The Canadian Journal of Neurological Sciences (2024), 1–3
doi:10.1017/cjn.2024.22

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Letter to the Editor: New Observation

Colpocephaly and Partial Agenesis of Corpus Callosum with High Neurodegenerative Marker Levels

Abrar Ahmed[1], Simrika Thapa[2,3], Anna Vasilevskaya[2,3], Paula Alcaide-Leon[4] and Maria Carmela Tartaglia[2,3]

[1]Schulich School of Medicine University of Western Ontario, London, Canada, [2]Tanz Centre for Research on Neurodegenerative disease. University of Toronto, Toronto, ON, Canada, [3]UHN Memory Clinic, Krembil Brain Institute, University Health Network, Toronto, ON, Canada and [4]Division of Neuroradiology, Joint Department of Medical Imaging, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, ON, Canada

Keywords: Alzheimer's disease; agenesis of corpus callosum; colpocephaly; neurodegeneration

Agenesis of the corpus callosum (AgCC) may occur with colpocephaly.[1] We present a case of elevated neurodegenerative biomarker levels in a patient with colpocephaly and partial AgCC.

A patient in their 50s complained of behavioral and progressive memory and cognitive issues beginning in their mid-forties after having sustained a fall related mild traumatic brain injury (mTBI). Post-concussion symptoms developed including headache, vertigo and dizziness. The physical symptoms largely resolved but the cognitive complaints slowly worsened. Although working full time, the patient reported difficulties remembering recent training sessions, and misplacing objects. They endorsed issues with word-finding, phonemic substitution and following conversations with multiple participants. The patient expressed frustration with multi-tasking, problem-solving, planning and navigating in familiar places.

The patient was independent for basic and most instrumental activities of daily life but their partner was managing finances due to reduced organizational skills. Although irritable, the patient denied other neuropsychiatric symptoms. They reported body, hands and legs paresthesia and pain in the right arm, bilateral legs and lower back. They had tension type headaches once a week, positional vertigo and right ear tinnitus.

The patient had normal physical and psychomotor development and no dysmorphic features were found on the exam. They smoked until their early 20s and drank wine and beer occasionally. The patient used CPAP 4–6 hours/night for their sleep apnea and oral cannabinoids for chronic pain but was on no other medications. There was no familial history of neurodegenerative disease, developmental delay, cognitive impairment, epilepsy or genetic syndromes, but the patient's father passed away from a stroke at age 60. The patient's mother was alive at first assessment.

The patient underwent four consecutive, yearly visits consisting of a neuropsychological assessment (Toronto Cognitive Assessment [TORCA])[2] or Montreal Cognitive Assessment (MOCA) and neurological exam. A lumbar puncture was performed according to Alzheimer's Disease Neuroimaging Initiative protocol.[3] Laboratory investigations included an evaluation of Alzheimer's disease (AD) biomarkers using an enzyme-linked immunosorbent assay to measure phosphorylated tau (pTau) (Innotest phospho-tau 181p, Fujirebio), total tau (T-Tau) (Innotest hTau-Ag, Fujirebio) and Amyloid beta 1-42 (Ab1-42) (Innotest B-Amyloid 1-42, Fujirebio) following the manufacturer's instruction. A SIMOA immunoassay Neurology 2-Plex B assay kit was performed on an SR-X instrument (Quanterix) to measure cerebrospinal fluid (CSF) neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP).

During visit one, the patient scored 311/330 on the TorCA, which is in the normal range, but verbal memory on CERAD was low (Supplementary table 1). One year later, the patient scored 19/22 on a telephone Blind MOCA (lost 2 points for delayed recall, 1 for serial 7s). One year afterwards, the patient scored 23/30 (lost 1 point for clock, 1 for serial 7s and 5 points for delayed recall). A repeat TorCA performed four years after the first time point showed no change in score (308/330) and better performance on CERAD (Supplementary table 1). Neurological exam revealed mild atrophy in the right hypothenar eminence with occasional fasciculations with full power, normal tone, symmetrical 2+ reflexes and downgoing plantar response. Their partner helps open jars and cut their food. EMG/NCS performed in Oct. 2019 was normal. An MRI of the brain was ordered to investigate the patient's reported dizziness. Incidentally, the T1 weighted 1.5T MRI showed partial AgCC and symmetrical biparietal atrophy (Fig. 1). Alzheimer's biomarkers (Ab1-42, phospho tau, total tau), neurodegenerative and astrocytic markers (Table 1), suggest that the patient was negative for AD.

To the best of our knowledge, this is the first description of elevated levels of CSF T-Tau, NfL and GFAP in a patient with partial AgCC and colpocephaly that was AD biomarker negative. While tau protein promotes the assembly of axonal microtubules, tau hyperphosphorylation results in pathological aggregation into neurofibrillary tangles, which is a neurodegenerative process.[9] NfL proteins aid neuronal stability but NfL is increased in neurodegenerative diseases.[10] GFAP acts to support cytoskeletal structure within astrocytes.[8] Neurodegenerative disease may injure astrocytes resulting in the extracellular release of GFAP.[8]

Corresponding author: M. C. Tartaglia; Email: carmela.tartaglia@uhn.ca

Cite this article: Ahmed A, Thapa S, Vasilevskaya A, Alcaide-Leon P, and Tartaglia MC. Colpocephaly and Partial Agenesis of Corpus Callosum with High Neurodegenerative Marker Levels. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2024.22

Table 1: Laboratory values of neurodegenerative markers found in the patient

Analyte	Values	Alzheimer Disease cutoffs
pTau	76 pg/mL	>68 pg/ml [4,5]
T-Tau	459 pg/ml	>300 pg/ml[4,5]
Ab1-42	1159 pg/ml	<557 pg/ml[6]
ATI:	1.48	<0.80[4,5]
NfL	661.24 pg/ml	>1024 pg/ml[7]
CSF GFAP	26,290.96 pg/ml	No cutoffs available. Mean ± SD Cognitively unimpaired group: 12,506 ± 5148 pg/mL AD: 16,314 ± 8513 pg/mL[8]

ATI = Amyloid Beta/Tau Ratio; NfL = Neurofilament light chain; CSF GFAP = Cerebrospinal Fluid Glial fibrillary acidic protein.

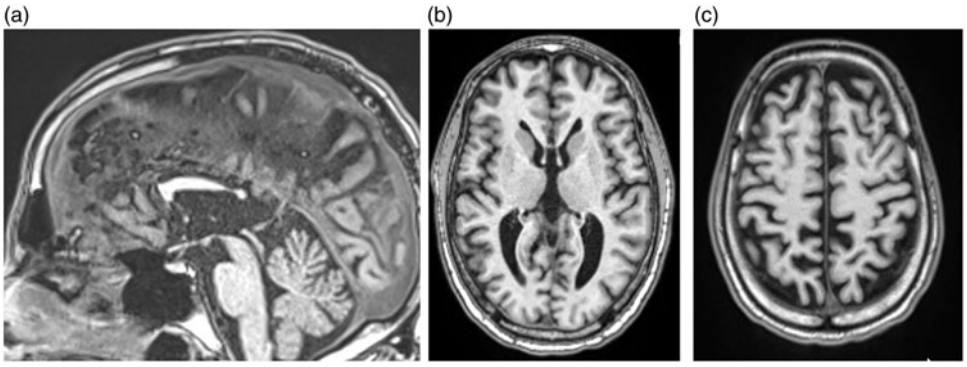

Figure 1: T1 weighted MRI images of a 51-year-old man with partial agenesis of the corpus callosum and colpocephaly. (***a***) Sagittal image showing dysgenesis of the corpus callosum with absent splenium.(***b***) Axial image illustrating the widely spaced bodies of the lateral ventricles (racing car sign) and the dilatation of the occipital horns of the lateral ventricles. (***c***) Axial image showing bilateral and symmetric parietal atrophy.

The patient reported experiencing a singular mTBI over five years prior to the assessment. While mTBI can lead to neuronal-axonal damage, and is associated with increased levels of NfL and GFAP following an injury, they return to baseline in most cases of mTBI.[11] Notably, a study on Swedish hockey players with mTBI, found that while serum Nfl levels are initially elevated, the levels normalized close to return to play.[11] Therefore this patient's elevated NfL and GFAP are unlikely related to mTBI. While previous cases of AgCC and colpocephaly did not measure neurodegenerative markers,[1,12] the patient described by Kosky et al 2022, had symptoms that may be secondary to accelerated aging.[12] The gentleman reported forgetting events, and complained of issues with attention and multitasking.[12] While the investigators concluded that the cognitive issues were likely to remain stable as the patient ages,[12] testing for neurodegenerative markers may have provided valuable information.

In conclusion, we present the first case of elevated neurodegenerative biomarkers in a patient with colpocephaly and partial AgCC despite being negative for AD biomarkers. It is unclear whether these markers reflect the colpocephaly and partial AgCC, which may be a form of brain injury with astrocytic reaction. While our patient had a mTBI, it is unlikely to be related as it was a single injury many years before assessment. Our current understanding of the long-term impact of AgCC and colpocephaly remains poor. It is notable that both NfL and GFAP are elevated in this patient. An increasing number of MRIs may lead to further incidental cases being discovered, and prompt subsequent biofluid analysis of neurodegenerative markers to better capture the pathophysiology of this condition. While this is a developmental lesion, there may be evidence of neuro-axonal injury and astrogliosis in patients who present with AgCC. The long term effects of developmental abnormalities are not well understood and may be associated with accelerated neurodegeneration that is detectable through cerebrospinal fluid analysis. Therefore, further research investigating the significance of these elevated markers in AgCC and colpocephaly is warranted.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2024.22.

Author contributions. All authors significantly contributed to, seen the final version of and approved the manuscript for submission. AA prepared the written case report and performed the supportive literature review. ST and AV conducted the necessary laboratory testing to measure the levels of neurodegenerative markers. PAL prepared the radiological images for the case. MCT was responsible for patient care, reviewed the case and reviewed and edited the manuscript

Funding statement. AV has received funding through endowments and scholarships from the University of Toronto. MCT has received grants from the Canadian Institute of Health Research, Weston Brain Institute and the National Institute of Health. MCT is also a scientific advisor to Brain Injury Canada, Women's Brain Project and Progressive Supranuclear Palsy Canada.

Competing interests. None.

Ethics approval. This study was approved by University Health Network ID: #22-5752.

Patient consent. The participant gave written informed consent to participate in the study before taking part as well as consent for this publication.

References

1. Parker C, Eilbert W, Meehan T, et al. Colpocephaly diagnosed in a neurologically normal adult in the emergency department. Clin Pract Cases Emerg Med. 2019;3:421–424. DOI: 10.5811/cpcem.2019.9.44646.
2. Freedman M, Leach L, Tartaglia MC, et al. The Toronto cognitive assessment (TorCA): normative data and validation to detect amnestic mild cognitive impairment. Alzheimers Res Ther. 2018;10:1–8. DOI: 10.1186/s13195-018-0382-y.

3. Jack CRJr, Bernstein MA, Fox NC, et al. The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. J Magn Reson Imaging. 2008;27:685–91. DOI: 10.1002/jmri.21049.
4. Blennow K, Dubois B, Fagan AM, et al. Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early Alzheimer's disease. Alzheimers Dement. 2015;11:58–69. DOI: 10.1016/j.jalz.2014.02.004.
5. Blennow K. Cerebrospinal fluid protein biomarkers for Alzheimer's disease. NeuroRx. 2004;1:213–25. DOI: 10.1602/neurorx.1.2.213.
6. Zwan MD, Rinne JO, Hasselbalch SG, et al. Use of amyloid-PET to determine cutpoints for CSF markers: a multicenter study. Neurology. 2016;86:50–8. DOI: 10.1212/WNL.0000000000002081.
7. Vermunt L, Otte M, Verberk IM, et al. Age-and disease-specific reference values for neurofilament light presented in an online interactive support interface. Ann Clin Transl Neur. 2022;9:1832–7. DOI: 10.1002/acn3.51676.
8. Benedet AL, Milà-Alomà M, Vrillon A, et al. Differences between plasma and cerebrospinal fluid glial fibrillary acidic protein levels across the alzheimer disease continuum. JAMA Neurol. 2021;78:1471–83. DOI: 10.1001/jamaneurol.2021.3671.
9. Wolfe MS. The role of tau in neurodegenerative diseases and its potential as a therapeutic target. Scientifica. 2012;2012:1–20. DOI: 10.6064/2012/796024.
10. Gaetani L, Blennow K, Calabresi P, et al. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019;90:870–81. DOI: 10.1136/jnnp-2018-320106.
11. Shahim P, Zetterberg H, Tegner Y, et al. Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports. Neurology. 2017;88:1788–94.
12. Kosky KM, Phenis R, Kiselica AM. Neuropsychological functioning in dysgenesis of the corpus callosum with colpocephaly. Appl Neuropsychol Adult. 2022;29:1681–7. DOI: 10.1080/23279095.2021.1897008.

https://doi.org/10.1017/cjn.2024.22 Published online by Cambridge University Press