The report of p.Val717Phe mutation in the APP gene in a Hungarian family with Alzheimer's disease – a phenomenological study

Dénes Zádori MD, PhD*, Judit Füvesi MD, PhD*, Erzsébet Timár MD**, Emese Horváth MD, PhD§, Renáta Bencsik#, Noémi Szépfalusi*, Anita Must MD, PhD*, László Vécsei MD, PhD, DSc*¶, Mária Judit Molnár MD, PhD, DSc#, Péter Klivényi MD, PhD, DSc*

*Department of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary
**Department of Psychiatry, Kálmán Pándy County Hospital, Gyula, Hungary
§Department of Medical Genetics, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary
#Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Budapest, Hungary
¶MTA-SZTE Neuroscience Research Group, University of Szeged, Szeged, Hungary

Corresponding author:
Péter Klivényi MD, PhD, DSc
Department of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary
H-6725 Szeged, Semmelweis u. 6.
E-mail: klivenyi.peter@med.u-szeged.hu
Phone: +36-62-545-351
Fax: +36-62-545-597

Running head: Phenomenology of p.Val717Phe mutation

Acknowledgement

This study was funded by Hungarian Brain Research Program – Grant No. KTIA_NAP_13-A_II/17. Dénes Zádori and Anita Must were supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.

Abstract

Autosomal dominantly inherited exonic mutations in the amyloid precursor protein (APP) gene may provide a relatively homogeneous patient pool for future therapeutic studies. Accordingly, the report of newly diagnosed families with APP gene mutations may have a special relevance. This case study aims at the first detailed phenotypic description of the Val717Phe mutation in the APP gene apropos of the first detected Hungarian family with this mutation. The symptoms of the proband consisted of memory impairment, disorientation, reduced attention, language impairment, apraxia, seizure, myoclonus, tongue protrusion and **P**arkinsonism starting to develop at the beginning of her 40s. The other affected members of the family presented similar alterations. These clinical characteristics**, i.e., amnestic Alzheimer's disease phenotype with seizures, myoclonus and Parkinsonism,** mostly resemble that of caused by Thr714Ile and Ile716Phe mutations with an early onset and severe **symptoms and signs**. In addition to prognostic and future therapeutic aspects, the identification of these conditions may have a special importance with regard to presymptomatic genetic counselling as well.

Keywords: Alzheimer's disease; hereditary; amyloid precursor protein; Val717Phe mutation; phenotype

1. Introduction

Autosomal dominantly inherited Alzheimer's disease (AD) is characterized by early onset (under the age of 65 years) and accounts for approximately 0.5% of all AD cases[1]. The underlying genetic alterations include mutations in the presenilin-1 (PSEN-1), PSEN-2 and amyloid precursor protein (APP) genes and duplication in the APP gene, out of which APP gene mutations are responsible for 18% of these genetic cases with a wide geographical distribution[2] (http://www.molgen.vib-ua.be/ADMutations; http://www.alzforum.org/mutations). Although the clinical features of APP gene mutations may be heterogeneous (Suppl. Table 1), the most prevalent symptoms are memory impairment, disorientation, language disturbances, apraxia, myoclonus, seizures, dyscalculia, **P**arkinsonism, apathy, depressive mood and aggressive behavior[1] (Suppl. Table 1). The age of onset and disease duration are variable as well, with a typical onset in their 40s and 50s (range: 30-82 years of age) and 10 years of duration (range: 2-18 years), respectively (Suppl. Table 1). Although the site of the mutation and the type of amino acid change clearly seems to affect the clinical characteristics (Suppl. Table 1), there may be several other influencing factors as well. The report of new families is clearly relevant in terms of better understanding of disease characteristics. Accordingly, the aim of the current study is to provide a detailed phenotypic description of the first Hungarian patient diagnosed with familial AD caused by the Val717Phe mutation in the APP gene.

2. Clinical details

The 48-year-old female patient (the proband, III-2 in Fig. 1) was first admitted to our clinic with the aim of the diagnostic work-up of her unknown cognitive disorder in 2015. Her symptoms started to develop at the beginning of her 40s. Besides the progressive deterioration of her memory functions, serious language impairment, sparing the sensorial part in some

extent evolved as well. Two years back her speech was almost incomprehensible. An epileptic seizure was reported one month prior to her admission and her relatives also regularly recognized myoclonus-like jerks. There is not any other relevant condition in her case history. With regard to her family history, the presence of an autosomal dominantly inherited neurocognitive disorder can be identified (Fig. 1). Her elder sister (III-1), her mother (II-1), her aunt (II-2) and one of her uncles (II-3) died at the age of 48, 61, 61 and 65 years of their age, respectively. The symptoms of patient III-1 started to develop at the beginning of her 40s as well. Initially she presented memory problems during household activities. Later, serious progressive language impairment with considerably reduced communication abilities, unspecified movement disorder, myoclonus-like jerks, epileptic seizures and agitation with aggressive behavior also developed. The symptoms of patients II-1, II-2 and II-3 were very similar to that of patients III-1 and III-2, but the symptoms started to develop later, at the beginning of their 50s. Patient II-1 was bedridden following femoral bone fracture in her last 4 years. Patient II-3 presented only memory impairment and disturbance of consciousness for several years following the onset of these symptoms.

On examination, our female patient presented severe impairment of short-term memory, disorientation, reduced attention, severe motor dysphasia or apraxia of speech (cannot be differentiated), apraxia affecting several modalities (ideational, ideomotor, dressing, constructional and limb kinetic), symmetric severe hypo- and bradykinesis, rigidity (**P**arkinsonism), hypomimia and occasional tongue protrusion. The clinical phenomena were consistent with Alzheimer's disease.

On the current admission, detailed neuropsychological assessment could not be implemented due to the severity of cognitive impairment. However, Mini-Mental State Examination, Addenbrooke's Cognitive Examination and Clock-Drawing Test were performed 2 years before with 9/30 points, 28/100 points (orientation: 4/10 points, attention/concentration: 1/8

points, memory 1/35 points, verbal fluency: 2/14 points, language: 20/28 points, visuoconstructional abilities: 0/5 points) and 0/10 points, respectively. The skull MRI revealed generalized atrophy **(Fig. 2)**. The EEG demonstrated temporo-parieto-occipital triphasic and delta waves and occasional left temporo-parieto-occipital sharp waves. The specific CSF diagnostics yielded normal hTAU (366 pg/ml), normal pTAU (50 pg/ml) and decreased β-amyloid$_{(1\text{-}42)}$ (443 pg/ml) levels. The genetic testing revealed a known pathogenic missense mutation in the APP gene in exon 17 (c.2149 G>T, p.Val717Phe).

3. Discussion

AD is a currently incurable condition with a relatively heterogeneous clinical phenotype. It affects a significant portion of mainly the elderly population resulting in high socioeconomic burden. Only symptomatic therapy is available and there is a great scientific effort to develop causative therapies. Although the autosomal dominantly inherited exonic mutations in the APP gene are responsible for only a very small percentage of Alzheimer's disease, but the pathogenic basis of disease development, i.e., alterations in APP processing, β-amyloid production (Aβ) and/or change in the ratio between $A\beta_{1\text{-}42}/A\beta_{1\text{-}40}$ are well-established in these cases[3]. Accordingly, the identification of these patients may yield a relatively homogeneous patient pool for future pharmaceutical studies[4]. Furthermore, the detailed clinical description of each mutation (Suppl. Table 1) may have an important prognostic value as well.

With regards to the Val717Phe mutation of the APP gene, only limited clinical data are available from previous reports[5,6]: almost exclusively, memory impairment was described with an approximate symptom onset at the beginning of their forties. In addition to this seemingly essential alteration in AD, patients in the currently presented family were demonstrated to have symptoms related to the impairment of other three cognitive domains as well (reduced attention, language impairment, apraxia). Perception and social interactions

were not affected at all. Furthermore, other prominent psychiatric and neurological alterations, such as disturbance of consciousness, agitation with aggressive behavior, seizure, myoclonus, **P**arkinsonism and occasional tongue protrusion were present as well. **Seizure and myoclonus are well delineated phenomena in AD including the familial forms[7]. A prospective study demonstrated that early onset familial AD patients had an 87-fold increase in seizures compared to the general population[8]. The altered processing of APP may be the mechanistic link between the development of cognitive dysfunction and seizures[7]. The development of Parkinsonism in patients with certain mutations in the APP gene is a well-known phenomenon as well and may be the consequence of Lewy body formation in addition to AD pathology[9]. Unfortunately, post mortem specimens are not available for neuropathological assessment in the presented pedigree, so this hypothesis, i.e. the presence of Lewy body formation in the background of Parkinsonian symptoms in this family cannot be verified.** There are three mutations (Thr714Ile, Val715Met, Ile716Phe), where the clinical phenotype is quite similar to that of in case of Val717Phe mutation, and diverse alterations in case of Val717Ile mutation show a considerable overlap as well (Suppl. Table 1). The Thr714Ile, Ile716Phe and Val717Phe mutations can be characterized by the lowest age of onset out of the mutations where at least 2 independent affected families are presented. Accordingly, excluding those autosomal dominant exonic mutations in the APP gene preferentially causing intracerebral hemorrhage due to cerebral amyloid angiopathy at young age, Ile716Phe, Val717Phe and especially Thr714Ile mutations seems to have the worst prognosis. The latter one is characterized by the highest increase in **CSF** $A\beta_{1-42}/A\beta_{1-40}$ ratio[3]. **With regard to biomarkers in the present study, the CSF $A\beta_{(1-42)}$ content of the proband decreased characteristically, but not as much as it may be expected in light of the severe clinical phenotype. However, it has been previously demonstrated that CSF β-amyloid$_{(1-42)}$ level did not correlate either with**

severity or rate of progression of dementia[10].

The identification of causative mutations in the background of clinical phenomena may provide a possibility for presymptomatic genetic counselling as well, involving clearly early onset cases of AD[11]. However, this option may have both advances and dilemmas[4,12]. The current guidelines mostly promote strictly regulated presymptomatic genetic testing in early onset autosomal dominantly inherited AD[13], which is always suggested to be carried out on individual basis following a detailed counselling and the acquisition of written informed consent. Accordingly, presymptomatic genetic counselling and testing was carried out in possible carriers (IV-2, IV-3), and proved the lack of pathogenic mutation in the APP gene. Although in light of the age and mental and cognitive status of the family members III-4 and III-5, the presence of pathogenic Val717Phe is improbable, the daughter (IV-4) and son (IV-5) of the family member III-4 even want to certainly exclude the possibility of carrying that mutation. However, one potential mutation carrier (V-1) rejected genetic counselling and testing.

In conclusion, this case study reports the first detailed clinical description of Val717Phe mutation**, demonstrating amnestic AD phenotype with seizures, myoclonus and Parkinsonism,** and yields an overview of related autosomal dominantly inherited exonic mutations in the APP gene.

4. Ethical approval

This study was performed following the acquisition of written informed consent for publication (institutional research committee registration number is 44/2016.). All procedures applied during the assessment of patients were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

5. Conflict of interest

The authors declare no conflict of interest.

6. References

1. Shea YF, Chu LW, Chan AO, et al. A systematic review of familial Alzheimer's disease: Differences in presentation of clinical features among three mutated genes and potential ethnic differences. *J Formos Med Assoc.* 2016;115:67-75.
2. Cruts M, Theuns J, Van Broeckhoven C. Locus-specific mutation databases for neurodegenerative brain diseases. *Hum Mutat.* 2012;33:1340-1344.
3. Theuns J, Marjaux E, Vandenbulcke M, et al. Alzheimer dementia caused by a novel mutation located in the APP C-terminal intracytosolic fragment. *Hum Mutat.* 2006;27:888-896.
4. Loy CT, Schofield PR, Turner AM, et al. Genetics of dementia. *Lancet.* 2014;383:828-840.
5. Finckh U, Kuschel C, Anagnostouli M, et al. Novel mutations and repeated findings of mutations in familial Alzheimer disease. *Neurogenetics.* 2005;6:85-89.
6. Murrell J, Farlow M, Ghetti B, et al. A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease. *Science.* 1991;254:97-99.
7. **Born HA. Seizures in Alzheimer's disease. *Neuroscience.* 2015;286:251-263.**
8. **Amatniek JC, Hauser WA, DelCastillo-Castaneda C, et al. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia.* 2006;47:867-872.**
9. **Rosenberg CK, Pericak-Vance MA, Saunders AM, et al. Lewy body and Alzheimer pathology in a family with the amyloid-beta precursor protein**

APP717 gene mutation. ***Acta Neuropathol.*** **2000;100:145-152.**

10. **Andreasen N, Hesse C, Davidsson P, et al. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease.** ***Arch Neurol.*** **1999;56:673-680.**
11. Zou Z, Liu C, Che C, et al. Clinical genetics of Alzheimer's disease. *Biomed Res Int.* 2014;2014:291862.
12. Fortea J, Llado A, Clarimon J, et al. PICOGEN: five years experience with a genetic counselling program for dementia. *Neurologia.* 2011;26:143-149.
13. Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. *Genet Med.* 2011;13:597-605.

7. Figure legend

Fig. 1. Pedigree of the assessed family. The generations are indicated with Roman numbers while individuals in each generation with Arabic numbers. The deceased members are crossed. The patients demonstrating symptoms are in black. The age at death (d.) and the current age of patients in years (y) are indicated where available. The proband is indicated with p, whereas the individuals seeking genetic testing with arrows. The results (positive (+) or negative (-)) of genetic examination (E) for the p.V717F mutation is also demonstrated. Family members, where the presence of pathogenic mutation cannot be certainly excluded and genetic testing was not performed, are indicated with question mark.

Fig. 2. T2-weighted skull magnetic resonance imaging (1.5 Tesla) of the proband with Val717Phe mutation in the amyloid precursor protein gene. The main characteristic

feature is generalized brain atrophy.