Presenilin 1 Mutation (A431V) Causing Features of Dementia with Lewy Bodies in a Chinese Family of Alzheimer’s Disease

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Abstract

Aim: We reported a family with a presenilin 1 (PSEN1) gene mutation whose clinical manifestations are similar to the Dementia with Lewy bodies.

Methods: We collected peripheral blood of the proband, his daughter and 100 normal Chinese individuals and extracted genomic DNA. PCR-sequencing of PSEN1 and microtubule associated protein tau (MAPT) were performed. We also gave them transcranial sonography test (TCS).

Results: We found that the proband and his daughter were heterozygous for a mutation 1292nd base in exon 12 of PSEN1, causing the amino acid alanine substituted by valine at codon 431 (A431V), but this was not found in normal controls. Meanwhile hyperechogenicity of bilateral substantia nigra could be seen in the two patients with the right-left asymmetry index >1.15.

Conclusion: This study identified a mutation A431V in the PSEN1 gene in Chinese patients. We considered it might play an important role in familial Alzheimer’s disease leading clinical manifestations similar to DLB.

Keywords: Alzheimer’s disease; Dementia with Lewy bodies; Mutation; Presenilin 1; Transcranial sonography

Introduction

Alzheimer’s disease (AD) and Dementia with Lewy bodies (DLB) are the two most common neurodegenerative diseases that cause progressive cognitive impairment. AD can be subdivided into sporadic type and familial type. The familial AD (FAD) is mostly early-onset, accounting for less than 5% of all AD cases, with Presenilin-1 (PSEN1) and Presenilin-2 (PSEN2) as its genes, of which PSEN1 stands at the top accounting for less than 5% of all AD cases, with Presenilin-1 (PSEN1) and Presenilin-2 (PSEN2) as its genes, of which PSEN1 stands at the top [1-4]. Though, DLB is found mostly sporadic, without any confirmed genetic risk factor. Here, we describe a family presented with the clinical manifestations of DLB, who have a PSEN1 gene mutation.

Methods

Patients' clinical data (Table 1)

The patients come from a Chinese family, which has 16 members, 8 males and 8 females. The pedigree is shown in Figure 1A. According to the revised 2005 International Criteria of Dementia with Lewy bodies [5], the proband (member II5) conformed to the diagnosis criteria of probable clinical DLB, 2005 International Criteria of Dementia with Lewy bodies [5], the proband (member II5) conformed to the diagnosis criteria of probable clinical DLB, and 8 females. The pedigree is shown in Figure 1A. According to the revised 2005 International Criteria of Dementia with Lewy bodies [5], the proband (member II5) conformed to the diagnosis criteria of probable clinical DLB, and 8 females, with an average age of 52.1, who were tested PSEN1 gene mutation and all have signed the informed consent.

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| Patient | Age | Gender | Clinical | Presenilin | Past History | MMSE | MOCA |
|---------|-----|--------|----------|------------|--------------|------|------|
| II 2    | 65  | F      | +        | +          | - HT        | 30   | 4    |
| II 4    | 62  | F      | +        | +          | -           | 30   | 4    |
| II 5    | 58  | M      | +        | +          | -           | 30   | 4    |
| III 3   | 31  | F      | +        | -          | -           | 30   | 4    |

D: Dementia; P: Parkinsonian Symptoms; H: Hallucination; MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment; F: Female; M: Male; HT: Hypertension; --: not detected

Table 1: Patients’ demographic and clinical data.

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We used BigDye (Applied Biosystems; Axyprep DNA Gel EXtraction kit) for test. The primer 3 online design (Sangon Biotech Beijing Co., Ltd.) was adopted. The polymerase chain reaction (PCR) amplification reaction system was No. 12 exon primer sequence: sense 5'-TCCAGATTGAATGAACGTCTGT-3', antisense 5'-AGACTTGGAAGGAAGCTGCA-3'. PCR products underwent electrophoresis on an ABI automated DNA sequencer (Perkin Elmer, Foster City, Calif). The data of electropherograms was analyzed using DNASTAR sequencing analysis software (Lasergene.v7.1).

Transcranial sonography (TCS) test

TCS was performed through the preauricular acoustic bone windows using a colour-coded phased-array ultrasound system equipped with a 2.5 MHz transducer (LOGIQ 9 ultrasound system). The ultrasound parameters were: penetration depth of 16 cm, dynamic range 50 dB. SN echogenic size measurements were performed on axial TCS scans automatically after manually encircling the outer circumference of substantia nigra (SN)'s echogenic area. SN echogenic sizes of less than 0.20 cm$^2$ are classified as normal. Additionally, echogenicity of thalami, lenticular nucleus and heads of caudate nucleus was investigated and classified as hyperechogenic when it was more intense than the surrounding white matter. For estimation of the right-left asymmetry index of SN echogenic sizes (SN+$R-L$ index), the larger size of bilateral measurements was divided by the smaller size. All TCS examinations were performed by one experienced sonographer (S.X.) who was blinded to diagnosis and clinical data of the patients.

Results

Imaging and laboratory test data

Proband II 5: Cranial magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed (Figure 2) global brain atrophy especially in hippocampus and temporal lobes as well as intracranial multiple focal ischemia lesions; D is the cranial MRA of proband showing no stenosis or occlusion of the intracranial blood vessels.

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proved that in addition to AD pathological features, Lewy Bodies (LBs) which is the key pathological feature of DLB is also a very frequent coexistent pathologic abnormality in FAD. It can be found wide spread in the brainstem, limbic areas, nigra and neocortex. Meanwhile, these pathological changes of LBs occur more frequently in FAD related to gene PSEN1 mutation than FAD related to Presenilin-2 gene mutation and sporadic AD [17]. It was speculated that in the normal condition PSEN1 plays an important role in certain intersections or interferences between β-amyloid and α-synuclein. This has been proved by Winslow [17] using immunoelectron microscopy found that PSEN1 together with α-synuclein and β-amyloid are closely related on the presynaptic vesicles, surfaces of mitochondria and plasma membrane. Aggregation of α-synuclein into Lewy bodies (LBs) can also be induced by PSEN1 mutation to an equal extent as β-amyloid pathology [15]. These above studies and assumptions provided proofs to the relationships between PSEN1 and α-synuclein and could state the mechanism of the AD patients of PSEN1 gene mutation presented with DLB clinical features.

It is noteworthy that by TCS hyperchogenicity of bilateral substantia nigra can be seen in the two patients of PSEN1 A431V mutation. TCS shows that 90% of the patients with Parkinson's diseases (PD) have abnormally enlarged SN+ [18]. In addition to PD, corticobasal ganglionic degeneration (CBD), DLB and many other neurodegenerative diseases also have SN+. Walter et al. [19] believed that the features of SN+ of DLB are the areas of SN+ ≥ 0.25cm2; and the bilateral asymmetry index <1.15. It is suggested that the SN+ is related to iron metabolism rather than Lewy body accumulation. In our research, the asymmetry index of SN echogenic sizes of both II 5 and III 3>1.15 and II 5 also has hyperchogenicity of bilateral lentiform nucleus. These are inconsistent with TCS features of the previously reported DLB. It is considered that our family is early-onset AD with DLB clinical features, not sporadic DLB, so the SN+ is not similar as sporadic DLB. But in a sense, it may give a hint that asymmetry of bilateral SN+ may be one of characteristic features in differentiating FAD with DLB from sporadic DLB.

**Conclusion**

This research reported that the early-onset FAD of PSEN1 gene A431V mutation has the clinical features of DLB for the first time. It helps understanding clinical manifestations of FAD with PSEN1 mutation and suggests that when we meet with familial DLB, early-onset FAD with PSEN1 mutation should be considered and TCS may be one of important methods to differentiate them. As a limitation of this research, the gene has not been detected in other family members, especially the other two patients. Furthermore, though positive in gene test, II3 has no symptoms. We will further follow up for more clinical data.
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References

1. Kamimura K, Tanahashi H, Yamanaka H, Takahashi K, Asada T, et al. (1998) Familial alzheimer’s disease genes in Japanese. J Neurol Sci 160: 76-81.
2. Campion D, Dumanchin C, Hannequin D, Dubus B, Belliard S, et al. (1999) Early-onset autosomal dominant alzheimer disease: Prevalence, genetic heterogeneity and mutation spectrum. Am J Hum Genet 65: 664-670.
3. Finckh U, Müller-Thomsen T, Mann U, Eggers C, Marksteiner J, et al. (2000) High prevalence of pathogenic mutations in patients with early-onset dementia detected by sequence analyses of four different genes. Am J Hum Genet 66: 110-117.
4. Athan ES, Williamson J, Ciappa A (2001) A founder mutation in presenilin 1 causing early-onset Alzheimer disease in unrelated caribbean hispanic families. JAMA 286: 2257-2263.
5. McKeith IG, Dickson DW, Lowe J, Enre M, O’Brien JT, et al. (2005) Diagnosis and management of dementia with Lewy bodies: Third report of the DLB Consortium. Neurology 65: 1863-1872.
6. Larner AJ (2013) Presenilin-1 mutations in Alzheimer’s disease: An update on genotype-phenotype relationships. J Alzheimers Dis 37: 653-659.
7. Matsuhashi S, Arai H, Okamura N, Ohmori T, Takasugi K, et al. (2000) Clinical and biomarker investigation of a patient with a novel presenilin-1 mutation (A431V) in the mild cognitive impairment stage of Alzheimer’s disease. Biol psychiatry 52: 907-910.
8. Borchelt DR, Thnakinara G, Eckman CB, et al. (1996) Familial alzheimer’s disease-linked presenilin 1 variants elevate a beta 1-42/1-40 ratio in vitro and in vivo. Neuron 17: 1005-1013.
9. Keller JN, Guo O, Holtsberg FW, Bruce-Keller AJ, Mattson MP (1998) Increased sensitivity to mitochondrial toxin-induced apoptosis in neural cells expressing mutant presenilin-1 is linked to perturbed calcium homeostasis and enhanced oxiradical production. J Neurosci 18: 4439-4450.
10. Takashima A, Murayama M, Murayama O, Kohno T, Honda T, et al. (1998) Presenilin 1 associates with glycogen synthase kinase-3beta and its substrate tau. Proc Natl Acad Sci U S A 95: 9637-9641.
11. Wehrl CC, Miller RJ, Roos RP (1999) The role of beta-catenin stability in mutant PS1-associated apoptosis. Neuroreport 10: 2527-2532.
12. De Ferrari GV, Inestrosa NC (2000) Wnt signaling function in Alzheimer’s disease. Brain Res Brain Res Rev 33: 1-12.
13. Gamblin TC, Chen F, Zambrano A, Abraha A, Lagalwar S, et al. (2003) Caspase cleavage of tau: Linking amyloid and neurofibrillary tangles in Alzheimer’s disease. Proc Natl Acad Sci U S A 100: 10032-10037.
14. Snider BJ, Norton J, Coats MA, Chakraverty S, Hou CE, et al. (2005) Novel presenilin 1 mutation (S170F) causing Alzheimer disease with lewy bodies in the third decade of life. Arch Neurol 62: 1821-1830.
15. Ishikawa A, Piao YS, Miyashita A, Kuwano R, Onodera O, et al. (2005) A mutant PSEN1 causes dementia with lewy bodies and variant Alzheimer’s disease. Ann Neurol 57: 429-434.
16. Leverenz JB, Fishel MA, Peskind ER, Montine TJ, Nochlin D, et al. (2006) Lewy body pathology in familial Alzheimer disease. Evidence for disease and mutation specific pathologic phenotype. Arch Neurol 63: 370-376.
17. Winslow AR, Moussaoud S, Zhu L, Post KL, Dickson DW, et al. (2014) Convergence of pathology in dementia with lewy bodies and Alzheimer’s disease: A role for the novel interaction of alpha-synuclein and presenilin 1 in disease. Brain 137: 1958-1970.
18. Berg D, Behnke S, Seppi K, Godau J, Lerche S, et al. (2013) Enlarged hyperechogenic substantia nigra as a risk marker for Parkinson’s disease. Mov Disord 28: 216-219.
19. Walter U, Dressler D, Wolters A, Wittstock M, Greim B, et al. (2006) Sonographic discrimination of dementia with Lewy bodies and Parkinson’s disease with dementia. J Neurol 253: 448-454.