Psychiatr. Pol. 2016; 50(2): 329–336
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: http://dx.doi.org/10.12740/PP/58937

Behavioural variant frontotemporal dementia with dominant gait disturbances – case report

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Summary

Introduction. Behavioural variant frontotemporal dementia is a clinically and pathologically heterogeneous neurodegenerative disorder, characterised by progressive behavioural changes and executive function impairment. It is the second most common neurodegenerative cause of dementia after Alzheimer's type dementia. Atypical course of the disease, including cases with other symptoms relevantly interfering with the clinical picture, provides a challenge in the diagnostic process.

Aim and material. The aim of this paper is to present a case of patient with BvFTD and gait disturbance as a main reported symptom masking behavioural changes and cognitive function impairment. Gait disturbance commonly occurs at the late stage of dementia disorders. It results from gait apraxia, extrapyramidal syndrome or motor neuron dysfunction. However, it is not a predominant symptom of behavioural variant frontotemporal dementia excluding terminal stage of the disease.

Conclusions. Presented case emphasises the significance of accurately gathered anamnesis with patient and his family. Behavioural variant frontotemporal dementia should be considered in cases of unexplained gait abnormalities.

Key words: frontotemporal dementia, gait disorder, case report

Introduction

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous group of dementia syndromes associated with degeneration of frontal and temporal lobes which was called frontotemporal lobar degeneration (FTLD) [1]. Three variants of FTD are distinguished: behavioural variant FTD (bvFTD), semantic dementia (SD) and progressive nonfluent aphasia (PNA) [1]. Degeneration process underlying FTD is heterogeneous. Currently, types of the proteins which form the intracellular

inclusions determine three major pathological features: FTLD-tau, FTLD-TDP and FTLD-FUS [2]. The prevalence of FTD is established to be 3–15/100000 [1, 3]. It is the second most common neurodegenerative cause of dementia after Alzheimer's type dementia (AD). In 40–50% cases of FTD, it runs in the family [1]. The onset of the disease typically occurs at 45–65 years of age, so it is earlier then the onset of AD [1].

The most common type of FTD is bvFTD characterised by behavioural disturbances including disinhibition, apathy, aspontaneity, inflexibility, irritability, loss of empathy, perseverations, stereotypies, compulsive behaviour, hyperorality and hypersexuality [1, 4, 5]. Executive function impairment typical for prefrontal cortex dysfunction is also distinctive for bvFTD [1, 4, 5]. Diagnostic criteria include frontal and anterior temporal lobes atrophy assessed in magnetic resonance imaging (MRI) as well as frontotemporal hypoperfusion on single-photon emission computed tomography (SPECT) and frontotemporal hypometabolism on positron emission tomography (PET) [4]. Pre-mortem differential diagnosis of dementia syndromes including FTD, especially clinical and neuropathological subtypes, often entails difficulties. Number of other symptoms not excepting extrapyramidal and pyramidal symptoms, extraocular movement impairment, gait and postural reflexes disturbance are relevant to identify aetiology of dementia syndrome [1, 2].

Gait disturbance is a component of FTD and other neurodegenerative disorders symptoms spectrum [6]. It may result from gait apraxia, extrapyramidal syndrome or muscle weakness caused by motor neuron disorder. Moreover motor disability may occur due to non-neurological causes such as blurred vision, bones and joints disorders. Gait impairment may also exist in nondemented elderly subjects and is associated with executive functioning [6]. However, relevant gait disturbance commonly occurs at the late stage of dementia disorders. It is not a predominant symptom of bvFTD, excluding terminal stage of the disease.

Aim

The aim of this report is to present a case of patient with bvFTD and gait disturbance as a main reported symptom masking behavioural changes and cognitive function impairment.

Case report

A 64-year-old female suffered from progressive gait impairment for 2 years. She reported lower extremities stiffness and imbalance. There was no collapse in the history. Patient was able to walk with the walker or with the assurance of another person. She managed to walk a few steps without assistance. Due to the presence of bilateral pyramidal symptoms including increased muscle tone, hyperactive stretch reflexes

and Babinski response MRI of the spine was performed earlier. However, it proved no relevant abnormality. The family reported increased irritability and inflexibility since motor difficulties occurred. These personality changes were explained by motor disability progression.

Patient's past medical history included uterine adenocarcinoma, she was subject to the hysterectomy and radiotherapy 10 years before neurological symptoms occurred. Hitherto there was no recurrence; bone scintigraphy performed one year after the symptoms had occurred showed no metastasis. Excluding this, she was not chronically ill. Non-neurological causes of gait disturbances, including blurred vision, bones and joints disorders, were excluded. There was no neurological disease, including dementia syndrome, in the family. She was taking baclofen in a daily dose of 30 mg due to the increased muscle tone.

Neurological examination showed: presence of the primitive reflexes, mildly increased muscle tone (spastic), mild reduction of strength (4+ on the Lovett scale) and hyperactive stretch reflexes in the lower extremities with bilateral Babinski response, mild and symmetric hypodiadochokinesia. Extraocular movement was normal; there was neither limb tremor, cerebellar signs nor sensory deficit. Romberg test was negative. Postural reflexes were slightly impaired. The patient presented gait disorder disproportionate with a degree of muscle weakness. Gait was moderately spastic with reduced stride length, reduced foot lifting (magnetic gait), moderately broad base of support. Difficulty in initiating movement was observed. Upper extremities swing was proper and the posture was upright.

Due to the suspicion of neurodegenerative disease, psychological examination was conducted. It proved behavioural changes including apathy, irritability, aspontaneity, reduced empathy, not keeping social rules and loss of insight. Frontal Behavioural Inventory (FBI) was performed with patient's family – the score was 32/70. The mood was mildly depressed; Montgomery-Asberg Depression Rating Scale score was 13. Executive functions were affected with relative sparing of memory functions. The results of neuropsychological tests were as follows: Mini Mental State Examination – 27/30, Alzheimer's Disease Assessment Scale – cognitive subscale – 14/70, Frontal Assessment Battery – 14/18, the Executive Interview (EXIT 25) – 12/50, Rey Auditory Verbal Learning Test: A1 – 6 words, A5 – 11 words, delayed recall – 10 words, recognition – 12 words, Digit Span: forward – 6 points, backward – 2 points, Stroop Test I – 26 sec., Stroop Test II – 101 sec. (9 mistakes), Trail Making Test: part A – 78 sec., part B – 345 sec. (with examiner's support).

Due to the uterine adenocarcinoma in the past, we tested patient for onconeural antibodies. Anti-titin antibodies were present (for one +). There were no myasthenic symptoms in this case. However, repetitive nerve stimulation (RNS) was performed – no abnormality was observed. Other laboratory tests results did not show any significant deviation. Brain MRI was performed. It revealed moderate supratentorial atrophy

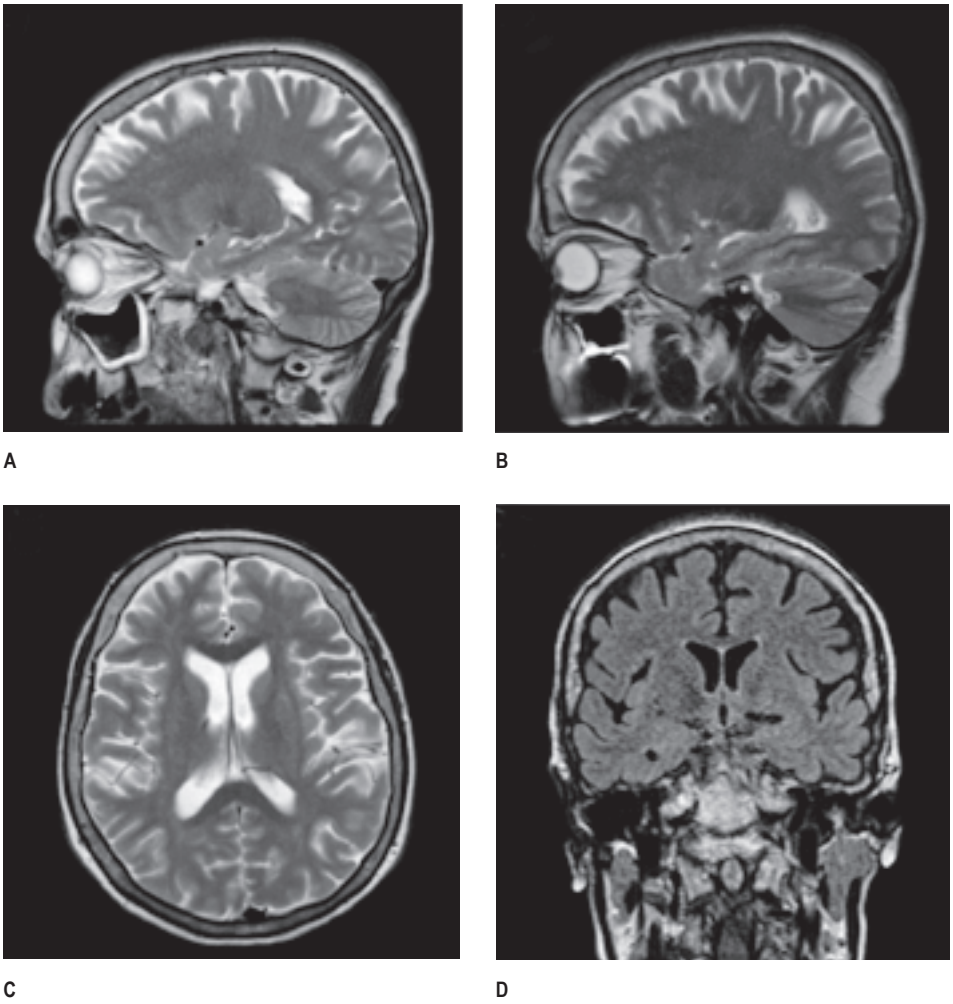
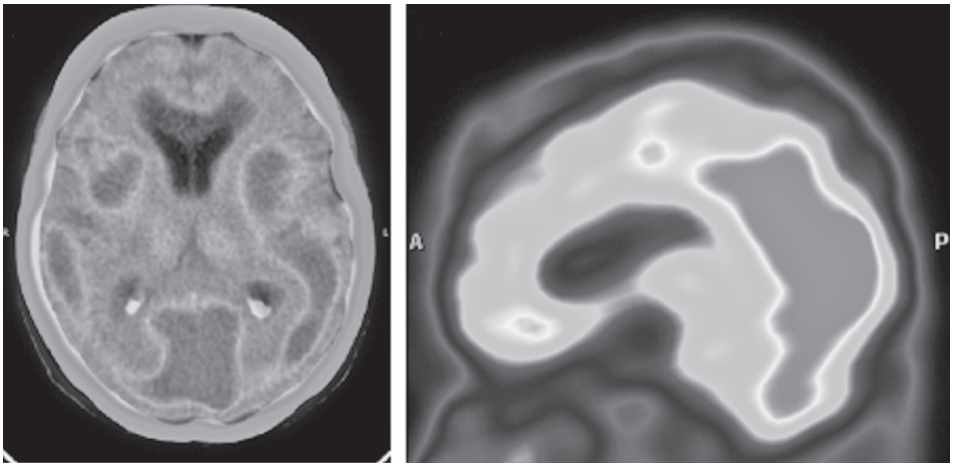


Figure 1. **MRI of the brain: A – sagittal T2-weighted image of the left hemisphere; B – sagittal T2-weighted image of the right hemisphere; C – axial T2-weighted image; D – coronal FLAIR image**

predominantly in frontal lobes (Figure 1). In EEG rare theta waves in the frontal derivations occurred. Tc-99m-HMPAO SPECT/CT proved relative hypoperfusion in the frontal and anterior parts of temporal lobes (Figure 2). Cerebrospinal fluid (CSF) was collected. β-amyloid 1-42 was not decreased, both β-amyloid 1-42 / β-amyloid 1-40 ratio and the level of tau protein were normal.

On the basis of the clinical data and results of the diagnostic tests we diagnosed probable bvFTD according to the criteria [4]. Venlafaxine at the initial daily dose of



A B

Figure 2. **SCEPT image of the brain: A – axial SPECT/CT fused image; B – sagittal SPECT image**

75 mg was recommended. The patient was directed to the neurological and cognitive rehabilitation. Regular psychogeriatric care was recommended.

Discussion

In this case the first reported symptom was gait disturbance. Bilateral pyramidal syndrome suggested the spinal cord disease, therefore the initial diagnostic was aimed at this direction. However, lack of both spinal sensory deficit, bladder and bowel dysfunction reduced the probability of spinal disease, but it could not be excluded. Behaviour and personality changes were treated as a consequence of motor disability progression. It was important to take neurodegenerative process into consideration in differential diagnosis. Psychological and neuropsychological examination proved behaviour changes and executive functions impairment specific for bvFTD.

Clinical presentation of this disease is heterogeneous. Abnormalities in the neurological examination at the early stage of bvFTD are rare [1]. As the disease progresses primitive reflexes, incontinence and parkinsonism may emerge [1, 5]. The signs of motor neuron disorder may also occur [1, 2]. Significant gait and posture reflexes disturbances emerge at the late stage of the majority of neurodegenerative dementia syndromes [6, 7]. However, it is not observed at the early stage. The correlation between prefrontal cortex functions and gait impairment was noticed in patients with dementia syndrome as well as in nondemented elderly subjects [7]. In the course of prefrontal cortex dysfunction, irrespectively from the aetiology, gait apraxia may be one of the symptoms besides behavioural and cognitive changes. Therefore it is well-founded to

state that gait is not an automatic motor activity independent of cognitive processes. Due to the prefrontal cortex disorder engagement in the clinical picture of bvFTD, the background of possible gait impairment seems to be clear. Patients suffering from bvFDT demonstrated worse gait parameters such as speed and stability compared to healthy and AD subjects [6]. However, it is still minor symptom of the disease and is not included in the diagnostic criteria. Reports of the patients suffering from bvFTD with gait disturbances as an essential symptom of the disease are not available.

Another possible cause of walking difficulties in the course of bvFDT is motor neuron disease (MND) which occurs in some patients [8]. Currently, common neuropathological and genetic factors underlying both FTD and MND are emphasised. The conception of FTD-MND spectrum became particularly relevant after the discovery of C9orf72 mutation which accounts for 40% of familial MND, 10% of sporadic MND, 5% of sporadic FTD and even 80% of familial FTD-MND cases [8]. In case of our patient the signs of upper motor neuron disorder were present. Lower motor neuron symptoms are typical for FTD [1], but these did not occur in the patient. However, gait disturbance was disproportionately severe in comparison with mild spastic paraparesis, suggesting both apraxia (predominantly) and upper motor neuron disorder engagement in walking difficulties.

The last relevant factor affecting gait in bvFTD is parkinsonism. It may occur in the late stage of the disease [1, 5] or earlier in case of frontotemporal dementia and parkinsonism associated with chromosome 17 (FTDP-17) [1]. Nevertheless, there were no evident extrapyramidal signs in this case and the character of gait was not parkinsonian, then parkinsonism was unlikely to be the cause of walking difficulties.

Brain MRI in our patient revealed moderate supratentorial atrophy predominantly in frontal lobes. This pattern is one of four patterns of atrophy distinguished in bvFTD – two with predominance of frontal atrophy and two with predominance of temporal atrophy [9]. Results of researches assessing the correlation between location of cerebral atrophy and clinical picture of the disease are inconsistent. Some researchers suggest faster progression in patients with predominance of frontal atrophy [1, 9]. There is no data on association between gait disturbances and the pattern of atrophy. As we mentioned prefrontal cortex functioning affects gait, then relation between frontal atrophy dominance and gait ability in bvFTD may be presumed. It requires further studies.

Other diagnostic tests were performed for further evaluation and to confirm the diagnosis. EEG revealed few theta waves in the frontal derivations. An absence of slow waves was regarded as a significant differentiating feature between FTD and AD in the past [10], however, studies conducted later did not confirm this correlation [11]. Currently EEG is not relevant for the diagnosis of bvFTD. Nevertheless, in this case slow waves occurrence could indicate a potential neurodegenerative process engagement irrespectively of the type. Frontal and anterior temporal hypoperfusion on SPECT as well as frontal and anterior temporal hypometabolism on PET are included

in bvFTD diagnostic criteria [4]. In this case frontal and anterior temporal perfusion was significantly lower than perfusion in other cerebral regions, therefore it increases the probability of bvFTD. Until now no significant biomarker for FTD diagnosis was discovered. The level of tau protein and β-amyloid 1-42 in CSF is used for differentiation between AD and other dementia syndromes including FTD [12]. Studies revealed normal CSF levels of tau and β-amyloid 1-42 in FTD. However, correlation between CSF level of tau and both more severe course of FTD and greater atrophy of left temporal lobe was noticed [13]. In our patient the level of β-amyloid 1-42 was not decreased and the level of tau protein was normal.

Despite gait disturbance dominance and pyramidal syndrome in the clinical picture, proper anamnesis and neuropsychological assessment revealed that the patient meets the diagnostic criteria for possible bvFTD. Diagnostic tests which were performed increased the probability of a proper diagnosis.

Conclusions

Behavioural changes and executive function impairment, despite heterogeneity, are the major symptoms of bvFTD. However, other symptoms, including gait disturbances, may significantly interfere with the clinical picture causing additional difficulties in proper diagnosis of the disease which is underdiagnosed in fact. Anamnesis gathered accurately with patient and his family and further psychological and neuropsychological assessment are essential for the diagnosis. It is worth to consider bvFTD in cases of unexplained gait abnormalities.

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