MEMORY & LEARNING AND EXECUTIVE FUNCTIONS PERFORMANCE IN PATIENTS WITH MULTIPLE SCLEROSIS: CLINICAL AND 3.0 TESLA MR IMAGING STUDY

Thesis

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By

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SUMMARY AND CONCLUSION

Multiple sclerosis is a common disease which affect patients in their productive period of life. Cognitive impairment is one of the most important manifestation of patients with MS. The interest in cognitive dysfunction is growing up especially in the last decade.

The aim of this study is to investigate the pattern of memory & learning and executive function impairment in MS patients and to explore its relationship to pathological changes obtained by high field MRI (3.0 Tesla) in MS.

The present study was conducted on 30 Egyptian patients diagnosed as clinically definite MS and 10 healthy control subjects, age, sex and educational level matched for comparison of the psychometric results.

All the patients were subjected to thorough neurological assessment, clinical evaluation of fatigue, depression and disability, as well as neuroradiological assessment by 3 Tesla MRI brain.The patients and controls underwent psychometric evaluation.

In the present study 80% of the patients showed abnormal test score in CVLT-DR. As long term memory recall was the only affected domain while the short term, the total memory recall and the recognition components were normal as appeared in the CVLT.

The impairment in long term memory recall in MS patients could be attributed to impaired retrieval from memory storage with an encoding preservation corresponding to the hallmark of subcortical dementia.

The impairment of long term recall could be also attributed to poor sustained attention ability during continuous retrieval of newly learned material, this was supported by the highly statistically significant correlation between the information processing speed and delayed memory recall in this study.

The MS patients showed impaired visuospatial memory performance as the both total and delayed memory recall were affected with intact recognition ability as appeared in BVMT. It was found that 46.67% of patients showed impaired delayed visuospatial memory recall , and 43.33% of the patients showed total impaired visuospatial memory recall. This could be explained by the poor retrieval of visual material with intact encoding in MS patients.

As regard the executive function performance, all aspects of executive functions were involved in MS patients. As the most frequently affected domains were information processing speed and represented 93% and 90% for the working memory.

The high percentage of involvement of information processing speed and working memory in MS patients could be attributed to the impairments in both the executive center and its connection loops systems. As an interruption of these loops due to white matter lesions may cause these cognitive domains impairment.

It was noted that 55.17% of the patients showed reduced percentage of conceptual responses, increased total and preservative errors scores representing concept formation impairment. While, 35% of the patients showed reduced number of categories achieved and increased trials to complete 1^{st} set representing ability of cognitive flexibility impairment.

Moreover, 65.51% of the patients showed failure to maintain the set representing inability to sustain mental set.

The verbal fluency had been found to be sensitive to impairment of executive functioning in MS patients. It was shown that the MS patients had a poor performance in both phonemic and semantic verbal fluency compared to the controls. It was noted that 90% of the patients had impaired semantic verbal fluency, while 40% of the patients showed impaired phonemic verbal fluency as appeared in COWAT. The greater impairment on measures of semantic fluency may be indicative of additional semantic memory dysfunction too.

It was suggested that the influence of the MS disease course is evident, as the working memory, information processing speed and executive function impairment particularly the concept formation, verbal fluency were present since the early stages of the disease and showed worsening with the progression of the disease. While, the verbal and visuospatial memory and learning impairment could be present later with the disease course.

Interestingly, it was shown in the current study that there was a significant effect of interferon on cognitive performance of the treated MS patients. Moreover, it had a selective effect on cognitive domains. So it could subsequently influence the patients' quality of life especially their vocational and academic performance. It was found that the interferon-*B* could improve the performance of the visual memory and learning, working memory and executive functions. But, it has no influence on verbal memory and learning and verbal fluency.

The relationship between cognitive impairment and physical disability in MS patients has produced highly conflicting results. But, it was found in this study that there was high negative correlation between the disability and information processing as well as phonemic verbal fluency. It could be

attributed to the diffuse brain damage causing different subcortical/cortical networks disconnection involved in information processing and disability. This was supported by the finding that the both EDSS and SDMT scores were highly correlated with the total T_2 lesion load.

Depression itself can compromise considerably cognitive performance in MS patients. The present study showed that there was significant correlation between the depression and the concept formation ability of executive functions as well as the information processing speed. It was suggested that delayed information processing speed may interfere with the ability of patients to develop effective adaptive coping skills. In particular, problems in planning, problem solving, self monitoring and flexibility.

The present study showed that there was no significant correlation found between fatigue or duration of illness with any psychometric tests.

The tests that assess the executive functions components including the working memory, information processing speed, verbal fluency and concept formation ability were correlated to health perception, mental health composite and emotional role limitation subscales of the MSQoL-54 test in this study. Deficits in information processing efficiency and executive dysfunction had an influence on their academic achievement, household and vocational activities resulting in poor quality of life. Moreover, the executive dysfunction could influence on the general sense of life satisfaction and, not surprisingly, on the patient's emotional state.

The present study showed high positive correlation between the physical disability and the number of the relapses with the total T_2 lesion load assessed by 3.0 Tesla MRI.

The total T_2 lesion load was statistically significantly correlated with tests assessing the information processing speed, long term verbal memory

recall, visuospatial memory delayed recall, phonemic verbal fluency and cognitive flexibility of executive functions in this study. it was hypothesized that the small lesions detected mostly at 3.0 T accounted for these findings.

It was shown that the total frontal T_2 lesions were significantly correlated with the information processing speed, cognitive flexibility and verbal fluency in this study. It could be attributed to the disruption of white matter circuits that connect the frontal areas to other cortical areas which were responsible for executive function performance.

Moreover, the frontal T_2 lesions were significantly correlated to the verbal and visuospatial memory& learning in this study. As the frontal lobe function is concerned with organized learning processes such as semantic clustering for verbal and visuospatial materials, and organizational schemes are associated with better recall consistency.

The total temporal T_2 lesion load was highly significantly correlated with the information processing speed and the phonemic verbal fluency in the current study. The contribution of the temporal lobe functioning to the SDMT performance may be explained by that short term memory activity is required for number/symbol pairings in this task**.** While the correlation with the verbal fluency could be explained by that the performance of verbal fluency is dependent on the information processing speed.

It was shown that the total and long term verbal memory recall memory recall were statistically significantly correlated with the temporal T_2 lesion load as the word-encoding tasks give rise to activity in the left frontal and temporal lobes.

The present study showed that the cortical T_2 lesion load was statistically significantly correlated with the long term verbal memory recall,

phonemic verbal fluency and the cognitive flexibility of the executive function.

The affected cognitive domains were also significantly correlated with total T_2 lesion load. The cortical T_2 lesion load was highly correlated with the total lesion load in this study suggesting that the underlying pathogenic processes might be related as the cortical lesion could be due to secondary wallerian degeneration.

The brain atrophy is likely to be the consequence of diffuse demyelination and axonal loss, The present study showed that the T_1 hypointense lesion load was statistically significantly correlated with the information processing speed, phonemic verbal fluency, delayed recall verbal memory, short term verbal memory recall, total recall visuospatial memory recall and the cognitive flexibility of executive functions.

Moreover, the present showed that the corpus callosum thickness at the splenuim was statistically significantly correlated with the information processing speed, working memory, total, long term and total verbal memory recall, total visuospatial memory recall, phonemic verbal fluency and concept formation of the executive functions. The corpus callosum thinning accounted for significant impairment in the performance of mental processing speed, working memory and verbal memory tasks as temporary storage and manipulation of new information may require rapid communication between different brain regions via white matter tracts.

The present study showed that the frontal cortical thickness was significantly correlated with total, short term verbal memory recall and total, delayed visuospatial memory. As the frontal neocortex which was activated during the encoding and consolidation process as well as managing transfer of information from working memory to long term memory and vice versa and responsible also for set shifting thinking.

Another measure of the grey matter atrophy is the third ventricular width which is increased secondary to thalamic atrophy. In this study, there was negative significant correlation between the total visuospatial memory recall and third ventricular width. The link between thalamic atrophy and memory & learning in MS could be attributed to that the thalamus is an integral component of memory and learning.

The present study showed positive significant correlation between the brain parenchymal fraction and cognitive flexibility of the executive function. While, no statistically significant difference was found between the other psychometric tests and the brain parenchymal fraction.

It is worth mentioning that cortical atrophy and central brain atrophy could occur in early MS and correlate to the cognitive impairment in MS in the early stages of the disease while the global brain atrophy could develop later in the disease. This could explain the lack of association of cognitive impairment and parenchymal brain fraction in this study due to the relatively short duration of illness of the participated patients.

الملخص العربي

يعدمرضالتصلبالمتعددمنأكثرالإمراضالتيتؤثرعلىالقدرةالإنتاجيةللمرضى.
كمايعدالخللالمعرفيمنأهمأعراضهذاالمرضحيثتشير الإحصائيات إلىأن 54- 65% منالمرضىيعانونمنهذاالعرضويصفكثيرمنهؤلاء المرضىأنهذاالعرضيعدمنأكثرالأعراضتأثيراعلىنشاطهماليومي.
وقداستهدفتهذهالدراسةتقييمنمطالخللفيالذاكرة و القدرةعلىالتعلموأداء الوظائفالتنفيذيةفيمرضىالتصلبالمتعددواستكشافالعلاقةبينالأداء المعرفيوالتغيراتالمرضيةللمخبالتصويرالرنينالمغناطيسيعاليالجودة 3 تسلا.
وقداشتملتهذهلدراسةعلى 30 مريضامصابينبمرضالتصلبالمتناثر و10 منالأصحاءللمقارنةبينننتائجالاختباراتالنفسية.

وقدتمتقييمالحالاتكالآتي:

- تقييمإكلينيكياعنطريقأخذالتاريخالمرضيوالفحصالإكلينيكي.
- تقييمدرجةالإعاقةباستخداممقياسEDSS.
- تقييمالأداء المعرفيو القدرةعلىالتعلمباستخدامكل من CVLT- II ,BVMT- R
- تقييمأداء الوظائفالتنفيذية:
- الذاكرةالعاملةباستخداممقياسPASAT .
- سرعةمعالجةالمعلوماتباستخداممقياسSDMT.
- الوظائفالتنفيذيةباستخداممقياسWSCT.
- الطلاقة اللفظية باستخدام مقياس COWAT
- تقييمدرجةالوهنباستخداممقياسشدةالوهن.
- تقييمالاكتئاببباستخداممقياسبيكللاكتئاب.
- تقييمجودةالحياةلمرضىالتصلبالمتناثرباستخداممقياسMSQoL -54
- بعملالرنينالمغناطيسيللمخعاليالجودة 3 تسلامتضمنةالصورالمحملةعلىالوقتالأول (T_1) والمحملةعلىالوقتالثاني (T_2) وصورFLAIR.

وقدأظهرتالنتائجمايلي:

- أن

80٪منالمرضىيعانونمنضعففياستدعاءالذاكرةعلىالمدىالطويلفقطفيحينلميتأثركلمناستدعاءالذاكرةعلىالمدىالقصيرأواستدعاءالذاكرةالكلية بينماكانتمكوناتالتعرفطبيعية .حيثيعزىالانخفاضفيالذاكرةعلىالمدىالطويلفيمرضىالتصلبالمتعددلضعفالاسترجاعمنذاكرةالتخزين.كمايعزىهذاالضعفأيضاً إلىافتقارقدرةالمرضىلسرعةمعالجةالمعلومات.

- وجدأن 46.67٪منالمرضىيعانونمنضعففياستدعاءالذاكرةالبصريةعلىالمدىالطويل و 43.33٪يعانونمنضعففياستدعاءالذاكرةالبصريةالكلية.كماكانتمكوناتالتعرفطبيعية. ويمكنتفسيرذلكلضعفالاسترجاعمنذاكرةالتخزين.

- أمافيمايتعلقبأداءالوظائفالتنفيذية،

فقدتبينإصابةجميعجوانبالمهاماتالتنفيذيةفيمرضىالتصلبالمتعدد.حيثكانأكثر المجالاتتعرضاًللإصابةهيسرعةمعالجةالمعلوماتوتمثل 93٪ بينماكانتللذاكرةالعاملة 90٪ .ويمكنأنيعزىارتفاع إصابةسرعةمعالجةالمعلوماتوالذاكرةالعاملةإلىإصابةحلقاتالاتصالالمسئولةعنإتمامالوظائفالتنفيذية.

- كمالوحظأن 55.17٪منالمرضىيعانونمننسبةانخفاضالاستيعابالفهمى،فيحينأظهر 35٪منالمرضىضعفقدرةالمرونةالإدراكية.

- وقدتبينأنمرضىالتصلبالمتعدديعانونمنضعفالأداءفيالطلاقةاللفظية. وكذلك لوحظأن 90٪منالمرضىيعانونمنضعفالطلاقةاللفظيةالدلاليةأيضامماىعطىمؤشراعلىضعفالذاكرةالدلاليةأيضا.

- كمالوحظوجودعلاقةذاتدلالةإحصائيةبينمسار المرضوالأداء المعرفي و القدرةعلىانجازالوظائفالتنفيذية .حيثتبينإصابةالذاكرةالعاملة،وسرعةمعالجةالمعلومات

و القدراتالتنفيذيةوكذلكضعفالطلاقةاللفظيةمنذالمراحلالمبكرةمنالنوعالانتكاسيللمرض،

وقدأظهرتتفاقماً معالتقدمفيالمرض.فيحينأناصابةالذاكرةاللفظيةوالذاكرةالبصريةظهرتمعالنوعالتقدميمسارالمرض.

- ومنالمثيرللاهتمامأنهقدتبينأنهناكتأثيررائعلعقارالانترفيرونعلىالأداءالتنفيذيوالمعرفيلمرضىالتصلبالمتناثر.وعلاوة علىذلكتبينوجودتحسناً انتقائياًفيالمجالاتالمعرفيةحيثيمكنلعقارالانترفيرونأنيحسنأداءالذاكرةالبصريةوالذاكرةالعاملةوالوظائفالتنفيذية.ولكنليسلهتأثيرعلىالذاكرةاللفظيةوالطلاقةاللفظية.

- وقدتبينفيهذهالدراسةأنهناكعلاقةسلبيةذاتدلالةإحصائيةبينارتفاعنسبةالإعاقةوالقدرةعلىمعالجةالمعلوماتوكذلكالط
لاقةاللفظية.ويمكنأنيعزىذلكإلىتلفالدماغالمنتشربسببالتصلبالمتعددالذيقديتسببفيانقطاعشبكاتمختلفةتحتالقشري
ة / القشريةالمسئولةعنإتماماالوظائفالتنفيذية.
- وأظهرتهذهالدراسةأنهناكعلاقةذاتدلالةإحصائيةبينالاكتئابوالقدرةعلىتشكيلمفهومالوظائفالتنفيذيةوكذلكسرعةمعا
لجةالمعلومات. ويعزىأنتأخرسرعةمعالجةالمعلوماتقدتتداخلمعقدرةالمرضىعلىالتكيفالفعاللتطويرمهاراتالتأقلم.
- وأظهر تهذهالدراسةأنهلايوجد علاقةذاتدلالةإحصائيةبينالإحساسبالإرهاقفيمرضىالتصلبالمتناثرأوالفترةالزمنيةللم
رضمعأيمنالاختباراتالنفسية.
- الاختباراتالتيتقيمالوظائفالتنفيذيةبمافيذلكوظائفالذاكرةالعاملة و سرعةمعالجةالمعلوماتوالقدرةاللفظية
و تشكيلمفهومالوظائفالتنفيذيةأظهرتارتباطاواضحابمقياس MSQoL-
54.فيهذهالدراسة،حيثكانالعجزفيكفاءةمعالجةالمعلوماتوالضعفالتنفيذيتأثيراعلىالأداءالأكاديميوالأنشطةالمهنية
وعلاوةعلىذلكيمكنأنتؤثرالوظيفةالتنفيذيةعلىالشعورالعامبالرضاعنالحياةو الحالةالنفسيةللمريض.
- وأظهرتهذهالدراسةعلاقةسلبيةذاتدلالةإحصائيةبيناختباراتتقييمسرعةمعالجةالمعلومات
و الذاكرةاللفظيةطويلةالمدى و الذاكرةالبصريةطويلةالمدى و الطلاقةاللفظية
و القدرةعلىالمرونةالإدراكيةفيهذهالدراسةبمجموعالإصابةفيصور T_2ويمكنأنيعزىذلكإلىإصابةالدوائرالعصبيةالم
سئولةعنأداءالوظائفالمعرفيةو التنفيذية.
- وعلاوةعلىذلكقدأظهرتهذهالدراسةعلاقةسلبيةذاتدلالةإحصائيةبيناختباراتالذاكرةاللفظية و الذاكرةالإبصارية
و حجمالإصابةفيالفصالجبهيللمخ.
- قدأظهرتهذهالدراسةعلاقةسلبيةذاتدلالةإحصائيةبيناختباراتسرعةمعالجةالمعلوماتوالطلاقةاللفظيةمعحجمالإ
صابة T
$_2$بالفصالصدغىللمخ.ويمكنتفسيرمساهمةالفصالصدغيلأداءمقياسSDMTوقياسالذاكرةعلىالمدىالقصيربالتز
اوجبينالعددو الرمزلهذهالمهمة.
- وقدتبينأنهناكعلاقةسلبيةذاتدلالةإحصائيةبيناستدعاءالذاكرةاللفظيةالكلية و علىالمدىالطويل
و الطلاقةاللفظيةوالمرونةالإدراكيةو حجمالإصابةبالصور T_2بالقشرةالمخية.
- وأظهرتالدراسةأنهناكسرعةعلاقةسلبيةذاتدلالةإحصائيةبينمعالجةالمعلوماتالطلاقةاللفظية
و استدعاءالذاكرةاللفظيةعلىالمدىالطويل و المدىالقصير
و استدعاءالذاكرةالبصريةوالمرونةالإدراكيةمنالمهامالتنفيذية
و حجمالإصابةبالصور T_1ممايؤكدارتباطالأداءالمعرفيوالأداءالتنفيذيبحجمضمورالمخ.

- وعلاوة علىذلك،قدأظهرتالدراسةأنهناكعلاقةسلبيةبينسمكالجسمالثفنيمعسرعةمعالجةالمعلومات و الذاكرةالعاملةواستدعاء الذاكرةاللفظيةطويلةالأجلوالإجمالية و استدعاء الذاكرةالبصرية و الطلاقةاللفظية و تشكيلمفهومالوظائفالتنفيذية.

و يعزىذلكإلىأنالأداء المعرفيوالأداء التنفيذيقديتطلبالتواصلالسريعبينمختلفمناطقالدماغعبر الجسمالثفنى.

- وأظهرتهذهالدراسةأنهناكعلاقةسلبيةبينسمكالقشريةالمخيةالجبهية و استدعاء الذاكرةاللفظيةقصيرةالأجلوالكلية و الذاكرةالبصريةطويلةالأجلحيثالقشرةالمخيةالجبهيةمسئولةعنعمليةالترميزفضلاعنإدارةنقلالمعلوماتمنالذاكر ةالعاملةإلىالذاكرةعلىالمدىالطويلكذلكمسئولةأيضاالمرونةالإدراكيةمنالوظائفالتنفيذية.
- كماوجدأنهناكعلاقةعكسيةبيناستدعاء الذاكرةالبصريةالإجمالية

و عرضالبطينالثالثاتجاهعنضمورالمهاد .ويمكنأنيعزىذلكإلىأنالمهادهوجزء لايتجزأمنالدائرةالعصبيةالمسئولةعنالذا كرةو التعلم.

- وأظهرتهذهالدراسةعلاقةطرديةبينحجمالمخوالمرونةالإدراكية ،فيحينلميوجدفرقذودلالةإحصائيةبينا لاختباراتالنف سيةالأخرىو حجمالمخ.

ومماسبقنستخلصأنالخللفيالذاكرة

و القدرةعلىالتعلموأداء الوظائفالتنفيذيةواضحفيمرضىالتصلبالمتناثرمنذالمراحلالأولىمنالمرضو يرتبطبشكلانتقائيبالتغيرا تالمرضيةمنحيثحجمالإصابةوكذلكضمور المخ.

دراسة الذاكرة والقدرة على التعلم وأداء الوظائفالتنفيذية في مرضى التصلب المتناثر:دراسة إكلينيكية وباستخدام تقنية حديثة من الرنين المغناطيسي 3 تسلا

رسالةمقدمةمن

الطبيبة/ لمياءإبراهيمعبدالعظيمداكر

بكالوريوس الطب والجراحة، ماجستير الأمراض العصبية والنفسية

توطنهللحصول على درجةالدكتوراه

في

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2012