Research and Reports of Medicine

Case Report

Case Report of a 47-Year-Old Long COVID Patient Diagnosed with Alzheimer's Disease

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INTRODUCTION

A 47-year-old female patient was diagnosed with Alzheimer Disease (AD) based on positive Amyloid-PET and Tau-PET imaging results, coupled with increased levels of plasma biomarkers (Aβ42/Aβ40, pTau181, and pTau217). In this report, we characterized this unusual AD case by integrating data from various diagnostic methods, including PET, MRI imaging, genetic testing, plasma biomarker testing, etc, to contribute to future research and guide clinical practice. Given that this case emerged after the peak of the COVID-19 pandemic, we suggest that the AD cases analogous to this one be categorized under a distinct subset within the long COVID syndromes, termed AD-like COVID syndromes.

CASE PRESENTATION

Early Onset Alzheimer Disease (EOAD) is a neurodegenerative dementing disorder that is relatively rare (<1% of all AD cases) [1]. Diagnosis of EOAD can be facilitated through the use of Amyloid-positron emission tomography (Amyloid-PET) and Tau-PET imaging, as well as plasma biomarkers. A female patient, born in 1974, began

exhibiting repetitive behavior, memory loss, and executive dysfunction since 2021, after the peak of the COVID-19 pandemic [2]. By the close of 2023, she received a diagnosis of AD, primarily based on positive results of both Amyloid-PET computed tomography (Amyloid-PET/CT) and Tau-PET/CT imaging, with the negative results of mGluR5-PET/MRI imaging.

However, we reached a different conclusion that this unusual case possesses substantial value for furture research. This conclusion was reached by integrating data from various diagnostic methods, such as PET, magnetic resonance imaging (MRI) imaging, genetic testing, plasma biomarker testing. The crucial finding was that magnetic resonance spectroscopy (MRS) results indicated a severer loss or damage of neurons in the left hippocampus compared to the right one, while Amyloid-PET/CT images showed a significantly higher abundance of amyloid plaques in the right hippocampus (Figure 1).

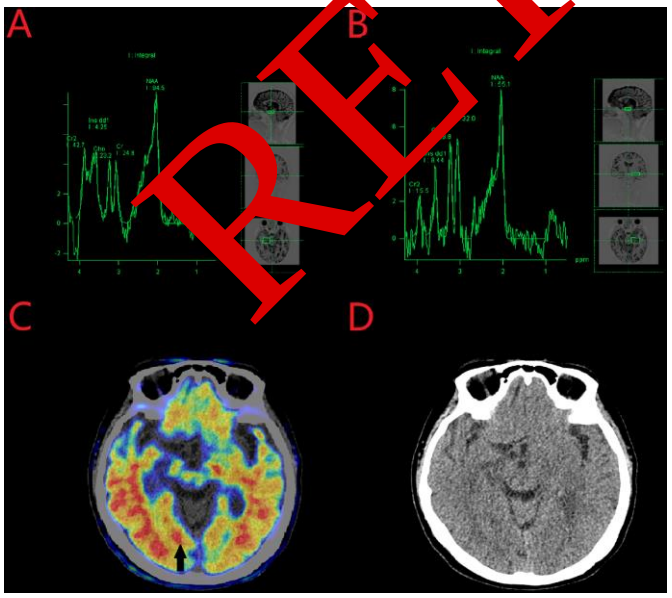

Figure (1): Comparison between MRS results and Amyloid-PET/CT images. MRS results (Date: 20240515) of the right hippocampus (A) were compared with those of the left one; (B): right NAA peak (ppm=2.0) > left peak, right Cr peak (ppm=3.03) < left peak, and right Cr peak (ppm=3.2) < left peak; (C) Amyloid plaques (in red color) of the right hippocampus (indicated by black arrow) were compared with the left one; (C) and (D) depict the same image in pseudocolor and grayscale styles, respectively. Amyloid-PET/CT report date is 20231227.

Our conclusion is validated preliminarily by subsequent clinical observations and diagnostic tests. Over the past 10 months since her AD diagnosis, no significant progressive cognitive decline was observed; instead, her health exhibited slight improvement. Notably, her Mini Mental State Examination (MMSE) score improved from 23/30 to 27/30. However, the demyelination in cerebral white matter showed no significant amelioration. Additionally, her plasma biomarkers (Aβ42/Aβ40, pTau181, and pTau217) remained positive, suggesting that the aggregated amyloid and Tau proteins in the brain have not been effectively cleared. In this report, we presented this case, along with our comprehensive analysis and all available data, to contribute to future research and guide clinical practice.

RESULTS AND DISCUSSION

PET Imaging Results and Previous Diagnosis

Amyloid-PET/CT and Tau-PET/CT imaging were conducted using 18F-AV45 (florbetapir) and 18F-MK6240, respectively. Images were taken over a 10-min period, 50 min after injection of PET tracers. Two individuals who are not

aware of any clinical information about the patient subsequently evaluated the images. In addition to visual assessment, the images were also evaluated quantitatively using the standard uptake value ratio (SUVr) in the specific regions of interest, relative to the cerebellum defined as the reference region. Both Amyloid-PET/CT and Tau-PET/CT scans (Date: 20231227 and 20240113) provided clear visualization across various brain regions, showing radioactivity uptake notably increased and diffusely distributed in the cerebral cortex, involving the bilateral temporal lobes (including the hippocampus and entorhinal cortex), frontal lobes, parietal lobes, occipital lobes, the posterior cingulate cortex, etc. Consequently, the patient was diagnosed with mild cognitive impairment (MCI) by a hospital and AD by another hospital. However, the quantification of Amyloid-PET/CT images yielded an average SUVr of 2.1 for the frontal lobe, 1.9 for the parietal, 1.9 for the temporal lobes, and 1.8 for the posterior cingulate gyrus. The pattern of these average SUVrs is different from the mean values (1.28, 1.24, 1.42 and 1.44) from AD patients in a previous study [3]. In addition, the PET/MRI results using ^{18}F-PSS232 showed no significant reduction in the distribution of mGluR5 in brain (Date: 20240515).

Genetic Testing Results and CircRNA Biomarker

As EOAD or autosomal dominantly inherited AD is substantially or even entirely genetically determined frequently associated with genetic causes [4], we performed genetic testing of the patient using whole exome sequencing (WES). The WES was performed by Innovo Biotechnology Co. Ltd, using 2×150 paired-end sequencing strategy on an Illumina sequencer, producing 32,769,278 pairs of reads. After data quality control, the cleaned reads (SRA: SRR31604084) were aligned to the reference human genome GRCh38. A total of 19,441 protein-coding genes and ORFs in the panel (VAHTS Target Capture Core Exome Panel) were covered with the average depth 148.7. As a result (Date: 20241026), no known deleterious mutations were detected in her AD-associated genes, particularly APP, PSEN1, PSEN2, MAPT, APOE, and CLU [5]. Her APOE genotype is ε3/ε3. Additionally, no known deleterious mutations has been detected in her son's genetic profile using WES, and there is no family history of AD among her parents. Based on these findings, it is unlikely that this AD case has a genetic origin. Notably, a circular RNA (circRNA) named circDENND1B-1, discovered as a potential diagnostic biomarker in a previous study [6], was tested separately using her plasma and blood cells. The negative results (qPCR Ct<40 indicates positive) indicated that this case is not a canonical AD case.

MRI Imaging Results and The Demyelination

The demyelination in cerebral white matter were identified by at least seven separate MRI scans (Data: 20231216, 20231221, 20240414, 20240427, 20240515, 20240701 and 20240826). The only suspected cause of this demyelination is COVID-19 infection or vaccination. Her symptoms emerged after the peak of the COVID-19 pandemic, when she was 47 years old, which is close to the median age of 44 identified in a study investigating 32 cases of central nervous system (CNS) demyelination following COVID-19 vaccination [7]. Since the patient underwent a comprehensive physical examination, using a variety of diagnostic methods to examine all parts of her body, we were

able to eliminate other potential causes. The only remaining possibility is the prolonged presence of inflammatory cytokines, as evidenced by the detection of high levels of IL-6 and IL-10 in the patient's blood following the peak of the COVID-19 pandemic. Using COVID-19 as a clue, the demyelination was associated with AD-like symptoms, thereby accounting for the earlier finding that people with COVID-19 were at significantly increased risk for new diagnosis of AD within 360 days after the initial COVID-19 diagnosis [8].

Primary Source of the Aggregated Amyloid and Tau Proteins

Our finding (Figure 1) suggested that dead or damaged neurons are not the primary source of aggregated amyloid proteins in the patient's brain. To pinpoint the actual primary source, a single-cell RNA sequencing (scRNA-seq) dataset was utilized to compare the expression levels of APP, MAPT, and ACE2 (Figure 2) across 13 major cell types [9]. Unexpectedly, the expression levels of APP and MAPT in oligodendrocytes were exceptionally higher than those in the other 12 cell types, exceeding twofold the levels in neurons. Remarkably, the expression level of ACE2 in pericytes was substantially higher, exceeding 13 times the combined levels across all other cells. Consequently, it is plausible that the demyelination initiated with the infection of pericytes in blood-brain barrier (BBB) by COVID-19 or its vaccine through ACE2. This process subsequently involved oligodendrocytes in the demyelination [10], potentially due to similar interactions observed between pericytes and oligodendrocyte precursor cells (OPSs) in the perivascular regions of cerebral white matter [11]. As a result, amyloid and Tau proteins were secreted from living oligodendrocytes or released from dying ones, serving as the primary source for plaque formation. This process can also account for a previous finding that oligodendrocytes produce amyloid-β and contribute to plaque formation [12,13].

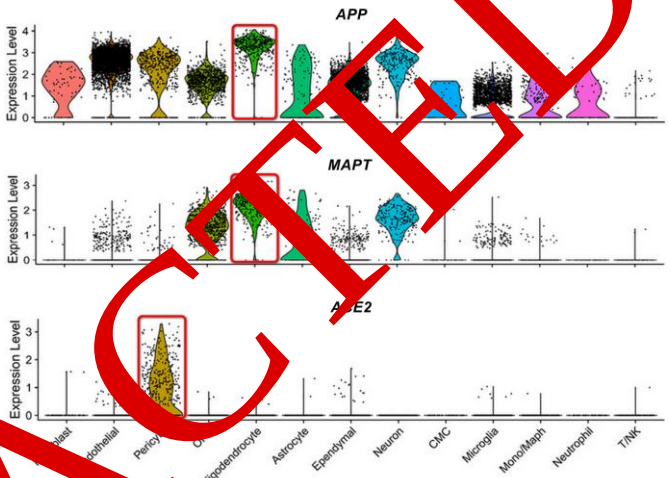

Figure (2): Cell-specific expression of APP, MAPT and ACE2.

The expression levels of (A)APP, (B)MAPT and (C)ACE2 in 13 major cell types (CMC, Neuron, Microglia, Mono/Maph, Neutrophil, T/NK, Fibroblast, Endothelial, Pericyte, OPC, Oligodendrocyte, Astrocyte, and Ependymal) were showed using a scRNA-seq dataset (GEO: GSE236293). Although this dataset was derived by sequencing cells from mouse spinal cords, the gene expression profile of these cell types in spinal cords is similar to that in brains. CMC: cycling myeloid cell; OPC: oligodendrocyte precursor cell; Mono: monocyte; Maph: macrophage; T: T cell; NK: natural killer cell.

CONCLUSION

CNS demyelination and "COVID fog" following COVID-19 infection or vaccination has been reported in previous studies. However, the

emergence of AD-like symptoms attributed to CNS demyelination is still an unexpected finding. The previous studies suggested that a considerable number of AD cases analogous to this one may had emerged after the peak of the COVID-19 pandemic. Therefore, we suggest that these analogous AD cases be categorized under a distinct subset within the long COVID syndromes, termed AD-like COVID syndromes. Given that plasma biomarker testing results align with those from Amyloid-PET/CT and Tau-PET/CT imaging, neither of these diagnostic methods can be used to reliably distinguish AD-like COVID syndromes from canonical AD. In this report, we characterized this unusual AD case by integrating data from various diagnostic methods, including PET, MRI imaging, genetic testing, plasma biomarker testing, etc, to aid in the identification of AD-like COVID syndromes in the future.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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