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# Mixed Cerebrovascular and Alzheimer's Type Pathology Mimicking Lewy Body Disease and Its Possible Contribution to Cognitive Impairment in Elderly Patients with Bipolar Disorder/Schizophrenia

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## Abstract

The fast aging human population requires new approaches to reliable diagnosis and proper treatment of dementia in elderly patients with psychiatric disorders such as bipolar disorder (BD) and schizophrenia (SCZ). As compared to other psychiatric disorders, BD and SCZ are characterized by increased and similar risk for dementia as well as cerebrovascular (CVD) and Parkinson's (PD) diseases independent of the patient's age. There are reports in the literature suggesting BD and SCZ in older patients could cause dementia without contribution from the neurodegenerative diseases, including Alzheimer's disease (AD), due to the absence of the known neuropathology associated with cognitive decline in such individuals. This view contradicts a plethora of data highlighting AD as a major cause of dementia in the elderly. This issue was addressed by examining postmortem cerebral pathology in an 83-year-old female diagnosed with BD, SCZ, and PD (D1) and comparing it to that of a second donor (D2), an age-matched male diagnosed with Lewy Body Dementia (LBD). Upon thorough histochemical and immunohistochemical examinations of both brains, the PD and LBD diagnoses in D1 and D2 were not confirmed. Instead, AD-related pathology was observed in both subjects with AD advancing to its clinical stage (mild to moderate) only in D1. Diffuse $\beta$-amyloid peptide 1-42 (A$\beta$1-42) staining, most likely reflecting a presence of the A$\beta$1-42 soluble form, was also detected in cerebellar neurons and cerebellar extracellular space in D1 and D2. Cerebrovascular pathology was pronounced and distinct in both brains and included amyloid angiopa-

thy, hyaline atherosclerosis, microbleeds, and dilated Virchow Robin spaces in D1 as well as thick-walled blood vessels with microbleeds in D2. It was concluded that a mixed AD and cerebrovascular pathology could mimic Lewy Body Disease and potentially contribute to dementia development in elderly BD and SCZ patients.

## Keywords

Bipolar Disorder, Schizophrenia, Alzheimer's Disease, Cerebrovascular Disease, Neuropathology

## 1. Introduction

Bipolar disorder (BD) is a common, chronic severe neuropsychiatric condition characterized by alternating depression and manic episodes. BD affects approximately 1.4% of the worldwide population and, in general, has an early onset of 13 - 30 years of age [1]. Because of the fast aging of the human population and despite a significantly lower life expectancy in comparison with the general population due to associated comorbidities [2], it is predicted that the number of patients with BD older than 60 years will account for ~50% of all BD patients by the year 2030 [3] [4]. Approximately 40% - 50% of those individuals will have cognitive impairment and, eventually, dementia [5] [6]. Older age BD (OABD) patients are at an increased risk of developing dementia not only because of their age but also due to BD itself, which in comparison to other major psychiatric disorders, is a significant risk factor for developing dementia [7] [8] [9] as well as Parkinson's (PD) and cerebrovascular (CVD) diseases in later life [9]. Therefore, the population of OABD patients can no longer be viewed as a subset of the younger BD patient group and for whom "…understanding of the disorder and recommended management can simply be extrapolated from experience in mixed-age groups" [10].

The most common cause of dementia, Alzheimer's disease (AD) [11], was absent in OABD patients with cognitive impairment when AD was probed by its biosignature, a combination of low amyloid beta-peptide 1-42 (A$\beta$1-42) and high total tau and phospho-tau levels in the cerebrospinal fluid (CSF) [12]. Based on these data, it was hypothesized that cognitive decline in BD was not attributable to AD-related pathology but rather to the intrinsic BD neurobiology, *i.e.* BD itself could trigger pathologic processes leading to the dementia development without contribution from other known neurodegenerative disorders [12]. A similar notion could be also extended to SCZ patients because no pathology associated with the neurodegenerative disease, including that of AD, was found in the elderly SCZ patients with dementia [13] [14] [15]. These data, along with those reported in [9], question AD's contribution to dementia development in patients with OABD and/or SCZ. Therefore, the main objective of this study was to probe this issue by examining postmortem AD-related pathology in two brains

of 83-year-old individuals. The first subject (D1) was diagnosed with BD, SCZ, PD, and underwent electroconvulsive therapy (ECT), whereas the second (D2) had Lewy Body Dementia (LBD). It should be noted, that SCZ has also an increased risk of developing dementia as compared to other psychiatric disorders and its level is similar to that of BD [9]. Additionally, PD, PD dementia, and LBD constitute Lewy Body Disease [16].

## 2. Methods

### 2.1. Human Cadaveric Body Procurement

The donor bodies were received through Saint Louis University (SLU) Gift Body Program from individuals who had given their written informed consent. Only bodies of individuals who died from natural causes, except those with infectious diseases, are accepted by the Program. The immediate cause of death for the D1 donor was chronic obstructive pulmonary disease while the underlying causes were Parkinson's Disease, Type 2 diabetes mellitus with complications, and hypertensive heart disease with heart failure. The manner of death for the D2 donor was listed as natural with an underlying cause of Lewy body dementia. The bodies were embalmed through the right femoral artery with a 2:1 mixture of water and a solution containing 33.3% glycerin, 28.8% phenol, 4.6% formaldehyde, and 33.3% methanol.

### 2.2. Anatomical Dissection

The brains were extracted from the bodies according to the Grant's dissector [17] and fixed in 10% neutral buffered formalin solution for 12 - 16 weeks. Following fixation, 10 mm coronal sections were made from the anterior aspect of the cerebrum to its posterior that was continued through the cerebellum and brainstem using a brain sectioning knife (Fine Science Tools, Foster City, CA, USA, Catalog # 10152-30).

### 2.3. Histochemical and Immunohistochemical Staining

The brain tissue excised from the specific brain regions was dehydrated, paraffin embedded, sectioned (4 - 5 μm), and stained with hematoxylin and eosin (H&E) according to standard procedures of the Research Microscopy and Histology Core, Department of Pathology, SLU School of Medicine). The immunohistochemical staining for phospho-tau was performed using phospho-tau (Ser202, Thr205) mouse monoclonal antibody (AT8) (Invitrogen, Rockford, IL, Catalog # MN1020). $\beta$-Amyloid peptide 1-42 (A$\beta$1-42) was detected with recombinant rabbit monoclonal antibody (H31L21) (Invitrogen, Rockford, IL, Catalog # 700254). The latter antibody is highly specific to A$\beta$1-42 as it does not react with A$\beta$1-37, A$\beta$1-38, A$\beta$1-40, or A$\beta$1-43. The primary antibodies were detected with a MACH 4TM micro-polymer system (Biocare Medical, Pacheco, CA, USA, Catalog # M4U534) where secondary antibodies were labeled with horseradish peroxidase and developed utilizing an intelliPATH FLX™ DAB Chromogen Kit

(Biocare Medical, Pacheco, CA, USA, Catalog # IPK5010). The immunohistochemical staining was performed at the abovementioned core facility according to the manufacturers provided protocols. The tissue stained without a primary antibody was used as a negative control.

### 2.4. Light Microscopy

Images were obtained with a Leica Leitz DMRB light microscope controlled by the Neurolucida software (MBF Bioscience, Williston, VT, USA) using the 10×, 20×, and 63× objectives.

## 3. Case Presentation

The study was conducted during the 2020-2022 calendar years. The initial step in the study was to assess LBD and PD diagnoses for the respective subjects. Upon examination of the hematoxylin and eosin (H&E) stained brain tissues, no Lewy Body Disease related pathologies were observed in both D1 and D2. Lewy bodies were not present in cortical areas, basal ganglia, and brainstem. In addition, the substantia nigra was well preserved in both brains, thereby not confirming the respective PD and LBD diagnoses (Figure 1).

However, D1 brain displayed Alzheimer's type pathology in the frontal, temporal, and occipital cortices as well as in the hippocampus. The respective pathological features identified by H&E staining included senile plaques and neurofibrillary tangles (NFTs) in the cortices (not shown) and hippocampus as well as granulovacuolar degeneration (GVD) in pyramidal neurons of the hippocampus (Figures 2(A)-(G)). In the D2 brain, the AD pathology was also present in the form of NFTs and GVD in the hippocampus (Figure 2(B) & Figure 2(D)) and was accompanied by a mild neuronal loss in the hippocampus and cortex (not shown). Senile plaques were undetectable in the D2 frontal and occipital cortices (Figure 2(F) & Figure 2(H)). The Alzheimer's type pathology in both donors was confirmed further by specific immunohistochemical staining for phospho-tau and $\beta$-amyloid (Figure 3). The phospho-tau staining identified NFTs in the D1 and D2 hippocampi (Figure 3(A) & Figure 3(B)), whereas $\beta$-amyloid

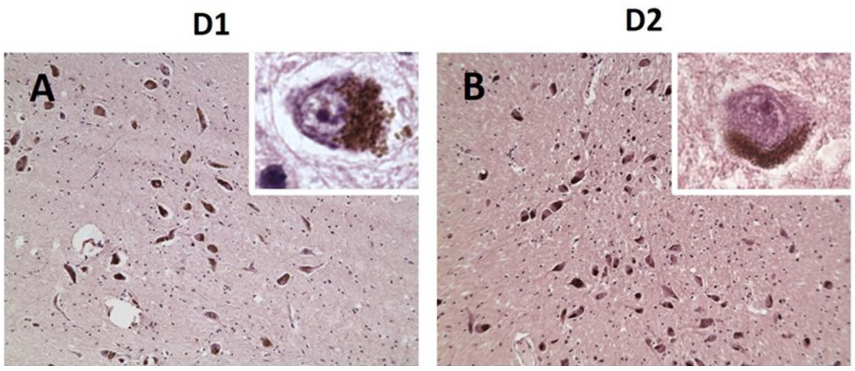


Figure 1. Absence of Lewy Body Disease related pathology in D1 and D2. The H&E-stained substantia nigra of D1 (A) and D2 (B) show well-preserved pigmented neuronal cells without Lewy bodies. Magnification ×200, inserts ×630.

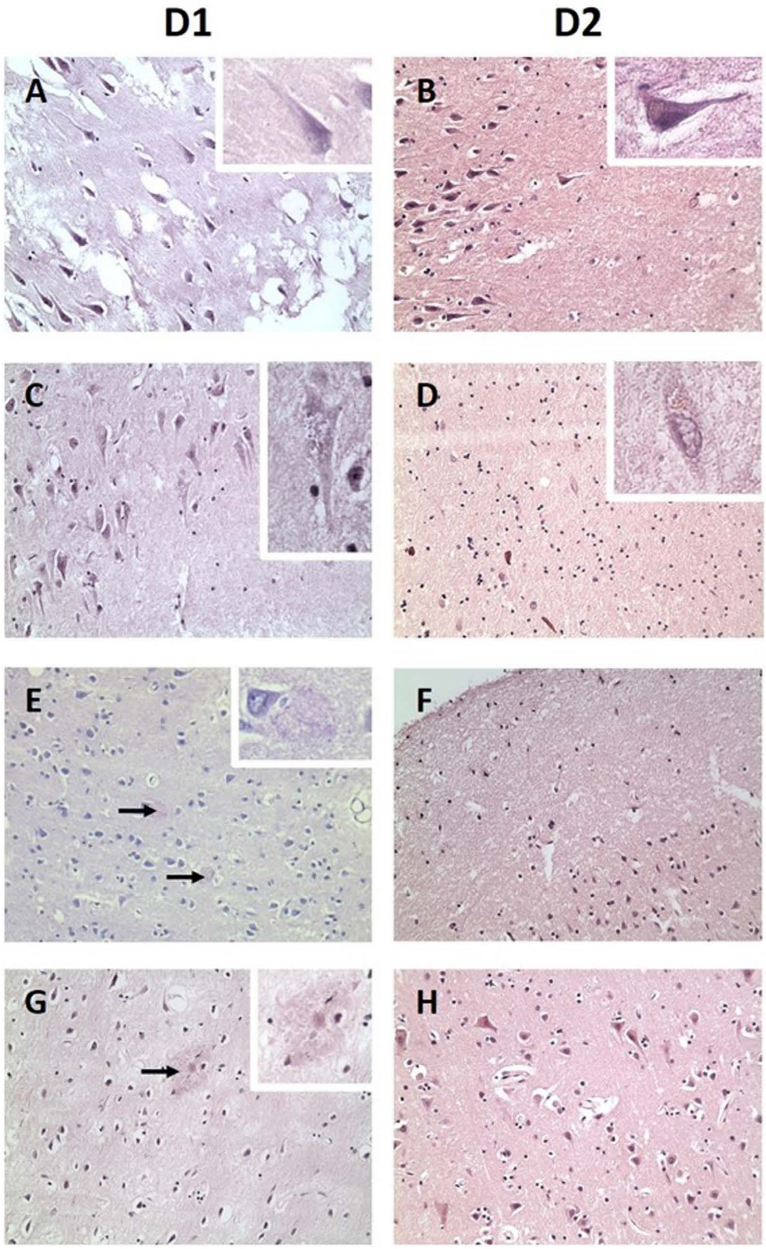


**Figure 2.** AD related pathology in D1 and D2. H&E staining shows neurofibrillary tangles in the hippocampi of D1 (A) and D2 (B). Granulovacuolar degeneration is evident in the hippocampi of both individuals (C and D). Amyloid plaques are present in both the frontal (E) and occipital cortices (G) of D1 (arrows) but are absent in the frontal (F) and occipital cortices (H) of D2. Magnification ×200, inserts ×630.

staining revealed abundant senile plaques only in the D1 hippocampus (**Figure 3(C)** & **Figure 3(D)**). Overall, the severity of the respective Alzheimer's type pathology in the D1 brain could be characterized by its clinical stage as mild to moderate. Unexpectedly, a specific and diffuse $\beta$-amyloid staining, which retained its presence upon a serial dilution of the primary antibody, was observed in the D1 and, to a lesser extent, in D2 cerebellar neurons, particularly in the Purkinje cells (**Figure 4**) and in the neurons of the dentate nucleus (**Figure 5**).

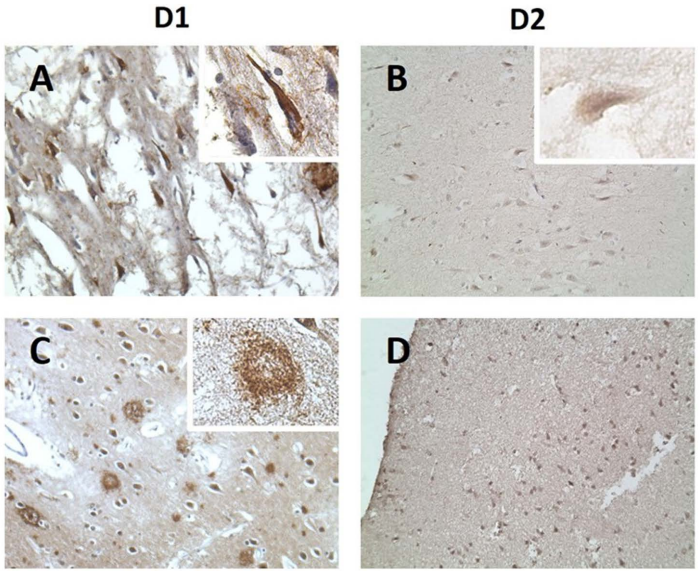


**Figure 3.** AD related pathology in D1 and D2 as probed by immunohistochemistry. Phospho-tau staining reveals neurofibrillary tangles in the hippocampi of D1 (A) and D2 (B). Staining for $\beta$-amyloid shows presence of abundant plaques in D1 (C) but their absence in D2 (D). Magnification ×200, inserts ×630.

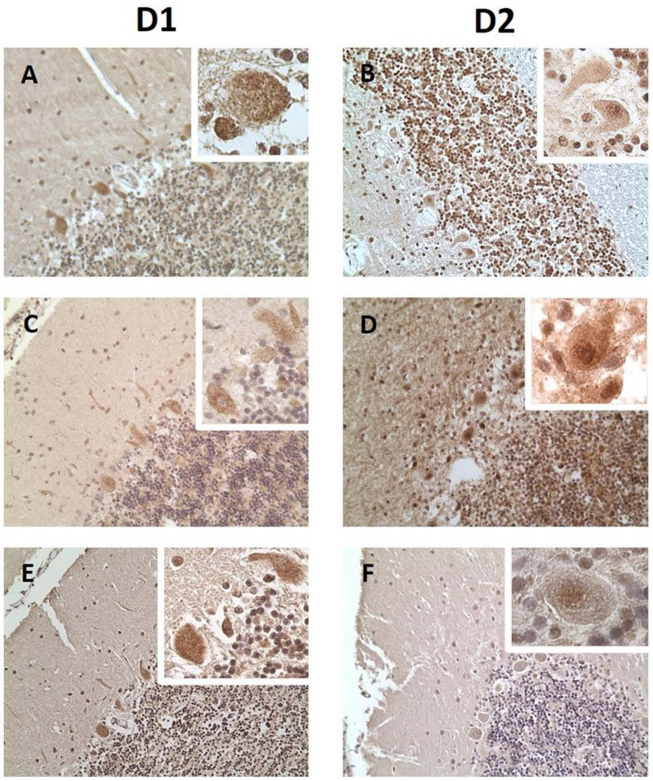


**Figure 4.** Immunohistochemical staining for $\beta$-amyloid in the D1 and D2 cerebelli. Specific, diffuse staining is most prominent within cerebellar Purkinje cells and is observed in D1 at the primary antibody dilutions of 1:500 (A), 1:1000 (C), and 1:2000 (E). In D2, similar $\beta$-amyloid staining is present at the primary antibody dilutions of 1:500 (B) and 1:1000 (D) but is almost absent at 1:2000 dilution (F). Sections were counterstained with hematoxylin. Magnification ×200, inserts ×630.

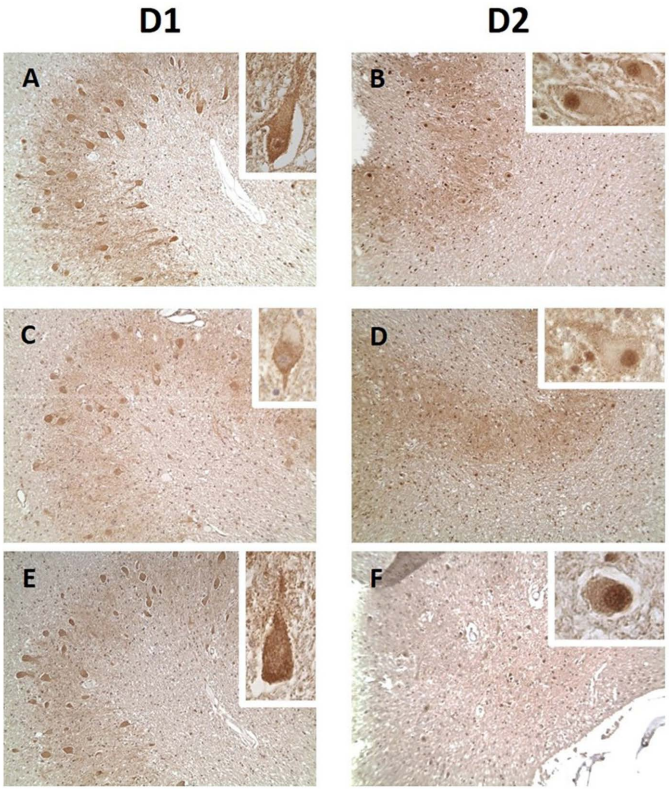


**Figure 5.** Immunohistochemical staining for $\beta$-amyloid in the dentate nucleus of the cerebellum of D1 and D2. Diffuse $\beta$-amyloid staining is observed in D1 at the primary antibody dilutions of 1:500 (A), 1:1000 (C), and 1:2000 (E). In D2, the $\beta$-amyloid staining is present at the primary antibody dilutions of 1:500 (B) and 1:1000 (D) but is almost absent at 1:2000 dilution (F). Sections were counterstained with hematoxylin. Magnification ×100, inserts ×630.

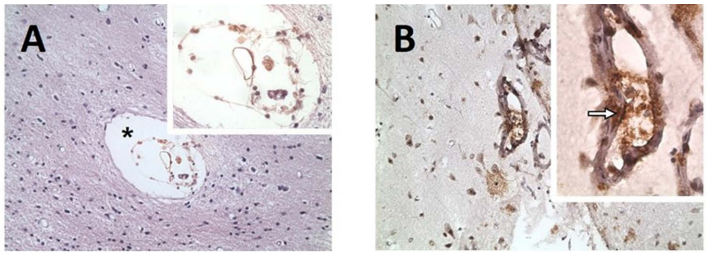


**Figure 6.** Cerebrovascular disease (CVD) related pathology in D1. H&E staining of the frontal cortex of Donor 1 (A) shows the presence of microbleeds and expanded Virchow Robin spaces (asterisk). $\beta$-amyloid immunohistochemical staining of the frontal cortex (B) reveals deposits of $\beta$-amyloid within the vessel wall (white arrow) and lumen. Magnification ×200, inserts ×630.

Importantly, there were also vascular changes in the D1 brain consistent with hypertensive CVD including hyaline atherosclerosis, microbleeds, and dilated Virchow Robin spaces (Figure 6(A)). Some blood vessels showed $\beta$-amyloid deposits within the vessel wall which is indicative of amyloid angiopathy (Figure 6(B)). A striking vascular pathology including thick-walled blood vessels with microbleeds was observed in D2 without evidence for amyloid angiopathy (Figure 7).

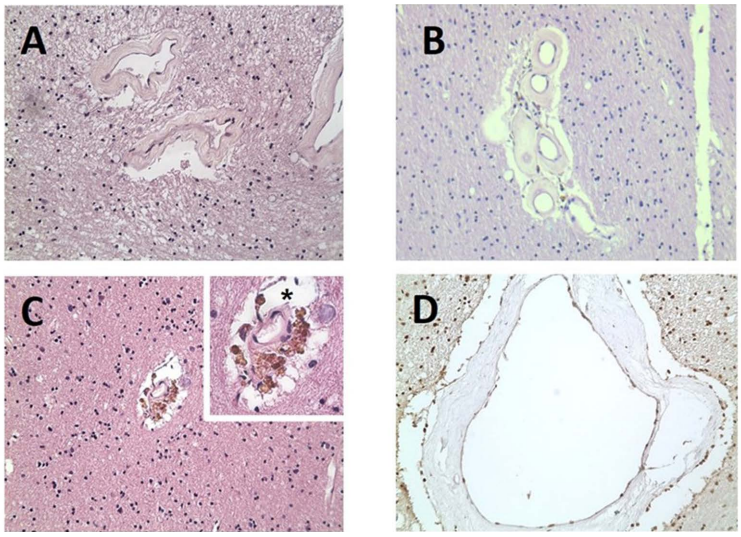


**Figure 7.** Cerebrovascular disease (CVD) related pathology in D2. H&E staining of Donor 2 shows concentric wall thickening of cerebral vasculature within the frontal cortex (A) and hippocampus (B) as well as microbleeds and expanded Virchow Robin space (asterisk) in the frontal cortex (C). $\beta$-amyloid immunohistochemical staining of the frontal cortex (D) shows an absence of $\beta$-amyloid within the vessel walls and lumen. Magnification ×200, insert ×630.

## 4. Discussion

The significance of the current findings is severalfold. First, the neuropathological examination of D1 demonstrated that AD could be present in elderly BD/SCZ patients and advance to its clinical stage associated with cognitive impairment, thereby potentially contributing to dementia development in OABD patients. Therefore, the reports such as [9] [12] not supporting the AD contribution to the latter process should be viewed with caution until more information becomes available from the respective studies including a larger number of postmortem cases unequivocally confirming the absence of AD related pathology in OABD patients with cognitive impairment.

Second, a mixed AD type and CVD pathology could mimic Lewy Body Disease in older individuals as it was demonstrated by both the D1 and D2 postmortem examination. This would emphasize a need for improved, or new diagnostic methodologies and/or diagnostic tools for the reliable assessment of Lewy Body Disease in older individuals.

Third, the observed diffuse intra- and extraneuronal staining in the D1 and D2 cerebelli is intriguing. Although the association of the $\beta$-amyloid plaque formation in the cerebellum with the clinical AD stage II (Phase 5) is well established [18], the role of soluble $\beta$-amyloid is much less known and appreciated. It was reported previously that the severity of dementia in AD, as well as the degree of the respective synaptic loss, is correlated strongly with the amount of soluble $\beta$-amyloid [19] [20], but correlates rather weakly with that of insoluble, fibrillar form of $\beta$-amyloid known to form senile plaques [21] [22]. These findings are supported by a study using a mouse model of familial AD where the accele-

rated neurodegeneration was demonstrated in the absence of $\beta$-amyloid plaques [23]. In rat brain, the amyloid beta precursor protein gene (App) expression is widespread with particularly strong levels in Purkinje cells and cerebellar granule cells [24]. The APP protein and its N-terminal fragments are accumulated in the cerebellum and Purkinje cells in the brain of aged rats [25]. Purkinje cells were reported to play an important role in the formation of the diffuse amyloid plaques in the cerebellum of patients with sporadic AD [26]. This process is initiated by the accumulation of A$\beta$1-42 peptide in the Purkinje cells perikaryons and dendrites, especially at the dendrite bifurcation points, which is then followed by dendritic rupture and the release of A$\beta$1-42 peptide into the extracellular space to form diffuse plaques in the cerebellum [26] [27] thereby contributing to dementia development in AD patients [28]. The monoclonal A$\beta$1-42 antibody used in the present study is highly specific and showed a similar staining pattern in D1 and, to a lesser extent, in D2 even when used at the concentrations 2 to 4-fold less than recommended by the manufacturer (see Supplementary Materials and **Figure 4** & **Figure 5**). Therefore, one could speculate that the observed diffuse intra- and extraneuronal staining in the D1 and D2 cerebelli represents, most likely, the soluble form of this peptide, monomeric or otherwise. If so, this would be indicative of the pathological changes in the stimulated APP metabolism in the cerebellum at the steps preceding those associated with the A$\beta$1-42 peptide fibrillar form accumulation and the subsequent neuritic plaque formation. It is tempting to speculate that those preceding steps in the pathologic APP metabolism and resultant diffuse A$\beta$1-42 staining in the cerebellum would bear significant importance for a correct AD diagnosis and staging in elderly individuals. In this regard, one could speculate that the failure to observe decreased levels of A$\beta$1-42 in the CSF of OABD patients with cognitive impairment as a component of AD biosignature [12] could be explained, at least in part, by the unabated supply of soluble A$\beta$1-42 peptide to CSF through the fourth cerebral ventricle adjacent to the cerebellum. Such cerebellar A$\beta$1-42 peptide outflow in AD setting could compensate for the diminished peptide entry into CSF from other cerebral locations where the majority of A$\beta$1-42 peptide is entrapped in amyloid plaques.

Fourth, the current report has a high educational value because it points to a possibility of the Lewy Body Disease misdiagnosis in elderly patients with BD/SCZ and/or dementia.

## 5. Conclusion

1) AD could be present in elderly BD/SCZ patients and advance to the clinical stage associated with cognitive impairment. 2) CVD in conjunction with AD could mimic Lewy Body Disease and contribute to dementia development in older BD/ SCZ patients. 3) A proper diagnosis of dementia associated with mixed CVD/AD pathology in elderly patients with BD/SCZ would be important for their adequate treatment and care.

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## Limitations

The study was performed with a small number of cases.

## Authors' Contributions

All authors have read and approved the final version of the manuscript.

## Funding

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## Disclosure

These data were presented in part at the Annual Experimental Biology Meeting (*FASEB J.* (2022), **36**: S1, Abstract 783.4).

## Conflicts of Interest

The authors declare that they have no competing interests.

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