Case report

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Severe Isolated Cognitive Relapse in Multiple Sclerosis - Indication for High Efficacy Therapy?

Marina Mioč[1], Barbara Barun[2], Marina Boban[2], David Ozretić[3], Mario Habek[2]

[1]Center for Sleep Disorders, University Psychiatric Hospital Vrapče, Zagreb, Croatia,
[2]Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia,
[3]Department for Diagnostic and Interventional Neuroradiology, University Hospital Centre Zagreb, Zagreb, Croatia

Abstract - Isolated cognitive relapses (ICRs) are transient deficits in cognitive performance that are not accompanied with other symptoms typical for multiple sclerosis (MS). They are often missed and can lead to long-term cognitive decline. Considering possible devastating consequences of cognitive impairment, especially in working adults, and high economic burden of MS, it is of great importance to establish whether ICRs are sufficient to start with high efficacy therapy. 42-year-old women with a recent diagnosis of relapsing-remitting multiple sclerosis developed significant impairment in almost all cognitive domains, with dominant difficulties in naming and low performance in phonemic fluency tasks, consistent with ICR. Her brain MRI showed new lesions affecting the anterior part of the thalamus and her condition partially improved on intravenous corticosteroid therapy. While waiting the disease-modifying therapy to begin, for what was now highly active MS, she developed subarachnoid haemorrhage which further narrowed the treatment options. This case illustrates the complexity of managing patients with MS and ICRs in at least three aspects. Firstly, the lack of uniform definition resulting in diagnostic delay of highly active MS and ICRs. Secondly, optimal treatment choices are often limited due to safety issues and reimbursement reasons. And thirdly, there is still an open question about the right treatment option for ICRs, so more research is needed.

Keywords: cognition; recurrence; multiple sclerosis

e-mail: apr.kbcsm@gmail.com • www.http://apr.kbcsm.hr

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating, neurodegenerative disease of the central nervous system and while changes in motor and sensory functions are easily recognizable with neurological examination, isolated cognitive relapses (ICRs) are often missed and data of their frequency are scarce. ICRs are transient deficits in cognitive performance that are the only presentation of MS and they have been associated with long-term cognitive decline and daily cognitive difficulties [1-2]. Traditional treatment strategy in MS has been an escalation approach, in which treatment was started with modestly effective, disease modifying therapy and subsequently escalated to a higher efficacy drug if there was evidence of clinical and/or radiologic disease activity. Development of higher efficacy therapies led to an induction approach in which high efficacy medications are started early in the disease

Correspondence to:
Marina Mioč, MD, Kraljevićeva ulica 24,10 000 Zagreb, Croatia,
Phone:+385 98 9889298
E-mail: marina.mioc29@gmail.com

course. Uniform criteria for defining patients with aggressive or highly active MS who might benefit from early treatment with high efficacy therapy are still lacking. Considering possible devastating consequences of cognitive impairment and high economic burden of MS there is a need to establish whether ICRs are sufficient criteria for high efficacy therapy. Here we report a case of highly active MS which presented with isolated cognitive relapse.

Case report

A 42 year old Caucasian female was hospitalized in September 2020 due to right hemiparesis and ataxic gait, EDSS 3.5 (Pyramid functional system FS 3, Cerebellar FS 3). MRI showed two periventricular T2 and one infratentorial T2 lesion with gadolinium enhancement, and cerebrospinal fluid analysis showed oligoclonal IgG bands fulfilling McDonald criteria for MS. After corticosteroid treatment her EDSS was 2.5 (Pyramid FS 2, Cerebellar FS 2) and treatment with glatiramer acetate was planned. On a follow up visit, in November 2020, significant cognitive impairment was observed. Extensive cognitive testing showed dominant difficulties in naming, low performance in phonemic fluency and discrete difficulties in understanding which could be explained with attention deficit, delayed visual and verbal memory recall, difficulties in executive functions and information processing (Table 1). EDSS was 4.5 (Cerebral FS 4, Pyramid FS 2, and Cerebellar FS 2). MRI showed two new periventricular gadolinium enhancing lesions, the bigger one in the left genu of internal capsule extending to the anterior part of thalamus (Figure 1a and 1b). ICR was confirmed and the patient was treated with 1g of intravenous methylprednisolone for five consecutive days with partial cognitive improvement (Table 1). Patient was characterized as highly active MS and high efficacy treatment was considered. Due to reimbursement issues in Croatia, only treatment with alemtuzumab was feasible. While waiting for the treatment to commence, in January 2021, the patient experienced a severe headache, nausea and vomiting. She was examined in the ER, her neurologic examination was stationary but brain CT detected a small amount of blood in the right frontal subarachnoid space (Figure 1c). DSA showed multiple narrowing's of third-order branches of intracranial arteries in a typical sausage-shape appearance (Figure 1d and 1e), as a presentation of Reversible Cerebral Vasoconstriction Syndrome. MRI showed reduction in size of the lesion in the left genu of the internal capsule (Figure 1f). She was treated symptomatically with complete resolutions of the symptoms. Because alemtuzumab is associated with rare but serious cases of stroke and arterial dissection, and other high efficacy medication like natalizumab, ocrelizumab, ofatumumab cladribin, fingolimod could not be given due to reimbursement reasons, in February 2021 she started treatment with dimethyl fumarate.

Table 1. Results of cognitive testing prior and post corticosteroid treatment

Cognitive test prior steroids 11/2020	Cognitive test post steroids 1/2021
MMSE = 15/30	MMSE = 21/30
CDT = 8/10	CDT = 10/10
SDMT = 25	SDMT = 35
RAVLT = 22/75	RAVLT = 31/75
ROCFT = 36/36	ROCFT = 36/36
ROCFT delayed = 11/36	ROCFT delayed = 14/36
BNT = 37/60	BNT = 42/60
Token test = 156/163	Token test = 161/163
Verbal fluency = PF3/SF11	Verbal fluency = PF3/SF12

MMSE: Mini Mental State Examination; CDT: Clock Drawing test; SDMT: Symbol Digit Modalities Test; RAVLT: Rey Auditory Verbal Learning Test; ROCFT: Rey-Osterrieth Complex Figure; BNT: Boston Naming Test

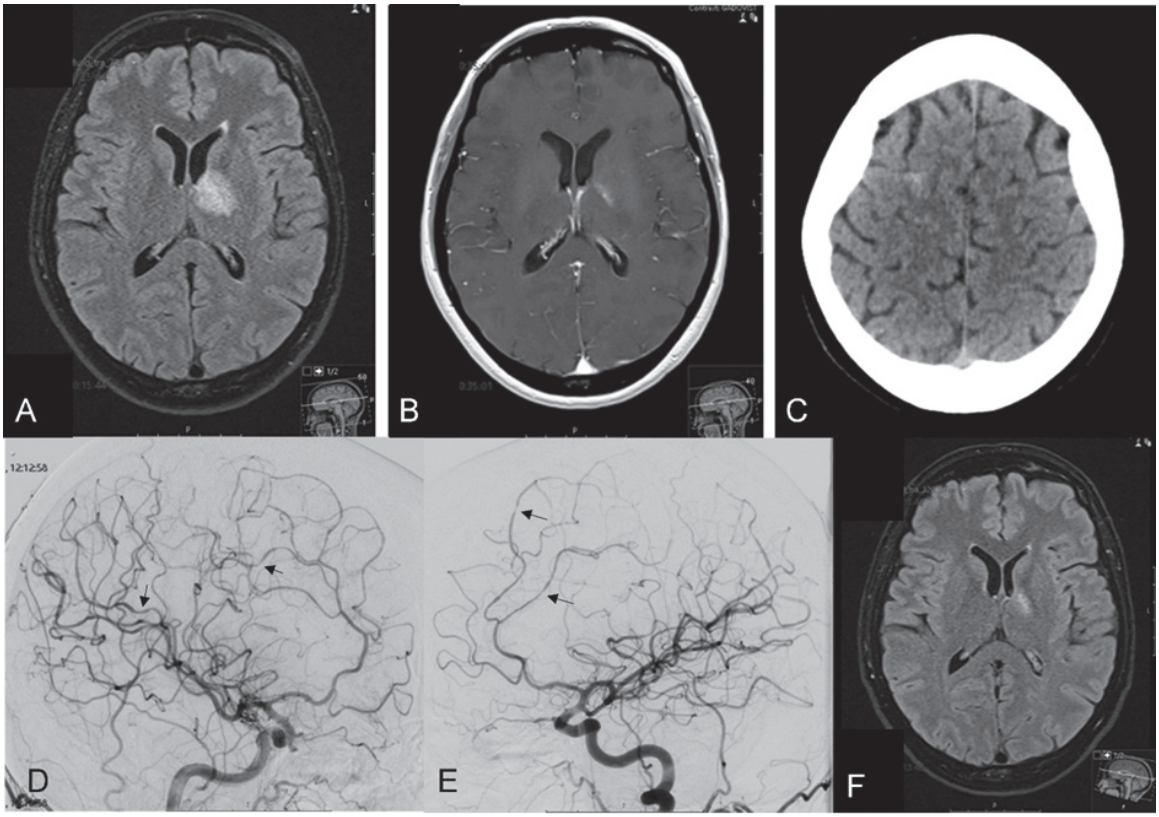

Figure 1. Brain MRI. Large MS lesion in genu of left internal capsule extending to anterior part of thalamus (a, b). Brain CT: small amount of SAH in right superior frontal sulcus (c). DSA: multiple narrowings on distal ACA and MCA branches on both sides (d, e). Follow up brain MRI after corticosteroids: reduction in size of MS lesion in genu of left internal capsule extending to anterior part of thalamus (f).

Discussion

We presented a patient fulfilling proposed criteria for an ICR: i) a transient cognitive decline in objective neuropsychological performance, ii) without clinical evidence of other new neurological signs and symptoms and iii) associated with brain disease activity defined as a positive gadolinium enhancing scan [1]. Uniform definition of highly active or aggressive MS is not yet established but there is an initiative to define this disease subtype, its treatment and management [3]. It is thought that patients with highly active MS could benefit if given more effective treatment earlier in the disease development. Our patient had cognitive impairment in the early stage of the disease which is a known predictor of earlier conversion to secondary progressive MS (1) so high efficacy therapy was considered.

Taking into account that during postmarketing pharmacovigilance, EMA issued assessment report on adverse reactions in close temporal relationship following alemtuzumab infusion, only possible medication that we could administer due to reimbursement reasons was casted off [4].

Conclusions

This case illustrates the complicity of managing patients with MS and ICRs for at least three aspects. Firstly, the lack of uniform definition and therefore diagnostic delay of highly active MS and ICRs. Additionally, optimal treatment choices for individual patients are often limited due to safety issues and reimbursement reasons. Thus, every effort should be made to raise awareness of ICRs in MS and future research is needed to establish whether ICRs are sufficient criteria for commencing high efficacy treatment.

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Conflict of interest

None to declare.

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