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Temporal variant of frontotemporal dementia in *C9orf72* repeat expansion carriers: two case studies

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Abstract

The temporal variant of frontotemporal dementia (tv-FTD) is a progressive neurodegenerative disease with a complex clinical picture mainly characterized by behavioral and language disorders. In this work, we describe clinical, genetic, neuroanatomical and neuropathological (only in one case) features of two patients with tv-FTD carrying *C9orf72* repeat expansion. The first patient (AB) presented with a 1-year disease duration showing focal right anterior temporal lobe (ATL) atrophy on magnetic resonance imaging (MRI). The second patient (BC) came to medical attention 13 years after disease onset and showed a prominent bilateral ATL involvement. Both patients showed naming deficits, impairment in identifying known faces and proper names, and personality changes with new onset behavioral rigidity, and progressing language difficulties to

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Informed consent Informed consent was obtained from all individual participants included in the study.

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single-word and sentence comprehension difficulties. They were classified as tv-FTD. Clinical, cognitive and MRI follow-up were performed. As cognitive impairment progressed, MRI atrophy worsened in ATL and frontotemporal areas in both patients. Both cases had clear family histories of neurological and/or psychiatric disease. Genetic testing revealed a *C9orf72* hexanucleotide repeat expansion in both cases. BC passed away after 15 years of disease and autopsy showed the expected TDP-type B pathology. These genetic cases of tv-FTD highlight the susceptibility of ATL to *C9orf72*-related pathology and emphasize the importance of genetical testing in FTD-spectrum disorders, regardless of the clinical phenotype.

Keywords

Temporal variant of frontotemporal dementia; *C9orf72*; Magnetic resonance imaging; Language; Social cognition; TDP-43

Introduction

The temporal variant of frontotemporal dementia (tv-FTD) is a progressive neurodegenerative disease that follows a characteristic cognitive and behavioral clinical picture and is usually associated with asymmetric anterior temporal lobe (ATL) degeneration (Seeley et al. 2005). In its classical form, it is associated with left ATL atrophy and clinically characterized at onset by language deficits such as loss of word and object meaning, surface dyslexia, and relatively preserved syntactic comprehension skills. This left tv-FTD is also known as semantic variant of primary progressive aphasia or semantic dementia (Gorno-Tempini et al. 2011). Approximately 25% of tv-FTD cases, however, present with predominant behavioral, emotional and interpersonal dysfunctions and right ATL atrophy (Chan et al. 2009; Edwards-Lee et al. 1997; Gainotti et al. 2003; Gorno-Tempini et al. 2004; Henry et al. 2014; Hodges et al. 2010; Josephs et al. 2009; Perry et al. 2001; Thompson et al. 2003). This right tv-FTD variant has been also named as ‘right semantic dementia’ (Kamminga et al. 2015; Kumfor et al. 2016) because patients often show also semantic deficits. However, despite the initial differences, the two tv-FTD progressively merge (Brambati et al. 2009). Therefore, behavioral disturbances emerge during disease course in left tv-FTD such as semantic/language deficits in the right tv-FTD (Seeley et al. 2005).

The right tv-FTD often leads clinician to challenges in the classification of these patients who do not perfectly fit the behavioral variant of FTD (bvFTD) criteria because they have early semantic deficits for famous people, places or food, and anomia (Henry et al. 2014; Mendez et al. 2004), but also might not fit the root primary progressive aphasia (PPA) criteria because of early behavioral symptoms.

In a study of familial heritability, tv-FTD was found to be the least heritable FTD syndrome (Goldman et al. 2011). Nevertheless, there have been few tv-FTD cases with established FTD associated gene mutations including the 43-kDa transactive response (TAR)-DNA-binding protein mutation (*TARDBP* +) (Caroppo et al. 2016; Floris et al. 2015; Gelpi et al. 2014), progranulin mutation (*GRN* +) (Cerami et al. 2013), MAPT mutation (*MAPT* +) (Bessi et al. 2010; Ishizuka et al. 2011), TBK1 mutation (*TBK1* +) (Caroppo et al. 2015; Hirsch-Reinshagen et al. 2019; Van Mossevelde et al. 2016) and *C9orf72* repeat expansion

(*C9orf72* +) (Le Ber et al. 2013; Majounie et al. 2012; Snowden et al. 2012). In the majority of genetic tv-FTD cases, MRI revealed ATL atrophy in the left hemisphere (Caroppo et al. 2015; Cerami et al. 2013; Gelpi et al. 2014; Hirsch-Reinshagen et al. 2019; Ishizuka et al. 2011; Le Ber et al. 2013; Snowden et al. 2012; Van Mossevelde et al. 2016). Only one *TARDBP* + (Floris et al. 2015) and one *MAPT* + (Bessi et al. 2010) patient showed prominent right-sided ATL involvement.

Here we describe in detail the clinical, neuropsychological and neuroanatomical features of two tv-FTD patients carrying *C9orf72* repeat expansion: one presented early with focal right ATL atrophy, and one who presented later with bilateral temporal involvement.

Informed consent was obtained from all individual participants included in the study.

Case report 1

History

A 60-year-old, right-handed woman, AB (arbitrary initials), was admitted to the Neurology Unit of San Raffaele Hospital (Milan, Italy) for first evaluation in 2016, and for follow-up in 2017. At baseline, AB and her husband reported one-year history of anomia in spontaneous speech and concomitant difficulties in managing her work activities as a health-care worker. Her husband noted she had significant language comprehension difficulties and personality changes. AB had become more anxious, irritable, and developed obsessive and ritualistic behaviors, such as eating the same type of food, or checking multiple times her work reports. She also became more apathetic and rigid and less empathetic, with overly strict routines and opinions in her life at home and at work. As a health-care provider, she lacked empathy for her clients' suffering; as a mother, she failed to understand and provide support for her daughter who was victim of a stalking episode. While she was worried and anxious about her performance difficulties at work, she could not point out what the cause of such impairment was and she was seemingly not concerned or aware of her behavioral and cognitive impairments. Consistently, she did not show any symptoms of depression or sadness. There was no significant past medical history. AB's father died at the age of 77 years for an unspecified dementia. Otherwise, her family history was unremarkable for neurological and/or psychiatric diseases.

Examination

Her general neurological exam was unremarkable, with no motor or sensory deficits; in particular, there were no pyramidal or extrapyramidal signs. Her demeanor was initially suspicious towards the examiner but during the visit she progressively shifted to an overly friendly approach. The Edinburgh handedness inventory showed strong right-handedness with a laterality index of 100 (Oldfield 1971). At bedside cognitive evaluation, AB's spontaneous speech was fluent, with no prosody, motor speech nor grammatical errors but she showed significant word finding difficulties and circumlocutions. AB exhibited difficulties in knowledge of low-frequency word and concepts, for example, she did not know what a positron emission tomographer (PET) was, despite working in a hospital

setting for decades. She also had trouble recognizing names and pictures of famous faces and pictures of landmarks.

Neuropsychological evaluation

At first evaluation, and at 1-year follow-up, AB underwent complete neuropsychological and functional testing. The presence of behavioral disorder was investigated through semi-structured interviews, as well as formal testing of her ability to identify emotions and attribute mental states to others (Theory of Mind, ToM). A detailed listing of the neuropsychological tests administered is available in the supplementary material. Raw cognitive test scores were transformed into Z scores (Table 1). AB's memory, visuo-spatial and attention domains were preserved. She showed difficulties in tests of abstract reasoning with tendency to provide simple, concrete responses. Language testing showed poor performance in confrontation naming and in discrimination between words/non-words on reading. Sentence and syntactic comprehension were intact and she did not show any difficulties with grammar comprehension or production. Visual semantic memory tests demonstrated difficulties in landmarks and famous faces identification and naming (Table 1). Despite these difficulties, she did not explicitly reported difficulty recognizing people in her daily life. AB was also tested on an extensive social cognition battery and was unable to recognize emotions or to use them in social context (a detailed list of neuropsychological testing is available in the supplementary material) (Table 2).

Neuroimaging

AB underwent a 1.5 Tesla MRI scan and an 18F-FDG-PET at baseline. MRI scans revealed severe right ATL atrophy, extending to the superior and middle temporal gyri with mild involvement of contralateral homologous regions (Fig. 1). FDG-PET showed severe hypometabolism in these atrophic regions and milder hypometabolism in fronto-medial cortex bilaterally, right orbitofrontal cortex, and right middle and inferior frontal gyri.

Laboratory testing

General metabolic panel, thyroid hormones, B12 and folate levels, autoimmune and infectious screening were within normal ranges. AB underwent lumbar puncture for amyloid and tau Alzheimer's disease biomarkers that were in the normal range.

Genetic testing

AB was first seen in 2016 and genetic testing was performed as part of standard research evaluation. The presence of the GGGGCC hexanucleotide repeat expansion in the first intron of the *C9orf72* gene was investigated using a repeat-primed PCR assay on an automated ABI3730 DNA-analyzer as previously described (Agosta et al. 2017). Additionally, mutations in the *MAPT*, *GRN* and *TARDBP* genes were excluded by Sanger sequencing (Agosta et al. 2017). Unexpectedly, AB's genetical analysis revealed the presence of the GGGGCC hexanucleotide repeat expansion in the first intron of the *C9orf72* gene. No mutations in the *MAPT*, *GRN* and *TARDBP* genes were found.

Diagnosis at baseline

Considering AB clinical, genetic and neuroimaging features, she was diagnosed by the clinical team with right tv-FTD. No medications were prescribed.

One-year follow-up visit (2017)

AB still did not show any pyramidal or extrapyramidal signs on neurological examination. Her husband commented on worsening anomia and impaired object recognition, as well as difficulties comprehending spoken language. AB's difficulty recognizing people became evident in everyday life. For example, she was no longer able to recognize her neighbor. With regard to her personality, she became more self-centered with no interest towards others' feelings. Her obsessive, rigid traits worsened, and she showed frequent inappropriate behaviors in social situations, switching easily from irritation to over friendliness. Despite progressive worsening, she still lacked insight into her cognitive and behavioral changes. There were no changes in her mood and she was even less concerned than the previous year, minimizing her cognitive difficulties and the complaints others voiced regarding her behavior. At this time, she was asked to retire from her job. On follow-up neuropsychological testing, memory, visuo-spatial abilities and attention were still relatively preserved and semantic impairment in visual and verbal tasks became more severe (Table 1). At this time, single word comprehension was significantly impaired while sentence comprehension was still relatively spared. She was unable to understand humor or empathic circumstances and showed a worsening of her ability to recognize emotions.

On examination, there was no change in weight, and there were no fasciculations, dysphagia or dysphonia. She underwent an electromyography of her limbs and tongue that was negative for secondary motor neuron involvement. At this time, MRI scan showed progression of atrophy in right more than left ATL, and milder involvement of the frontal regions (Fig. 1).

Case report 2

History

A 69-year-old, right-handed English/German bilingual man, BC (arbitrary initials), presented to UCSF Memory and Aging Center (MAC) in 2007, with a 13-year history of behavioral changes and a 4-year history of global cognitive decline. He had a successful business, which he sold in 1999 because he was 'burnt out'. Following retirement, his wife started to notice behavioral changes. He became more stressed and more mentally rigid. He aggressively asserted his opinion about the house plans, including construction and electrical work, even though he was not knowledgeable about this. In the following years, he became more particular about his clothing and food, began having repetitive behaviors, and became more confrontational. He became obsessed with eating the same food and developed a regimented schedule that was specifically arranged around his meals. He started collecting objects, did not discard anything, and started recycling more. He spent hours on certain activities, such as playing Sudoku, gardening and collecting worms. He was a mushroom-expert and started having difficulties recognizing them. He also became less empathic. A few months later, he started to show involuntary buccal movements, such as mouth shaking

and tongue jutting, classified as tardive dyskinesia. Beginning in 2002, he noticed short-term memory loss. He started losing personal items and began writing reminders down on Post-It notes. These included reminders to himself such as “smile more” or “hug your wife”. He could not recognize friends and once mistook a friend for his cousin. Regards to language, he started having word-finding difficulties and paraphasia. As an example, he used the word “avocado” instead of “arugula”. His sentences were grammatically correct but shorter. His comprehension seemed unaffected except that he occasionally asked people to repeat. With regard to his motor and cognitive changes, he was quite aware of these deficits; in stark contrast he was completely unaware of the behavioral changes listed above.

He initially saw a psychiatrist in December of 2006 and was thought to potentially have Alzheimer’s disease (AD). He was on Donepezil for about 2 years with little or no improvement in his symptoms. He has also tried Memantine but noted no improvement.

His past medical history was notable for stomach ulcers, cataract surgery, right retinal tear status after surgery, hernia repair, and one ER visit secondary to severe constipation. He still tended to have constipation. His medications included Rivastigmine 3 mg twice daily, Escitalopram 20 mg once a day (which he has taken for 1 year), a bulk-forming laxative p.r.n., vitamin C 500 mg once a day, saw palmetto 160 mg twice daily, and a multivitamin product once daily.

He was born in a foreign country and learned English during his adolescence when he moved to the US. He denied/endorsed significant alcohol and drug use. His family history was notable for personality changes in his mother and sister, for which his sister had received a diagnosis of FTD.

Examination

In 2007, BC was seen at the Memory and Aging Center (MAC) of University of California, San Francisco (CA, US). His neurological exam was notable only for mild oral-buccal dyskinesia.

Neuropsychological evaluation

Neuropsychological testing at first examination (Kramer et al. 2003) (for details see supplementary material) revealed moderate deficits in episodic verbal and visual memory, as well as executive functions. On language testing (Caso et al. 2013), BC showed poor confrontation naming and difficulty in object conceptual knowledge and showed markedly impaired ability to identify famous faces (Table 1) of which he did not complain during his interview. Sentence comprehension was relatively spared. Social cognition testing revealed difficulties in perspective taking and empathic concerns (Table 2).

Neuroimaging

In 2007 (13 years after symptoms’ onset), BC performed a first 3D T1-weighted MRI scan (4 Tesla) which revealed bilateral severe ATL atrophy, mainly in the poles, moderately extending to medial and lateral regions. Orbitofrontal and cingulate (anterior and posterior) cortices were also clearly atrophic (Fig. 1). In order to explore the possibility of an

underlying AD pathology, in 2007 the patient underwent a PiB-PET, which was deemed negative, not only based on visual read, but also based on quantification of the cortical uptake that was estimated at −6 centiloid, below the 12 centiloid positivity threshold (La Joie et al. 2019). EMG was also performed and it was normal.

Laboratory testing

Laboratory data included a complete blood count and a basic metabolic panel, erythrocyte sedimentation rate, vitamin B12, rapid plasma regain, and thyroid-stimulating hormone, which were unremarkable. Lumbar puncture was not performed.

Diagnosis at baseline

A differential diagnosis between atypical AD and tv-FTD was initially proposed. After PiB-PET results, tv-FTD became the main diagnostic hypothesis. Memantine was started in order to control behavioral symptoms.

One-year follow-up visit (2008)

BC became more apathetic, showing emotional blunting and a tendency to withdraw from social events, including quitting many hobbies and outside activities. BC continued to manifest obsessive-compulsive behaviors, mental rigidity, picky eating, and started to take less care of his hygiene. In terms of cognition, he still complained of difficulties in memory for recent events, in multitasking and problem solving. Even his language worsened, with frequent anomia and paraphasic errors. He showed also clear word comprehension impairment. He spoke less and with shorter phrases. He also had some mild problems recognizing faces of friends. No depression, anxiety, delusions, or hallucinations were reported. General neurological exam performed in 2008 was unremarkable and no buccofacial dyskinesia was detected. BC referred that mouth movements improved with memantine treatment. Neuropsychological testing showed worsening of verbal/visual memory, naming, and visuospatial function. Language evaluation revealed a still fluent and grammatically correct speech and he was still able to follow three-step commands. However, his semantic and naming impairments worsened, and he exhibited surface dyslexia (Table 1).

MRI showed a global progression of atrophy, mainly in fronto-temporal regions, with a prominent bilateral ATL involvement still evident (Fig. 1). Taking into account both clinical and imaging data, the tv-FTD diagnosis was confirmed.

Two-year follow-up visit (2009)

BC’s wife reported further worsening of his behavioral disturbances, especially in compulsions, perseverations and fixations. He had episodes of agitation, delusions and inappropriate behavior. He occasionally encountered difficulties in recognizing familiar people such as his daughter. In 2009, during a general neurological exam, the patient appeared only partially oriented in time and space. No pyramidal or extrapyramidal signs were detected. He showed clear difficulties following commands. Trazodone was prescribed for behavioral symptoms.

Neuropathology

BC died in 2010 and autopsy was performed. Neuropathological examination was conducted as previously described (Spinelli et al. 2017). Immunohistochemical analysis showed unequivocal evidence of TDP-43-Type B inclusions, with frequent granular, compact, or skein-like neuronal cytoplasmic inclusions, as well as sparse neuritic and glial inclusions in anterior cingulate cortex, ventral striatum, inferior temporal gyrus, CA1/subiculum, and entorhinal cortex. Frequent similar inclusions were also found in affected brainstem and in anterior horn cells of cervical spinal cord structures. In addition, there was contributing AD pathology characterized by moderate density of neuritic plaques in frontal cortex and neurofibrillary degeneration in limbic and paralimbic regions, constituting Braak stage IV, as well as moderate cerebral amyloid angiopathy. According to the recent Mackenzie's criteria, the case was classified as frontotemporal lobar degeneration (FTLD)-TDP, type B with MND, and concomitant intermediate AD pathology (A1B2C2 score) (Mackenzie et al. 2010).

Genetic testing

Post-mortem genetic analyses were performed on blood sample collected from the patient in 2011. In order to detect the presence of expanded GGGGCC hexanucleotide repeats in *C9orf72*, the hexanucleotide repeat was PCR amplified using 1 fluorescently labeled primer followed by fragment length analysis on an automated ABI3730 DNA analyzer as previously described (Khan et al. 2012; Sha et al. 2012). Blood sample collected from the patient revealed the presence of hexanucleotide (GGGGCC/CCCCGG) repeat expansion in the non-coding region of *C9orf72* gene. In 2013, the presence of mutations of *MAPT, GRN* and *TARBPD* genes were also explored as previously reported (Lee et al. 2013; Moreno et al. 2015) and excluded.

Discussion

We described clinical, cognitive and neuroanatomical features of two temporal variant of frontotemporal dementia (tv-FTD) cases with predominantly right or bilateral ATL atrophy carrying pathogenic *C9orf72* hexanucleotide repeat expansion. Despite differences in the specific circumstances and disease stage, both cases presented with similar essential features and highlight that these genetic mutations should be considered in the molecular differential diagnosis of the tv-FTD/bvFTD without motor neuron disease.

Both patients showed significant naming difficulties and behavioral changes early in the disease. As often seen in right temporal involvement, mental rigidity, lack of empathy and tendency for stereotyped behavior dominated the clinical picture (Seeley et al. 2005). There was also lack of insight for mood and/or behavioral changes that were particularly striking in AB, who was a health-care provider. While AB showed a very focal clinical and neuroimaging presentation consistent with focal right ATL degeneration, BC presented with a longer disease duration and a more complicated history in 2007, when the *C9orf72* hexanucleotide repeat expansion had not been discovered yet. Therefore, diagnoses at first visits were different in the two cases: AB was classified as right tv-FTD with predicted TDP-C pathology, although it is questionable whether language or behavioral symptoms

were dominant; BC's first diagnosis was quite controversial and included both tv-FTD and atypical AD. Then, language difficulties and ATL atrophy drove clinicians to a possible tv-FTD diagnosis, and PIB negativity towards TDP-C pathology. We could speculate that BC's disease also started in the right ATL. These two cases highlight the overlap between tv-FTD with severe right temporal involvement and behavioral symptoms, and bvFTD (Henry et al. 2014; Mendez et al. 2004). Both patients did not fit perfectly the criteria of primary progressive aphasia (PPA) (Gorno-Tempini et al. 2011) for their early and significant behavioral disturbances and conversely, they cannot be classified as typical bvFTD (Rascovsky et al. 2011) due to their semantic deficits. However, behavioral hallmarks of right tv-FTD are an obsessive and rigid behavior with personality changes, and significant difficulties in emotion processing (Edwards-Lee et al. 1997; Kamminga et al. 2015; Seeley et al. 2005), as we observed in our cases. Conversely, bvFTD patients show more frequently apathy/social withdrawal (Kamminga et al. 2015). Our patients also exhibited the cognitive hallmarks of tv-FTD, such as naming difficulties, impairment in familiar face naming/recognition, and deficit in visual recognition memory, (i.e., topographic agnosia in AB) (Kamminga et al. 2015). Differently, bvFTD patients often show attentive-executive problems (Kamminga et al. 2015).

In both cases, dominant genetic mutations were not predicted as tv-FTD is thought to be the least genetic of the FTD-spectrum clinical syndromes (Blauwendraat et al. 2018). However, looking back, both our patients showed a family history positive for dementia (AB's father and BC's sister), and BC's mother was reported as having had some personality changes. In the case of AB, clinicians could have hypothesized an autosomal dominant inheritance but for BC the situation was not as clear. In fact, in 2007 *C9orf72* and its heterogeneous clinical correlates had not been discovered yet (DeJesus-Hernandez et al. 2011) and an autosomal dominant inheritance of a tv-FTD syndrome (BC) from a parent (mother) with unclear behavioral disorder was not expected. The identification of genetic cases is not always supported by family history (Murphy et al. 2017). This might be due to the difficulty of anamnestic data collection, to the different type of inheritance of genes, and to heterogeneous clinical phenotype expressed in the same family, as for *C9orf72+* carriers (Devenney et al. 2015; Mahoney et al. 2012; Murphy et al. 2017). Notable tv-FTD cases due to genetic mutations have been described in previous papers in which they were often classified as having a 'semantic dementia' (Bessi et al. 2010; Caroppo et al. 2015; 2016; Cerami et al. 2013; Floris et al. 2015; Gelpi et al. 2014; Hirsch-Reinshagen et al. 2019; Ishizuka et al. 2011; Le Ber et al. 2013; Majounie et al. 2012; Snowden et al. 2012; Van Mossevelde et al. 2016). From the available literature, family history was negative in one *TARDBP+* patient (Caroppo et al. 2016) whereas familial data were not available for one *MAPT+* (Bessi et al. 2010) and seven *C9orf72+* tv-FTD patients (Majounie et al. 2012). All other tv-FTD genetic cases had significant family history for dementia and/or amyotrophic lateral sclerosis (Bessi et al. 2010; Caroppo et al. 2015; 2016; Cerami et al. 2013; Floris et al. 2015; Gelpi et al. 2014; Hirsch-Reinshagen et al. 2019; Ishizuka et al. 2011; Le Ber et al. 2013; Snowden et al. 2012; Van Mossevelde et al. 2016). The majority of genetic tv-FTD cases described so far showed left ATL atrophy (Caroppo et al. 2015; Cerami et al. 2013; Gelpi et al. 2014; Hirsch-Reinshagen et al. 2019; Ishizuka et al. 2011; Le Ber et al. 2013; Snowden et al. 2012; Van Mossevelde et al. 2016). The only two genetic tv-FTD cases with

prominent right-sided ATL involvement were a *TARDBP+* (Floris et al. 2015) and a *MAPT+* (Bessi et al. 2010) carrier with a clinical phenotype characterized by severe prosopoagnosia, language (semantic) deficits and behavioral disorders. In addition, except for two *TARDBP+* (Caroppo et al. 2016) and three *TBK1* (Caroppo et al. 2015; Hirsch-Reinshagen et al. 2019) patients developing a motor neuron disease, genetic tv-FTD cases exhibited an unremarkable neurological exam at time of their first evaluation and during the follow-up. Detailed data are available for one *C9orf72+* patient who received a clinical diagnosis of semantic dementia/FTD (Snowden et al. 2012). She was a 47 years-old woman with language and behavioral disorders. She showed loss of empathy and insight, repetitive and obsessive behavior beside of cognitive impairment such as naming deficits and facial/object agnosia. MRI revealed left more than right brain atrophy that involved in equal manner frontal and temporal lobes (Snowden et al. 2012). Our patient BC was quite similar to this case (Snowden et al. 2012) in terms of symptomatology. However, BC's MRI showed more bilateral temporal than frontal impairment compared to the previous patient (Snowden et al. 2012).

Considering clinico-pathological associations, there is an established correlation between a clinical diagnosis of tv-FTD/semantic dementia and FTLD Mackenzie's C subgroup pathology (Rohrer et al. 2010). These findings, however, pertain to sporadic cases. The expected pathology in *C9orf72*+ subjects, as in our AB and BC patients, is TDP-43 type B, and in *GRN*+ subjects is TDP-43 type A (Mackenzie et al. 2011). Moreover, with regard to pathological findings, we might hypothesize a co-occurrence of FTLD and AD pathology in BC patient with both contributing to cognitive symptoms, or an incidental finding of co-morbid amyloid plaques in a dementia driven by FTLD pathology (Rabinovici et al. 2017). Accordingly, PiB negativity in BC patient with post-mortem finding of AD pathology most likely represents a false negative case due to imperfect sensitivity of PiB-PET to detect mild-to-moderate amyloid burden (La Joie et al. 2019; Villeneuve et al. 2015). Indeed, although BC's neuropathological examination detected neuritic plaques in a "moderate" density, the plaques were found only in the frontal lobe, not on all slices, suggesting that the overall cortical burden was quite low.

We reported extensive clinical, genetical and neuroanatomical description of two tv-FTD cases due to *C9orf72* repeat expansion. We also described the first case of right tv-FTD carrying *C9orf72* repeat expansion. A multidisciplinary approach was essential to reach an accurate diagnosis. Genetical testing allowed us to correctly identify the TDP-type B pathology underlying the tv-FTD clinical syndrome.

Conclusions

We described two tv-FTD cases due to *C9orf72* repeat expansion. These cases have implications for the clinical care of patients diagnosed with a syndrome falling under the clinical umbrella of FTD. Our results highlight the importance to offer genetic testing to tv-FTD patients, especially in those with even a vaguely positive family history of neurological/psychiatric diseases. Such testing allows correct prediction of the underlying pathology and provides crucial information to patients and families. In this perspective, genetic testing in tv-FTD patients might allow to identify, among the majority of FTLD-TDP

type C cases, the patients with a different TDP-subtype who might be eligible for specific targeted therapies as they became available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Two cases of tv-FTD with *C9orf72* repeat expansion are described.

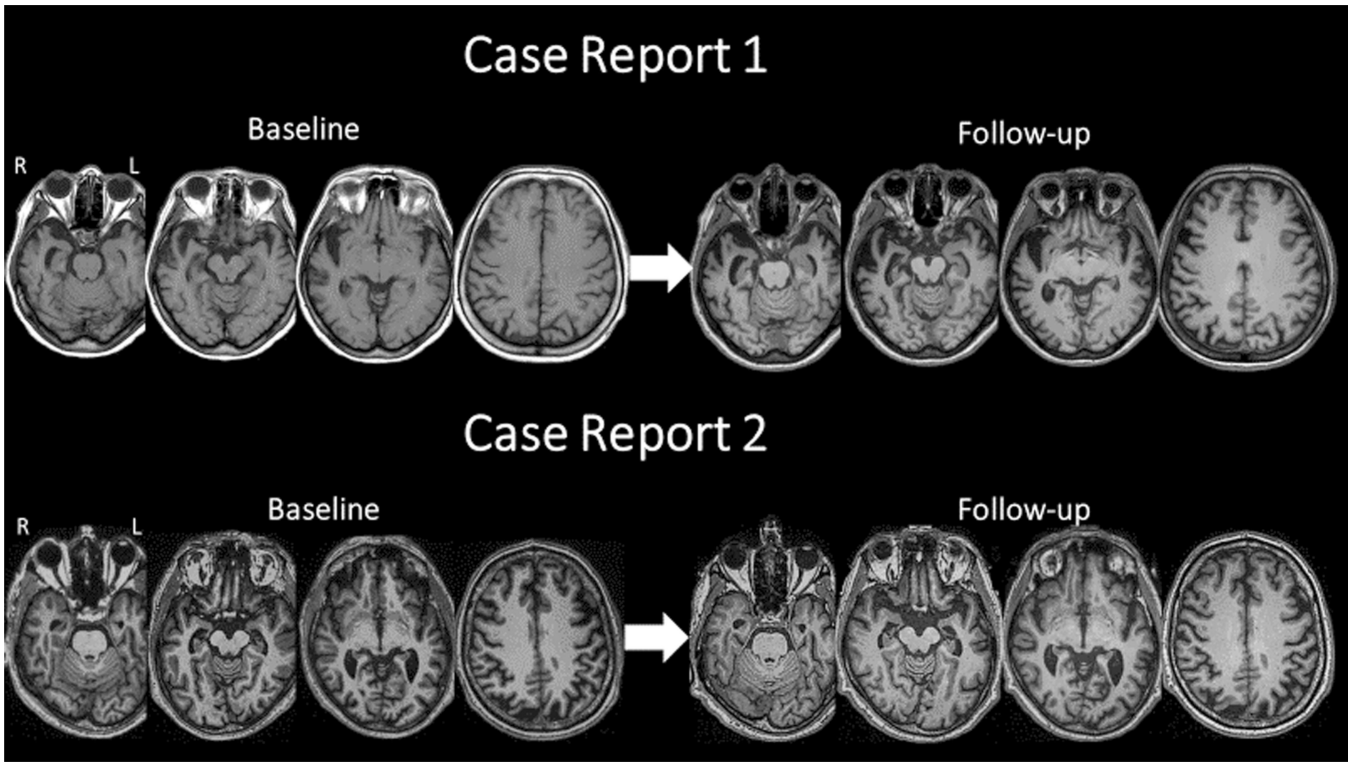

Fig. 1.

Axial T1 MR images at baseline and follow-up visits in Case Report 1 and Case Report 2. Images are shown in radiological convention (right is left).

Table 1

General cognition and language assessment in Case Report 1 and Case Report 2

	Case report 1		Case report 2	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Global cognitive status				
MMSE (< 24)	29	30	26	25
CDR (>0)	O.5	0.5	2	1
CDR-sb (>0)	1.5	2.5	9	l
Attentive and executive functions	m(z): −0.2	m(z): −1.43	Z = −1.26	Z = −1.31
Visuo-spatial abilities	Z: O.O6	Z: −0.53	Z = 0.10	Z = −1.55
Face perception abilities	Z: 2.42	Z: 0.5	Z = 0.04	Z = −0.34
Short-term verbal memory	Z: 0.21	Z:−0.84	Z = −0.54	Z = −0.08
Long-term verbal memory	m(z): 0.62	m(z):−0.53	**m(z) = −5.94**	**m(z) = −4.27**
Visuospatial memory	Z:1.1	Z:−1.76	Z = −1	Z = −2.79
Visual semantic memory	m(z): −1.78	**m(z): −2.57**	**m(z) = −4.61**	**m(z) = −6.23**
PPT- pictures	Z:-1.18	**Z: −3.55**	**Z = −7**	**Z = −12**
Famous faces test-naming	**Z: −2.16**	**Z: −2.16**	**Z = −3.96**	**Z = −4.26**
Famous face test-recognition	**Z:−2**	**Z: −2**	**Z = −2.86**	**Z = −2.44**
Speech and language	**m(z): −2.64**	**m(z): −4.95**	**m(z): −2.56**	**m(z): −2.77**
Motor speech	Z:0	Z:0	Z=0	Z=0
Semantic fluency	Z:0.143	**Z:−2.38**	**Z = −3.11**	**Z = −2.28**
Sentence comprehension	Z:−0.28	Z:−0.47	Z = 0.44	Z = −1.20
Picture naming	**Z:−7.99**	**Z:−15.75**	**Z = −6.29**	**Z = −7.71**
Single word comprehension	Z:0	**Z:-6**	Z = 0	Z = 0
Reading	**Z:-4.3**	**Z:-5**	**Z= −3.2**	**Z = −3.27**

Raw scores or average Z-score of the main cognitive domains. Bold values represent abnormal values in reference to normative data (2 SD below mean). For ‘Visual semantic memory’ and ‘Language and speech’ domains the specific tests used are shown with the relative Z-score

Abbreviations: *m(z)* average Z-score of the domain, *CDR-sb* clinical dementia rating scale-sum of boxes, *MMSE* mini mental state examination, *MSE* motor speech evaluation, *PPT* Pyramid and Palm Trees-pictures

Table 2

Social cognition assessment in Case Report 1 and Case Report 2

Social Cognition	Case Report 1			Case Report 2		
	Test	**Baseline**	**Follow-up**	**Test**	**Baseline**	**Follow-up**
Behavior	NPI	20	9	NPI	49	60
Empathy and ToM	SET-EA	**Z: −4.13**	**Z: −4.13**	IRI-EC	**Z: −2.57**	**Z: −3.33**
	SET-IA	Z: −1.7	Z:−1.7	IRI-PT	**Z: −2.12 (m:20.19;sd:6.23)**	Z:−1.96
	SET-CI	Z:−0.99	Z: 0.13	TASIT-Lie	–	**Z: −2.7**
	Reading the mind in the eyes	Z:−1.77	**Z: −2.94**	TASIT-Sarcasm	–	**Z: −4.7**
Emotions	CATS-Affect discrimination	–	Z:− 0.35	CATS-Affect discrimination	Z = −0.08	Z = 0.24
	CATS-Match Affect	–	Z: −1.48	CATS-Name Emotional Prosody	–	**Z = −2.51**
	BLED Humor	**Z:−2**	**Z:−2**			
	BLED Inference	Z:−1.89	**Z:−2**			

Raw scores or Z-scores of the social cognition test battery. Bold values represent abnormal values in reference to normative data (2 SD below mean)

Abbreviations: – test not administered, *BLED* language battery of right hemisphere (Batteria del Linguaggio dell'Emisfero Destro), *CATS* comprehensive affect testing system, *IRI-EC* Interpersonal Reactivity Index-Empathic Concern, *IRI-PT* Interpersonal Reactivity Index-Perspective taking, *NPI* neuropsychiatric inventory, *SET* story-based empathy test (*IA* intention attribution, *CI* causal inference, *EA* emotion attribution), *TASIT* The Awareness of Social Inference Test, *ToM* theory of mind