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Single Case Report

Symptomatic conversion in a case of sporadic frontotemporal dementia: Longitudinal neuroimaging of the presymptomatic stage

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ABSTRACT

Background: Identifying preclinical stages of behavioral variant frontotemporal dementia (bvFTD) is exclusively possible in familial bvFTD. In non-genetic (sporadic) cases this is prevented by the lack of biomarkers. In particular, serial neuroimaging might preview early abnormalities in asymptomatic genetic bvFTD, whereas such data are lacking in sporadic bvFTD.

Case: Here, we present a pathology-confirmed case of sporadic bvFTD in a 61-year-old male with the unique availability of multiple presymptomatic magnetic resonance imaging (MRI) scans following a resection of meningioma 20 years prior to disease onset. This study aims to provide a detailed description of his clinical disease course, symptom onset, and early cortical changes on MRI using visual rating scales (VRS), as well as post-mortem evaluation.

Methods: Eight T1-weighted MRI scans (2000–2023) were assessed using previously developed and validated VRS, scored for both hemispheres separately by two independent raters (DML, and GGF). The scales used were: Anterior cingulate (AC), orbitofrontal (OF), frontoinsular (FI), anterior temporal (AT), medio-temporal atrophy (MTA), and posterior atrophy (PA). Four MRI scans were available in the presymptomatic stage, and four after reported symptom onset in 2016. Clinical data was collected from medical charts, and a structured retrospective interview with the patient's family and caregivers.

Conclusions: In this case of sporadic bvFTD due to Pick's disease, structural changes in frontoinsular and anterior temporal cortices preceded symptom onset by 5–9 years. Exploring patient populations with repeated follow-up imaging, particularly outside of

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dementia clinics, could provide valuable insights into longitudinal changes in neurodegenerative diseases.

1. Introduction

Frontotemporal dementia (FTD) refers to a group of neurodegenerative disorders marked by progressive atrophy of the frontal and temporal lobes, leading to changes in behavior, personality, language, and executive functions (Olney, Spina, & Miller, 2017). Clinically, FTD is classified into several phenotypes, each defined by predominant changes in behavior, semantic appraisal, or language. The FTD disease spectrum also includes cases with motor involvement, such as FTD with motor-neuron disease as well as tau-associated subtypes like progressive supranuclear palsy and corticobasal degeneration.

The most common clinical phenotype is the behavioral variant of FTD (bvFTD) (Hogan et al., 2016). Clinical consensus criteria for possible bvFTD require progressive deterioration of behavior and/or cognition, with at least three of the following features: early behavioral disinhibition, apathy or inertia, loss of sympathy or empathy, perseverative or compulsive behaviors, hyperorality or dietary changes, or a dysexecutive neuropsychological profile with relative sparing of memory and visuospatial functions (Rascovsky et al., 2011). Levels of diagnostic certainty are further defined by the presence or absence of biomarkers. Presently, a definite diagnosis can only be given based on genetic or post-mortem pathology data.

In North-America and Europe, approximately a third of FTD-cases is familial and caused by an autosomal dominant genetic mutation, most commonly in the microtubule-associated protein tau (MAPT), progranulin (GRN), or chromosome 9 open reading frame 72 (C9orf72) genes (Moore et al., 2020). Prospective cohort studies monitoring at-risk presymptomatic mutation-carriers have shown distinct atrophy patterns on structural magnetic resonance imaging (MRI) up to 10 years before symptom onset using volumetric analyses (Chen & Kantarci, 2020; McKenna, Lope, Tan, & Bede, 2022). Although atrophy patterns can vary between pathogenic FTD mutations, studies show early alterations in the insular and temporal cortices during the presymptomatic stage. These changes are followed by atrophy in the frontal cortex and subcortical structures, with further progression to the parietal and cingulate cortices around expected symptom onset (Rohrer et al., 2015). However, similar longitudinal studies assessing presymptomatic changes in sporadic (non-familial) bvFTD remain absent. The lack of reliable biomarkers in sporadic cases limits targeted presymptomatic screening and hampers prospective enrollment in large-scale studies comparable to those in familial bvFTD.

Visual rating scales (VRS) to assess atrophy on MRI are commonly used in clinical practice and research settings (Harper, Barkhof, Fox, & Schott, 2015), and are shown to correlate strongly with atrophy in the same region on volumetric analyses, aiding clinical diagnostic accuracy (Harper et al., 2016). Compared to data-driven imaging approaches, like Voxel-based morphometry (VBM), the use of VRS does not require highly specialized software and expertise, thus providing an accessible and applicable tool for clinicians (Davies et al., 2009; Harper et al., 2015). In the context of Alzheimer's disease (AD), the well-known VRS of medial temporal atrophy (MTA-scale) developed by Scheltens et al. (1992) is widely used in clinical settings for diagnostic purposes. In the context of familial bvFTD, VRS showed distinct atrophy patterns between genetic mutation carrier groups (Fumagalli et al., 2018), and they have been included in research criteria for prodromal FTD assessing presymptomatic changes and phenoconversion (Benussi et al., 2024).

In this study, we present a pathology-confirmed case of sporadic bvFTD with the unique availability of longitudinal MRI scans spanning both presymptomatic and symptomatic stages, aiming to discern and compare early cortical changes during the disease course using VRS.

2. Methods

2.1. Informed consent and data collection

Written informed consent was obtained to retrospectively assess clinical, demographic, and imaging data for this study, according to the declaration of Helsinki (Assembly, 1964). A structured interview was performed with the patient's spouse to gather retrospective information on the presence of cognitive symptoms and the progression of the disease. Additionally, medical records from previously visited clinics were requested following written consent. Dementia severity was retrospectively evaluated using the Clinical Dementia Rating + National Alzheimer's Coordinating Center–Frontotemporal lobar degeneration (CDR + NACC-FTLD) scale based on available clinical data (Knopman et al., 2008). MRI scans were acquired retrospectively as part of routine clinical follow-up after meningioma resection and therefore did not follow a standardized research protocol. Detailed information on scanner models, field strength, and sequence parameters is provided in Supplementary Table S5.

2.2. Visual rating scales (VRS) protocol

A protocol of six visual rating scales (VRS) was used to assess T1-weighted MRI images. Two independent raters (GGF and DML), both experienced with VRS assessment, rated the scans while blinded to clinical information and scan dates. Scans were presented in a random order.

This protocol was previously validated (Harper et al., 2016), applied in familial FTD research (Fumagalli et al., 2018), and

incorporated into research criteria for prodromal FTD (Benussi et al., 2024). Reference images for each scale were provided. When no coronal T1-weighted scan was available (e.g. 2011 scan), a reconstructed image was generated using multiplanar reformatting (MPR) from axial sequences, which may have reduced interpretability in some regions.

VRS were used to assess intra-individual longitudinal changes within this single case, rather than for cross-sectional diagnostic classification. Accordingly, no control scans were included. To determine presymptomatic atrophy, an increase of $\geq$1 point on a VRS, sustained in subsequent scans, was considered a relevant change. Given that VRS scores of 0–1 may reflect normal aging, a score of $\geq$2 by *both* raters was interpreted as evidence of FTD-related atrophy.

The following VRS were used to evaluate both hemispheres separately: orbitofrontal (OF), anterior cingulate (AC), frontoinsular (FI) (Davies et al., 2009; Harper et al., 2016), anterior temporal (AT) (Davies et al., 2006; Kipps et al., 2007), medial temporal atrophy (MTA) (Scheltens et al., 1992), and posterior atrophy (PA) (Koedam et al., 2011).

Inter-rater reliability (IRR) was assessed using quadratic weighted Cohen's kappa for each VRS and hemisphere. For scale–hemisphere combinations with zero variance in one rater's scores, weighted kappa could not be estimated and observed agreement was reported instead.

2.3. Post-mortem evaluation and protocol

The patient was registered as a brain donor at the Netherlands Brain Bank (NBB) conform national ethical guidelines. After death, autopsy was performed according to the NBB rapid autopsy protocol. The left hemisphere was used for sampling of fresh-frozen tissue, while the right hemisphere was fixed in formalin for neuropathological evaluation.

After fixation, macroscopic examination was performed and diagnostic regions were dissected according to a standardized frontotemporal dementia dissection protocol. Formalin-fixed, paraffin-embedded tissue was sectioned at 8 μm and stained with hematoxylin and eosin (H&E) and immunohistochemistry.

Immunohistochemistry staining included amyloid-β, phosphorylated tau (AT8), TDP-43 (phosphoSer409), α-synuclein (KM51), and p62, performed at the NBB. Additional staining performed at the Amsterdam UMC pathology department included 3R tau (RD-3), 4R tau (RD-4), proteolipid protein (PLP), glial fibrillary acidic protein (GFAP), HLA-DR, and neurofilament. All stained slices were digitized using the Olympus VS200 slide scanner.

3. Case presentation

MS is a 61-year-old Caucasian man, who was referred to our center for a second opinion due to changes in language and behavior.

Twenty years prior to symptom onset, in 1996, a benign suprasellar meningioma was resected *via* right-sided craniotomy. The meningioma extended into the tuberculum sellae, as well as the right orbitofrontal cortex. At that time his complaints were right-sided vision loss and headache, which subsided after resection. No cognitive or behavioral symptoms were reported before or directly after the resection. Following the resection, the patient underwent regular MRI monitoring. There was no family history of dementia.

3.1. Clinical course

Symptoms began in 2016 with subtle behavioral changes, including inappropriate conversational responses, social withdrawal, and more frequent disagreements with family members. He started to occasionally change into his wife's clothes. Over the following months, he developed word-finding difficulties. His language became more descriptive and simple with the use of circumlocutions such as: "That thing that keeps things cold", when referring to a refrigerator. During the day he was tired, inattentive, and forgetful, yet after a sleep-registration assessment no diagnosis of sleep disorder was made.

In 2017 his symptoms started to interfere with his daily life. He experienced trouble doing groceries (remembering items, lack of initiative) and neglected household chores leading to increased tension within the family. He became more rigid in his routines, adhered to a fixed daily schedule, and displayed mild hoarding tendencies.

At initial evaluation in 2018 (age 55), MRI showed subtle atrophy in the prefrontal and anterior temporal regions, presumed to be post-operative changes from the meningioma resection. MS was referred to a geriatrician for further (cognitive) evaluation. In the meantime, his symptoms worsened, including agitation, executive dysfunction, decreased self-care/hygiene, and more pronounced (sexually) disinhibited behaviors. Cognitive screening tests did not suggest an underlying neurodegenerative cause, with a Mini-Mental State Examination (MMSE) score of 28/30. Neuropsychological evaluation (NPE), including memory, language, executive, visuoconstruction, attention, and processing speed measures, showed formal deficits only in processing speed (particularly on Stroop I-III, and trail-making test A-C). However, upon review, lower scores were also observed for episodic memory tasks (poor encoding, flat learning curve, and low recognition scores on Rey Auditory Verbal Learning Test (RAVLT)). Recall of verbally mediated information (RBMT) was also reduced and there were low scores for verbal fluency, although the available language measures did not establish a formal language disorder. Visuoconstruction functions remained relatively preserved. No social cognitive tests were carried out at the time. MS got the diagnosis mild cognitive impairment (MCI) with unspecified etiology.

At a follow-up visit in 2020, progression was reported by his partner, and cognitive screening tests showed worse scores, with a Montreal Cognitive Assessment (MOCA) score of 15/30 and a MMSE score of 19/30. Repeated NPE showed a broadly similar cognitive profile, although verbal learning and recognition had further declined (RAVLT; RBMT), alongside visuospatial associative learning (VAT), while executive function test scores (fluency, set-shifting) remained comparable to before. Cerebrospinal fluid (CSF) analysis showed normal levels of amyloid-beta 42, total tau, and phosphorylated tau, leading to a diagnosis of possible frontotemporal dementia

(FTD). To manage increasing agitation, aggression, and disinhibition, he was prescribed risperidone.

The patient's condition continued to deteriorate, exhibiting aggressive behavior towards his children and a lack of empathy, eventually necessitating a move to a nursing home in 2021.

In 2022, MS was referred to our center for a second opinion, and the desire to contribute to science. Behavioral symptoms included lack of empathy, apathy, disinhibition, changes in appetite, stereotypy, and executive dysfunction. Based on clinical evaluation, language symptoms had progressed, including anomia, circumlocution, and impaired semantic processing and abstraction, although no repeat NPE was performed at this timepoint. There was no apraxia or prosopagnosia. MRI showed frontotemporal atrophy with anterior temporal white-matter involvement. Serum levels of neurofilament light chain (NfL) were substantially elevated for his age, at 43.1 pg/ml. Genetic testing (panel listed in Supplementary material S1) showed no pathogenic variants. Based on the clinical presentation, MS met criteria for probable sporadic bvFTD according to the Rascovsky-criteria (Rascovsky et al., 2011).

By 2023, MS had progressed to a state of severe cognitive impairment, with minimal verbal output limited to stereotyped responses. During a visit to the nursing home, he was found to be too cognitively impaired for formal testing. A comprehensive timeline of his clinical course can be found in Fig. 1.

3.2. *Imaging progression*

Eight MRI scans (2000–2023) were included and evaluated, comprising four presymptomatic and four post-symptomatic scans. Longitudinal progression of structural changes and VRS scores per hemisphere can be found in Fig. 2.

Inter-rater reliability (IRR) for VRS was generally high, with substantial to almost perfect agreement across most scale–hemisphere combinations (quadratic weighted κ = .64–1.00). Agreement was lower for MTA-L (κ = .27). For MTA-R, weighted κ could not be estimated due to zero variance in one rater's scores; observed agreement for this scale was .62. Full IRR estimates and observed agreement values are provided in Supplementary Table S3, and Supplementary Fig. S4.

Scan-level analysis indicated variability in rating reliability across time points. The reconstructed 2011 MRI showed the lowest exact agreement across all scales (.33) and a high absolute inter-rater difference (.67), indicating limited reliability). Lower agreement was also observed for the 2018 and 2023 scans, primarily driven by discordance in MTA ratings, while other scales showed more consistent agreement. Full VRS scores by both raters are provided in Supplementary material S2.

During the presymptomatic phase (2000–2011), VRS scores were largely within the range of 0–1 across most regions. Early increases were observed in the AT scale, with higher right-sided scores observed on the 2007 scan. Subtle presymptomatic increases were also observed on the PA-scale. Orbitofrontal (OF), anterior cingulate (AC), and medial temporal atrophy (MTA) scores remained low and mostly symmetric during this phase.

From symptom onset (2016) onwards, progressive increases in VRS scores were observed across multiple regions. Frontoinsular (FI) and posterior atrophy (PA) scores showed early and pronounced increases, with consistently higher values in the left hemisphere. AT scores continued to increase, with a shift from initial right-sided predominance to greater left-sided involvement from 2020 onwards.

OF and AC scores increased from 2018, while MTA scores showed progression later in the disease course (from 2020 onwards). Despite limited interpretability, the 2011 scan showed patterns consistent with adjacent time points, including higher left-FI, left-PA, and right-AT scores.

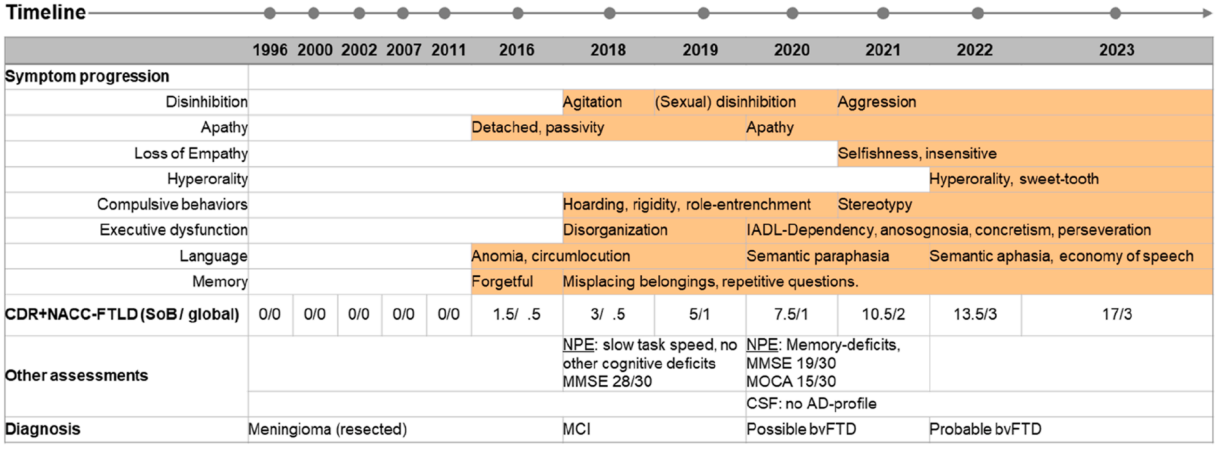

Fig. 1 – Timeline of clinical course. ***Summary of symptom progression and functional changes in our bvFTD case from 1996 to 2023, based on an interview with the patient's caregiver and medical chart review. Orange coloring in the timeline indicates symptom onset.***

Abbreviations: AD; Alzheimer's disease, CDR + NACC-FTLD SoB; Clinical Dementia Rating + National Alzheimer's Coordinating Center–Frontotemporal Lobar Degeneration sum of boxes, CSF; Cerebrospinal fluid, FTD; Frontotemporal dementia, MCI; Mild cognitive impairment, MMSE; Mini-Mental state examination, MOCA; Montreal Cognitive Assessment, NPE; Neuropsychological evaluation.

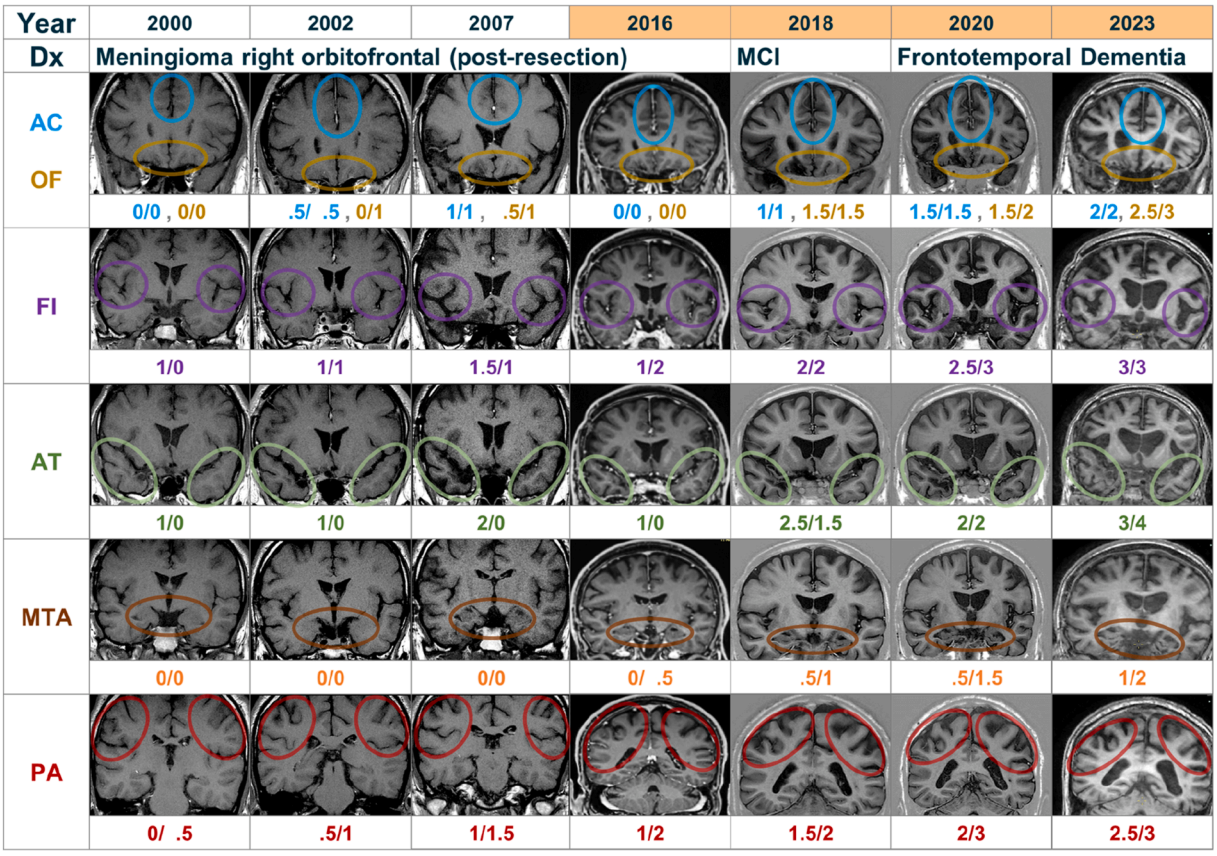

Fig. 2 – Longitudinal evaluation of MRI scans using Visual rating scales. ***T1-weighted MRI images were independently evaluated by two raters (GGF and DML) using a previously validated visual rating scale (VRS) protocol applied to both hemispheres. The assessed regions and their respective score ranges were: anterior cingulate (AC, 0–3), orbitofrontal (OF, 0–3), frontoinsular (FI, 0–3), anterior temporal (AT, 0–4), mediotemporal (MTA, 0–3), and posterior atrophy (PA, 0–3). Considering the generally high inter-rater reliability (weighted k = .64-1.00), VRS scores are presented right/left as the mean score of the two raters. Due to limited quality, and reliance on reconstructed images, the 2011 scan is not shown here. Orange coloring in the timeline indicates symptom onset.*** **Abbreviations: Dx; Diagnosis, MCI; Mild cognitive impairment**

Overall, early changes were most prominent in FI, AT, and PA regions, whereas OF, AC, and MTA regions showed later involvement.

3.3. *Post-mortem evaluation*

Neuropathological examination showed asymmetric frontotemporal-predominant atrophy (brain weight 1055 g), more pronounced in the right hemisphere, involving frontal, temporal, parietal, and insular cortices.

Microscopy showed severe neuronal loss and gliosis with numerous ballooned neurons and tau-positive neuronal inclusions consistent with Pick bodies (Fig. 3). Immunohistochemistry demonstrated 3R tau-positive pathology (RD3-positive, RD4-negative), with widespread involvement of cortical layers (predominantly layer II), hippocampus (dentate gyrus), basal ganglia, and brainstem. Additional tau pathology included coiled bodies, axonal tau positivity, and ramified astrocytes. Pathology extended to the substantia nigra, medulla oblongata, and cervical spinal cord, indicating advanced disease stage. There was no relevant co-occurring neuropathology [e.g. no Alzheimer's disease neuropathologic change (ADNC), α-synucleinopathy, or TDP-43 proteinopathy].

A focal white matter lesion in the right anterior temporal horn showed severe astrogliosis, demyelination, axonal disorganization, and increased corpora amylacea, consistent with focal leukoencephalopathy, likely related to prior meningioma resection (Supplementary materials S7). Importantly, tau pathology within and adjacent to this lesion was comparable to surrounding regions.

Overall, findings were consistent with advanced Pick's disease (3R tauopathy) with widespread cortical and subcortical involvement and right-sided predominance. The full autopsy report can be found in Supplementary materials S6.

4. Discussion

As far as we are aware, we present the first case of pathology-confirmed sporadic bvFTD with available longitudinal neuroimaging over a long presymptomatic stage. We observed early structural changes in anterior temporal and posterior regions

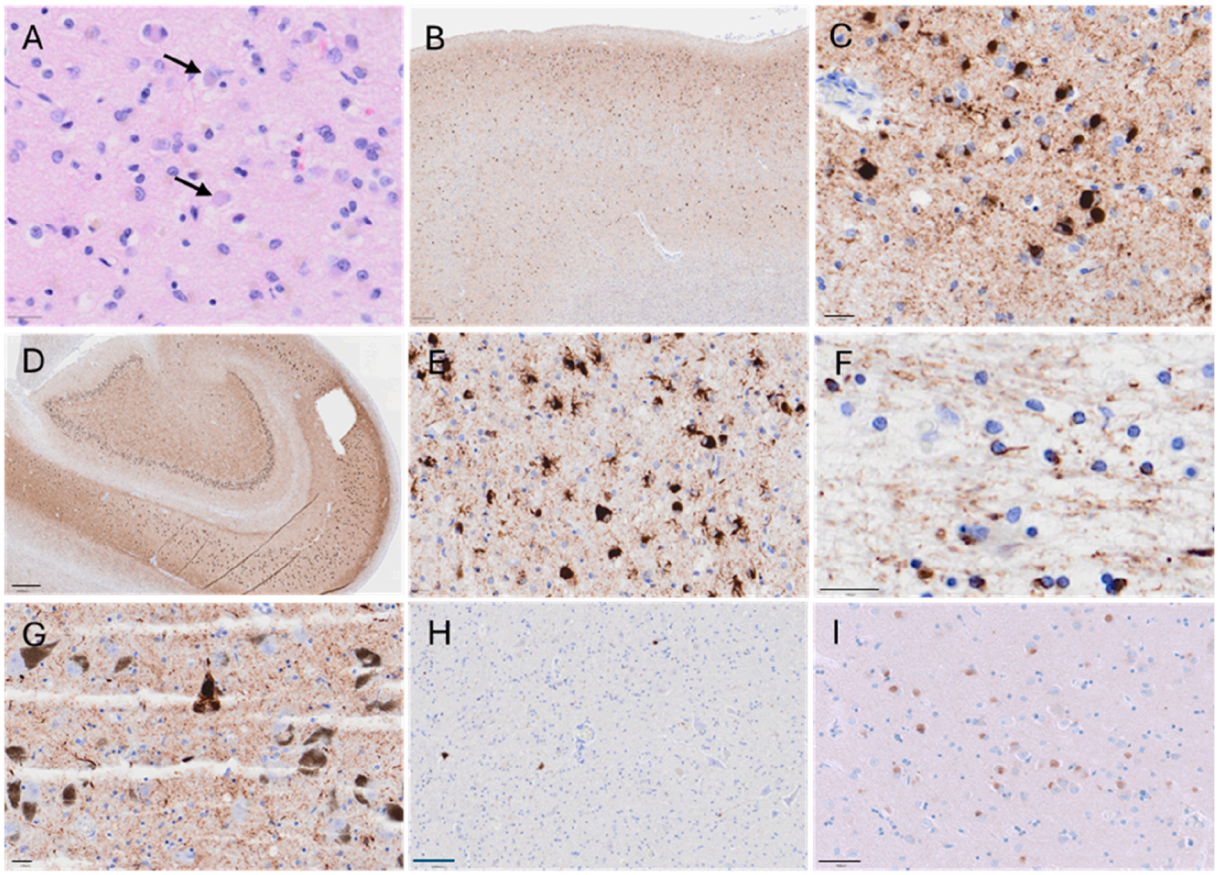

Fig. 3 – Neuropathological diagnosis of Pick's disease. ***HE of frontal cortex demonstrating neuronal loss, gliosis and Picks bodies (arrows) (A). AT8 immunohistochemistry demonstrating: Picks bodies in all cortical layers of frontal cortex (B), high magnification of frontal cortex showing compact sharp round neuronal inclusions and diffuse neuronal cytoplasmic staining (C). Hippocampus with many Picks bodies severely affecting the gyrus dentatus (D). Ramified astrocytes in grey matter especially prominent in parietal cortex (E), coiled bodies in the white matter (F). Advanced spread of tau pathology also involving substantia nigra (G), brainstem (not shown) and spinal cord (H). 3R Tau staining revealed 3R positive neuronal and glial inclusions (I), 4R Tau was negative (not shown).***

up to 5–9 years prior to reported symptom onset, followed by progressive involvement of frontal, insular, and medial temporal regions after clinical conversion. Neuropathological evaluation confirmed advanced Pick's disease (3R tauopathy) without co-occurring pathology, supporting that the observed imaging changes reflect the natural course of primary sporadic FTLD rather than secondary or mixed pathology. Together, these findings provide a rare clinicoradiological and pathological perspective on the early stages and progression in sporadic bvFTD.

4.1. *Clinicoradiological associations*

Following clinical onset, progressive atrophy on the AC and OF scales paralleled the development of behavioral symptoms such as agitation, disinhibition, and rigidity. Disinhibition has been linked to both anterior cingulate (Chu et al., 2021; Rosen et al., 2005), and orbitofrontal atrophy (Massimo et al., 2009), which is found to be among the earliest changes in bvFTD (Peet, Castro-Suarez, & Miller, 2021). In the present case, however, increasing OF scores should be interpreted cautiously, given the history of right orbitofrontal meningioma resection and the limited interpretability of post-operative changes in this region. Similarly, the emergence of hyperorality in 2022 in this case coincided with increased OF and FI atrophy scale scores, reflecting associations described previously by Woolley et al. (2007) between hyperorality and orbitofrontal-insular-striatal atrophy.

After 2016, left anterior temporal lobe atrophy surpassed the right, corresponding with reported worsening of semantic language symptoms and stereotyped behaviors. These findings align with studies linking left anterior temporal atrophy to semantic impairments (Snowden et al., 2018), and repetitive behaviors (Peet et al., 2021). In contrast, early right anterior temporal abnormalities did not clearly co-occur with corresponding clinical features. Similarly, we observed more severe right-sided atrophy at autopsy. The shift from early right-sided and later left-dominant imaging patterns to right-predominant end-stage pathology suggests that regional asymmetry may evolve dynamically over the disease course rather than remain fixed.

Although forgetfulness was an early informant-reported symptom, notable increases in MTA scores were only observed after the bvFTD diagnosis was made in 2020, suggesting medial temporal atrophy as a secondary feature in this case. This finding is consistent with its limited early role in bvFTD compared to Alzheimer's disease (Scheltens et al., 1992; van de Pol et al., 2006). However, inter-rater reliability for MTA was lower and more variable than for other scales, warranting cautious interpretation of these findings.

Additionally, post-symptomatic scans showed increasing PA scores, fitting with a more generalized atrophy pattern. However, posterior atrophy's clinical relevance in this case is less direct, as posterior regions such as the precuneus and posterior cingulate are primarily associated with visuospatial, executive and attentional dysfunction (Holden, Bettcher, & Pelak, 2020). Although these were not primary deficits in this case, the reported early forgetfulness could potentially have been misinterpreted inattention, fitting with observed increases in PA-scale scores prior to symptom onset.

4.2. *Potential role of prior meningioma resection*

It is conceivable that the prior meningioma resection contributed to the emergence of bvFTD or an FTD-like syndrome. Although it has been described that a meningioma in the frontal lobe clinically might present with psychiatric or behavioral symptoms whilst in situ (Hunter, Blackwood, & Bull, 1968), we are not aware of any literature reporting this relationship postoperatively. Notably, in the case we present here, no behavioral or cognitive symptoms were reported while the meningioma was in situ, nor did they emerge for nearly 20 years post-resection. Postoperative structural changes following the meningioma resection in 1996 were visible on MRI but remained stable over time.

Neuropathological findings provide further context. Although a focal leukoencephalopathy was present in the right anterior temporal white matter, likely related to prior surgery, tau pathology within and around this region was comparable to surrounding tissue. Moreover, the widespread distribution of 3R tau pathology affecting frontotemporal cortices, hippocampus, basal ganglia, and brainstem, together with the absence of co-occurring neuropathology, is consistent with a primary sporadic Pick's disease process rather than secondary neurodegeneration originating from a focal lesion.

It is plausible that postoperative changes damaged frontotemporal network structures and might indirectly contribute to selective vulnerability of other structures as part of this network, potentially explaining early asymmetrical imaging findings. Similar hypotheses have been proposed in other contexts, such as traumatic brain injury (TBI), linking head trauma to increased dementia risk, including FTD (Deutsch, Mendez, & Teng, 2015; Shively, Scher, Perl, & Diaz-Arrastia, 2012). Mechanisms such as Wallerian-like degeneration and proteoform toxicity have been proposed (Graham & Sharp, 2019), but whether intracranial surgery triggers similar processes remains uncertain. Neuroinflammation may also play a role; Alam, Hana, Jin, Suen, and Ma (2018) suggest systemic inflammatory response (SIRS) post-surgery can contribute to cognitive dysfunction and even dementia. In MS's postoperative course, there was no direct clinical evidence of neuroinflammation, though the persistence of inflammatory markers or a delayed inflammatory response cannot be ruled out entirely.

Overall, while prior meningioma resection may have influenced local structural integrity and potentially modulated regional vulnerability, the clinical, imaging, and neuropathological findings do not support a causal or initiating role in the development or spread of the underlying Pick's disease. Nevertheless, retrospective identification or prospective follow-up of post-meningioma patients might provide insights into potential links between resected meningiomas and neurodegeneration, though evidence remains sparse.

4.3. *Comparison with familial FTD*

Longitudinal neuroimaging in familial FTD has shown presymptomatic changes in mutation carriers up to a decade before expected symptom onset (Bocchetta et al., 2023; Cash et al., 2018; Jiskoot et al., 2019; McKenna et al., 2022; Rohrer et al., 2015). Grey matter volume loss of the cingulate cortex consistently predicts symptom onset (Jiskoot et al., 2019). Here, anterior cingulate atrophy emerged during the transition from MCI to FTD, rather than preceding symptoms. However, early involvement of salience network structures (Seeley et al., 2007), including insula and anterior temporal regions, mirrors presymptomatic patterns seen in familial bvFTD (Rohrer et al., 2015).

A study using the same VRS protocol found presymptomatic MTA-scale changes in MAPT mutation carriers but no changes in other genetic groups (Fumagalli et al., 2018). Despite the heterogeneity in atrophy patterns between sporadic and familial bvFTD, and even between genetic groups, early salience network involvement seems present across groups, suggesting a shared disease pathway.

4.4. *Strengths & limitations*

This study's strengths lie in its rare availability of longitudinal imaging data spanning both presymptomatic and symptomatic phases in a pathology-confirmed sporadic bvFTD case. This enables us to relate early imaging changes to both clinical progression, underlying pathology, and cautiously compare this to the body of work performed in familial FTD.

This study does have several limitations. First, the use of VRS provides a qualitative and subjective measure for brain atrophy, which may be less accurate than data-driven approaches like VBM. Nonetheless, the VRS used in this study are all well described, validated, and shown to correlate with data-driven methods (Davies et al., 2009; Fumagalli et al., 2018; Harper et al., 2016), as well as showing high inter-rater reliability in this study. Furthermore, limitations of VRS are offset by the benefits in terms of applicability and accessibility for clinical use. Second, the retrospective design of this study affects data quality, including variable technical quality of MRI scans, acquisition protocols, and occasional absence of the ideal rating slice, requiring the use of reconstructed images. This may have affected rating reliability, as shown by the limited interpretability of the 2011 scan. Similarly, detailed NPE data were only available for the 2018 and 2020 timepoints, limiting reconstruction of objective domain-specific cognitive

decline. In addition, recall bias may have influenced caregiver-reported symptoms, though cross-referencing with medical charts reduced its impact.

Third, orbitofrontal assessment was complicated by prior meningioma resection, potentially affecting both anatomical interpretation and rating reliability in this region. Finally, as a single-case study, findings must be generalized cautiously.

Despite these limitations, our findings may prompt future studies to assess opportunistic imaging in non-genetic bvFTD, particularly in patients undergoing routine scans for seemingly unrelated conditions.

4.5. *Conclusions*

Within the scarcity of presymptomatic data in sporadic bvFTD, our case contributes to a better understanding of early pathological changes and their clinical implications in sporadic FTD. Here, we observed structural changes several years prior to symptom onset, particularly within salience network regions. The combination of longitudinal imaging and neuropathological confirmation supports a temporo-insular onset pattern with subsequent spread to frontal and medial temporal regions in Pick's disease. Furthermore, exploring patient populations with repeated follow-up imaging, particularly outside of dementia clinics, could provide valuable insights into longitudinal changes in neurodegenerative diseases.

CRediT authorship contribution statement

Willem Lucas Hartog: Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Diederick M. de Leeuw:** Writing – review & editing, Investigation, Formal analysis. **Sterre C.M. de Boer:** Writing – review & editing, Resources, Project administration, Data curation. **Nina L. Fransen:** Visualization, Resources, Project administration, Methodology, Investigation. **Ramón Landin-Romero:** Writing – review & editing, Resources, Data curation. **Betty M. Tijms:** Writing – review & editing, Supervision, Resources, Conceptualization. **Giorgio G. Fumagalli:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yolande A.L. Pijnenburg:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

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Scientific transparency statement

DATA: Some raw and processed data supporting this research are publicly available, while some are subject to restrictions: https://osf.io/xg5up/overview?view_only=e2173c05238c4c57b22473335a8c80b8 Data contained in the manuscript or supplemental files.

CODE: All analysis code supporting this research is publicly available: https://osf.io/xg5up/overview?view_only=e2173c05238c4c57b22473335a8c80b8.

MATERIALS: All study materials supporting this research are publicly available: https://osf.io/xg5up/overview?view_only=e2173c05238c4c57b22473335a8c80b8 Materials are contained in the manuscript or supplemental files.

DESIGN: This article reports, for all studies, how the author(s) determined all sample sizes, all data exclusions, all data inclusion and exclusion criteria, and whether inclusion and exclusion criteria were established prior to data analysis.

PRE-REGISTRATION: No part of the study procedures was pre-registered in a time-stamped, institutional registry prior to the research being conducted. No part of the analysis plans was pre-registered in a time-stamped, institutional registry prior to the research being conducted.

For full details, see the *Scientific Transparency Report* in the supplementary data to the online version of this article.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2026.06.021.

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