

ELECTIVE (SSC5c) REPORT (1200 words)

A report that addresses the above four objectives should be written below. Your Elective supervisor will assess this.

Treatment of Cognitive Decline in Multiple Sclerosis

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Summary

Multiple Sclerosis (MS) is a chronic demyelinating disorder of central nervous system that causes varying degrees of physical and cognitive impairment. My elective time enabled me to gain further insights into clinical care of some neurological conditions, particularly, MS which is in line with my objectives. One of the important challenges in the current management of MS is treatment of MS-associated cognitive dysfunction. Here I discuss some of the recent developments in the treatment of MS-associated cognitive decline.

Introduction

Multiple sclerosis is a chronic neurological disorder that can be debilitating. In addition to apparent physical disability, there is increasing evidence that MS may also impair cognitive functioning (1). Cognitive deficits are common in MS patients. Estimates of the prevalence of cognitive impairment in MS vary but typically range between about 40-70% (2,3) highlighting the burden. Cognitive problems have been noticed in all the stages of MS (4) including clinically (5) and radiologically isolated syndromes (6). Cognitive deficit in MS tends to be related to the type of MS with the most frequent and severe forms seen in secondary progressive MS (7). Different forms of cognitive deficits have been identified in MS patients. Common examples described by previous studies include: executive dysfunction, memory problems, impairment of visuo-spatial processing, language and communication difficulties as well as delayed information processing speed (3,4). Cognitive decline impacts negatively on the quality of life of MS patients quite independent of the degree of physical impairment (8). It affects general functioning, activities of daily living, employment and social life. As a result, there is growing need for treatment strategies to limit or reverse cognitive problems in MS patients.

In order to treat cognitive decline, it is imperative to assess the type and quantify the extent of impairment. Previous studies showed that patient reports of extent of cognitive deficit in MS are quite unreliable and more related to depressive symptoms (9). As a result, a number of neuropsychological tests have been developed. Initially, elaborate tests such as Multiple Sclerosis Functional Composite (MSFC) were developed (10). Detailed cognitive assessments are better reliable however these tests are time consuming hence less adaptable to clinical practise. There has been a paradigm shift towards shorter screening tools such as the Brief Repeatable Battery of Neuropsychological (BRNB) tests (11), the Minimal Assessment of Cognitive Function in MS (MACFIMS) (12), and more recently the Brief International Cognitive Assessment for MS (BICAMS) (13). The BICAMS is particularly favoured because it is newer and targeted for universal use (14). Both MACFIMS and BICAMS have been validated in Czech, demonstrating potential for cross-cultural

applications (15). BICAMS has recently been applied in Italian MS population with promising results (16).

There a number of the treatment modalities that has been tried in an attempt to reduce or reverse cognitive decline in MS. This report focuses specifically on recent trials of cognitive rehabilitation approaches and pharmacological therapies.

Cognitive Rehabilitation

Cognitive rehabilitation applies neuropsychological approaches to ameliorate dysfunctional thinking, memory and other brain processes in disease states. Investigators have tested different types of cognitive rehabilitation approaches in MS patients. Memory rehabilitation programmes have been attempted with some reported benefits (17-19). One of these studies involved a double-blind placebo controlled RCT, which showed that learning by use of context and imagery resulted in significant improvement of neuropsychological tests performance and patient report of daily activities (20). In keeping with this, the investigators demonstrated increased activation in brain areas in MS patients, who were trained in learning by use of context and imagery as compared with placebo controls in a follow up study (21). Nonetheless, a recent systematic review concluded that the quality of available evidence for memory rehabilitation in MS is weak (22). The reviewers suggested that higher quality Randomized Control Trials (RCTs) on memory rehabilitation are necessary.

Computer-assisted cognitive rehabilitation methods aroused increasing research interests since late 1990s. There have been a number of computer-based rehabilitation studies demonstrating some improvements in different aspects of cognition including attention (23,24), spatial construction abilities (18), and executive function (24). Computer-assisted cognitive rehabilitation programmes designs have recently focused on home-based training(17,23) to improve adherence. The impact of subtle improvements in cognition observed in rehabilitation studies on daily activities and quality of life of MS patients are subjects for future research.

Some vocational rehabilitation approaches have also been tested with the goal of improving the ability of MS patients to participate in workforce. Whilst there have been some promising results, the evidence in support of vocational rehabilitation remains inconclusive. A recent systematic review judged that quality of evidence in support of vocational rehabilitation is weak suggesting the need for higher quality clinical trials in that area (25).

The MS-Line is a new cognitive rehabilitation programme, which applies written, manipulative and computer-based materials of varying difficulty that can be used at early stages of MS (26). The MS-Line was recently tested in a randomized controlled single-blinded 6 month study. The study showed some improvement in cognitive function with regards to learning, visual memory, executive function, attention, naming ability and speed of information processing (27).

Pharmacological Therapies

The potential for medications to prevent, delay or even reverse MS-associated cognitive dysfunction is increasingly being investigated. Pharmacological agents that alter CNS function (such as stimulants) and neurotransmission (acetylcholinesterase inhibitors) have been tested. In addition to this, the putative beneficial effects of MS Disease Modifying Therapies (DMTs) on cognitive functioning are subjects of active investigations. The ensuing paragraph summarises some of the important findings on roles of pharmacological therapies in treatment of cognitive decline in MS.

CNS stimulants like methylphenidate and amphetamine were considered as possible ways of reversing slowed mental processing, which frequently coexists with disturbances in various aspects of cognition in MS such as working memory. Harel and colleagues conducted double blinded placebo controlled RCT in MS patients using a single dose of methylphenidate. The investigators showed improvement in attention during Paced Auditory Serial Addition Tests (28). Studies examining effects of single dosing of amphetamine showed similar findings to methylphenidate however the continuous dosing of amphetamine in larger-sample study failed to replicate the effects (29-31). These may suggest that potential beneficial effects of stimulants on attention may be short lived. Nonetheless, because there potential effects on memory for the initial studies, a recent study re-investigated the effects of amphetamine on MS patients specifically selected for impaired memory relative to those who had normal memory. The results were quite promising but requiring further validation (29-31). Owing to possible benefits of acetylcholinesterase inhibitors on memory in Alzheimers Disease, investigators have examined the benefits of donepezil and rivastigmine on cognitive function in MS patients. Overall the results of these studies haven't been positive. Although one of the studies (32) reported potential benefits of donepezil on cognitive function, the findings were not replicated by the other studies (33,34). Controlled studies with some DMT like Natalizumab and interferon β -1a and 1b have reported benefits on Cognitive function in Relapsing Remitting MS (35,36).

Conclusion and Reflection

Development of therapeutic strategies to limit or reverse cognitive decline in MS is an important ongoing challenge as highlighted in this report. MS affects people living in many countries of the world, albeit in an uneven pattern with prevalence increasing in countries farther away from the equator. My elective allowed me to gain insights into current clinical care of MS patients in UK and areas for future improvements/research. One of the areas requiring improvements is the treatment of cognitive impairment. During my participation in clinics and wards, I gained some appreciation of both physical and cognitive disability associated with MS. I also realized the immense impact of the MS on the lives of patients, their family and society. My current report on treatment of cognitive decline in MS integrates my current thinking and literature on this topic. I also gained understanding of some cross-cultural issues in clinical care for instance the applicability of neuropsychological tests for cross-cultural use. Overall, the elective experience has leaned me towards future training in Neurology. I gained insight into other areas of neurology including motor neuron disease, epilepsy and pediatric neurology. I have been shortlisted to submit a report for paediatric neurodisability clinical observation award, The Geoffrey Udall prize.

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