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Highlights

- We compared MRI and neuropsychological test data in twins discordant for VCP mutation.
- Affected twin revealed rapid cognitive decline in a span of 1 year.
- FTD related cognitive features may precede behavioral changes in VCP disease.
- Cognitive–behavioral impairment may be missed on routine neurological exam and MMSE.
- Need for a dedicated screening measure to recognize the neurological impairment.

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Case report

A case report comparing clinical, imaging and neuropsychological assessment findings in twins discordant for the VCP p.R155C mutation

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Abstract

Inclusion body myopathy, Paget disease of bone and/or frontotemporal dementia is an autosomal dominant disease caused by mutations in the *Valosin Containing Protein* (VCP) gene. We compared clinical findings including MRI images and neuropsychological assessment data in affected and unaffected twin brothers aged 56 years from a family with the p.R155C VCP gene mutation. The affected twin presented with a 10 year history of progressive proximal muscle weakness, difficulty swallowing, gastroesophageal reflux, fecal incontinence, and peripheral neuropathy. Comprehensive neuropsychological testing revealed rapid cognitive decline in the absence of any behavioral changes in a span of 1 year. This case illustrates that frontotemporal dementia related cognitive impairment may precede behavioral changes in VCP disease as compared with predominance of behavioral impairment reported in previous studies. Our findings suggest that there is a need to establish VCP disease specific tools and normative rates of decline to detect pre-clinical cognitive impairment among affected individuals.

Keywords: VCP; Inclusion body myopathy; Frontotemporal dementia screening; Multisystem proteinopathy; Neuropsychological assessment

1. Introduction

Hereditary inclusion body myopathy (h-IBM), Paget disease of bone (PDB) and/or frontotemporal dementia (FTD), also called multisystem proteinopathy or IBMPFD; (OMIM 167320) is caused by dominantly inherited mutations in the *Valosin Containing Protein* (VCP) gene mapped to the human chromosomal region 9p13.3-12 [1–4]. One of the main functions of the protein is as a chaperone for proteasomal and autophagic protein degradation with dysfunction leading to protein aggregation [5–8]. IBMPFD is a heterogeneous disorder with variable penetrance [9,10]. Approximately 90% of the affected individuals develop myopathy usually in their 30s–40s which clinically manifests as shoulder and pelvic girdle muscle weakness and atrophy and muscle weakness progressively involves the other groups in the later stages [2,10–14]. Approximately 50% develop PDB typically in their 30s [1,3]. A third of the affected individuals may suffer from a degenerative condition of the frontal and anterior temporal lobes, which typically manifests later in the fifth to sixth decade

Abbreviations: 7MS, 7 Minute Screen; ALP, alkaline phosphatase; ALS, amyotrophic lateral sclerosis; ALS-CBS, ALS Cognitive Behavioral Screen; AMT, Abbreviated Mental Test; BNT, Boston Naming Test; CDT, Clock Drawing Test; CK, creatine kinase; DEXA, dual emission X-ray absorptiometry; EMG, electromyography; FCSRT, Free and Cued Selective Reminding Test; FTD, frontotemporal dementia; h-IBM, hereditary inclusion body myopathy; IBMPFD, inclusion body myopathy, Paget's disease of bone and frontotemporal dementia; ICTS, Institute for Clinical & Translational Science; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MIS, Memory Impairment Screen; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PDB, Paget's disease of bone; PFT, Pulmonary Function Testing; SPMSQ, Short Portable Mental Status Questionnaire; TICS, Telephone Interview for Cognitive Status; *TDP 43*, TAR DNA-binding protein 43; *VCP*, Valosin Containing Protein; WMS-R, Wechsler Memory Scale – Revised.

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as FTD. FTD is characterized by comprehension deficits, relative preservation of memory, paraphasic errors, dysnomia, dyscalculia, and social unawareness [10]. In later stages, auditory comprehension deficits for simpler one-step commands, alexia, and agraphia may be seen [1,3]. FTD typically accelerates the progression of the disease [15]. Currently, there are no curative treatments for the myopathy or FTD. However, selective serotonin reuptake inhibitors are sometimes used in patients to control obsessive symptoms and mood [16]. Affected individuals typically die in their 50s from respiratory insufficiency or cardiac failure or complications from early stage dementia [5,10,17]. Less common phenotypic features reported in VCP disease include cardiomyopathy, hepatic steatosis, cataracts, sensory motor axonal neuropathy, pyramidal tract dysfunction, sphincter disturbance, sensorineural hearing loss, and amyotrophic lateral sclerosis (ALS) [11,12,18–20]. Histologically, the affected muscle and brain typically show the presence of rimmed vacuoles, ubiquitin and TDP-43 positive inclusions [3,11,12,18–22]. TDP-43 is the major component of inclusions characteristic of VCP-associated FTD and ALS-like pathology, placing VCP disease in a novel category of neurodegenerative diseases termed TDP-43 proteinopathies [23,24].

Because of the heterogeneity in VCP disease, studying fraternal twin brothers discordant for VCP disease provides a unique opportunity to highlight differences in the neuropsychological studies, key MRI findings of brain and muscle and pulmonary function studies. The diagnosis of FTD requires a thorough understanding of family history of dementia, with assessment of behavioral and personality changes, in addition to an extensive battery of neuropsychological testing. With increasing focus on formulating a concise screening tool to detect cognitive and behavioral impairment in various FTD syndromes in a clinical setting, the literature is full with examples of various screening measures that is being utilized and validated in ALS [22,25], and non-ALS [26] patient populations. However, no screening tool has been validated or used in VCP disease. This case report emphasizes the need to establish a VCP disease specific standardized screening tool to monitor cognitive and behavioral status in a busy clinical setting to diagnose pre-clinical FTD in VCP disease. The tool could also be useful in deciding if a patient requires the extensive diagnostic neuropsychological testing.

2. Case report

The twins who were discordant for the p.R155C VCP mutation were recruited and evaluated at the University of California, Irvine ICTS (Institute of Clinical and Translational Science) for a 2 day visit. Informed consent was obtained from the individuals for the study which was approved by the Institutional Review Board of the University of California, Irvine. The diagnosis of VCP disease was confirmed or excluded by molecular genetic testing in the Mitomed CLIA certified laboratory. Clinical evaluations, review of records, analysis of serum alkaline phosphatase (AP), creatine kinase (CK), X-rays, dual-emission x-ray absorptiometry (DEXA), pulmonary function testing (PFT), magnetic resonance imaging (MRI) of brain (Fig. 1), MRI of lower limbs (Fig. 2), and psychometric testing were obtained (Table 1) The autopsy report of the deceased twin was reviewed.

Both brothers underwent MRI scanning and psychometric testing at the age of 55 years at the University of Kentucky, Lexington, and at age 56 years at UC Irvine. The diagnostic comprehensive neuropsychological test batteries administered were similar for both the twins. The test batteries were administered at the same center by the same psychometrist/psychologists (BTG/SW, CN), all of whom had special training in FTD. The comprehensive neuropsychological test batteries included Mini-Mental State Examination (MMSE), HANDS screening depression tool [27], The Stroop Interference subtest, Victoria version [28,29], Trails A and Trails B [30], The Digit

Table 1
Comparison of neuropsychological assessment findings in twins discordant for VCP mutation at 1 year intervals.

Assessment Tools	Affected twin age 56 years	Unaffected twin age 56 years	Affected twin age 55 years	Unaffected twin age 55 years
MMSE *(Max score – 30)*	26	29	27	28
PERMP Pre-Test	Easy level	Moderate level	NT	NT
FAS test	23	32	32	25
BNT test	46; 14 phonemic cues needed	60, no cues needed	57, no cues needed	58, no cues needed
Trail Making Test A and B	Trails A: 36 sec Trails B: 282 sec, 3 errors	Trails A: 31 sec, 1 error Trails B: 81 sec	Trails A: 42 sec, 0 error Trails B: 95 sec, 1 error	Trails A: 19 sec Trails B: 49 sec
WSM test (Total Digits)	10	14	14	16
Category Fluency Test (Animal) (# correct)	14	23	NT	NT
BDI-II	9	0	9	2
Hands Depression Screening Tool (T-score)	3	0	NT	NT
PERMP Assigned Level of Difficulty (problems correct/problems attempted)	Easy level (2) 108/115	Moderate level (3) 78/80	NT	NT
Paragraph Immediate Recall test	NT	NT	30	32
Paragraph Delayed Recall test	NT	NT	17	16
FBI	NT	NT	1	0

MMSE = Folstein Mini-Mental State Exam; BNT = Boston Naming Test; FAS = Controlled Word Association/Letter Fluency; WSM = Wechsler Memory Digit Span Test; BDI-II = Beck Depression Inventory-II, FBI = Frontal Behavioral Inventory (Max score – 72); NT = Not Tested.

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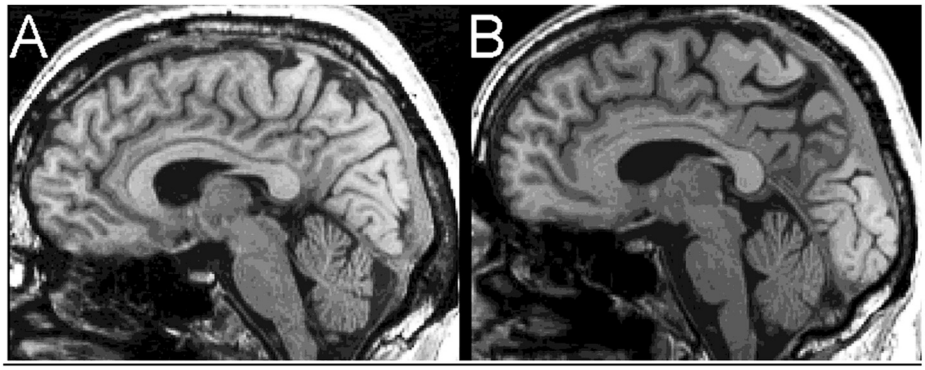

MRI Brain Measure	Affected twin age 55 (06/09/2008)	Unaffected twin age 55 (07/01/2008)
Total Intracranial Volume (TIV), cc	1,667.7	1,604.6
Total Brain Volume, cc	1,229.3	1,242.6
Cerebral White Matter Volume, cc	517.3	525.4
Cerebral Grey Matter Volume, cc	483.6	493.1
Frontal Cortex (% of TIV))	5.44	5.76

*Free surfer was used to estimate volumes

Fig. 1. T1-weighted sagittal MRI images of the affected (A) and unaffected (B) twins at age 55 years and brain volumes from MRI scans performed at age 55 years.

Span subtests from the Wechsler Memory Scale – Revised (WMS-R) [31], The Letter Fluency Test [28], and The Boston Naming Test [32].

On review of the family history, several members were diagnosed with muscle weakness, Paget's disease and FTD. Their mother developed myopathy at age 37 years and passed away at age 64 years. The maternal grandmother developed myopathy and passed away at age 65 years. A brother and a sister developed myopathy at age 37 and 50 years respectively. Three first cousins had myopathy and one of them also developed Paget's disease. A maternal aunt had myopathy and FTD. The affected twin has a daughter and a son who are mutation positive but are currently asymptomatic.

Case 1 is the affected non-ambulatory twin brother with a 10 year history of worsening muscular weakness in his both upper and lower limbs. He was first diagnosed with inclusion body myopathy and Paget's disease at the age of 46 years when he developed difficulty climbing stairs. Later the diagnosis was confirmed by molecular testing. Genomic DNA sequencing at the Mitomed Laboratory (UC Irvine) detected a heterozygous deleterious mutation at position c.463 C > T in exon 5 of the VCP gene causing an amino acid arginine to cysteine substitution at position p.R155C. About 2 years after the disease onset he claimed disability and at age 55 years he became wheel chair bound. He experienced difficulty swallowing, gastroesophageal reflux with epigastric pain and fecal incontinence secondary to both functional incontinence and poor anal sphincter control. He experienced dyspnea on mild exertion and orthopnea. Chest examination revealed decreased breath sounds in bilateral lower lung fields. He also showed signs of 2+ pitting edema in his lower extremities, extending up to the knees, and this being attributed to relative inactivity. On appearance, he was well dressed, alert and oriented to place and time. He was able to recall his past events without any difficulty. He was cooperative throughout the visit and maintained eye contact. He was well articulated with normal perception but a little depressed about his condition. He did not manifest any positive symptoms including delusions, hallucinations or suicidal ideation. Neurological examination identified extreme proximal and distal muscular weakness and restricted movements in all four extremities. Scapular winging was noted which was more pronounced on his left side. Neurological exam also revealed diminished sensations to tuning fork over the left toe, and dysdiadochokinesia of the upper extremities.

2.1. Brain pathology

The affected twin ultimately succumbed to disease at the age of 58 years and consent for an autopsy was provided by the family. Brain weight was 1310 g. Detailed microscopic examination revealed mild thinning of the cerebral gyri with widening of the sulcal spaces. Ubiquitin immunostains performed in frontal, temporal with hippocampal sections revealed faint cytoplasmic staining in rare cortical neurons and occasional faint neuronal nuclear staining, but no definite

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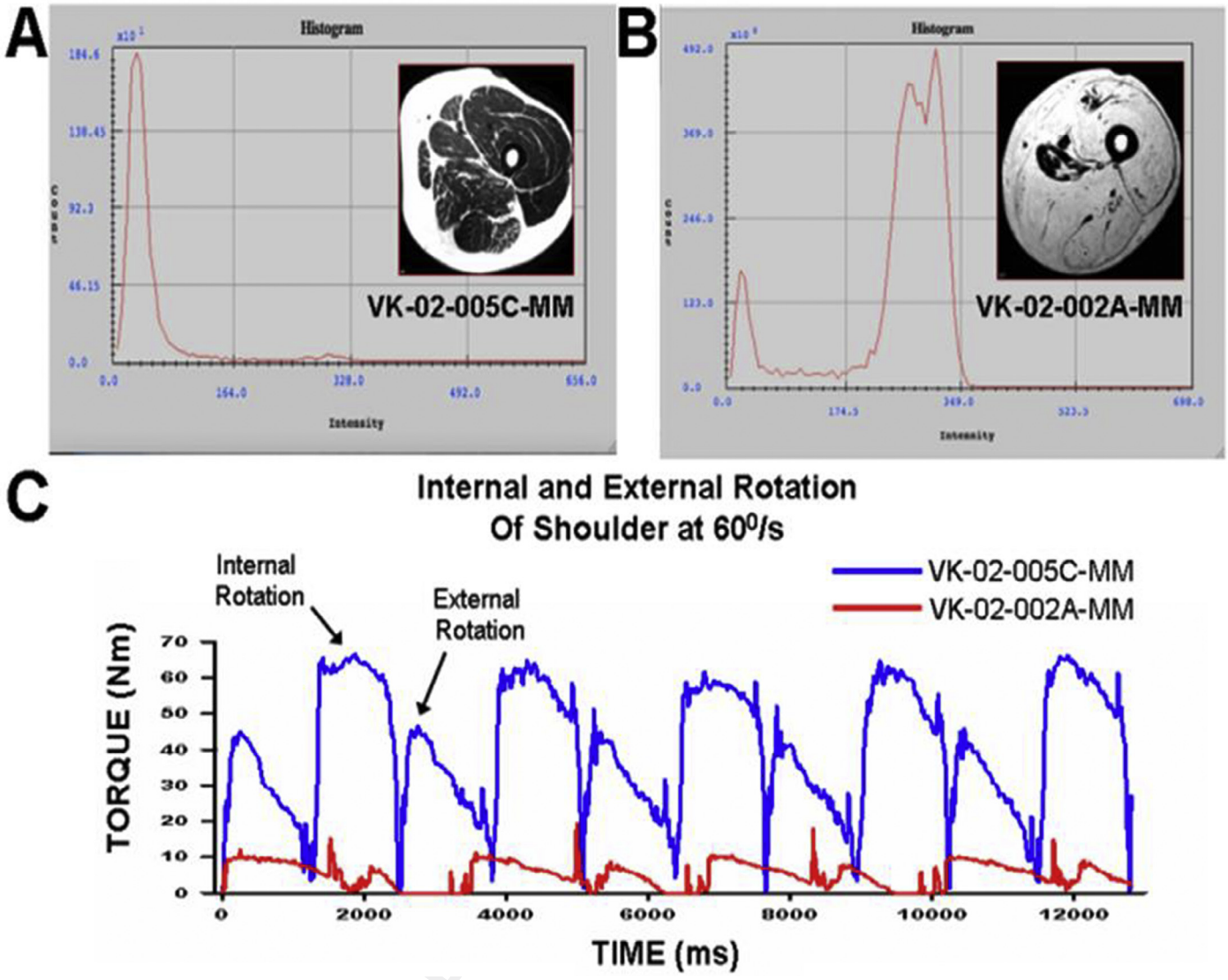

Fig. 2. MRI of thighs and Biodex measurements from twins discordant for the VCP disease. Pixel-intensity histograms of the segmented muscle group in T2-weighted histograms of (A) Control twin and (B) Affected twin. (C) Biodex measurements of control and affected twins of VCP disease.

nuclear or cytoplasmic inclusions were seen. Scattered small perinuclear vacuoles were seen in the cortical pyramidal neurons (Fig. 3). There was staining of the white matter with a granular pattern and rare axonal corkscrews, and glial nuclear staining. There was considerable fibrosis of the deep white matter arteries, with pigmented macrophages and rare cuffs of lymphocytes in the perivascular spaces. There was pallor, microvacuolation and abundant deposits of corpora amylacea in the subventricular white matter of the cingulum (long standing gliosis), and scattered corpora amylacea in the subpial spaces of the cortical sections. There was mild neuronal loss in the substantia nigra, with groups of pigmented macrophages. There were very rare degenerating enlarged axons. No neurofibrillary tangles or neuritic plaques, Lewy pale bodies or other intraneuronal inclusions were identified. There were petechial

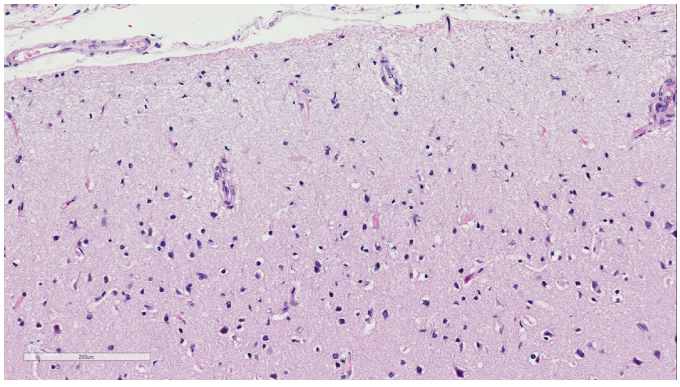

Fig. 3. Frontal cortex stained with hematoxylin and eosin shows nonspecific perineuronal vacuolation. Ubiquitin immunohistochemistry was nonspecific in the cerebral cortex and white matter. Scale bar = 200 μm.

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hemorrhages in the medullary section, some in the dorsal aspect, below the fourth ventricle, and some perivascularly. TDP-43 immunohistochemistry (rabbit polyclonal antibody to C-terminal TDP-43 peptide corresponding to amino acids 355–369) of the frontal and temporal cortices showed a normal pattern of nuclear immunoreactivity with no TDP-43-positive cytoplasmic inclusions or neurites identified.

Case 2 is the 56 year old unaffected twin brother tested negative for the familial VCP gene mutation. He had no specific health complaints except for hypertension. His muscle strength and activity level were normal for his age. He underwent a similar battery of testing for comparison with his affected twin.

Neuropsychological Assessment showed normal FBI scores at age 55 years, indicating no behavioral features of early FTD. Repeat testing approximately 1 year later demonstrated a decline in the affected brother, particularly on the Category Fluency test, Boston naming and Trails B tests, whereas global MMSE and Beck depression scale scores were preserved (Table 1) on comparison with his unaffected twin. Detailed neuropsychological examination 1 year later revealed impairment on the Boston Naming test indicative of dysnomia, difficulties on the Trail Making Test A and B, suggesting impaired attention and visual sequencing and difficulties on the Digit Span Test, suggesting impaired working memory functioning. In addition, the affected twin showed reduced performance on the same tests compared with his own level of performance 1 year previously. He also displayed difficulty in verbal fluency from Controlled Word Association (FAS) and Letter Fluency Category Test (Animal). He displayed dysnomia, clear deficiency of short-term memory and executive functions. His cognitive language decline was evident with minimal depression. In contrast the relatively low fluency score at the first test at 55 years in the unaffected twin raises the possibility that the letter fluency may be a less sensitive measure for assessment of behavioral features in individuals with VCP mutation. However, given the normal score on this test at second visit, and that this test has well-established sensitivity to features of FTD, it is more likely that the low score at first testing in the unaffected twin could have been influenced by motivational factors, medications, lack of sleep, or distraction. Nevertheless, the discordance in scores highlights the importance of repeat neuropsychological testing in establishing accurate diagnoses.

MRI of the brain of both affected and unaffected twin at age 55 years showed no generalized atrophy or focal atrophy in the frontal region or elsewhere in the affected twin. Brain volumes were similar at age 55 years (Fig. 1) [33]. Both brothers underwent MRI scans of the legs (Fig. 2) and shoulders.

Additional studies showed *plasma alkaline phosphatase (ALP)* (70 IU/L; normal range 26–110 IU/L) and *plasma creatinine phosphokinase (CK)* (99 IU/L; normal range 22–269 IU/L) for the affected twin were within the normal range. *Electromyography/nerve conduction studies* revealed myopathic changes with early recruitment and increased polyphasic motor units of the right deltoid in the affected twin.

A *bone scan* of the affected twin at 54 years revealed sclerotic lesions and cortical thickening of diaphysis and metaphysis of the distal bilateral humerus, bilateral femur and anterior aspects of bilateral ribs. He also had compression deformities at mid thoracic vertebral bodies, multilevel lumbar chronic degenerative disease and mild scoliosis consistent with PDB. Radiographs of the chest of the affected twin revealed bibasilar atelectasis of the lungs. *DEXA analysis* of the affected twin at 56 years revealed 50.30% body fat compared with 31% in unaffected twin partly attributable to fatty replacement of muscle fibers seen in advanced stage of myopathy. The bone mineral density of the affected twin of the total left hip was 0.682 g/cm^2 with a corresponding T score of −2.3 g/cm^2 indicative of osteopenia and increased risk for bone fractures. *Magnetic resonance imaging (MRI)* (Fig. 2) in both flexor and extensor muscles of the thigh in the affected twin showed diffuse high signal intensity resulting from the nearly total fatty replacement of the muscles. Thigh muscles in the unaffected twin (left) revealed normal uniform low signal intensity. *Dynamometry testing* using the hydraulic hand dynamometer showed the mean upper extremity muscle strength in the affected twin on right and left side were 29.4 and 45.4 lbs respectively compared with 80 and 76.8 lbs for the unaffected twin revealing muscle weakness compromising the physical function in the affected twin.

Echocardiogram of the affected twin revealed mild global hypokinesia, moderate concentric left ventricular hypertrophy, ejection fraction of 56% and a normal left ventricular systolic function. *Pulmonary function studies* in him revealed his best Forced Vital Capacity was 1.54 L. His Forced Expiratory Volume was 1.12 L. The Peak Expiratory Volume was 3.08 L; the Maximal Inspiratory Pressure was recorded at 53 mmHg and Maximal Expiratory Pressure at 52 mmHg suggesting a severe restrictive ventilatory impairment. Pulmonary function studies in the unaffected twin were entirely normal.

3. Discussion

Studying twins discordant for the disease provides a unique opportunity to study the effects of the VCP mutation since the effects of the prenatal environment, age, and sex are common. There are some limitations however since dizygotic twins share on an average 50% of their genes and are exposed to diverse environmental and other genetic influences [34]. The Swedish Twin Registry data on longevity studies reported that over the total age range examined, one third of the variance in longevity is attributable to genetic factors, and almost all of the remaining variance is due to non-shared, individual specific environmental factors. Data on cognitive ability in this population indicated that 50% variation in general is due to genetic differences and approximately 40% of general cognitive abilities are environmental [35].

We have reported that approximately 33% of affected individuals have FTD at late stages of the disease. However, identified VCP carriers have not always had a comprehensive evaluation, and it is likely that more individuals with early behavioral and cognitive alterations would be detected using a uniform assessment protocol. Differences between the affected and unaffected twin were not apparent on the global MMSE scores. However, in-depth neuropsychological testing revealed

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performance declines on similar semantic and executive tests in the affected twin over a relatively short, 1-year follow up period. In contrast, classic FTD behavioral changes were notably absent. This suggests that FTD-related cognitive features may precede behavioral changes in VCP disease as compared with predominance of behavioral impairment reported in previous studies [10] [36] [37].

Neuropathological findings in more advanced FTD are atrophy and neuronal loss in the frontal and temporal lobes with ubiquitin and TDP-43 positive inclusions that co-localize with ubiquitin [21,23]. Forman et al. (2006) studied the neuropathology in eight subjects. All six with clinical FTD or dementia and one of the two individuals without dementia had some degree of brain atrophy with associated neuron loss, spongiosis, and gliosis, extensive ubiquitin-positive intranuclear inclusions and dystrophic neurites throughout the neocortex but most severe in the temporal lobe [38]. The autopsy report in the affected twin indicated only mild neurodegenerative changes. The rapid demise of the patient within 2 years after cognitive testing was due to severe neuromuscular complications, and not apparently related to FTD. The affected twin did not show ubiquitin or TDP-43 inclusions, which suggests that these changes occur with progression of the disease that may have occurred if death had not supervened. This case illustrates that cognitive decline can occur in the absence of these features, possibly resulting from more subtle metabolic cerebral alterations not assessed here.

Although the MMSE remains the most thoroughly studied instrument, from this report it is clear that MMSE is not sensitive in screening for frontotemporal dementia in VCP patients associated with problems in verbal fluency, short-term memory and executive function domains of cognition. The comprehensive neuropsychological assessment thus remains the 'gold standard' in the diagnosis of FTD. There is a need for a rapid screening test for FTD associated with VCP disease. The most recent evidence update from the U.S. Preventive Services Task Force 2013 [39] reported test performance, diagnostic accuracy of brief screening instruments to detect cognitive impairment. Pooled estimates across 14 studies for MMSE ($n = 10{,}185$) resulted in 88.3% sensitivity (95% CI, 81.3–92.9) and 86.2 specificity (95% CI, 81.8–89.7) for a cut-point of 23/24 or 24/25 to detect dementia. Other screening instruments including Clock Drawing Test (CDT), Mini-Cog, Memory Impairment Screen (MIS), Abbreviated Mental Test (AMT), Short Portable Mental Status Questionnaire (SPMSQ), Free and Cued Selective Reminding Test (FCSRT), 7-Minute Screen (7MS), Telephone Interview for Cognitive Status (TICS), self-administered or informant-based screening tool Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) showed much wider range of sensitivity and specificity. This case also illustrates that cognitive decline can occur relatively rapidly. Establishing an appropriate screening measure which is simple, easy to administer and brief for administration at regular intervals in busy clinical settings is desirable. Utilizing tests for cognition including attention, concentration, working memory, fluency and existing dementia screening measures would also be useful in detecting preclinical frontotemporal dementia. Patients with VCP disease should therefore have monitoring of their cognitive and behavioral status at regular basis since there is an increased risk for cognitive impairment. The extensive battery of neuropsychological assessment is limited by need for trained staff, screening time and funding. An alternative simple, easy to administer, sensitive screening measure that can be administered at regular intervals in clinical settings will recognize cognitive and behavioral impairment that will not be detected on routine neurological examination. Woolley et al. (2010) [22] developed and validated a screening tool, the ALS Cognitive Behavioral Screen tool (ALS-CBS), to accurately differentiate ALS-FTD from other ALS patients. This test could be very helpful in VCP disease, but nevertheless needs to be validated in this group of patients.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2014.10.003.

References

[1] Watts GD, Thorne M, Kovach MJ, Pestronk A, Kimonis VE. Clinical and genetic heterogeneity in chromosome 9p associated hereditary inclusion body myopathy: exclusion of GNE and three other candidate genes. Neuromuscul Disord 2003;13(7–8):559–67.

[2] Kovach MJ, Waggoner B, Leal SM, et al. Clinical delineation and localization to chromosome 9p13.3-p12 of a unique dominant disorder in four families: hereditary inclusion body myopathy, Paget disease of bone, and frontotemporal dementia. Mol Genet Metab 2001;74(4):458–75.

[3] Kimonis VE, Kovach MJ, Waggoner B, et al. Clinical and molecular studies in a unique family with autosomal dominant limb-girdle muscular dystrophy and Paget disease of bone. Genet Med 2000;2(4):232–41.

[4] Kimonis V, Donkervoort S, Watts G. Inclusion body myopathy associated with Paget disease of bone and/or frontotemporal dementia. Seattle: Gene GeneTests (www.genetests.org) and University of Washington; 2011 <http://www.ncbi.nlm.nih.gov/pubmed/20301649>.

[5] Weihl CC, Pestronk A, Kimonis VE. Valosin-containing protein disease: inclusion body myopathy with Paget's disease of the bone and fronto-temporal dementia. Neuromuscul Disord 2009;19:308–15.

[6] Nalbandian A, Donkervoort S, Dec E, et al. The multiple faces of valosin-containing protein-associated diseases: inclusion body myopathy with Paget's disease of bone, frontotemporal dementia, and amyotrophic lateral sclerosis. J Mol Neurosci 2011;42:522–31.

[7] Vesa J, Su H, Watts GD, et al. Valosin containing protein associated inclusion body myopathy: abnormal vacuolization, autophagy and cell fusion in myoblasts. Neuromuscul Disord 2009;19:766–72.

[8] Ju JS, Weihl CC. Inclusion body myopathy, Paget's disease of the bone and fronto-temporal dementia: a disorder of autophagy. Hum Mol Genet 2010;19:R38–45.

[9] Waggoner B, Kovach MJ, Winkelman M, et al. Heterogeneity in familial dominant Paget disease of bone and muscular dystrophy. Am J Med Genet 2002;108(3):187–91.

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[10] Kimonis VE, Fulchiero E, Vesa J, Watts G. VCP disease associated with myopathy, Paget disease of bone and frontotemporal dementia: review of a unique disorder. Biochim Biophys Acta 2008;1782:744–8.

[11] Guyant-Marechal L, Laquerriere A, Duyckaerts C, et al. Valosin-containing protein gene mutations: clinical and neuropathologic features. Neurology 2006;67:644–51.

[12] Haubenberger D, Bittner RE, Rauch-Shorny S, et al. Inclusion body myopathy and Paget disease is linked to a novel mutation in the VCP gene. Neurology 2005;65:1304–5.

[13] Watts GD, Thomasova D, Ramdeen SK, et al. Novel VCP mutations in inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia. Clin Genet 2007;72(5):420–6.

[14] Gidaro T, Modoni A, Sabatelli M, Tasca G, Broccolini A, Mirabella M. An Italian family with inclusion-body myopathy and frontotemporal dementia due to mutation in the VCP gene. Muscle Nerve 2008;37(1): 111–14.

[15] Mehta SG, Khare M, Ramani R, et al. Genotype-phenotype studies of VCP-associated inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia. Clin Genet 2013;83(5):422–31.

[16] Roberson ED. Contemporary approaches to Alzheimer's disease and frontotemporal dementia. Methods Mol Biol 2011;670:1–9.

[17] Mehta SG, Watts GD, McGillivray B, et al. Manifestations in a family with autosomal dominant bone fragility and limb-girdle myopathy. Am J Med Genet A 2006;140(4):322–30.

[18] Djamshidian A, Schaefer J, Haubenberger D, et al. A novel mutation in the VCP gene (G157R) in a German family with inclusion-body myopathy with Paget disease of bone and frontotemporal dementia. Muscle Nerve 2009;39(3):389–91.

[19] Kumar KR, Needham M, Mina K, et al. Two Australian families with inclusion-body myopathy, Paget's disease of bone and frontotemporal dementia: novel clinical and genetic findings. Neuromuscul Disord 2010;20(5):330–4.

[20] Miller TD, Jackson AP, Barresi R, et al. Inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD): clinical features including sphincter disturbance in a large pedigree. J Neurol Neurosurg Psychiatry 2009;80(5):583–4.

[21] Neumann M, Mackenzie IR, Cairns NJ, et al. TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. J Neuropathol Exp Neurol 2007;66(2):152–7.

[22] Woolley SC, York MK, Moore DH, et al. Detecting frontotemporal dysfunction in ALS: utility of the ALS Cognitive Behavioral Screen (ALS-CBS). Amyotroph Lateral Scler 2010;11:303–11.

[23] Cairns NJ, Neumann M, Bigio EH, et al. TDP-43 in familial and sporadic frontotemporal lobar degeneration with ubiquitin inclusions. Am J Pathol 2007;171(1):227–40.

[24] van der Zee J, Pirici D, Van Langenhove T, et al. Clinical heterogeneity in 3 unrelated families linked to VCP p.Arg159His. Neurology 2009; 73:626–32.

[25] Gordon PH, Wang Y, Doorish C, et al. A screening assessment of cognitive impairment in patients with ALS. Amyotroph Lateral Scler 2007;8:362–5.

[26] Flaherty-Craig C, Brothers A, Dearman B, Eslinger P, Simmons Z. Penn State screen exam for the detection of frontal and temporal dysfunction syndromes: application to ALS. Amyotroph Lateral Scler 2009;10: 107–12.

[27] Baer L, Jacobs DG, Meszler-Reizes J, et al. Development of a brief screening instrument: the HANDS. Psychother Psychosom 2000;69 (1):35–41.

[28] Gaddes WH, Crockett DJ. The Spreen-Benton aphasia tests, normative data as a measure of normal language development. Brain Lang 1975;2(3):257–80.

[29] Spreen O, Benton AL, Fincham RW. Auditory agnosia without aphasia. Arch Neurol 1965;13:84–92.

[30] Aita JA, Armitage SG, Reitan RM, Rabinovitz A. The use of certain psychological tests in the evaluation of brain injury. J Gen Psychol 1947;37:25–44.

[31] Bowden SC, Bell RC. Relative usefulness of the WMS and WMS-R: a comment on D'Elia et al. (1989). J Clin Exp Neuropsychol 1992; 14(2):340–6.

[32] Kaplan E, Goodglass H, Weintraub S. Boston naming test. Philadelphia: Lea and Febiger; 1983.

[33] Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex 2004;14(1):11–22.

[34] Ljungquist B, Berg S, Lanke J, McClearn GE, Pedersen NL. The effect of genetic factors for longevity: a comparison of identical and fraternal twins in the Swedish Twin Registry. J Gerontol A Biol Sci Med Sci 1998; 53(6):M441–6.

[35] McClearn GE, Johansson B, Berg S, et al. Substantial genetic influence on cognitive abilities in twins 80 or more years old. Science 1997; 276(5318):1560–3.

[36] Stojkovic T, Hammouda EH, Richard P, et al. Clinical outcome in 19 French and Spanish patients with valosin-containing protein myopathy associated with Paget's disease of bone and frontotemporal dementia. Neuromuscul Disord 2009;19(5):316–23.

[37] Jacquin A, Rouaud O, Soichot P, et al. Psychiatric presentation of frontotemporal dementia associated with inclusion body myopathy due to the VCP mutation (R155H) in a French family. Case Rep Neurol 2013;5(3):187–94.

[38] Forman MS, Mackenzie IR, Cairns NJ, et al. Novel ubiquitin neuropathology in frontotemporal dementia with valosin-containing protein gene mutations. J Neuropathol Exp Neurol 2006;65(6):571–81.

[39] Lin JS, O'Connor E, Rossom RC, editors. Screening for cognitive impairment in older adults: an evidence update for the U.S. preventive services task force. Rockville, MD: Agency for Healthcare Research and Quality (US); 2013, Report No.: 14–05198-EF-1. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews.

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