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Letter to the Editor

SARS-CoV-2 vaccinations may reduce the frequency of COVID-19 associated Miller-Fisher syndrome

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We read with interest the review article by Martins Filho *et al*. about 11 patients with SARS-CoV-2 associated Miller-Fisher syndrome (SC2-MFS) collected from the literature by a Pubmed search spanning the period 1st January 2020 and 31st January 2021 [1]. It was found that SC2-MFS is a rare manifestation of COVID-19, without virus RNA in the cerebro-spinal fluid (CSF), only rarely associated with ganglioside antibodies, but favourably responding to intravenous immunoglobulins (IVIG) [1]. The study is appealing but raises comments and concerns.

The first limitation of the study is that the spectrum of clinical presentation exceeded that of MFS sensu strictu, which is characterised by ophthalmoparesis, ataxia, and reduced tendon reflexes. Thus, these patients should be rather classified as "MFS plus" than as "MFS". There is also a need for discussing if patients with an "AIDP" pattern on nerve conductions studies (NCSs) shouldn't be rather classified as AIDP with involvement of the cranial nerves than as MFS. A further argument for the MFS plus classification is that three patients had autonomic dysfunction which is rather a manifestation of Guillain-Barre syndrome (GBS) than of MFS.

There is also a need to delineate the clinical presentation from that of polyneuritis cranialis (PNC), another subtype of GBS. Weakness of facial muscles in six patients suggests that the VIIth cranial nerve was affected, which has been repeatedly reported in COVID-19 patients (table 1) [1]. Dysphonia or dysarthria, reported in three patients suggests that the IXth and Xth cranial nerves were additionally affected. Deviation of the tongue in 2 patients suggests that the XIIth cranial nerve was additionally involved. The two cases of SC2-MFS reported by Guttierez-Ortiz *et al*. and those reported by Dinkin *et al*. had PCN or MFS plus [1].

Table 1: SC2-MFS cases published until September 2021 in addition to the 11 cases mentioned in the review

Reference	Age	Sex	LCM	Plus	TR	OC
Costa *et al*. [6]	21	f	mr	mydriasis, eyelid nystagmus	IVIG	PR
Ramirez *et al*. [7]	55	m	NPC	limb weakness, III, IV, VI, VII affected	PE	CR
Tran *et al*. [8]	42	m	nr	limb weakness, facial hypoesthesia, dysarthria	IVIG	PR
Raghunathan [9]	7	m	10d	quadruparesis, VII, IX, X affected	IVIG, PE	CR
Aljomah *et al*. [10]	9	m	>2d	VII, IX, X	IVIG	PR
Lantos *et al*. [2]	36	m	4d	limb paresthesis	IVIG	PR
Lowery *et al*. [4]	45	m	14d	quadruparesis	IVIG	no
Garnero *et al*. [3]	55	m	20d	AIDP	nr	PR
Julian Caamani [5]	61	m	10d	no	Steroids	CR

CR: complete recovery, LCM: latency between onset of COVID-19 and onset of MFS+, IVIG: intravenous immunoglobulins, NPC: neurologiy preceeds COVID_19, nr: not reported, OC: outcome, PE: plasma exchange, PR: partial recovery, Pyr: pyridostigmine, TR. treatment

Another limitation of several of the included studies is that NCSs were carried out only in five of eleven patients. As MFS is characterised by reduced tendon reflexes, as MFS frequently overlaps with features of AIDP or acute motor axonal neuropathy (AMAN), and as GBS is diagnosed according to the Brighton criteria, according to which NCSs are a prerequisite for their application, it is crucial that all patients with MFS also undergo NCSs of the peripheral nerves.

It is not comprehensible why the SC2-MFS cases reported by Lantos *et al*. [2], Garnero *et al*. [3], Lowery *et al*. [4], and Juliao Caamano *et al*. [5] were not included in the review. All four articles were published within in the search period. Adding these four cases to the 11 papers included in the review, it becomes obvious that the reports of SC2-MFS cases significantly declined since the introduction of SARS-CoV-2 vaccinations. Whether this reduced number of reports (15 until 1/210 and 5 since February 2021) (table 1) is truly a vaccination effect or simply a reduced interest in publishing SC2-MFS cases, remains speculative. It is also conceivable that MFS plus cases were published under the term "GBS".

Missing is a discussion about the three cases in whom MFS started before onset of COVID-19 symptoms. We should know if this mismatch was due to only mild clinical manifestations of COVID-19 which were not recognised as such, due to extra-pulmonary onset manifestations of COVID-19, or due to a subclinical infection, which nonetheless triggered an immune response.

Overall, the interesting study has limitations which should be addressed to further strengthen the conclusion and their interpretation.

Declarations

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