

Long-Term Cognitive Outcomes in Patients with Autoimmune Encephalitis

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ABSTRACT: Background: A need exists to characterise the long-term cognitive outcomes in patients who recovered from autoimmune encephalitis and to identify the modifiable factors associated with improved outcomes. **Methods:** We retrospectively analysed data from patients diagnosed with autoimmune encephalitis in our outpatient autoimmune encephalitis clinic over a 5-year period, where the Montreal Cognitive Assessment (MoCA) is routinely administered. **Results:** In total, 21 patients met the inclusion criteria, of whom 52% had persistent cognitive impairment at their latest follow-up (median delay to testing = 20 months, range 13-182). Visuospatial and executive abilities, language, attention, and delayed recall were predominantly affected. Patients with status epilepticus at presentation had lower total MoCA scores at their last follow-up (median total score 21, range 15-29) compared with patients without status epilepticus at presentation (median total score 27.5, range 21-30; $r^2 = 0.366$, $p = 0.004$). Patients who experienced delays of more than 60 days from symptom onset to initiation of treatment (either immunosuppression or tumour removal) were more likely to have a MoCA score compatible with cognitive impairment at their last follow-up ($r^2 = 0.253$, $p = 0.0239$; z -score = -2.01 , $p = 0.044$). **Conclusions:** Our study suggests that the MoCA may be used to evaluate cognition in recovering patients with autoimmune encephalitis. Delays to treatment shorter than 60 days and absence of status epilepticus at onset were associated with better performance on the MoCA obtained more than 1 year after symptom onset, and may predict better long-term cognitive outcomes.

RÉSUMÉ: Évolution à long terme des capacités cognitives de patients atteints d'encéphalite auto-immune. Contexte: Il nous reste encore à décrire l'évolution à long terme des capacités cognitives de patients qui se rétablissent de l'encéphalite auto-immune et à identifier les facteurs modifiables associés à une évolution favorable. **Méthodes:** Nous avons analysé de façon rétrospective les données de patients chez qui l'on avait diagnostiqué, dans notre clinique externe d'encéphalite auto-immune, une telle inflammation aiguë, et ce, au cours d'une période de cinq ans. Fait à noter, l'Évaluation cognitive de Montréal (ou MoCA) est couramment utilisée dans notre clinique. **Résultats:** Vingt-et-un patients ont répondu à nos critères d'inclusion. De ce nombre, 52 % montraient une forme d'incapacité cognitive persistante au moment de leur dernier suivi médical (délai médian des tests = 20 mois ; étendue 13-182). Tant leurs fonctions visuo-spatiales, exécutives et langagières que leur attention et leur mémoire différée étaient alors principalement affectées. Les patients atteints de l'état de mal épileptique au moment de consulter ont donné à voir, lors de leur dernier suivi, des scores totaux inférieurs au MoCA (score total médian = 21 ; étendue 15-29) en comparaison avec ceux n'étant pas atteints de cette complication au moment de consulter (score médian total = 27,5 ; étendue 21-30; $r^2 = 0,366$; $p = 0,004$). Par ailleurs, les patients qui ont dû attendre plus de soixante jours après l'apparition de leurs symptômes pour qu'on débute un traitement, que ce soit au moyen de l'immunosuppression ou de l'ablation de leurs tumeurs, étaient plus susceptibles, au moment de leur plus récent suivi, d'obtenir un score au MoCA indiquant une forme d'incapacité cognitive ($r^2 = 0,253$; $p = 0,0239$; cote Z = $-2,01$; $p = 0,044$). **Conclusions:** Notre étude suggère donc que le test dit MoCA peut être utilisé pour évaluer la cognition de patients se rétablissant d'une encéphalite auto-immune. Des délais de traitement inférieurs à 60 jours et l'absence de l'état de mal épileptique au moment de l'apparition des symptômes ont été associés à de meilleurs résultats au test MoCA plus d'un an après l'apparition de ces mêmes symptômes. En cela, il est possible que ces résultats nous permettent de prédire une évolution à long terme plus favorable de leurs capacités cognitives.

Keywords: Autoimmune encephalitis, Cognitive outcomes, Montreal Cognitive Assessment

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INTRODUCTION

As experience with the diagnosis and management of patients with autoimmune encephalitis (AE) continues to improve,¹ the need to characterise the long-term outcomes in recovering patients

has become important. This need is most apparent in patients with AE associated with autoantibodies against cell-surface receptors who retain the greatest potential for meaningful recovery following diagnosis and treatment. To date, several large studies have

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reported “good” long-term outcomes in patients recovering from *N*-methyl-D-aspartate receptor (NMDAR) encephalitis,²⁻⁴ and AE associated with voltage-gated potassium channel complex (VGKC) autoantibodies.⁵⁻⁸ These studies confirm that between 70% and 80% of patients regain the ability to ambulate within 2 years of first presentation, defined as a score of ≤ 2 on the modified Rankin Scale (mRS).^{2-4,7-9} However, it is increasingly apparent that “good outcomes,” as quantified by measures emphasising motor function, may overlook outcomes of importance to recovering patients—particularly those related to cognitive capacity.¹⁰ In support of this statement, studies applying comprehensive cognitive assessments report multi-domain dysfunction in the acute phase of NMDAR encephalitis, with persistence of deficits in memory, executive function, and attention at long-term follow-up.¹¹⁻¹³ Similar patterns of deficits are observed in patients with encephalitis associated with leucine-rich glioma inactivated 1 (LGII) autoantibodies.¹⁴

Although sensitive and informative, full neuropsychological assessment is not practical in most clinical settings owing to the length and high cost associated with administration. There is a need to develop and validate measures that can be reliably and rapidly applied to assess and monitor progression in recovering AE patients. The Montreal Cognitive Assessment (MoCA) is a sensitive and adaptable method for detecting mild cognitive impairment, with normative data available.^{15,16} In this study, we used the MoCA to estimate cognitive impairment in patients recovering from AE and determined the clinically measurable factors that affect performance on the MoCA.

METHODS

Study Population and Data Collection

Data were ascertained through chart review from patients assessed and diagnosed with AE at our tertiary care AE clinic (Toronto Western Hospital, Toronto, Ontario, Canada) from September 1, 2012, to September 1, 2017. Patients included in the study presented with a clinical diagnosis of “probable” or “definite” AE.¹ The MoCA is routinely administered in the clinic. In addition, a 1-minute animal category word generation task was performed in the majority of patients. Information was collected through chart review concerning patient demographics and disease characteristics, including antibody type, presence of tumour, type of symptoms at onset, delay to first treatment, nature of first treatment, and number of relapses. Study protocols were approved by the University Health Network Research Ethics Board.

Data Analysis

MoCA scores were stratified into “early” (the earliest MoCA collected within 1 year of symptom onset) and “long-term” intervals (the latest MoCA collected after 1 year from symptom onset). Clinical data were analysed using SPSS Statistics (IBM Corp., Version 24.0. Armonk, NY, USA). Correlations between disease characteristics and MoCA scores were evaluated using a Pearson’s correlation coefficient. Correlated factors were subsequently analysed using regression analysis and a Mann-Whitney *U*-test. Statistical significance was defined as $p < 0.05$, unless otherwise stated.

RESULTS

In total, 22 patients were diagnosed with AE during the study period (Table 1). One patient was excluded from further analyses as accurate data outlining the treatment course were not available. In total, 21 patients were therefore included in the study.

Early MoCA scores were available from 13 subjects. Early scores were lower than long-term MoCA scores ($p = 0.045$). Visuospatial/executive abilities, language, attention, and delayed recall were predominantly affected in the early phase of the disease. A similar pattern was observed at last follow-up, with the exception of delayed recall, which demonstrated a trend towards improvement ($p = 0.0949$) (Table 2). Letter-fluency was consistently more impaired than category fluency. The most common source of errors for visuospatial/executive skills involved reproducing a geometrical shape, either a cube, rectangular prism, or cylinder, depending on the MoCA version used. In total, 11 (52%) patients had persistent cognitive impairment at their last follow-up, defined as a MoCA score of $< 26/30$.

Patients with status epilepticus at presentation had lower total MoCA scores at last follow-up (median 21, range 15-29) compared with patients without status epilepticus at presentation (median 27.5, range 21-30; $r^2 = 0.366$, $p = 0.004$). There was a trend towards lower long-term MoCA scores in patients with heavier antiepileptic burden ($r = -0.408$, $p = 0.104$). No correlation was found between long-term MoCA scores and admission to

Table 1: Patients’ characteristics

Total number of patients (<i>n</i>)	21
Age at disease onset (median [range]) (years)	35 (14-73)
Females (<i>n</i> [%])	11 (52.3%)
Seizures at onset (<i>n</i> [%])	16 (76.2%)
Status epilepticus at onset (<i>n</i> [%])	7 (33.3%)
Underlying tumour found (<i>n</i> [%])	6 (28.6%)
Delay from symptom onset to first treatment (median, days [range])	59 (14-3285)
Relapse after initial treatment (<i>n</i> [%])	8 (38.1%)
Delay from disease onset to last follow-up (median, months [range])	22 (12-182)
Seronegative (<i>n</i> [%])	5 (23.8%)
Antibody associated with presentation	
Anti-NMDAR (<i>n</i> [%])	10 (47.6%)
Anti-LGII (<i>n</i> [%])	4 (19.0%)
Anti-GAD (<i>n</i> [%])	1 (4.8%)
Anti-Ma2 (<i>n</i> [%])	1 (4.8%)
Symptoms at presentation	
Seizures (<i>n</i> [%])	16 (76%)
Status epilepticus (<i>n</i> [%])	7 (33%)
Cognitive decline (<i>n</i> [%])	8 (38%)
Psychiatric symptoms (<i>n</i> [%])	15 (71%)
Initial treatment	
Intravenous immunoglobulin (<i>n</i> [%])	14 (66.7%)
Intravenous steroids (<i>n</i> [%])	18 (85.7%)
Plasmapheresis (<i>n</i> [%])	4 (19.0%)
Tumour removal (<i>n</i> [%])	6 (28.6%)

Table 2: Montreal Cognitive Assessment (MoCA) results by cognitive domain

MoCA domain	Early follow-up (median [range])*	Long-term follow-up (median [range])**
Total score	24/30 (11-28)	25/30 (15-30)
Executive/visuospatial	4/5 (0-5)	4/5 (0-5)
Naming	3/3 (2-3)	3/3 (1-3)
Language	2/3 (0-3)	2/3 (0-3)
Letter fluency	10.5 (4-16)	10 (4-21)
Attention	5/6 (3-6)	6/6 (2-6)
Abstraction	2/2 (0-2)	2/2 (0-2)
5-word learning	5/5 (0-5)	5/5 (3-5)
5-word delayed recall	2/5 (0-5)	3/5 (0-5)
Orientation	6/6 (2-6)	6/6 (4-6)
Animal fluency***	19 (12-27)	17 (9-30)

LGI1 = leucine-rich glioma inactivated 1; NMDAr = *N*-methyl-D-aspartate receptor

*For the first MoCA obtained before 1 year, median delay to testing = 6 months, range 2-12 months

**For the last MoCA obtained after 1 year, median delay to testing = 20 months, range 13-182 months

***Not part of original MoCA testing

the intensive care unit ($r = -0.117$, $p = 0.613$), or length of hospital stay ($r = -0.237$, $p = 0.3$). Delays >60 days from symptom onset to initiation of treatment were associated with a higher probability of MoCA score <26 at last follow-up ($r^2 = 0.253$, $p = 0.0239$; z -score = -2.01 , $p = 0.044$). In the long term, there was no statistically significant difference between the MoCA scores of patients with cell-surface antibodies (median 27, range 21-29) and patients with intracellular antibodies (median 23.5, range 22-25, $p = 0.502$). Furthermore, no difference was observed when seronegative cases (median = 25, range 21-30, $p = 0.55$) were considered. The long-term MoCA score was not correlated with the first total MoCA score ($r^2 = 0.12$, $p = 0.22$), female gender ($r^2 = 0.03$, $p = 0.44$), presence of a tumour ($r^2 = 0.069$, $p = 0.249$), or occurrence of relapses after initial presentation ($r^2 = 0.032$, $p = 0.44$). There was a trend towards lower long-term MoCA scores in older patients ($r^2 = 0.16$, $p = 0.07$). Time from symptom onset to testing predicted higher total MoCA scores ($r^2 = 0.16$, $p = 0.002$).

DISCUSSION

In all, 52% of recovering adult AE patients had cognitive impairment at their last follow-up, defined as a total MoCA score <26. This compares to rates of ~50% reported in other studies that have considered long-term outcomes in a predominantly paediatric population with cell-surface antibody-mediated AE.^{17,18} In the acute phase of AE, delayed recall was more severely affected in our cohort. Impaired recall presumably reflected impairment in retrieval of stored information, recognising that most patients successfully encoded the five-word list following presentation (median 5/5 words in both trials; range 0-5 early, and 3-5 late at long-term follow-up). Performance on measures of visuospatial/executive,

language, and attention were mildly impaired, whereas naming, abstraction, and orientation were largely preserved. This cognitive pattern was relatively preserved at the last follow-up, except for delayed recall impairments, which tended to improve. The persistent discrepancy between letter fluency and animal fluency suggests preferential frontal impairment.¹⁹ These findings are similar to what was previously reported in the literature in patients with various forms of antibody-mediated AE,²⁰ including NMDAR^{12,13} and VGKC encephalitis.¹⁴

In the subgroup of 10 patients with NMDAR encephalitis, 30% of patients had cognitive impairment at last follow-up, higher than the 10% reported in the literature using the MMSE (defined as total score <26).^{3,4} Three of four (75%) patients recovering from LGI1 encephalitis exhibited cognitive impairment at a median follow-up of 35 months (range 18-100 months). By comparison, a rate of 29% of moderate to severe cognitive impairment has been reported at 24 months in 76 patients with LGI1 encephalitis, using a non-validated measure of cognitive outcomes,⁵ and 28% (19/67) of patients were shown to have some form of cognitive impairment using the Clinical Dementia Rating ($CDR \geq 0.5$).^{8,21}

Delay to initial treatment >60 days was a measured potentially modifiable risk factor associated with long-term cognitive impairment (MoCA < 26). This finding adds to a growing body of literature emphasising the importance of early consideration of AE, and initiation of empiric treatment.^{1-3,13} A statistically significant difference was observed in early and long-term MoCA scores, suggesting that overall performance on cognitive testing tended to improve over time.

The presence of status epilepticus at onset was identified as a potential risk factor associated with poorer long-term cognitive outcomes, with a trend towards poorer performance on the MoCA in the long term with greater burden of anti-epileptic drug required. There was a non-statistically significant trend towards poor long-term cognitive performance in older patients. Although no statistically significant difference was observed in this study between long-term MoCA scores of patients with cell-surface antibodies compared with other types of encephalitis, we suspect we would find such a difference if our sample size was larger.^{20,22} Unlike previous studies,²⁻⁴ we did not find that extended hospital stay was related to poorer long-term cognitive impairment.

Rates of cognitive impairment reported in this study (52%) are considerably lower than the 80-90% prevalence reported in smaller case series ($n \leq 10$ patients) using formal neuropsychological testing.^{12-14,20} These differences may be attributed to the lower sensitivity of the MoCA for the detection of cognitive impairment. This limitation may be counterbalanced by relative advantages of the MoCA as applied to routine follow-up in the outpatient population, including the low cost of use, the wide availability of published normative data across different ethnicities and languages,²³⁻²⁶ and the ease of administration. In addition, the MoCA offers comparative advantages to other widely used bedside screening measures, particularly the MMSE.¹⁵ Compared with the MMSE, the MoCA exhibits superior sensitivity for the detection of incipient cognitive decline,¹⁶ while also permitting more detailed assessment of visuospatial, attention, and memory functions—of particular relevance when assessing patients recovering from AE, who may manifest with disproportionate dysfunction in these areas.^{15,16} Nevertheless, there is a clear need to develop and validate cognitive assessment tools for

outpatient follow-up of patients with AE, including direct comparisons between performance on bedside measures and formal neuropsychological tests. In lieu of these data, we advocate for the routine use of the MoCA in outpatient follow-up of patients with AE, with addition of a word-category generation task.

Limitations of this study include its retrospective nature, and reporting within a single outpatient specialty clinic. As a result, our results may overestimate the rate of cognitive impairment seen in other clinical environments, recognising that patients who fully recover following their hospitalisation may be less likely to be referred for further assessment. Furthermore, rates and types of AE may vary across centres, challenging the generalisability of our results. Prospective studies in other clinical environments are ultimately required to confirm our findings. Another limitation of our study is its modest sample size. As a result, this study was probably underpowered for the detection of the relationship between potentially important modifiers of outcomes (e.g., effect of antibody subtype on cognitive outcomes, duration of treatment, medication use, and so on). A final limitation is that data for early MoCA testing were not available for all patients. This is unsurprising given that, during the acute phase of the disease, inpatient health care teams often focus on stabilising more pressing issues such as seizure activity and dysautonomia, and it may be impossible to administer formal cognitive testing in patients who are sedated and intubated.

CONCLUSIONS

The MoCA may be used to evaluate cognition in recovering patients with AE. Shorter delays to treatment and absence of status epilepticus at onset predict better performance on the MoCA ≥ 1 year following acute presentation, and may predict better long-term cognitive outcomes.

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DISCLOSURES

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STATEMENT OF AUTHORSHIP

JH: data collection, design of study, drafting of manuscript, and revision of the manuscript; GSD and CS: data collection, study design, and revision of the manuscript; RAW and DTW: Study design and revision of the manuscript.

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