Conversion to major neurocognitive disorder after COVID-19 in a woman with bipolar disorder: A 6-year longitudinal case report

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1 CASE PRESENTATION

The patient is a 78-year-old female with longstanding history of bipolar disorder. Her first documented psychiatric concern was a remote episode of post-partum depression that required hospitalization for approximately 2 weeks in the 1960s. She was treated on and off for the diagnosis of bipolar disorder, and she was noted to be non-compliant with the treatment. Decades later, at age 72, the patient was admitted to St. Joseph’s Healthcare Hamilton for two and a half months and was discharged with a diagnosis of bipolar type I mixed episode in 2015. To manage her condition, the patient was prescribed 450 mg of lithium, 4 mg of perphenazine, and 25 mg of amitriptyline daily. Additionally, the patient underwent neuropsychological testing, and she demonstrated weaknesses in processing speed, attention, and executive functioning. The results were described as consistent with moderate white matter changes identified on brain magnetic resonance imaging (MRI), in addition to her psychiatric diagnosis of bipolar disorder. She was diagnosed with minor neurocognitive disorder due to vascular disease.

The patient was followed up 1 year later and appeared stable. In the months ahead, the patient was readmitted with a bipolar type I mixed episode. It was the opinion of the physicians treating the patient that it would be beneficial for the patient to be followed in an environment with intense case management and a family health team. Thus, the patient was transferred from an acute psychiatric facility to a psychiatric hospital approximately 8 months later. Following this transition, the patient presented with a bipolar type I mixed episode in the context of non-compliance with medications. She reported several weeks of decreased sleep of 2 to 3 h per night and feeling agitated with racing thoughts and pressured speech. She had difficulty maintaining her personal hygiene and upkeep of her apartment. Repeat neuropsychological testing revealed a stable cognitive profile (Table A1). She continued to meet criteria for minor neurocognitive disorder due to vascular disease.

Two years later (2018), the patient was followed up as an outpatient and inpatient, and once again appeared cognitively stable. She had subjective cognitive concerns but reported functioning independently. Repeat neuropsychological testing showed a stable cognitive profile, and she continued to meet criteria for minor neurocognitive disorder due to vascular disease (Figure A1).

On February 2, 2021, the patient tested positive for COVID-19 following an outbreak at a satellite health facility where she was admitted waiting for long-term care due to care needs related to her bipolar disorder. Initially, the patient was asymptomatic. Unfortunately, she did worsen from the infection, and had recurrent fevers and hypoxia around February 12–14, 2021. Due to the consideration of SARS-CoV-2 infection playing a role in her condition, she was also treated with dexamethasone 6 mg IV/PO q24h for up to 10 days and remdesivir 200 mg IV load then 100 mg IV daily for 4 days as part of a research study. Her
The course of the patient’s SARS-CoV-2 infection was associated with deterioration of the patient’s behavior and mental status. Initially the patient was somewhat agitated at times and yelled intermittently but was overall communicating appropriately. When the patient began to experience symptoms of COVID-19 in mid-February, she became considerably less responsive. The patient had a fragile cognitive and psychological state prior to her admission, although there was a clear deterioration in the context of her systemic illness and SARS-CoV-2 infection, representing a new pathologic process at play separate from the patient’s prior state of delirium. The clinical picture is not one of neuroleptic malignant syndrome or serotonin syndrome.

An electroencephalogram (EEG), MRI scan, and an extensive blood work panel was conducted to investigate SARS-CoV-2-related neuropsychiatric disorder as well as other causes of encephalopathy. Following the SARS-CoV-2 infection, the results of the EEG were abnormal with poorly organized and suppressed background activity in the theta and delta range. There was poorly organized 4-7CPS suppressed background activity with occasional 2-3CPS components occurring randomly. The patient appeared to be awake during the recording. Taken together, all EEG findings were abnormal, and the patient’s presentation was consistent with a toxic metabolic multifocal or diffuse degenerative state.

An MRI report dated February 21, 2021, following the SARS-CoV-2 infection, described moderate generalized atrophy and white matter changes, which was noted to be worse compared with 2017 (Figure 1). Specifically, white matter hyperintensities located in the periventricular regions, frontal regions, and deep white matter were observed, indicating microangiopathic disease. Additionally, the MRI indicated volumetric atrophy in corpus callosum and cerebellum as well as both supratentorial and infratentorial atrophy. The degree of cerebral atrophy was slightly progressed compared with a recent CT of the brain in December 2019. In addition, since 2017, the corpus callosum was diffusely thinned, mild cerebellar atrophy appeared, but brainstem atrophy was unchanged. A CT report following the SARS-CoV-2 infection described persistent left frontal lobe hypoaxenation involving periventricular/deep white matter with apparent hypodensity of the subcortical white matter and overlying cortex.

On repeat neuropsychological assessment, 3 months after the SARS-CoV-2 infection, the patient performed within normal limits for her age on tests of verbal intelligence, short-term auditory attention span, confrontation naming, expressive vocabulary, single word reading, and object perception. In contrast, she performed below age expectations on tests of orientation, processing speed, executive functioning, memory, spatial perception, and visual construction. Regarding executive functioning, she demonstrated problems with cognitive flexibility, abstract reasoning, impersistence on verbal fluency, and working memory. Regarding memory, the pattern on testing indicated variable problems with encoding and retention of recent information, at least on less structured tasks (e.g., word list), which place demand on executive skills related to self-initiated and strategic encoding processes. Her memory was relatively stronger for contextualized information. In terms of visuospatial processing, she had difficulty with spatial perception and visual construction tasks, including draw to command and copy tasks. Clock drawing performance revealed conceptual errors, indicating degradation of semantic knowledge (Figure A1). Overall, the evaluation showed a decline in cognitive performance compared with multiple prior neurocognitive evaluations (Figure 2). More specifically, fluid intelligence declined from the average range to borderline. She is now disoriented to time, place, and person. Executive functioning has worsened, although some degree of executive dysfunction has been present since her first assessment in 2015, this was relatively stable until the most recent evaluation. Her executive difficulties are now more extensive, encompassing more aspects of executive functioning. Similarly, memory and visuospatial processing showed a pattern of relative stability across assessments, until the marked decline on the recent evaluation. She also appears to have less insight into her
cognitive abilities, compared with prior evaluations, as she has fewer subjective cognitive complaints on interview.

The patient shows deficits in multiple cognitive domains, and there is evidence of cognitive decline relative to the previous assessment 3 years ago in 2018. As such, the present findings are consistent with dementia. Regarding etiology, her history and cognitive profile are most consistent with major vascular neurocognitive disorder, as per DSM-5, which is supported by the MRI findings of

**FIGURE 1** Neuropsychological test scores from baseline and follow-up evaluations. (A) The graph depicts age-corrected standardized test scores in the memory domain. KBNA: Kaplan Baycrest Neurocognitive Assessment; WMS-IV LM: Wechsler Memory Scale, Fourth Edition, Logical Memory. (B) The graph depicts age-corrected standardized test scores in non-memory domains. FSIQ, Full Scale Intelligence Quotient; KBNA, Kaplan Baycrest Neurocognitive Assessment; TOPF, Test of Premorbid Functioning; VOSP, Visual Object and Space Perception Battery; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; WASI-II, Wechsler Abbreviated Test of Intelligence, Second Edition

**FIGURE 2** Supporting figure. Brain MRI post COVID-19 infection
moderate cerebral atrophy and microangiopathic changes. It is possible that her multiple episodes of delirium over the past year, including the delirium associated with her recent COVID-19 infection, have accelerated her cognitive decline. The converse is also likely, that her underlying cerebrovascular disease has heightened her susceptibility to delirium following infection. Other contributing factors include bipolar disorder and medication side effects, which can impact processing speed and executive functioning. Her cognitive profile does not support co-existing Alzheimer’s disease, although this cannot be entirely ruled out by a clinical examination.

ACKNOWLEDGEMENTS
Not applicable.

AUTHOR CONTRIBUTIONS
Emma L. Tolsdorf, Dante Duarte, and Christina Gojmerac drafted the manuscript. Flavio Kapczinski, Benicio N. Frey, and Jonathan Crowson reviewed the draft and revised the paper prior to submission.

COMPETING INTERESTS
The authors declare that they have no competing interest.

CONSENT
Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author, ET. The data are not publicly available due to containing information that could compromise the privacy of the research participant.

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REFERENCES
1. Bianchetti A, Rozzini R, Guerini F, et al. Clinical presentation of COVID19 in dementia patients. J Nutr Health Aging. 2020;24(6):560-562. doi:10.1007/s12603-020-1389-1
2. Toubasi AA, AbuAnzeh RB, Tawileh HBA, Aldebei RH, Alryalat SAS. A meta-analysis: the mortality and severity of COVID-19 among patients with mental disorders. Psychiatry Res. 2021;299:113856. doi:10.1016/j.psychres.2021.113856
3. Pandharipande PP, Girard TD, Ely EW. Long-term cognitive impairment after critical illness. N Engl J Med. 2014;370(2):185-186. doi:10.1056/NEJMc1313886
4. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Crit Care. 2020;24(1):176. doi:10.1186/s13054-020-02882-x
5. Kieseppä T, Tuulio-Henriksson A, Haukka J, et al. Memory and verbal learning functions in twins with bipolar-I disorder, and the role of information-processing speed. Psychol Med. 2005;35(2):205-215. doi:10.1017/s0033291704003125. PMID: 15841678.

APPENDIX

FIGURE A1 Clock drawing and copying samples
| Domain               | Test                                | 2015          | 2016          | 2018          | 2021          |
|----------------------|-------------------------------------|---------------|---------------|---------------|---------------|
|                      |                                     | Score         | Range         | Score         | Range         | Score         | Range         |
| IQ                   | TOPF                                | Std. Scr. = 96| Average       | -             | -             | Std. Scr. = 93| Average       | Std. Scr. = 92| Average       |
|                      | WASI-II FSIQ                         | Std. Scr. = 95| Average       | -             | -             | -             | -             | Std. Scr. = 78| Borderline    |
| Attention            | KBNA Orientation                     | >16%ile       | WNL           | >16%ile       | WNL           | >16%ile       | WNL           | <2%ile        | Impaired      |
|                      | WAIS-IV Digit Span Forward          | SS = 7        | Average       | SS = 12      | High average  | SS = 10       | Average       | SS = 8        | Average       |
|                      | WAIS-IV Digit Span Backward         | SS = 9        | Average       | SS = 9       | Average       | SS = 6        | Low average   | SS = 6        | Low average   |
|                      | Digit Span Sequencing               | SS = 11       | Average       | SS = 6       | Low average   | SS = 9        | Average       | SS = 4        | Borderline    |
|                      | Trails A                             | T = 37        | Average       | T < 20       | Impaired      | T < 20        | Impaired      | T = 20        | Impaired      |
| Executive            | Trails B                             | T < 20        | Impaired      | T < 20       | Impaired      | D/C           | Impaired      | D/C           | Impaired      |
| Functioning          | WASI-II Matrix Reasoning            | T = 44        | Average       | -            | -             | -             | -             | T = 25        | Impaired      |
|                      | KBNA Practical Reasoning/Conceptual | SS = 8        | Average       | SS = 7       | Low average   | SS = 8        | Average       | SS = 4        | Borderline    |
|                      | Shifting                             |                |               |               |               |               |               |               |               |
|                      | KBNA Phonemic Fluency               | SS = 8        | Average       | SS = 7       | Low average   | SS = 8        | Average       | SS = 3        | Impaired      |
|                      | KBNA Semantic Fluency               | SS = 8        | Average       | SS = 4       | Borderline    | SS = 5        | Borderline    | SS = 2        | Impaired      |
| Language             | WASI-II Vocabulary                  | T = 51        | Average       | -            | -             | -             | -             | T = 49        | Average       |
|                      | Boston Naming Test                  | T = 44        | Average       | T = 44       | Average       | T = 41        | Low average   | T = 46        | Average       |
| Visuospatial         | KBNA Clocks and Figure              | SS = 11       | Average       | SS = 9       | Average       | SS = 8        | Average       | SS = 4        | Borderline    |
| Processing           | VOSP: Degraded Letters              | -             | -             | -            | -             | Raw = 20/20   | Pass          | Raw = 20/20   | Pass          |
|                      | VOSP: Cube Analysis                 | -             | -             | -            | -             | Raw = 10/10   | Pass          | Raw = 6/10    | Fail          |
(Continues)
| Domain        | Test                        | 2015                | 2016                | 2018                | 2021                |
|--------------|-----------------------------|---------------------|---------------------|---------------------|---------------------|
|              | Domain Test                 | Score | Range  | Score | Range  | Score | Range  | Score | Range  | Score | Range  |
| Memory       | KBNA Word Lists             |       |        |       |        |       |        |       |        |       |        |
|              | Lists 1                     | SS = 10 | Average | SS = 9 | Average | SS = 10 | Average | SS = 3 | Impaired |       |        |
|              | Lists 2                     | SS = 13 | High avg. | SS = 12 | High Avg. | SS = 10 | Average | SS = 2 | Impaired |       |        |
|              | Lists 2 Recognition         | SS = 15 | Superior | SS = 15 | Superior | SS = 13 | High avg. | SS = 3 | Impaired |       |        |
|              | WMS-IV LM                   |       |        |       |        |       |        |       |        |       |        |
|              | LM I                        | SS = 10 | Average | SS = 11 | Average | SS = 12 | High avg. | SS = 10 | Average |       |        |
|              | LM II                       | SS = 11 | Average | SS = 10 | Average | SS = 11 | Average | SS = 6  | Low Avg.  |       |        |
|              | LM II Recognition           | 17–25%ile | Avg.-low avg. | 51–75%ile | Avg.-high avg. | >75%ile | High avg. | 10–16%ile | Low Avg.  |       |        |
| KBNA Figure  | Figure 1                    | SS = 7  | Low avg. | SS = 5  | Borderline | -               | -               | SS = 4  | Borderline |       |        |
|              | Figure 2                    | SS = 6  | Low avg. | SS = 3  | Impaired  | -               | -               | SS = 3  | Impaired  |       |        |
|              | Figure 2 Recognition        | SS = 10 | Average | SS = 6  | Low Avg.  | -               | -               | SS = 3  | Impaired  |       |        |

Abbreviations:
- %ile, percentile; -, no data available; D/C, discontinue; FSIQ, Full Scale Intelligence Quotient; KBNA, Kaplan Baycrest Neurocognitive Assessment; SS, scaled score; Std. Scr, standard score; T, t-score; TOPF, Test of Premorbid Functioning; VOSP, Visual Object and Space Perception Battery; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; WASI-II, Wechsler Abbreviated Test of Intelligence, Second Edition; WMS-IV, Wechsler Memory Scale, Fourth Edition; WNL, within normal limits.