4-9-2021

Predicting Cognitive Rehabilitation Needs in Patients with Central Nervous System Infections Using Montreal Cognitive Assessment

Matilde Ørum

Merete Storgaard

Paul Denton

Trine Hyrup Mogensen

Christina Kjærgaard Højbjerg

See next page for additional authors

Authors

Matilde Ørum, Merete Storgaard, Paul Denton, Trine Hyrup Mogensen, Christina Kjærgaard Højbjerg, Mathilde Pedersen, and Jesper Damsgaard Gunst

Predicting Cognitive Rehabilitation Needs in Patients with Central Nervous System Infections Using Montreal Cognitive Assessment

SN Comprehensive Clinical Medicine

April 2021

Body

Introduction

Cognitive impairments are prevalent among patients following central nervous system (CNS) infections, even after good recovery [–]. This is unsurprising for bacterial meningitis (BM) and encephalitis (EN) considering the severity of these diseases with extensive inflammation in the CNS [–]. However, several studies indicate that ***cognitive*** impairments also occur after aseptic meningitis (AM), which is otherwise considered a relatively benign disease [, , –]. AM is defined as a CNS infection with laboratory and clinical signs of meningeal inflammation. Pleocytosis is found in the cerebrospinal fluid with negative tests for bacteria. AM can be caused by viruses, mycobacteria, fungi, spirochetes, malignancy, and medications []. Recent studies showed that quality of life was reduced among three groups of adult patients with AM in the months following discharge compared to healthy controls [,]; however, there were indications of good recovery with no/minimal ***cognitive*** sequelae 12 months after discharge []. In support of good recovery, studies among patients with AM showed long-term health comparable to the general population [,]. Importantly, another recent study showed that the risk for developing mental disorders after CNS infection was higher among patients with AM compared to that with BM []. The following impairments have been reported among patients with AM after discharge: impairment of concentration; loss of memory and/or executive functions; decreased speed of ***cognitive*** function; reduced psychomotor performance; and sleeping disorders [,]. Such ***cognitive*** impairments can affect the patient's health-related quality of life including their ability to work []. Thus, being able to identify patients with ***cognitive*** impairments at the time of, or soon following, discharge would be of great value to individuals as well as to the society as a whole.

The Montreal ***Cognitive*** Assessment (MoCA) is a brief, ***cognitive*** test developed to identify mild ***cognitive*** impairment. MoCA has previously been validated, primarily in patients with neurological diseases or injuries. Recently, the MoCA was also validated in adolescents and young adults with congenital heart disease [,]. Because of its reproducibility as well as its ease of use, we have previously speculated whether MoCA could be used as a screening tool to identify mild ***cognitive*** impairment in patients with AM []. We designed the current study to address this question. Specifically, the aims of this study were (i) to evaluate the prevalence of patients with CNS infections (subdivided into the diagnosis of aseptic meningitis, bacterial meningitis, and encephalitis) in need of ***rehabilitation*** at/after discharge and (ii) to determine the extent to which MoCA could be used as a screening tool to identify a need of ***cognitive rehabilitation*** following CNS infection.

Methods

Participants

A total of 239 patients with CNS infections were included such that our data set was composed of all persons in our study area who were diagnosed with AM, BM, or EN. Patients with non-infectious CNS inflammation (n = 6), Lyme neuroborreliosis (n = 11), brain abscess (n = 8), neurosyphilis (n = 3), or unknown CNS infection were excluded (n = 38) to keep the study populations well defined. Seven patients died during their hospital stay and were excluded from the study population (all aged ≥ 65: AM n = 2, BM n = 4, and EN n = 1). The remaining 166 patients constituted the study population (Table). They were admitted with AM (n = 77), BM (n = 53), and EN (n = 36). Occupational assessments were not performed among 23 individuals; therefore, the need for ***rehabilitation*** among these individuals was clinically determined by physicians alone. MoCA was not performed in 71 individuals and

these individuals are excluded from the adjusted binary logistic regression model for this particular variable. This research study was conducted retrospectively from data obtained for clinical purposes. We consulted the Danish National Committee on Health Research Ethics who determined that our study did not need ethical approval. The study was approved by the Danish Data Protection Agency (record no. 1-16-02-399-16).

Baseline patient characteristics according to diagnosis

	Total	**Aseptic meningitis (AM)**	**Bacterial meningitis (BM)**	**Encephalitis (EN)**
	166 (100)	**77 (46)**	**53 (32)**	**36 (22)**
Need for ***rehabilitation***[A]				
Yes	96 (58)	37 (48)	33 (62)	26 (72)
Cognitive	*44 (46)*	*26 (70)*	*9 (27)*	*9 (35)*
Physical	*7 (07)*	*5 (14)*	*2 (06)*	*0 (00)*
Cognitive + *physical*	*29 (30)*	*4 (11)*	*17 (52)*	*8 (30)*
Inpatient specialized neurorehabilitation	*16 (17)*	*2 (05)*	*5 (15)*	*9 (35)*
No	70 (42)	40 (52)	20 (38)	10 (28)
Age (years)				
16?43	68 (41)	51 (66)	8 (15)	9 (25)
44?64	37 (22)	9 (12)	18 (34)	10 (28)
? 65	61 (37)	17 (22)	27 (51)	17 (47)
Sex				
Female	82 (49)	37 (48)	27 (51)	18 (50)
Male	84 (51)	40 (52)	26 (49)	18 (50)
Symptomatic period pre-admission (days)				
? 2	87 (52)	43 (56)	34 (64)	10 (28)
> 2 and ? 7	46 (28)	20 (26)	11 (21)	15 (42)
> 7	21 (13)	11 (14)	3 (06)	7 (19)
Missing data	*12 (07)*	*3 (04)*	*5 (09)*	*4 (11)*
ICU[B]				
Yes	18 (11)	0 (00)	13 (25)	5 (14)
No	148 (89)	77 (100)	40 (75)	31 (86)
GOS score[C]				
< 4	21 (13)	4 (05)	5 (09)	12 (33)
? 4	145 (87)	73 (95)	48 (81)	24 (67)
MoCA score[D]				
< 26	43 (26)	16 (21)	17 (32)	10 (28)
? 26	52 (31)	32 (42)	15 (28)	5 (14)
Missing data	*71 (43)*	*29 (38)*	*21 (40)*	*21 (58)*

Data are n (%)

AAt discharge or follow-up in the outpatient clinic

BDuring admission

COne month after discharge during outpatient visit

DDuring admission or follow-up in the outpatient clinic

GOS, Glasgow Outcome Scale; ICU, intensive care unit; MoCA, Montreal ***Cognitive*** Assessment

Design

From 1 January 2015 to 31 December 2016, the need for ***rehabilitation*** was assessed among patients (age 16 and older) with CNS infections admitted to the Department of Infectious Diseases, Aarhus University Hospital in Central Denmark Region.

Procedures

The need for ***rehabilitation*** among patients with CNS infections was clinically determined by physicians with the aid of occupational therapy assessments at discharge or at 1- or 3-month outpatient follow-up visits. In addition, a MoCA screening was made after grading the need for ***rehabilitation***. Thereafter, we identified the clinical characteristics of the study population in the national Danish Study Group of Infections of the Brain (DASGIB) database and retrieved data on age, sex, duration of symptoms pre-admission, admission to intensive care unit (ICU), and GOS score at 1-month follow-up (Table) []. The occupational therapy assessment consisted of an occupation-focused interview that was theoretically based on the first step in the Occupational Therapy Intervention Process Model []. In short, this model is a top-down, patient-centered, occupation-centered model. It focuses on the person, the environment, and any circumstances specific for the occupation of the person being assessed. The first step in implementing the model is to establish a client-centered performance context. At this step, the occupational therapist gathers information about relevant factors affecting the person's ability to perform their occupation including why and how they perform different tasks. This is then extended to ensure the identification of specific daily tasks affecting the individual's participation in society [].

Outcomes

The need for ***rehabilitation*** was graded as either (1) no need or (2) need for outpatient ***rehabilitation*** (either ***cognitive*** or/and physical therapy), or (3) need for inpatient specialized neurorehabilitation. In those graded as (3), MoCA was not performed (total, n = 16; AM, n = 2; BM, n = 5; and EN, n = 9). The MoCA was used as a potential screening tool to identify patients in need of ***rehabilitation***. The overall score ranges between 0 and 30; scores of ≥ 26 are considered normal []. The Glasgow Outcome Scale (GOS) was used to depict clinical outcomes on an ordinal scale for incorporation into the binary logistic regression model. The GOS is a well-validated tool to assess outcomes within the following categories: 1 = death; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; and 5 = good recovery [].

Statistical Analysis

Categorical variables were compared pairwise using Fisher's exact test. p values below 0.05 were considered statistically significant, and Bonferroni correction was used to counteract problems associated with multiple comparisons. We evaluated the odds of needing either ***cognitive*** or physical ***rehabilitation*** using a binary logistic regression forced entry model. We considered both an unadjusted and adjusted model for the clinical characteristics listed in the table. A correlation matrix of the adjusted variables showed no significant intercorrelations. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla, CA, USA, www.graphpad.com) and StataCorp. 2013 (Stata Statistical Software: Release 162. College Station, TX: StataCorp LP).

Results

There are several key observations within the baseline patient characteristics (n = 166) that should be emphasized (Table). Overall, 58% of the patients with CNS infections needed ***rehabilitation***. Because our study focused on understanding the need for AM patients to have ***rehabilitation*** relative to BM or EN patients, we constrained our

analyses to comparisons made between AM and BM or AM and EN (Table). For completeness in data reporting, we have also provided comparisons of BM vs EN. However, we do not discuss these data further. First, AM patients were distinguished from BM patients in several ways. They were younger and not admitted to the ICU. Conversely, there were multiple parameters where AM patients were indistinguishable from BM patients. Specifically, these comparisons revealed no differences in need for ***rehabilitation***, sex, GOS scores (< 4 vs. ≥ 4), or MoCA score (< 26 vs. ≥ 26). Next, we compared AM patients to EN patients. For these comparisons, we found that the AM patients were again younger and not admitted to the ICU relative to EN patients. Furthermore, the AM patients were admitted earlier according to the symptomatic period and had higher GOS scores (< 4 vs. ≥ 4) relative to EN patients. No differences between these groups were noted for need for ***rehabilitation***, sex, or MoCA score (< 26 vs. ≥ 26).

Comparisons of baseline patient characteristics across diagnoses

	Variable 1		**Variable 2**	***p* value**
AM vs. BM		vs		0.152
	Need for ***rehabilitation***		No need for ***rehabilitation***	
Age 16?43	*vs*	*Age 44?64*	*< 0.001*	
Age 16?43	*vs*	*Age ? 65*	*< 0.001*	
Age 44?64	vs	Age ? 65	0.801	
Female	vs	Male	0.859	
Symptomatic period pre-admission (days) ? 2	vs	Symptomatic period pre-admission (days) > 2 and ? 7	0.518	
Symptomatic period pre-admission (days) ? 2	vs	Symptomatic period pre-admission (days) > 7	0.145	
Symptomatic period pre-admission (days) > 2 and ? 7	vs	Symptomatic period pre-admission (days) > 7	0.492	
Admitted to ICU	*vs*	*Not admitted ICU*	*<0.001*	
GOS score < 4	vs	GOS score ? 4	0.485	
MoCA < 26	vs	MoCA score ? 26	0.105	
AM vs. EN		vs		0.025
	Need for ***rehabilitation***		No need for ***rehabilitation***	
Age 16?43	*vs*	*Age 44?64*	*0.002*	
Age 16?43	*vs*	*Age ? 65*	*0.001*	
Age 44?64	vs	Age ? 65	1.000	
Female	vs	Male	1.000	
Symptomatic period pre-admission (days) ?2	*vs*	*Symptomatic period pre-admission (days) > 2 and ? 7*	*0.018*	
Symptomatic period pre-admission (days) ? 2	vs	Symptomatic period pre-admission (days) > 7	0.112	
Symptomatic period pre-admission (days) > 2 and ? 7	vs	Symptomatic period pre-admission (days) > 7	1.000	
Admitted to ICU	*vs*	*Not admitted ICU*	*0.003*	

	Variable 1		Variable 2	*p* value
GOS score < 4	*vs*	*GOS score ? 4*	*0.001*	
MoCA <26	vs	MoCA score ?26	0.035	
BM vs. EN	Need for ***rehabilitation***	vs	No need for ***rehabilitation***	0.368
Age 16?43	vs	Age 44?64	0.353	
Age 16?43	vs	Age ? 65	0.391	
Age 44?64	vs	Age ? 65	1.000	
Female	vs	Male	1.000	
Symptomatic period pre-admission (days) ? 2	*vs*	*Symptomatic period pre-admission (days) > 2 and ? 7*	*0.005*	
Symptomatic period pre-admission (days) ?2	vs	Symptomatic period pre-admission (days) > 7	0.007	
Symptomatic period pre-admission (days) > 2 and ? 7	vs	Symptomatic period pre-admission (days) > 7	0.706	
Admitted to ICU	vs	Not admitted ICU	0.286	
GOS score < 4	vs	GOS score ? 4	0.007	
MoCA < 26	vs	MoCA score ? 26	0.529	

Statistical test was performed pairwise of the variable noted using Fisher's exact test with a Bonferroni correction of (0.05/11) 0.005

AM, aseptic meningitis; BM, bacterial meningitis; EN, encephalitis; GOS, Glasgow Outcome Scale; ICU, intensive care unit; MoCA, Montreal ***Cognitive*** Assessment

Next, we related the categorical patient data to whether ***rehabilitation*** was required. As shown in Table , patients with CNS infections were more likely to need ***rehabilitation*** if the diagnose was EN (unadjusted odds ratio (OR) = 2.81), admission to the ICU had occurred (unadjusted OR = 6.8), GOS score 1 month after discharge was < 4 (unadjusted OR = 5.15), or MoCA score was below 26 (unadjusted OR = 4.38). In the adjusted analyses a MoCA score < 26 was the only variable strongly associated with higher odds of needing ***rehabilitation*** (adjusted OR = 10.8). Accordingly, patients with CNS infection and a low MoCA score had a higher probability of needing ***rehabilitation*** and vice versa (Fig.). The steepest part of the curve was around the score of 26 (a cutoff value of 26 ***predicted*** the highest odds of needing ***rehabilitation***). The probability of needing ***rehabilitation*** increased with older age, but the widest CI was seen among younger and older ages (Fig.). Nevertheless, there was no association between the need for ***rehabilitation*** and increasing age according to the regression analysis (Table). Plotting the MoCA score from 62 patients with either AM, BM, or EN in need of ***rehabilitation*** showed that 26 (42%) had a MoCA score ≥ 26 (Fig.). The patients in need of ***rehabilitation*** and with a MoCA score ≥ 26 were primarily young adults (16–43 years) (69%) followed by the group of middle aged (44–64 years) (23%) and aged (≥ 65 years) (8%). There was no statistical difference between the age groups in whether or not ***rehabilitation*** was needed (16–43 vs ≥ 65, p = 0.08; 44–64 vs ≥ 65, p = 0.54; 16–43 vs 44–64, p = 0.36). The need for ***rehabilitation*** among these groups was graded as either ***cognitive*** or physical (Fig.). The ***cognitive*** impairments primarily involved fatigue (25%), attention (25%), and memory deficits (23%) (Fig.).

Correlates of needing ***cognitive*** and/or physical ***rehabilitation***

	Odds of needing *rehabilitation*		
	Unadjusted OR (95% CI)	**Adjusted OR[A] (95% CI)**	***p* value**

	Odds of needing ***rehabilitation***		
	Unadjusted OR (95% CI)	**Adjusted OR[A] (95% CI)**	***p* value**
Diagnosis			
Aseptic meningitis	1 (Reference)	1 (Reference)	
Bacterial meningitis	1.78 (0.87?3.64)	1.40 (0.34?5.89)	0.640
Encephalitis	2.81 (1.19?6.61)	2.37 (0.39?14.5)	0.352
Age (years)			
16?43	1 (Reference)	1 (Reference)	
44?64	1.47 (0.65?3.30)	1.20 (0.30?4.90)	0.796
? 65	1.90 (0.94?3.88)	0.29 (0.05?1.61)	0.158
Sex			
Female	1 (Reference)	1 (Reference)	
Male	0.57 (0.31?1.07)	0.37 (0.13?1.05)	0.061
Symptomatic period pre-admission (days)			
? 2	1 (Reference)	1 (Reference)	
> 2 and ? 7	1.68 (0.80?3.55)	1.23 (0.40?3.84)	0.717
> 7	0.89 (0.34?2.32)	0.59 (0.11?3.12)	0.539
ICU[B]			
Yes	6.8 (1.50?30.6)	1.81 (0.24?13.8)	0.567
No	1 (Reference)	1 (Reference)	
GOS score[C]			
< 4	5.15 (1.45?18.3)	2.69 (0.23?31.0)	0.428
? 4	1 (Reference)	1 (Reference)	
MoCA score[D]			
< 26	4.38 (1.71?11.2)	10.8 (2.52?46.0)	0.001
? 26	1 (Reference)	1 (Reference)	

CI, confidence interval; GOS, Glasgow Outcome Scale; ICU, intensive care unit; MoCA, Montreal ***Cognitive*** Assessment; OR, odds ratio

AModel adjusted for all variables listed in this table

BDuring admission

COne month after discharge during outpatient visit

DDuring admission or follow-up in the outpatient clinic

Montreal ***Cognitive*** Assessment (MoCA) score among patients with central nervous system infection. a MoCA score according to the probability of needing ***rehabilitation***. b Age according to the probability of needing ***rehabilitation***. Panels a and b are ***predicted*** mean with 95% confidence interval. c MoCA score among patients in need of ***rehabilitation***. d The distribution of ***cognitive*** and/or physical ***rehabilitation*** needs among patients with MoCA 26 (highlighted gray box in c). e The ***cognitive*** impairments depicted in Panel d represent the predominant ***cognitive*** impairment experienced in each patient with ***cognitive rehabilitation*** needs among patients with MoCA 26 (highlighted gray box in c). ● Young adults (16–43 years), ■ middle aged (44–64 years), and ♦ aged (65 years)

Discussion

We found that more than half of the adults admitted into our hospital with CNS infections needed ***rehabilitation*** at/after discharge. This was true when considering AM, BM, and EN in aggregate. This included a need for

rehabilitation in a large proportion of AM patients—a somewhat surprising result given that AM is considered a relatively benign disease compared to BM and EN [, , ,]. Because of the need for ***rehabilitation*** in a population that was not anticipated, we sought an accurate method for rapidly identifying individuals in need of ***rehabilitation*** that is independent of their clinical diagnosis.

Towards this goal, we found that a MoCA score < 26 shows a high probability of needing ***rehabilitation***. However, the MoCA test cannot stand alone. This is exemplified by the fact that 26 (42%) patients in need of ***rehabilitation*** had a MoCA score ≥ 26 and the majority of these 26 individuals were young adults (16–43 years). This finding shows the importance of a systematic assessment for need of ***rehabilitation*** [], especially in young adult patients. Such an assessment should be performed even if a MoCA score ≥ 26 was obtained. There is precedent for such a need. Specifically, in a separate study of patients with CNS infections caused by varicella zoster virus infection, five of twelve patients had mild ***cognitive*** impairment as well as a significantly lower MoCA score compared to the age- and gender-matched controls []. One patient of the five had a MoCA score < 26 []. This led the authors to hypothesize that younger patients with a high educational level were able to compensate for a ***cognitive*** decline when taking the MoCA. This could be because the MoCA has a maximum score. Our data are also consistent with a MoCA outcome driven by compensation for ***cognitive*** decline by younger adults. Furthermore, ***cognitive*** complaints after CNS infection could be more subtle during admission in the group of young adults (16–43 years of age). ***Cognitive*** complaints may then be exacerbated after discharge once these patients are confronted with obligations and demands upon returning home to family and careers. The concept that return to “normal” life exacerbates ***cognitive*** symptoms is supported by studies among patients with EN and viral meningitis [, ,]. These studies found similar trends towards reduced quality of life, especially in the age groups 35–44 and 25–35 years, respectively [, ,]. Together, prior data plus the data we present indicate that special care must be taken to ensure that young adults in need of ***rehabilitation*** following CNS infection are identified and given access to ***rehabilitation***. The steps required to identify such young adults may be greater than required for identifying older patients needing ***rehabilitation***. It is critical that health care providers be aware of this age disparity and ensure that MoCA outcomes are properly supplemented with occupational therapy assessments, particularly in younger adults.

Our study has some limitations. The criterion for needing ***rehabilitation*** was based on the clinical evaluation made by the physician with the aid of occupational therapy assessments. These criteria might not be comparable to what can feasibly be obtained given the infrastructure present in other sites. The MoCA was not conducted among all enrolled patients. Moreover, MoCA was not compared to any other neuropsychological tests. Our results were challenged by the fact that we studied a relatively small patient population with a clinical follow-up limited to 3 months. Since the occupational therapy assessment and/or MoCA was not repeated during outpatient visits, our data do not address whether the ***cognitive*** complaints were improved, persistent, or worse. Fatigue is a common self-reported symptom after neurological diseases in general, and should also be assessed when evaluating the need for ***rehabilitation*** after CNS infection []. The state of fatigue and ***cognitive*** impairment might affect each other.

In conclusion, many patients will have a need for ***cognitive rehabilitation*** after a CNS infection, regardless of the diagnosis. There is a definite need for systematic assessment for need-of-***rehabilitation*** among younger adult patients. Identifying which patients with CNS infections are at risk of ***cognitive*** impairment and whether these impairments can be prevented or reduced by specific ***rehabilitation*** initiatives during admission or at/after discharge needs to be prioritized, especially in younger adults.

Acknowledgements

We would like to acknowledge DASGIB for providing access to the database.

Notes

Classification

Language: ENGLISH

Publication-Type: Magazine

Journal Code: 42399

Subject: BACTERIA (93%); MENINGITIS (91%); DISEASES & DISORDERS (90%); INFECTIOUS DISEASE (90%); INFLAMMATORY DISEASES (90%); NEUROLOGICAL DISORDERS & INJURIES (90%); RESEARCH REPORTS (90%); INTELLIGENCE & COGNITION (89%); ADOLESCENTS & TEENS (78%); EXPERIMENTATION & RESEARCH (78%); LYME DISEASE (78%); MEMORY (78%); MEMORY DISORDERS (78%); NEUROSCIENCE (78%); ADULTS (74%); CARDIOVASCULAR DISEASE (73%); CONGENITAL DISORDERS (73%); HEART DISEASE (73%); MENTAL ILLNESS (73%); SLEEP DISORDERS (73%)

Organization: UNIVERSITY OF NEBRASKA (59%); Department of Infectious Diseases; Aarhus University Hospital; Department of Internal Medicine; Randers Regional Hospital; Department of Biology; University of Nebraska at Omaha; Department of Physiotherapy and Occupational Therapy; Aarhus University Hospital

Person: Ørum Matilde; Storgaard Merete; Denton Paul W.; Mogensen Trine Hyrup; Højbjerg Christina Kjærgaard; Pedersen Mathilde; Gunst Jesper Damsgaard

Geographic: OMAHA, NE, USA (58%); NEBRASKA, USA (79%)