Psychiatr. Pol. ONLINE FIRST Nr 159: 1–7
Published ahead of print 20 January 2020
www.psychiatriapolska.pl
ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
DOI: https://doi.org/10.12740/PP/OnlineFirst/114122

Early onset Alzheimer's disease – a case study

Beata Łabuz-Roszak[1], Magdalena Torbus-Paluszczak[2], Janusz Becelewski[3], Michał Becelewski[1], Paweł Dobrakowski[4], Krystyna Pierzchała[2]

[1]Department of Basic Medical Sciences, Faculty of Health Sciences in Bytom, Medical University of Silesia in Katowice

[2] Department of Neurology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice

[3] Upper Silesian Rehabilitation Centre "Repty", Tarnowskie Gory

[4] Institute of Psychology, Humanitas University in Sosnowiec

Summary

Dementia syndromes constitute problem not only for the elderly. Early-onset dementia (EOD) starts below the age of 65 years. It accounts for 4–10% of all cases of dementia. EOD has significant psychosocial consequences because it affects people in their most productive years of life, with numerous family, professional and social responsibilities. There are many diseases that have been identified as the cause of the EOD. Among them, the most common are Alzheimer's disease, vascular dementia, fronto-temporal dementia, Lewy body dementia, traumatic brain injury, alcohol related dementia, Huntington's disease, Parkinson's disease, mixed dementia, Creutzfeldt-Jakob disease and Down syndrome. Most studies have demonstrated Alzheimer's disease as the most common etiology of EOD. The article presents the case of a 33-year-old patient hospitalized in the Department of Neurology in Zabrze, with cognitive dysfunction, speech disorders and features of Parkinson's extrapyramidal syndrome that have been progressing for about 15 months. The MR of the head revealed cortical and subcortical atrophy, especially in parietal and temporal lobes. The cerebrospinal fluid examination showed decreased level of β-amyloid and significantly elevated level of H-tau. The patient was diagnosed with early-onset Alzheimer's disease, which was confirmed by genetic testing – the sequence change was identified in the gene for presenilin 1 in a heterozygous system.

Key words: dementia, early-onset dementia, Alzheimer's disease

Introduction

Dementia syndromes constituted a significant health problem for older people, but they also occur in young adults and middle-aged people. Early-onset dementia (EOD) accounts for 4–10% of dementia syndromes and is defined as dementia starting below the age of 65 years [1]. EOD has catastrophic psychosocial consequences because it affects people in their most productive years of life with family responsibilities. It is estimated that 67–98 cases per 100,000 people aged 45–64 suffer from EOD [2]. The number of people with EOD is constantly increasing, and the disease is becoming a significant clinical problem.

There are many diseases and disorders that have been identified as the cause of EOD. These include Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal lobe dementia (FTLD), dementia with Lewy bodies (DLB), traumatic brain injury (TBI), alcohol-related dementia (ARD), Huntington's disease (HD), Parkinson's disease dementia (PDD), mixed dementia (MD), Creutzfeldt-Jakob disease (CJD), and Down syndrome (DS). Most studies have demonstrated AD as the most common etiology of EOD (prevalence ratios ranging from 1 to 66.7%). The second place is for VaD (6.1–44%), whereas FTLD constitutes the third cause (3–26.6%) [2]. DLB is rare in young people (1–7%). On the other hand, TBI is common in young people (1.8–24%) [2]. In turn, ARD is found in 1–14% of cases of EOD, HD – in 1–16.6%, and PDD – in 1–4% [2]. One should also remember about other, sometimes reversible forms of EOD, such as inflammatory disease (multiple sclerosis, neurosarcoidosis, paraneoplastic and autoimmune limbic encephalitis), infectious diseases (dementia in the course of HIV infection, nerve syphilis, Whipple's disease and progressive multifocal leukoencephalopathy) and toxic disorders (alcohol, drugs and poisoning with heavy metals). One should also not forget about searching for metabolic diseases such as Wilson's disease, anemia associated with vitamin B12 deficiency, Gaucher disease, Niemann-Pick disease, Lesch-Nyhan syndrome or metachromatic leukodystrophy [3].

A case report

A 33-year-old patient with progressive memory and behavioral disturbances, progressing for about 15 months, was admitted in June 2014 to the neurological department for diagnosis. 3 months earlier the patient also noticed problems with writing and reading. In the last month before admission, speech disorders and movement disorders, mainly tremor of the limbs, additionally appeared. Until that, the patient has not been diagnosed for this reason. Interview for risk factors for cardiovascular diseases as well as other chronic diseases was negative. The patient was a smoker (20 cigarettes per day for 15 years), but denied the abuse of alcohol, as well as taking any other stimulants. He did not take any medications chronically. He worked as a security officer, was divorced, and had a son and a daughter. He has recently lived with his mother.

In the neurological examination at admission, the patient had normal autopsychic orientation but allopsychic orientation was disturbed, his behavior was inadequate to

the situation; his speech was blurred and dysarthric. In addition, there was an increased extra-pyramidal muscle tone in the right limbs ('gear' type), asymmetry of tendon reflexes P>L, resting tremor and ataxia in the lower limbs, presence of pathological symptoms (Rossolimo's sign, Hoffman's sign, Jacobsohn's finger flexion sign, and Babinski sign) bilaterally. Extrapyramidal-pyramidal syndrome with accompanying cerebellar syndrome was found. Laboratory tests (complete blood count, glucose, CRP, creatinine, Na, K, cholesterol, triglycerides, TSH, fT3, fT4) and abdominal ultrasound showed no deviations. The level of copper and ceruloplasmin in the serum was normal. MRI of the head indicated cortical and subcortical atrophy, especially in the area of parietal and temporal lobes. No pathological signals were found after intravenous administration of the contrast agent. Areas of pathologically limited diffusion were not found. The supratentorial ventricular system was undisturbed, moderately wide, asymmetric (L>P), the aqueduct and the fourth chamber were normal. The lumbar puncture showed normal cerebrospinal fluid (pleocytosis 4/3, protein 445 mg/dl, glucose 62 mg/dl, oligoclonal bands not present, normal proteinogram). The 14-3-3 protein was also not found in the cerebrospinal fluid. In the EEG, a basal activity consisting of low-voltage rapid beta activity in the temporo-occipital region was seen with a significant admixture of the activity of 5–6 Hz theta in the temporal region with periodic right-sided lateralization.

The following tests were performed: *the Mini Mental State Examination* (MMSE), *Short Test of Mental Status* (STMS) and *Clock Drawing Test* (CDT). In the MMSE, the patient scored 16 points, after correction 18 points [4]. In addition to recalling, memorizing and attention disorders, linguistic functions and constructional praxis were significantly reduced. The study of language functions has been extended by the naming test of *the Addenbrooke's Cognitive Examination* (ACE-R) [5]. The patient scored 10/12 points, the score was decreased due to the paraphasias. A simplified test of connecting dots (created on the basis of *the Trail Making Test* – TMT B) from the MoCA questionnaire was also used [6]. There were irregularities in the switching of attention, the path was drawn very slowly, the patient made one mistake. CDT was made in the version presented by Hausz-Piskorz and Buczkowski [7]. In the first attempt, a long performance time was found, the second attempt was correct, in the third attempt the patient repeated the layout of the clues from the previous clock. The STMS, in which the patient obtained 19 points, revealed acquired memory disorders. Orientation and abstract thinking were well preserved. During the test, slow speed of reading and writing as well as typing with typing errors was noticed. The consultant psychologist observed a slowdown in the rate of psychomotor reactions and forced crying. He found a significant degree of cognitive dysfunction (moderate dementia) and the presence of anxiety and depression in the course of the illness.

Relevant data on family burden were obtained by collecting an interview with the patient's mother. The father of the patient, as well as uncle, aunt, grandmother and great-grandfather – on his father's side – all died before the age of 40, with a clinical picture of severe dementia. In each of them, the first symptoms of the illness occurred between 30 and 34 years of age, and neuroimaging studies performed in some of them showed a significant atrophy of the brain. The patient was referred to the Department

of Neurology at the Institute of Psychiatry and Neurology in Warsaw for further diagnosis. In the cerebrospinal fluid collected there, a significantly reduced level of β-amyloid (268 pg/ml; cut off point for AD < 609 pg/ml) and a significantly elevated level of H-TAU (1,104 pg/ml; cut off point for AD > 277) and phospho-TAU (139.8 pg/ml; cut off point for AD > 55) were detected. The final confirmation of early-onset Alzheimer's disease was a genetic test – the alteration of the presenilin 1 (PSEN 1) gene sequence in the heterozygous system was identified; g.44656A> T (reference sequence: AF109907.1), p.I213F, described in the Alzheimer Disease & Frontotemporal Dementia Mutation Database[1] as a mutation causally associated with AD. Genetic testing was performed at the Institute of Experimental and Clinical Medicine of the Polish Academy of Sciences. The patient was under the care of the neurological outpatient clinic. Progressive memory, speech and motor disorders have been observed. In addition, swallowing disorders appeared. In May 2015, psychological consultation was carried out, and the patient did not give his consent to next ones. Compared to the first examination, in the MMSE, the time orientation deteriorated (the corrected result was 17 points). The STMS revealed deterioration of abstract thinking (15 points). In CDT, incorrect performance in all attempts, lines instead of hours, single arm or lack thereof, perseveration (Figure 1).

The psychologist observed the increased difficulty in performing CDT also due to problems with holding a pen. Despite the negation of suicidal thoughts during the examination, the patient reported the willingness to consider suicide if the present symptoms were to correspond to the disease that affected his father.

During one of the appointments in 2016, the patient was diagnosed with epilepsy (based on the interview collected from the mother – the patient had two general epileptic tonic-clonic seizures), valproic acid was included in the treatment with a good effect. The last visit to the Neurological Outpatient Clinic took place in October 2017. At that time, the patient was diagnosed with total sensorimotor aphasia and spastic tetraparesis (RUE – grade II, LUE – grade II, LLE – grade I, RLE – grade I according to the Lovett scale) with bilateral (+) pathological symptoms in the upper and lower extremities. A few months before this appointments, the patient stopped walking, became completely dependent on the other people (he remained under the care of his mother). He died in December 2017.

Discussion

The described case of a 33-year-old patient with a family history of early-onset Alzheimer's disease may be interesting for the practice of physicians due to the rare occurrence of this disease. Besides, so far few studies on EOD have been conducted.

Most epidemiological studies of dementia are focused on patients over the age of 60 years. According to Harvey et al. [8], the incidence of dementia in the population aged 30–64 was 54 cases per 100,000 people in the United Kingdom. In turn, Ikejima et al. [9] found that in Japan prevalence rate was 42.3 per 100,000 people aged between

[1] http://www.molgen.ua.ac.be/ADMutations/.

20 and 64 years. The *World Alzheimer's Report* 2009 stated that 2–10% of all dementia cases begun before the age of 65 [10]. Similarly to late-onset dementia, also in EOD, incidence ratios have been increasing with age.

AD is the leading cause of EOD. The neuropathological features of the disease are the occurrence of extracellular amyloid deposits in the form of amyloid plaques and neurofibrillary degeneration [11]. The etiology of AD, despite many years of research, is still not fully understood, but probably it is the result of the coexistence of both genetic and environmental factors. According to many authors, the younger the age of occurrence of EOD is, the more likely the participation of genetic factors is, although often coexistence of other diseases may cause that the person at risk of late-onset dementia experiences symptoms at younger age [12]. Rare mutations of the amyloid precursor protein (APP) and within the presenilin 1 (PSEN 1) and presenilin 2 (PSEN 2) genes were found in familial early-onset Alzheimer's disease. These mutations are characterized by strong penetration, they are usually inherited in an autosomal dominant manner and cause an increase in the relative level of the Aβ42 peptide, followed by its aggregation and early onset of the disease, which starts in the fourth or fifth decade of life [11].

The mutation identified in this patient has already been described and placed in the Alzheimer Disease & Frontotemporal Dementia Mutation Database as a mutation associated with Alzheimer's disease. This mutation was previously found in one Caucasian patient – a Pole aged 33 [13]. Other data on the phenotype accompanying this mutation are not described in the database. In 2007, a PSEN 1 gene mutation (L250F) associated with early-onset Alzheimer's disease was identified in the large First Nation family living in dispersed communities in British Columbia, Canada. It turned out that this rare disease is a 100% penetrant with a typical beginning of the disease between 47 and 59 years of age. Currently, one hundred of members of the family at risk of the disease are known [14].

Early-onset dementia is characterized by rapid progress compared to the dementia of the elderly age [15]. Early-onset Alzheimer's disease is also characterized by a rapid progression of cognitive impairment. In addition, pyramidal and extrapyramidal symptoms, myoclonus and epileptic seizures are very common. Linguistic and visual-spatial disorders are clearly marked [16]. However, according to Kay et al. [17], in some patients the course of the disease does not differ from late-onset dementia. Survival of patients with early-onset dementia, with a beginning between 45 and 65 years of age, is usually around 6 years.

The patient described by us survived 5 years from the onset of the first symptoms (3.5 years from the diagnosis). The disease was also characterized by a rapid course and rich symptomatology. The patient had pyramidal, extrapyramidal and cerebellar symptoms as well as epileptic seizures. As it resulted from the mother's report, the course of the disease of the patient's father was similar.

Recapitulation

Due to the fact that EOD concerns young people, in the procreation period and professionally active, it constitutes a significant medical and social problem. Nowadays, the number of EOD diagnoses has been increasing because of better diagnostic possibilities. EOD requires more and more intensive research on modern diagnostics and effective treatment.

References

1. Levine DA. *Young-onset dementia unanswered questions and unmet needs*. JAMA Intern. Med. 2013; 173(17): 1619–1620.
2. Harvey RJ, Rossor MN, Skelton-Robinson M. *Young onset dementia: Epidemiology. Clinical symptoms, family burden, support and outcome*. London: Dementia Research Group; 1998.
3. Kuruppu DK, Matthews BR. *Young-onset dementia*. Semin. Neurol. 2013; 33(4): 365–385.
4. Mungas D, Marshall SC, Weldon M, Haan M, Reed BR. *Age and education correction of Mini Mental State Examination for English and Spanish speaking elderly*. Neurology. 1996; 46(3): 700–706.
5. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. *The Addenbrooke's Cognitive Examination Revised (ACE-R): A brief cognitive test battery for dementia screening*. Int. J. Geriatr. Psychiatry. 2006; 21(11): 1078–1085.
6. Gierus J, Mosiołek A, Koweszko T, Kozyra O, Wnukiewicz P, Łoza B, Szulc A. *The Montreal Cognitive Assessment 7.2 – polish adaptation and research on equivalency*. Psychiatr. Pol. 2015; 49(1): 171–179.
7. Hausz-Piskorz B, Buczkowski K. *Diagnostyka i leczenie choroby Alzheimera w warunkach praktyki lekarza rodzinnego*. For. Med. Rodz. 2013; 7(4): 198–207.
8. Harvey RJ, Skelton-Robinson M, Rossor MN. *The prevalence and causes of dementia in people under the age of 65 years*. J. Neurol. Neurosurg. Psych. 2003; 74(9): 1206–1209.
9. Ikejima C, Yasuno F, Mizukami K, Sasaki M, Tanimukai S, Asada T. *Prevalence and causes of early-onset dementia in Japan: A population-based study*. Stroke. 2009; 40(8): 2709–2714.
10. Prince M, Jackson J. *World Alzheimer's Report 2009*. London: Alzheimer's Disease International; 2009.
11. Maeyux R, Stern Y. *Epidemiology of Alzheimer's disease*. Cold Spring Harb. Perspect. Med. 2012; 2(8): a006239.
12. Masellis M, Sherborn K, Neto PR, Sadovnick DA, Hsiung GY, Black SE et al. *Early – onset dementias: Diagnostic and etiological considerations*. Alzheimers Res. Ther. 2013; 5(Suppl 1): S7.
13. Zekanowski C, Styczynska M, Peplonska B, Gabryelewicz T, Religa D, Ilkowski J et al. *Mutations in presenilin 1, presenilin 2 and amyloid precursor protein genes in patients with early-onset Alzheimer's disease in Poland*. Exp. Neurol. 2003; 184(2): 991–996.
14. Cabrera LY, Beattie BL, Dwosh E, Illes J. *Converging approaches to understanding early onset familial Alzheimer disease: A First Nation study*. SAGE Open Med. 2015; 3: 2050312115621766.
15. Vieira RT, Caixeta L, Machado S, Silva AC, Nardi AE, Arias-Carrión O, Carta MG. *Epidemiology of early-onset dementia: A review of the literature*. Clin. Pract. Epidemiol. Ment. Health. 2013; 9: 88–95.

16. Miyoshi K. *What is 'early onset dementia?* Psychogeriatrics. 2009; 9(2): 67–72.
17. Kay DW, Forster DP, Newens AJ. *Long-term survival, place of death, and death certification in clinically diagnosed pre-senile dementia in northern England – follow – up after 8–12 years*. Br. J. Psychiatry. 2000; 177: 156–162.

Address: Beata Łabuz-Roszak
Department of Basic Medical Sciences
Faculty of Health Sciences in Bytom,
Medical University of Silesia in Katowice
41-902 Bytom, Piekarska Street 18
e-mail: broszak@sum.edu.pl