

Editorial on the Research Topic
Case reports in aging psychiatry

Introduction

Case reports are an important part of scientific literature, where exceptional or novel situations, for which there exist no clear or deterministic data or evidence, are presented. These reports have immense educational value, and at times, they propose new hypotheses for further empirical evidence generation (1). In this special section of Aging Psychiatry, unusual presentations of dementing disorders, and their clinical expressions, are described from an etiopathological point of view.

Autoimmune dementia

Neural antibodies have been reported to cause neuroinflammation and, therefore, cognitive impairment. Hansen, Sagebiel et al. from the University of Goettingen, Germany, report three distinct cases of dementia syndrome associated with neural antibodies. The identification of these types of patients can have significant treatment implications and requires further research to characterize these patients for clinical identification. In a series of three cases, the first case describes the presence of autoantibodies toward VGlut2 (vesicular glutamate transporter 2) in addition to Alzheimer's pathology (Hansen, Teegen, Hirschel, Willfang, Schott, Bartels et al.).

Subsequently, a 75-year-old patient diagnosed with dementia exhibited moderate cerebral microangiopathy upon neuroimaging and tested positive for anti-CARPVIII autoantibodies during serum analysis. In light of both cerebrovascular alterations and the presence of neuroinflammation, the patient was diagnosed with mixed dementia, encompassing both vascular and autoimmune components (Hansen, Teegen, Hirschel, Willfang, Schott, Malchow et al.).

Finally, Hansen, Sagebiel et al. describe two patients who presented with mild cognitive impairment, and brain MRI showed microangiopathy. Neurofascin 186 antibodies were detected in serum in both patients. These cases highlight that neurofascin 186 antibodies not only cause peripheral neuropathy but can also induce central neuroinflammation. These cases add to the expanding literature on autoimmune dementia and argue for more research in this direction.

Unusual presentation of Lewy body dementia

Lewy body dementia (LBD) is the second most common neurodegenerative dementia, and its diagnosis, especially in early stages, can be challenging. Depression is a common comorbidity with LBD. The question of whether late-onset depression serves as a risk factor or a prodrome of dementia remains to be answered (2). Valença et al. present a case of a 73-year-old patient who was treated for refractory depression for 3 years while his cognitive functions deteriorated. The patient was eventually found to have biomarkers that confirmed LBD. This case highlights the importance of a clear understanding of the depression–dementia relationship.

In another noteworthy case series on LBD, Taomoto et al. reported two cases in which patients exhibited clinical symptoms of LBD accompanied by delusions of infestation. While hallucinations, particularly visual ones, are well-established features of LBD, this case series underscores the significance of recognizing tactile hallucinations as potential symptoms of LBD. Furthermore, it highlights the potential efficacy of acetylcholinesterase inhibitors in mitigating these distressing symptoms.

Unusual presentation of encephalitis

Porpiglia et al. present an unusual clinical presentation of anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis, a type of limbic encephalitis, which presented as a manic episode with cognitive symptoms. Treatment with intravenous immunoglobulins led to improvement of neuropsychiatric symptoms and corresponding changes in functional neuroimaging. This case not only serves to inform us about this unique and atypical presentation but also emphasizes the significance of identifying warning signs for the diagnosis. Additionally, complete recovery of this patient with immune system modulators provides a direction for future treatment research.

In summary, these cases present unique clinical scenarios that may not typically be considered during a routine clinical examination and treatment planning process. Moreover, the collection of such case studies provides a framework for initial data collection, eventually leading to newer conceptual categories. For example, autoimmune dementia and encephalopathies can present with a variety of symptoms as described by Hansen, Teegen, Hirschel, Willfang, Schott, Malchow et al.. These case reports prompt consideration of autoimmune phenomena in similar clinical presentations and propose a new research context. Research findings and learning from this area can have implications for more common neurocognitive disorders secondary to neurodegenerative and cerebrovascular disorders.

Author contributions

RB: Writing—original draft, Writing—review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Packer CD, Katz RB, Iacopetti CL, Krimmel JD, Singh MK. A case suspended in time: the educational value of case reports. *Acad Med.* (2017) 92:152–6. doi: 10.1097/ACM.0000000000001199

2. Piras F, Banaj N, Porcari DE, Piras F, Spalletta G. Later life depression as risk factor for developing dementia: epidemiological evidence, predictive models, preventive strategies and future trends. *Minerva Med.* (2021) 112:456–66. doi: 10.23736/S0026-4806.21.07571-6

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 10 November 2022
DOI 10.3389/fpsyt.2022.1051067

Check for updates

OPEN ACCESS

EDITED BY
Takuma Inagawa,
National Center of Neurology and Psychiatry, Japan

REVIEWED BY
Sanjeev Kumar,
University of Toronto, Canada
Sayuri Suwa,
Chiba University, Chiba, Japan
Yuki Konishi,
University of Occupational and Environmental Health Japan, Japan
Daichi Morioka,
Yamagata University, Japan

*CORRESPONDENCE
Hideki Kanemoto
hkanemoto@psy.med.osaka-u.ac.jp

SPECIALTY SECTION
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

RECEIVED 22 September 2022
ACCEPTED 28 October 2022
PUBLISHED 10 November 2022

CITATION
Taomoto D, Kanemoto H, Satake Y, Yoshiyama K, Iwase M, Hashimoto M and Ikeda M (2022) Case report: Delusional infestation in dementia with Lewy bodies.
Front. Psychiatry 13:1051067.
doi: 10.3389/fpsyt.2022.1051067

COPYRIGHT
© 2022 Taomoto, Kanemoto, Satake, Yoshiyama, Iwase, Hashimoto and Ikeda. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Case report: Delusional infestation in dementia with Lewy bodies

Daiki Taomoto[1], Hideki Kanemoto[1]*, Yuto Satake[1], Kenji Yoshiyama[1], Masao Iwase[1], Mamoru Hashimoto[1,2] and Manabu Ikeda[1]

[1]Department of Psychiatry, Osaka University Graduate School of Medicine, Suita, Japan, [2]Department of Neuropsychiatry, Kindai University Faculty of Medicine, Osakasayama, Japan

Background: Delusional infestation is characterized by delusions of being infested with parasites, vermin, or small insects and is frequently accompanied by tactile and visual hallucinations. Herein, we report two cases of dementia with Lewy bodies (DLB) with delusional infestation.

Case presentation: Case 1 was an 83-year-old man. At the age of 75, he began to show symptoms of rapid eye movement sleep behavior disorder. At the age of 83, he began to complain of visual hallucinations of people and delusional infestation with tactile and visual hallucinations of insects, resulting in the use of insecticides for non-existent insects. He also complained of mild amnesia and was admitted to our psychiatric ward for evaluation and treatment. After admission, the delusional infestation disappeared without any new medication. Based on our examinations, he was diagnosed with probable DLB with delusional infestation. He was treated with 5 mg/day of donepezil hydrochloride; his visual and tactile hallucinations disappeared, and the delusional infestation had not recurred at the 1-year follow-up. Case 2 was a 69-year-old woman. At the age of 60, she underwent clipping for subarachnoid hemorrhage (SAH). At the age of 65, she began to have visual hallucinations of people. At the age of 67, she began to complain of visual illusions in which she mistook lint for insects. At the age of 69, she developed delusional infestation and mild amnesia. She took various actions to get rid of these non-existent insects, including insecticide use, consulting an exterminator, and visiting several dermatologists. She eventually burnt her leg in an attempt to kill the non-existent insects. Based on our examinations, she was diagnosed with prodromal DLB in addition to SAH sequelae. We determined that her delusional infestation was caused by DLB rather than SAH sequelae based on the course of her symptoms. She was treated with a combination of 3 mg/day of donepezil hydrochloride and 12.5 mg/day of quetiapine. Thereafter, the delusional infestation partially improved, and she took no further action against non-existent insects.

10.3389/fpsyt.2022.1051067

Conclusion: Delusional infestation may be caused by DLB. Acetylcholinesterase inhibitors (AChEI) may be effective for delusional infestation in DLB, although antipsychotics may also be needed in severe cases.

KEYWORDS

Ekbom syndrome, delusional infestation, delusional parasitosis, tactile hallucination, dementia with Lewy bodies

Introduction

Delusional infestation, also known as delusional parasitosis or Ekbom syndrome, is characterized by delusions of being infested with parasites, vermin, or small insects (1), as well as tactile and visual hallucinations (2). Although patients with this syndrome are sometimes diagnosed with delusional disorders, schizophrenia, depression, and dementia, the neurobiological mechanisms are not fully understood (3).

Dementia with Lewy bodies (DLB) is the second most common type of neurodegenerative dementia in older adults after Alzheimer's dementia (4). Hallucinations and delusions are more common in patients with DLB than in patients with Alzheimer's dementia (5). Psychosis in older people are frequently developed in prodromal stage and early stage of dementia (6). However, there are only a few reports on delusional infestation in DLB (7–9). Herein, we report our experience with two patients with DLB and delusional infestation who were both safely treated with medication.

Case presentation

Case 1

This patient was an 83-year-old man with a junior high school education who worked in the printing industry until the age of 73. His past medical history included hypertension, hyperuricemia, and inguinal hernia, with no history of substance abuse or heavy drinking or a family history of neuropsychiatric illness. At the age of 75, he began moving his limbs while sleeping and falling out of bed, which was thought to be caused by rapid eye movement sleep behavior disorder. At the age of 83, he began to complain of visual hallucinations of people and delusional infestation with tactile and visual hallucinations of insects. He used insecticides for non-existent insects, although he had some insight into his own symptoms. He stated, "I saw some insects that were 5 mm to 1 cm in size. I couldn't touch them because they moved when I tried to touch them," "The insects crawled on my body and bit me. They sometimes come out of my anus," and "I think that this is a strange experience." When we pointed out that there were no insects, he agreed with us" He also complained of mild amnesia and was admitted to our psychiatric ward for evaluation and treatment. After admission, his delusional infestation disappeared without any new medication; however, he developed visual and tactile hallucinations of people. He said "I saw a man last night. He painted me with a slimy thing," and "A person in white clothes like a nurse touched me." The patient had no visible skin abnormalities, and no neurological abnormalities, including parkinsonism, were observed. His Mini-Mental State Examination (MMSE) scores fluctuated from 18 to 23, reflecting his fluctuating cognition level. Blood and cerebrospinal fluid test results were normal. An electroencephalogram showed unremarkable findings. Cranial magnetic resonance imaging (MRI) revealed diffuse very mild atrophy including the bilateral hippocampus (**Figure 1**). N-isopropyl-p-[^{123}I] iodoamphetamine (^{123}I-IMP) single-photon emission computed tomography (SPECT) revealed hypoperfusion in the bilateral occipital and parietal lobes (**Figure 1**). Furthermore, cardiac ^{123}I-metaiodobenzylguanidine scintigraphy revealed reduced myocardial uptake (heart-to-mediastinum ratio = early: 1.55; delayed: 1.26; **Figure 1**). Considering the results of all examinations, the patient was diagnosed with dementia because he showed progressive cognitive decline that interfered with his daily activities. Moreover, the patient had three core clinical features (rapid eye movement sleep behavior disorder, fluctuating cognition level, visual hallucinations) and one indicative biomarker (abnormal cardiac ^{123}I-metaiodobenzylguanidine scintigraphy) and was therefore diagnosed with probable DLB (10) with delusional infestation. He was administered 5 mg/day of donepezil hydrochloride; his tactile and visual hallucinations disappeared, and the delusional infestation did not recur. Therefore, we did not increase the donepezil hydrochloride to the recommended dose of 10 mg/day. At the follow-up examination 1 year later, his symptoms had not recurred and his MMSE score remained unchanged (11), as did his ability to perform activities of daily living. His family members expressed understanding of the cause of and required treatment for delusional infestation.

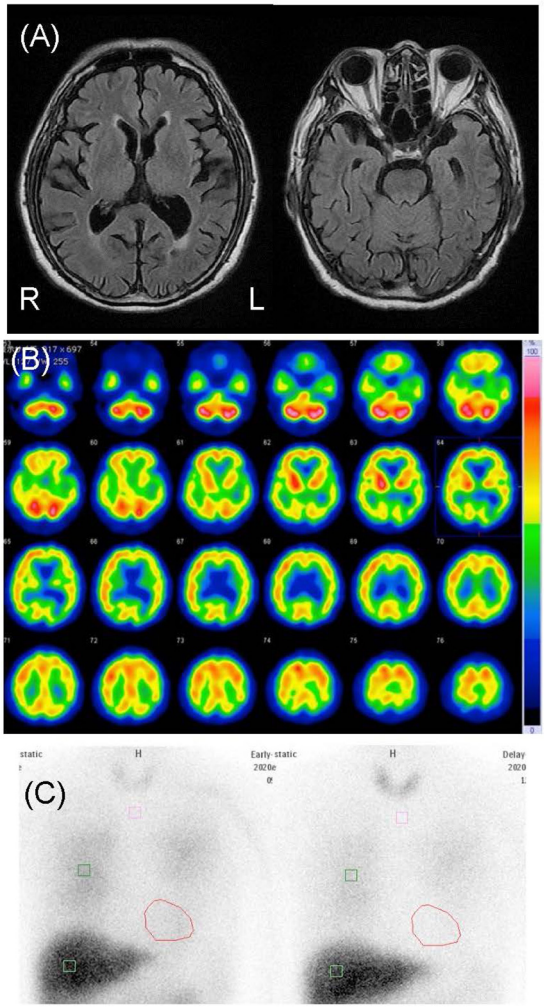


FIGURE 1
Neuroimages of case 1. **(A)** Cranial magnetic resonance images revealed diffuse mild atrophy including the bilateral hippocampus. **(B)** N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography revealed hypoperfusion in the bilateral occipital and parietal lobes. **(C)** Cardiac [^{123}I]-metaiodobenzylguanidine scintigraphy revealed heart-to-mediastinum ratios of 1.55 and 1.26 in the early and delayed phases, respectively.

Case 2

This patient was a 69-year-old woman who dropped out of high school and worked as a fashion model. Her past medical history included subarachnoid hemorrhage (SAH), symptomatic epilepsy following SAH, and hypertension. She had no family history of neuropsychiatric illness, nor did she have a history of substance abuse or heavy drinking. At the age of 60, she underwent clipping for SAH. At the age of 65, she began to have frequent visual hallucinations of people, although she had previously experienced visual hallucinations temporarily for a short period after the SAH clipping. She remembered the visual hallucinations she experienced after the clipping well, and these temporary visual hallucinations were not considered postoperative delirium. At the age of 67, she began to complain of visual illusions in which she mistook lint for insects. At the age of 69, she developed delusional infestation and saw insects crawling on her body. She had no insight into her symptoms and took various actions to get rid of these non-existent insects, including insecticide use, consulting an exterminator, moving to a different house, and visiting several dermatologists. Despite all evidence to the contrary, she had a fixed belief of being infested with insects. She also complained of mild amnesia. Her partner brought her to our psychiatric clinic for evaluation and treatment. Her delusion was severe. She stated, "There are white insects in my body. They come out of my skin," "Sometimes I can see crawling insects. But I can't see insects when they crawl in my clothes," and "They crawled on the skin of my neck, trunk, and limbs. I felt tingling." She showed us pictures of lint on her limbs, claiming they were pictures of insects (Figure 2). Her partner said, "When I pointed out that there were no insects, she disagreed with me and insisted that they were present." Neurological examination revealed mild paralysis and sensory deficits in the left upper and lower limbs as sequelae of SAH, although she did not have parkinsonism. Her MMSE scores ranged from 21 to 26, reflecting her fluctuating cognition

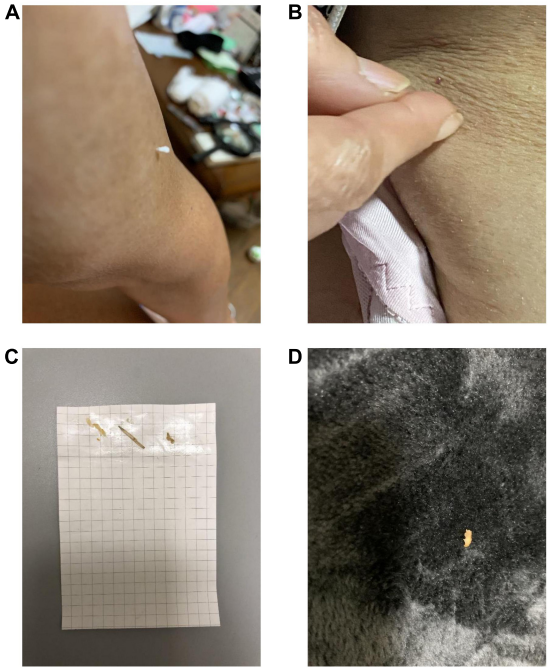


FIGURE 2
The patient in case 2 showed us pictures of lint that she thought looked like insects, which is known as the "specimen sign" or "matchbox sign". **(A,B)** Picture of an object on her skin. **(C)** She pasted the object onto a paper and **(D)** found the object on the carpet.

10.3389/fpsyt.2022.1051067

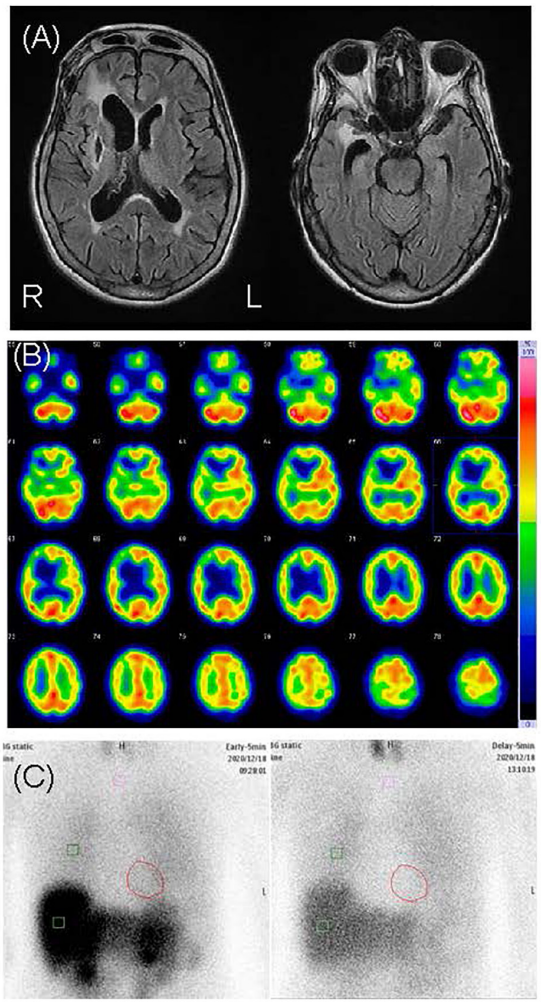


FIGURE 3
Neuroimages of case 2. **(A)** Cranial magnetic resonance revealed right dominant bilateral diffuse atrophy and right putamen chronic hemorrhage. **(B)** N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography revealed hypoperfusion in the right basal ganglia and the frontal, temporal, and parietal lobes. **(C)** Cardiac [^{123}I]-metaiodobenzylguanidine scintigraphy revealed heart-to-mediastinum ratios of 1.91 and 1.32 in the early and delayed phases, respectively.

level. The blood and cerebral spinal fluid test results showed no abnormalities. An electroencephalogram showed sharp waves in the right frontal area, which was considered an effect of SAH, with no obvious slow wave. Cranial MRI revealed an old hemorrhagic lesion in the right putamen and right dominant bilateral diffuse atrophy with ischemic changes secondary to SAH (Figure 3). ^{123}I-IMP SPECT revealed hypoperfusion in the right basal ganglia and the frontal, temporal, and parietal lobes (Figure 3). Furthermore, cardiac ^{123}I-metaiodobenzylguanidine scintigraphy revealed reduced myocardial uptake (heart-to-mediastinum ratio = early: 1.91; delayed: 1.32; Figure 3). Considering the results of all examinations, the patient was diagnosed with mild cognitive impairment because she showed progressive cognitive decline that did not to interfere with her daily activities. She had two clinical features (fluctuating cognition level, visual hallucinations) and one indicative biomarker (abnormal cardiac ^{123}I metaiodobenzylguanidine scintigraphy) and was therefore diagnosed with prodromal DLB (12) in addition to SAH sequelae. We determined that her delusional infestation was caused by DLB rather than SAH sequelae based on the course of her symptoms. Seven days after the initiation of 3 mg/day of donepezil hydrochloride, she visited another hospital because she had burnt her own leg in an attempt to kill the non-existent insects. When she visited our outpatient clinic after treatment for her burns, we determined that her behavior was not due to drug-induced impulsivity related to donepezil hydrochloride, but rather to behavioralization associated with the delusional infestation with visual hallucinations. Therefore, donepezil hydrochloride was increased to 10 mg/day with the aim of improving her symptoms. After donepezil hydrochloride was increased to 10 mg/day, her visual hallucinations of people improved. However, the delusional infestation with visual illusions of insects continued. Therefore, she was admitted to our hospital for treatment of delusional infestation. She persistently complained of delusional infestation and repeatedly showed us lint that looked like insects to her. She was prescribed 12.5 mg/day of quetiapine, and her delusional infestation partially improved. Donepezil hydrochloride was reduced to 3 mg/day because of frequent urination. Ultimately, she was treated with a combination of 3 mg/day of donepezil hydrochloride and 12.5 mg/day of quetiapine. The delusional infestation partially improved, and she took no further action against non-existent insects until a year later at our last follow-up. At the follow-up examination 1 year later, her MMSE score was 25, which was not significantly difference from 1 year earlier, and her impairment regarding activities of daily living remained unchanged. Her partner expressed understanding regarding the cause of and treatment for delusional infestation, and stated that he had stopped to point out the absence of the insects because he found that this was ineffective.

Discussion

We report our experience with two cases of DLB with delusional infestation. Both patients complained of insects coming out of their bodies and used insecticides for non-existent insects. Case 1 had some insight into his symptoms. After he was admitted, his delusional infestation disappeared without any new medication; however, he developed tactile hallucinations of people. The content of the tactile hallucinations depended on the content of his visual hallucinations. He did not take any other action against the non-existent insects other than insecticide use. On the contrary, Case 2 had no insight into her

symptoms. After she was admitted, her delusional infestation continued, and she had no tactile hallucinations other than those of insects. Her tactile hallucinations and delusional infestation sometimes appeared in the absence of visual hallucinations. She took various actions against these non-existent insects, including consulting an exterminator, moving to a different house, visiting several dermatologists, and insecticide use. She eventually burnt her leg in attempt to remove the non-existent insects, similar to the patient reported by Von Ekbom (1). Case 2 showed us pictures of lint that she thought looked like insects (**Figure 2**), which is known as the "specimen sign" (13) or "matchbox sign" (14). The differences in delusional infestation and tactile hallucinations between these two patients indicate that the delusional infestation in case 2 was more severe than that in case 1. Differences in the severity of delusional infestation may affect the patient's treatment response.

Case 1 was diagnosed with probable DLB (10) and case 2 was diagnosed with prodromal DLB (12). Both patients had visual hallucinations, which is one of the core clinical features of DLB. Among four prior cases of delusional infestation diagnosed with DLB, two patients had visual hallucinations (7–9). Even in cases of suspected dementia in which a diagnosis of DLB had not been made, the coexistence of complex visual hallucinations and delusional infestation have been reported (15–17). The patient reported by Kanazawa and Hata was suspected of having Alzheimer's dementia (15), and the case was reported before the publication of the first criteria for DLB (18). Although the patient reported by Rocha et al. showed cognitive impairment, the diagnosis was unclear because the patient refused detailed examinations and evaluation and was also limited by visual deficits and hypoacusis (16). Another case reported by Hirakawa et al. was suspected of having DLB, and donepezil hydrochloride was prescribed (17). Delusional infestation occasionally accompanies visual hallucinations (13), possibly suggesting the presence of a certain number of cases of undiagnosed DLB among patients with dementia and delusional infestation. In fact, if the indicative biomarkers were not available, Case 2 might have been diagnosed with delusional infestation caused by SAH.

Although little is known about the pathophysiology of delusional infestation (3), a promising hypothesis involves deterioration of the striatal dopamine transporter function (19), which is a hallmark of DLB. If this hypothesis is correct, it is possible that some patients with delusional infestation without dementia may also have the psychiatric-onset type of prodromal DLB (12). We recently compared the characteristics of patients with very-late-onset schizophrenia-like psychosis with and without positive results for the indicative biomarkers of DLB and the prevalence of visual hallucination was higher in patients with very-late-onset schizophrenia-like psychosis and suspected prodromal DLB (20). Visual hallucinations may be a symptom suggestive of DLB, even in older patients with delusional infestation.

There is limited existing evidence related to brain images in cases of delusional infestation, with only a few case reports and one case series available in the literature (21). Huber et al. reported a possible relationship between the striatum, particularly the putamen, and delusional infestation (21). Other case reports suggest that various regions of brain damage affect delusional infestation, such as damage in the right temporo-parietal (22, 23), right temporo-occipital (11, 24), left temporo-occipital (25), and right frontal lobes (22). In case 1, cranial MRI revealed diffuse very mild atrophy, including the bilateral hippocampus, and a ^{123}I-IMP SPECT revealed hypoperfusion in the bilateral occipital and parietal lobes (**Figure 1**). These results are consistent with the characteristics of DLB, and we could not find an apparent difference in brain images between case 1 and DLB patients without delusional infestation. In case 2, cranial MRI revealed an old hemorrhagic lesion in the right putamen, right dominant bilateral diffuse atrophy, and ischemic changes secondary to SAH, while ^{123}I-IMP SPECT revealed hypoperfusion in the right basal ganglia and the frontal, temporal, and parietal lobes (**Figure 3**). This patient's brain lesions in the right putamen and the frontal, temporal, and parietal lobes were consistent with those in past reports. Therefore, we considered that SAH might have partially affected her severe delusional infestation. However, we determined that her delusional infestation was mainly caused by DLB rather than SAH sequelae based on the course of her symptoms. Therefore, we considered that case 2 had increased vulnerability for delusional infestation after SAH, and that her delusional infestation appeared after the onset of DLB.

After admission, the patient in case 1 had no further complaints of delusional infestation. His visual and tactile hallucinations, which frequently accompanied his delusional infestation, disappeared with donepezil hydrochloride administration, and his delusional infestation had not recurred at the 1-year follow-up with continued donepezil hydrochloride use, even after discharge. Although case 2 continued to complain of delusional infestation with visual illusions, severity of the delusional hallucination was apparently improved, and her visual hallucinations disappeared after the initiation of donepezil hydrochloride. Moreover, her delusional infestation further improved after adding quetiapine to her medication regimen. Mori et al. reported that donepezil hydrochloride was effective for visual hallucinations in patients with DLB (26). In cases 1 and 2, donepezil hydrochloride was effective for reducing the frequency of or eliminating visual hallucinations. However, the efficacy of donepezil hydrochloride for delusional infestation in patients with DLB differed between cases 1 and 2. There have been some case reports of treatment for delusional infestation in DLB. Magierski et al. reported two cases of delusional infestation in patients with DLB who were treated with a combination of acetylcholinesterase inhibitor (AChEI) therapy and 50 mg/day of quetiapine or 2.5–5 mg/day of olanzapine (7). Ochiai et al. reported a patient with delusional

infestation and depressive symptoms with DLB who was treated with a combination of 5 mg/day of donepezil hydrochloride and 1.5 mg/day of aripiprazole, with temporary administration of mirtazapine (8). de Mendonça et al. reported a DLB patient with delusional infestation and depressive symptoms who was treated with a combination of rivastigmine and citalopram (9). All patients in all cases, including ours, were safely treated with medication. According to the past cases and our case 2, antipsychotics may be necessary for partial or full remission of delusional infestation in patients with DLB. However, de Mendonça et al.'s patient and our case 1 were successfully treated without antipsychotics. Recent reviews for the treatment of delusional infestation recommend antipsychotics but do not include AChEI as a treatment option (27, 28). However, DLB has severe sensitivity to antipsychotics, which may cause worsening cognition, sedation, acute onset parkinsonism, and symptoms resembling neuroleptic malignant syndrome (29). Thereafter, it may be more beneficial to use AChEI initially and antipsychotics only when AChEI is ineffective.

Case 2 burnt her leg in an attempt to kill non-existent insects after the initiation of donepezil hydrochloride. Carrasco et al. reported that the frequency of agitation was 1.1% among patients with Alzheimer's dementia who were prescribed donepezil hydrochloride (30). After our patient burnt her leg, she continued with an increased dose of donepezil hydrochloride with no further agitation or impulsive behavior. Therefore, we cannot conclude that her impulsive behavior, that is burning her own legs, was a side effect of donepezil hydrochloride. However, in patients with DLB with delusional infestation such behavior may occur due to increased impulsivity induced by donepezil hydrochloride, which should therefore be administered with caution.

In summary, delusional infestation is rare and can occur in patients with DLB. It is often accompanied by visual hallucinations related to the delusion. Our findings indicate that it may be beneficial to use AChEI as priority and antipsychotics only when AChEI is ineffective for delusional infestation in patients with DLB. Further studies on the underlying pathophysiology and treatment of delusional infestation in patients with DLB are required.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DT conducted the neuropsychological assessments of patients, collected the data, and wrote the initial draft of the manuscript. MIk conducted the outpatient treatments. HK, YS, KY, MIw, MH, and MIk offered treatment advice and participated in the discussion of the results. All authors contributed to the manuscript and approved the final version for submission.

Funding

This work was supported by the Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research (KAKENHI) (Grant Number T21K157300 to HK).

Acknowledgments

We would like to thank Tamiki Wada, Shunsuke Sato, Takashi Suehiro, Kyosuke Kakeda, Sumiyo Umeda, Hirotaka Nakatani, Fuyuki Koizumi, Maki Yamakawa, Maki Suzuki, Yuki Yamamoto, Natsuho Hirakawa, and Sakura Hikita for their useful comments on the study data.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor TI declared a shared consortium group with the authors MIw, MH, and KY at the time of review.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Von Ekbom KA. Der präsenile dermatozoenwahn. *Acta Psychiatr Scand.* (1938) 13:227–59. doi: 10.1111/j.1600-0447.1938.tb06569.x

2. Munro A. Monosymptomatic hypochondriacal psychosis. *Br J Psychiatry Suppl.* (1988) 2:37–40. doi: 10.1192/S0007125000298978

3. Reich A, Kwiatkowska D, Pacan P. Delusions of parasitosis: an update. *Dermatol Ther.* (2019) 9:631–8. doi: 10.1007/s13555-019-00324-3

4. Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. *Psychol Med.* (2014) 44:673–83. doi: 10.1017/S0033291713000494

5. Hashimoto M, Yatabe Y, Ishikawa T, Fukuhara R, Kaneda K, Honda K, et al. Relationship between dementia severity and behavioral and psychological symptoms of dementia in dementia with Lewy bodies and Alzheimer's disease patients. *Dement Geriatr Cogn Dis Extra.* (2015) 5:244–52. doi: 10.1159/000381800

6. Utsumi K, Fukatsu R, Hara Y, Takamaru Y, Yasumura S. Psychotic features among patients in the prodromal stage of dementia with Lewy bodies during longitudinal observation. *J Alzheimers Dis.* (2021) 83:1917–27. doi: 10.3233/JAD-210416

7. Magierski R, Magierska J, Kloszewska I, Sobow T. P4-042: dementia with lewy bodies manifested as delusional parasitosis (Ekbom's syndrome). *Alzheimers Dement.* (2015) 11:781–2. doi: 10.1016/j.jalz.2015.06.1746

8. Ochiai S, Sugawara H, Kajio Y, Tanaka H, Ishikawa T, Fukuhara R, et al. Delusional parasitosis in dementia with Lewy bodies: a case report. *Ann Gen Psychiatry.* (2019) 18:29. doi: 10.1186/s12991-019-0253-3

9. de Mendonça FJP, Teixeira IA, Marinho V. Ekbom syndrome associated with Lewy body dementia: a case report. *Dement Neuropsychol.* (2020) 14:83–7. doi: 10.1590/1980-57642020dn14-010014

10. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology.* (2017) 89:88–100. doi: 10.1212/WNL.0000000000004058

11. Yoon TH, Ahn TB. Delusional parasitosis in a patient with an infarction in the territory of the right posterior cerebral artery. *Dement Neurocogn Disord.* (2019) 18:149–51. doi: 10.12779/dnd.2019.18.4.149

12. McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology.* (2020) 94:743–55. doi: 10.1212/WNL.0000000000009323

13. Freudenmann RW, Lepping P. Delusional infestation. *Clin Microbiol Rev.* (2009) 22:690–732. doi: 10.1128/CMR.00018-09

14. Lancet. The matchbox sign. *Lancet.* (1983) 2:261.

15. Kanazawa A, Hata T. Coexistence of the Ekbom syndrome and lilliputian hallucination. *Psychopathology.* (1992) 25:209–11. doi: 10.1159/000284774

16. Rocha FL, Caramelli P, Oliveira LC. Complex visual hallucinations and delusional infestation comorbidity. *Arq Neuropsiquiatr.* (2012) 70:553–4. doi: 10.1590/s0004-282x2012000700017

17. Hirakawa H, Terao T, Kanehisa M, Ninomiya T, Ishii N. Coexistence of delusional parasitosis and complex visual hallucinations with micropsia. *J Neuropsychiatry Clin Neurosci.* (2016) 28:e10–2. doi: 10.1176/appi.neuropsych.15070168

18. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology.* (1996) 47:1113–24. doi: 10.1212/wnl.47.5.1113

19. Huber M, Kirchler E, Karner M, Pycha R. Delusional parasitosis and the dopamine transporter. a new insight of etiology? *Med Hypotheses.* (2007) 68:1351–8. doi: 10.1016/j.mehy.2006.07.061

20. Kanemoto H, Satake Y, Taomoto D, Koizumi F, Sato S, Wada T, et al. Characteristics of very-late onset schizophrenia like psychosis as prodromal dementia with Lewy bodies: a cross-sectional study. *Alzheimers Res Ther.* (2022) 14:137. doi: 10.1186/s13195-022-01080-x

21. Huber M, Karner M, Kirchler E, Lepping P, Freudenmann RW. Striatal lesions in delusional parasitosis revealed by magnetic resonance imaging. *Prog Neuropsychopharmacol Biol Psychiatry.* (2008) 32:1967–71. doi: 10.1016/j.pnpbp.2008.09.014

22. Adunsky A. Early post-stroke parasitic delusions. *Age Ageing.* (1997) 26:238–9. doi: 10.1093/ageing/26.3.238-a

23. Narumoto J, Ueda H, Tsuchida H, Yamashita T, Kitabayashi Y, Fukui K. Regional cerebral blood flow changes in a patient with delusional parasitosis before and after successful treatment with risperidone: a case report. *Prog Neuropsychopharmacol Biol Psychiatry.* (2006) 30:737–40. doi: 10.1016/j.pnpbp.2005.11.029

24. Haas NL, Nicholson A, Haas MRC. Delusional parasitosis as presenting symptom of occipital lobe cerebrovascular accident. *Am J Emerg Med.* (2019) 37:1990.e3–e5. doi: 10.1016/j.ajem.2019.158368

25. Nagaratnam N, O'Neile L. Delusional parasitosis following occipito-temporal cerebral infarction. *Gen Hosp Psychiatry.* (2000) 22:129–32. doi: 10.1016/s0163-8343(00)00064-5

26. Mori E, Ikeda M, Kosaka K. Donepezil-DLB study investigators. donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. *Ann Neurol.* (2012) 72:41–52. doi: 10.1002/ana.23557

27. Mumcuoglu KY, Leibovici V, Reuveni I, Bonne O. Delusional parasitosis: diagnosis and treatment. *Isr Med Assoc J.* (2018) 20:456–60.

28. Katsoulis K, Rutledge KJ, Jafferany M. Delusional infestation: a prototype of psychodermatological disease. *Int J Dermatol.* (2020) 59:551–60. doi: 10.1111/ijd.14709

29. McKeith I, Fairbairn A, Perry R, Thompson P, Perry E. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ.* (1992) 305:673–8. doi: 10.1136/bmj.305.6855.673

30. Carrasco MM, Agüera L, Gil P, Moríñigo A, Leon T. Safety and effectiveness of donepezil on behavioral symptoms in patients with Alzheimer disease. *Alzheimer Dis Assoc Disord.* (2011) 25:333–40. doi: 10.1097/WAD.0b013e318212ab7a

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 19 December 2022
DOI 10.3389/fpsyt.2022.1059150

Check for updates

OPEN ACCESS

EDITED BY
Vincenza Frisardi,
Santa Maria Nuova Hospital, Italy

REVIEWED BY
Junichi Iga,
Ehime University, Japan
Sanjeev Kumar,
University of Toronto, Canada

*CORRESPONDENCE
Gustavo C. Oliveira
psiquiatragustavo@gmail.com

SPECIALTY SECTION
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

RECEIVED 30 September 2022
ACCEPTED 22 November 2022
PUBLISHED 19 December 2022

CITATION
Valença AM, Studart Leal CC, Oliveira GC, de Moraes TM, Nardi AE and Mendlowicz MV (2022) Case Report: Depression × dementia with Lewy bodies in the elderly: The importance of differential diagnosis.
Front. Psychiatry 13:1059150.
doi: 10.3389/fpsyt.2022.1059150

COPYRIGHT
© 2022 Valença, Studart Leal, Oliveira, de Moraes, Nardi and Mendlowicz. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Case Report: Depression x dementia with Lewy bodies in the elderly: The importance of differential diagnosis

Alexandre M. Valença[1], Cláudia Cristina Studart Leal[1], Gustavo C. Oliveira[2,3]*, Talvane M. de Moraes[4], Antonio E. Nardi[1] and Mauro V. Mendlowicz[5]

[1]Department of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [2]Department of Psychiatry, University Center of Brasilia, Brasília, Brazil, [3]Department of Psychiatry, University of Brasília, Brasília, Brazil, [4]Department of Psychiatry, Academia Nacional de Medicina, Rio de Janeiro, Brazil, [5]Department of Psychiatry, Fluminense Federal University, Rio de Janeiro, Brazil

Background: Dementia is a clinical syndrome which is more common in elderly people. Dementia with Lewy bodies (LBD) is not so rare in elderly people, with cognitive impairment in about 30% over age 65. The clinical picture is characterized by fluctuation in cognitive functions, recurrent, well-formed, detailed visual hallucinations, and Parkinsonism, with rigidity, tremor, bradykinesia, and slurred speech.

Case presentation: We present a case report of LBD in a 73-year-old retired teacher, which a initial wrong diagnosis of refractory depression for at least 3 years. We also conduct a review of recent works on theme.

Conclusion: LBD diagnosis can be neglected for years, with a legal and clinical issues to patients and their families. Detailed medical research, including differential diagnosis, are very necessary on those cases, specially when they are called refractory. We encourage new research and adequate clinical training to prevent damage.

KEYWORDS

depression, dementia, Lewy bodies (LBD), diagnosis, legal medicine assessment

Introduction

Dementia is a clinical syndrome characterized by multiple, acquired, and persistent cognitive deficits, capable of substantially interfering in the patient's daily activities. It is more prevalent in segments of the population with advanced age, especially in those older than 75 years. The increase in the population with dementia is a major concern for health professionals and lawmakers around the world (1). Alzheimer's

disease (AD) and dementia with Lewy bodies (LBD) are the main representative types of the neurodegenerative dementias (2).

LBD is a common form of cognitive impairment, accounting for 30% of cases of dementia in people over age 65. Early diagnosis of LBD can be challenging, particularly in the context of the differentiation between Parkinson's disease dementia and other forms of dementia, such as Alzheimer's disease, and mood disorders such as depression (3).

The clinical picture of LBD is characterized by fluctuation in cognitive functions, recurrent, well-formed, detailed visual hallucinations, and Parkinsonism, with rigidity, tremor, bradykinesia, and slurred speech. Memory deficit usually occurs later, and attention deficits, cognitive impairment, and loss of visual-spatial skills become more frequent. Other characteristics are behavioral REM (rapid eye movement) sleep disorder, increased sensitivity to the adverse effects of antipsychotics, and reduced dopamine uptake in the basal ganglia (4).

A retrospective study found that the diagnosis of major depression was initially made in 19% of the 962 patients with LBD (5). Seventeen of the 90 patients with probable LBD (18.9%) reported depression and concomitant antidepressant use before or at the onset of memory loss. The mean prodromal duration of depression before the onset of memory loss was 7.2 ± 12.0 years (6).

Depression in elderly people, diagnosed as senile depression (SD), includes heterogeneous symptoms and clinical profile findings. The pathophysiology remains unclear because it should be different (7). SD may be risk factor for developing dementia or a prodromal stage. Disturbance of neural circuity, imbalance of monoaminergic systems, dysregulation of the hypothalamic–pituitary–adrenal axis, and elevated neuroinflammatory status where studied and are involved with the syndrome (7). A very recent Guideline from Japanese Society of Mood disorders (8) (2022) of diagnosis and treatment of SD emphasizes the need of differential diagnosis from bipolar disorders, organic brain diseases, drug effects and dementia. Determine the comorbidity between late-life depression and dementia is also necessary, according to this society (8).

The objective of this report is to describe and analyze a case of LBD that for several years was erroneously diagnosed and treated as depression.

Case description

Mr. John is a 73-year-old retired teacher. His wife had requested a Social Security disability benefit for him, but the psychiatric examiner made a diagnosis of "major depression" and the benefit was denied. According to the patient's wife, he began complaining about "forgetfulness" early in 2015. She noticed "strange things," such as "sleep attacks," even in front of the guests invited by the couple. The "forgetfulness" remained relatively mild for three years. However, a further decline in Mr. John's cognitive skills was observed from 2018 on, when, for instance, he went shopping in a grocery store and forgot several items there but could not acknowledge that loss.

In 2020, the memory deficits of Mr. John became more severe. On one occasion, he attempted to drive his car but could not find the accelerator pedal. This same year, he got lost trying to get to his son's home and had to ask for directions, although the neighborhood was quite familiar to him. Mr. John could not understand movies or TV shows anymore. He complained of sadness, anguish, ideas of death, and of not sleeping all night. Several psychiatrists assessed the patient during the last five years, made a diagnosis of refractory depression, and medicated him with a variety antidepressant drugs. At the beginning of 2021, Mr. John underwent electroconvulsive therapy that resulted in limited improvement.

The patient's depression was accompanied by cognitive problems, such as forgetting events, appointments, and people's names and frequent losses of his belongings. He reported false memories, such as having been present at a specific musical show, a fact that never really did occur. Mr. John also reported visions of "dead people and butterflies."

Diagnostic

There were report of episodes of exacerbation of the parkinsonism with the prescription of antipsychotic medications such as quetiapine. After being medicated with this drug, the patient remained in bed for three days due to severe muscle rigidity. He walked very slowly, took a long time to eat meals, and had hand tremors. He suffered several falls to the ground while standing or walking. His wife reported that he had many nights of agitated sleep, in which he talked almost non-stop, and repeatedly moved his arms.

A neuropsychological assessment carried out in 2021 identified difficulties in recognizing shapes and parts of objects and of integrating them into a whole. The patient also showed deficits in attention and cognitive flexibility, in the ability to plan and monitor tasks, in the inhibitory control, and in verbal fluency. In a screening test, he could spontaneous say 9 animals' names in one minute. According to Brucki et al. (9), 13 names is expected in Brazilian population. In 2019, it was related that the patient could say 20 names doing the same test, for comparison. Now, in this neuropsychological it was also found: five digit test (FDT) showed less than 5 score in 95,9" and 74,8" for alternance and flexibility respectively, which is a severe impairment. WAIS-III (Wechsler Adult Intelligence Scale) showed operational memory affected. Other findings included impairment in the ability of naming figures, to express the meaning of words, and of learning new material, after previous exposure to new content.

Cerebrospinal fluid analysis of neurodegeneration biomarkers identified increased levels of T-Tau protein and decreased levels of beta-amyloid ratio (AB42/AB40). Nuclear magnetic resonance imaging (MRI) of the skull showed foci of ischemic gliosis at the posterior margins of the ventricular bodies. Preservation of neurons in the pars substantia nigra and hippocampus. Dilated supratentorial ventricles, with type 4 hydrocephalus described. Spectral analyses of MRI with proton spectroscopy revealed glutamine/glutamate peaks and increased levels of myo-inositol in the frontal lobes, notably in the right one. Basal cisterns, fissures, and cerebral convexity grooves were more evident, notably in high parietal convexities bilaterally. Scintigraphy of the dopaminergic neurons of the base nuclei showed a bilaterally reduced concentration of the radiotracer in the basal nuclei, a finding compatible with severe nigrostriatal dopaminergic dysfunction (**Figure 1**). Despite the increase of T-tau protein usually indicates the presence of Alzheimer Disease, the decrease of AB42/AB40 is not going to confirm. The alterations in image exams and the detailed clinical history of our case are more suggestive to LBD (10).

Dopamine transporter (DAT) single-photon emission tomography showed a markedly reduced bilateral concentration of the radiotracer in the basal ganglia, a finding that is compatible with severe nigrostriatal dopaminergic depletion. The usefulness of this test in distinguishing dementia with LBD from Alzheimer's disease is well established, having a sensitivity of 88% and specificity of 100% in the exclusion of cases with other dementias other than LDB (3).

The latest mental state examination was performed three months ago. The patient was awake and fully oriented in time and space. However, he was unable to remember several relevant information, like the year he retired or his wedding day. Mr. John was little attentive to the interview, and it was necessary to repeat questions or rephrase them to further his understanding. Data about his psychiatric history had to be provided by his wife, and he was unable to establish a chronological link between his complaints and the symptoms he presented. Memories of recent and remote events were impaired. There are reports of paramnesias (memories of events that do not correspond to reality). The Mini-mental state examination (MMSE) was applied and the score was 25/30. Orientation and recent memory were affected with loss of 1 point of score each, and loss of attention was the responsible for other 3 points loss. The decrease of verbal fluency was confirmed with just 9 names spontaneously spoken by him. Mr. John complained about "depression, discouragement, forgetfulness, and bad mind." The content of his thinking was poor, and the flow of ideas was impaired. He reported visual hallucinations in the past. His mood was apathetic and the affectivity was faded. Willpower and pragmatism were greatly impaired. His wife said he still affected, even using Rivastigmin for near to one year. He is also using Olanzapine, Mirtazapine, Zolpidem, Pramipexole and Alprazolam. She considers that he is calmer, but with some changes in his mood, which are not very predictable. He is probably stable, not better or worse than a year ago in cognition skills, and he still need support in his self-care. On the other hand, his behavior and his sleep are better now. The time-line (**Figure 2**) show the case progression.

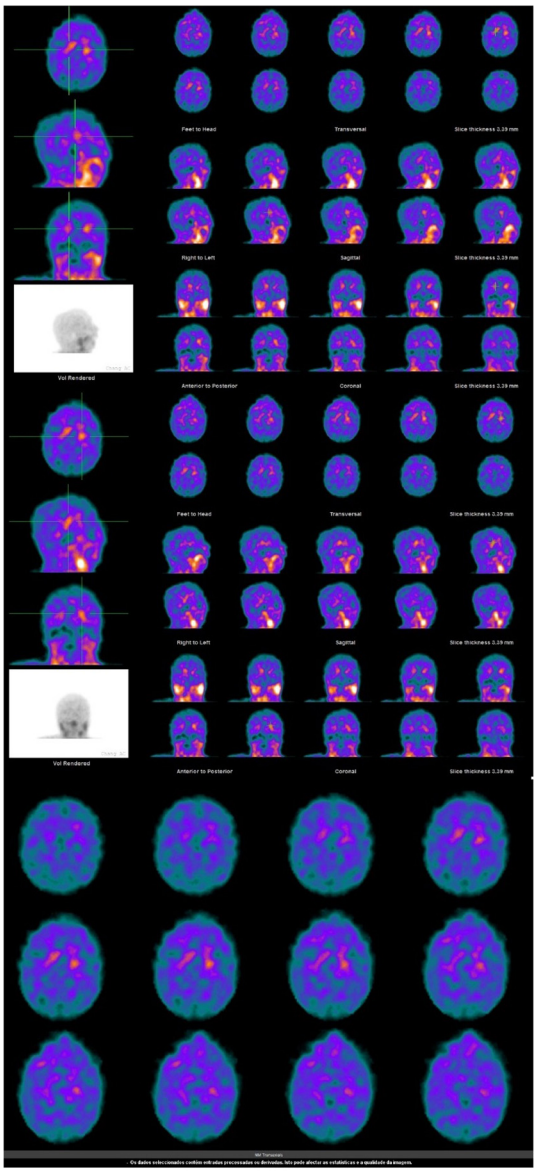


FIGURE 1
Patient's exams.

Discussion

Holistically, the examination of the patient's mental state, added by ancillary exams, neuropsychological evaluation, and history data, strongly points to the presence of degenerative dementias, such as Alzheimer's dementia and LBD (11, 12).

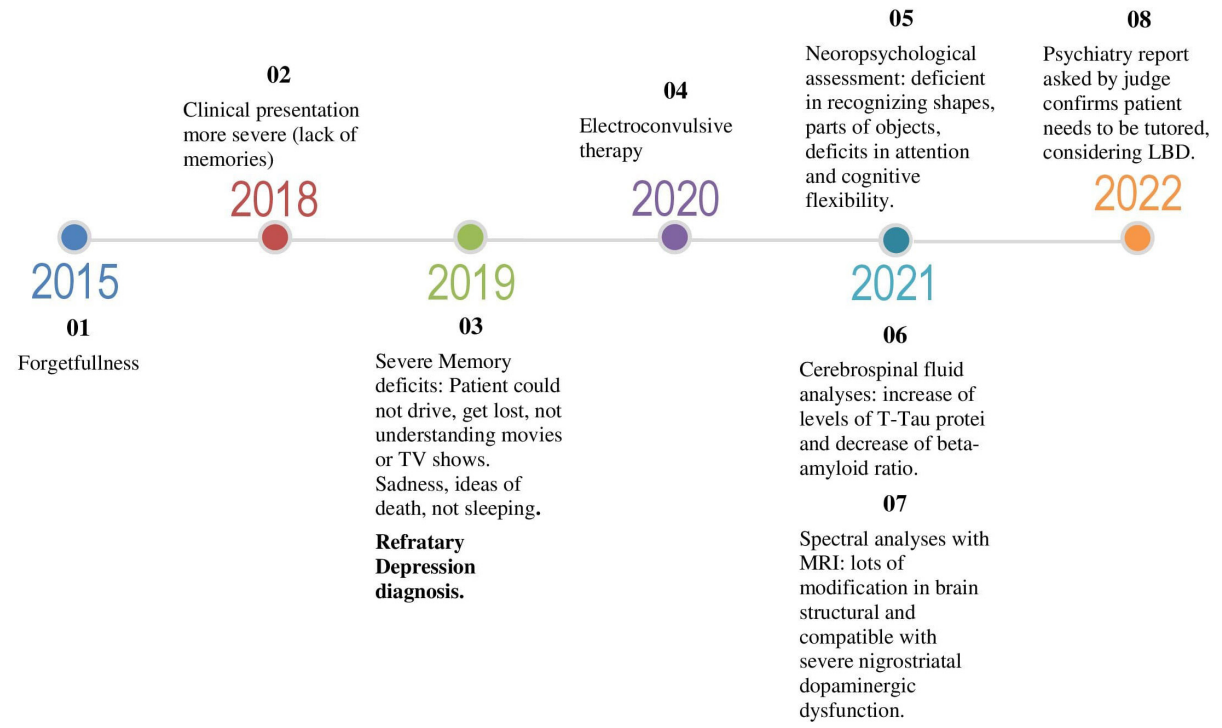


FIGURE 2
Time-line.

According to the Alzheimer's Association (13), LBD can occur either alone or in association with Alzheimer's disease or with vascular dementia. There are many studies in Alzheimer's disease about its neuropathological perspective Lewy Bodies, plaques, tangles and proteins may increase the risk of Dementia, in different perspective. LBD seems clearly to affect younger ages than the usual modification from Alzheimer's and other Dementia (14). Mr. John also had several signs and symptoms related to LBD, such as visual hallucinations, hypersensitivity to antipsychotics, neuropsychiatric symptoms, parkinsonism, and behavioral sleep disorder. Regarding visual hallucinations in LBD they are complex in terms of content and can be well-structured, vivid, and detailed, involving people or animals. More than 80% of patients with this type of dementia report these experiences (15), as in the case in question. In these cases, there is also a hypersensitivity to antipsychotic drugs. Even the hypersensitivity to antipsychotics has become a support criterion for the diagnosis of LBD (16). In the present case, Mr. John presented severe extrapyramidal symptoms after the use of quetiapine and it continued despite stopping this medication.

The patient also had depression and reported previous suicidal ideation. This is a common neuropsychiatric symptom in LBD. One cannot fail to consider the impact of dementia on the current depressive condition, including contributing to the genesis of depression, its worsened prognosis, and its refractoriness to pharmacological treatment and electroconvulsive therapy, as in the present case.

The patient has presented symptoms of parkinsonism in his daily life, such as postural instability (report of falls), bradykinesia, and slowing of movements. It is important to note that spontaneous parkinsonism affects more than 85% of patients with LBD (17).

It is important to note that although LBD was not listed in ICD-10 (18) but in ICD 11 (19) it is featured as a dementia associated with Lewy body disease (6D82). ICD-11 (19) describes it as follows: "Dementia associated with Lewy body disease is the second most common form of dementia in elderly disease after Alzheimer's." The onset is insidious, with attention and executive functioning deficits usually reported as the complaint initially presented. These cognitive deficits are often accompanied by visual hallucinations and symptoms of REM sleep behavioral disorder. Hallucinations in other sensory modalities, depressive symptoms, and delusions may also be present. The presentation of symptoms generally varies significantly over days requiring longitudinal observation. The spontaneous onset of parkinsonism within approximately 1 year of the onset of cognitive symptoms is characteristic of the disease." It should be noted that this description corresponds entirely to the case in question. According to the last Consensus of LBD (2017) (20) new information has been incorporated about aspects of DLB, with increased

diagnostic weighting given to REM sleep behavior disorder and 123iodine-metaiodobenzylguanidine (MIBG) myocardial scintigraphy. The patient hasn't do does tests, but his sleep became bad, since the diagnosis and the disease progress. Despite that, the case can be consider a probable LBD, as he has Fluctuating cognition with pronounced variations in attention, recurrent visual hallucinations well-formed and detailed and rigidity, rest tremor, rigidity and bradykinesia, with at least 3 clinical features, so not just the positive biomarkers. The treatment is also based on specialist opinion, as there are few randomized controlled trials in DLB, also according to consensus (20).

Patient perspective

A case as the reported brings many problems to the patient and his family, as a late diagnosis implied inadequate therapy, with side effects resulting from this, as reported. In addition, legal repercussions are a big issue, as a diagnosis of refractory depression rather than dementia, which is a serious mental illness. This situation limits patient's access to rights and even to a better care, through tutoring, for example, and it also become difficult to their families.

Conclusion

The present case illustrates how in a dementia syndrome related to LBD, cognitive functioning and the social and daily life of the individual are greatly impaired. The study of clinical, neurological, and psychopathological characteristics of patients with depression who present symptoms of degenerative dementias such as LBD can contribute to elucidating the differential diagnosis between these conditions. Depression in old age can be a prodromic presentation of degenerative dementias (15). Certainly, the study of this relationship deserves to be further studied.

Detailed medical research is extremely important in these cases, including differential diagnosis with depression, to provide adequate treatment, and family guidance and enable financial benefits provided by social security when necessary, thus contributing to social justice and better quality of life for these patients.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. The patient's next of kin/legal guardian provided written informed consent for the publication of this case report.

Author contributions

AN, TM, GO, and CS contributed to conception and design of the study, analyzed the case, and reviewed literature. MM reviewed and organized the sections of the manuscript, rewriting parts of the manuscript. AV wrote the first draft of the manuscript and support review of publication. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* (2013) 9:63–75. doi: 10.1016/j.jalz.2012.11.007

2. Cummings JL, Reichman WE. Dementia. 3rd Edn. In: Duthie EHJ, Katz PR editors. *Practice of Geriatrics*. Philadelphia, PA: WB Saunders Company (1998).

3. Yousaf T, Dervenoulas G, Valkimadi P, Politis M. Neuroimaging in Lewy body dementia. *J Neurol.* (2019) 266:1–26.

4. Mckeith I, Dickson D, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report f the DLB Consortium. *Neurology.* (2005) 65:1863–72.

5. Galvin JE, Duda JE, Kaufer DI, Lippa CF, Taylor A, Zarit SH. Lewy body dementia: The caregiver experience of clinical care. *Parkinsonism Relat Disord.* (2010) 16:388–92.

6. Fujishiro H, Nakamura S, Sato K, Iseki E. Prodromal dementia with Lewy bodies. *Geriatr Gerontol Int.* (2015) 15:817–26. doi: 10.1111/ggi.12466

7. Kawakami I, Iga JI, Takahashi S, Lin YT, Fujishiro H. Towards an understanding of the pathological basis of senile depression and incident dementia: implications for treatment. *Psychiatry Clin Neurosci.* (2022) [Epub ahead of print].

8. Baba H, Kito S, Nukariya K, Takeshima M, Fujise N, Iga J, et al. Guidelines for diagnosis and treatment of depression in older adults: a report from the Japanese Society of mood disorders. *Psychiatry Clin Neurosci.* (2022) 76:222–34. doi: 10.1111/pcn.13349

9. Brucki SMD. Dados Normativos para o Uso do Teste de Fluência Verbal (Categoria Animais) em Nosso Meio. *Rev Neuroci.* (1997) 5:40–1.

10. Aerts MB, Esselink RA, Claassen JA, Abdo WF, Bloem BR, Verbeek MM. CSF tau, Aβ42, and MHPG differentiate dementia with Lewy bodies from Alzheimer's disease. *J Alzheimers Dis.* (2011) 27:377–84. doi: 10.3233/JAD-2011-110482

11. Bjerke M, Engelborghs S. Cerebrospinal fluid biomarkers for early and differential Alzheimer's Disease Diagnosis. *J Alzheimers Dis.* (2018) 62:1199–209. doi: 10.3233/JAD-170680

12. Nardi AE, da Silva AG, Quevedo J. *Tratado de Psiquiatria da Associação Brasileira de Psiquiatria*. Porto Alegre: Artmed (2022).

13. Alzheimer's Association. *Dementia with Lewy Bodies*. Chicago, IL: Alzheimer's Association (2022).

14. Robinson JL, Richardson H, Xie SX, Suh E, Van Deerlin VM, Alfaro B, et al. The development and convergence of co-pathologies in Alzheimer's disease. *Brain.* (2021) 144:953–62. doi: 10.1093/brain/awaa438

15. Walker Z, Possin KL, Boeve BF, Aarsland D. Lew body dementias. *Lancet.* (2015) 386:1683–97. doi: 10.1016/S0140-6736(15)00462-6

16. Ferman TJ, Boeve BF, Smith GE, Lin SC, Silber MH, Pedraza O, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. *Neurology.* (2011) 77:875–82. doi: 10.1212/WNL.0b013e31822c9148

17. World Health Organization [WHO]. *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision*, 2nd Edn. Geneva: World Health Organization (2004).

18. World Health Organization [WHO]. *ICD-11: International Classification of Diseases (11th revision)*. Geneva: World Health Organization (2019).

19. Fujishiro H. Late-life depression and lewy body disease. *Am J Geriatr Psychiatry.* (2019) 27:287–9. doi: 10.1016/j.jagp.2018.11.001

20. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology.* (2017) 89:88–100. doi: 10.1212/WNL.0000000000004058

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 12 January 2023
DOI 10.3389/fpsyt.2022.1054461

Check for updates

OPEN ACCESS

EDITED BY
Vincenza Frisardi,
Santa Maria Nuova Hospital, Italy

REVIEWED BY
Jeffrey Dupree,
Virginia Commonwealth University, United States
Salvatore Iacono,
University of Palermo, Italy

*CORRESPONDENCE
Niels Hansen
✉ niels.hansen@med.uni-goettingen.de

SPECIALTY SECTION
This article was submitted to Aging Psychiatry, a section of the journal Frontiers in Psychiatry

RECEIVED 26 September 2022
ACCEPTED 22 December 2022
PUBLISHED 12 January 2023

CITATION
Hansen N, Sagebiel A, Rentzsch K, Hirschel S, Wiltfang J, Schott BH and Claudia B (2023) Case report: Amnestic mild cognitive impairment in multiple domains associated with neurofascin 186 autoantibodies: Case series with follow-up and review. *Front. Psychiatry* 13:1054461. doi: 10.3389/fpsyt.2022.1054461

COPYRIGHT
© 2023 Hansen, Sagebiel, Rentzsch, Hirschel, Wiltfang, Schott and Claudia. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Case report: Amnestic mild cognitive impairment in multiple domains associated with neurofascin 186 autoantibodies: Case series with follow-up and review

Niels Hansen[1,2]*, Anne Sagebiel[1], Kristin Rentzsch[3], Sina Hirschel[1], Jens Wiltfang[1,4,5], Björn H. Schott[1,4,6] and Bartels Claudia[1]

[1]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany, [2]Department of Psychiatry and Psychotherapy, Translational Psychoneuroscience, University Medical Center Göttingen, Göttingen, Germany, [3]Clinical Immunological Laboratory Prof. Stöcker, Groß Grönau, Germany, [4]German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany, [5]Department of Medical Sciences, Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), University of Aveiro, Aveiro, Portugal, [6]Leibniz Institute for Neurobiology, University of Magdeburg, Magdeburg, Germany

Background: Neurofascin 186 autoantibodies are known to occur with a diseased peripheral nervous system. Recently, also additional central nervous system (CNS) involvement has been reported in conjunction with neurofascin 186 autoantibodies. Our case enlarges the spectrum of neurofascin 186 antibody-related disease to include mild cognitive impairment (MCI).

Methods: We report here a case after having examined the patient files retrospectively, including diagnostics such as blood and cerebrospinal fluid (CSF) analysis involving the determination of neural autoantibodies, brain magnetic resonance imaging (MRI), brain fluorodesoxyglucose positron emission tomography (FDG-PET), and extensive neuropsychological testing.

Results: We report on two patients with MCI. Brain MRI showed cerebral microangiopathy in both patients, but brain FDG-PET demonstrated pathology in the right prefrontal cortex, in the right inferior parietal cortex, and in both lateral occipital cortices in one patient. Neurofascin 186 antibodies were detected in serum in both patients, and neurofascin 186 autoantibodies were also detected in the CSF of one of these patients. At follow-up six month later, neurofascin 186 autoantibodies disappeared in one patient while persisting in the other.

Conclusion: We report on two individuals presenting MCI associated with neurofascin 186 antibodies, thus expanding the potential spectrum of neurofascin 186-associated disease. This report supports the recommendation to consider also neurofascin 186 autoantibodies in not just

peripheral nerve disease, but also in disorders involving CNS autoimmunity. More studies are needed to clarify the lack of association between neurofascin 186 autoantibodies and cognitive decline.

KEYWORDS

autoantibody, autoimmunity, cognition, neurofascin 186 antibody, mild cognitive impairment

1. Introduction

The spectrum of the diseases associated with neurofascin 186 antibodies is limited mainly to peripheral neuropathy (1) such as chronic demyelinating inflammatory polyneuropathy (2) as well as subacute nodopathy (3) and to amyotrophic lateral sclerosis (4). Recently, also central nervous system (CNS) involvement in neurofascin 186 autoantibody-associated peripheral neuropathy has been demonstrated (5). However, cognitive impairment has been rarely reported in association with neurofascin 186 antibodies (5), and there might be structures in the CNS involved in primary neuroinflammation in the peripheral nervous system. Here we report two patients predominantly presenting with cognitive impairment as a clinical phenotype in which primary neuroinflammatory locus is probably not the peripheral nervous system. Our report thus highlights the novelty of a neurofascin 186 autoantibody-related affectation of the CNS through a possible inflammatory process associated with cognitive impairment.

2. Case reports

2.1. Case 1

A 75-year-old woman presented complaining of short-term memory disturbances, word-finding difficulties and depressive symptoms starting about a year earlier. She is a multimorbid patient with high care needs. Her comorbidities comprised essential tremor, lung empyema, steatosis hepatis with multiple liver cysts, cholecystolithiasis, coronary heart disease, arterial hypertension, mitral valve insufficiency, hyperlipoproteinemia, hypothyreosis, and polyneuropathy. She also has a knee total endoprothesis on the left and coxathrosis on the right. She also has about 60 pack years involving nicotine abuse, but has probably been abstinent since 2019. Her mother suffered from dementia. She has been categorized as care level two and is about 70% disabled (i.e., severely disabled). Her daughter serves as a complete health care proxy for her. She acquired a secondary school level 1 certificate and worked as a telephone assistant in telecommunications. Concurrent mediation comprised the following: pantoprazole 20 mg/d, atorvastatin 20 mg/d, L-thyroxin 50 mikrog/d, fexofenadin 180 mg/d and bupropion 150 mg/d. Psychopathological examination revealed a loss of drive and a slowed psychomotor speed. Furthermore, she was also suffering from depression (ICD-10: F33.1: recurrent major depression, moderate, Geriatric Depression Scale (GDS) score: 6, i.e., depressive symptoms of mild to moderate severity). Neurological examination demonstrated pallanesthesia in her legs. At cognitive screening, she scored 29 of 30 points on the Mini Mental Status Examination (MMST), but neuropsychological testing revealed an amnestic mild cognitive impairment (MCI) with deficits in information processing speed (attention), visuospatial cognition, verbal and figural memory (**Figure 1**). Together with cognitive deterioration in multiple domains, a caregiver rating (Bayer Activities of Daily Living Scale, B-ADL) resulted in mild impairments of ADL competence (mean B-ADL: 3.3). Magnetic resonance imaging (MRI) revealed cerebral microangiopathy with Fazekas grade 1. Cerebrospinal fluid (CSF) analysis showed elevated S100 protein (4.7 μg/l, pathological if > 2.7 μg/l) (**Table 1**) and ptau 181 protein (**Table 1**).We also identified intrathecal IgG synthesis (**Table 1**). We also detected anti-neurofascin 186 autoantibodies in serum at 1:32 intensity via anti-neural antigen IgG immunofluorescence testing with BIOCHIP-mosaic with brain tissue and recombinant cells. At follow-up six months later, no serum neurofascin 186 autoantibodies were detectable. Her familiar MCI was evident over the course, but dementia-like syndrome was not.

2.2. Case 2

A 66-year-old man presented complaining of memory problems for the past two years. His medical history included nicotine dependency, hyperlipidemia, presbyacusis and post prostate cancer. Psychopathology was indicative of recurrent major depression, moderate (ICD-10: F33.1, Beck Depression inventory (BDI-II) score 31, i.e., depressive symptoms of severe severity). He is married, living with his wife, and has a daughter. He worked as a professional mason. He completed eight years of school and has a secondary school diploma, and has been retired for 3 years. His mother has severe dementia at an age of 87 years and requires constant health supervision. His father died of a myocardial infarction at

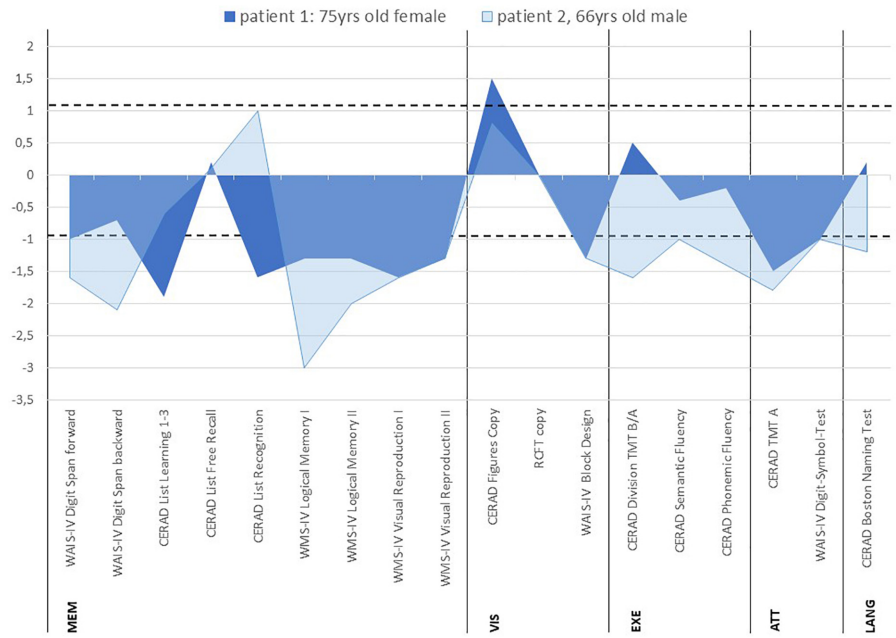


FIGURE 1
Neuropsychological profiles of patients with anti-neurofascin 186 autoantibody-associated cognitive impairment *z*-scores. The area between dotted lines denote the normal range. CERAD, consortium to establish a registry for Alzheimer's disease; WMS IV, wechsler memory scale – 4th edition; RCFT, rey-osterrieth complex figure test; WAIS-IV, wechsler adult intelligence scale – 4th edition; TMT, trail making test; MEM, memory; VIS, visuospatial cognition; EXE, executive functions; ATT, attention; LANG, language.

the age of 46 years. At the time-point of neuropsychological testing, he reported Cognitive screening resulted in mild cognitive impairment (MMST 26/30). At neuropsychological testing, mild difficulties were detected in confrontation naming (language), and more severe cognitive deficits became apparent in information processing speed (attention), phonematic word fluency (language/executive functions), cognitive flexibility (executive functions), visuospatial cognition, working memory, visual memory and partly in verbal memory (Figure 1). His cognitive performance profile was classified as MCI in multiple domains together with mildly reduced ADL-competency (B-ADL: 4.4). His MRI revealed cerebral microangiopathy, but his brain fluorodesoxyglucose positron emission tomography (FDG-PET) yielded pathological Z-scores in the right prefrontal cortex, in the parietal inferior cortex on the right side, lateral occipital cortex on both sides, visual cortex on both sides, and temporal lateral cortex on the right side. Anti-neurofascin 186 autoantibodies were detected in his serum (1: 320) and CSF 1: 32 via anti-neural antigen IgG immunofluorescence testing with BIOCHIP-mosaic with brain tissue and recombinant cells. The neurofascin 186 autoantibodies were still present six months later (1:32). At follow-up he showed speech anomalies primarily entailing a stutter. However, he claims to have already stuttered when young, so that it is not clear whether this should be interpreted as a speech disorder or reactivation. The cognitive disturbances did not appear to be significantly progressive in his follow-up examination. He also denies suffering from hypomimia, vigilance fluctuations, REM sleep disturbances, and hallucinations.

3. Discussion

Our main finding here is the novelty of CNS involvement in neurofascin 186 antibody-associated autoimmunity over

TABLE 1 Neurofascin 186 autoantibodies in neuropsychiatric disease.

Neuropsychiatric disease	References
Amyotrophic lateral sclerosis	(4)
Anti-pan neurofascin-associated neuropathy	(13)
Cerebellar disease	(5)
CIDP	(14)
Guillian Barré Syndrome	(15)
Multifocal motor neuropathy	(16)
Peripheral neuropathy	(1)
Pontocerebellar degeneration	(17)
Subacute nodopathy	(3)
Vision impairment	(5)
Multiple sclerosis	(8)

CIDP, chronic inflammatory demyelinating polyneuropathy.

10.3389/fpsyt.2022.1054461

TABLE 2 Clinical and laboratory characteristics of patients.

Parameter	Patient 1	Patient 2
Demographic parameters		
Gender	Female	Male
Age in years	75	66
Psychopathology		
Disorientation	No	No
Attentional dysfunction	No	No
Memory disturbances	Yes	Yes
Formal thought disorder	No	Yes
Affective disturbance	Yes	Yes
Drive and psychomotor disturbance	Yes	Yes
CSF		
Cell count (<5µg/L)	1	3
Albumin mg/L	229	226
Tau protein (<450pg/ml)	163	128
P Tau protein 181 (<61pg/ml)	91	49
Aß42 (>450pg/ml)	2,185	1,082
Aß40	16,403	9,982
Ratio Aß42/40 × 10 (>0.5)	1.3	1.1
Blood brain barrier disturbance	No	No
Intrathecal IgG synthesis	Yes	No
MRI		
Generalized atrophy	Yes	No
Focal atrophy	No	No
Hippocampal atrophy	No	No
Vascular pathology	Yes	Yes

Aß42, Amyloid-ß 42; Aß40, amyloid-ß 40; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; P Tau Protein 181, phosphorylated tau protein 181; ratio Aß42/40, ratio of amyloid-ß 42/ratio of amyloid-ß 40; y, years. For laboratory data normal ranges are shown in brackets. Reference values: refers to reference values from the Neurochemistry Laboratory, Neurology Department, University Medical Center Göttingen.

a follow-up of six months in two paradigmatic patients. Neurofascin 186 interacts with Neuropilin-1, which mediates axon guidance and adhesion during the formation of gamma amino butyric (GABA)ergic synapses in the cerebellum (6). Neurofascin 186 antibodies might have an impact on the function of GABAergic synapses in the cerebellum. Dysfunctional cerebellar GABAergic synapses might in turn affect cognitive functions via functional and anatomical connections between the cerebellum and hippocampus (7) as a potential mechanism of action of how neurofascin 186 antibodies might act. Another mechanism of action is based on axonal pathology with complement deposition induced by neurofascin 155 and 186 antibodies, which selectively target the nodes of Ranvier in multiple sclerosis (8). Other reports support the role of neurofascin autoantibodies in demyelinating diseases such as multiple sclerosis (9). Neurofascin antibodies appear to be much more common in primary progressive multiple sclerosis than in relapsing-remitting multiple sclerosis (10) (**Table 1**). These studies suggest that axonal pathology associated with neurofascin 186 autoantibodies may contribute to the progressive course. In one of our patients, we also detected elevated ptau181, suggesting axonal brain damage. Considering the mechanistic studies of how neurofascin 186 autoantibodies might contribute to axonal brain pathology, the ptau181 elevation in one patient can be partially explained. However, axonal pathology in our cases was not caused by multiple sclerosis. The neuroaxonal CNS damage in strategically cognitively relevant areas may contribute to cognitive dysfunction. Mild cognitive dysfunction could also coincide with multiple sclerosis, but further progression to dementia would be entirely atypical for multiple sclerosis. However, the exact mechanism of cognitive dysfunction in association with neurofascin 186 autoantibodies remains unclear in our patients, especially when considering the Bradford-Hill criteria (11). In our patient 2, it seems unlikely that dysimmune neuropathy and a combined central and peripheral demyelinating syndrome cause the neurofascin 186-associated cognitive dysfunction because of increased brain injury proteins and evidence of intrathecal IgG synthesis suggesting a central inflammatory process. Note that FDG-PET results demonstrate hypometabolism of the frontal, temporal, and parietal lobes in the second patient. Frontotemporal degeneration might therefore be the probable cause of cognitive dysfunction in patient 2, although clinical features for FTD behavioral variant or primary progressive aphasia were not met. In addition, the cognitive impairment began at age 64 years, suggesting possible disease from frontotemporal lobar degeneration. However, the clinical and neuropsychological profiles do not suggest FTD in the second patient.

Our follow-up investigations showed persistent neurofascin 186 autoimmunity only in one of the two patients; a peripheral nervous system affectation is also clinically conceivable with persisting neurofascin 186 autoantibodies. Although not formally retested, cognitive impairment was still obvious at follow-up and in both cases. We do not finally know whether autoantibodies against neurofascin 186 play a causal role in cognitive impairment in these two patients. Additionally, both patients suffered from major depression and were positive for cardiovascular risk factors, the latter most probably having caused cerebral microangiopathy found in both MRIs. This might in turn have contributed – at least in parts – to the observed cognitive impairment. Moreover and most interestingly, both patients had a positive family history for dementia. As patient 1 suffered peripheral nerve damage, the presence of neurofascin 186 antibodies should be regarded in conjunction with her peripheral nerve system affectation while considering the main manifestations of neurofascin 186-related disease described so far (**Table 2**: overview of neurofascin 186 antibody-related disease).

4. Limitations

The main limitation of our case report is that we had no neuropsychological follow-up in either patient. In addition, the origin of MCI in both patients could also be influenced by vascular pathology, as evidenced by cerebral microangiopathy on MRI and the neuropsychological profile showing impairments in several cognitive domains. However, the mild degree of microangiopathy argue against a pronounced vascular pathology as a cause of MCI in these patients. In addition we cannot completely rule out that neurofascin 186 antibodies were false positive in the first case, as these were not replicated six months later. However, the clinically evident severe cognitive impairment and circumstantial evidence for neuroaxonal cell damage in the brain as well as intrathecal IgG synthesis support the possible role of these neurofascin 186 autoantibodies according to the recently published criteria for autoimmune-based psychiatric syndromes (12). It would be beneficial to measure ptau181 levels in a future study to see whether tau levels normalize over the time course of neurofascin 186-associated cognitive impairment, which we would expect to be the case in autoimmune-mediated cognitive impairment. In the second case, the repeated findings of neurofascin 186 antibodies in addition to brain abnormalities also argue against a false-positive effect of the autoantibody results. Another point worth mentioning is that no patient so far underwent immunotherapy as an individual drug trial, so the we cannot assess any benefit of immunotherapy which would have delivered potential evidence of a possible link between the cognitive impairment and an autoimmune basis of the neurofascin 186 autoantibodies.

5. Conclusion

Our results demonstrate that neurofascin 186 autoantibodies associated with amnestic MCI occur in multiple domains that should be considered in the differential diagnosis for mild cognitive impairment. The strength of this case series is the careful differential diagnosis with a large panel of neural autoantibodies, especially neurofascin 186 autoantibodies, and the longitudinal follow-up in both patients with MCI. Follow-up in both patients with stable cognitive impairment is also suggestive of an autoimmune-mediated time course and reveals no obviously progressive clinical course as in neurodegenerative diseases. These patients have not undergone immunotherapy because of the lack of evidence. More research is needed to investigate the presence of these autoantibodies in association with cognitive impairment in a larger homogeneous cohort without peripheral nervous system involvement and to include comprehensive clinical follow-up to better assess the clinical significance of autoantibody findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

Ethics statement

Ethical approval is given for this study. The patients provided their written informed consent to participate in the study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this study.

Author contributions

NH and BC wrote the manuscript. All authors revised the manuscript for important intellectual content.

Funding

JW was supported by an Ilídio Pinho professorship, iBiMED (UIDB/04501/2020) at the University of Aveiro, Portugal. This study was funded by the Open Access fund of the University of Göttingen.

Acknowledgments

We thank Carole Cürten for editing and proofreading the English language in this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Ng J, Malotka J, Kawakami N, Derfuss T, Khademi M, Olsson T, et al. Neurofascin as a target for autoantibodies in peripheral neuropathies. *Neurology.* (2012) 79:2241–8. doi: 10.1212/WNL.0b013e31827689ad

2. Delmont E, Manso C, Querol L, Cortese A, Berardinelli A, Lozza A, et al. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain.* (2017) 140:1851–8. doi: 10.1093/brain/awx124

3. Vallat J, Mathis S, Magy L, Bounolleau P, Skarzynski M, Heitzmann A, et al. Subacute nodopathy with conduction blocks and anti-neurofascin 140/186 antibodies: an ultrastructural study. *Brain.* (2018) 141:e56. doi: 10.1093/brain/awy134

4. Liu S, Zhang Y, Zhao H, Liu T, Shi J. Anti-neurofascin 186 antibody in amyotrophic lateral sclerosis: a case report. *Acta Neurol Belg.* (2022). doi: 10.1007/s13760-022-01989-y [Epub ahead of print].

5. Xie C, Wang Z, Zhao N, Zhu D, Zhou X, Ding J, et al. From PNS to CNS: characteristics of anti-neurofascin 186 neuropathy in 16 cases. *Neurol Sci.* (2021) 42:4673–81. doi: 10.1007/s10072-021-05101-9

6. Telley L, Cadilhac C, Cioni J, Saywell V, Jahannault-Talignani C, Huettl R, et al. Dual function of NRP1 in axon guidance and subcellular target recognition in cerebellum. *Neuron.* (2016) 91:1276–91. doi: 10.1016/j.neuron.2016.08.015

7. Rondi-Reig L, Paradis A, Fallahnezhad M. A liaison brought to light: cerebellum-hippocampus, partners for spatial cognition. *Cerebellum.* (2022) 21:826–37. doi: 10.1007/s12311-022-01422-3

8. Mathey E, Derfuss T, Storch M, Williams K, Hales K, Woolley D, et al. Neurofascin as a novel target for autoantibody-mediated axonal injury. *J Exp Med.* (2007) 204:2363–72. doi: 10.1084/jem.20071053

9. Kira J, Yamasaki R, Ogata H. Anti-neurofascin autoantibody and demyelination. *Neurochem Int.* (2019) 130:104360. doi: 10.1016/j.neuint.2018.12.011

10. Stich O, Perera S, Berger B, Jarius S, Wildemann B, Baumgartner A, et al. Prevalence of neurofascin-155 antibodies in patients with multiple sclerosis. *J Neurol Sci.* (2016) 364:29–32. doi: 10.1016/j.jns.2016.03.004

11. Hill A. The environment and disease: association or causation?. *Proc R Soc Med.* (1965) 58:295–300. doi: 10.1177/003591576505800503

12. Hansen N, Lipp M, Vogelgsang J, Vukovich R, Zindler T, Luedecke D, et al. Autoantibody-associated psychiatric symptoms and syndromes in adults: a narrative review and proposed diagnostic approach. *Brain Behav Immun Health.* (2020) 9:100154. doi: 10.1016/j.bbih.2020.100154

13. Fels M, Fisse A, Schwake C, Motte J, Athanasopoulos D, Grüter T, et al. Report of a fulminant anti-pan-neurofascin-associated neuropathy responsive to rituximab and bortezomib. *Peripher Nerv Syst.* (2021) 26:475–80. doi: 10.1111/jns.12465

14. Tan C, Goh K, Oh A, Devaux J, Shahrizaila N. Autoantibody profile in a Malaysian cohort of chronic inflammatory demyelinating polyneuropathy. *Neuromuscul Disord.* (2022) 32:255–62. doi: 10.1016/j.nmd.2022.01.006

15. Devaux JJ, Odaka M, Yuki N. Nodal proteins are target antigens in guillain-barré syndrome. *J Peripher Nerv Syst.* (2012) 17:62–71. doi: 10.1111/j.1529-8027.2012.00372.x

16. Notturno F, Di Febo T, Yuki N, Fernandez Rodriguez B, Corti D, Nobile-Orazio E, et al. Autoantibodies to neurofascin-186 and gliomedin in multifocal motor neuropathy. *J Neuroimmunol.* (2014) 276:207–12. doi: 10.1016/j.jneuroim.2014.09.001

17. Klehmet J, Staudt M, Diederich J, Siebert E, Meinl E, Harms L, et al. Neurofascin (NF)155- and NF186-specific T cell response in a patient developing a central pontocerebellar demyelination after 10 years of CIDP. *Front Neurol.* (2017) 8:724. doi: 10.3389/fneur.2017.00724

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 05 May 2023
DOI 10.3389/fpsyt.2023.1133302

Check for updates

OPEN ACCESS

EDITED BY
Shaheen E. Lakhan,
Click Therapeutics, Inc., United States

REVIEWED BY
Daichi Morioka,
Yamagata University, Japan
Sanjeev Kumar,
University of Toronto, Canada

*CORRESPONDENCE
Niels Hansen
✉ niels.hansen@med.uni-goettingen.de

RECEIVED 28 December 2022
ACCEPTED 10 April 2023
PUBLISHED 05 May 2023

CITATION
Hansen N, Teegen B, Hirschel S, Wiltfang J, Schott BH, Malchow B and Claudia B (2023) Case report: Anti-CARPVIII autoantibody-associated mixed dementia.
Front. Psychiatry 14:1133302.
doi: 10.3389/fpsyt.2023.1133302

COPYRIGHT
© 2023 Hansen, Teegen, Hirschel, Wiltfang, Schott, Malchow and Claudia. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Case report: Anti-CARPVIII autoantibody-associated mixed dementia

Niels Hansen[1,2]*, Bianca Teegen[3], Sina Hirschel[1], Jens Wiltfang[1,4,5], Björn H. Schott[1,4,6], Berend Malchow[1] and Bartels Claudia[1]

[1]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Germany, [2]Translational Psychoneuroscience, Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany, [3]Clinical Immunological Laboratory Prof. Stöcker, Groß Grönau, Germany, [4]German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany, [5]Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal, [6]Leibniz-Institute of Neurobiology, University of Magdeburg, Magdeburg, Germany

Background: Anti-carbonic anhydrase-related protein VIII (CARPVIII) is reported to be associated with paraneoplastic cerebellar degeneration. Our case extends the spectrum of anti-CARPVIII-associated disease to severe cognitive impairment.

Methods: We present the case of a 75-year-old woman who presented to our Department of Psychiatry and Psychotherapy with a dementia syndrome. The diagnostic approach included magnetic resonance imaging (MRI), cerebrospinal fluid analysis (CSF) analysis involving autoantibody determination, and neuropsychological examination.

Results: Neuropsychological examination revealed severe cognitive impairment meeting the criteria for dementia. MRI showed evidence of moderate cerebral microangiopathy. CSF analysis revealed mild pleocytosis, and serum analysis revealed anti-CARPVIII autoantibodies. Based on the dementia syndrome entailing signs of CNS inflammation such as pleocytosis and the repeated detection of anti-CARPVIII autoantibodies in serum, we diagnosed autoimmune dementia as a component of mixed dementia with additional vascular dementia components.

Conclusion: Our finding adds severe cognitive impairment to the spectrum of anti-CARPVIII-associated disease. However, detecting anti-CARPVIII antibodies may also be an incidental finding in conjunction with typical mixed dementia. Further studies are needed to evaluate the relevance of these clinical findings.

KEYWORDS

anti-CARPVIII autoantibody, dementia, psychiatry, autoimmunity, mixed dementia

1. Introduction

Anti-carbonic anhydrase-related proteins such as anti-carbonic anhydrase-related protein VIII (CARPVIII) were detected in paraneoplastic cerebellar degeneration (1–3). Carbonic anhydrase-related proteins play a role in various biological processes (4). CARPV III is a catalytically active protein in the carbonic anhydrase (CA) gene family; it has been associated with colorectal cancer (5) and breast cancer (6). There has been no report to date of progressive cognitive impairment associated with CARPVIII autoantibodies. We present the case of a

10.3389/fpsyt.2023.1133302

75-year-old woman with a dementia syndrome associated with CARPVIII autoantibodies. In addition to her dementia's possible autoimmune origin we detected circumstantial evidence of a vascular component.

2. Case presentation

A 75-year-old woman presented to the memory outpatient clinic of the Department of Psychiatry and Psychotherapy of the University Medical Center Göttingen because of concentration difficulties as well as memory and retentiveness disorders that had been gradually developing for 2 years (Table 1; Figure 1). She could not always remember orders for certain activities. No episodes of transient loss of consciousness have been reported. Similarly, there was no clinical evidence of delirium. She also complained of a gait disorder, but is unsure about when exactly it started. Her recurrent depressive disorder had been documented; she currently suffers mild to no specific depressive symptoms involving reduced drive, impaired concentration, brooding cognitions, apathy, and social withdrawal. The patient is already dependent on her grandson's help, as he lives with her in the house. She was a saleswoman, and worries a lot about her daughter. Her psychopathological examination confirmed the reported disturbances of memory and retention, but there was no other psychopathology evident. Neurological examination revealed an extinguished patellar reflex on the right side and extinguished Achilles tendon reflexes on both sides. She also revealed mild foot jack paresis on the right. We found no evidence of rigor, tremor, or cogwheel phenomenon. She also complained of urinary incontinence and occasional fecal incontinence. Pre-existing conditions are a chronic pain syndrome with psychological and somatic factors of unclear onset. She has ventrolisthesis of LWK3 versus LWK4 and LWK4 versus LWK5, in addition to facet joint atresia and osteochondrosis intervertebralis. In addition, she has two artificial knee joints, as well as arterial hypertension, obesity, and presbycusis. She suffered a Weber B fracture on the left side in 2017. Neuropsychological testing revealed impaired semantic and phonematic word fluency, reduced cognitive processing speed, faulty switching ability, a pathological clock test, and verbal memory deficits (encoding and delayed recall of verbal, non-associated information, encoding and delayed recall of complex verbal content) (Figure 2). Results from her thorough neuropsychological tests are in Figure 2. The other parameters tested, such as confrontation recognition, action planning, working and figural memory, verbal discriminability, visuoconstructive skills, and visuospatial perception, corresponded to her educational level. Her profile was thuson the borderline between mild amnestic cognitive impairment and an incipient dementia syndrome. Taking into account her significantly impaired daily living skills (B-ADL = 7.8) (according to her daughter), the dementia criteria are clinically fulfilled. Her magnetic resonance imaging (MRI) findings (Table 1) revealed a Fazekas grade II and medial temporal lobe atrophy score of 2 suggesting mixed dementia. In more detail: the MRI examination she had December of last year showed evidence of a general, primarily internal cerebral volume reduction with an advanced microangiopathic damage pattern. We detected Fazekas grade II microangiopathic anomalies. When she underwent MRI, her cognitive symptoms had been present for 1 year. The computed

TABLE 1 Clinical and laboratory characteristics of patient.

Parameter	
Demographic parameter	
Sex	Female
Age y	75
Age of onset y	73
Psychopathology	
Orientation dysfunction	0
Attentional dysfunction	1
Memory disturbances	1
Formal thought disorder	0
Affective disturbance	0
Drive and psychomotor disturbance	0
CSF	
Cell count (<5 µL)	6
Albumin mg/L	273
Tau protein (<415 pg/mL)	418
P Tau protein 181 (<50 pg/mL)	54.8
Aß42 (>570 pg/mL)	1,218
Aß40	13,283
Ratio Aß42/40 (>0.06)	0.092
Blood brain barrier disturbance	0
Intrathecal IgG synthesis	0
Serum autoantibodies	Anti-CARPVIII++1: 32
MRI	
Generalized atrophy	1
Focal atrophy	1
Hippocampal atrophy	1
Vascular pathology	1

Aß42, Amyloid-ß 42; Aß40, amyloid-ß 40; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; P Tau Protein 181, phosphorylated tau protein 181; ratio Aß42/40, ratio of amyloid-ß 42/ ratio of amyloid-ß 40; y, years. The values are depicted as mean ± standard deviation. For laboratory data normal ranges are shown in brackets. Reference values: refers to reference values from the Laboratory for Clinical Neurochemistry and Neurochemical Dementia Diagnostics, Department of Psychiatry and Psychotherapy, University Hospital Erlangen. *0 = item not present, # 1 = item present.

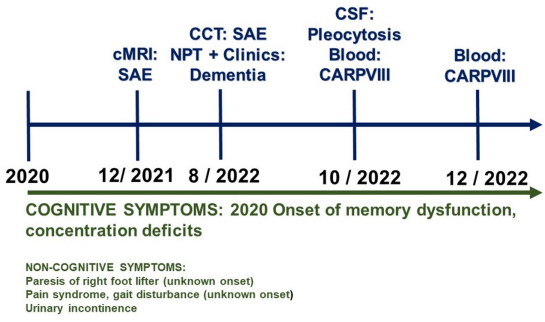


FIGURE 1
Time course of the patient's symptoms and diagnostics. CARPVIII, Anti-carbonic anhydrase-related protein VIII; MRI, magnetic resonance imaging; NPT, neuropsychological testing; SAE, subcortical arteriosclerotic encephalopathy.

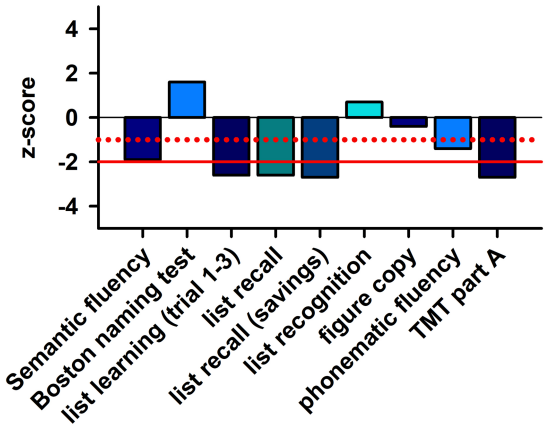


FIGURE 2
Neuropsychological profile of patient. TMT part A, trial making test part A. The dotted red line indicates the level of the single standard deviation and the solid red line shows the level of the double standard deviation.

tomography taken 1 year later (2 months after she presented in our outpatient memory clinic) also showed a dilated ventricular system with widespread brain atrophy. Her (123) I N-omega-fluoropropyl-2beta-carbomethoxy-3beta-{4-iodophenyl}nortropane single photon emission computed tomography examination showed no reduced dopaminergic uptake in the nigrostriatal system. A differential-diagnostic cerebrospinal fluid (CSF) puncture showed mild pleocytosis (6/µL, reference: ≤ 5/µL, Table 1) with a predominant pattern of lymphocytes (93%), elevated phosphorylated tau protein 181 (54.8 pg/mL, pathological: > 50 pg/mL, Table 1) and total tau protein (418 pg/mL, reference, <415 pg/mL), and anti-CARPVIII autoantibodies in the serum at 1:32 intensity (Table 1; Figure 1). The CSF analysis revealed no abnormalities in the beta amyloid peptides: amyloid beta 42 (Aß42), amyloid beta 40 (Aß40) and the amyloid beta 42/40 (Aß42/40) ratio were all in the normal range. In a repeated blood test 2 months later, we detected anti-CARPVIII autoantibodies again at a greater intensity of 1:32 (Figure 1). The autoantibodies were determined in the Clinical Immunological Laboratory from Prof. Stöcker. Relying on the dementia syndrome involving signs of CNS inflammation such as pleocytosis and after detecting anti-CARPVIII autoantibodies in serum, we diagnosed an autoimmune dementia as a component of mixed dementia with additional vascular dementia components present. Our repeated detection of anti-CARPVIII autoantibodies in her serum confirmed their presence as a relevant finding. Portions of the dementia syndrome may also be vascular in origin. There was no evidence of dementia with Lewy bodies or dementia due to Parkinson's disease. In case of an inconspicuous ratio Aß42/40, an Alzheimer pathology as a second etiology of mixed dementia is equally unlikely, but cannot be excluded in the presence of elevated ptau181. Thus, we cannot entirely rule out a typical mixed dementia with both vascular components and Alzheimer pathology, but that is quite unlikely. Furthermore, as her ptau181 was only slightly elevated, Alzheimer's disease is unlikely as the cause of her cognitive impairment. She suffered from a gait disturbance, urinary incontinence, and dementia-like syndrome, thus fulfilling the Hakim triad, so we considered the differential diagnosis of normal pressure hydrocephalus. However, there was no evidence of normal pressure hydrocephalus on imaging, and the gait disturbance could be attributable to her pre-existing spinal anomalies and foot lifter paresis. Her cognitive impairments could also be explained differently *via* the mixed dementia, thus ruling out a normal pressure hydrocephalus as a differential diagnosis. Our patient underwent her last follow-up examinations as an inpatient in December last year. She has not undergone any additional follow-up examinations since then. Therapeutically speaking, we limited ourselves to treating her vascular risk factors by prescribing telmisartan 80 mg/d and atorvastatin 20 mg/d. She has not been offered immunotherapy given the slow progression of her symptoms and mixed dementia. However, should her symptoms begin again to deteriorate and were we to detect anti-CARPVIII autoantibodies again, immunotherapy would be an option as an individualized curative approach.

3. Discussion

Our results demonstrate the novelty of a progressive cognitive impairment associated with CARPVIII autoantibodies. CARPs are involved in acid–base regulation and motor coordination, as studies in zebrafish showed (7). In particular, CARPVIII is involved in motor coordination functions in mice and humans (8). Interestingly, a homozygous missense mutation in CARPVIII protein impaired the function of inositol 1,4,5-trisphosphate to bind to inositol 1,4,5-trisphosphate receptor I, resulting in ataxia associated with mild cognitive impairment (9). Inositol 1,4,5-trisphosphate, which binds to the inositol receptor, is important in regulating the intracellular calcium concentration as a calcium channel in the endoplasmic reticulum membrane. In addition, inositol 1,4,5-trisphosphate, which binds to the inositol receptor, is very abundant in Purkinje cell neurons. Because the cerebellum is also involved in cognitive processes through anatomical fiber projections to the cortex and hippocampus (10), it is conceivable that cognition may be chronically impaired in patients with persistent CARPVIII autoantibodies due to dysfunctional connectivity between the cerebellum and hippocampus. Another possibility is that preexisting vascular dementia characterized by severe cerebral microangiopathy is exacerbated by an inflammatory process detected by CARPVIII antibodies and pleocytosis. Autoantibodies have even been detected in classic forms of dementia such as Alzheimer's disease (11) and Creutzfeld-Jacob disease (12). Vascular dementia is reportedly associated with antiphospholipid antibodies (13). Thus, in our patient, a mixture of autoimmune and vascular processes is probably responsible for her worsening cognitive functions, although we cannot demonstrate a direct causal relationship. Viral CARPs, for example, have the important function of binding to host cells. Therefore, autoantibody production could also be directed against the process of virus docking to the host cell. In this sense, anti-CARPVIII autoantibodies may reflect a mechanism in our immune system's antiviral defense strategy.

Weaknesses in our case report include the low evidence level inherent to a case report. In addition, as we detected no CARPVIII antibodies in the CSF and also found no evidence of intrathecal IgG synthesis, our claim that she may have an autoimmune-related cognitive disorder is somewhat weakened. Ultimately, it is unclear whether the vascular anomalies are contributing substantially to her

cognitive disorder. Strengths of our report are that, to our knowledge, anti-CARPVIII autoantibodies have not previously been reported in association with cognitive disorder. Furthermore, the fact that we detected anti-CARPVIII antibodies repeatedly suggests that this is a relevant finding. We therefore believe that this case report's novelty represents a clear strength – and one that outweighs the weakness of a low evidence level. The anti-CARPVIII autoantibody has extremely seldom been reported in a clinical context, but it has already being investigated in a few patients in research studies addressing neuroimmunological disorders (2, 14).

Our case highlights the need for further research on the occurrence of anti-CARPVIII autoantibodies in dementia and, in particular, in mixed dementia coinciding with vascular pathology. The prognosis is unclear, as we have no experience with anti-CARPVIII associated cognitive impairment. The vascular damage with no evidence of Alzheimer's pathology suggests a rather slow progression, which, however, could also be stepwise and not quite uniform. Thus, the outcome with the present course is rather favorable with regard to an incipient need for care and a rapid loss of independence. However, the possibility of a typical mixed dementia involving neurodegenerative and vascular pathology cannot be excluded, and our detection of CARPVIII autoantibodies might thus be an incidental finding. In conclusion: our report broadens the spectrum of autoantibodies occurring in autoimmune dementia and mixed dementia with vascular co-pathology.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

Ethics statement

The study involving human participants was reviewed and approved by Ethics committee of the University Medical Center Göttingen. The patient provided their written informed consent to publish the clinical data. Written informed consent was obtained from the individual for the publication of any potentially identifiable images included in this article.

Author contributions

NH wrote the article. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Höftberger R, Sabater L, Velasco F, Ciordia R, Dalmau J, Graus F. Carbonic anhydrase-related protein VIII antibodies and paraneoplastic cerebellar degeneration. *Neuropathol Appl Neurobiol*. (2014) 40:650–3. doi: 10.1111/nan.12118

2. Mitoma H, Nanri K. Autoantibodies associated with autoimmune-mediated cerebellar ataxia. *Brain Nerve*. (2013) 65:355–64.

3. Sakai K. Paraneoplastic cerebellar degeneration. *Brain Nerve*. (2010) 62:357–64.

4. Taniuchi K, Nishimori I, Takeuchi T, Fujikawa-Adachi K, Ohtsuki Y. Onishi S developmental expression of carbonic anhydrase-related proteins VIII, X, and XI in the human brain. *Neuroscience*. (2002) 112:93–9. doi: 10.1016/s0306-4522(02)00066-0

5. Miyaji E, Nishimori I, Taniuchi K, Takeuchi T, Ohtsuki Y, Onishi S. Overexpression of carbonic anhydrase-related protein VIII in human colorectal cancer. *J Pathol*. (2003) 201:37–45. doi: 10.1002/path.1404

6. Prevezianou A, Tzartos JS, Dagklis IE, Bentenidi E, Angelopoulos P, Bostantjopoulou S. Paraneoplastic cerebellar degeneration in a patient with breast cancer associated with carbonic anhydrase-related protein VIII autoantibodies. *J Neuroimmunol*. (2020) 344:577242. doi: 10.1016/j.jneuroim.2020.577242

7. Aspatwar A, Syrjänen L, Parkkila S. Roles of carbonic anhydrases and carbonic anhydrase related proteins in zebrafish. *Int J Mol Sci*. (2022) 23:4342. doi: 10.3390/ijms23084342

8. Aspatwar A, Tolvanen MEE, Barker H, Syrjänen L, Valanne S, Purmonen S, et al. Carbonic anhydrases in metazoan model organisms: molecules, mechanisms, and physiology. *Physiol Rev*. (2022) 102:1327–83. doi: 10.1152/physrev.00018.2021

9. Tada M, Nishizawa M, Onodera O. Roles of inositol 1,4,5-trisphosphate receptors in spinocerebellar ataxias. *Neurochem Int*. (2016) 94:1–8. doi: 10.1016/j.neuint.2016.01.007

10. Rochefort C, Lefort JM, Rondi-Reig L. The cerebellum: a new key structure in the navigation system. *Front Neural Circuits*. (2013) 7:35. doi: 10.3389/fncir.2013.00035

11. Hansen N, Malchow B, Teegen B, Wiltfang J, Bartels C. Case report: Alzheimer's dementia associated with cerebrospinal fluid Neurochondrin autoantibodies. *Front Neurol*. (2022) 13:879009. doi: 10.3389/fneur.2022.879009

12. Grau-Rivera O, Sánchez-Valle R, Saiz A, Molinuevo JL, Bernabé R, Munteis E, et al. Determination of neuronal antibodies in suspected and definite Creutzfeldt-Jakob disease. *JAMA Neurol*. (2014) 71:74–8. doi: 10.1001/jamaneurol.2013.4857

13. Mosek A, Yust I, Treves TA, Vardinon N, Korczyn AD, Chapman J. Dementia and antiphospholipid antibodies. *Dement Geriatr Cogn Disord*. (2000) 11:36–8. doi: 10.1159/000017211

14. Jarius S, Metz I, König FB, Ruprecht K, Reindl M, Paul F, et al. Screening for MOG-IgG and 27 other anti-glial and anti-neuronal autoantibodies in 'pattern II multiple sclerosis' and brain biopsy findings in a MOG-IgG-positive case. *Mult Scler*. (2016) 22:1541–9. doi: 10.1177/1352458515622986

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 18 May 2023
DOI 10.3389/fpsyt.2023.1168302

Check for updates

OPEN ACCESS

EDITED BY
Vincenza Frisardi,
Santa Maria Nuova Hospital, Italy

REVIEWED BY
Luiz Eduardo Betting,
São Paulo State University, Brazil
Jerome Aupy,
Université de Bordeaux, France

*CORRESPONDENCE
Alexandre Morin
✉ alexandre.morin@chu-rouen.Fr

RECEIVED 17 February 2023
ACCEPTED 02 May 2023
PUBLISHED 18 May 2023

CITATION
Porpiglia F, Guillaume M, Bliaux E, Psimaras D, Decazes P, Guillin O, Rothärmel M and Morin A (2023) Anti-leucine-rich glioma-inactivated 1 encephalitis revealed by a manic episode: insights from frontal lobe dysfunction in neuropsychiatry through neuropsychology and metabolic imaging. A case report.
Front. Psychiatry 14:1168302.
doi: 10.3389/fpsyt.2023.1168302

COPYRIGHT
© 2023 Porpiglia, Guillaume, Bliaux, Psimaras, Decazes, Guillin, Rothärmel and Morin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Anti-leucine-rich glioma-inactivated 1 encephalitis revealed by a manic episode: insights from frontal lobe dysfunction in neuropsychiatry through neuropsychology and metabolic imaging. A case report

Federica Porpiglia[1], Maxime Guillaume[2], Evangeline Bliaux[2], Dimitri Psimaras[3], Pierre Decazes[4], Olivier Guillin[1], Maud Rothärmel[1] and Alexandre Morin[1,2]*

[1]Department of Psychiatry, Rouvray Hospital, University of Rouen, Rouen, France, [2]Department of Neurology and CNR-MAJ, CHU Rouen, Univ Rouen Normandie, UNIROUEN, Rouen, France, [3]Department of Neurology 2-Mazarin AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Paris, France, [4]Department of Nuclear Medicine, Centre Henri-Becquerel, Rouen, France

Background: Anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis is a limbic encephalitis that rarely presents as an isolated psychiatric syndrome.

Case presentation: A 70-year-old patient first presented with behavioral disorder including hyperactivity, euphoria, with disinhibition and accelerated speech associated with severe insomnia and cognitive disorder. A manic episode was diagnosed and he received various psychotropic medications with no improvement. Invesitgations were negative (MRI showed T2 aspecific hyperintensities with no hyperintensities in limbic regions and EEG was normal). He was transferred to a nursing home, with a diagnosis of neurodegenerative condition. Later, he was referred to our unit for further investigations. A cerebral 18F-FDG-PET revealed an association of frontal hypometabolism and temporal and striatum hypermetabolism and CSF analysis revealed slightly increased white blood cell counts. Plasmatic anti-LGI1 antibodies were detected. The patient was treated with intra-venous immunoglobulin (Ivlg) but showed no improvement. Second-line treatment (a combination of rituximab and cyclophosmphamide) was then administered for a year, leading to an improvement of neuropsychiatric symptoms and normalization of metabolic impairment on 18F-FDG-PET.

Conclusion: In this report, we describe a novel case of a patient withanti-LGI1 encephalitis with a predominant long-term psychiatric presentation. An atypical presentation (such as atypical psychiatric symptoms, neurocognitive disorder, and hyponatremia) should prompt further investigations such as CSF analysis, considering that MRI and EEG may be normal. FDG-PET might be of interest but few data are available in the literature. Early treatment of anti-LGI1 encephalitis is crucial for overall prognosis and may delay the development of dementia in some cases.

KEYWORDS

anti-LGI1 encephalitis, limbic encephalitis, autoimmune manic syndrome, FDG-PET, behavior

Background

Limbic encephalitis (LE; also known as antibody-mediated encephalitis) represents a group of conditions which present essentially with neuropsychiatric symptoms (1). Initial presentation can vary and is often aspecific. In particular, psychiatric-onset LE can blur a clinician's judgement leading to a misdiagnosis, delayed immunotherapy and poor prognogis (2).

Although psychiatric symptoms are observed in 90% of patients (3), they often mask neurological manifestations, making the diagnosis of this disease challenging (2, 4–6). Patients are often first diagnosed with psychiatric disease, thus delaying immunotherapy.

Therefore, the aim of this report was to describe a case of anti-leucine-rich glioma-inactivated 1 (anti-GLI1) encephalitis with a predominant psychiatric presentation that caused a delay in diagnosis and treatment and a chronification of cognitive impairment.

Case report

A 70-year-old man presented to our unit for evaluation of behavioral and cognitive disturbance.

The patient was married and he had two children. Previously, he had worked in a heating company, but he was retired at the time of the visit. Prior to disease onset, he was totally self-sufficient.

The patient's medical history showed no evidence of psychiatric or neurological conditions beforehand. At the age of 57, he had colorectal cancer, which was in remission (annual colonoscopy). At the age of 67 (August 2018), he developed various behavioral symptoms such as hyperactivity, euphoria, with disinhibition and accelerated speech, and he had many renovation projects for his house. Moreover, he suffered from severe insomnia and reduced cognitive performance (for example, he was not able to recognize his own home or to remember dates). In October 2018, he started to present hallucinations, such as a sensation of bugs moving on his legs, seeing people in the woods, and hearing the phone ringing constantly. He also presented with persecutory delusion. At the same time, several episodes of confusion and temporospatial disorientation were reported by his wife. By December 2018, he started to exhibit cognitive impairment and memory loss together with insomnia and psychomotor agitation.

In January 2019, he was admitted to the psychiatric department of Dieppe Hospital (Normandy). Behavioral symptoms such as psychomotor agitation, insomnia and persecutory delusions were predominant. A diagnosis of manic episode with psychotic symptoms was discussed and further investigations were performed due to the atypical presentation. Magnetic resonance imaging (MRI) showed aspecific white matter hyper intensities, electroencephalogram (EEG) was normal and no neurological diagnosis was retained. At this time, laboratory testing showed hyponatremia (i.e., 132 mmol/L; reference range 136–145 mmol/L). The patient was treated with risperidone 2 mg but he experienced severe side effects such as confusion and hypothermia. He was then treated with sodium valproate 1 g.

Despite neuroleptic and mood-regulating treatments, the patient showed no improvement in clinical presentation whilst cognitive symptoms worsened. In August 2019, he was discharged with a diagnosis of dementia and was transferred to a nursing home.

Because of the severity of the disease a new visit was scheduled. In December 2019, the patient was admitted to our memory clinic at Rouen University Hospital, 1½ year after symptom exacerbation.

The neuropsychiatric examination pointed to mood fluctuations, apathy, delusions with a prominent Capgras syndrome, and insomnia. The patient did not present hallucinations or suicidal tendencies and had normal appetite. On the other hand, severe attention disorder, disinhibition, episodic memory impairment together with severe temporospatial disorientation and illogical speech were detected.

Neurological examination revealed no pyramidal or extrapyramidal syndrome, no sensorimotor disorder, no dysarthria, no facio-brachial dystonic seizures, no sign of dysautonomia, no ataxia.

Cerebrospinal fluid (CSF) analysis showed mildly elevated leukocytes (9/uL, normal range 0–8/uL) and an elevated protein level (49 mg/dL, normal range 20–40 mg/dL). Anti-LGI1 antibodies were positive both in serum and CSF. Sodium level and other laboratory blood tests were within normal ranges. Multiple EEGs including one sleep-deprived EEG were performed with no epileptiform discharges or patterns suggesting encephalitis. Cranial MRI exhibited few aspecific hyperintensities on T2-weighted fluid-attenuated inversion recovery sequences with no hyperintensities in limbic regions.

A cerebral FDG-PET examination revealed the association of frontal hypometabolism and temporal and striatum hypermetabolism (Figure 1). A whole-body FDG-PET/computer tomography scan revealed no structural or metabolic abnormalities.

Neuropsychological testing showed a deficit in Mini Mental State Examination (24 out of a maximum of 30 points), frontal syndrome [Frontal Assessment Battery (7) = 12/18] and severe difficulties in episodic memory (8, 9) as presented in Table 1.

The patient was diagnosed with anti-LGI1 autoimmune encephalitis and was initially treated with intra-venous immunoglobulins (IvIg) but showed no improvement of neuropsychiatric symptoms. A second-line treatment was then proposed to the patient, and he was administered immunotherapy combining rituximab and cyclophosphamide (rituximab on Day 1 (D1) and D15, cyclophosphamide on D30 and then once a month).

In October 2020, 6 months after the beginning of treatment, neuropsychiatric examination showed an improvement of behavioral and delusional symptoms but only a mild improvement of cognitive impairment: progress in memory tests but persistency of frontal lobe syndrome (Table 1).

Immunotherapy was pursued for 6 months followed by a rituximab perfusion twice a year with no adverse event.

New assessments were performed in April 2021, 1 year after the beginning of treatment. Clinical evaluation showed a consistent improvement of psychiatric symptoms, with normal thought and attention, no more mood fluctuations, disinhibition or apathy, no hallucinations or delusion. Sleep disturbances were still present, and a specialized examination ruled out obstructive sleep apnea (OSA). Cerebral FDG-PET showed a normalization of metabolic impairment (Figure 1).

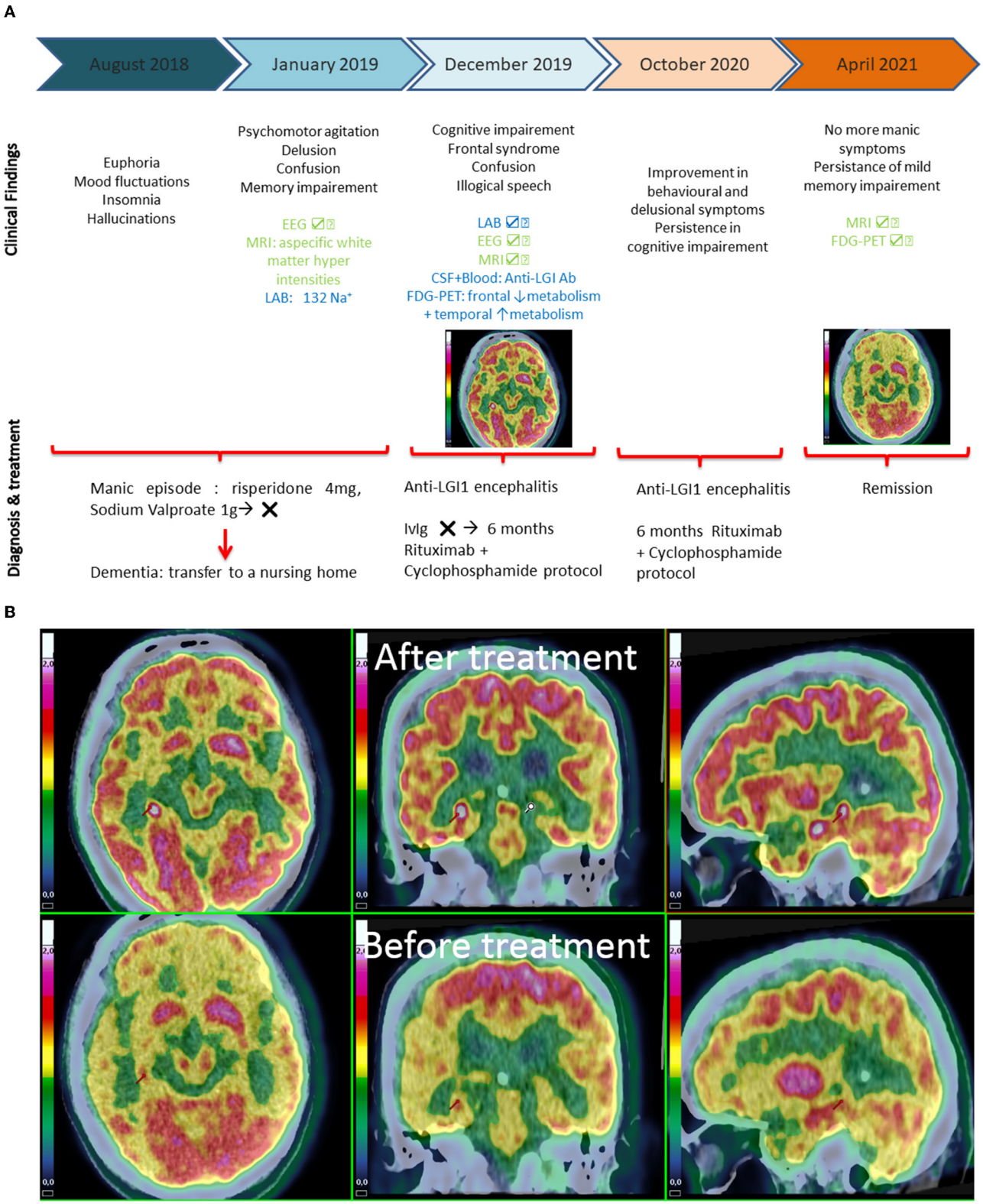


FIGURE 1
(A) Timeline from first symptoms to diagnosis and final treatment. **(B)** Brain FDG-PET: axial, coronal and sagittal orientation. Before treatment: diffuse frontal and temporal hypometabolism and striatum hypermetabolism. After treatment: improvement of orbito-frontal lobe and temporal hypometabolism and, to a smaller extent, of dorsolateral lobe hypometabolism. Anatomical orientation (right hemisphere on the right part of the figure). SUV ranging from 0 (blue) to 2 (red).

10.3389/fpsyt.2023.1168302

TABLE 1 Neuropsychological assessment before treatment (March 2019 and January 2020) and after treatment (October 2020).

	Neuropsychological test	Maximum	Mar-19	Jan-20	Oct-20	N/P
Global cognition	MMSE	30	24	18	20	**P**
Praxis	Gestures	8	8	7	8	N
Visuo-constructive skills	Rey's figure (copy)	36	36	35	33	N
Episodic memory	Free and cued selected recall test	list	A	A	B	
	Immediate recall	16	8	Aborted	14	N
	Free recall 1	16	2		4	**P**
	Total recall 1	16	2		8	**P**
	Free recall 2	16	0		4	**P**
	Total recall 2	16	Aborted		11	**P**
	Free recall 3	16			5	**P**
	Total recall 3	16			8	**P**
	Delayed free recall	16			2	**P**
	Delayed total recall	16			3	**P**
Frontal lobe dysfunction	Frontal Assesment Battery	18	12	13	12	N
	Trail Making Test					
	Trail Making Test A		46		64	N
	Trail Making Test B		223		95	N
	Trail Making Test Errors A		0		0	N
	Trail Making Test Errors B		0		0	N
Language	Naming	80	79	78	78	N
	Verbal fluency					
	Phonologic fluency		14	7	20	N
	Semantic fluency		11	5	16	N

N, normal range; P, pathological range. Bold values means "pathological scores".

Discussion

This report outlines the case of a patient presenting chronified anti-LGI1 encephalitis who had exhibited predominant manic syndrome with atypical symptoms including cognitive impairment for 1½ years. Our patient showed an obvious recovery after 1 year of immunomodulating treatment, from both a clinical and a metabolic point of view.

The predominant psychiatric manifestation of anti-LGI1 encephalitis over the course of almost 2 years without brachio-facial seizures or other neurological symptoms apart from cognitive disorder is rare. The clinical features of the present case are essentially those of a manic episode with insomnia, disinhibition, psychomotor agitation, flight of ideas and delusion. Neurocognitive symptoms, which are present in 97% of cases (10), appeared secondarily.

Classically, insomnia is more associated with a psychiatric condition, but it is also common in LGI1 encephalitis. This could have been misleading and could explain why no lumbar puncture or FDG-PET was proposed for the patient.

Disinhibition, agitation, working memory deficits can point to a frontal lobe syndrome as encountered in neurological conditions, but is also common in manic episodes (11). Cognitive disorders can sometimes be misleading in psychiatric conditions. It is often difficult to disentangle neurological from psychiatric frontal lobe dysfunction during the acute manic phase. Nevertheless, cognitive disorder should not evolve negatively in bipolar disorder, apart from long-term bipolar disorder (12) which was not the case here. Furthermore, episodic memory was involved which is more specific to neurological conditions.

Thus, rapidly evolving cognitive disorders, even when associated with psychiatric symptoms, should prompt extensive neurological workup. Most frequent diagnoses are sporadic Creutzfeldt-Jakob disease, autoimmune encephalitis and require MRI, EEG and lumbar puncture (13).

Three cases of patients presenting anti-LGI1 encephalitis with psychiatric presentation have been published, two with psychotic symptoms and memory loss (one of whom presenting faciobrachial seizures) (4, 14), and one with manic syndrome. However, unlike two of the above-cited cases (14), our patient's atypical presentation led to a delayed diagnosis as he presented symptoms for almost 2 years before being treated. Secondly, he did not have neurological symptoms and, in particular, he did not experience epileptic seizure, a feature which motivated clinicians to perform further tests in the above-cited case (15). Finally, our patient did not respond to first-line treatments but improved considerably after

1 year of rituximab-endoxan protocol, as opposed to one of these cases.

The concept of "autoimmune psychosis," including schizophrenia and manic episodes, was recently suggested, and red flags and consensus statements have been published (6). In this case, there were three red flags for a hidden autoimmune encephalitis: firstly, the atypical psychiatric presentation associated with severe cognitive impairment; secondly, the atypical age of onset of psychiatric symptoms, bipolar disorder being mostly diagnosed at a young age; and finally the clinical deterioration despite psychopharmacological treatment.

The positivity of anti-LGI1 antibodies in serum and CSF together with metabolic impairment revealed on FDG-PET led to a final diagnosis of anti-LGI1 encephalitis. The EEG of the present case is rare in this context (16). However, typical electro encephalographic features have not been described in the literature (17), and our patient did not have epileptic seizures which could explain the absence of EEG impairment. Hyponatremia, an emblematic feature of anti-LGI1 encephalitis, was initially observed. It has been reported in 60% of patients suffering from the disease, although the underlying mechanism has been investigated in a limited number of patients (18).

Meaningfully, cerebral FDG-PET findings were consistent with the association of temporal or basal ganglia hypermetabolism and frontomesial hypometabolism as described in other auto-immune encephalitis (18–20). Two case reports identified the presence of hypermetabolism in the basal ganglia as well as in the left hippocampus and amygdala in their patients a few months after clinical onset of anti-LG1 encephalitis (8, 21). In addition, Shin et al. showed temporal and bilateral basal ganglia hypermetabolism in most of their patients (3 days to 2 years further to diagnosis), suggesting that the anti-LGI1-induced brain metabolic pattern may depend on the disease evolution and delay between clinical onset and treatment administration.

Moreover, our patient's clinical improvement assessed 1 year after the beginning of the treatment was congruent with the disappearance of metabolic impairment on FDG-PET.

Our patient's poor response to anti-inflammatory first-line medications may be associated with the delayed diagnosis and therefore the start of treatment, as it is well-known that early medication is associated with better prognosis in autoimmune encephalitis (22). This concept is even more outstanding when considering anti-LGI1 encephalitis, as it is rarely associated with cancer comorbidities and has for this reason a better long-term prognosis if treated rapidly (10).

A recently published case report introduced the concept of a difference between "acute inflammatory state" and "state of organ damage" regarding autoimmune encephalitis (4). In the first case, anti-inflammatory treatment can control or completely suppress disease activity and thus possibly prevent irreversible damage, as opposed to the "state of organ damage" in which organ dysfunction has already occurred due to inflammatory activity. In the present case, the patient might have suffered from both lesions.

Some inflammatory lesions with altered metabolism on FDG PET might have been medication-responsive, such as behavioral symptoms (related to the orbito-frontal region) and improved memory impairment (related to the mesial temporal region). Some damage might have been out of reach of immunotherapy, especially regarding executive dysfunction (related to the dorso-lateral cortex), which remained impaired after 1 year of treatment.

Moreover, the severity of disease presentation required not only to use a second-line protocol, but also to extend the treatment period from 6 months to a year. Such treatments are not without side effects and the state of induced immunodeficiency could potentially lead to other infectious diseases. Future studies should focus on identifying biomarkers or clinical markers (red flags) of "acute inflammatory state" in predominantly psychiatric forms of anti-LGI1 encephalitis, in order to promote early treatment and therefore prevent the "state of organ damage."

Conclusion

A predominantl neurocognitive and manic presentation of anti-LGI1 encephalitis can lead to delayed diagnosis and treatment (2), therefore inducing a poorer response to medication. The detection of red flags for the presence of autoimmune encephalitis in patients with atypical psychiatric presentation is essential to treat the disease as rapidly as possible and to achieve full recovery. In this report, we describe a novel case of a patient with chronified anti-LGI1 encephalitis which improved both clinically and radiologically after 1 year of second-line treatment.

Patient's perspective

The patient was relatively anosognosic and did not express any improvement or side effects. His spouse reported a major subjective improvement of behavior and cognition and was prone to pursue intensive therapeutics.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AM and FP: substantial contributions to the conception or design of the work and drafting the work. AM, FP, EB, DP, and PD: acquisition, analysis, and the interpretation of data for the work. FP, MG, DP, PD, OG, and MR: revising the work critically for important intellectual content. AM: final approval of the version to

be published. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Sonderen A, Thijs RD, Coenders EC, Jiskoot LC, Sanchez E, de Bruijn MAA, et al. Anti-LGI1 encephalitis: Clinical syndrome and long-term follow-up. *Neurology.* (2016) 87:1449–56. doi: 10.1212/WNL.0000000000003173

2. Jang Y, Lee S-T, Lim J-A, Kim T-J, Jun J-S, Moon J, et al. Psychiatric symptoms delay the diagnosis of anti-LGI1 encephalitis. *J Neuroimmunol.* (2018) 317:8–14. doi: 10.1016/j.jneuroim.2018.02.005

3. Arino H, Petit-Pedrol M, Armangue T, Saiz A, Dalmau J, Graus F. Anti-LGI1-associated cognitive impairment: Clinical profiles and long-term outcome (P6.124). *Neurology.* (2016) 86(16Suppl.):3009.

4. Endres D, Prüss H, Dressing A, Schneider J, Feige B, Schweizer T, et al. Psychiatric manifestation of anti-LGI1 encephalitis. *Brain Sci.* (2020) 10:60375. doi: 10.3390/brainsci10060375

5. Honnorat J, Plazat LO. Autoimmune encephalitis and psychiatric disorders. *Rev Neurol.* (2018) 174:228–36. doi: 10.1016/j.neurol.2017.11.004

6. Herken J, Prüss H. Red flags: Clinical signs for identifying autoimmune encephalitis in psychiatric patients. *Front Psychiatry.* (2017) 8:25. doi: 10.3389/fpsyt.2017.00025

7. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: A frontal assessment battery at bedside. *Neurology.* (2000) 55:1621–6. doi: 10.1212/WNL.55.11.1621

8. Nakaoku Y, Maki T, Kanazawa K, Matsumoto R, Fukuyama H, Takahashi R, et al. *A Case of Smoldering Anti-leucine Rich Glioma Inactivated 1 (LGI1) Antibody-associated Limbic Encephalitis With Faciobrachial Dystonic Seizure*. Tokyo: Rinsho Shinkeigaku.

9. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. *Neurology.* (1988) 38:900–900. doi: 10.1212/WNL.38.6.900

10. Ariño H, Armangué T, Petit-Pedrol M, et al. Anti-LGI1–associated cognitive impairment: Presentation and long-term outcome. *Neurology.* (2016) 87:759–65. doi: 10.1212/WNL.0000000000003009

11. Abé C, Ekman CJ, Sellgren C, Petrovic P, Ingvar M, Landén M. Manic episodes are related to changes in frontal cortex: A longitudinal neuroimaging study of bipolar disorder 1. *Brain.* (2015) 138:3440–8. doi: 10.1093/brain/awv266

12. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, et al. A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord.* (2006) 93:105–15. doi: 10.1016/j.jad.2006.02.016

13. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. *Ann Neurol.* (2008) 64:97–108. doi: 10.1002/ana.21430

14. Wang D, Hao Q, He L, Wang Q. LGI1 antibody encephalitis and psychosis. *Australas Psychiatry.* (2018) 26:612–4. doi: 10.1177/1039856218771513

15. Tu TH, Chan YLE, Bai YM. Anti-leucine-rich glioma-inactivated 1 encephalitis with manic symptoms as the initial manifestation. *Aust N Z J Psychiatry.* (2018) 52:714–5. doi: 10.1177/0004867417742522

16. van Sonderen A, Schreurs MWJ, Wirtz PW, Sillevis Smitt PAE, Titulaer MJ. From VGKC to LGI1 and Caspr2 encephalitis: The evolution of a disease entity over time. *Autoimmun Rev.* (2016) 15:970–4. doi: 10.1016/j.autrev.2016.07.018

17. Aupy J, Collongues N, Blanc F, Tranchant C, Hirsch E, De Seze J. Encéphalites dysimmunitaires, données cliniques, radiologiques et immunologiques. *Rev Neurol.* (2013) 169:142–53. doi: 10.1016/j.neurol.2012.05.014

18. Shin YW, Lee ST, Shin JW, Moon J, Lim JA, Byun JI, et al. VGKC-complex/LGI1-antibody encephalitis: Clinical manifestations and response to immunotherapy. *J Neuroimmunol.* (2013) 265:75–81. doi: 10.1016/j.jneuroim.2013.10.005

19. Fauser S, Talazko J, Wagner K, Ziyeh S, Jarius S, Vincent A, et al. FDG-PET and MRI in potassium channel antibody-associated non-paraneoplastic limbic encephalitis: Correlation with clinical course and neuropsychology. *Acta Neurol Scand.* (2005) 111:338–43. doi: 10.1111/j.1600-0404.2005.00406.x

20. Wegner F, Wilke F, Raab P, Tayeb SB, Boeck AL, Haense C, et al. Anti-leucine rich glioma inactivated 1 protein and anti-N-methyl-D-aspartate receptor encephalitis show distinct patterns of brain glucose metabolism in 18F-fluoro-2-deoxy-d-glucose positron emission tomography. *BMC Neurol.* (2014) 14:136. doi: 10.1186/1471-2377-14-136

21. Kamaleshwaran KK, Iyer RS, Antony J, Radhakrishnan EK, Shinto A. *18F-FDG PET/CT Findings in Voltage-Gated Potassium Channel Limbic Encephalitis.* Clinical Nuclear Medicine, Philadelphia: Lippincott.

22. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol.* (2016) 15:391–404. doi: 10.1016/S1474-4422(15)00401-9

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 12 July 2023
DOI 10.3389/fpsyt.2023.1227824

Check for updates

OPEN ACCESS

EDITED BY
Takuma Inagawa,
National Center of Neurology and Psychiatry, Japan

REVIEWED BY
Yuto Uchida,
Johns Hopkins Medicine, United States
Masafumi Yoshimura,
Kansai Medical University, Japan
Hiroki Okano,
National Center of Neurology and Psychiatry, Japan

*CORRESPONDENCE
Niels Hansen
✉ niels.hansen@med.uni-goettingen.de

RECEIVED 23 May 2023
ACCEPTED 19 June 2023
PUBLISHED 12 July 2023

CITATION
Hansen N, Teegen B, Hirschel S, Wiltfang J, Schott BH, Bartels C and Bouter C (2023) Case report: Mixed dementia associated with autoantibodies targeting the vesicular glutamate transporter 2.
Front. Psychiatry 14:1227824.
doi: 10.3389/fpsyt.2023.1227824

COPYRIGHT
© 2023 Hansen, Teegen, Hirschel, Wiltfang, Schott, Bartels and Bouter. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Case report: Mixed dementia associated with autoantibodies targeting the vesicular glutamate transporter 2

Niels Hansen[1]*, Bianca Teegen[2], Sina Hirschel[1], Jens Wiltfang[1,3,4], Björn H. Schott[1,3,5], Claudia Bartels[1] and Caroline Bouter[6]

[1]Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany, [2]Clinical Immunological Laboratory Prof. Stöcker, Groß Grönau, Germany, [3]German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany, [4]Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal, [5]Leibniz Institute for Neurobiology, University of Magdeburg, Magdeburg, Germany, [6]Department of Nuclear Medicine, University Medical Center Göttingen, Göttingen, Germany

Background: Autoantibodies against the vesicular glutamate transporter type 2 (VGlut2) can trigger impaired synaptic signaling and are described here for the first time in association with mixed dementia.

Methods: We report on a 71-year-old female patient with a dementing syndrome who underwent a thorough dementia diagnosis including neuropsychological testing, magnetic resonance imaging (MRI), ^{18}F-fluorodesoxyglucose positron emission tomography (FDG-PET), and a spinal tap to search for neural autoantibodies.

Results: Our patient exhibited mixed dementia. Her CSF revealed elevated ptau 181 protein and a reduced Aß42/40 ratio indicating Alzheimer's disease (AD) pathology. In addition, neuropsychological testing showed a profile consistent with AD with impaired memory, reduced semantic word fluency, naming disorder, and impaired visuoconstructive skills. Nevertheless, in-depth neuropsychological testing also revealed marked psychomotor slowing and visuospatial perceptual impairments that are more indicative of the presence of DLB. Overall, her dementia is more likely of mixed pathology. In addition, we repeatedly detected VGlut2 autoantibodies in her serum.

Conclusion: To the best of our knowledge, this report is the first to describe mixed dementia associated with VGlut2 autoantibodies.

KEYWORDS

autoimmunity, cognition, VGlut2, autoantibodies, Alzheimer's dementia, depression

1. Introduction

An undisturbed glutamatergic excitatory neurotransmission between synapses can only occur when glutamate is transported *via* vesicles such as the vesicular glutamate transporter 2 (VGlut2). Several lines of evidence (1, 9) support the notion that Alzheimer's disease (AD) can be understood as a synaptopathy. The vesicular glutamate transporter 2 (VGlut2) as part of the glutamatergic systems is involved in AD. This assumption is based on observations that VGlut2 expression in the dorsolateral prefrontal cortex is reduced in Alzheimer's disease patients (2) as well as the fact that increased amyloid beta peptide accumulation takes place in the VGlut2 terminals (3). Antibodies against the VGlut2 transporter could cause synaptic dysfunction. In our case report, we describe the diagnosis of clinically and cerebrospinal fluid (CSF)-based AD associated with VGlut2 autoantibodies, which has never been

described to our knowledge. The role of VGlut2 autoantibodies in AD is unknown, but they may be associated with synaptic dysfunction, supporting the hypothesis of AD as synaptopathy. Through this report, the potentially diverse spectrum of neuronal autoantibodies in cognitive disorders (4, 5) can be supported.

2. Case report

A 71-year-old female patient presented to the emergency ward in our psychiatric clinic. For about half a year, she had been suffering from a depressed mood, pronounced restlessness, a concentration disorder, diffuse anxiety, and sleep disturbances (Figure 1). The depressive symptoms had been very obvious for 3 weeks. She had no appetite and cried more often during conversations. Her sense of joy was reduced, and there was general listlessness. She suffers from early waking, feeling depressed in the morning, and feeling a deep sense of shame. She also described passive death wishes, but no concrete suicidal thoughts. She reports no relevant psychosocial stress factors and even when asked, describes no stress factors. After careful questioning of her daughter, we learned that her retention and memory disorders had already existed for a year (Figure 1). The daughter also spoke of her considerably impaired daily living skills, stating that she could probably no longer manage alone at home and depended on her daughter for help with self-care. Nursing help would also be needed at home to ensure that her medications are taken. The patient is a Kazakhstan native who has lived in Germany for 30 years. She is a widow with two children. She is a trained hotel manager, a pensioner, and lives alone. Her daughter has the power of attorney for her healthcare. There are no known psychiatric diseases in her family history. She had no known somatic diseases. In her psychopathological examination, we observed indications of concentration and comprehension disturbances as well as impaired retentiveness and memory. Furthermore, she worries about the future. Her emotional state was depressed, and there was a disturbance of vital feelings. She also reported being less able to feel joy, a loss of interest, and reduced drive. She had also become socially withdrawn. Her neurological examination, however, was inconspicuous apart from the cognitive dysfunction. Her physical examination revealed no pathologies. Due to her serious memory problems that started before the depressive symptoms, we conducted extensive neuropsychological testing to make a differential diagnosis. The detailed neuropsychological examination revealed significant impairments in several cognitive domains such as orientation, semantic word fluency, confrontation naming, cognitive processing speed, visuomotor coordination, the clock test, action planning, working and figural memory, encoding and consolidation of verbal non-associated information, encoding

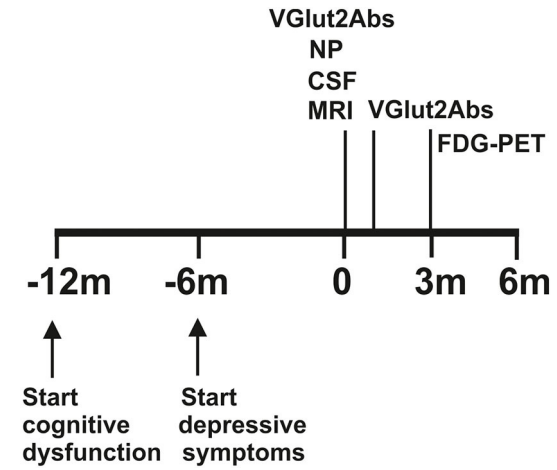


FIGURE 1
Time course of symptoms and investigations. MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; FDGPET, fluorodesoxyglucose positron emission computed tomography; M, month; MRI, magnetic resonance imaging; NP, neuropsychological testing; VGlut2 abs, vesicular glutamate transporter 2 autoantibodies.

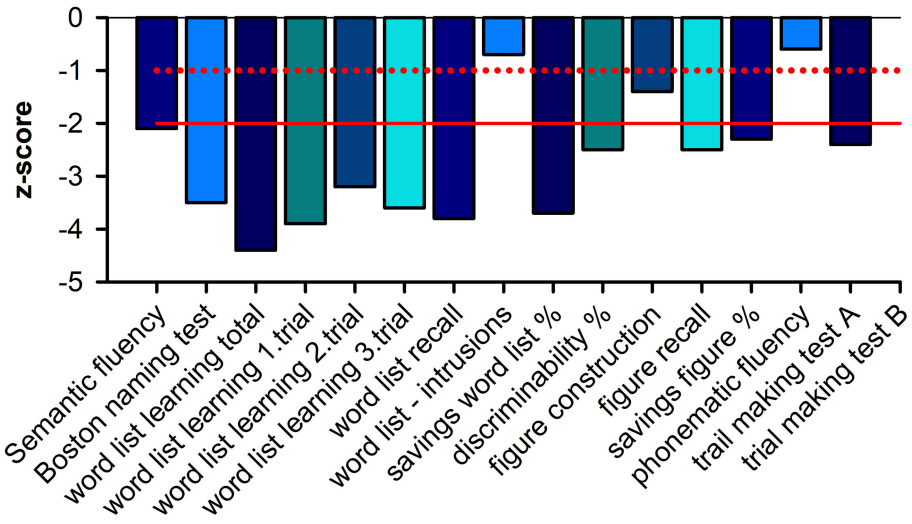


FIGURE 2
Neuropsychological profile.

10.3389/fpsyt.2023.1227824

TABLE 1 Data of neuropsychological testing.

Language	Raw value	Percentual rank
CERAD (age and education corrected standard)		
Boston Naming Test	7	0
Semantic word fluency	7	2
Phonematic word fluency	8	27
Attentional and executive functions		
WAIS-IV (age corrected standard)		
Number Symbol Test	16	1
TMT (age/education corrected standard)		
Part A seconds	112	1
Visuoconstruction		
Clock test	3	na
CERAD		
Constructive practice: Signing off	8	8
WAIS-IV (age corrected standard)		
Mosaic test	16	5
Learning and memory		
WAIS-IV (age corrected standard)		
Number span forward	7	16
Number span backward	5	9
CERAD (age and education corrected standard)		
Learn word list: Sum Trial 1-3	7	0
Word list free retrieval	0	0
Savings word list (%)	0	0
Word List Recognition (%)	80	1
WMS-IV (age corrected standard)		
Logical memory I	9	0,1
Logical memory II	0	0,1
CERAD (age and education corrected standard)		
Constructive praxis: free recall	1	1
Saving figures (%)	13	1

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition; WMS-IV, Wechsler Memory Scale - Fourth edition; TMT, Trial Making Test.

and delayed recall of complex verbal content, visuoconstructive skills, and visual-spatial perception objectified (Figure 2, Table 1). However, her phonematic word fluency was not age appropriate. From a neuropsychological point of view, the aforementioned dysfunctions go beyond depression-related cognitive impairments and are compatible with dementia syndrome. Her major memory impairment, reduced semantic word fluency with naming disorders, and limited visuoconstructive skills indicate AD dementia. Atypical for AD dementia is the pronounced psychomotor slowing and visual-spatial perceptual disturbances. To enable additional differential diagnosis of neurodegenerative dementia, she underwent magnetic resonance imaging (MRI).

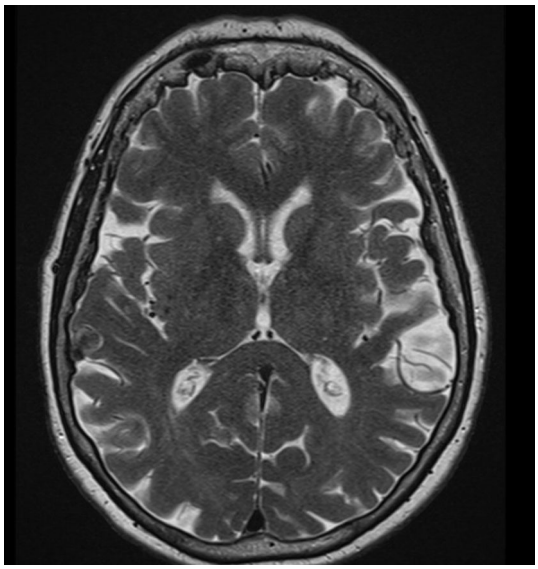


FIGURE 3
Magnetic resonance imaging. Magnetic resonance imaging (MRI) of the brain shows minor cerebral microangiopathy with periventricular vascular lesions in the white matter.

Cranial MRI showed isolated cerebral lesions in the periventricular white matter (Figure 3). Cerebrospinal fluid was collected to ensure a differential diagnosis of inflammatory and neurodegenerative causes of dementia syndrome. Cerebrospinal fluid (CSF) revealed a constellation of biomarkers compatible with AD, e.g., a reduced Aß42 /40 ratio (0.05, reference level: >0.06) and elevated ptau 181 protein (70 pg/ml, reference level: <50 pg/ml). We detected VGlut2 autoantibodies (1:100) in serum samples, observed again in serum samples (1:1000) 1 month later. In addition, after incubating the patient's serum with rat and monkey brain tissues, immunohistochemistry revealed relevant spotty fluorescence of the granular layer in the hippocampus and streaky fluorescence in the thalamus and molecular layer in the cerebellum caused by the antibody against VGlut2. ^{18}F-fluorodesoxyglucose positron emission tomography (^{18}F-FDG-PET) of the brain showed left parietal and left temporal hypometabolism (Figure 4). In addition, a reduced tracer uptake was also detected in the right cerebellum consistent with diaschisis. Furthermore, the lower ^{18}F-FDG uptake was detected in the left primary visual cortex (Figure 4). Overall, her PET provided evidence compatible with a DLB pattern or a pattern associated with a logopenic variant of primary progressive aphasia. To summarize her status, we suspect mixed dementia with Alzheimer's pathology and Lewy body pathology. The presence of AD is suggested by the CSF findings and her neuropsychological exam indicating impaired memory, reduced semantic word fluency and naming disorders, and impaired visuoconstructive skills. However, neuropsychological findings include marked psychomotor slowing and visuospatial perceptual disturbances, which are more indicative of the presence of DLB. However, note that biomarkers to diagnose DLB such as (123)-I-2-ß-carbomethoxy-3ß-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane single photon emission computed tomography (123I-FP-CIT SPECT) or [^{123}I] metaiodobenzylguanidine (MIBG)

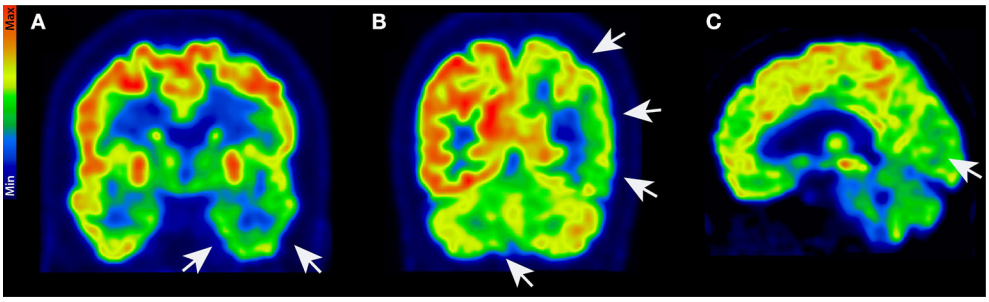


FIGURE 4
^{18}F-FDG-PET. ^{18}F-FDG-PET in coronal **(A, B)** and sagittal **(C)** view with distinct hypometabolism in the left temporal **(A)**, left parietal, and right cerebellar cortex **(B)**. Furthermore, hypometabolism in the left primary visual cortex was detected **(C)**. White arrows show brain areas with lower tracer uptake.

cardiac scintigraphy were not explored. However, as she presented no other DLB symptoms other than her cognitive symptoms, i.e., evidence of Parkinson's, a REM sleep behavior disorder, or visual hallucinations, we did not investigate this potential component of Lewy pathology further. Overall, therefore, hers is probably a mixed pathology. As we consistently detected VGlut2 autoantibodies in her serum, that finding is relevant. We, therefore, diagnosed mixed dementia associated with VGlut2 autoantibodies. We ruled out an acute inflammatory CNS event because of her CSF results. To exclude a tumor, she also underwent whole-body FDG PET, which revealed a suspicious nodule near the anterior sternum. An additional dermatologic workup revealed nothing conclusive. Due to mixed dementia with components of Alzheimer's pathology, we started anti-dementia therapy with the acetylcholinesterase inhibitor donepezil at a 10 mg/d dosage. In the absence of evidence of inflammation in the CSF, we have refrained from immunotherapy with methylprednisolone off-label for the time being. We also had this patient undergo antidepressant effective therapy with sertraline 100 mg/day and quetiapine 150 mg/day. Quetiapine was discontinued during the course in favor of mirtazapine 45 mg/day after observing the lack of efficacy under mirtazapine. We find it quite tempting to postulate that her depressive symptoms are an expression of the underlying neurodegenerative mixed dementia associated with VGlut2 autoantibodies. Overall, her diagnosis is probably consistent with the prognosis of mild dementia syndrome due to AD, but it remains unclear whether the additional association with VGlut2 tends to favor the prognosis. After inpatient treatment, the patient experienced two more outpatient follow-up visits. Under antidepressant and anti-dementia therapy, her cognitive symptoms remained stable, and the depressive symptoms largely disappeared. She now presents a euthymic mood with no significant loss of drive and no dangerous behavior. Her medical therapy has been well tolerated, and no relevant side effects have occurred.

3. Discussion

Our report is the first to describe to the best of our knowledge an AD associated with the presence of VGlut2 autoantibodies in serum. Moreover, we provide a new perspective on a possible autoimmune involvement in AD, our data broadly support the hypothesis of AD synaptopathy by postulating a pathogenic role of VGlut2 autoantibodies resulting in synaptic dysfunction. However, note that this report only demonstrates an association between VGlut2 autoantibodies and AD but not their pathogenic role. On the other hand, one can argue that our patient presents no clear AD clinically and laboratory-diagnostically since marked psychomotor slowing and visual-spatial perceptual disturbances are both neuropsychologically evident. The pattern of cerebral hypometabolism also supports the diagnosis of alpha-synucleinopathy, so we suspect a mixed etiology of AD pathology and alpha-synucleinopathy, which has not previously been reported in association with VGlut2 autoantibodies. Interestingly, there is evidence that in alpha-synucleinopathy Parkinson's disease, VGlut2 receptor expression is upregulated in the dopaminergic neurons remaining after neurodegeneration (6). Assuming at least a co-pathology of alpha-synuclein in our patient, the presence of VGlut2 autoantibodies could thus be relevant if pathogenicity is postulated (by penetrating the blood–brain barrier). The cerebral cortex contributes to memory performance (7), supporting our hypothesis that by blocking VGlut2 function, autoantibodies may impair cognitive function and lead to dementia.

3.1. Limitations

To date, VGlut2 autoantibodies have not been reported in association with mixed dementia; therefore, this is an atypical clinical syndrome that should be interpreted with caution in a single case report.

3.2. Conclusion

Our case highlights the occurrence of VGlut2 antibodies in mixed dementia, supporting an additional dimension of neural autoantibody-associated dementia. The strength of the case report lies in the new observation of the occurrence of VGlut2 autoantibodies in dementia syndrome. Although the pathophysiological basis of the symptoms can be traced back to a disturbed glutamate vesicle transport and altered synaptic information transmission and encoding, such a pathophysiological

basis as the cause of the symptoms remains speculative and cannot be proven at present. However, this report highlights a new rare autoantibody not previously described in the context of cognitive impairment that should be further investigated in larger cohorts, particularly in relation to AD pathology but also alpha-synucleinopathy. Recently, in a large study of 920 patients with neurodegenerative dementias, 0.8% were found to have neural autoantibodies (8). In this study, no abnormalities were found on MRI, and a small proportion was found with pleocytosis in CSF (8). This study confirms that autoantibody-associated predominantly neurodegenerative dementias that exist would benefit from a modified therapeutic approach. Such a therapeutic approach with immunotherapy and standard therapy should be investigated in larger studies. In addition, the low evidence level of this case report limits the significance considerably, and it remains to be seen whether it is not a purely indeterminate finding. Nevertheless, this case report appears to be a landmark and is therefore important to be reported.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

Ethics statement

The study involving human participants was reviewed and approved by the Ethics Committee of the University Medical Center Göttingen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NH wrote the manuscript. All authors have read, edited, and agreed to the submitted version of the manuscript.

Funding

Funding was received from the Fund for Open Access Publishing from the University of Göttingen. JW is supported by an Ilídio Pinho professorship, iBiMED (UIDB/04501/2020) at the University of Aveiro, Portugal.

Acknowledgments

The authors would like to thank Carole Cürten for editing and proofreading the English language in this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Pelucchi, S., Gardoni, F., Di Luca, M., and Marcello, E., (2022). Synaptic dysfunction in early phases of Alzheimer's Disease.[[i]]Handb Cl[[/i]]in Neurol.184, 417–438. doi: 10.1016/B978-0-12-819410-2.00022-9

2. Kashani A, Lepicard E, Poirel O, Videau C, David JP, Fallet-Bianco C, et al. Loss of VGLUT1 and VGLUT2 in the prefrontal cortex is correlated with cognitive decline in Alzheimer disease. *Neurobiol Aging.* (2008) 29:1619–30. doi: 10.1016/j.neurobiolaging.2007.04.010

3. Sokolow S, Luu SH, Nandy K, Miller CA, Vinters HV, Poon WW, et al. Preferential accumulation of amyloid-beta in presynaptic glutamatergic terminals (VGluT1 and VGluT2) in Alzheimer's disease cortex. *Neurobiol Dis.* (2012) 45:381–7. doi: 10.1016/j.nbd.2011.08.027

4. Hansen N, Lipp M, Vogelgsang J, Vukovich R, Zindler T, Luedecke D, et al. Autoantibody-associated psychiatric symptoms and syndromes in adults: a narrative review and proposed diagnostic approach. *Brain Behav. Immun. Health.* (2020) 9:100154. doi: 10.1016/j.bbih.2020.100154

5. Hansen N. Current nosology of neural autoantibody-associated dementia. *Front Aging Neurosci.* (2021) 13:711195. doi: 10.3389/fnagi.2021.711195

6. Steinkellner T, Conrad WS, Kovacs I, Rissman RA, Lee EB, Trojanowski JQ, et al. Dopamine neurons exhibit emergent glutamatergic identity in Parkinson's disease. *Brain.* (2022) 145:879–86. doi: 10.1093/brain/awab373

7. Cheng XR, Yang Y, Zhou WX, Zhang YX. Expression of VGLUTs contributes to degeneration and acquisition of learning and memory. *Neurobiol Learn Mem.* (2011) 95:361–75. doi: 10.1016/j.nlm.2011.01.010

8. Bastiaansen AEM, van Steenhoven RW, Te Vaarwerk ES, van der Flier WM, Teunissen C. Antibodies associated with autoimmune encephalitis in patients with presumed neurodegenerative dementia. *Neurol Neuroimmunol Neuroinflamm.* (2023) 10:e200137. doi: 10.1212/NXI.0000000000200137

9. Babaei P. NMDA and AMPA receptors dysregulation in Alzheimer's disease. *Eur J Pharmacol.* (2021) 908:174310. doi: 10.1016/j.ejphar.2021.174310

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 08 January 2024
DOI 10.3389/fpsyt.2023.1329171

Check for updates

OPEN ACCESS

EDITED BY
Florian Riese,
University of Zurich, Switzerland

REVIEWED BY
Julia Jockusch,
University of Zurich, Switzerland
Pia Lopez Lopez Jornet,
University of Murcia, Spain

*CORRESPONDENCE
Motoko Watanabe
✉ totoompm@tmd.ac.jp

RECEIVED 28 October 2023
ACCEPTED 18 December 2023
PUBLISHED 08 January 2024

CITATION
Watanabe M, Araki W, Takao C, Maeda C, Tominaga R, Kimura Y, Nayanar G, Tu TTH, Asada T and Toyofuku A (2024) A case with burning mouth syndrome followed by dementia with Lewy bodies: a case report. *Front. Psychiatry* 14:1329171. doi: 10.3389/fpsyt.2023.1329171

COPYRIGHT
© 2024 Watanabe, Araki, Takao, Maeda, Tominaga, Kimura, Nayanar, Tu, Asada and Toyofuku. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

A case with burning mouth syndrome followed by dementia with Lewy bodies: a case report

Motoko Watanabe[1]*, Wataru Araki[2,3], Chihiro Takao[1], Chizuko Maeda[1], Risa Tominaga[1], Yasuyuki Kimura[1], Gayatri Nayanar[1], Trang Thi Huyen Tu[1,4], Takashi Asada[3] and Akira Toyofuku[1]

[1]Department of Psychosomatic Dentistry, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [2]Department of Neurology and Neurological Science, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [3]Memory Clinic Ochanomizu, Tokyo, Japan, [4]Department of Basic Dental Sciences, Faculty of Odonto-Stomatology, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam

Burning mouth syndrome (BMS) is characterized by persistent oral burning sensations without corresponding organic findings. Dementia with Lewy bodies (DLB) is a common type of dementia and generally presents visual hallucination and parkinsonism as motor dysfunction besides cognitive decline. In this case report, we present a case in which DLB emerged during the treatment for BMS, with a relatively positive outcome for BMS. A 74 years-old female complained of burning pain in her mouth and a subsequent decrease in food intake. Following a diagnosis of BMS, pharmacotherapy was initiated. BMS was much improved with mirtazapine 15 mg and aripiprazole 1.0 mg, leading to the restoration of her food intake by day 180. However, BMS flared up again triggered by deteriorating physical condition of herself and that of her husband. With aripiprazole 1.5 mg and amitriptyline 25 mg, her BMS gradually improved by day 482. However, by day 510, an increase in anxiety was noted, accompanied by the occasionally misidentification of her husband on day 566. Her cognitive impairment and disorientation were also reported by her husband on the day 572, she was then immediately referred to a neurologist specialized dementia and diagnosed with DLB on the day 583. Her treatment was adjusted to include the prescription of rivastigmine which was titrated up to 9.0 mg. Considering the potential impact of amitriptyline on cognitive function, it was reduced and switched to mirtazapine; however, her oral sensations slightly got worse. Following the consultation with her neurologist, amitriptyline 10 mg was reintroduced and aripiprazole was discontinued on day 755. Remarkably, BMS gradually improved without deteriorating DLB. This case indicated the reaffirmed necessity of careful interviews for changes in daily life not only with the patients but also with their families through the medical assessments. It highlights the vigilance regarding potential cognitive decline underlying or induced as an adverse event especially when treating elderly patients with BMS. While the interaction between BMS and DLB remains unclear, this case underscores the importance of prudent diagnosis and constructing collaboration with specialists in managing BMS with the early phase of DLB.

KEYWORDS

burning mouth syndrome, dementia, dementia with Lewy bodies, elderly patient, cognitive decline, hallucination, Capgras syndrome, antidepressant

1 Introduction

Burning mouth syndrome (BMS) is characterized by persistent oral burning sensations without corresponding organic findings. While a potential association between cognitive decline and several chronic pain disorders has been indicated (1), no definitive connection has yet been established in individuals with burning mouth syndrome (2). Nevertheless, as the elderly population diagnosed with BMS continues to grow in the context of aging society (3), it is becoming progressively important to carefully consider the potential presence of underlying cognitive decline and the risk of adverse events associated with psychopharmacotherapy for BMS throughout the course of treatments, including the diagnosis phase, especially for elderly patients.

Dementia with Lewy bodies (DLB) is one of the most prevalent types of dementia, accounting for 10%–15% of dementia cases (4). The main features are visual hallucination and parkinsonism as motor dysfunction besides cognitive decline. Delusional oral sensations such as oral cenesthopathy has been reported as prodromal sensations for DLB (5–7). However, there is currently only a single case report in French describing development of DLB in a patient previously diagnosed with BMS. In this report, we describe a case in which DLB manifested during the treatment for BMS and remarkably, BMS showed a favorable prognosis without severe exacerbation of DLB.

2 Case presentation

A 74 years-old female complained of persistent burning pain in her mouth which was exacerbated on consuming foods or drinks. This discomfort had first emerged in October X-1 years without any apparent triggers and had had gradually worsened over time. By January X years, her condition had deteriorated to the point where she could tolerate specific foods such as rice, sweet breads, or pudding due to the severe pain. Her symptoms did not improve despite previous treatment with polaprezinc and antifungal drug for *Candida albicans*. Mirtazapine was prescribed by her physician considering her decreased appetite and normal blood examination results; however, she discontinued it due to drowsiness. Additionally, she could not take mirogabalin either because of dizziness. By May X years, her condition had deteriorated to extent that she required intravenous drips 4 times a week as she could only consume liquid or soft foods at room temperature. This worsening oral condition had gradually started impacting her ability to enjoy playing tennis and sewing hand-made crafts with her friends. Subsequently, she was referred to our clinic in June X years for a comprehensive evaluation and further management.

She had been diagnosed with primary Sjogren's syndrome since January X-1 years. Since her primary symptom was only salivary dysfunction, she was prescribed sodium gualenate hydrate by her rheumatologist. Although she had no psychiatric comorbidities, her physician reported her psychological characteristics as anxiety and a pessimistic outlook. To address this, she had been prescribed alprazolam and brotizolam, to use on an as-needed basis for over 10 years.

Accompanied by her husband, with whom she had been living alone since their children had become self-sufficient, she visited our clinic. They seemed to care for each other. During her visit, she was able to walk into our clinic unassisted, dressed neatly, and left a bright and lively impression. There were no signs of paralysis or movement disorders in the orofacial region. Although a slight tongue coating was observed, it did not cause pain upon touch (Figure 1). Decreased salivation was found but no abnormal mucosal changes were detected, including atrophy of tongue papillae. Taste dysfunction was not evident. Her self-rating depressive scale (SDS) score was 58, and visual analogue scale (VAS) which indicates pain intensity was notably high at 86/100. Furthermore, she showed a tendency for pain catastrophizing, scoring 30/52 on the pain catastrophizing scale (PCS).

On being diagnosed with BMS, she was initially prescribed 0.5 mg of aripiprazole considering her previous medication sensitivity. However, she experienced nocturnal awakening when the dose was increased to 1.0 mg. Consequently, a low dose (3.75 mg) of mirtazapine was re-prescribed to promote sleep and a transition of augmenting mirtazapine with aripiprazole was made on day 19 (Figure 2). By day 33, mirtazapine 7.5 mg and aripiprazole 0.5 mg yielded a marginal reduction in BMS symptoms. A considerable improvement was noted in BMS symptoms with 15 mg of mirtazapine and 1.0 mg of aripiprazole by day 61, paralleled by a decrease in intravenous drips to twice in a week. She regained the ability to eat meat and vegetable and her condition stabilized with further improvements by day 180. Her physician observed increased food intake and reduced frequency of intravenous drips to once a week, alongside absence of spontaneous crying. The PCS scores also decreased along with decrease in VAS scores. However, BMS flared up again on day 264, triggered by her and her husband's deteriorating physical condition and with increase of PCS (50/52). Although BMS improved temporarily with alprazolam as a rescue medication, the events such as her lumbar compression fracture and acute deteriorating of her husband's physical condition made her more anxiety and worsened her BMS symptoms. A cessation of tennis or sewing activities with her friend was observed since she became unable to walk by herself after lumbar compression fracture, accompanied by apatite loss and about 3 to 4 kg weight decline. Her pain and anxiety symptoms fluctuated. Aripiprazole was then gradually increased up to 3.0 mg which initially improved BMS. However, since tremor and irritability occurred on day 440, aripiprazole had to be decreased to 1.5 mg and 15 mg of mirtazapine was substituted with 25 mg of amitriptyline. By day 482, her BMS gradually improved, and food intake also increased.

However, by day 510, an increase in anxiety, led to cautious approach to treatment with more frequent consultations. On day 566, her husband reported that she often made remarks such as "I wonder if my husband is going out and meeting someone else." Her physician also reported escalated anxiety and emotional incontinence although her responses were clear and obvious recognitive decline could not be found through the medical interviews. While her BMS symptoms remained stable in the improved state, the score of SDS decreased to 36 and the frequency of intravenous drip reduced to once in 3 weeks, her husband reported cognitive impairment and disorientation. He described instances where she would say "even if you are next to me, you are not my husband but someone else with his face, and I will not sleep until real one returns" and other comments like, "this is not my house" and she could not be reassured of by going outside to confirm it was her own house. These alarming developments promoted immediately referral to a neurologist specializing in dementia on day 583.

10.3389/fpsyt.2023.1329171

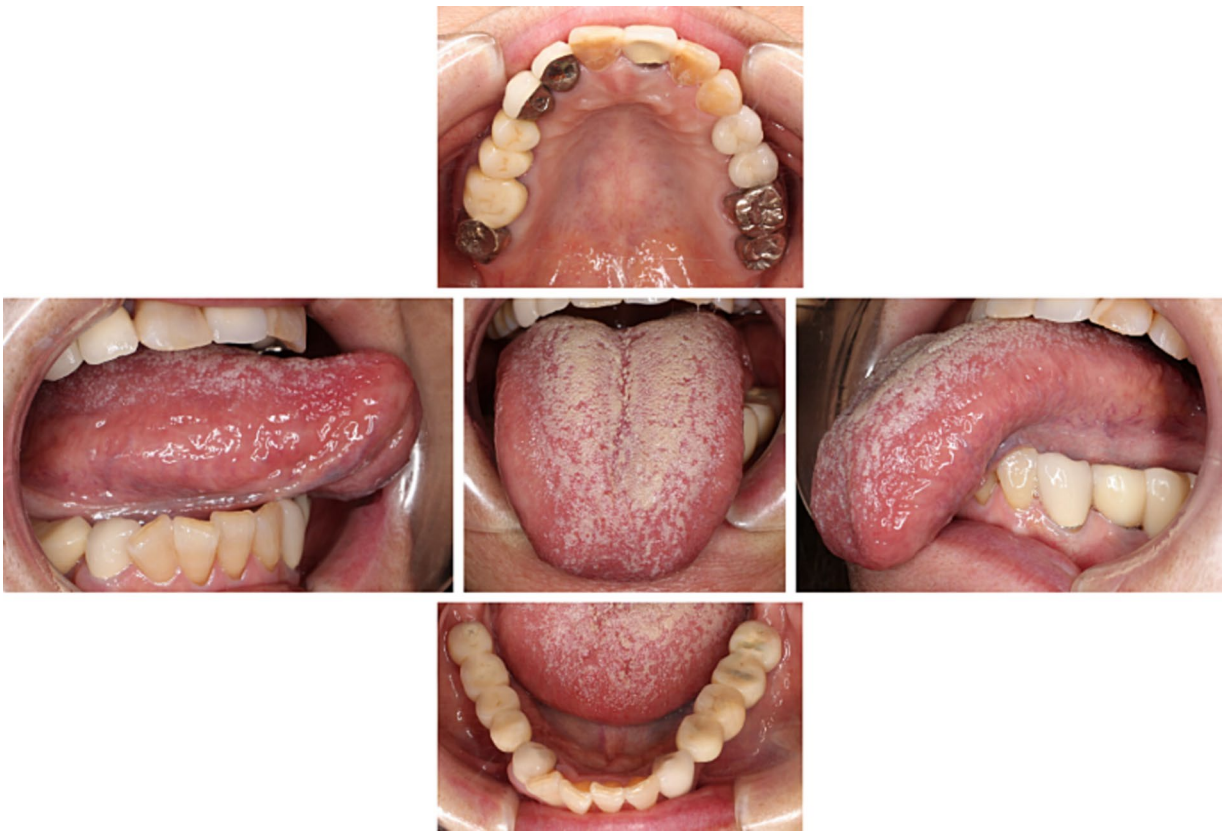


FIGURE 1
Intraoral findings. There were no abnormal findings in her oral cavity except slight tongue coating.

There were no abnormalities detected in magnetic resonance images and electro encephalography. Moreover, the hypoperfusion was detected only in the right posterior region, which was not significant enough to meet to the threshold of DLB, according to the easy *Z* score imaging system of single photon computed tomography with 99mTc-ECD (Figure 3). However, symptoms indicative of misidentification and Capgras syndrome were also observed besides decline of recognition (mini mental state examination: MMSE; 17/30, Hasegawa dementia rating scale—revised: HDSR; 15/30). Consequently, she was then diagnosed with dementia with Lewy bodies and was prescribed a 4.5 mg of rivastigmine on day 674, which was later increased to 9 mg on day 702. Considering the impact of amitriptyline on cognitive function, it was reduced and switched to mirtazapine; unfortunately, this resulted into slight worsening of her oral sensations. Since discontinuation of mirtazapine induced sleep disturbance, mirtazapine 7.5 mg and aripiprazole was prescribed again on day 733. After consultation with her neurologist, amitriptyline at 10 mg was reintroduced, and aripiprazole was discontinued on day 755. Subsequently, BMS symptoms gradually improved without adverse effects on her DLB condition (MMSE: 18/30, HDSR: 14/30). She marked high VAS scores (85/100) but noted that the burning pain manageable provided she avoided certain foods that irritated her tongue. This improvement was accompanied by a lower PCS score (22/52) by day 818, indicating a good prognosis of BMS without severe exacerbation of DLB.

3 Discussion

This case report is the first to document a BMS patient who developed DLB during BMS treatment. Notably, the BMS prognosis was favorable, with DLB progressing mildly.

In the initial stages of dementia, differentiating it from mood disorders is difficult since depression and anxiety often coexists (8, 9). The patients with BMS also have higher risks for depression and anxiety, although no significant increase in dementia risk has been reported in comparison to healthy subjects (10). In the sole case report describing BMS as pseudo-psychiatric symptoms (11), the patient was initially diagnosed with BMS but gradually showed delusional sensations and depressive complaints. By the time DLB was diagnosed, the disease had advanced to a stage where treatment was ineffective. The authors highlighted the complex symptom overlapping between BMS and DLB, which posed challenges in diagnosis and treatment. In the present case, symptoms such as anxiety, uncontrolled emotions, and unstable burning sensations could retrospectively be seen as signs of DLB. However, her underlying predisposition to high anxiety, excessively pessimistic psychological characteristics, and coupled with her husband's physical condition, initially obscured the DLB diagnosis. What ultimately facilitated her prompt referral was the detailed reports provided by her husband regarding the changes in her daily behavior that only he had noticed. As a result, she received appropriate treatment for DLB in the early stages. Visual hallucination is one of the main symptoms of DLB and more found in females than in males

10.3389/fpsyt.2023.1329171

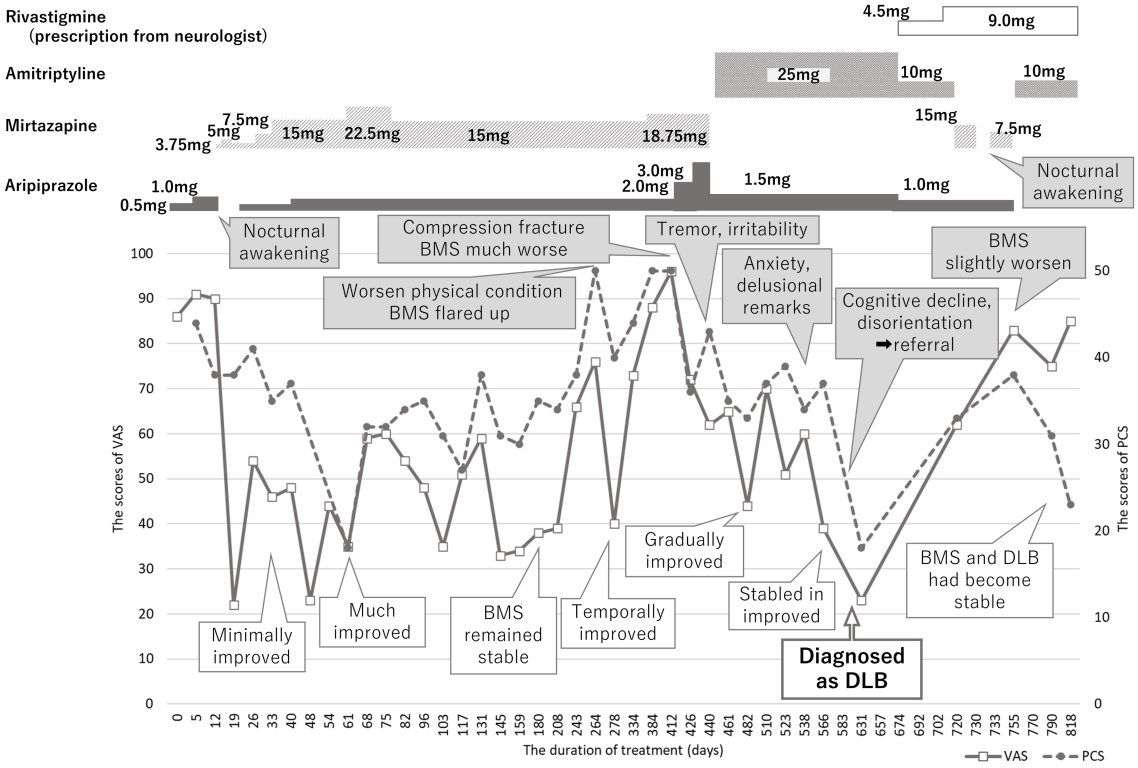


FIGURE 2
Time course of treatment. Burning mouth syndrome (BMS) was improved with mirtazapine 15 mg and aripiprazole 1.0 mg; however, it had been exacerbated relating with physical conditions of herself and her husband. While BMS had been improved, the sudden cognitive dysfunction and disorientation were reported by her husband. She was immediately referred to neurologist and diagnosed with dementia with Lewy bodies (DLB). BMS got in a good prognosis with slow progression of DLB by amitriptyline 10 mg besides rivastigmine prescribed by her neurologist. VAS, visual analogue scale, PCS, pain catastrophizing scale, BMS, burning mouth syndrome, DLB, dementia with Lewy bodies.

(8). Capgras syndrome is a visual hallucination where the patent misidentifies close family members to someone else, is more easily detected by someone really close to patient, as was with the husband in the present case. While significant parkinsonism was not observed in this case, decrease of daily activity level caused by her lumbar compression fracture might have masked movement disorder such as gait disturbance. This case emphasized the reaffirmed necessity of careful interviews regarding changes in daily life, not only with the patients but also with their families, during the medical interview.

Moreover, two main features of DLB, visual hallucinations and parkinsonism are related to dopaminergic system. Aripiprazole which is a dopamine partial agonist might have a negative impact on DLB although it was not evident in the present case. Conversely, anticholinergic medications, commonly used as a first-line treatment for BMS, have been associated with cognitive decline (12). Both BMS and DLB can hardly be improved completely since pathophysiology and effective medications are interact in a complex manner. In the present case, treatments were challenging. Decreasing amitriptyline and switching to mirtazapine, while considering the potential effects on cognitive decline, led to a slight exacerbation of BMS, and discontinuing mirtazapine resulted in sleep disturbances. Maintaining a low dose of amitriptyline consequently had kept BMS stable without severe adverse events, in close collaboration with her neurologist. In addition, rivastigmine, which is a medication for dementia inhibiting acetylcholinesterase and butyrylcholinesterase in the central nervous system, may have had a beneficial effect on both DLB and BMS. Aging induces increase of cholinesterase enzyme which lead to

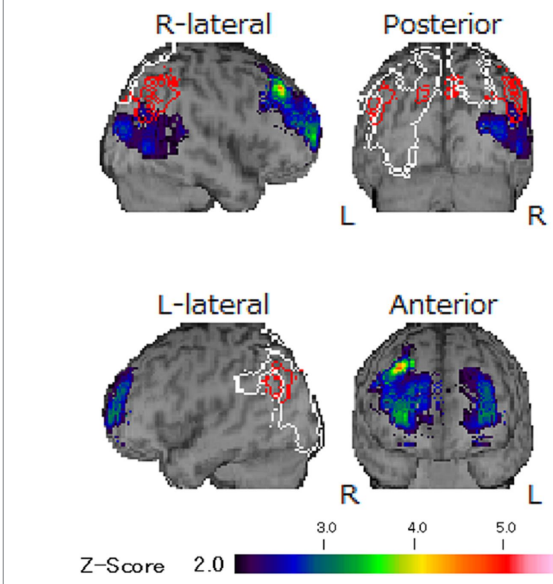


FIGURE 3
The images of single photon computed tomography. The hypoperfusion was detected only in right posterior region and any other abnormalities were not revealed according to the easy *Z* score imaging system of single photon computed tomography with 99mTc-ECD. The observed unilateral hypoperfusion is not typical finding in DLB and its degree was not enough to meet the threshold of DLB.

acetylcholine degrading followed by pain exacerbation (13). However, acetylcholine esterase inhibitors including rivastigmine inhibit cholinesterase and activate acetylcholine action by increasing acetylcholine in the synaptic cleft. While amitriptyline activates descending pain inhibitory pathway, rivastigmine also effects on the pain control system (13). These mechanisms may have synergistically contributed to favorable prognosis of BMS without sever exacerbation of DLB in the present case.

In conclusion, the possibility of cognitive decline underlying or induced as adverse events should be considered during the treatment of BMS, especially in the elderly patients, despite the unclear interaction between BMS and DLB. Moreover, a prudent approach to diagnosis and collaboration with specialists are important in managing BMS with the early phase of DLB for improving the prognosis.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethical Committee of Tokyo Medical and Dental University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The patient provided her written informed consent to participate in this case report. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

MW: Writing – original draft, Writing – review & editing, Data curation, Investigation. WA: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – review & editing. CT: Data curation, Investigation, Writing – review & editing. CM: Data curation, Investigation, Writing – review & editing. RT: Data curation, Investigation, Writing – review & editing. YK: Data curation, Investigation, Writing – review & editing. GN: Writing – review & editing, Data curation. TT: Investigation, Writing – review & editing. TA: Investigation, Writing – review & editing, Supervision. AT: Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by KAKENHI from the Japanese Society for the Promotion of Science (JSPS) Grant Number 22K10141 to AT. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Zhao W, Zhao L, Chang X, Lu X, Tu Y. Elevated dementia risk, cognitive decline, and hippocampal atrophy in multisite chronic pain. *Proc Natl Acad Sci U S A*. (2023) 120:e2215192120. doi: 10.1073/pnas.2215192120

2. Yuan H, Ahmed WL, Liu M, Tu S, Zhou F, Wang S. Contribution of pain to subsequent cognitive decline or dementia: a systematic review and meta-analysis of cohort studies. *Int J Nurs Stud*. (2023) 138:104409. doi: 10.1016/j.ijnurstu.2022.104409

3. Suga T, Watanabe T, Aota Y, Nagamine T, Toyofuku A. Burning mouth syndrome: the challenge of an aging population. *Geriatr Gerontol Int*. (2018) 18:1649–50. doi: 10.1111/ggi.13548

4. Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. *Lancet*. (2015) 386:1683–97. doi: 10.1016/S0140-6736(15)00462-6

5. Sawada Y, Konishi Y, Ikenouchi A, Yoshimura R. Oral Cenesthopathy proceeding dementia with Lewy body: a case report. *SN Compr Clin Med*. (2021) 3:1206–9. doi: 10.1007/S42399-021-00817-3

6. Umezaki Y, Asada T, Naito T, Toyofuku A. A case of oral cenesthopathy in which dementia with Lewy bodies developed during treatment. *Psychogeriatrics*. (2020) 20:766–8. doi: 10.1111/psyg.12541

7. Ochiai S, Sugawara H, Kajio Y, Tanaka H, Ishikawa T, Fukuhara R, et al. Delusional parasitosis in dementia with Lewy bodies: a case report. *Ann General Psychiatry*. (2019) 18:29. doi: 10.1186/s12991-019-0253-3

8. Fei M, Wang F, Wu H, Liu S, Gan J, Ji Y. Characteristics of initial symptoms in patients with dementia with Lewy body disease. *Front Neurol*. (2022) 13:1024995. doi: 10.3389/FNEUR.2022.1024995/BIBTEX

9. Jellinger KA. Depression in dementia with Lewy bodies: a critical update. *J Neural Transm*. (2023) 130:1207–18. doi: 10.1007/s00702-023-02669-8

10. Kim JY, Kim YS, Ko I, Kim DK. Association between burning mouth syndrome and the development of depression, anxiety, dementia, and Parkinson disease. *JAMA Otolaryngol Head Neck Surg*. (2020) 146:561–9. doi: 10.1001/jamaoto.2020.0526

11. Varvat J, Thomas-Anterion C, Decousus M, Perret-Liaudet A, Laurent B. Atypical Lewy body disease revealed by burning mouth syndrome and a pseudo-psychiatric syndrome. *Rev Neurol*. (2010) 166:547–9. doi: 10.1016/J.NEUROL.2009.10.018

12. Chahine B, Al Souheil F, Yaghi G. Anticholinergic burden in older adults with psychiatric illnesses: a cross-sectional study. *Arch Psychiatr Nurs*. (2023) 44:26–34. doi: 10.1016/J.APNU.2023.03.006

13. Eldufani J, Blaise G. The role of acetylcholinesterase inhibitors such as neostigmine and rivastigmine on chronic pain and cognitive function in aging: a review of recent clinical applications. *Alzheimers Dement*. (2019) 5:175–83. doi: 10.1016/J.TRCI.2019.03.004

frontiers | Frontiers in Psychiatry

TYPE Case Report
PUBLISHED 08 January 2024
DOI 10.3389/fpsyt.2023.1325145

Check for updates

OPEN ACCESS

EDITED BY
Hirofumi Hirakawa,
Oita University, Japan

REVIEWED BY
Christoph Born,
Klinikum am Weissenhof, Germany
Mariusz Stanisław Wiglusz,
Medical University of Gdansk, Poland

*CORRESPONDENCE
Iolanda Batalla
✉ ibatalla@gss.cat

RECEIVED 20 October 2023
ACCEPTED 15 December 2023
PUBLISHED 08 January 2024

CITATION
Llorca-Bofí V, Batalla I, Ruiz-Julián M, Adrados-Pérez M, Buil-Reiné E, Piñol-Ripoll G, Gallart-Palau X and Torrent A (2024) Lithium management of periodic mood fluctuations in behavioural frontotemporal dementia: a case report.
Front. Psychiatry 14:1325145.
doi: 10.3389/fpsyt.2023.1325145

COPYRIGHT
© 2024 Llorca-Bofí, Batalla, Ruiz-Julián, Adrados-Pérez, Buil-Reiné, Piñol-Ripoll, Gallart-Palau and Torrent. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Lithium management of periodic mood fluctuations in behavioural frontotemporal dementia: a case report

Vicent Llorca-Bofí[1,2], Iolanda Batalla[2,3,4]*, Maria Ruiz-Julián[5], Marina Adrados-Pérez[2], Esther Buil-Reiné[2], Gerard Piñol-Ripoll[3,4,5], Xavier Gallart-Palau[6,7,8] and Aurora Torrent[2,3]

[1]Department of Medicine, University of Barcelona School of Medicine, Barcelona, Spain, [2]Department of Psychiatry, Hospital Universitari Santa María, Lleida, Spain, [3]Institut de Recerca Biomèdica de Lleida (IRBLleida), Lleida, Spain, [4]Medicine Department, Universitat de Lleida (UdL), Lleida, Spain, [5]Cognitive Disorders Unit, Hospital Universitari Santa Maria, Lleida, Spain, [6]Biomedical Research Institute of Lleida Dr. Pifarré Foundation (IRB Lleida), Neuroscience Area, +Pec Proteomics Research Group (+PPRG), University Hospital Arnau de Vilanova (HUAV), Lleida, Spain, [7]Psychology Department, University of Lleida (UdL), Lleida, Spain, [8]Faculty of Health Sciences, Valencian International University, Valencia, Spain

The behavioural variant of Frontotemporal Dementia (bvFTD) is a neurodegenerative condition characterized by behavioural and cognitive symptoms. Mood disturbances, including manic-like episodes, can occur in bvFTD, posing diagnostic and therapeutic challenges. This case report presents a 62-year-old male with bvFTD exhibiting weekly mood fluctuations alternating between manic and depressive-like states. While initial treatment with quetiapine and trazodone showed partial improvement, the periodicity of mood fluctuations persisted. Subsequently, lithium was introduced, resulting in a notable reduction in symptom severity for both manic and depressive episodes. This report highlights the potential use of lithium as a mood stabilizer in bvFTD patients with periodic mood fluctuations, refractory to standard treatments. Further research is needed to elucidate the mechanisms underlying lithium's efficacy in bvFTD and to establish treatment guidelines.

KEYWORDS

behavioural frontotemporal dementia, mood fluctuations, manic-like episodes, lithium, case report

1 Introduction

Frontotemporal Dementia is the third leading cause of neurodegenerative dementia, with the most common form being the behavioural variant (bvFTD) (1). Initial mood and personality disturbances are a characteristic feature of bvFTD, often manifesting as a loss of empathy, apathy or abulia, and disinhibition or impulsivity. However, bvFTD presents a wide range of behavioural symptoms, which is why many patients are eventually referred to the Psychiatry service (2). In this setting, the differential diagnosis between bvFTD and a primary psychiatric disease (3) is stablished, and if needed, appropriate adjustments are made to psychopharmacological interventions.

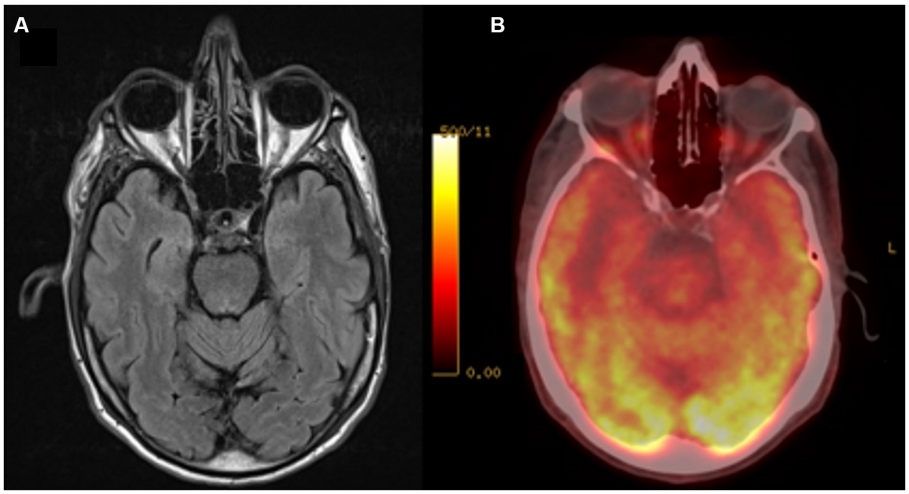


FIGURE 1
Neuroimaging Exams. **(A)** Brain MRI, FLAIR sequence; **(B)** Brain PET/CT with 18F-FDG. A decrease in glycidic metabolism is observed at the bilateral anterior temporal level.

Among the initial behavioural changes, patients may present with euphoria, increased energy, loquacity and racing thoughts, irritability, distractibility, and disinhibition. This presentation resembles a manic or hypomanic episode and there are numerous reports of manic behaviour as an initial manifestation of bvFTD (4). However, the occurrence of periodic mood fluctuations resembling bipolar disorder in bvFTD is relatively rare. Additionally, the use of lithium for managing bvFTD has been infrequent and is currently under study (5, 6). This case report describes a patient with bvFTD who experienced weekly mood fluctuations consisting of manic and depressive-like symptoms. Subsequently, lithium was introduced as a treatment option after a partial response to conventional therapy.

2 Case description

We present the case of a 62-year-old man who was evaluated by the Neurology service for functional decline and progressive behavioural alteration. The patient had a tobacco use disorder but did not exhibit any other toxic habits. He had a history of successfully treated chronic hepatitis caused by hepatitis C virus and no prior psychiatric history. Apart from a first-degree relative who experienced a stroke in old age, there was no other family history of neurological diseases, including dementia, or psychiatric disorders.

At the neurologic assessment, his spouse explained an insidious onset of behavioural changes approximately three years earlier, which ranged from irritability to apathy and anergy in the same week with progressive deterioration of functionality at home. The patient lacked insight and relativized his functional deficits. In the initial evaluation, no alterations were observed in the screening tests, including MMSE, clock test, praxis, Luria motor sequence and graphic alternations. A blood test with cobalamin, folic acid, TSH and luetic serology was performed with normal results. A brain MRI did not show atrophy or other significant findings. Glucose PET showed mild hypometabolism at the bilateral anterior temporal level, with preservation of metabolism in the rest of the cortical and subcortical structures (Figure 1). The neuropsychological examination revealed a deficit in executive functions (cognitive flexibility and alternation) and low performance in immediate visual memory, with normality in the rest of the cognitive areas evaluated. Quetiapine 25 mg was started at night, yielding limited efficacy, most likely attributable to suboptimal adherence resulting from the reported sensation of weakness. Subsequently, the patient was referred to the Psychiatry service for comprehensive assessment of the observed behavioural alteration.

On psychiatric assessment, the wife explained a fluctuant behavioural pattern with a weekly frequency. During manic-like episodes, the patient was particularly happy and full of energy, but would become irritable if contradicted in any way. They spent most of the day in a heightened state, rearranging furniture at home and making unrealistic plans. They repeatedly confronted the neighbours, displaying uninhibited behaviour, and slept only a few hours, claiming to have enough energy to not sleep. In the psychopathological examination the patient was awake, conscious and oriented in all 3 spheres. He was approachable and collaborative and at times presented loss of social distance. The patient appeared partially well-groomed, with some internal tension and the contact was syntonic. The speech was accelerated and under pressure, circumstantial and sometimes disorganised, with a loss of purpose and with humorous content standing out. The affect was expansive with hyperthymia. He did not present suicidal ideation. He also had no psychotic symptoms or altered sensory perception. He highlighted basal anxiety with irritability. Sleep decreased to 2–3 h despite quetiapine treatment. No self or hetero-aggressive behaviour was shown. Insight was null with a marked lack of empathy. During this period the clinical scores were YMRS (7): 33 and MADRS (8): 9.

In the following 4–5 days, the patient remained calm, correct and adequate, resting all night but listless, sad and lacking in energy. He presented pessimistic thoughts of guilt but without suicidal ideation. In the subsequent psychopathological examination, the patient was approachable and cooperative, well-groomed and did not present alterations in psychomotricity. The contact was syntonic. His speech was limited, concrete and impoverished with little fluency and

without reaching objectives. Affect was flattened and he presented hypothymia with negative cognitions, apathy, abulia, and hypohedonia. He did not present suicidal ideation. He also had no psychotic symptoms or altered sensory perception. During this period there was no anxiety or irritability and sleep was pharmacologically corrected. No self or hetero-aggressive behaviour was shown. The insight was null. Clinical scores were YMRS: 7 and MADRS: 22. Throughout these periods, he presented difficulties in planning his day-to-day activities, which was accentuated as the week went by until the start of the 2–3 mania-like days and the cycle started again.

A strict application of the DSM-5 criteria (9) for bipolar disorder ruled out this diagnosis. The patient did not meet criterion A (showed less than one week of manic symptoms) for a manic episode. He also did not meet criterion A (showed less than two weeks of depressive symptoms) for a major depressive episode. He did not meet criterion B (he showed more than two consecutive months with symptoms present) for cyclothymic disorder. He also did not meet the criteria for rapid cycling bipolar disorder because he did not meet the definitions of mania or major depressive disorder. Some authors have proposed the term "ultra-rapid cycling" when cycles occur with a frequency of days to weeks (10). Although it is not included in the DSM-5 specifiers, this presentation could bear resemblance to that of our patient if not for the pronounced presence of neurocognitive disturbances.

Regarding the potential classification as a mixed episode, the patient did not concurrently manifest symptoms of both polarities. Instead, distinct periods of manic or depressive-like symptoms were evident. Furthermore, the patient did not satisfy criterion A (failed to meet all the criteria for a depressive or manic episode) for a mixed episode. Concerning bipolar disorder due to another medical condition, the development of neurocognitive difficulties oriented more toward a dementia-type process and therefore excluded criterion C (better explained by another medical condition) for this diagnosis. He was diagnosed with periodic mood fluctuations in a probable behavioural frontotemporal dementia based on the 2011 Rascovsky diagnostic criteria (11). Following current recommendations (3), C9orf72 mutation was studied, which was negative.

Based on the results of the clinical trial by Lebert et al. (12), trazodone was started in ascending doses up to 300 mg at night with good tolerance and quetiapine was stopped. Mania-like episodes were reduced in duration (from three to one day) and severity (YMRS: 26) and depressive-like episodes were reduced in severity (MADRS: 16), but the fluctuations of the mood periods remained weekly and insight remained impaired.

After six months of treatment with trazodone at the maximum dose, we introduced lithium to leverage its mood-stabilizing effects. We started with a nightly dose of 200 mg, gradually increasing it by 200 mg every seven days, reaching a daily dose of 600 mg within one month. Despite achieving blood lithium levels of 0.86 mmol/L in the subsequent month (see Figure 2, month 10), minimal effects on both mania and depression were observed (YMRS 25 to 24; MADRS 16 to 15), and the weekly cyclicity persisted.

During the next visit (see Figure 2, month 11), following the recommendations for managing acute mania (13), we adjusted the dosage to 800 mg/day, resulting in a blood lithium level of 1.02 mmol/L. Over the following ten months, a significant reduction in symptom intensity occurred during both manic and depressive phases, yielding scores of YMRS: 15 and MADRS: 8 at month 24, albeit with ongoing weekly cyclicity.

Subsequently, following the current recommendations for maintenance treatment (14), we reverted to a dose of 600 mg/day with blood lithium levels stabilizing at 0.81 mmol/L. We continued monitoring the patient up to 36 months since the initial contact, with no significant changes in clinical severity observed. Throughout both the acute episode and the follow-up, the patient reported no relevant adverse effects. Kidney and thyroid function remained within normal ranges, and calcium levels were also normal.

3 Discussion

Cognitive and behavioural symptoms are the hallmark of bvFTD (1). However, mood disturbances, such as depression, and less frequently, manic episodes, can also manifest in this condition (2). Managing mood fluctuations in neurological disorders presents significant challenges, as it deviates from the established diagnostic criteria for bipolar disorder or other psychiatric conditions (15, 16). This case report provides evidence of the potential effectiveness of lithium in treating periodic mood fluctuations in bvFTD.

The management of mood disturbances in bvFTD is complex and often requires a multimodal approach. Pharmacological interventions for mood disturbances in bvFTD have primarily focused on selectively targeting the serotonergic system affected in FTD (15). Trazodone, at doses of at least 300 mg/day, has shown both acute and long-term benefits in managing behavioural alterations in bvFTD (12, 17). Lithium has also been proposed as a potential treatment for manic symptoms in bvFTD (18). However, the existing evidence comes from case reports describing favourable outcomes with the use of lithium in the treatment of mood symptoms (5). Nonetheless, a phase II randomized clinical trial is currently underway to evaluate the efficacy of low-dose lithium on behavioural symptoms in patients with bvFTD, which will provide valuable evidence in this field (6).

In the present case, the patient exhibited periodic mood fluctuations with weekly periodicity, alternating between manic-like and depressive-like periods. Initial treatment with quetiapine and trazodone provided partial relief, but the weekly cyclicity of mood fluctuations persisted. To address the mood instability observed in the patient, lithium was added to the treatment regimen. Notably, the addition of lithium with serum until 1.2 mmol/L resulted in a significant reduction in the intensity of both manic and depressive symptoms. In a published case series of three patients with bvFTD or semantic variant-primary progressive aphasia, lithium used at serum concentrations ranged between 0.4 and 0.8 mmol/L daily improved behavioural disturbances notably agitation with or without psychotic features (5). However, in our approach, higher doses of lithium were used in the acute episode, with a focus on mood disturbances rather than behavioural symptoms. These clinical findings support the consideration of lithium as a potential therapeutic option for managing mood fluctuations in bvFTD that have not shown a response to the currently recommended treatments (19).

Lithium is a well-established mood stabilizer primarily utilized in the treatment of bipolar disorders (20). Its therapeutic effects stem from diverse mechanisms, including the modulation of intracellular signaling pathways, neuroprotective actions, and regulation of neurotransmitter systems (21). In the context of bvFTD, the mood-stabilizing effects of lithium are believed to result from its capacity to modulate intracellular signaling pathways (20, 21). Specifically, lithium exhibits inhibitory

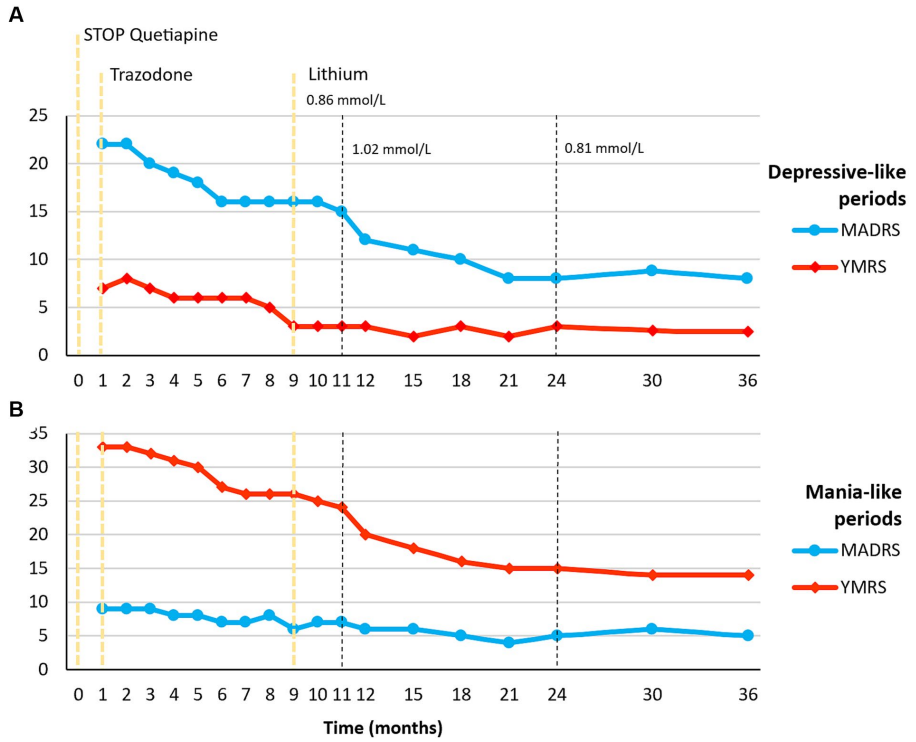


FIGURE 2
Timeline of Pharmacological and Psychopathological Changes. **(A)** Psychopathological changes measured by MADRS and YMRS in depressive-like periods; **(B)** Psychopathological changes measured by MADRS and YMRS in mania-like periods. An initial improvement in both mania and depressive-like symptoms was observed during trazodone treatment, reaching a plateau in the response at month 9. Subsequently, the addition of lithium resulted in a greater improvement, and this response was sustained for up to 3 years of follow-up. MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale.

effects on glycogen synthase kinase-3β (GSK-3β), a factor involved in tau phosphorylation. By influencing abnormal protein aggregation, lithium is hypothesized to act as a neuroprotective agent against tauopathies, including bvFTD. However, the precise mechanism of action for treating mood disturbances in bvFTD remains speculative. Translational research suggests neurotrophic and neuroprotective effects that contribute to the modulation of multiple homeostatic mechanisms, which are core pathological processes in dementia (22). Additional research is necessary to clarify the specific mechanisms through which lithium operates in bvFTD.

It is important to note that the response to lithium in bvFTD-associated mood fluctuations can be variable, and not all patients may experience significant benefit. In our case report, the addition of lithium to the treatment regimen resulted in a reduction in symptom severity (Figure 2), but the weekly cyclicity of mood fluctuations persisted. Insight remained impaired, indicating that lithium may primarily target mood symptoms rather than underlying cognitive deficits. However, we recognize the limited generalizability inherent in single-case studies. To address this, we advocate for further research with larger samples. The ongoing randomized clinical trial (6) will surely provide valuable information on the acute effects, but longitudinal studies will also be necessary to investigate the sustained efficacy of the intervention. These efforts will contribute to a more robust evidence base and guide the development of targeted treatment guidelines for this challenging condition.

In conclusion, this case report provides evidence for the potential use of lithium as a mood stabilizer in the management of periodic mood fluctuations in bvFTD after an unsatisfactory response to conventional treatments. While the exact mechanisms underlying the therapeutic effects of lithium in bvFTD are not fully understood, its neuroprotective properties and modulation of neurotransmitter systems may play a role. Further research is needed to validate these findings and to guide the use of lithium in bvFTD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Arnau de Vilanova University Hospital – GSS, Lleida, Spain (CEIC-2341). The studies were conducted in accordance with the local legislation and institutional requirements. The participant provided his written informed consent to participate in this study. Written informed consent was obtained from the individual

for the publication of any potentially identifiable images or data included in this article.

Author contributions

VL-B: Writing – original draft, Writing – review & editing. IB: Writing – original draft, Writing – review & editing. MR-J: Data curation, Formal analysis, Investigation, Writing – review & editing. MA-P: Writing – review & editing. EB-R: Writing – review & editing. GP-R: Writing – review & editing. XG-P: Writing – original draft, Writing – review & editing. AT: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research received financial support from the Diputació de Lleida and Projectes d'Impuls a la Recerca en Salut 2022 (PIRS22/03).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Elahi FM, Miller BL. A clinicopathological approach to the diagnosis of dementia. Nature reviews. *Neurology*. (2017) 13:457–76. doi: 10.1038/nrneurol.2017.96

2. Woolley JD, Khan BK, Murthy NK, Miller BL, Rankin KP. The diagnostic challenge of psychiatric symptoms in neurodegenerative disease: rates of and risk factors for prior psychiatric diagnosis in patients with early neurodegenerative disease. *J Clin Psychiatry*. (2011) 72:4437. doi: 10.4088/JCP.10M06382OLI

3. Ducharme S, Dols A, Laforce R, Devenney E, Kumfor F, van den Stock J, et al. Recommendations to distinguish behavioural variant frontotemporal dementia from psychiatric disorders. *Brain*. (2020) 143:1632–50. doi: 10.1093/BRAIN/AWAA018

4. Mendez MF, Parand L, Akhlaghipour G. Bipolar disorder among patients diagnosed with frontotemporal dementia. *J Neuropsychiatry Clin Neurosci*. (2020) 32:376–84. doi: 10.1176/APPI.NEUROPSYCH.20010003/FORMAT/EPUB

5. Devanand DP, Pelton GH, D'Antonio K, Strickler JG, Kreisl WC, Noble J, et al. Low-dose lithium treatment for agitation and psychosis in Alzheimer disease and frontotemporal dementia. *Alzheimer Dis Assoc Disord*. (2017) 31:73–5. doi: 10.1097/WAD.0000000000000161

6. Huey E. Low-dose lithium for the treatment of Behavioral symptoms in frontotemporal dementia. ClinicalTrialsGov identifier: NCT02862210 n.d. Available at: https://clinicaltrials.gov/study/NCT02862210 (accessed June 26, 2023).

7. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. (1978) 133:429–35. doi: 10.1192/BJP.133.5.429

8. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. (1979) 134:382–9. doi: 10.1192/BJP.134.4.382

9. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, *5th* edn. Washington, DC: American Psychiatric Association. (2013).

10. Tillman R, Geller B. Definitions of rapid, Ultrarapid, and Ultradian cycling and of episode duration in Pediatric and adult bipolar disorders: a proposal to distinguish episodes from cycles. *J Child Adolesc Psychopharmacol*. (2004) 13:267–71. doi: 10.1089/104454603322572598

11. 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) 134:2456–77. doi: 10.1093/BRAIN/AWR179

12. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. *Dement Geriatr Cogn Disord*. (2004) 17:355–9. doi: 10.1159/000077171

13. Pacchiarotti I, Anmella G, Colomer L, Vieta E. How to treat mania. *Acta Psychiatr Scand*. (2020) 142:173–92. doi: 10.1111/ACPS.13209

14. Nolen WA, Licht RW, Young AH, Malhi GS, Tohen M, Vieta E, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI task force on treatment with lithium. *Bipolar Disord*. (2019) 21:394–409. doi: 10.1111/BDI.12805

15. Buoli M, Serati M, Caldiroli A, Galimberti D, Scarpini E, Altamura AC. Pharmacological management of psychiatric symptoms in frontotemporal dementia: a systematic review. *J Geriatr Psychiatry Neurol*. (2017) 30:162–9. doi: 10.1177/0891988717700506

16. Al-Diwani A, Handel A, Townsend L, Pollak T, Leite MI, Harrison PJ, et al. The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data. *Lancet Psychiatry*. (2019) 6:235–46. doi: 10.1016/S2215-0366(19)30001-X

17. Lebert F. Behavioral benefits of trazodone are sustained for the long term in frontotemporal dementia. *Therapy*. (2006) 3:93–6. doi: 10.1586/14750708.3.1.93

18. Limanaqi F, Biagioni F, Ryskalin L, Busceti CL, Fornai F. Molecular mechanisms linking ALS/FTD and psychiatric disorders, the potential effects of lithium. *Front Cell Neurosci*. (2019) 13:450. doi: 10.3389/FNCEL.2019.00450/BIBTEX

19. Khoury R, Liu Y, Sheheryar Q, Grossberg GT. Pharmacotherapy for frontotemporal dementia. *CNS Drugs*. (2021) 35:425–38. doi: 10.1007/S40263-021-00813-0

20. Damri O, Shemesh N, Agam G. Is there justification to treat neurodegenerative disorders by repurposing drugs? The case of Alzheimer's disease, lithium, and autophagy. *Int J Mol Sci*. (2021) 22:189. doi: 10.3390/IJMS22010189

21. Lauterbach EC, Shillcutt SD, Victoroff J, Coburn KL, Mendez MF. Psychopharmacological neuroprotection in neurodegenerative disease: heuristic clinical applications. *J Neuropsychiatry Clin Neurosci*. (2010) 22:130–54. doi: 10.1176/JNP.2010.22.2.130/ASSET/IMAGES/LARGE/AR02100002LT2.JPEG

22. Shim SS, Berglund K, Yu SP. Lithium: an old drug for new therapeutic strategy for Alzheimer's disease and related dementia. *Neurodegener Dis*. (2023) 23:1–12. doi: 10.1159/000533797

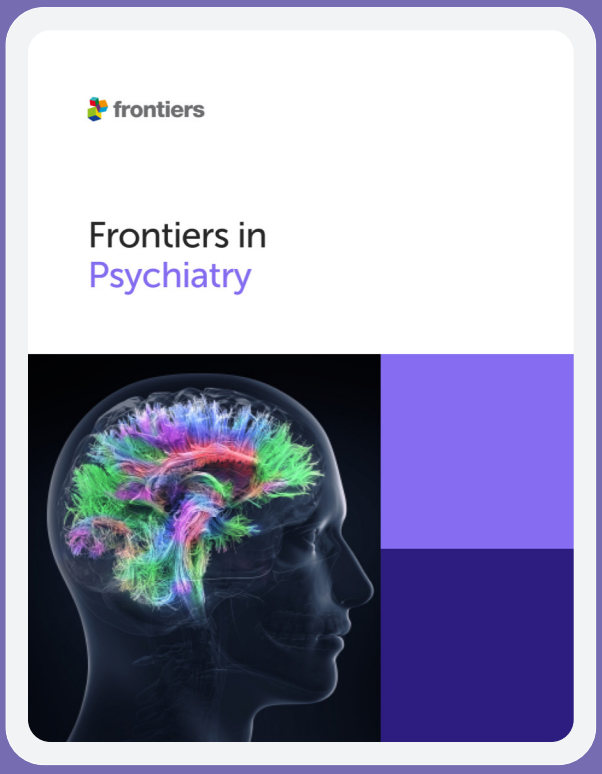
Frontiers in Psychiatry

Explores and communicates innovation in the field of psychiatry to improve patient outcomes

The third most-cited journal in its field, using translational approaches to improve therapeutic options for mental illness, communicate progress to clinicians and researchers, and consequently to improve patient treatment outcomes.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact