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Psychosis and Hallucinations in FTD with C9ORF72 mutation: A detailed clinical cohort

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Abstract

OBJECTIVE—To describe in detail the presenting symptoms and clinical course of a cohort of patients with Frontotemporal dementia and the recently described *C9ORF72* repeat expansion.

BACKGROUND—Recent discovery of the *C9ORF72* repeat expansion linked to familial frontotemporal dementia and ALS has permitted retrospective evaluation of potential defining clinical characteristics that may distinguish *C9ORF72* mutation carriers from other patients with FTD. Prior reports have identified a subset of patients with an increased incidence of psychosis, specifically delusions, though the detailed nature of these symptoms is not yet well described.

METHODS—We conducted a retrospective chart review of to report the detailed case histories of 7 patients with *C9ORF72* mutations from a cohort of 61 patients with FTD.

Results—Detailed histories available from these patients reveal an increased incidence of psychosis, including visual and auditory hallucinations and delusions compared to sporadic FTD patients in our cohort.

CONCLUSIONS—This cohort confirms and adds symptom-related details to prior reports of increased incidence of psychotic phenomenon in FTD and ALS patients with *C9ORF72* mutations, to enhance future clinical identification and diagnosis of patients presenting with these symptoms.

Keywords

frontotemporal dementia; psychosis; C9ORF72 mutation; motor neuron disease

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Readers of this article will become familiar with some of the range of neuropsychiatric symptoms which patients with FTD and C9 mutations may present with, which can be misdiagnosed as primary psychiatric disorders for decades prior to development of other symptoms of FTD.

1. Introduction

Expanded GGGGCC hexanucleotide repeats in the *C9ORF72* gene have recently been identified in frontotemporal dementia (FTD), Amyotrophic Lateral Sclerosis (ALS) and ALS-FTD[1, 2] and appear as the most common genetic cause of familial (FALS) and sporadic (SALS) forms of ALS[3–6]. In patients with the *C9ORF72* mutation, the most common presenting clinical syndromes are behavioural variant frontotemporal dementia and primary progressive aphasia with concomitant ALS[4, 7]. In a multi-centre survey 6% of Europeans with sporadic FTD had the mutation (59 of 981), as did 25% of Europeans with familial FTD (99 of 400)[4]. Comparison of the presenting neuropsychiatric symptoms has demonstrated an increased incidence of delusions in *C9ORF72* mutation carriers vs. noncarriers with FTD[8, 9]. Predominant temporal atrophy on neuroimaging is present in approximately half of patients, while in comparison to non-carriers, *C9ORF72* carriers also show significant thalamic and parietal atrophy[9]. Pathological examination of brain tissue from patients with the *C9ORF72* mutation has nearly always revealed FTLD-TDP-43 of variable type, size and morphology[7, 8, 10, 11].

In this report we describe seven cases in detail to contribute to the clarification of the clinical phenotype of this new and important mutation. We were struck by the high incidence of psychosis, beyond the otherwise severe behavioural manifestations of FTD.

2. Methods

2.1 Case Ascertainment

From 2004 to 2012, 350 patients seen in our centre were diagnosed with FTD. Clinical diagnosis made prior to 2011 were based on Neary Criteria[12] and subsequently based on the revised consensus criteria[13]. Of the 350 patients, 62 patients with FTD consented to participate in genetic testing in research protocols and were tested for the *C9ORF72* expanded repeats (23 with behavioral variant FTD (bvFTD), 18 with semantic dementia, 6 with progressive nonfluent aphasia, 7 with FTD+MND, 5 with corticobasal syndrome (CBS) and 3 with progressive supranuclear palsy (PSP)). Data on the clinical symptoms, family histories, neuropsychological testing, neuroimaging and autopsy results were extracted from clinic charts and reviewed by two neurologists (AK and EF). Chi-square analysis were then conducted on the frequency of psychotic symptoms in *C9ORF72* carriers vs. non-carriers.

2.2 Genotyping

C9ORF72 mutation analysis was performed using a two-step protocol. First, in all samples, the hexanucleotide repeat was PCR amplified using one fluorescently labelled primer followed by fragment length analysis on an automated ABI3730 DNA-analyzer as described[14]. All patients that appeared homozygous in this assay were further analyzed using the repeat primed PCR method. A characteristic stutter amplification pattern on the electropherogram was considered evidence of a pathogenic repeat expansion.

3. Results

Of the 62 patients tested, 7 patients from 6 different families were found to have expanded repeats in *C9ORF72* (Table). Each of the patients with expanded repeats in *C9ORF72* is described in detail below. We also describe one additional patient from the 6 families who was followed in our centre and had autopsy proven FTD but did not undergo genetic testing. Clinical charts were available from 44 of the remaining 55 patients without *C9ORF72* expanded repeats, and these were reviewed for the presence of hallucinations, delusions or other psychotic symptoms.

3.1 Case Histories

3.1.1 Patient 1

Pre-diagnosis behaviour: Patient 1 was a 57 year old retired minister and courier driver with 16 years of education. At age 24 he had a psychotic breakdown when he reported he "saw the devil" and he thought he was dying. In his thirties he was hospitalized again because he thought he was possessed by the devil and thought people were talking about him and were out to get him. He developed food fads and indiscriminate eating of sweets, a year before he was evaluated in our centre. He hoarded orange pop in his fridge and would eat a box of chocolates or a whole cake in one sitting. He started eating dinner before anyone else and would eat off of others' plates. He stored food in his mouth without swallowing. He was first demoted at work to a job in the warehouse and eventually was fired because he was observed to eat leftovers from the shipments destined for garbage. The family had to intervene to stop his overspending. He would give money to charities or door-to-door solicitors. His personal hygiene also suffered. He would not bathe or brush his teeth and was very resistant to suggestions to do this. When he was challenged by family, he would say that it was none of their business. He was also indifferent to family issues and events. His speech output decreased and he stopped engaging in conversation. He mumbled, lost his normal inflection and his singing voice. He was arrested for assaulting his second wife. In the year prior to presentation, he had 6 syncopal episodes.

Presentation at time of diagnosis: He was referred to the clinic at age 58 initially for loss of initiative and changes in his voice and language. On examination, he was noted to lack spontaneous speech. When asked a question, he responded in clichés with mumbling and stuttering. He had orofacial movements consistent with tardive dyskinesia secondary to neuroleptics medications. His posture was slouched, with slow movements and a shuffling gait with decreased arm swing. His right hand was held in a curled position at times. His family history indicated dominantly inherited FTD/ALS. His brother, patient #2 described below, had bvFTD. A maternal aunt had ALS. His mother and a maternal uncle had early onset dementia, probably FTD. There was no other known history of psychiatric disease in the family. Neuropsychological testing showed word finding and comprehension difficulties, semantic paraphasias and circumlocutions. MMSE was 29/30, Raven's colored progressive matrices were also normal, but he had problems with clock drawing, although he copied well. The Frontal Behavioural Inventory (FBI) score was 45, diagnostic of FTD. MRI showed considerable left parietal atrophy in addition to more diffuse frontal and temporal atrophy.

Post-diagnosis course: Follow up 7 years after his initial visit found him in a group home, displaying inappropriate behaviour, drinking large quantities of Coca-Cola and holding his right arm in the air levitating and rigid, suggesting corticobasal degeneration.

3.1.2 Patient 2

Pre-diagnosis behaviour: Patient 2, the brother of patient #1, age 52 at the time of his wife's death, appeared somewhat detached, inattentive and confused about what to do. He did not seem to be listening to what was being said. He also became careless with his money, giving it away to a church and other charitable organizations. He ran red lights and was in several accidents, until his driver's licence was withdrawn. Subsequently, he developed disinhibition and bizarre behaviour. From being a rather shy person he became rather bold. He joined a senior's walking group, but after a while his walking became incessant roaming. When the group was finished for the day, he often stayed to continue roaming the mall and went home by taxi. He became obsessed about getting to his walking group on time and he became very upset if he could not go. He also developed strange eating habits. He would finish a chocolate cake if it was left in front of him, and always asked for seconds when they ate out; he did not seem to know when to stop. Once in the mall he reached over some stranger's shoulder to dig into their popcorn. He would take napkins from each stall of the food court and bring them home. Pop cans, collected on his walks, crushed and stuffed in his pockets ruined his jacket. He would sit down at someone's table and take a section of their paper without asking and took a book from a store without paying for it. He neglected his hygiene and he had to be reminded to shower. He repeated questions, sounding like an echo and when his daughter asked him to pass the salt he would repeat under his breath, "pass the salt…pass the salt…pass the salt". He also repeated phrases from the radio that he heard.

Presentation at time of diagnosis: He presented for evaluation at age 55. On examination he had a vacuous smile and echoed what was said to him, repeating instructions such as "hold your hands out." He had a persistent glabellar tap reflex and "gegenhalten". On the Frontal Behavioural Inventory his daughter endorsed many symptoms, such as impulsivity, restlessness, social inappropriateness, poor judgement, excessive jocularity, perseverations, obsessions, disorganization, personal neglect, concreteness, inflexibility, indifference, aspontaneity, and apathy.

Post-diagnosis course: His language became impoverished, he did not speak spontaneously as much as he did before, and he had word finding difficulty. His childish stubbornness and single-mindedness seemed like a "tunnel vision." He was put on Trazodone with a modest decrease in his restlessness. His supervised day program became one of his adopted routines and he particularly enjoyed dancing. There he would walk to the fridge to get food, which was not his. Another time he followed the custodian up onto the roof. He was impatient and impulsive. If he had to wait for a few minutes he would walk around rubbing his hands and clapping his thighs and then he may disappear. Subsequently he developed severe apraxia and "parkinsonism" doubtfully responsive to Levodopa. He became progressively rigid and mute, except for echolalic whispers, singing songs and lip synching movies. He had marked axial neck and asymmetric limb rigidity and dystonic plantar responses. He also had a strong

grasp reflex in the right arm and gripped his own left arm causing bruising. He could not manipulate objects with his right hand, as if his right arm did not belong to him. He had fixed, dystonic facial expressions, grimacing, rhisus sardonicus, and frontalis hypertonicity. A partial vertical gaze palsy and square wave horizontal saccades were also observed. He died in a nursing home 7 years after onset at age 59.

Neuropathology: Autopsy showed widespread cortical atrophy, most severe in the frontal lobes with ubiquitin positive tau negative inclusions and degeneration of the basal ganglia, thalamus and substantia nigra. Subsequently, TDP-43 immunostaining revealed cytoplasmic expression of TDP-43 in the cortical neurons, dentate granular neurons, hippocampal pyramidal neurons and spinal motor neurons, as well as some staining in the white matter tracts, compatible with type B of the Mackenzie classification[15].

3.1.3 Patient 3

Pre-diagnosis behaviour: Patient 3 was a 43 year old right handed mechanic with 13 years of education who noticed some word finding difficulty two years before his evaluation but didn't think much of it. Later his speech was described as sounding like he was drunk on the telephone (he lived far from the informant). At times he didn't seem to understand what was being asked and he repeated things over and over again. He would even perseverate with single words. When he couldn't follow a conversation he would hang up on his wife. A year later his speech was very much decreased, he began to cry easily and his telephone calls were restricted to yes and no responses. He had no ambition to do anything and he quit his job. He didn't like to go out to see people. He would get up if he had company and go out of the room to be alone. He was stubborn and rigid in thinking and his personal hygiene declined. He took one shower in 3 weeks. His wife had to tell him to change his clothes. He childishly did not want to share money. He also developed gluttony and he would eat two large plates of food at supper time. He grabbed at food and shoved it into his mouth with his hands. He also developed a sweet tooth and liked to eat ice cream, which he never liked before, by the bowl full. Social disinhibition was evidenced by the compulsion to tell everyone he had to go to the bathroom. He was inattentive, easily distractible and disorganized. He was unaware of any of the above changes and denied any when he asked about them. Family history was positive for a maternal uncle who was diagnosed with Pick's disease.

Presentation at time of diagnosis: He presented at age 45. On examination he had dysarthric speech which was borderline fluent, and perseverative, with some paraphasias, repetition and word finding difficulties. His MMSE score was 23/30, but notably he remained well oriented in place. His drawings of a pentagon or a clock were spatially correct, but he couldn't set the hands appropriately which appeared to be a language problem. He did poorly on a logical memory paragraph. On the Western Aphasia Batter the overall Aphasia Quotient (A.Q.) was 80.6. He showed difficulties with reading, spelling, drawing and praxis. Dementia Rating Scale-2 (DRS-2) score was 100/144, in the significantly impaired range. Severe disinhibition behaviours, perseverations, apathy, indifference, aspontaneity, obsessions, irritability, and inappropriateness were reported on the FBI.

The clinical diagnosis frontotemporal dementia/Pick's disease was made, but his dysarthria was atypical and motor neuron disease and brainstem vascular abnormalities were also considered. Neuroimaging showed left, predominantly perisylvian, frontotemporal atrophy on CT, MRI and SPECT imaging.

Post-diagnosis course: He died without an autopsy 3 years after symptom onset at age 46.

3.1.4 Patient 4

Pre-diagnosis behaviour: Patient 4 was a 56 year old part time bus driver, still working in a warehouse when he developed personality changes 3 years prior to presentation. He became angry and repetitive and had episodes of road rage while at the same time was apathetic and disinterested. He started to eat ice cream all the time, developed rigid routines, eating cereal at the same time from the same bowl, rubbing his hand repetitively and he appeared restless. He also developed word finding difficulty and slurred speech. His arms became weak; he could not lift them above his head. He started to choke on liquid a year after the behavioural onset of his disease.

Presentation at diagnosis: At age 59, he presented to our clinic. He endorsed auditory hallucinations of voices on direct inquiry. On examination he was restless and dysarthric with severe verbal and orofacial apraxia. Significant weakness in his deltoids, biceps, hip flexors and legs was associated with fasciculations, including in his tongue. He could not complete cognitive testing, but was noted to have word finding difficulty in addition to his severe dysarthria and comprehension difficulty for complex sentences. Family history was negative for similar illnesses. Neuroimaging with CT and MRI showed bifrontal and left perisylvian atrophy.

Post-diagnosis course: The diagnosis of FTD/ALS was made and he was referred to the ALS unit, where electrodiagnostic studies confirmed Motor Neuron Disease and he was admitted to palliative care. He died within a year of his diagnosis at age 60. Autopsy was declined.

3.1.5 Patient 5

Pre-diagnosis behaviours: Patient 5 was a 53-year-old housewife who was well until 3 years prior to presentation, when she was said to be depressed, increasingly bizarre and delusional after her husband died suddenly. Prior to his death others had commented on her echolalia. Subsequently, she believed that she had inherited a home from another man. She was admitted to nursing home as a result of her decline in mental status, but they were no longer able to manage her, as she was leaving the nursing home wandering and looking for children from this man and she was admitted to psychiatry. In the psychiatric unit she was initially diagnosed with psychotic depression. She was treated with ECT, olanzapine and intramuscular risperidone. She developed parkinsonism presumably from the psychotropic medications.

Presentation at time of diagnosis: She was referred to our Cognitive Neurology Clinic for evaluation of dementia 3 years after onset at age 56. Her medications were weaned, resulting

in improvement of her tremor. Her daughter noticed, particularly, when the patient was still living at home, a significant decline in personal hygiene. She bathed infrequently and for very short amounts of time. She followed her daughter everywhere and was very dependent. She did not change her clothes appropriately. She ate food quickly and shoveled it in, even guzzling down hot coffee. She continued to display apathy or lack of interest in most things, but loved to participate in music at the nursing home and said spontaneously several times during the evaluation "I love country music." She slept a lot and was not interested in engaging conversations with her children or grandchildren even when they came to visit. In contrast, when they were at Wal-Mart she approached babies and when they passed by a playground she went on the swings, consistent with change towards childlike behaviors. Although she was disinterested and withdrawn initially, over time she became excessively jocular and impulsive. She seemed to lose her manners and often burped in public. On one occasion, she emailed a picture of her own daughter's deceased baby to acquaintances. She became restless, fidgety, and made frequent humming noises.

Her family history was suggestive of FTD and ALS in a dominantly inherited pattern. The patient had 3 brothers and 3 sisters. One sister was diagnosed with ALS with probable cognitive changes in her fifties, and the patient's mother was diagnosed with a dementia (thought to be Alzheimer's disease) with onset in her sixties. One other sister was diagnosed with depression.

On neurologic examination she displayed a child-like affect. Her speech was sparse but she engaged in near constant echolalia, mumbling and small humming noises. She was able to follow verbal commands and gestures, named 4/6 items but was not able to indicate the meaning of more complicated words. She displayed a mild action tremor in the left arm, bilateral grasp reflexes and a positive snout reflex.

Neuropsychological testing: She scored 14/30 on the Mini-Mental Status exam, but she was correctly oriented to the month, year and day, as well as the city. She lost points for attention, concentration, repetition, following commands, writing and copying the design. She was notably laughing and quite childlike throughout the testing. Her visual spatial skills such as assessed on clock drawing were generally good, with impaired hand placement on clock and which improved when copying. Trails A was impaired, with a score at the 10^{th} percentile. She could not complete Trails B. Neuroimaging (CT scan) showed bilateral anterior temporal lobe and medial frontal lobe atrophy.

Post-diagnosis course: A progressive decline in language and speech was also noted. She began to say "yup" or "okay" in a stereotypic way, even when it was an inappropriate response to the question. She developed mild dysphagia and became incontinent of urine. Now age 59, she currently resides in a nursing home.

3.1.6 Patient 6

Pre-diagnosis behaviours: Patient 6 was a 67 year old accountant, who began to forget the name of things. His wife noted that he would say "that thing there" instead of using actual concrete nouns. When putting away the dishes, a familiar chore, he often asked "where does this go?" He did not ask what specific words mean but on one occasion asked what a tire

gauge was when he saw it (he typically carried a tire gauge with him when driving). On another occasion he confused strawberries with raspberries. When speaking, he emphasized the wrong syllable. He spent $500 on Reader's Digest books convinced that he would win a prize. On another occasion, he ordered many CDs, yet did not take them out of the plastic covers. He told detailed stories to others about his medical condition to the point that it embarrassed them.

Presentation at diagnosis: He presented for evaluation at age 68. Although he was very aware of the familial history of disease, he had no insight into the changes described. On examination he demonstrated some difficulty with fluency and made a few phonemic paraphasic errors, calling a kite a "pipe" or a "pike" and a flag a "flang". Semantic fluency was mildly, while phonemic fluency was mild to moderately impaired. His family history was significant for FTD in his sister, who had FTLD-TDP-43 type b. His MRI demonstrated mild frontal, temporal and parietal atrophy bilaterally.

Post-diagnosis course: Now at age 71 he has become very routine bound and was easily upset with change. He is still described as being emotionally sensitive. Many times unable to find an object, he thinks that someone had "stolen it." He accuses his son who is living with them of stealing food from the refrigerator. His hoarding tendencies have increased. He is reluctant to throw out old expired food. He has developed obsessive behaviors, such as using a saline nasal spray so frequently he ends up with nosebleeds.

3.1.7 Patient 7

Pre-diagnosis behaviours: Patient 7, a 62 year old man developed argumentativeness, disinhibition and social inappropriateness at age 52, 10 years before his evaluation, eventually resulting in losing his project manager job. His previously serious, aggressive personality became malleable, indifferent, and "happy-go–lucky". He brought noisy ornaments to the company Christmas party and yelled at coworkers. He developed incontinence, possibly related to his drinking diet coke constantly. When his wife had surgery at Halloween, he went out trick and treating. He obsessively collected fishing gear, records and tapes. He did not change his clothes. He spent impulsively and lost interest in managing his finances, even though he was an accountant. Nearly 20 years before his presentation he developed visual hallucinations, seeing people. These occurred only at night, in dark rooms. He described these people as funny and friendly, and would at times laugh out loud when having a conversation with them, suggesting potential auditory hallucinations as well. His wife found him downstairs in the dark one night, telling the hallucinations to be quiet because otherwise his wife was going to wake up and come downstairs. He said the faces were not full, and were not recognizable. He refused to see a doctor, because he did not want to have Pick's disease diagnosed like his sister had. Nine months before diagnosis he developed slurred speech, drooling and later weakness in his legs. Five years prior to presentation he developed coughing, which progressed to dysarthria and dysphagia. His family history indicated an autosomal dominant familial pattern of FTD. His sister was diagnosed to have FTD (see below 3.1.7). His mother was diagnosed with ALS and described as "very goofy" though no formal diagnosis of dementia was made. Two maternal uncles and one maternal cousin had ALS. Another maternal uncle was said to have dementia

and a relative in Ireland had “creeping paralysis” and a maternal aunt in Ireland had been described to be “crazy”.

Presentation at time of diagnosis: He presented at age 62. Examination demonstrated a jovial disposition with a spastic dysarthria and fasciculations in the tongue and arms. Reflexes were brisk in the left arm and legs bilaterally. He had a brisk jaw jerk and positive rooting reflex. Neuropsychological testing showed a loss of executive functions, with generally preserved memory, language and visuospatial performance. MRI showed moderate bitemporal and inferior frontal atrophy.

Post-diagnosis course: The patient’s jovial affect has continued. His visual hallucinations subsided. His bulbar symptoms have continued to progress, but he remains active without weakness in the limbs.

3.1.8 Patient 8

Pre-diagnosis behaviour: Patient #8 was the sister of Patient #7 above. She was fired from her job as a receptionist at age 47, about 8 years prior to her evaluation at age 55. At that time she started to eat too much, such as whole bag of candies in one sitting (she worked for Weight Watchers), became indifferent about the family, and started to shop and hoard clothes excessively. She bought thousands of dollars worth from catalogues at Christmas. She told her doctor he was “cute” and perseverated about irrelevant topics. She often appeared impatient, watching the clock and walked ahead of everybody. She hugged and kissed the neighbours’ teenage son, danced in public and became intimate with strangers. She also described visual hallucinations of people for several years prior to her presentation that were similar to the experiences of her brother. The hallucinations occurred at night in dark rooms, and she often had conversations with them. She would try to keep them quiet so they would not wake up her husband who was sleeping next to her, also suggesting a concurrent auditory hallucination.

Presentation at diagnosis: She presented at age 63 for evaluation in our centre. At that time she became inattentive and her conversation became simplified and childish. She did not understand movies and she often laughed without reason. She became apathetic, disorganized, stopped cooking and neglected her hygiene.

On examination she appeared euphoric, hugged the examiner, interrupted her daughter, spoke tangentially, and had long periods of not talking at all. At other times speech was echolalic. She was apraxic on alternating hand movements and had low scores on executive function. Family history was as noted for patient #7. Neuroimaging showed severe bifrontal and greater right than left temporal atrophy on CT and MRI.

Post-diagnosis behaviours: Later she touched everything and stroked velvet repeatedly. She claimed to “hate food” but ate very well. She reported nightly visual hallucinations as described above. She developed incontinence and signs of motor neuron disease included a drop foot. She died 9 years after her presentation, at age 64.

3.19 Psychosis, hallucinations and delusions in FTD patients without C9ORF72 expanded repeats—Chart review of the available information from 44 patients without C9ORF72 expanded repeats in the cohort revealed 2 patients with visual hallucinations (one of a dog on the ceiling, the other patient saw people who were deceased, snakes, dogs and bulls), no patients with auditory hallucinations, and 8 patients with delusions. Of the patients with delusions, 5 had paranoid delusions common to Alzheimer's disease, of theft or spousal infidelity. Of the other three patients with delusions, one believed that her children had been in a car crash and would tell strangers her children had been killed. The other two patients were sisters and both were convinced that others were encouraged to be physically abusive towards them. Chi-square analysis demonstrated a significant association between C9ORF72 status and the presence of any psychotic symptom $\chi^2(1)=8.68$, $p<0.005$.

4. Discussion

These eight cases reflect our experience with the *C9ORF72* mutation in our clinically diagnosed FTD population of 350, of whom 63 were tested for *C9ORF72* repeat expansions. In the present *C9ORF72* cohort, three out of eight patients had prominent psychiatric histories or presenting symptoms. One of our patients was treated for psychotic breakdowns at age 24 and one had auditory hallucinations on systemic enquiry at age 58. Another one was hospitalized because of paranoid delusions and psychotic depression at age 53. A fourth was mildly paranoid without actual psychiatric diagnosis, which is not uncommon in FTD or AD. The patients as a rule presented with behavioral variant of FTD with a pattern of disinhibition, compulsions, gluttony, indifference, and irritability not different from tauopathies or other TDP-43 confirmed cases. The exceptions were one patient who was mildly aphasic at the onset and another who had psychosis 20 years before the onset of FTD. Two patients were echolalic, but not obviously aphasic and another one had elements of semantic dementia. In comparison to other FTD patients in our cohort, the prevalence of hallucinations in patients with C9ORF72 expanded repeats was significantly greater: 50% for C9 carriers vs. 5% for non-carriers. The presence of delusions was found in 25% of the C9ORF72 mutation carriers, in contrast to 18% in non-carriers.

The prevalence of this new mutation in our clinic population is commensurate to the combined experience of other centres. The reported prevalence of hexanucleotide repeat expansions in *C9ORF72* in familial FTD ranges in European cohorts is 25–28% and 2–6% in patients with sporadic frontotemporal dementia[4, 7]. The mean age at onset in our cohort was 52.4 years (range 43–58) compared to 56.9 ± 8.3 years (range 39–76) in the Sanchez et al. 2012 study. The diagnosis at onset was bvFTD in 6 patients, aphasia in one and depression in another. All patients developed the typical pattern of significant behavioural disturbance, food obsessions and gluttony, loss of hygiene, indifference, inattention, irritability and disinhibition. Eventually all but one became aphasic as well. Two developed ALS, one the typical spinal and bulbar type with rapid progression, and another one with only bulbar features thus far. A family history of ALS was present in the other 4 families. Three patients developed apraxia, and two developed an extrapyramidal disorder resembling corticobasal syndrome after a typical course of bvFTD. Another patient developed parkinsonism, presumably after antipsychotic medication. There is another report of

corticobasal syndrome and parkinsonism with the *C9ORF72* mutation[16]. In our series, though only 2 of the 8 patients met criteria for probable ALS and one for possible ALS, this is still higher than the ~15% one would expect in a general FTD clinic population[17].

The most interesting difference in our cohort of patients with *C9ORF72* mutations compared to the general FTD population is the incidence of psychosis with visual or auditory hallucinations or psychotic delusions in 4 patients and paranoid ideation in another. Observations of psychiatric illness in bvFTD literature have typically described the florid behavioural abnormality that is the essence of bvFTD. Psychosis in FTD or FTD/ALS was considered rare, and at times listed as an exclusion criteria[18]. We reported the case of a woman with sporadic bvFTD with visual hallucinations and delusions of sexual content or erotomania (deClerambault syndrome) who had fronto-temporal and parietal atrophy and TDP-43 pathology on autopsy[19]. A small series of patients meeting criteria for both FTD and LBD with hallucinations were also noted to have TDP-43 pathology[20]. Others have described psychosis and Parkinsonism in C9 linked families before the specific mutation was discovered[21] and in patients with progranulin mutations[22]. While psychosis is not considered a feature of ALS, small numbers of patients have been described. Three patients with FTD/ALS and psychosis with visual hallucinations were described by Nitrini et al.[23]. Subsequently it was reported that delusions occur more frequently in patients with FTD/ALS than with FTD alone[24].

Psychiatric presentations have been described in patients with C9ORF72 mutations, but 2/3 of the patients had “psychiatric symptoms” compatible with bvFTD and one had mystical delirium with auditory hallucinations at 44 years of age, and did not present neurological symptoms over a 7-year follow up[25]. In a series of 32 patients with the C9ORF72 mutation presented with psychosis and another 28% were paranoid or delusional[8]. Mutations in the C9ORF72 gene may be a major cause not only of frontotemporal dementia with motor neuron disease but also of late onset psychosis. In another series, 22% of patients with FTD or ALS and *C9ORF72* mutations had a higher frequency of delusions as rated on the Neuropsychiatric inventory, compared with non-carriers (0%)[9]. One of our patients with visual hallucinations experienced these 20 years before the onset of FTD and one could argue that he had an independent psychiatric illness. In the other depressed patient, the delusional content of her psychiatric illness had some possible basis in reality, and in the other two patients with paranoid ideation and auditory hallucinations, the symptoms were elicited on direct questioning and were not treated as psychiatric illness as such.

5. Conclusions

In summary, we report a case series of 8 patients with FTD and *C9ORF72* mutations, in whom we found a higher than expected incidence of psychosis, hallucinations and delusions. In several of the patients the psychotic symptoms predated other changes more typical of bvFTD, often resulting in initial misdiagnosis of a psychiatric disorder. The series is also notable for the frequent occurrence of both ALS and hallucinations. Future larger scale studies of the presence and the detailed nature of psychotic symptoms in bvFTD and *C9ORF72* mutation carriers are required to determine whether and how these features may be differ in patients with FTD compared to other psychiatric disorders.

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TABLE 1

Clinical Details and Neuroanatomic Findings in Patients With Frontemporal Dementia (FTD) and *C9ORF72* Expanded Repeats

Patient # and Sex	Age at Onset	Mode of Onset	Nature of Psychosis	Other bvFTD-Related Symptoms	Aphasia	Motor Neuron Disease	Neuroimaging Findings	Family History	FBI Score*	Age at Death, Autopsy Findings
1 Man	57	Behavior change	Visual hallucinations, psychotic delusions	Food, poor hygiene, impulsiveness, indifference	Anomia	No	Left parietal, bifrontal, and temporal atrophy	Brother (Patient 2) had FTLD-U; mother and maternal uncle had early-onset dementia, probably FTD; maternal aunt had ALS	45	
2 Man	52	Behavior change		Food, poor hygiene, indifference, compulsions	Echolalia	No	No testing	Brother (Patient 1) had FTD; same family history as Patient 1	43	59, FTLD-U + TDP-43 type B
3 Man	43	Behavior change		Food, poor hygiene, irritability, indifference	Anomia, conduction	Possible bulbar	Left > right frontal and temporal atrophy	Maternal uncle had Pick disease	42	46, declined
4 Man	56	Behavior change	Auditory hallucinations	Food, irritability, indifference, compulsions	Mild anomia	Yes	Bifrontal and left temporal atrophy	No family history	32	60, declined
5 Woman	53	Depression	Bizarre delusions	Food, poor hygiene, indifference, inappropriate behaviors	Echolalia	No	Medial frontal and anterior temporal atrophy	Sister had ALS and cognitive deficits; mother had early-onset dementia	39	
6 Man	67	Aphasia	Paranoid delusions	Food, compulsions, irritability, disinhibition, impulsiveness	Semantic paraphasias	No	Mild bifrontal, temporal, and parietal atrophy	Sister had FTD/ALS: FTLD-U TDP-43 type b	32	
7 Man	52	Behavior change	Visual and auditory hallucinations	Food, poor hygiene, inappropriate behaviors, indifference, obsessions	Dysarthria	Yes	Right temporal and inferior frontal atrophy	Sister (Patient 8) had bvFTD; mother had ALS and suspected behavioral changes; 2 maternal uncles and 1 cousin had ALS; another maternal uncle had dementia	46	
8 Woman	47	Behavior change	Visual and auditory hallucinations	Food, inappropriate behavior, compulsions	Decreased speech output	Yes	Bifrontal and right > left temporal atrophy	Brother (Patient 7) had bvFTD; same family history as Patient 7	46	64, FTLD-U +TDP-43 type B

* A Frontal Behavioral Inventory score of 27 or higher is considered sensitive and specific for a diagnosis of bvFTD (Kertesz et al, 1997).

FBI = Frontal Behavioral Inventory. FTLD-U = frontotemporal lobar degeneration with ubiquitin-positive inclusions. ALS = amyotrophic lateral sclerosis. bvFTD = behavioral variant frontotemporal dementia. TDP-43 = transactive response DNA-binding protein 43 kDa (kiloDalton).