

High Risk of Suicide in Behavioral Variant Frontotemporal Dementia

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Abstract

Aim: The purpose of the study was to determine the prevalence of suicidal ideation and attempts in patients with behavioral variant frontotemporal dementia (bvFTD), evaluating possible risk factors for suicidality. **Methods:** Risk of suicide was assessed using the Scale for Suicide Ideation (SSI) in 35 patients with bvFTD and 25 controls. **Results:** According to SSI, 40% of patients with bvFTD had suicidal ideation in comparison to 8% of controls ($P = .009$). Four patients with bvFTD have attempted suicide versus none control ($P = .006$). Patients with bvFTD with suicide risk showed higher levels of anxiety, depression, stress, and hopelessness than patients without suicide risk ($P < .001$). Patients who attempted suicide were younger and had a longer disease duration than those with only suicide ideation. Intriguingly, 40% of patients with parkinsonism presented high level of suicide ideation. **Conclusions:** Our findings show that patients with bvFTD have a high risk of suicide. Additional studies in larger populations are needed to confirm our results.

Keywords

bvFTD, frontotemporal dementia, FTD, suicide, SSI, parkinsonism

Introduction

The term frontotemporal dementia (FTD) encompasses a spectrum of neurodegenerative diseases clinically characterized by a progressive decline in both behavior and language, related to deposition of misfolded proteins in frontal and temporal lobes. Behavioral variant FTD (bvFTD), semantic dementia (SD), and progressive nonfluent aphasia are the main clinical subtypes of FTD.¹

Frontotemporal dementia is the second cause of presenile dementia, and bvFTD represents the most frequent subtype.^{2,3} This form is clinically characterized by prominent behavioral disturbances, including disinhibition, impulsivity, perseverations, and loss of empathy, that are associated with deterioration in social conduct and impairment of cognition.^{1,4} Recently, a complex and intriguing relationship between bvFTD and several psychiatric disorders has been described. Psychiatric symptoms may represent the first clinical signs of bvFTD, even several years before the onset of behavioral and cognitive symptoms.⁵

In patients with overall dementia, the risk of suicide is generally considered low.⁶⁻⁸ However, a growing body of research suggests that mood changes, severity of cognitive impairment, and awareness of disease may lead patients with different forms of dementia to be more vulnerable to suicidal behavior.⁸⁻¹² To date, literature is scarce about the suicide risk in patients with bvFTD. In 2012, a first case report described a patient with bvFTD who committed suicide a few months after the

diagnosis.¹³ Subsequently, a retrospective study reported a higher risk of suicidal behavior in patients with bvFTD when compared to controls.¹⁴ At present, prevalence and risk factors for suicide have not been adequately investigated in bvFTD.

Thence, the primary aim of our study was to determine the prevalence of both suicidal ideation and suicidal attempts in a cohort of patients with bvFTD according to a case-control strategy. A secondary aim was to evaluate the possible neuropsychological and neuropsychiatric risk factors correlated with suicidality.

Methods

Participants

Thirty-five patients with a diagnosis of probable bvFTD (18 men, 17 women; mean age \pm standard deviation [SD]:

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70.1 ± 6.3 years) attending the Aging Brain and Memory Clinic of the Department of Neuroscience "Rita Levi Montalcini," University of Torino, Italy, were recruited for the study. The diagnosis of bvFTD was performed according to Rascovsky et al's criteria.¹⁵

Patients underwent extensive clinical, neuropsychological, and neuroimaging investigations (brain magnetic resonance imaging and 18-fluorodeoxyglucose positron emission tomography). The clinical diagnosis was supported by cerebrospinal fluid biomarkers (beta amyloid, total tau, and phosphorylated tau) in order to exclude Alzheimer's disease pathology. Patients were screened for genetic variants in the major FTD-related genes (*MAPT*, *GRN*, and *C9orf72*).¹⁶ A group of 25 healthy age- and education-matched patients (8 men, 17 women; mean age ± SD: 68.1 ± 7.4 years) served as controls. Patients were excluded from the study if they had (1) an Anosognosia Questionnaire–Dementia (AQ-D)¹⁷ score ≥32, (2) a Mini-Mental State Examination (MMSE)¹⁸ score <24, and (3) a Token Test (TT)¹⁹ score <26.5. Written informed consent was obtained from all participants, and the study was approved by the Hospital Ethics Committee.

Assessment of Suicidality

Suicide risk was measured using the Scale for Suicide Ideations (SSI)²⁰ as suggested by the Italian Society of Psychiatry [www.psichiatria.it]. The SSI is a 19-item semistructured interview performed by a clinician, based on patient's answers, evaluating self-destructive and suicide thoughts within the last 7-days period. In addition, data on previous suicide attempts are collected by the test. In detail, SSI consists of 5 screening domains: 3 items exploring the wish to live or die and 2 items evaluating the desire to attempt suicide. Each item consists of a 3-point scale, ranging from 0 to 2, to quantify suicidal intensity. Fourteen additional questions are administered if the patients report any active or passive thoughts to commit suicide. Answers include duration and frequency of ideation, sense of control over making an attempt, number of deterrents, and amount of actual preparation for a contemplated attempt. The overall score ranges from 0 to 38, and according to the literature, a score ≥6 has been used as threshold for suicidal ideation.^{21,22} Suicide attempt refers to potentially self-injurious behavior thought and performed with the purpose to kill oneself.

Neuropsychological Assessment

Global cognitive impairment was assessed through MMSE,¹⁸ Clinical Dementia Rating Scale,²³ and Frontal Assessment Battery.²⁴ Other cognitive domains were also investigated: attention and executive functions with Trail Making Test,^{25,26} verbal learning and memory with Rey 15 Words Auditory Learning Test,²⁷ and language comprehension with TT.^{19,25} In addition, Reading the Mind in the Eyes Test has been used to evaluate the ability to recognize the mental state of others using the expressions of the eyes.^{28,29} Patients' awareness of

Table 1. Demographic Characteristics of Patients With bvFTD and Controls.

	bvFTD	Controls
Gender, M/F	18/17	8/17
Age, years, mean ± SD	70.14 ± 6.32	68.12 ± 7.44
Education		
8 years	62.86% (22)	32.00% (8)
13 years	25.71% (9)	40.00% (10)
>13 years	11.43% (4)	28.00% (7)
Onset of disease, years	65.00 ± 7.82	–
Duration of disease, years	4.08 ± 3.27	–

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; F, female; M, male; SD, standard deviation.

disease was assessed using the AQ-D scale.¹⁷ Finally, autonomy in daily living was estimated with both activities of daily living (ADL)³⁰ and the instrumental ADL Scale.³¹

Neuropsychiatric Assessment

Each group underwent specific questionnaires on behavioral and mood changes. Apathy was assessed with Apathy Evaluation Scale–Clinician Version,³² depression was examined with Hamilton Depression Rating Scale,³³ and anxiety and stress were evaluated with Hamilton Anxiety Rating Scale³⁴ and Perceived Stress Scale, respectively.³⁵ Finally, Barratt Impulsiveness Scale³⁶ and Beck Hopelessness Scale³⁷ were also used to evaluate patient's impulsiveness and hopelessness.

Statistical Analysis

All data were analyzed using SPSS version 21.0 for Windows (IBM SPSS Statistics, Inc, Chicago, Illinois). Demographic and clinical variables were compared using *t* test and χ^2 . Neuropsychological and neuropsychiatric characteristics were analyzed using *t* test and multivariate analysis of variance. Pearson ρ with Bonferroni correction was used to evaluate the correlation between suicidal ideation and performance on the neuropsychological and neuropsychiatric tests. The significance level was set at $P < .05$ for all analyses, and $P < .01$ for Bonferroni correction.

Results

Assessment of Suicidality

Demographic and clinical characteristics of patients and controls are summarized in Table 1. According to SSI scale, 40% of patients with bvFTD showed suicide ideation in comparison to 8.0% of controls ($P = .009$). Subsequently, according to the obtained scores, all the patients involved in the study were divided into 2 different groups: (1) patients with risk of suicide (SR), and (2) patients without risk of suicide (NS).

When looking at overall bvFTD group, 14 patients with bvFTD had a risk of suicide (bvFTD-SR) and 21 patients with bvFTD showed no suicide risk (bvFTD-NS). In the subgroup of

bvFTD at risk of suicide, 10 (71.4%) patients showed a suicide ideation alone, whereas 4 (28.6%) patients in addition to suicidal ideation also had attempted suicide. In detail, 3 patients with bvFTD had attempted suicide with a nonfatal self-poisoning, while 1 patient with bvFTD tried to defenestrate himself. When patients with bvFTD attempted suicide, they were not taking any L-dopa or dopaminergic treatments. In control group, according to the SSI, 2 (8%) controls had a risk of suicide (Cont-SR), whereas the remaining patients showed no suicide risk (Cont-NS).

Patients with bvFTD who attempted suicide showed a higher global SSI score in comparison to those who presented suicidal ideation alone ($P < .001$). No differences were found in global SSI scores between male and female patients with bvFTD at risk of suicide.

Neuropsychological Assessment

The overall group of patients with bvFTD showed higher levels of functional and cognitive impairment ($P < .005$) and were more apathetic and impulsive ($P < .001$) when compared to controls as expected. Interestingly, in the bvFTD group, no differences in the neuropsychological characteristics were found when comparing patients with bvFTD at suicide risk and patients with bvFTD with no suicide risk (Table 2).

Neuropsychiatric Assessment

Using multivariate analysis for the neuropsychiatric data, patients with bvFTD presented higher levels of apathy, impulsivity, and hopelessness ($P < .001$) when compared to controls. In the bvFTD group, patients at suicide risk showed higher scores in depression, anxiety, stress, and hopelessness ($P < .001$) in comparison to patients with bvFTD with no suicide risk (Figure 1).

Clinical Characteristics

Evaluating the clinical characteristics of patients with bvFTD, we observed that the patients who attempted suicide were younger ($P = .023$) and had a longer duration of the disease ($P = .007$) than patients with bvFTD with only suicide ideation. In addition, gender and education did not influence the suicide risk in bvFTD.

In the overall bvFTD group, 7 out of 35 patients showed parkinsonism, mainly presenting with bradykinesia and axial rigidity. Notably, patients with bvFTD with extrapyramidal signs had higher level of suicide ideation (odds ratio = 15; 95% confidence interval: 1.55-145.23, $P = .019$) than remaining patients.

In this data set of patients with bvFTD, one patient carried a missense mutation in *GRN* gene and one an expansion in *C9orf72* gene. However, we did not detect any clear link between suicide risk and mutations in known FTD-related genes due to the paucity of patients with mutations.

Table 2. Neuropsychological, Neuropsychiatric, and Functional Assessment Synopsis of Patients With bvFTD According to the Presence of the Suicide Risk.^a

	bvFTD-SR	bvFTD-NS	P Value
MMSE	24.1 ± 3.4	23.7 ± 2.8	.685
CDR	1.0 ± 0.7	1.1 ± 0.5	.858
FAB	10.7 ± 3.6	10.9 ± 3.2	.881
TMT-A	121.9 ± 124.1	103.4 ± 76.9	.755
TMT-B	312.7 ± 137.9	290.8 ± 174.1	.706
TMT B-A	232.2 ± 130.9	201.3 ± 149.8	.624
RAVLT	21.3 ± 7.7	22.3 ± 6.7	.725
TT	33.0 ± 2.4	32.1 ± 2.6	.579
RMET	16.6 ± 4.1	18.0 ± 5.7	.349
AES-C	13.9 ± 12.3	23.7 ± 18.7	.940
HDR-S	26.4 ± 9.0	11.5 ± 5.5	.000
HAR-S	24.6 ± 7.5	10.1 ± 5.7	.000
PSS	27.6 ± 3.2	16.1 ± 5.2	.000
BIS-11	78.4 ± 8.1	73.1 ± 13.0	.188
BHS	15.5 ± 4.7	8.6 ± 5.1	.000
AQ-D	-2.5 ± 10.4	4.3 ± 9.0	.075
ADL	4.8 ± 1.5	5.7 ± 5.0	.070
IADL	5.2 ± 2.4	5.0 ± 2.2	.754

Abbreviations: ADL, Activity of Daily Living Scale; AES-C, Apathy Evaluation Scale—Clinician Version; AQ-D, Awareness Questionnaire Disease; BHS, Beck Hopelessness Scale; BIS-11, Barratt Impulsiveness Scale; bvFTD, behavioral variant frontotemporal dementia; bvFTD-NS, bvFTD without risk of suicide; bvFTD-SR, bvFTD patients with risk of suicide; CDR, Clinical Dementia Rating Scale; FAB, Frontal Assessment Battery; HAR-S, Hamilton Anxiety Rating Scale; HDR-S, Hamilton Depression Rating Scale; IADL, Instrumental Activity of Daily Living Scale; MMSE, Mini-Mental State Examination; PSS, Perceived Stress Scale; RAVLT, Rey 15 Words Auditory Learning Test; RMET, Reading the Mind in the Eyes Test; SD, standard deviation; TMT, Trial Making Test; TT, Token Test.

^aAll data are presented as mean ± SD.

Discussion

To the best of our knowledge, this is the first study evaluating both the suicidal behavior and the suicidal ideation in patients with bvFTD. Our findings showed that patients with bvFTD are at higher risk of suicide, since approximately 40% of our patients showed a suicidal ideation and more than 10% attempted suicide.

Worldwide, suicidal behavior is a major cause of disability and the 15th cause of death according to World Health Organization (WHO) reports.³⁸ Globally, the lifetime prevalence of suicidal ideation is 9.2% and of suicidal attempts is 2.7%.³⁹ Therefore, investigating the prevalence of suicidal behavior as well as its neurobiological bases in patients with major neurocognitive disorders is paramount. The risk of committing suicide in dementia is generally low, and suicide attempts are present in <1% of patients.^{40,41} However, a recent study investigating the suicidal behavior in patients with FTD showed a higher risk of attempt of suicide in respect to controls.¹⁴ In our study, we confirmed these results in patients with bvFTD, the main subgroup of FTD, and we further showed that not only the suicidal behavior but also the suicidal ideation is high in these patients. It is of interest to note that, in our bvFTD population, the frequency of suicide behavior overlaps the one observed in

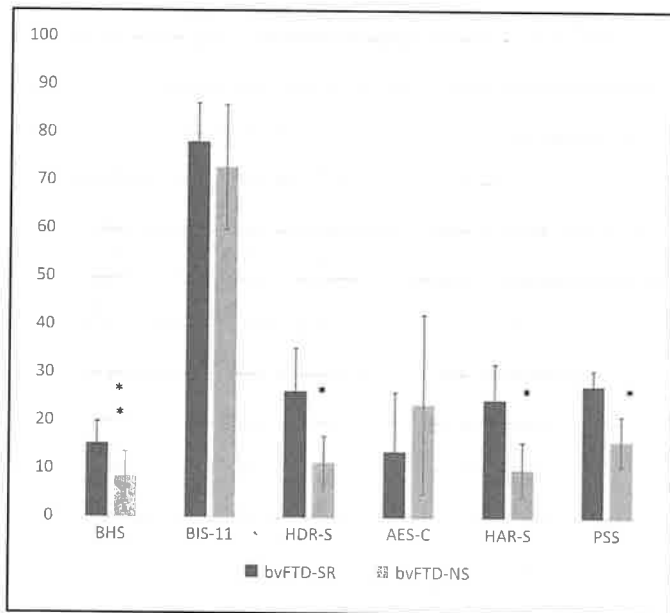


Figure 1. Levels of hopelessness, impulsivity, depression, apathy, anxiety, and stress in patients with behavioral variant frontotemporal dementia (bvFTD). Data are presented as means \pm SD of patients' scores in questionnaires on behavioral and mood changes according to the presence of suicide risk. Patients with bvFTD with the risk of suicide (bvFTD-SR) show higher levels of hopelessness, depression, anxiety, and stress than bvFTD without risk of suicide (bvFTD-NS). * $P < .01$. AES-C indicates Apathy Evaluation Scale—Clinician Version; BHS, Beck Hopelessness Scale; BIS-11, Barratt Impulsiveness Scale; HAR-S, Hamilton Anxiety Rating Scale; HDR-S, Hamilton Depression Rating Scale; PSS, Perceived Stress Scale.

Huntington disease, a neurodegenerative disease known to be associated with high risk of suicide.^{42,43} Therefore, additional clinical and epidemiological studies are warranted in order to better investigate the risk of suicide in different neurodegenerative disorders.

In our study, patients with bvFTD who have attempted suicide were younger and showed a longer duration of the disease than patients with only suicide ideation. Our findings are supported by a growing body of researches on suicidality in patients with dementia, reporting that young age is a risk factor for suicide behavior.^{9,11} Intriguingly, no association between gender and risk of suicide was found in our patients. This finding is in line with other research focused on suicide behavior in patients with neurodegenerative disorders, that did not confirm a higher tendency of suicidality in females.⁴⁴ Recently, a case-control study on neurological disorders and suicide attempts showed that males with neurological diseases had a higher risk of attempting suicide than female patients.⁴⁵ Therefore, further studies assessing the risk of suicide in patients with chronic neurological disorders according to gender are needed.

Psychological aspects as anxiety and depression related to the diagnosis of a neurodegenerative disorder at an earlier age could drive to suicidal behavior.^{11,12} In our patients, risk factors for suicide include depression, anxiety, stress, and hopelessness. Since no therapies for the disease are currently

available, patients with bvFTD may experience an elevated stress and a sense of hopelessness for their future, leading to suicidal ideations.

Neurobiological bases of suicidal behavior have been investigated only in recent years. Some studies suggested a role for the prefrontal regions in suicide.⁴⁶ Postmortem studies reported a reduction in presynaptic serotonin transporter sites in the prefrontal cortex, including the inferior frontal gyrus and the orbitofrontal cortex,⁴⁷ brain areas typically involved in the pathogenesis of bvFTD. In addition, an increased in 5-HT1A binding was found in these regions, suggesting that the serotonergic dysfunction in suicide victims might be due to gene expression changes in dorsal and ventral regions of the prefrontal cortex.⁴⁷ Finally, reduced concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid are associated with suicidal behavior in patients with depressive disorders and schizophrenia.⁴⁸ All these findings support the role of the serotonergic system in the pathogenesis of suicide behavior.

In our study, approximately 20% of the overall patients presented extrapyramidal signs that are consistent with previously reported on the prevalence of parkinsonism in bvFTD.⁴ Intriguingly, we observed that 40% of patients with bvFTD with extrapyramidal signs showed higher level of suicide ideation than patients without parkinsonism. A recent case report described a suicide attempt in a patient with bvFTD with parkinsonian symptoms.¹³ These clinical findings could be of importance for clinicians treating these patients. This could also suggest an involvement of subcortical regions and basal ganglia in the risk of suicide. In literature, suicidal ideations have been reported to occur in approximately in 23% of patients with Parkinson disease.⁴⁹ In addition, there are some evidences in depressed suicide victims for a reduced dopamine turnover in the nucleus accumbens, caudate, and putamen.⁵⁰ Furthermore, gene polymorphisms of the dopaminergic system have been reported to be involved in the biological susceptibility to suicide.⁵¹ Finally, a recent study showed that a haplotype in the dopamine receptor *DRD2* gene is involved in suicidal behaviour in alcohol-dependent patients.⁵² Further investigations on the genetic susceptibility of suicide are therefore suggested in patients with bvFTD.

Finally, we suggest that suicide risk should be considered when evaluating patients with bvFTD, in particular in young age. Suicide ideation and attempts are strongly predictive of suicide deaths, but the risk of suicide in patients with dementias other than Alzheimer's disease has often been underestimated. Therefore, this study can have several potential clinical implications. First, a better understanding of risk factors associated with suicidal behavior in patients with bvFTD can increase the use of routine suicide evaluations. Secondly, an early identification of patients who have suicidal ideation can help the clinicians to suggest psychological supports and to prescribe more effective individualized pharmacological therapies. In schizophrenia, there are some evidences that the typical antipsychotic drugs, associated or not with antidepressants, as well as the atypical neuroleptic drugs such as clozapine have an effect

on suicidal behavior and reduce the risk of suicide.⁵³ This therapeutic approach could also be applied to patients with bvFTD.

Our study has some limitations that deserve to be mentioned. First, the study population is relatively small; however, the patients recruited for the study have been extensively investigated in order to exclude any other forms of dementia. Second, our work involves only bvFTD and does not capture the language forms of FTD. Previously, in patients with SD, it has been reported that the risk of committing suicide is particularly high along with an accompanying awareness of their cognitive impairment.¹⁴ Contrariwise, a previous retrospective study on frontotemporal lobar degeneration reported that all the patients with suicidal behavior had the behavioral variant of FTD.¹⁴ Third, our control population is unbalanced in terms of gender. Notwithstanding, in our controls, the prevalence of suicide ideation overlaps that reported in WHO findings.³⁸ Fourth, in our study, patients with bvFTD present a lower level of education in respect to controls. However, in Italian population, the attainment of high level of education is associated with a greater risk of suicide; thence, the lower level of schooling in bvFTD may not have influenced the suicide ideation.⁵⁴ Fifth, in our study, suicide risk was assessed using the SSI as suggested by Italian psychiatric guidelines, and the use of combined suicide scales might provide additional clinical data. Finally, the majority of the patients involved in the study are aware of their disorder. In the literature, it is unclear whether a preserved insight potentially increases the risk of suicidal behavior in patients with neurodegenerative disorders.

In conclusion, our data showed that patients with bvFTD are at high risk of suicide. Additional studies are needed in order to further investigate the suicide risk in bvFTD and to elucidate the underlying neurobiological and neurocognitive mechanisms.

Authors' Note

Milena Zucca and Elisa Rubino authors equally contributed to the manuscript.

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