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Short Communication

Phenotypic Variability associated with the *C9ORF72* Hexanucleotide Repeat Expansion: A Sporadic Case of Frontotemporal Lobar Degeneration with Prodromal Hyposmia and Predominant Semantic Deficits

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Abstract. We describe a sporadic case of frontotemporal lobar degeneration, associated with the *C9ORF72* mutation, with prominent behavioral changes and semantic deficits. Predominant deficits in naming, vocabulary, word comprehension, and face and object recognition emerged on neuropsychological assessment. Amnesia, behavioral changes, and isolated psychotic symptoms were also present. Hyposmia was an unspecific prodromal sign. Brain imaging showed basofrontal and temporopolar hypometabolism bilaterally, and predominantly left-sided atrophy. Levels of cerebrospinal fluid biomarkers (amyloid-β, tau and p-tau) were normal. This description further confirms the heterogeneous presentation of the *C9ORF72* mutation.

Keywords: *C9ORF72*, frontotemporal lobar degeneration, hyposmia, phenotype, semantic dementia

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INTRODUCTION

A hexanucleotide repeat expansion in the *C9ORF72* gene has been shown to be responsible for many cases of familial amyotrophic lateral sclerosis or frontotemporal lobar degeneration, with or without concomitant motor neuron disease [1, 2]. The clinical phenotype of the *C9ORF72* carriers is widely heterogeneous, even within the same family. The most common presentation is the behavioral variant of frontotemporal dementia (bvFTD), sometimes accompanied by features of amyotrophic lateral sclerosis [3–10]. Psychosis, obsessive-compulsive disorders, and memory impairment are also frequent symptoms at disease onset [4, 9, 11–13]. In a more limited number of patients, clinical features of progressive nonfluent (PNFA) [4, 5, 7, 10] or semantic variant (SD) [4, 6, 9, 10, 14, 15] of primary progressive aphasias have been reported. Some authors [6] have observed that the occurrence of SD associated with the *C9ORF72* mutation was unexpected since patients with SD usually have a negative family history [16], suggesting a masked genetic dominant pattern of inheritance. Therefore, further clinical studies are needed to confirm the association between the repeat expansion in the *C9ORF72* gene and the SD phenotype as well as to elucidate the genetic contribution to SD [6]. Here, we describe a sporadic Italian case of frontotemporal lobar degeneration associated with the *C9ORF72* mutation, exhibiting a clinical phenotype with predominant semantic deficits.

METHODS

A neurological, neuropsychological, behavioral, functional, and instrumental evaluation was carried out. Global cognitive functioning was assessed with the Mini-Mental State Examination (MMSE) and the Clock Drawing test (CDT). The neuropsychological assessment included multiple tests to evaluate a range of cognitive functions (i.e., logical-deductive reasoning abilities, pre-frontal functions, insight, psychomotor speed, visuospatial attention [17, 18], anterograde, semantic [19–21] and retrograde memory [22], short-term memory, language, limb and limb-kinetic praxis, constructional functions, object recognition [23]) (Table 1). Behavior was assessed with the Neuropsychiatric Inventory Battery (NPI), functional autonomy with the Activities of Daily Living (ADL) and Instrumental ADL (IADL) scales, and depression with the Geriatric Depression Scale (GDS). Electroencephalography (EEG), brain magnetic resonance (MR), and [^{18}F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) were performed. Lumbar puncture was carried out, and cerebrospinal fluid (CSF) amyloid-β (Aβ), tau, and phosphorylated tau (p-tau) were evaluated by ELISA (Innogenetics, Ghent, Belgium). Progranulin plasma levels were determined by ELISA (Adipogene, Korea). Genomic DNA was extracted from blood using a salting-out method [24] and the *C9ORF72* genotyping was accomplished by Repeat-Primed PCR and sequencing [1] which allows detection of about 30 repeats. According to the current literature [3], a characteristic stutter amplification pattern (>30 repeats) on the electropherogram is considered evidence of a pathogenic repeat expansion. Both patient and caregiver provided written informed consent to participation in the study.

CASE REPORT

The patient came to our attention in 2012 because of subjective memory complaints. He was a right-handed, 69-year-old man, with 13 years of education. His family history was negative for dementia and/or for motor neuron disease. His mother died at 67 years of age due to long-term consequences of a prior stroke, and his father at 69 years of age because of a heart attack. The patient has three siblings, aged 73, 72 and 68, who, so far, do not appear to have any cognitive or motor disturbances. His only known medical condition was mild hypertension. At the visit, his relatives described a complex clinical picture including behavioral changes, cognitive impairments, and psychotic symptoms, all with a subtle onset about three years earlier and a slowly progressive course. The patient had left his wife and family and had gone off to live on his own. He had grown apathetic, progressively losing interest in social interactions as well as emotional involvement with his family. He had taken to keeping the money for himself and spending it on compulsive gambling. Increasing inertia concurrently emerged: he had to be encouraged to properly attend to his personal hygiene. Moreover, his diet had become very restricted. Mild psychotic symptoms were also evident: he had become extremely religious and sometimes manifested mystic/megalomaniac and theft delusions. He had developed subtle dysfunctions in episodic and retrograde as well as semantic memory (e.g., although he owned a small business he no longer knew what "bank loan" meant). Interestingly, hyposmia was a possible unspecific prodromal sign, appearing five years

Table 1
Neuropsychological assessment

Test	Patient raw score	Maximum score	Cut-off score	Impairment
General				
Mini mental state examination	29	/30	24	
Raven coloured progressive matrices	30	/36	17.5	
Executive functioning				
Trail Making Test (TMT) part A	44”		93”	
Trail Making Test (TMT) part B	89”		282”	
Digit span backward	3			
Short stroop test (time)	52.5”		36.92”	Impaired
Short stroop test (errors)	7.5		4.24	Impaired
Verbal fluency (phonological one)	13		17	Impaired
Verbal fluency (semantic one)	12		24	Impaired
Cognitive estimates test (CET) total	17	/42	18	
Cognitive estimates test (CET) bizarre	5	/21	4	Impaired
Weigl’s sorting test	5	/15	8.1	Impaired
Clinical Insight Rating Scale (CIR)	3	/8		Impaired
Memory				
Short term memory				
Digit span forward	5		3.75	
Anterograde long term memory				
Prose memory	12.3	/16	4.75	
Paired-associate word	2	/22.5	6.5	Impaired
Rey-Osterrieth complex figure (recall)	4	/36	9.47	Impaired
Semantic memory				
Picture to picture matching task	23	/30	25	Impaired
Word to word matching task	14	/30	24	Impaired
Celebrities identification task	0	/60		Impaired
Vocabulary task	1	/10		Impaired
Retrograde memory test (verbal section)	0	/44		Impaired
Language				
Picture naming task	58	/80	61	Impaired
Achener Aphasia Test (AAT)				
Token test	10	/0	7	Impaired
Repetition	142	/150	142	
Written language	88	/90	81	
Naming	97	/120	104	Impaired
Comprehension	102	/120	108	Impaired
Praxis				
De Renzi test (right)	72	/72	53	
De Renzi test (left)	70	/72	53	
Visual attention				
Bell’s test	34	/35	30	
Digit cancellation task	47	/60	31	
Visuospatial functions				
Clock Drawing Test (CDT)	5	/5	3	
Copy of geometrical figures	13	/14	8	
Rey-Osterrieth complex figure (copy)	35	/36	28.88	

Impaired = score <5th percentile.

before cognitive and psychotic symptoms. The neurological examination was unremarkable, apart from mild hypomimia. No signs of motor neuron disease were observed. Cognitive screening was normal (MMSE = 29/30; CDT = 5/5). Behavioral examination was mildly pathological (NPI = 19/144), the GDS was negative for depression (2/30), and functional autonomy was still preserved (ADL = 6/6; IADL = 5/5). The neuropsychological examination disclosed severe deficits in all semantic tasks, involving word-, object-, and face-processing. The verbal matching task was more impaired than its visual counterpart (Table 1). There were also severe deficits in the vocabulary task, a mild pre-frontal dysexecutive syndrome, and a slight loss of insight (CIR = 3/8). Moreover, mild social inappropriateness and verbal disinhibition emerged at the clinical interview. Anterograde amnesia was revealed by the visual delayed recall and verbal learning tasks. Retrograde amnesia emerged on recalling medical history and autobiographical information, and was

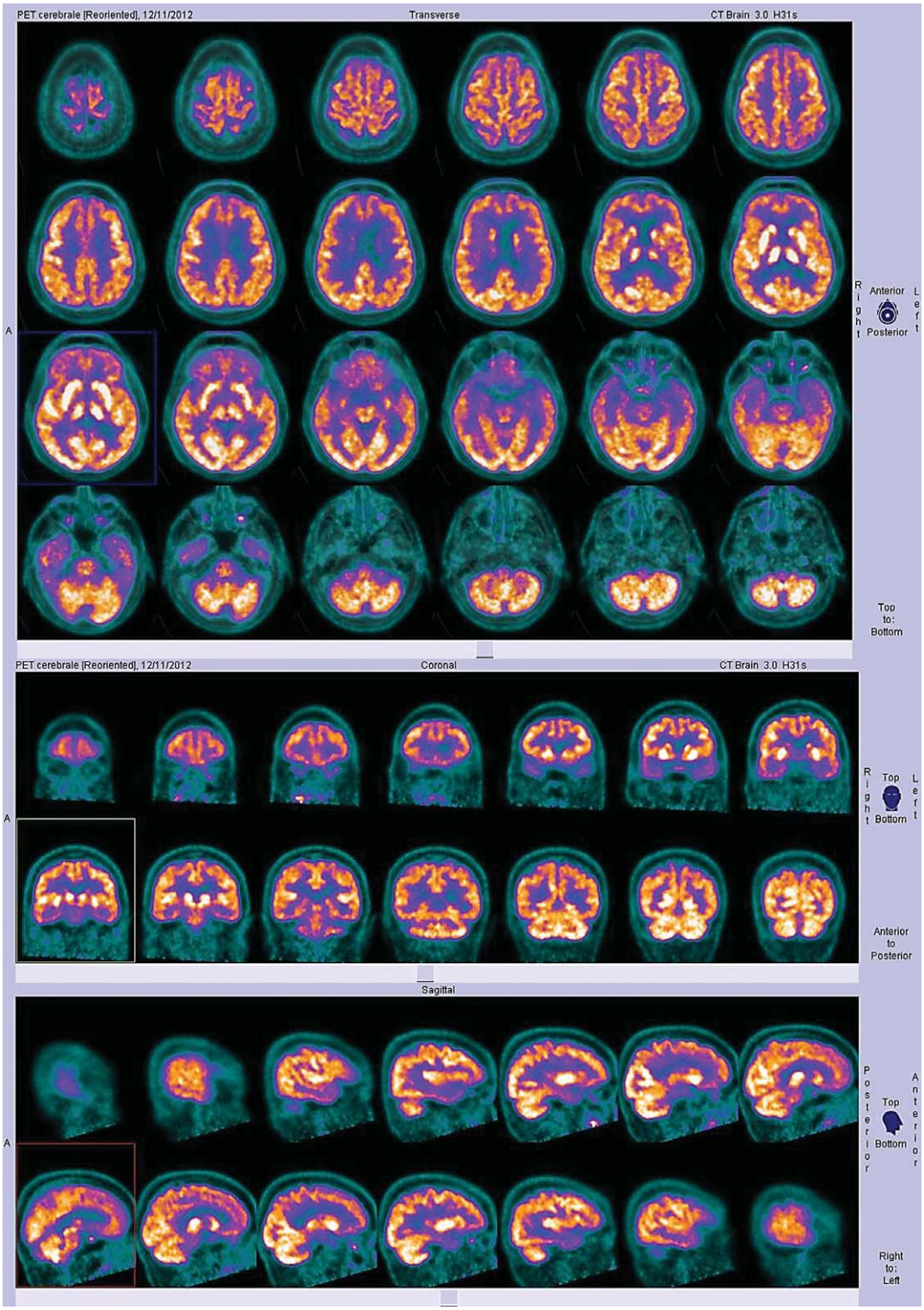

Fig. 1. FDG-PET scan demonstrating diffuse cortical hypometabolism, more pronounced on bilateral basal frontal and temporal polar cortex.

confirmed by a retrograde memory test. Short-term memory was preserved. Speech was fluent, with rare pass-partout words and perseverations, and there were no signs of dysartria. Repetition was preserved, while significant deficit were found in naming tasks (Table 1). There were some difficulties in comprehension tasks (AAT), more pronounced for single words (48/60) than for sentences (54/60). There was no dyslexia and dysgraphia (AAT), no impairment in visual attention and visuospatial functions, and no limb and limb-kinetic apraxia. There was evidence of both temporal and contextual disorientation. From the instrumental examinations, different findings emerged. EEG showed a minimal hyperventilation-induced slowing across the fronto-temporal regions, with a left-sided predominance. The brain MRI scan showed diffuse cortical and subcortical atrophy, particularly affecting the left hemisphere, and mild subcortical vascular damage. The FDG-PET scan demonstrated diffuse cortical hypometabolism, with a more marked involvement of the basofrontal and temporopolar cortex bilaterally (Fig. 1). With regard to biomarkers, CSF Aβ, tau, and p-tau were not altered (1242 pg/ml, 375 pg/ml, and 31 pg/ml, respectively) and nor were plasma progranulin levels (215 ng/ml). On genetic testing the patient was found to be a carrier of the *C9ORF72* hexanucleotide repeat expansion. Based on the genetic, instrumental, clinical, and neuropsychological data, a tentative diagnosis of SD was therefore made, according to current criteria [25–27]. At a follow-up visit, one year later, the patient's relatives reported further worsening of both apathy and cognitive impairment. The neurological examination was unchanged. While the CDT was still normal (5/5), the MMSE had dropped to 22, the NPI score was a little higher (25/144), and there was a decrease in functional autonomy (ADL = 5/6; IADL = 0/5).

DISCUSSION

In this report, we describe a patient with the repeat expansion in the *C9ORF72* gene, presenting with a clinical phenotype with prominent behavioral changes and semantic deficits. The core clinical feature was a profound semantic dysfunction, with loss of word meaning, impaired face and object recognition, and better comprehension for sentences than for single words. The bilateral basofrontal and temporopolar cortex hypometabolism found on brain imaging is compatible with an intermediate stage of SD [26]. Moreover, the asymmetric pattern of atrophy, with left sided predominance, well matches the more severe impairment of the verbal than visual semantics. Interestingly, the patient reported early hyposmia, in accordance with previous data showing a severe impairment in olfactory identification in SD patients, despite normal perceptual discrimination [28]. Moreover, the loss of olfactory as well as of visual knowledge has been supposed to contribute to the dietary changes observed in such patients [28]. Another patient with the *C9ORF72* mutation and a SD phenotype has been reported to be apparently unable to recognize foods by taste [14]. Although semantic dysfunction was predominant, behavioral changes, other cognitive deficits, and mild psychotic symptoms were found to be associated with semantic disorders in this case. Indeed, behavioral changes, like the ones displayed by our patient, have been described in SD [26] even if compulsive gambling and signs of social disinhibition are not typical SD features. Anterograde dysmnesia with temporal disorientation and delusions appear to be less compatible with SD, but memory impairment [7–9, 14] and psychotic symptoms [3, 4, 11, 13, 14] have often been reported in *C9ORF72* mutation carriers. Actually, considering the imaging pattern and the heterogeneity of the clinical features, an alternative diagnosis of bvFTD with temporal involvement and associated semantic deficits cannot be excluded.

In conclusion, we described a patient with the repeat expansion in the *C9ORF72* gene presenting with behavioral changes and semantic deficits, thus supporting the heterogeneity of the clinical presentation of the *C9ORF72* mutation. However, the method used allowed us to visualize 30 repetitions. Therefore, we cannot rule out a correlation between the length of the expansion and the clinical phenotype, age at onset, and course of the disease. In this regard, additional genetic, epigenetic, or environmental factors could contribute to determining the age at onset as well as the heterogeneity of symptoms, although no definite conclusions on this issue have been reached yet.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2078).

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