https://doi.org/10.22364/lmahc.fd.24.03

Frontotemporal Dementia and Amyotrophic Lateral Sclerosis Associated with *C9orf72* Gene Mutation: Case Report and Literature Review

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Timely differential diagnosis of neurodegenerative disorders remains a clinical challenge. The cognitive profile and other clinical symptoms are often nonspecific, overlapping, and may occur in various pathologies. Even advanced diagnostic methods (imaging and cerebrospinal fluid biomarkers) are sometimes not sufficient to differentiate frontotemporal degeneration from Alzheimer's disease. Genetic counselling and testing is becoming increasingly important in clinical practice, but is still limited due to cost and late results. The presented clinical case illustrates that the accurate description of clinical signs and symptoms, evaluation of anamnesis data, interpretation of the course of the disease, monitoring of the cognitive and neurological status, remains an important, perhaps even a key part of the diagnostic process of neurodegenerative dementias.

Keywords: cognitive impairment, differential diagnosis, C9orf72 gene mutation

Introduction

Despite improving diagnostic capabilities in Lithuania, diagnosing and treating cognitive disturbances remain a major challenge. Accurate identification of the first symptoms and their dynamics is crucial for timely diagnosis and treatment, preserving cognitive function and independence, while alleviating non-cognitive symptoms. However, patients often do not seek treatment at an early stage, and as the disease progresses, they can no longer identify the symptoms themselves. Relatives of the patients likewise do not seek help immediately after noticing the first signs and in most cases not until the patient's cognitive and behavioural changes begin to cause difficulties. On the other hand, establishing a diagnosis is a complex and time-consuming process, and the final diagnosis is often not made until the patient has been observed for months or even years. In recent years, the incidence of dementia has been increasing rapidly due to longer life expectancy. In 2019, the Alzheimer Europe organization presented

data in the yearbook *Estimating the Prevalence of Dementia in Europe*, according to which the number of people with dementia will double by 2050 compared to 2019 [1]. This compels the search for new, simpler, more accessible options for early diagnosis of cognitive impairment, as well as creation and development of national dementia management strategies, increasing public and specialist awareness of dementia. When treating individual patients, it is crucial to assess the history critically and comprehensively, to evaluate the combination of symptoms, clinical signs, and diagnostic test results. It is also essential to follow the defined diagnostic criteria and revise the diagnosis dynamically as new data is discovered.

We present a clinical case investigated and observed at the Department of Neurology of the Hospital of Lithuanian University of Health Sciences (HLUHS) Kauno klinikos, which reveals the diverse symptoms of frontotemporal dementia (FTD), the complexity of its differential diagnosis and the challenges in the practical work of a neurologist.

1. Clinical case

At the beginning of 2021, a 69-year-old man, urged by his wife, came to the Outpatient Department of Neurology at HLUHS Kauno klinikos for a neurological consultation. The patient himself did not indicate any clear complaints. According to his wife, the patient's condition had been worsening for about 6 months: his memory had deteriorated (he kept forgetting the keys, and left the water running), it was often difficult for him to find the right words, he no longer knew how to use the TV remote control, and often confused dates. The patient's coordination, perception of space, and distance estimation were disturbed (the patient was no longer able to drive the car to the garage), he became irritable, found it difficult to assess his capabilities and risks (the patient walked on foot to a friend who lived 8 kilometres away). The wife emphasized that her husband's character had changed, his eating and hygiene habits had deteriorated, and the patient had become less independent in the household. The behavioural changes were more noticeable in the evening. At that time, the patient was taking ginkgo medication and Pramiracetam. The patient had type 2 diabetes mellitus and myocardial infarction. There was no history of neuro-infections, brain injuries, or mental disorders. The man had 8 years of education and worked as a brigade leader. The patient's maternal cousin had Alzheimer's disease (AD).

During the neurological examination, the patient was observed to have poor speech, had difficulty fixing his sight upon the object of observation, and did not immediately understand all commands. No other focal neurological or extrapyramidal symptoms were found. The patient was consulted by a psychiatrist. During the examination, the patient was conscious, correctly aware of himself,

and partly in place and time. He was available for meaningful verbal contact but did not answer all questions correctly, frequently questions had to be repeated and simplified. The patient was a little tense during the interview. The mood was euthymic, emotions lacked adequacy. The thinking was slow, concentration and memory were impaired. Criticism regarding the condition was formal. Psychological assessment of cognitive functions with specialized tests showed reduced working memory capacity, impaired memory retention and ability to transfer to long-term memory (Mini-Mental State Examination (MMSE) score was 21 points, Blessed Dementia Scale score was 9 points). The condition was assessed as mild dementia syndrome. Tiapride was prescribed to correct mental and behavioural symptoms. Extended neuropsychological assessment of executive functions, verbal fluency, and other frontal functions was not possible at the time.

Laboratory test analysis of peripheral blood showed no significant abnormalities, chronic infections were also excluded. Carotid artery ultrasound revealed moderate atherosclerotic lesions without hemodynamically significant stenosis. An arachnoid cyst in the right front-temporal region, front-temporal hypoplasia/atrophy, asymmetric communicating hydrocephalus, asymmetric atrophy of the hippocampal heads, and a possible small cavernoma in the right parietal lobe was revealed by brain magnetic resonance imaging (MRI). No serum antibodies associated with paraneoplastic neurological syndromes were detected. ApoE ε 2/4 genotype was identified. Differentiating the causes of neurodegenerative dementia (Alzheimer's disease or FTD), a brain positron emission tomography (PET) was performed, but the data were not sufficient for classic AD. Areas of hypometabolism in the front-temporal lobes corresponded to cystic lesions and hypoplastic changes.

Diagnostics were performed on an outpatient basis and took about 3 months. At the follow-up visit, the patient's wife reported deterioration in the patient's condition: memory impairment was evident, the patient lost the ability to use tools he would previously use with ease, and, above all, behavioural changes progressed: he was getting irritated very easily, became aggressive at least once a week, could no longer eat properly (he would cram two eggs in his mouth and not chew), was not able to name objects and could not understand the meaning of words. The patient himself had no health complaints and disagreed with the information provided by his wife. Since the patient lived in another region of the country, he was hospitalized at the Department of Neurology in a planned manner for lumbar puncture and cerebrospinal fluid (CSF) examination. Cytological and biochemical examination of the CSF was non-pathological. Samples were taken for AD biomarkers (amyloid beta and tau protein). It is worth mentioning that when the patient was in the hospital, he became disoriented, gathered his belongings, and left the department arbitrarily. While waiting for the results of the AD biomarkers, Donepezil was prescribed to maintain cognitive function and Tiapride was continued at the doses recommended by the psychiatrists.

Five months after the first visit and neuropsychological evaluation, the patient has been consulted again on an outpatient basis. Rapid regression of cognitive functions and marked impairment of daily functions were observed (MMSE – 7 points, Blessed Dementia Scale – 23 points). Also, the brain MRI was repeated, in which the congenital arachnoid cyst and moderate hypoplasia of the adjacent parts of the brain were observed, which were unchanged compared to the previous examination. In addition, moderate atrophic lesions, more pronounced in the frontal lobes, were seen, which did not allow the exclusion of FTD diagnosis. However, the pronounced hippocampal atrophy also did not permit to exclude the diagnosis of AD. The CSF AD biomarker profile was ambiguous, with decreased (positive) Abeta42, a positive Abeta42 and Abeta40 ratio, negative pTau181, and tTau – at the upper range limit. The diagnosis of atypical AD was formed, and it was decided to investigate other genetic factors. Due to poor tolerance, agitation, and rapid cognitive decline, Donepezil was substituted with Memantine. Quetiapine was additionally prescribed for sleep induction, anxiety and behaviour control.

At the end of 2021, the patient's condition worsened: he became irritable, threatened to strangle his wife, lost control of urination, disregarded personal hygiene, did not wash himself, and did not brush his teeth. He was often at a loss for words, unable to carry out a sequence of actions – he would mix up the order of his clothes and could no longer cross himself. He had a strong craving for sweets – he would stuff his mouth full when eating, unable to chew or swallow, and had to be supervised to ensure that he would not choke. The wife noticed that his muscles twitched when he slept, and that he moved his leg involuntarily ("my husband sleeps and his muscles twitch"). During the examination, the patient smiled inadequately, his speech was marked by echolalia components and perseveration of movements. During the neurological examination, multiple fasciculations were observed in the shoulder strap and chest muscles, and the patient's toes and feet twitched. No extrapyramidal symptoms were noticed. The patient was poorly oriented in time and space. Difficulty in following instructions, markedly impaired concentration, and impaired calculation and copying skills were observed.

Considering frontotemporal dementia with concomitant amyotrophic lateral sclerosis (ALS), an electroneuromyography study was performed – signs of focal demyelination of the sensory and motor fibres of the right median nerve in the carpal tunnel were observed. The responses of the other tested peripheral nerves were within normal limits. Single fasciculations without symptoms of acute denervation were registered in the examined limb muscles. The patient was consulted by a geneticist, and it was agreed to test for the most common dementia-related gene mutations. Disappointingly, the results were obtained only a few months later – the new-generation sequencing method (CeGaT, Germany) identified the c.-45+163G_4C_2 repetitive sequence of the *C9orf72* gene. This confirmed the final clinical diagnosis of FTD + ALS, but the patient's condition was already too severe for an outpatient consultation. As the disease progressed, the patient died due

to thromboembolic complications and progressive respiratory failure 22 months after the initial visit with a complaint of cognitive impairment to the neurologist.

2. Frontotemporal dementia and amyotrophic lateral sclerosis associated with *C9orf72* gene mutation

Frontotemporal dementia is a rare form of dementia caused by degeneration of the anterior temporal and frontal lobes. This disease usually manifests in a progressive decline in executive functions, behaviour, and language [2, 3]. There are several main clinical subtypes of FTD: behavioural variant, semantic dementia, and primary progressive aphasia. Behavioural type is the most common subtype, and it is characterized by behavioural and personality changes that occur in the early stages of the disease. Such changes can manifest in apathy, loss of empathy, impulsivity, and reduced judgment. Most patients are unaware of their behavioural changes. Delusions, hallucinations, psychotic and anxiety episodes are also characteristic of this illness [4, 5].

Symptoms of FTD often occur in association with motor neuron disease. About 15% of patients with frontotemporal dementia show symptoms of amyotrophic lateral sclerosis, and up to 50% of patients with ALS have varying degrees of cognitive deficits [6]. Worldwide, the *C9orf72* gene mutation is associated with FTD (especially the behavioural variant) and ALS [7]. Alterations in this gene are inherited in an autosomal dominant pattern, and ALS plus FTD patients have a multiple repeat sequence in G_4C_2 [5, 7].

FTD and ALS associated with the *C9orf72* gene mutation can occur at any age, most commonly around 50–60 years [8]. In these cases, the clinical symptoms of amyotrophic lateral sclerosis do not have significant differences from the classical variant of the disease. In *C9orf72*-related ALS, spinal onset (e.g. muscle weakness and changes in muscle tone, spasticity, fasciculations) are more common observed than bulbar onset (including speaking and swallowing functions) (54%>39%) [9]. Cognitive and behavioural impairment occurs more often in individuals with ALS, who have been diagnosed with a mutation in the *C9orf72* gene, than in the classic form of the disease without this gene [10].

In addition to the neurological examination, neuropsychological assessment of the patient, and genetic testing for the *C9orf72* gene and its number of G_4C_2 repeated sequences, various neuroimaging testing are also important for clinical diagnosis. In the *C9orf72*-FTD form of the disease, the atrophy observed on brain MRI is exceptionally symmetrical and generalized but develops slowly. Atrophy in the frontal and temporal cortex may be observed, as well as in the cerebellum and subcortical structures (e.g., the thalamus) [7, 11]. During the PET scan, the areas of hypometabolism match with the areas of atrophy detected on MRI, but it is important to note that the PET scan can detect abnormalities about 10 years before the symptoms may appear [11].

In FTD cases, in the cerebrospinal fluid (CSF) pathological aggregates of tau, TDP-43, or FET proteins are detected while in ALS superoxide dismutase-1 (SOD1), TDP-43, or FET proteins may be found in CSF. Abnormal TDP-43 aggregates are found in about 50% of FTD cases and 95% of ALS cases [12]. Moreover, TDP-43 has been found to be associated with the *C9orf72* gene mutation and its repeated sequence expansion in both frontotemporal dementia and amyotrophic lateral sclerosis [13].

C9orf72-FTD/ALS are typically rapidly progressive neurodegenerative diseases, and survival from the onset of symptoms often lasts only a few years (median 6.4 years) [14]. The treatment and follow-up of these patients require a multidisciplinary team consisting of a neurologist, nurses with special training, a pulmonologist, a physical therapist, a speech and language therapist, an occupational therapist, a psychologist, a nutritionist, a social worker, and a genetic consultant [5]. Treatment depends on the presenting clinical symptoms. However, therapeutic options are currently limited and there is no treatment that can fundamentally alter the course of ALS or FTD caused by changes in the *C9orf72* gene. The main treatment for ALS is riluzole and for FTD the medications for mental and behavioural symptom correction [15]. In 2017, the free radical-scavenger drug edaravone was approved by U.S. Food and Drug Administration (FDA) [16] for patients with ALS. Unfortunately, no single treatment can improve cognitive or motor impairment, but riluzole and edaravone can slightly slow the progression of ALS [15].

Conclusions

The literature shows that frontotemporal dementia and amyotrophic lateral sclerosis are often diagnosed together. This clinical case reveals that the combination of these pathologies is difficult to detect even with modern diagnostic methods, and it has to be differentiated from other neurodegenerative diseases. The ability of the patient and their relatives to communicate and accurately describe the symptoms and experienced difficulties, the doctor's professionalism in asking essential questions, and the time taken from the onset of symptoms to the time when the patient is referred to a diagnostic and treatment centre, is of a great importance. A standardized diagnostic and treatment protocol, interpreted and applied the same way throughout Lithuania, or even the whole Baltic region, would be an extremely valuable tool in the care of neurodegenerative diseases, and, as societies age, this should become a priority for health care system. Repeated neurological examinations and monitoring of cognitive function dynamics are necessary to provide comprehensive care as the disease progresses. Although there is no effective treatment for this disease, it is important to make the diagnosis as early as possible to be able to control the symptoms, maintain the patient's dignity and ensure the quality of life by all available means.

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