Frontotemporal dementia presenting as pathological gambling

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Background. A 69 year-old woman presented to an interdisciplinary medical group with pathological gambling, and went on to develop disinhibition, loss of empathy, and perseverative, stereotyped and ritualistic behavior. An initial neuropsychological evaluation showed selective impairment on the Iowa Gambling Task similar to that of patients with behavioral variant frontotemporal dementia, despite normal performance on standard neuropsychological tasks. MRI scans showed frontal lobe atrophy, which was consistent with findings on hexamethylpropyleneamine oxime single photon emission CT (HMPAO-SPECT).

Investigations. Physical examination, neuropsychiatric and neuropsychological assessments, MRI brain scan, HMPAO-SPECT.

Diagnosis. Behavioral variant frontotemporal dementia.

Management. Pharmacological treatment with the selective serotonin reuptake inhibitor paroxetine for impulsive behavior and carbamazepine to stabilize mood. The patient and her family also received counseling to advise on behavioral and legal issues.

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The case

A 69 year-old woman was referred to a memory clinic by her family to be evaluated and treated by an interdisciplinary group after developing pathological gambling (Box 1). The patient was right-handed, unmarried and had an unremarkable medical history. She had a family history of minor depression, but not dementia.

Before developing pathological gambling the patient had been tidy and meticulous, and careful with her money. Approximately 1.5 years before presentation to the clinic, she started to visit a casino during her holidays and, on returning home, she continued to gamble at a local venue. Over a period of around 6 months, she visited the casino at increasing frequency to gamble alone, and eventually attended every night. The patient spent her entire salary and savings, sold her possessions and valuable objects that belonged to her family (without their permission), and borrowed money from friends and relatives, making up extraordinary excuses so that she could continue to bet. On one occasion she was forced to borrow money from the staff at the casino to return home. She felt constantly exhausted owing to the fact that she hardly slept or rested, as she would rush to the casino after work and gamble until the early morning, sometimes staying through the night and going to work straight from the casino.

The patient's emotional state worsened, and her family became aware of her pathological gambling and its deleterious effects. She was dismissed from her job managing a student residence after stealing money assigned for maintenance of the residence. Her family restricted her funds, made sure that she no longer attended the casino, and referred her to our interdisciplinary group. At that time, the patient exhibited a notable lack of personal hygiene and care. Her family reported apathy and socially disinhibited behavior. The patient lacked insight and considered that her family's concerns were unfounded. She complained about their money restrictions and controls, stating that she understood she had to refrain from gambling, but was uncertain what she would do if she had no money available.

Physical and neurological examinations, performed at initial presentation, were unremarkable and laboratory values were normal. The behavioral deficits were not accounted for by a medical disorder (such as hypothyroidism) or a substance-induced condition. The patient was not using any medications associated with pathological gambling, such as dopamine agonists. On the first assessment, the patient's cognitive performance was entirely normal even on executive tasks, with the exception of the Iowa Gambling Task (a task that detects compulsive behavior in a card game; Box 2).[1] In this task, the patient impulsively selected the riskiest decks and needed to request new loans to continue playing. Statistical comparison of her scores with controls (measured in 20-card blocks, by means of single-case methodology[2]) showed significant differences in block 4 ($P<0.01$) and block 5

Competing interests
The authors declare no competing interests.

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Box 1 | Pathological gambling and decision-making capabilities

- Pathological gambling differs from ordinary gambling in that it is a persistent and maladaptive behavior that has disruptive consequences on familial, occupational and social functions
- Recent studies have suggested that pathological gamblers with dysfunction of the prefrontal cortex share certain characteristics with patients with frontal lobe damage
- The Iowa Gambling Task[1] can detect impairments in some cases of substance addiction, which shares vulnerability mechanisms with pathological gambling
- These measures of decision making are sensitive to pathology in the prefrontal cortex

Box 2 | The Iowa Gambling Task

The Iowa Gambling Task requires the individual to make 100 choices from four decks of cards, labeled A–D.[1] Each choice results in the individual either winning or losing money, but the reward and punishment contingencies of the different decks are unknown to the participant. Healthy controls typically sample from the four decks and realize that the decks fall into two categories. Decks A and B provide high rewards, but their occasional high punishment ends in a net loss over time ('high-risk' decks). By contrast, decks C and D provide smaller immediate wins but the punishments are also less severe, and repeated picks result in overall profit ('low-risk' decks). The dependent variable on this task is the net score, calculated by subtracting the number of choices from the risky decks (A + B) from the choices from the safe decks (C + D). Participants who develop a safe strategy will consistently choose cards from decks C or D, because they come to realize that although the immediate reward is small relative to that of decks A and B, the chances of losing money or the magnitude of such losses are smaller, ensuring an overall ultimate profit. However, patients with pathological gambling may fail to foresee the long-term consequences of consistently choosing cards from decks A and B, which may be more appealing because of their higher immediate gain, but which will lead to severe net losses owing to the high monetary punishments.

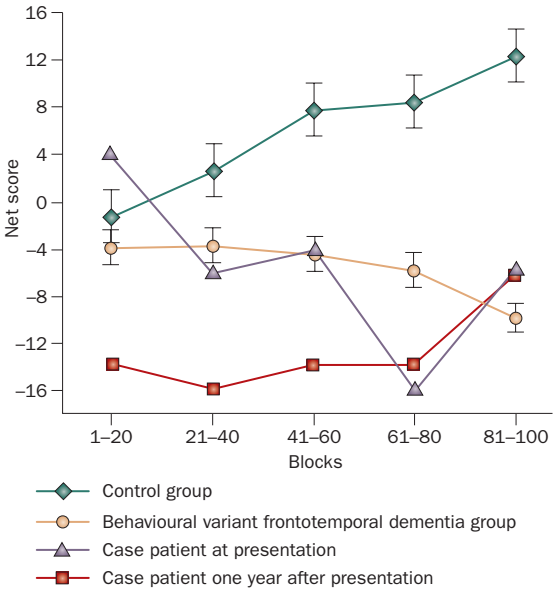

Figure 1 | Iowa Gambling Test performance. Mean (± standard error of the mean) net score on each block of 20 cards for the control group, the behavioral variant frontotemporal dementia group, and the case patient's performance at presentation and 2 years later.

(P <0.05). The patient's performance did not differ significantly from that of patients with behavioral variant frontotemporal dementia (bvFTD; Figure 1), and showed a substantial decline over 12 months of follow-up. The patient met the DSM-IV® (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, American Psychiatric Publishing, Inc., Arlington, VA) diagnostic criteria for pathological gambling. A diagnosis of FTD was established according to Lund–Manchester criteria.[3] Progressive frontal lobe atrophy was detected on MRI scans taken at initial presentation and after 2 years (Figure 2), which were assessed using a validated visual rating scale.[4] Marked hypoperfusion of the frontal and temporal lobes was detected by hexamethylpropyleneamine oxime single photon emission CT (HMPAO-SPECT). These findings supported a diagnosis of bvFTD (Box 3).

On the Neuropsychiatric Inventory (NPI), a diagnostic tool designed to evaluate neuropsychiatric symptoms and behavioral disorders in dementia, the patient's profile was characteristic of bvFTD, with high scores in the domains of apathy, disinhibition and stereotyped behaviors.

Table 1 shows the neuropsychological performance of the patient (at presentation and 2 years later) and comparison groups of 20 patients with bvFTD and 14 normal controls. The 20 patients with bvFTD presented with prominent changes in personality and social behavior, which were verified by a caregiver and met international consensus criteria for a diagnosis of FTD.[3] Healthy controls were recruited within the same geographical area as the study patients, and were matched for age and level of education.

The case was reviewed in the context of a multidisciplinary clinical meeting, where cognitive neurologists, psychiatrists and neuropsychologists discuss each patient's case in detail. Following this review, a diagnosis of bvFTD was agreed. At this point we started treatment with paroxetine (in doses increasing from 20 mg/day to 40 mg/day) for impulsive behavior,[5,6] and carbamazepine (initial dose 200 mg/day increasing to 600 mg/day) to stabilize mood.[5,7] Compulsivity and impulsivity were reduced with treatment. In addition to drug therapy, we implemented psychoeducation, behavioral intervention, and assistance to the caregivers as part of a nonpharmacological treatment program.

Over 1–2 years, the patient's executive symptoms progressed, and her behavioral changes increasingly worsened, with severe frontal lobe dysfunction, perseveration, echolalia, and poor emotional and cognitive awareness. In assessments made 2 years after the initial presentation, clear deterioration was evident on a range of tasks, in particular those evaluating executive functions: the Frontal Assessment Battery[8] (detailed analysis revealed deficits in verbal fluency, Luria motor series, conflictive instructions, and the go–no go test), verbal fluency, backwards digits span, and Part B of the Trail Making Test.[9] With regard to tests of memory, the patient performed poorly on tests with a strong executive component (Table 1). The patient continued on paroxetine and carbamazepine and her mood temporarily

stabilized. At this point, the patient received cognitive rehabilitation, especially aimed at improving memory and executive functions.[10] Cognitive rehabilitation showed some temporary efficacy on the patient's performance, although cognitive and behavioral difficulties increased over time. Behavioral management techniques for socially disruptive behavior were also attempted in this patient, resulting in a small improvement in behavior, an effect that was only temporary. We did not use acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) as these agents may increase the risk of exacerbating disinhibition–impulsivity behavior.[5]

Discussion of diagnosis

Background

The behavioral variant of FTD is characterized by various changes in personality, including impaired social interaction, a lack of empathy, apathy, disinhibition, compulsive behavior, and a decline in self-interest. These features, together with other cognitive and memory deficits, are indicative of frontal and/or anterior temporal atrophy (Box 3). To date, only one published report exists of a patient with bvFTD presenting with pathological gambling.[11] The authors of this report implicated abnormal functioning of the orbitofrontal cortex in the pathophysiology of gambling behavior, although no neuropsychological and neuroradiological data were presented. In 2007, Nakaaki *et al.* reported pathological gambling presenting late in the disease course of a patient with bvFTD.[12] The 48 year-old man initially showed a pathological tendency to hoard litter and exhibited changes in food preference. Almost 3 years later, he began to show pathological gambling. SPECT showed orbitofrontal–basal forebrain, cingulate, and medial frontal hypoperfusion. We have now comprehensively documented a case of bvFTD presenting with late-onset pathological gambling, and may be the first team to apply a test of decision making, the Iowa Gambling Test—which is highly sensitive in the early stages of bvFTD (Box 2)—to such a case.[13] Even when first evaluated, and despite normal performance on standard neuropsychological tasks, our patient showed an abnormal pattern of performance on the Iowa Gambling Task similar to that of patients with a confirmed diagnosis of bvFTD (Figure 1). Decision making, as assessed in the Iowa Gambling Task, seems to involve a complicated collection of psychological processes that recruit a large prefrontal network.[14] Neuropsychological evidence indicates a critical role for the orbitofrontal cortex in the pathophysiology of pathological gambling.[15]

FTD is a common cause of presenile dementia, and the prevalence of FTD in people below the age of 65 years approaches that of Alzheimer disease (AD).[16,17] For FTD, the age of presentation is typically between 45 and 65 years, although onset can even occur after 75 years of age. Different clinical and motor variants are now recognized as part of the clinical spectrum of FTD. Clinical variants include bvFTD and primary progressive aphasia (encompassing agrammatic or nonfluent, semantic, and logopenic or phonological progressive aphasia subvariants). Motor variants include progressive supranuclear palsy, corticobasal degeneration and amyotrophic lateral sclerosis.

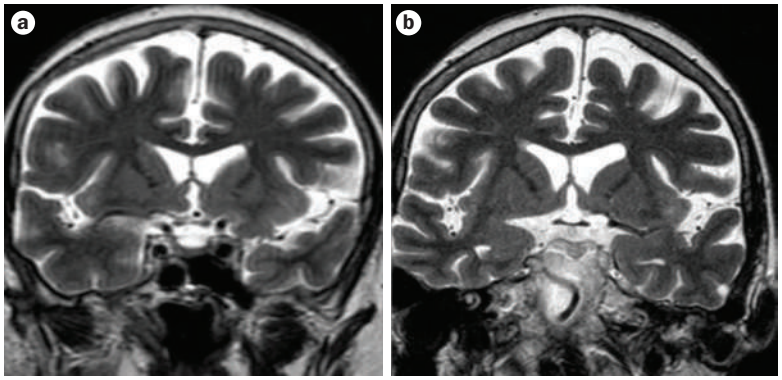

Figure 2 | Brain MRI scans from a patient with behavioral variant frontotemporal dementia. Coronal MRI scans through the frontal lobes, indicating progressive frontal lobe degeneration. Frontal atrophy was assessed by means of a validated visual rating scale,[4] which uses T1-weighted coronal images through the frontal and anterior temporal lobes and rates regional atrophy on a four-point scale (0 = no atrophy; 1 = mild atrophy; 2 = moderate atrophy; 3 = marked atrophy). **a** | MRI scan of the case patient taken on initial presentation; frontal atrophy rated at grade 1. **b** | MRI scan taken 2 years after initial presentation showing more-severe frontal atrophy (grade 2).

Box 3 | Behavioral variant frontotemporal dementia

The behavioral variant of frontotemporal dementia is characterized by the following:

- Insidiously progressive changes in personality and in social interaction, which typically precede other cognitive deficits
- Disinhibition, impulsiveness and lack of empathy
- Perseverative, stereotyped or compulsive and/or ritualistic behavior
- Withdrawal, apathy and diminished interest for activities or hobbies
- Impaired self-care
- Increased appetite with a tendency for sweet foods is frequent, and hypersexuality and hyperorality may develop, especially toward more advanced stages of the disease
- Perception, episodic memory, visuospatial abilities and praxis are intact or relatively well preserved
- Frontal and/or anterior temporal atrophy on MRI

Differential diagnosis

An early diagnosis of FTD can be difficult to make when behavioral problems dominate the clinical picture while cognitive functions remain relatively normal. A number of differential diagnoses must be taken into consideration (Box 4). Patients with bvFTD develop manifest changes in personality and social conduct and present with the following symptoms: disinhibition; impaired empathy, concern for others and emotional responsiveness; apathy; mental rigidity; altered patterns of eating; and stereotyped and obsessive behaviors. These symptoms overlap with those seen in a range of neuropsychiatric

Table 1 | Neuropsychological background tests

Test	Case patient at presentation	Case patient 2 years after presentation	Patients with bvFTD ($n=20$)	Control ($n=14$)
Mini-Mental State Examination	30	27	27.9 (1.6)	29.5 (0.8)
Addenbrooke's Cognitive Evaluation[24]*	94	81‡	85.6 (8.6)	94.8 (5.8)
Frontal Assessment Battery at bedside[8]§	16	11‡	14.3 (4.1)	17.7 (0.5)
Rey Auditory–Verbal Learning test:[25]‖				
Immediate recall	44	31	28.1 (10.1)	47.1 (7.4)
Delayed recall	4	4	3.77 (3.0)	8.1 (2.5)
Recognition	12	10	9.6 (3.5)	14.3 (0.9)
Logical memory[25]‖				
Immediate recall	19	17	18.8 (8.3)	24.5 (4.6)
Delayed recall	14	13	12.8 (9.0)	19.2 (5.3)
Digit span forward[26]¶	7	7	6.0 (1.5)	7.1 (0.9)
Digit span backward[26]#	5	4	4.1 (1.4)	4.8 (1.0)
Trail Making Test A[9]¶	55 s	68 s	65.2 s (29.2 s)	39.7 s (15.6 s)
Trail Making Test B[9]#	74 s	113 s	123.5 s (59.1 s)	97.7 s (9.8 s)
Boston Naming Test[27]**	18	18	18.8 (1.0)	19.8 (0.4)
Phonological verbal fluency[26]#	14	9‡	13.3 (7.1)	15.9 (4.5)
Semantic verbal fluency**	17	12‡	13.4 (6.0)	19.2 (2.3)
Rey complex figure test:[25]‡‡				
Immediate copy	36	36	31.5 (6.1)	35.4 (0.5)
Delayed recall (45 mins)	18	16	9.9 (6.1)	20.1 (5.6)
Wisconsin Card Sorting Test (modified version):[28]#				
Categories	6	6	3.9 (1.7)	5.5 (0.6)
Perseverative errors	2	4	7.2 (3.1)	2.2 (0.3)
Other errors	5	5	4.5 (2.1)	0.5 (0.1)
Pyramid & Palm Tree[29]**	51	51	49.7 (3.4)	51.8 (0.4)

Control and bvFTD group values are shown as mean (SD). *Test for screening dementia. ‡Denotes significant decline over the two assessments. §Test used as a brief screening of executive dysfunction. ‖Tests for assessing memory. ¶Assessments of attention and concentration. #Further tests of executive dysfunction. **Assessments of several features of language. ‡‡Measure of visual memory. Abbreviation: bvFTD, behavioral variant frontotemporal dementia.

conditions, including bipolar disorder, late-onset atypical psychosis, personality disorders, age-related personality change, obsessive–compulsive disorder, mid-life and late-life attention-deficit hyperactivity disorder, and alcohol abuse. The case patient had no history of psychiatric disorders or gambling. Perhaps the most likely alternative diagnosis would be mania, but our patient did not show the elevation of mood that characterizes this disorder, and had no abnormal beliefs or disturbance of the sleep–wake cycle. Other psychiatric syndromes that must be considered in the differential diagnosis of bvFTD include late-onset schizophrenia and depression. Our patient did not show hallucinations, delusion or thought disorders, and depressive symptoms were not reported by either the patient or her family. On formal psychiatric interview, neither schizophrenia nor depression was felt to be the likely explanation for our patient's condition.

Pathological gambling is a potential adverse effect associated with the use of dopamine agonists. The full syndrome related to overuse of dopamine agonists includes gambling, shopping, overeating, hypersexuality and punding.[18] Pathological gambling and other compulsive behaviors can occur independently, and they normally improve after dose reduction, discontinuation or switching to different dopamine agonists. Although the reports of pathological gambling with dopamine agonists was originally related to Parkinson disease, this adverse effect has also been reported in patients with restless legs syndrome after long periods of treatment with dopaminergic agonists.[19] Our patient had not taken any dopamine agonists, ruling out the possibility of a substance-induced condition, and she did not have any symptoms of Parkinson disease or parkinsonian syndromes. MRI scans showed no evidence of other structural abnormalities, such as trauma, vascular dementia, anoxic encephalopathy, normal pressure hydrocephalus, or tumors. Moreover, there was no clinical evidence of motor neuron disease.

A common misdiagnosis for bvFTD is AD but, although behavioral changes predominate in bvFTD, AD is dominated by deficits in episodic memory.[20] Apathy is a common feature of AD, but disinhibition and stereotyped patterns of behavior are not reported in the early stages of this condition.[21]

The diagnosis of bvFTD in our patient was supported by the finding of frontotemporal atrophy on MRI and hypometabolism in the frontotemporal regions on HMPAO-SPECT, neither of which is compatible with a functional psychiatric diagnosis. Moreover, the neuropsychological profile in our patient was typical of that described in bvFTD, with disproportionate impairment of a decision making task.[13,22]

Treatment and management

No disease-modifying therapies are available for the treatment of FTD; however, environmental and pharmacological interventions can help to manage behavior. Patients with bvFTD show a profound presynaptic serotonergic deficit, and selective serotonin reuptake inhibitors (SSRIs) have been used with some success.[5] Indeed, in our patient, treatment with the SSRI paroxetine seemed to reduce compulsivity and impulsivity. Patients showing high levels of agitation and/or aggression may need atypical antipsychotics, but these should be avoided for routine management. Although patients with FTD may respond to small doses of atypical antipsychotics, we avoided these drugs because of their potential adverse effects (especially extrapyramidal symptoms). Impulse control disorders, such as those seen in bvFTD, are a set of behaviors that include pathological gambling, compulsive shopping, compulsive eating and hypersexuality, among others. The underlying pathophysiology of these behaviors is poorly understood, and limited data exist to support any particular therapeutic strategy. Thus, management must be designed for each patient in their particular clinical setting. We used the mood stabilizer carbamazepine, which can diminish long-term emotional fluctuation[5] and has produced positive results in patients with pathological gambling.[7] Our patient's mood stabilized following this treatment.

The patient also received nonpharmacological treatment, including behavioral management such as occupational therapy, and cognitive rehabilitation, which were aimed at managing both pathological gambling and the impulse control disorder of bvFTD. These approaches met with little success.

Box 4 | Main differential diagnoses of bvFTD

Alzheimer disease

Trauma (frontotemporal contusions)

Infections such as Creutzfeldt–Jakob disease, HIV or neurosyphilis

Vascular dementia

Anoxic encephalopathy

Normal pressure hydrocephalus

Tumors such as glioblastoma multiforme

Motor neuron disease

Parkinson syndromes

Hashimoto encephalopathy

Psychiatric diagnoses

- Bipolar disorder
- Late-onset atypical psychosis
- Personality disorders
- Age-related personality change
- Obsessive–compulsive disorder
- Alcohol abuse
- Atypical depression
- Mid-life and late-life attention-deficit hyperactivity disorder

Abbreviation: bvFTD, behavioral variant frontotemporal dementia.

Conclusions

This Case Study exemplifies many of the typical features of bvFTD and highlights presentation with pathological gambling. Physicians should look out for features indicative of bvFTD, such as frontal executive impairment or frontal atrophy, when confronted with a patient manifesting personality changes, and a shift towards impulsive, aggressive and socially inappropriate behavior. Early and accurate diagnosis is critical.

Patients with bvFTD present unique legal and ethical problems related to competency, as these individuals may perform normally on standard neuropsychological tests, yet have severe deficits in judgment and decision making. In 2006, Burns and Bechara[23] claimed that the idea of free will, on which many legal systems are based, is not supported by the neuroscience of decision making. Human decision making is influenced by implicit processes that do not necessarily reach consciousness, and which can be disturbed by frontal damage. Under the current legal system, patients with bvFTD who have preserved cognitive functions would be held guilty for unlawful behavior resulting from frontal damage. From a practical perspective, current legal regulations and laws derived to deal with dementia similar to that observed in AD are inadequate in patients with bvFTD. Standards for determining competence are typically based on cognitive screenings or classical neuropsychological test evaluations. Patients with early bvFTD might perform well in these cognitive batteries yet show gross deficits in real-life decision making, accompanied by profound changes in personality. Caregivers need clear guidelines on the likely progression and outcome so that they can plan long-term management. The involvement of a multidisciplinary team including clinical psychologists, occupational and speech therapists, neurologists, and psychiatrists is highly desirable. Our case highlights the urgent necessity to develop specific policy and legal alternatives to help families cope with bvFTD.

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