A curious case of early-onset dementia

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This article was published on 14 Jun 2023 at www.hkmj.org.

Hong Kong Med J 2023;29:359.e1-3
https://doi.org/10.12809/hkmj2210106

A 63-year-old woman was referred to the memory clinic of Queen Mary Hospital, Hong Kong in September 2021 for early-onset dementia (defined as onset before age of 65 years). Three months previously, she had developed stepwise deterioration in cognitive function and self-care ability following a right occipital lobe infarction. After a course of rehabilitation, her Montreal Cognitive Assessment–Hong Kong version and the Barthel Index scores were 5/30 and 9/20, respectively. The Montreal Cognitive Assessment–Hong Kong version score would have remained below the 2nd percentile even if the visual components, affected due to her potential visual deficit from stroke, had been excluded from the total score. A detailed review of her medical history revealed that she had had progressive anterograde amnesia since the age of 56 years. She worked previously as a professional accountant but had retired since the onset of cognitive impairment. Within 1 year, she developed executive dysfunction and personality change with aggressiveness. She reportedly had disorientation, prosopagnosia, and apraxia prior to her stroke in 2021. ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography and Pittsburgh Compound B positron emission tomography at the age of 61 years, before the episode of stroke, showed bilateral temporoparietal hypometabolism (Fig 1) and diffuse amyloid load, especially over bilateral frontal lobes, parietal lobes, and posterior cingulate gyrus (Fig 2). The imaging findings were compatible with Alzheimer's disease (AD). Further examination of her family history revealed multiple first-degree relatives with early-onset dementia with an autosomal dominant inheritance pattern (Fig 3).

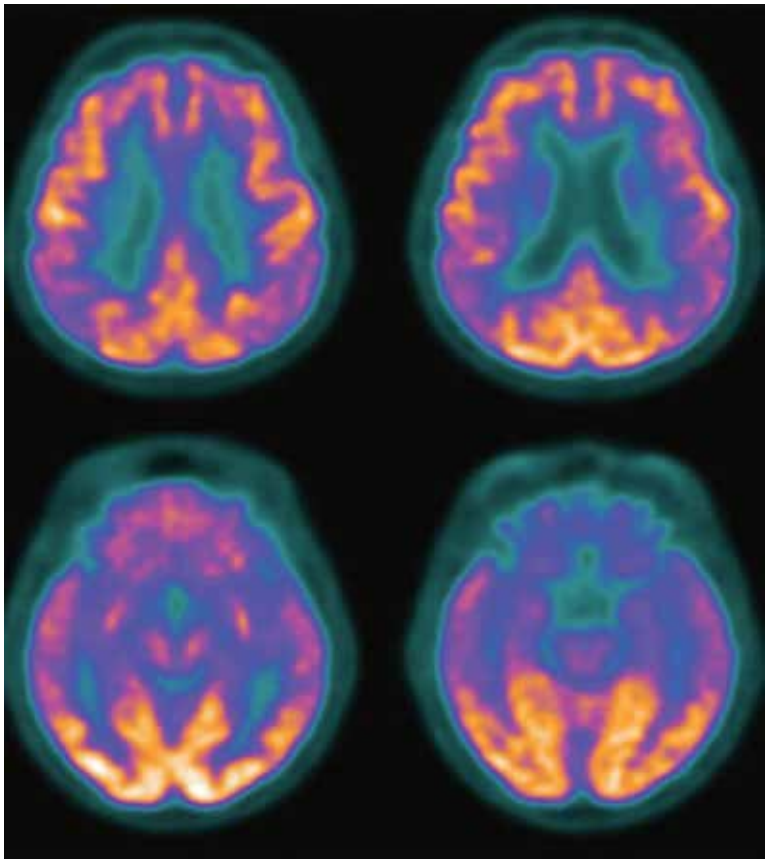

FIG 1. ^{18}F-fluorodeoxyglucose positron emission tomography–computed tomography showing bilateral temporoparietal hypometabolism

Given the strong family history of early-onset dementia, familial AD gene panel, which included amyloid protein precursor (*APP*), presenilin-1 (*PSEN1*), and presenilin-2 (*PSEN2*), by next-generation sequencing was performed. Presenilin-1 was positive for a heterozygous mutation with a missense variant (c.786G>C, p.Leu262Phe), confirming the diagnosis of familial AD. No known pathogenic variants were detected in *APP* or *PSEN2* genes. The family was referred for genetic counselling.

Familial AD accounts for less than 0.5% of early-onset AD cases.[1] It is caused by mutations in the *PSEN1*, *PSEN2* or *APP* gene, resulting in early deposition of amyloid plaques due to overproduction and deposition of Aβ42 leading to early neurodegeneration (the amyloid hypothesis).[1] Nonetheless a newer presenilin hypothesis suggests alternative mechanisms, eg, loss-of-function of *PSEN1* with suppressed γ-secretase activity and increased Aβ42/Aβ40 ratios, resulting in neurodegeneration.[2] Presenilin-1 mutations account for up to 71.5% of Asian cases of familial AD.[1] These patients may have an atypical presentation such as parkinsonism or spastic paraparesis.[1] With a few exceptions, familial AD mutations are considered fully penetrant with the development of dementia at a predictable age. Families should be referred for genetic counselling since carriers may have half the chance of transmitting the mutation to a child. Carriers may be referred to a tertiary centre for potential pre-implantation genetic testing. There have been three reported families in Hong Kong with familial AD and different mutations.[3,4] Patients

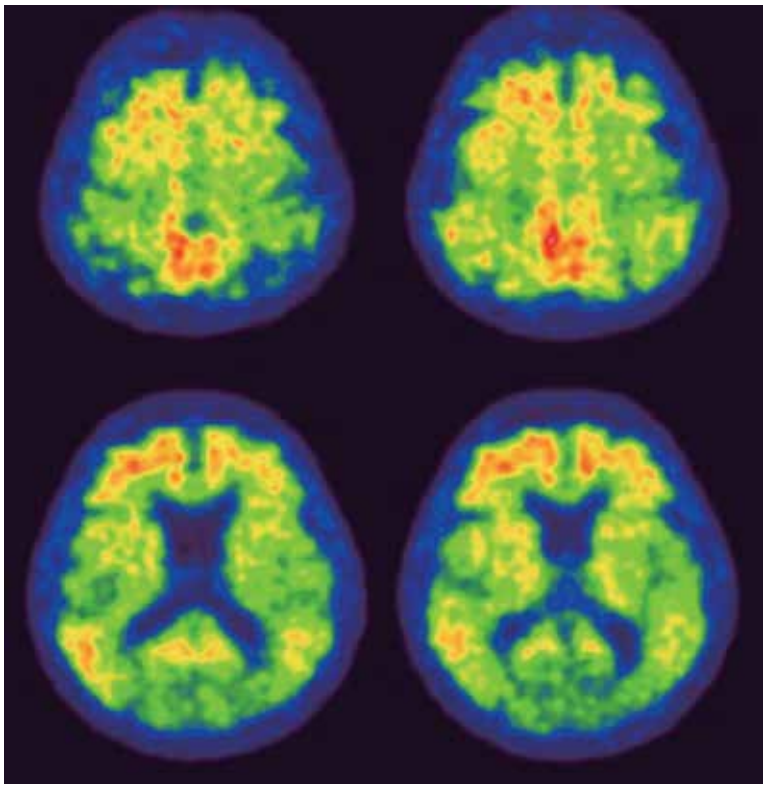

FIG 2. Pittsburgh Compound B positron emission tomography showing diffuse amyloid load over the brain as depicted by the reddish-yellowish areas, especially over the bilateral frontal lobes, parietal lobes, and posterior cingulate gyrus

with *PSEN1* p.Leu262Phe tend to have a decreased word-finding ability.[5]

In summary, familial AD should be considered when a patient presents with early-onset cognitive impairment and a strong family history of early-onset dementia. Referral to chemical pathologists for genetic testing is important for family planning and advance care planning.

Author contributions

All authors contributed to the concept or design of the study, acquisition of the data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. Patient consent was obtained for all investigations including treatment, procedures, and publication.

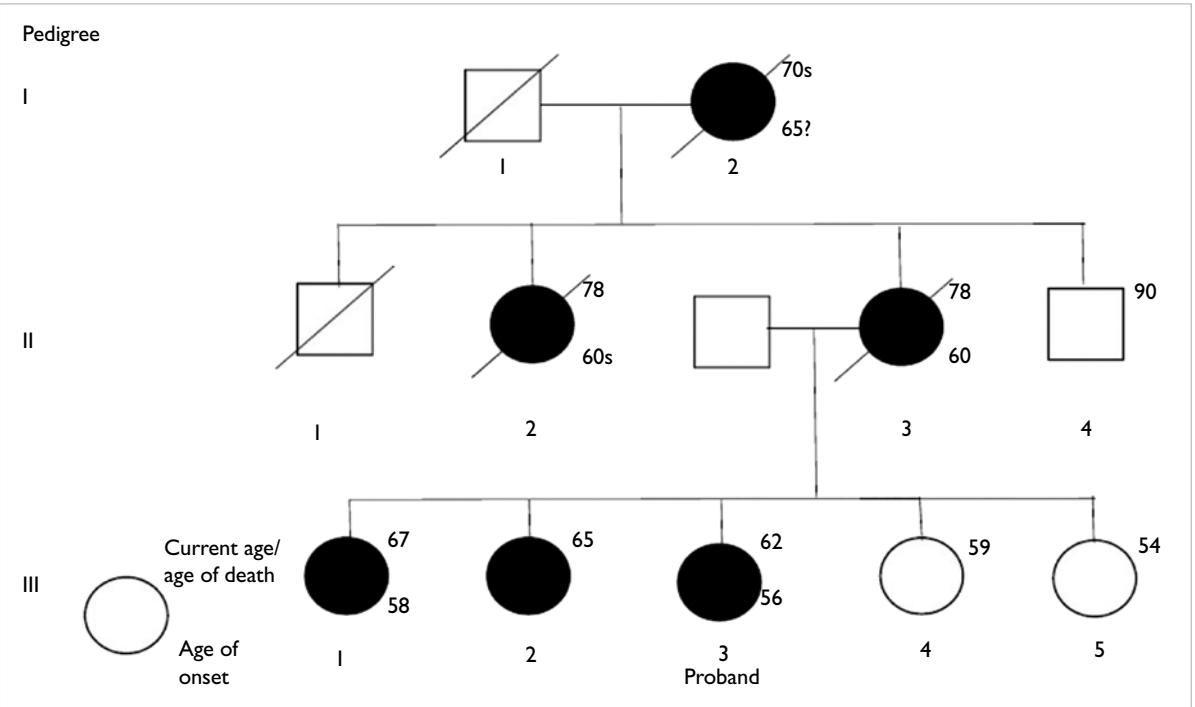

FIG 3. Pedigree of the patient's family showing an autosomal dominant inheritance pattern

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