Scientific Research Publishing

Open Journal of Pathology, 2025, 15(3), 99-109
https://www.scirp.org/journal/ojpathology
ISSN Online: 2164-6783
ISSN Print: 2164-6775

Unique Case of Remarkably Delayed Dementia in an Elderly Individual after a Massive Stroke: Neuropathological and Genetic Insights

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How to cite this paper: Frolov, A., Meyer, D., Guzman, M.A. and Martin, J.R. (2025) Unique Case of Remarkably Delayed Dementia in an Elderly Individual after a Massive Stroke: Neuropathological and Genetic Insights. *Open Journal of Pathology*, **15**, 99-109.
https://doi.org/10.4236/ojpathology.2025.153009

Received: April 3, 2025
Accepted: May 10, 2025
Published: May 13, 2025

Abstract

Stroke is a neurological disorder defined as an interruption of blood delivery to the brain resulting in impairment of brain function often leading to patient's death or major disability. Stroke survivors face a high risk of developing dementia which is a major cause of post-stroke morbidity and mortality. Dementia occurring 3 - 6 months after stroke is termed late-onset post-stroke dementia (LOPSD) and has gained a significant interest from researchers because such delay, which could last for several years, offers a reasonable time window for early dementia diagnosis and preventive treatment. However, little is known about biological process (es) underlining LOSPD. To address this issue, we studied a case of an 85-year-old individual who had stroke with right-side paralysis and aphasia with dementia onset 22 years later. The cause of death for this individual was bladder cancer. By using a combination of post-mortem neuropathological examination and genetic screening by whole exome sequencing (WES) on the Illumina next generation sequencing (NGS) platform we identified the respective pathological and genetic underlining. The former was characterized by pronounced cerebral small vessel disease (cSVD) and Alzheimer's disease (AD) related pathologies that were known to be associated with LOSPD. The latter revealed a presence of multiple pleiotropic genes with rare (minor allele frequency, MAF ≤ 0.01) pathological/deleterious variants that were grouped into the following categories: Cardiovascular Disease, Stroke, Vascular Pathology, Cognitive Impairment/Dementia, Alzheimer's Disease, Vascular Dementia, and Parkinson's Disease. Surprisingly, the genetic pleiotropy was observed not only across those categories but also across an additional category "Cancer" including bladder cancer. The mucin gene family members *MUC2*, *MUC4*, and *MUC6* were the ones of such

pleiotropic genes. The results obtained pointed toward a potential involvement of the gut-brain and bladder-gut-brain axes as well as a putative crosstalk between cancer and dementia in the development of LOPSD in an elderly individual.

Keywords

Stroke, Post-Stroke Dementia, Alzheimer's Disease, Cerebrovascular Disease, Whole Exome Sequencing, Next Generation Sequencing

1. Introduction

Stroke is a leading cause of disability in the United States [1] [2]. Approximately 610,000 Americans suffer from an incident stroke each year, with the probability of death in the following 5 years ranging from 19% to 67%, depending on demographics [2] [3]. Along with focal neurological deficits, dementia is another common result of stroke found among survivors with up to one third estimated to have post-stroke cognitive impairment [4]. The latter along with dementia represents a major underlining cause for morbidity and mortality in patients after stroke [1]. As stroke mortality rates have been slowly decreasing and life expectancy increasing, possibly due to advances in patient care, delayed-onset post-stroke dementia (PSD) has begun to receive increased attention primarily because of its high disability and mortality risks [2] [5]. In contrast to early-onset PSD, which defines the development of dementia within 3 - 6 months after stroke onset, delayed-onset PSD describes dementia development any time thereafter and has a prevalence of 4.4% - 23.9% [5]. Early-onset dementia is mostly associated with dementia-prone stroke lesions, *i.e.* cerebral infarcts affecting large brain areas or infarcts targeting brain cognition centers, whereas delayed-onset dementia is mostly driven by severe cerebral small vessel disease (cSVD) (60% of delayed-onset PSD cases) and Alzheimer's disease (AD) related pathologies (less than 20% of delayed-onset PSD cases) [5].

Given the complex etiology of post-stroke dementia, particularly of its delayed-onset form, there is a paucity of information regarding the molecular mechanism (s) governing those processes which resulted in disappointing outcomes of clinical trials aimed at development of an efficient treatment for post-stroke cognitive impairment and dementia [5]. With that in mind, we took advantage of a unique opportunity to study post-mortem a case of an 85-year-old male with a history of stroke and PSD onset delayed by 22 years. The results of this study where we used a combination of neuropathological examination and genetic screening by WES on the NGS Illumina platform are presented in this report. It was concluded that such a long delay in LOPSD observed in the current case could be explained, at least in part, by an aberrant activation of the gut-brain and bladder-gut-brain axes with a potential contribution from cancer-dementia crosstalk.

2. Methods

2.1. Human Cadaveric Body Procurement

The body of an 85-year-old male was received through the Saint Louis University (SLU) Gift Body Program with signed informed consent. This individual had a stroke at the age of 59 with the right-side paralysis and aphasia followed by dementia onset 22 years later. The cause of death was bladder cancer. The body was 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 brain extraction and dissection were performed as previously described [6].

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) and Bielschowsky Silver stain according to standard procedures of the Advanced Spatial Biology and Research Histology Facility (Department of Pathology, SLU School of Medicine). The immunohistochemical staining for phospho-tau and β-Amyloid peptide 1-42 (Aβ1-42) was performed exactly as previously described [6] 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 equipped with a DFC7000 T camera and controlled by the Neurolucida software (MBF Bioscience, Williston, VT, USA) using the 10×, 20×, and 63× objectives.

2.5. Genetic Analysis

The postmortem genetic screening by WES on the Illumina NGS platform and the respective bioinformatics analysis were performed as previously described [7] [8]. The cumulative exome coverage for 50× depth of coverage was 92%.

3. Results

3.1. Neuropathological Examination

Gross anatomical examination of the excised brain revealed a large necrotic area present in the left cerebral hemisphere, affecting parts of the frontal, parietal, and temporal lobes (**Figure 1(a)**). An enlarged frontal horn of the left ventricle (arrow), a common observation in those with AD, was also seen in a coronal section through the anterior commissure (**Figure 1(b)**).

Histological examination of the brain tissue stained with hematoxylin and eosin

(H&E) revealed neuronal loss throughout much of the frontal and parietal cerebral cortices, with white matter rarefaction (Figure 2).

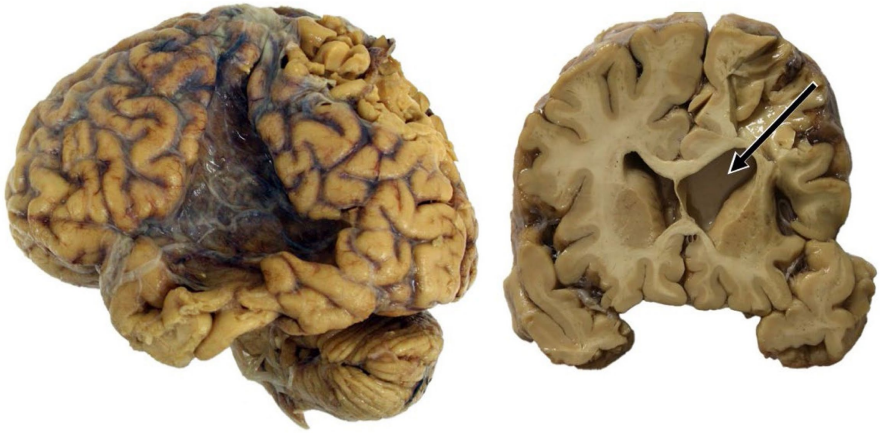

Figure 1. (a). Macroscopic lateral view of the left hemisphere displaying the necrotic area. (b). Coronal section showing the enlarged left frontal horn of the lateral ventricle (arrow).

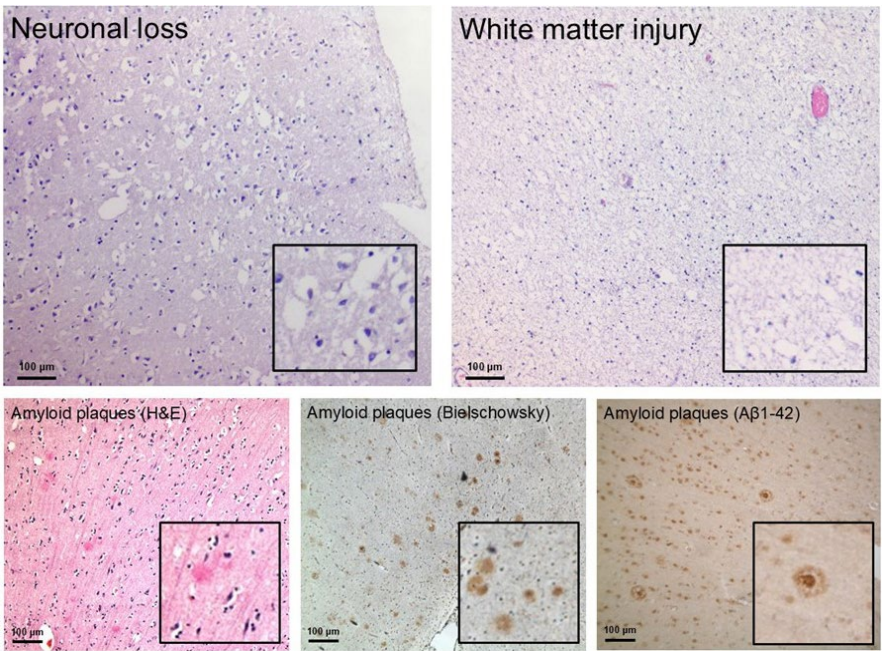

Figure 2. Alzheimer's disease pathology in the cerebral hemisphere.

AD related pathology was observed with numerous amyloid plaques identified in the cortex and hippocampus as well as by neurofibrillary tangles (NFT)s present in the hippocampus (Figure 3).

Additionally, several pathological changes of cerebral vasculature were found in the frontal cortex, hippocampus, and basal ganglia. These included arteriosclerosis, cerebral amyloid angiopathy, cerebral microbleeds, and enlarged perivascular spaces (PVS) (Figure 4).

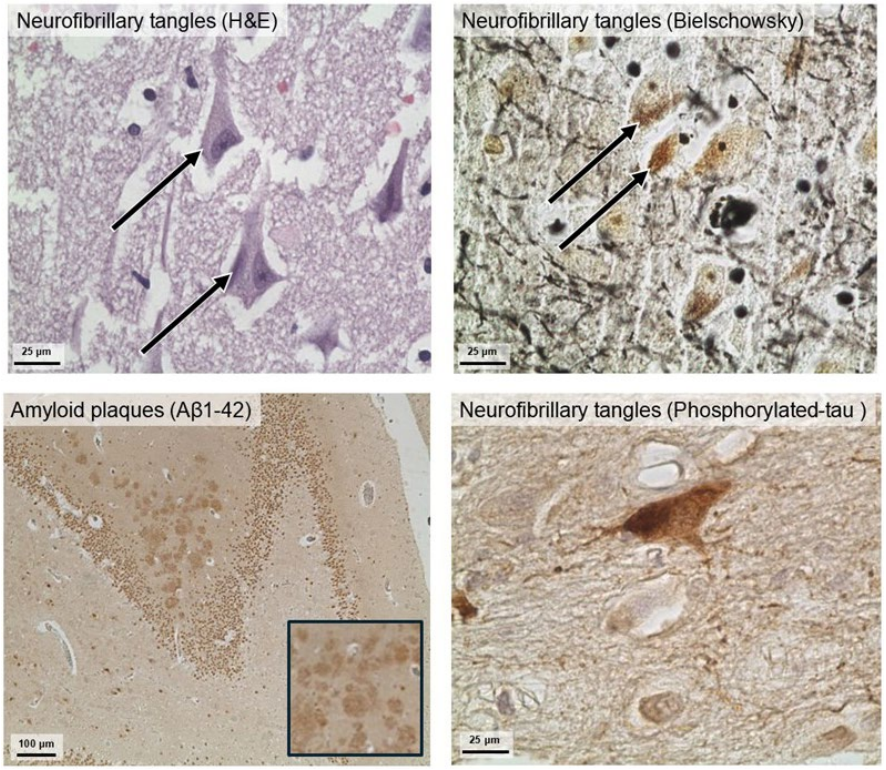

Figure 3. Alzheimer's disease pathology in the hippocampus. Neurofibrillary tangles (NFTs) are indicated by arrows.

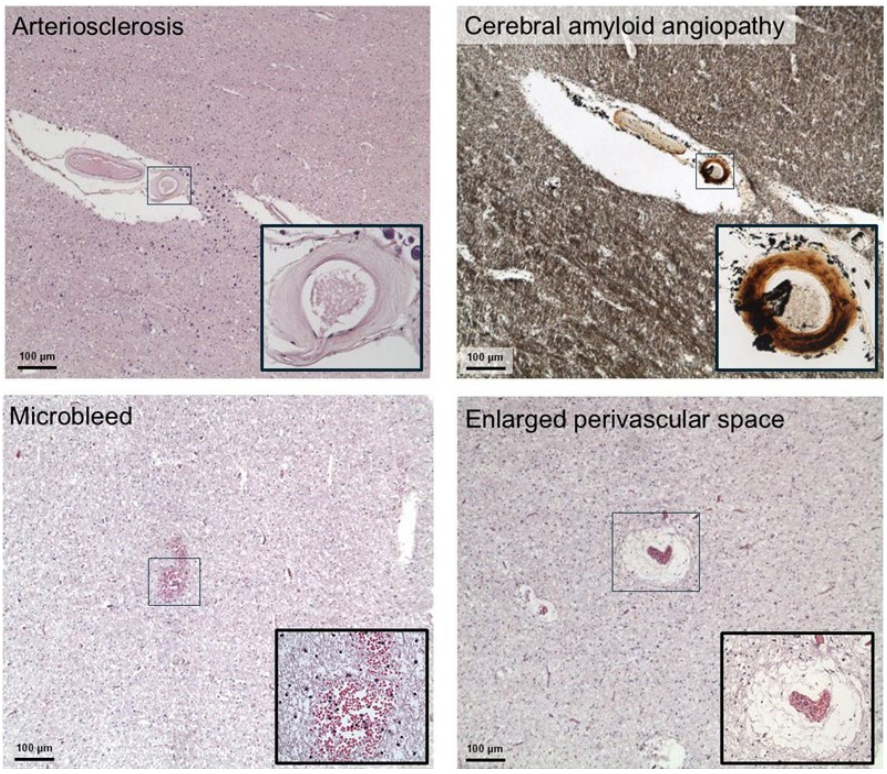

Figure 4. Vascular pathology in the cerebral hemispheres. Cerebral amyloid angiopathy is shown by Bielschowsky staining.

3.2. Genetic Screening

Following a very stringent filtering process [7] [8], genes with rare (minor allele frequency, MAF ≤ 0.01) pathological/deleterious variants were grouped based on the GeneCards, Google Scholar, and PubMed searches into the following categories: Cardiovascular Disease, Stroke, Vascular Pathology, Cognitive Impairment/Dementia, Alzheimer's Disease, Vascular Dementia, and Parkinson's Disease (Table 1).

Table 1. Genes with rare pathological/deleterious variants in the present case linked to cardiovascular and neurological pathologies.

Categories	Genes
Cardiovascular Disease	*ABHD16B*, *ABHD17A*, *C16ORF47*, *CAVIN2*, *CEL*, *CELSR1*, *ERV3-1*, *FLNB*, *FRMD4B*, *KCNJ12*, *KMT2C*, *LIPI*, *MTHFSD*, *MUC2*, *MYCT1*, *NCEH1*, *NEBL*, *NR4A1*, *PCK2*, *PDE1A*, *PLXND1*, *PSMF1*, *SEPTIN10*, *SLC22A6*, *SLC35G1*, *SLC9B1*, *SPOCD1*, *THBS2*, *TTN*, *ZNF561*
Stroke	*AQP7*, *CFHR5*, *DNASE1*, *FCGBP*, *FLNB*, *G6PC2*, *GPBP1L1*, *GRIN2C*, *GTF2H2**, *HAVCR1*, *HMMR*, *ITSN2*, *KIR2DL1*, *MUC2*, *MUC4*, *NR4A1*, *PDE1A*, *SENP6*, *SHANK1*, *SLC22A6*, *SLIT1*, *TCIRG1*, *THBS2*
Vascular Pathology	*C16ORF47*, *CPZ*, *HMMR*, *SLC12A9*, *SMG7*
Cognitive Impairment/ Dementia	*CKAP2*, *COL11A2*, *DNAH10*, *DNASE1*, *FBLN7*, *FCGBP*, *G6PC2*, *HLA-DRB5*, *HYDIN*, *IRF2BPL*, *MUC2*, *MUC4*, *NEBL*, *NGEF*, *NR4A1*, *PRSS1*, *PSMF1*, *TH*, *UBXN11*, *ZNF717*, *ZNF778*
Alzheimer's Disease	*ANKRD20A1**, *AQP7*, *ASIC2*, *BRD3BP*, *C9*, *CDC14C*, *CKAP2*, *DNAH10*, *DNASE1*, *EHBP1*, *ELFN2*, *FCGBP*, *FIBCD1*, *FRMD4B*, *GRIN2C*, *GTF2H2**, *HAVCR1*, *HKDC1*, *HLA-DRB5*, *HMMR*, *ITSN2*, *MUC6*, *MYO18A*, *NEBL*, *NGEF*, *PCK2*, *PLXND1*, *PSMF1*, *RHBDD3*, *SEC63*, *SHANK1*, *SLC22A6*, *SLC35G1*, *SLIT1*, *SMG7*, *SPATA31A1*, *SPOCD1*, *TCIRG1*, *TH*, *THBS2*, *WDR87*, *ZMIZ2*
Vascular Dementia	*FCGBP*, *THBS2*
Parkinson's Disease	*BRD3BP*, *DNAH1*, *ELFN2*, *KCNJ12*, *NGEF*, *PDCD2*, *PDE1A*, *PSMF1*, *PSMF1*, *TBP*, *TTC38*

*Biallelic variant.

These particular categories were chosen as being the most relevant to the present case based on the respective pathologies noted in the donor's medical history as well as on the current results of neuropathological examination of the donor (see above). As is seen from Table 1, each of the above categories had multiple entries pointing to a very complex genetic underlining of the present case. Unexpectedly, many of the genes listed in Table 1 appeared to be pleiotropic as they were not only present in more than one category but could also be linked to can-

cer, including bladder cancer, the cancer type causing the donor's death (Table 2).

Table 2. Genes with rare pathological/deleterious variants in the present case linked to cancer as well as to cancer shared with cardiovascular and neurological pathologies.

Categories	Genes
Cancer	*ARSD*, *CCDC*39, *CDRT*1, *CGB*2¶, *CNTNAP*3*B**, *CST*5, *DENND*6*B*, *FICD*, *FIGN***, *FIP*1*L*1, *FOXD*4*L*5, *FOXD*4*L*6, *GANAB*¶, *GOLGA*6*L*3, *HEATR*3¶, *HGC*6.3, *HMMR*, *HRNR*¶, *IGSF*3, *KMT*2*C*, *KRTAP*10-6, *KRTAP*2-2, *LIPM*, *MAP*3*K*19, *MED*16, *MST*1*L*, *NFE*2, *OR*10*K*1***, *PKHD*1, *POTEG*, *POTEH*, *PRAMEF*1, *PRAMEF*18*, *PRSS*3, *RPP*30, *STARD*8*, *TEKT*4, *TRIM*48, *TUT*1, *ZDBF*2, *ZNF*585*A*¶
Cancer/Cardiovascular Disease	*ABHD*17*A*, *C*16*ORF*47, *CAVIN*2, *CELSR*1**, *ERV*3-1¶, *FLNB*, *FRMD*4*B*, *HAVCR*1, *HEATR*5*B*, *KCNJ*12***, *LIPI*, *MUC*2¶, *MYCT*1, *NR*4*A*1, *PCK*2, *PDE*1*A*, *PLXND*1, *SEPTIN*10, *SLC*22*A*6, *SLC*9*B*1, *SPOCD*1, *THBS*2, *ZNF*561
Cancer/Stroke	*CFHR*5, *FCGBP*, *FLNB*, *GPBP*1*L*1, *GRIN*2*C*, *GTF*2*H*2* *HAVCR*1, *HMMR*, *ITSN*2, *KIR*2*DL*1, *KPNA*2, *MUC*2¶, *NR*4*A*1, *PDE*1*A*, *SENP*6, *SHANK*1**, *SLC*22*A*6, *SLIT*1, *TCIRG*1, *THBS*2
Cancer/Vascular Pathology	*C*16*ORF*47, *CPZ*, *PSMF*1, *SLC*12*A*9, *SMG*7
Cancer/Cognitive Impairment/Dementia	*BAGE*2, *C*9, *CKAP*2, *FBLN*7, *FCGBP*, *HYDIN*, *MUC*2¶, *MUC*4¶, *NR*4*A*1, *PRSS*1, *PSMF*1, *TH*, *UBXN*11, *ZNF*717
Cancer/Alzheimer's Disease	*ANKRD*20*A*1*, *AQP*7¶, *BRI*3*BP*, *C*9, *CKAP*2, *DNAH*10, *DNAH*8, *DNAJB*7, *EHBP*1, *ELFN*2**, *FCGBP*, *FIBCD*1, *FRMD*4*B*, *GRIN*2*C*, *GTF*2*H*2*, *HAVCR*1, *HEATR*5*B*, *HKDC*1, *HMMR*, *ITSN*2, *MUC*6¶, *MYO*18*A*, *NR*4*A*1, *PCK*2, *PSMF*1, *RHBDD*3, *SEC*63, *SHANK*1**, *SLC*22*A*6, *SLIT*1, *SMG*7, *SPATA*31*A*1*, *SPOCD*1, *TCIRG*1, *TH*, *THBS*2, *WDR*87, *ZMIZ*2
Cancer/Vascular Dementia	*FCGBP*, *THBS*2
Cancer/Parkinson's Disease	*BRI*3*BP*, *DNAH*1, *ELFN*2**, *KCNJ*12***, *PDCD*2, *PDE*1*A*, *PSMF*1, *PUSL*1, *PSMF*1, *TBP*, *TTC*38

*Biallelic variant; **Oncogene; ***Driver mutation gene in cancer; ¶Bladder cancer.

4. Discussion

The current case of remarkably delayed, by more than two decades, dementia in an elderly individual after a massive stroke and who eventually succumbed to bladder cancer could provide important insights into the etiology of stroke and

post-stroke dementia. *First*, the results of neuropathological examination revealed this case as a massive stroke affecting predominantly the left hemisphere of the donor's brain being consistent with the right-side paralysis and aphasia noted in the donor's medical history. The detection of pronounced neuropathologies related to AD (amyloid plaques and NFTs), and vascular dementia (arteriosclerosis and microbleeds) point toward a possible development of mixed dementia at the terminal stage of the donor. *Second*, the presence of multiple mutated genes linked to stroke, including those involved in post-stroke recovery, *MUC*2 [9], *MUC*4 [9], and *SLIT*1 [10], was consistent with stroke having a polygenic underlining. *Third*, very interesting was an association of three affected mucin gene family members with dementia and AD—*MUC*2 [11], *MUC*4 [11], and *MUC*6 [12]—which point toward a potential role of the gut-brain axis in the development of post-stroke dementia in the present case [13] [14]. Intriguingly, the same genes were also linked to bladder cancer: *MUC*2 [15] [16], *MUC*4 [16], and *MUC*6 [15]. Therefore, given an intricate inverse relationship between cancer and dementia in general [17] and between cancer and AD in particular [18]-[22] we may conclude that remarkably delayed (by 22 years) post-stroke dementia in the current case could be explained, at least in part, by mutually opposing effects of co-developing mixed dementia and bladder cancer in the donor. An adversely activated bladder-gut-brain axis [23] [24] may also serve as a contributing factor in the above process. It is worth noting that mutated genes associated with dementia were detected earlier in cancer patients [25] and affected cancer related pleiotropic genes have been recently found in an individual with amyotrophic lateral sclerosis [26].

5. Conclusions

The results of the current study highlight potential involvement of the gut-brain and bladder-gut-brain axes as well as cancer comorbidity in the development of a remarkably delayed post-stroke dementia in the elderly individual.

The presence of a plethora of mutated pleiotropic genes involved in both cancer and stroke, cognitive impairment/dementia, AD, PD, and vascular dementia warrants a closer look at a putative link between cancer and neurological disorders.

Given that the current case describes a post-mortem, single-patient study, the respective results and conclusions should be viewed as an important lead for follow-up ante-mortem studies using a large cohort of patients diagnosed with post-stroke dementia and comorbid cancer.

Acknowledgements

We are grateful to all individuals and their families for their invaluable contribution to SLU Gift Body Program. We also like to thank Dr. Paul Cliften (Genome Technology Access Center, Washington University in St. Louis, St. Louis, MO, USA) for his expert assistance with the bioinformatics analysis as well as Caroline Murphy (Advanced Spatial Biology and Research Histology Core, SLU SOM) for her skillful help with the histology slides preparation.

Limitations

The study was performed with a small number of cases.

Authors' Contribution

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

Disclosure

These data were presented in part as an abstract at the Experimental Biology Meeting on April 27-30, 2021.

Funding

This study was supported by the Center for Anatomical Science and Education, SLU School of Medicine.

Conflicts of Interest

The authors declare that they have no competing interests.

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