Article published online: 2022-12-23

Gender Differences in Executive Functions of Patients Operated for Mild to Moderate Epidural Hematoma

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Indian J Neurosurg 2024;13:20–26.

Abstract

Background Impairment in neurocognitive functions are commonly followed by Epidural hematoma (EDH) . This cross-sectional study was aimed to study gender differences in neurocognitive functions in mild to moderate epidural hematoma patients (43 male and 19 female patients) post-surgery using standardized assessment tools of comprehensive neurocognitive function attention, speed, working memory, fluency, set-shifting, perseveration, planning and response inhibition.

Methods Descriptive statistics, i.e., mean and standard deviation (SD) values were computed, and a *t*-test was applied for further exploration.

Results The analysis of results shows that on the test of working memory, female group scored better as significant differences were found on N-Back (2 Back versions) and digit span-backward. On the verbal fluency test (COWA), significant difference was found as females scored higher than the male group on total responses. However, the male group was higher in total time and error than the female group on the test of sustained attention and divided attention.

Conclusion This study shows interesting results in terms of gender differences in executive function of patients operated for mild to moderate epidural hematoma. These findings have significant clinical and implications for planning intervention. The neuropsychological rehabilitation of patients operated for mild to moderate epidural hematoma has a crucial role in enhancing their recovery and overall functioning. Inputs about gender differences in neuro psychological functioning of these patients would help in decision making regarding neuropsychological rehabilitation incorporating the gender related differences too in their intervention plan.

Keywords
- traumatic brain injury
- epidural hematoma
- neurocognitive functions
- executive functions

Traumatic brain injury (TBI) is a major public health concern.[1] Epidural hematoma (EDH) constitutes 10% of TBI. It is a condition when blood collects between the skull and thick membrane (dura mater) which covers the brain.[2] Collection of blood exerts pressure on the brain and causes inflammation, which damages the brain's tissue resulting in transient and long-lasting cognitive impairments in attention, comprehension, working memory fluency, set-

article published online
December 23, 2022

DOI https://doi.org/10.1055/s-0042-1757918.
ISSN 2277-954X.

shifting, perseveration, response inhibition and planning which affect personal, social and occupational life of the patient.[3,4]

Variables such as age, severity of injury, and neurological status have been found to play a crucial role in clinical manifestation and outcome of EDH. Apart from these variables, gender is by far the most controversial in the literature. Earlier studies showed the absence of gender differences in problem-solving performance between college students[5] as well as nursery students.[6] Recently, gender differences have been revealed by studies examining cognitive functions and the role of gender in patients of TBI. Schopp, Shigaki, Johnstone, and Kirlpatrick.[7] concluded that men underperformed women on certain memory tasks specifically, on verbal memory, after a TBI. Research, using Traumatic Brain Injury Model Systems [8] also revealed the effect of gender on executive function, wherein women outperformed men. Women were also reported to achieve better composite scores on verbal memory in comparison to men.[9] In contrast, differing conclusions exist for gender effect on verbal and visuo-spatial domains of patients with TBI. Broshek et al[10] reported that women had more verbal and visuospatial memory deficits after an injury as compared with men. However, Harness et al[11] found that though there were insignificant gender differences in verbal recall task, women performed better on visuospatial tasks.

Review of preceding manuscript shows that gender is most controversial in the research community, especially when it comes to brain injury. Furthermore, existing literature on gender differences in neurocognitive outcome of EDH have been equivocal. Hence, current inquiry was aimed to explore gender differences in terms of comprehensive executive functions of recovered post-surgery EDH male and female patients matched for age, duration, and severity of injury using standardized assessment tools. In light of previous studies, we hypothesized that there will be gender differences in executive functions of males and females recovered post-surgery EDH patients.

Methods

This was a cross-sectional, case–controlled study planned to investigate gender differences in comprehensive neurocognitive functions in recovered EDH patients visiting the Neurosurgery Department at a tertiary care hospital in north India. The protocol was accepted by Institutional Ethics Committee (64th ECM II-B/P28). Patients were purposively sampled, and gender-wise matching was done for age, duration, and injury severity.

Participants

Sixty-two EDH patients (aged 20–60 years) were sampled for the study after consulting the neurosurgeons and radiologists. The patients were diagnosed with epidural hematoma with a history of sustaining TBI and presented to Emergency Services of the Department of Neurosurgery within 24 hours. Patients were screened by consultant neurosurgeons using clinical evaluation, MRI, and surgical intervention (craniotomy and evacuation). Glasgow Coma Scale (GCS) was used to determine the severity of TBI on a scale of 9 to 15.[12]

The inclusion criteria of the patients were (a) aged between 20 and 60 years at the time of brain injury, (b) diagnosis of EDH following injury, (c) treatment through surgical intervention with the past 3–5 months, (d) mild-moderate severity of TBI (GCS = 9–15) [12], (d) post-traumatic unconsciousness of duration < 24 hours, and (e) literate in verbal and written Hindi language.

The exclusion criteria for the patients were (a) it they had history of any present or past substance abuse except for nicotine, (b) presence of any neurological disorder (stroke, or tumors, CVAs), (c) significant medical condition, (d) diagnosis of any psychiatric disorder (evaluated by MINI International Neuropsychiatric Interview),[13] (e) clinical impression suggestive of intellectual disability, (f) gross visual/hearing/perceptual/motor impairment, which could inhibit cognitive assessment, (g) severe TBI (screened through GCS score if $\leq$ 9),[12] (h) medications expected to interfere with cognitive functions (anti-dementia medications, lithium, tricyclic antidepressants, etc.).

Tools

MINI International Neuropsychiatric Interview

To rule out any co-morbid psychiatric illnesses in the patients, MINI was used.[13] It is a structured interview schedule put together by clinicians and psychiatrists and is also an integral part of DSM IV and ICD 10.

NIMHANS Neuropsychological Battery

This test battery was used to assess neurocognitive functions of participants. The NIMHANS[14] battery is also used internationally, and normative data regarding percentiles and cut-off scores have been established for Indian adults between the ages of 16 and 65. It includes the following sets of tests:

Digit Symbol Test measures sustained attention and visuomotor coordination. The test taker needs to substitute the number inside the cell with a symbol, using the key for number-symbol substitution at the top as a guide. The numbers range from 1 to 9 and are arbitrarily assigned in four rows of 25 cells each.

Color Trails test is a more cross-cultural test involving the use of focused attention. Sustained attention, perceptual tracking, and sequencing are included in part 1 of the test, and mental flexibility is involved in part 2.

Digit Vigilance Test measures sustained attention and psychomotor speed. Numbers 1–9 are arranged randomly in rows through the entire sheet. The subject has to selectively focus on the target stimuli, i.e., cancelling out only 6s and 9s among the other distractor digits.

Digit Span test includes forward and backward span tests. The forward span measures attention efficiency when the subject needs to repeat the numbers in the identical sequences as said aloud by the tester. In backward span, the executive function of working memory plays the major role, wherein the subject repeats the numbers in reverse order as said aloud by the tester.

Controlled Oral Word Association Test (COWA) evaluates verbal fluency. The subject has to rapidly produce words of the same designated letter (phonetics), such as F, A, S. To accommodate Hindi speaking participants, phonetics such as "Ka," "Ra," and "Pa" were used.

Animal Names Test assesses category fluency. The test needs the subject to bring as many animal names as possible within a minute, thereby evaluating a sematic category fluency at a time.

N back tests involve encoding and working memory. The 1-back version requires the subject to point out if the letter (n) being narrated has been repeated n-1 time, requiring verbal storage and rehearsal. On the contrary, the 2-back version needs the subject to point out if the letter (n) has been narrated n-2 times in the sequence of intervening letters. The scores are calculated based on hits and errors made in both tests.

Tower of London test is used to evaluate mental preplanning in participants. The test entails two matching wooden boards having three round pegs with different colored beads/balls in each. First, a stimulus board (model of pegs and beads) is presented to the participant, and then the target pegs and beads have to be arranged to match the stimulus board.

Stroop Test assesses response inhibition. The stimuli are different names of colors, written in an ink not corresponding to their color name, e.g., the word "blue" is noted in the color green. The subject is first asked to read all the names of colors irrespective of their ink color. The test progresses, asking the subject to ignore the name of the color and start naming the ink color of each stimulus. The duration of both phases is recorded.

Auditory Verbal Learning Test[15] measures attention, concentration during learning, and under overloaded conditions too. It contains of two lists, A and B. List A (15 words) is presented to the subject five times, followed by a recall of the list after each presentation. After five such recalls, List B of 15 different words is presented, and an immediate recall is asked. After that a recall of List A without presentation is asked, followed by a presentation of a recognition list to identify all the words belonging to List A. This test successfully measures delayed recall and recognition of stimuli too.

Complex Figure Test[16] assesses visuospatial/ constructional ability and visual memory ability through immediate recognition and recall of a complex figure of lines that are abstract in nature. Accordingly, it is scored depending on the overall copied structure and multiple subcomponents of the reproduced drawing.

Letter Number Sequencing Test

Auditory working memory was evaluated by Letter Number Sequencing Test[17] that includes auditory stimuli by using subtests **Wechsler Memory Scale** 3rd edition includes 11 subtests, i.e., 6 primary subtests and 5 optional ones. Dr. Pushpalatha Gurappa (NIMHANS, Bengaluru) has adapted it according to the Indian population to assess immediate, delayed recall, and working memory.

Wisconsin Card Sorting Test

Wisconsin Card Sorting Test (WCST)[18] consists several cards with different figures, with respect to color, quantity, and shape, which are offered to participants. It is used to evaluate "set-shifting" and problem-solving strategies.

Procedure

The process of screening participants, sampling, and collecting data was carried from February 2017 to October, 2017. The database of the patients diagnosed with TBI in the past 3 to 5 months in the Neurosurgery Department of a tertiary care center in North India was retrieved. The individuals meeting the inclusion criteria were reached out through phone calls and were elucidated the objectives of the study. Meetings with those who agreed to cooperate were arranged according to mutual convenience. Written informed consent was taken, and neuropsychological assessment was conducted according to the protocol in the Psychiatry Department. Patients were instructed to be off of any sedatives, anticholinergic medications or benzodiazepines for at least 12 hours before the commencement of assessment. For recruitment of healthy controls group, the patient's attendants and hospital employees of the department of Neurosurgery were contacted and screened using the General Health Questionnaire (GHQ)[19]. The individuals scoring less than 3 on GHQ were sampled as controls in the study. A semi-structured proforma was used to record the controls and study subjects' socio- demographic and other essential details. Following this, neuropsychological assessment using standardized tools was conducted on study and control participants.

Statistical Analysis

Mean and standard deviations were used for summarizing the pool of data. The control and study group's performance were compared using the student *t*-test. Mean scores of groups were statistically analyzed for test of significance by *t*-test. A two-tailed ($\alpha = 2$) $p < 0.05$ was set as statistically significant. Microsoft Excel 2010 software and GraphPad Prism 7.00 for Windows (GraphPad Software, La Jolla, California, USA, www.graphpad.com) were used to tabulate the data.

Results

A database of TBI patients of the past 3 to 5 months was reviewed, revealing that 216 patients with EDH were operated. The screened data revealed that 17 patients were deceased, 21 patients had severe TBI, 11 did not fall in the age range of 20 to 60 years, and 18 were illiterate. Other 9 patients were excluded because of medical illnesses, 15

Table 1 Socio demographic characteristics of male and female TBI patients' groups

Sociodemographic characteristics		Male $n = 43$ (69.35%)	Female $n = 19$ (30.64%)
Age	Minimum–maximum	19–61	18–51
	Mean ± SD	37.95 ± 14.06	29.42 ± 10.65
Mean years of education [y]		15	14
Hemisphere	Right	28 (65.12%)	14 (73.68%)
	Left	15 (34.88%)	05 (26.32%)
Mean GCS score on severity		14.7	14.2
Mean Duration post- surgery [mo]		4.3	4.8
Site of injury	Frontal lobe	9 (20.93%)	6 (31.58%)
	Frontotemporal lobe	15 (34.88%)	2 (10.53%)
	Frontoparietal lobe	11 (25.58%)	4 (21.05%)
	Temporal-parietal lobe	6 (13.95%)	4 (21.05%)
	Fronto-tempo-parietal lobe	2 (4.65%)	3(15.79%)

patients had some co-morbid neurological conditions (1 patient reported for CVA, 2 had stroke, 2 reported having hippocampal sclerosis, 4 had stroke, and 6 patients had dementia), 8 patients were excluded because of co- morbid psychiatric illness (generalized anxiety disorder-1, bipolar disorder- 2 and five patients had depression), 17 patients had record of substance abuse and 2 patients were intellectual disable. Exclusion was also based on disagreement with participation in the study. The patients recruited using the inclusion criteria mostly suffered TBI due to injury in road accidents. Seventy-three such patients were enrolled, out of which 11 were unable to complete the entire assessment. The clinical and demographic details of the participants recruited are listed in ►**Table 1**.

A comparison of means of neuropsychological tests between males and females revealed that the female group had better performance in some executive function tests than male patients [►**Table 2**].

Mean scores showed that males to be higher in total time and total error than females on tests of attention (divided and sustained), concentration, and mental speed measured by the Color Trails Test and Digit Symbol Test; however, differences between group mean are insignificant. On test of working memory, female group scored better as significant differences were found on N-Back (2 Back) and digit span-backward. Here, again male group took more time and committed more errors than the females. On COWA (total response), a significant difference was revealed as females scored higher than males. Both genders performed equally on WCST (except percentage perseverative responses), Stroop test, and Tower of London Test, which suggest no difference in the planning aspect of executive functioning among both genders.

Discussion

The present study investigated gender differences in executive functions among patients operated for EDH. Most patients in this study had a history of frontal lobe involvement, which is considered the seat of executive functions [attention, reasoning, judgment, problem-solving]. It is shown that disruptions in executive functions become more evident in patients with frontotemporal lesions followed by a TBI.[20,21]

Findings suggest that on tasks related to working memory assessed by the N-Back test and B-Working, females had a higher mean score than males in both tests. In addition, the former also has a lower N-Back error score, which suggests better working memory function in general. Results on COWA indicate that even after suffering neurological effects of EDH, the ability to generate words is less impaired in women as compared with men. Research reveals that females, compared with males, have a skewed brain organization wherein language specialization in the left hemisphere progresses earlier in females, leading to smoother verbal skills.[22,23] Males, in contrast, have an advantage over spatial skills owing to more bilateral brain organization. Levy[23,24] noted a heavy reliance on verbal processing in left hemisphere and spatial tasks on the right hemisphere. He concludes that females' more "bilateral" brain organization would mean that both left and right hemispheres are structured to execute verbal task performances. In contrast, males have a more asymmetric brain organization with superior execution of spatial tasks instead of verbal tasks.

A left-hemispheric laterality in females compared with the right-hemispheric laterality in males reflects the cognitive sex differences regarding verbal-working memory tasks.[25] This finding is per the previous research concluding superior performance of females in verbal task performance.[26] The pediatric population also showed a similar trend in which girls with TBI performed significantly better than boys on verbal skills and working memory tasks.[27] Females also outperform on sub-tests of verbal ability[28] and other tasks such as sentence formations,

Table 2 Mean ± SD and *t*-values of various Neuropsychological Tests between male and female TBI patients

Tests		Gender		SED	*t*-Value	*p*-Value
		Male $n = 43$	Female $n = 19$			
		Mean ± SD	Mean ± SD			
I. Attention (sustained attention and divided attention)						
1	Digit vigilance (Total Errors)	6.23 ± 1.74	5.68 ± 1.60	0.469	1.170	0.247
2	Digit vigilance (total time)	372.86 ± 74.23	336.84 ± 98.96	22.708	1.586	0.118
3	Digit symbol (total time)	611.14 ± 95.70	580.16 ± 87.04	25.671	1.207	0.232
4	Color trial-1 (total time)	105.83 ± 25.14	95.47 ± 15.73	6.261	1.655	0.103
5	Color trial-2 (total time)	258.74 ± 71.53	239.0 ± 47.59	17.983	1.098	0.277
II. Executive Function						
1	1 Back (responses) Immediate memory	5.28 ± 0.91	5.53 ± 0.091	0.249	−0.989	0.327
2	1 Back (errors) Immediate memory	3.19 ± 1.32	2.74 ± 1.15	0.349	1.288	0.203
3	2 Back (responses)	3.58 ± 1.12	4.42 ± 1.22	0.316	−2.655	0.010**
4	2 Back (errors)	4.56 ± 1.45	3.53 ± 1.71	1.032	2.440	0.018*
5	Letter Number Sequence (responses)	7.42 ± 2.24	7.84 ± 2.31	0.623	−0.680	0.499
6	Digit Span-Forward (Responses)	4.37 ± 1.05	4.84 ± 1.21	0.303	−1.551	0.126
7	Digit Span-Backward (Responses)	2.53 ± 0.85	3.05 ± 1.10	0.265	−1.952	0.049*
8	COWA (total responses)	3.67 ± 1.13	4.32 ± 1.06	0.305	−2.103	0.040*
9	Animal naming–(responses)	7.74 ± 1.91	8.53 ± 2.19	0.552	−1.417	0.162
10	WCST-Percentage Errors	54.05 ± 5.89	52.47 ± 6.83	1.706	0.922	0.360
11	WCST-percentage perseverative responses	25.83 ± 2.52	27.84 ± 4.56	0.901	−2.224	0.030*
12	WCST-percentage perseverative error	34.56 ± 4.98	33.32 ± 6.18	1.479	0.840	0.404
13	WCST-correct**responses	48.26 ± 4.16	48.4 ± 5.34	1.252	−0.132	0.896
14	Tower of London-levels	2.56 ± 0.91	2.79 ± 1.32	0.288	−0.802	0.426
15	Tower of London-mean moves (attempts)	4.67 ± 1.66	4.32 ± 1.97	0.484	0.740	0.462
16	Tower of London–(problems solved)	3.51 ± 1.83	3.84 ± 1.98	0.517	−0.639	0.525
17	Stroop effect (time)	287.93 ± 43.21	271.84 ± 45.25	12.075	1.332	0.188
III- Visuospatial memory						
1	Auditory verbal	31.02 ± 4.58	29.21 ± 5.36	1.329	1.363	0.178
2	Copying-complex figure test	34.09 ± 1.90	34.10 ± 2.21	0.550	−0.022	0.982
3	Immediate recall-complex figure test	15.47 ± 3.06	16.16 ± 3.83	0.913	−0.759	0.451
4	Delayed recall-complex figure test	11.28 ± 2.06	11.05 ± 2.48	0.605	0.374	0.710

*Indicates statistical significance at $p < 0.05$.

spellings, reading, and pronunciation.[29] These cognitive sex differences also highlight a better performance by females in verbal episodic memory tasks[30] and in remembering past episodes.[31]

This difference in cognitive ability and associated neurological functioning on verbal–working memory tasks has been consistently noted in previous research.[32,33] Females have been recorded to better execute verbal memory tasks post anterior temporal lobectomy.[34] They are also recorded to outperform tasks involving distraction inherent visuospatial working memory tasks[11] and event-based tasks.[35]

However, keeping in view contradictory findings of other research where women showed attenuated recall of verbal stimuli compared with men,[25] further research is suggested to come to a generalization.

Authors have also noted that females perform better on tasks involving executive functions of strategic planning, organized searching, and set-shifting, such as the Wisconsin Card Sorting Test and in other frontal lobe functions. Females have better percentage perseverative responses on WCST than males. Research suggests that females hold a higher ground in self-regulation and adapt to environmental changes[36] due to better performance on six

WCST scores (errors, categories, perseverative errors, perseverative responses, to conceptual level responses and trials to first category). This suggests, females have fewer deficits in their set shifting ability post-surgery and were able to maintain some aspects of mental flexibility better than males after TBI.[37] Females are concluded to outperform males on WCST irrespective of educational levels and ethnicity, highlighting an independent gender effect.[9]

The findings of present study add to the current body of growing literature on fewer behavioral and cognitive impairments and better recovery in females. Findings indicate TBI due to brutal injury in males and higher behavior and adjustment difficulties after TBI than in female patients.[38,39]

No gender-based differences were found in attention (sustained and divided), concentration, and mental speed, measured through Color Trails Test, Triads Test, and Digit Symbol Test from NIMHANS battery. Both genders performed equally on the Tower of London Test, which suggested no difference in the planning aspect of executive functioning among both genders. On task measuring response inhibition, results were similar as well. On attention task performance, no gender-based differences in mean values was found.[40]

Major strengths of the study include the administration of an expansive range of standardized executive functions tests for assessing holistic neurocognition in the subjects. A rigorous inclusion–exclusion criteria is also a major strength of the study. However, in light of findings of this research, it is also essential that we discuss certain limitations of this study. First, the representative sample of each gender was disproportionate, which further hampered the authors to make generalizations from this study. Second, findings from this study are not sufficient to comment upon a wide range of gender-based differences which might be present in patients with EDH in their executive functioning post-surgery. Further research is essential to reflect on additional differences after injury across genders and examine any differing additional recovery symptoms. In addition, a few variables where further areas should be explored such as ethnicity, education, and age concerning gender and post-injury dysfunction.

Conclusion

The study findings show that on the test of working memory female group scored better as significant differences were found on N-Back (2 Back versions) and digit span-backward. In addition, significant difference was registered on the verbal fluency test (COWA) in total responses, as females scored higher than the male group. However, the male group is higher in total time and error than the female group on the attention test (sustained and divided). This study shows interesting results with significant clinical implications for planning neuropsychological management.

Conflict of Interest
None declared.

Acknowledgement
The authors of this paper are highly thankful to Ms. Kriti Sapra (Research Scholar, Department of Psychiatry, King George's Medical University, Lucknow) for her valuable time to edit this manuscript.

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