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Behavioral variant of frontotemporal dementia in carriers of biallelic TREM2 variants: cases study

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Abstract

Introduction: *First reports associated mutations in triggering receptors expressed on myeloid cells 2 (TREM2) with autosomal recessive Nasu-Hakola disease characterized by painful bone cysts and progressive presenile dementia with psychotic symptoms; however, recent TREM2 biallelic rare variants are suggested to be causative also for the behavioral variant of frontotemporal dementia (bvFTD) without bone involvement.*

Material and methods: *Clinical data of three unrelated bvFTD patients carrying TREM2 biallelic variants were evaluated. All patients underwent neurological, psychiatric, and cognitive evaluation and neuroimaging. A full neuropsychological assessment was performed in two cases.*

Results: *Two patients carried compound heterozygous TREM2 variants, p.R62C and p.T66M, and one carried the homozygous p.D87N variant. Based on all obtained clinical and neuroimaging data, a behavioral variant of frontotemporal dementia was diagnosed in all cases. Their clinical manifestation was typical with neuropsychiatric and cognitive features, without bone abnormalities.*

Conclusions: *Despite all three subjects partially resembling clinical manifestations of Nasu-Hakola disease with TREM2 mutations, we reveal some distinct features, including age of onset, neuroimaging findings, or disease course.*

Key words: *neuropsychological assessment, compound heterozygosity, biallelic variants, bvFTD.*

Introduction

Triggering receptors expressed on myeloid cells 2 (TREM2) in the central nervous system are primarily expressed in microglia. Activation of the TREM2 receptor stimulates phagocytosis activity and decreases microglial pro-inflammatory responses [28]. Therefore, it is proposed that TREM2 is essential for clearing cellular debris without excessive inflammation and tissue destruction. Causative homozygous loss-of-function mutations in the *TREM2* gene were described for the first time in patients with autosomal recessive Nasu-Hakola disease (NHD) characterized by painful bone cysts, psychotic symptoms and progressive presenile dementia [17,24]. Further investigation associated heterozygous *TREM2* rare variants with neurodegenerative disorders both as causative factors and/or risk ones with late-onset Alzheimer's disease (LOAD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD) spectrum, mainly in the primary progressive aphasia (PPA), and the behavioral variant of frontotemporal dementia (bvFTD) [5,13]. Cognitive deterioration in bvFTD includes executive and language dysfunctions without episodic memory deficits, along with altered personality and behavior. It results in delayed diagnosis or misdiagnosis of psychiatric disorders [14].

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Biallelic variants (compound heterozygous or homozygous) in the *TREM2* gene have been reported in several families and associated with bvFTD. Besides the early age of onset (mainly in the third and fourth decade of life), personality and behavioral changes occur with executive and language impairments with relatively spared memory. Seizures, callosal atrophy, and diffuse white matter lucency were also described in patients [2-4,8,11,12,22,23]. *TREM2* rare variants are likely to be the first recessive determinants for FTD. Here, we report a clinical description of three bvFTD cases carrying *TREM2* biallelic variants identified in Polish patients.

Material and methods

Among 135 FTD patients from the Polish cohort, we identified three subjects with biallelic variants of the *TREM2* gene using a next-generation sequencing-based gene panel. All three patients were initially diagnosed with FTD [21] and later confirmed as a behavioral variant of FTD [27]. Two female patients carried the same putative causative compound heterozygous variants: p.R62C (c.184C>T, NM_018965.4) and p.T66M (c.197C>T, NM_018965.4). One male patient was a carrier of homozygous *TREM2* p.D87N (c.259G>A, NM_018965.4). The biochemical and epidemiological characteristics of the identified variants were described previously [25].

We found no mutations in known genes (*PSEN1*, *APP*, *MAPT*, *C9orf72*, and *PGRN*) associated with neurodegeneration.

All subjects underwent clinical evaluation, including detailed medical interviews, neurological and psychiatric examination, cognitive screening, and full neuropsychological assessment in Cases 2 and 3 [7]. Standard laboratory testing and computed tomography (CT) were performed in all patients, and Case 3 underwent single positron emission computed tomography (SPECT).

Results

Case 1 – TREM2 (p.[R62C]; [T66M])

A 60-year-old female farmer with primary school education was referred to the Neurodegenerative Department in 2000 with behavioral and speech problems. No cognitive or psychiatric disorders were present in the family history, according to relatives' knowledge. The subject's first symptoms at the age of 50 manifested in increased apathy, jocular attitude, excessive joy, and disinhibition. Three years later, the patient developed memory decline and language perseverations in speech. It was followed by disorientation in space, which resulted in being lost in the neighborhood. At the age of 59, the patient had manifested severe dressing and cutlery apraxia and personal care neglect with bowel and bladder incontinence.

The first epileptic seizures were also present at that time. Neither aggression nor psychotic features were reported. She was physically healthy except for the medical issues with the knee joints due to a rheumatologic condition.

The psychiatric examination unveiled increased apathy. The neurological examination revealed mild both-sided Babinski and pyramidal signs, parkinsonism manifesting with bradykinesia, hypomimia, bradyphrenia, and disturbances in the basic reflexes. CT scan showed general cortico-subcortical atrophy. Routine blood laboratory testing showed no abnormalities.

The clinical assessment at the age of 60 revealed severe behavior and cognition impairment. The Mini-Mental State Examination (MMSE) [6] scale score was 1, as the subject could repeat only one word, with the presence of echolalia, the lack of insight and logical contact. She failed to follow any commands and managed to copy a circle with later preservations. Detailed scores of used assessment scales are in Table I.

Based on the history of symptoms and the subject's examination, she was then diagnosed with FTD in the severely advanced stage and later confirmed as bvFTD.

The patient's condition was stable, with persistent epileptic seizures (once a month). Due to the further progression of movement problems, the family resigned from 3-month apart visits. No follow-up data were possible to obtain.

Case 2 – TREM2 (p.[R62C]; [T66M])

A 51-year-old female with a high school degree, working as an office clerk for a short period, was admit-

Table I. Screening assessment scores

Test (ranges)	Case 1	Case 2	Case 3
MMSE (0-30)	1	24	26
CDT (0-10)	1	n/a	6
GDS (1-7)	6	n/a	3
CDR (0-3)	n/a	1	0,5

MMSE – Mini-Mental State Examination, CDT – Clock Drawing Test, GDS – Global Dementia Scale, CDR – Clinical Dementia Rating

ted to a Neurology Clinic in 2010 with an unconfirmed diagnosis of cognitive disorders manifesting in language and behavioral problems for the last six months. At 49, she was hospitalized in the Psychiatric Unit with depression symptoms and diagnosed with unspecified personality and behavioral disorders with a history of alcohol abuse. The subject's mother reported verbal and physical aggression, socially inappropriate behavior, emotional liability, and the neglect of personal care. The patient was agitated and loquacious, with accelerated, slurred, and unintelligible speech. It was accompanied by elevated mood and disinhibition. No family history of dementia or psychiatric disorders was reported.

Except for the elevated cholesterol level, all laboratory results were normal. No other neurological problems were observed. CT scans revealed bilateral frontotemporal atrophy with the enlargement of ventricles. Screening cognitive diagnosis (MMSE score 24) and the patient's behavioral disorders pointed to mild dementia. See Table I for details.

During the neuropsychological assessment, the patient lacked insight, denied cognitive deficits, and was disinhibited with utilization behavior. She had only mild problems with time and place orientation. There was a dominant executive impairment, mainly in poor verbal fluency and mental inflexibility, with disturbed abstractive thinking. She presented with dysfunctions in repeating digits backward, spatial planning, and organization, with difficulties learning hand movement sequences. Serial subtractions and attention were mildly impaired. Problems with verbal learning, as the typical frontal lobe damage "plateau" curve during the words-learning task were noted. Her episodic memory was relatively spared, with slightly decreased recognition due to intrusions. Semantic memory was also disturbed as the patient recognized or recalled 11 of 20 contouring objects. The visuospatial functions were intact. A mild psychomotor slowing was observed in the initiation and execution of task times. See Table II for details. She was diagnosed with early-onset dementia due to FTD.

A diagnosis of bvFTD, according to criteria from 2011 [27], was established a year later. The patient's condition was relatively stable, with slurred and accelerated speech, increased apathy, slowness of gait, and agitation, along with verbal and physical aggression. She was treated with mood stabilizers without improvement. Another CT scan revealed more pronounced left-sided brain atrophy. The observation two months later showed the diminishing of loquacity, but the rest of the psychiatric symptoms remained stable. At 53 years old, the subject required full care as the extrapyramidal signs became severe with the adverse reaction to levodopa treatment. In addition, there were bladder and bowel incontinence and advanced problems with gait. Her worsening physical condition was the reason that her family stopped follow-up visits.

Case 3 – TREM2 (p.[D87N]; [D87N])

A 66-year-old male with a high school degree working as a plumber was referred to the Neurodegenerative Department in 2002 with behavioral problems starting two years earlier. His father was diagnosed with young-onset dementia of unknown etiology at 58 and died four years later. The subject suffered from diabetes and had a history of alcohol abuse until 63. He manifested mainly irritability, verbal and physical aggression, and poor control, together with withdrawal and apathy. His disturbed circadian cycle – waking up at sunrise with the immediate need to go outside without any purpose caused distress for his family. According to the subject's son, the patient always presented a self-control prob-

Table II. Neuropsychological assessment scores

List of tasks (ranges)	Case 2	Case 3
Blessed's Information, Memory, and Concentration Scale/Address (0-37)	24/0	32/2
Verbal fluency: animals/letter K	11/2	8/5
Complex Figure Copy (0-36) (score/time)	30/131 sec	32/219 sec
Complex Figure Recall (0-36) (score/time)	6/92 sec	15/ 112 sec
Serial sevens task (0-14) (score/time)	10/160 sec	6/170 sec
8 Words List Learning task (first trial/last trial/recall/recognition)	3/5/3/6	4/6/3/7
Digit span forward/backward (0-7)	4/3	6/2
WAIS-R Similarities subtest (0-28)	6	11
Naming of 20 contouring pictures (0-20)	11	17
Trial Making Test A (0-24) (score/time)	23/61 sec	n/a
Trial Making Test B (0-24) (score/time)	11/347 sec	n/a

WAIS-R – Wechsler Adult Intelligence Scale-Revised

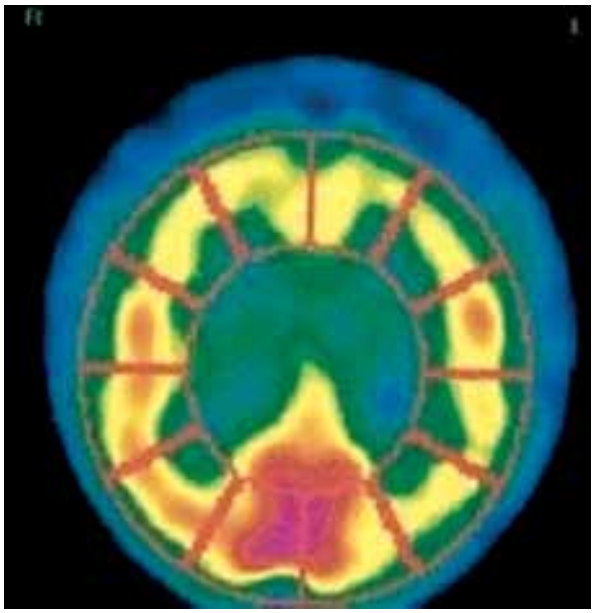

Fig. 1. Single positron emission commuted tomography of Case 3.

lem, but these symptoms became more apparent and impossible to handle. At 66, he lost his driving license as he caused three mild vehicle collisions. There were no neurological problems during the clinical evaluation at the age of 66, but psychiatric assessment revealed aggression and irritability. He scored 26 points on MMSE (see Table I for details). Standard laboratory testing showed no abnormalities. CT revealed general atrophy of the brain and cerebellum with a small hypertensive focal change in the left lenticular nucleus. SPECT suggested the FTD-like pattern – with decreased perfusion in bilateral frontal and anterior temporal lobes and basal ganglia regions (Fig. 1).

Neuropsychological assessment revealed a lack of insight, disinhibition, and poor cooperation during testing, as the patient constantly complained about non-localized pain in his right arm. He was fully oriented, with extensive executive impairments, mainly in poor verbal fluency, difficulties with serial sevens subtractions, repeating digits backward, planning, and spatial organization, and the subject could not follow the rules of Trail Making Test Part A [19]. It was accompanied by severe hand motor sequencing and reciprocal coordination impairments. He had problems in verbal learning, with a flat curve, but episodic memory and recognition were relatively intact. No semantic memory, visuospatial, or abstractive thinking impairment was noted, but psychomotor slowing was observed (see Table II for details). Based on the data, the subject was diagnosed with FTD in its initial phase, which was later confirmed as bvFTD.

The patient was under observation for the following months, attended psychiatric consults, and was treated with mood stabilizers. At 67, he refused any further visits, probably due to his behavior dysfunctions and the contact with him and his family was lost.

Discussion

TREM2 is a relevant part of the functional network involved in the efficient functioning of the nervous system. The transmembrane receptor takes part in the activation of immune response and phagocytosis in microglia and the differentiation of dendritic cells and osteoclast. It was shown that the *TREM2* variant burden is more likely to increase the risk for a broader spectrum of neurodegeneration disorders. The biallelic variants underlie the development of NHD and, as reported in recent years, might be responsible for bvFTD.

Homozygous splice site mutation (c.40+3delAGG) as a cause of bvFTD was described for the first time in the Lebanese family (consanguine marriage) [3]. Further homozygous mutations were found in the Colombian (p.W198*) [8], Italian (p.T66M) [18], Chinese families (c.391+1G>A) [20], South Asian (p.R47C) [22], and Turkish subjects (p.Q33*; p.T66M; p.Y38C; p.D86V) [10,29]. Compound heterozygosity was described in the Turkish family (p.Y38C and p.D86V) [10], Hungarian (p.A105Rfs*84 and p.R47C) [4] and German (p.A105Rfs*84 and p.H67Tfs*9) [2] patients. It was not possible to differentiate between the possibilities of co-inheritance or compound heterozygosity in one Colombian patient (p.H157Y and p.R62H) [23]. It is noteworthy that the mentioned p.R62H variant with p.D134Vfs*55 variant was identified only in compound heterozygous patients with Alzheimer's disease [1]. This seems to expand the spectrum of clinical phenotypes. In cases where the pedigree analysis was possible, these mutations segregate with disease in the autosomal recessive manner. No biallelic variants in healthy individuals have been reported yet. There is still not enough available data (reported cases) to ascertain correlations between *TREM2* rare variants and the course of the disease (cognitive and behavioral profile). It was observed that some variants e.g., c.40+3delAGG, p.Q33*; p.T66M, p.Y38C (firmly damaging ligand-binding domain in both alleles in the *TREM2* gene) result in more rapid disease progression. All aforementioned patients present with bvFTD clinical features but with some atypical signs: early seizures, white matter lesions, and corpus callosum thickness on magnetic resonance imaging (MRI). The discrepancy in age of onset (ranging from 20 to 50 years), the disease progression rate, and the severity of symptoms are worth

emphasizing. However, additional features like the pattern of behavioral disturbances, neurological signs, and neuroimaging changes seem more dependent on the overall genetic makeup and environmental impact.

The presented study allowed us to report three new cases: two unrelated compounds heterozygous: p.[(R62C)]; [(T66M)] and one homozygous (p.D87N). p.R62C and p.T66M variants were described as probably impairing and severe impairing (respectively) protein function [15,16,26,31], while p.D87N was reported only as a risk factor.

Our subjects with different severity of symptoms (from mild to very advanced ones) were initially diagnosed as FTD, according to criteria from 1998 [21], and later confirmed with bvFTD according to criteria from 2011 [27]. None of our patients presented with different dementia within the frontotemporal lobar degeneration spectrum. Semantic problems (naming difficulties) presented by Case 2 are observed in half of the bvFTD population [30].

Our two female subjects had neither a positive family history nor any relationship. The lack of a strong inheritance pattern or even a family history record is often for recessive mutations. Our male subject (Case 3) had a father diagnosed with early-onset, rapidly evolving dementia of uncertain diagnosis. Due to the lack of any clinical data (relatives' statements), the nature of the patient's father's dementia was unclear.

Older age of onset (about 50 years in females and 64 years in Case 3) was one of the most distinctive differences between our subjects and previously reported cases with TREM2 mutations. Differences in phenotype presentations allow to speculate about pathogenicity spectrum of TREM2 variants. Most bvFTD patients due to the TREM2 mutations were extremely young (present with first symptoms in their twenties or thirties) [18] and Colombian subjects presenting with symptoms in their forties [8] and the Chinese patient in his fifties were similar to ours [10].

Neuroimaging data of previously described patients suggested frontal and temporal atrophy with or without parietal involvement but with the presence of white matter changes rather unusual for bvFTD [10] and callosal thickness [11,18]. Except for general or frontotemporal atrophy of the brain, we found no other significant changes in the scans of our subjects. The recent data suggest that the combination of white matter changes, enlarged ventricles, atrophy of the caudate nucleus, and thinning of the corpus callosum in MRI in patients with FTD syndrome might strongly suggest the presence of NHD [29]. Structural or functional changes in our cases were different, however typical for bvFTD, in accordance with clinical diagnosis in Cases 2 and 3; moreover, they failed to point to any other specific neurodegenerative disease.

All of our cases presented with different severity of extrapyramidal symptoms dependent on the advancement of cognitive impairment, as it was not a primary clinical feature in any of our subjects. In bvFTD, parkinsonism is frequent (up to 80%), mainly manifesting in bradykinesia, parkinsonian gait/posture, and rigidity [14].

Despite seizures being a rare symptom in bvFTD without *TREM2* pathology compared to other dementias [9], TREM2 mutation carriers from Italian [18], Turkish [11,29], and Colombian [9] families were presenting with seizures, in some cases even preceding cognitive and behavioral symptoms. Among our patients, only Case 1 developed epileptic seizures nine years after onset, probably due to disease progression.

All previously reported carriers of TREM2 biallelic mutations presented with a clinical manifestation similar to the NHD with behavioral change and subsequent cognitive impairment but without bone-associated phenotypes, in like manner to our patients as their physical condition was excellent until they had developed extrapyramidal symptoms (Cases 1 and 2).

Cases 2 and 3 also had a history of alcohol abuse, but it was excluded as a direct reason for cognitive worsening (they stopped drinking before the onset of the symptoms). It differs from the report on the Turkish siblings [8] whose increased drinking was a part of the clinical manifestation of behavioral problems. According to other data, somatic complaints and sleep disturbances manifested by Case 3 are one of the earliest symptoms in bvFTD patients [30], and many preclinical bvFTD patients present with psychiatric symptoms or even law-violation behavior (Case 3 caused traffic collisions) [9]. Misdiagnosis of psychiatric disorders is common among bvFTD patients and often precedes the actual diagnosis [14]. All our cases presented with psychiatric features, but only Case 2 had a previously documented psychiatric disorder diagnosis. bvFTD is usually characterized by initial psychiatric symptoms followed by progressive executive and cognitive impairment with poor reaction to pharmacological treatment. This pattern was present in previously published cases as well as in our subjects.

Conclusions

Biallelic *TREM2* variants contribute to the risk of developing bvFTD, regardless of their significant associations with other forms of neurodegenerative diseases.

Our findings support the presence of a bvFTD-like clinical profile in biallelic *TREM2* variants carriers. It is still open to discussing whether it should be considered as NHD without bone involvement or an FTD variant. It seems that among subjects with biallelic *TREM2*

mutations and bvFTD-like clinical profiles, an extremely young age of onset (20s and 30s), early seizures, colossal thinness, white matter changes, are more suggestive of the NHD without bone involvement. On the other hand, behavioral and cognitive features fulfilling the diagnostic criteria for bvFTD, the onset of symptoms in 50s or 60s, typical FTD-like brain changes pattern, and the lack of strong family history are more likely to be bvFTD caused by *TREM2* mutation.

This study demonstrates that genetic testing of a sporadic or autosomal recessive form of FTD, mainly in its behavioral presentation should also include *TREM2* screening.

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Disclosures

Approval of the Bioethics Committee was not required.

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