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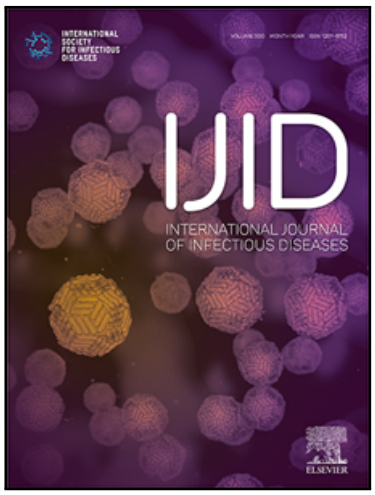

Persistent IgG anti-cardiolipin autoantibodies are associated with post-covid syndrome

Daniel Bertin , Elsa Kaphan , Samuel Weber , Benjamin Babacci , Robin Arcani , Benoit Faucher , Amélie Ménard , Alexandre Brodovitch , Jean Louis Mege , Nathalie Bardin

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Highlights:

- No biological marker has been yet proposed to predict post-COVID syndrome (PCS)
- IgG anti-cardiolipin autoantibodies (aCL) are associated with COVID-19 severity
- We report here a persistent IgG aCL positivity in a patient developing PCS
- Persitence of aCL positivity could be a potential biological predictor of PCS

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Persistent IgG anti-cardiolipin autoantibodies are associated with post-covid syndrome

Daniel Bertin [1]; Elsa Kaphan [2]; Samuel Weber [1]; Benjamin Babacci [1] ; Robin Arcani [3,7] ; Benoit Faucher[4]; Amélie Ménard [5]; Alexandre Brodovitch [1]; Jean Louis Mege [1,6]; Nathalie Bardin [1,7]

[1] Service d'Immunologie, Pôle de Biologie, Hôpital de la Conception, Assistance Publique-Hôpitaux de Marseille (AP-HM), France

[2] Service de Neurologie, Pôle de Neurosciences Cliniques, Hôpital de la Timone, Assistance Publique-Hôpitaux de Marseille (AP-HM), Marseille, France

[3] Service de Médecine Interne et d'Immunologie Clinique, Hôpital de la Conception, Assistance Publique-Hôpitaux de Marseille (AP-HM), France

[4] Service de Médecine Interne, Aix-Marseille Université, AP-HM, Hôpital La Timone, Marseille, France.

[5] Institut Hospitalo-Universitaire (IHU) Méditerranée Infection, Hôpital Nord, Assistance Publique-Hôpitaux de Marseille (AP-HM), Aix Marseille Université, Marseille, France.

[6] Aix-Marseille Université, IRD, MEPHI, IHU-Méditerranée Infection, Marseille, France

[7] Aix Marseille Université, C2VN, INSERM UMR_S 1263, Marseille, France

Corresponding author:

Dr Daniel Bertin: Pôle de Biologie - Laboratoire d'immunologie - Hôpital de la Conception - Pavillon Cornil - 147, Bd Baille - 13005 Marseille – France - Phone: +33(0)491383907 ; Fax : +33(0)491383633

E-mail: daniel.bertin@ap-hm.fr

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Abstract

Persistence of various symptoms in patients who recovered from COVID-19 was recently defined as long COVID or post-COVID syndrome (PCS). We report a case of a 58-year-old woman who, although recovering from COVID-19, has novel and persistent symptoms such as neurological complications, not explained by another cause apart from PCS. In addition to a low inflammatory response, we found a persistence of IgG aCL positivity and eosinopenia, one year after the COVID-19 acute infection, both previously defined as independent factors associated with disease severity. The pathophysiological mechanism of PCS is not known, but the possibility of persistence of the virus, especially in the nervous system, could be suggested, with a post-infectious inflammatory or autoimmune reaction.

Introduction

Growing data show the persistence of various symptoms in patients who recovered from COVID-19, recently defined as long COVID or post-COVID syndrome (PCS) (Tenforde et al., 2020). While markers associated to COVID-19 severity such as IL6, IgG anticardiolipin autoantibodies (aCL), eosinopenia, hemogram-derived ratios, have been described in the acute phase of the disease (Bertin et al., 2020; Liang et al., 2020; Lindsley et al., 2020; Zhou et al., 2020) , no biological marker has been yet proposed to predict PCS.

Case presentation

With a one-year follow-up, we report a case of a 58-year-old woman who, although recovering from COVID-19, has novel and persistent symptoms such as neurological complications. COVID-19 was diagnosed in March 2020, on the basis of positive SARS-CoV-2 RT-PCR, followed in June 2020 by positive anti- SARS-CoV-2 serology (Table 1). She had asthma, arterial hypertension, insulin-dependent diabetes and overweight in her medical history (BMI =35.3kg/m2). During the acute

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phase, the patient presented febrile hypoxemic pneumonia with dyspnea and cough, which required hospitalization in intensive care unit without intubation and was treated by azithromycine, hydroxychloroquine and then ceftriaxone for one week. One year later, she still complains of asthenia, weekly sleepless headaches, memory problems related to dysexecutive syndrome, exertional dyspnea (stage 2 according to MMRC scale), chest pain and digestive disorders such as intermittent diarrhea, bloating, and belching. The scores on the neuropsychological tests were 23/30 on the Mini-Mental Score, 14/18 on the Frontal Assessment Battery, while the word memorization test revealed a deficit of information recall without encoding disorder. Cardiological examination showed minimal left ventricular hypertrophy with preserved ejection fraction. Pertinent laboratory data on admission and in the follow-up of the patient summarized in Table 1, showed persistent inflammatory biological syndrome with elevated CRP and fibrinogen, but not IL6. Interestingly, among antiphospholipid autoantibodies tested, only aCL IgG was positive and persistent one year later. A light but persistent eosinopenia was also observed. Other biological data were normal. Apart from the headaches, which persist, without a definite etiology, the clinical examination did not find any clinical sign of antiphospholipid syndrome (absence of skin lesion, renal or cardiac involvement or thrombosis). She has 5 children, and no known history of miscarriage or thrombosis.

Because of persistent neurological complaint, cerebrospinal fluid (CSF) analysis was performed and showed normal CSF-protein, without oligoclonal band nor pleïocytosis. Cerebral MRI showed isolated temporal lacunar stroke of old appearance. Cerebral 18F-FDG-PET scan showed moderate hypometabolism of amygdala, and mild hypometabolism of fronto-mesial lobe, insula, brainstem and cerebellum, as it has already been described in patients with long COVID (Guedj et al., 2021). Whole body 18F-FDG-PET scan did not show any systemic pathological hypermetabolism.

Discussion

Until now, most of the clinical studies of COVID-19 have focused on symptoms during the acute phase of the disease. Mainly, patients present fever (≥ 38 °C), cough, chest pain, dyspnea, diarrhea

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and fatigue or myalgia, and in about 15% of case, they may develop acute respiratory distress syndrome (ARDS) or end-organ failure. More recently, a "post-covid syndrome" (PCS) has been described in patients who exhibit at least one persistent symptom, 12 weeks after disease onset, which cannot be explained by another cause (Tenforde et al., 2020). This syndrome seems to be frequent after COVID-19 acute infection, and not only after a severe form of the disease. The most common signs of this clinical picture are persistent fatigue, dyspnea, and anosmia or memory complaint. In this case, we evidenced neurological disorders, not explained by another cause apart from PCS. In addition to a low grade inflammatory process, we evidenced the persistence of IgG aCL positivity and eosinopenia, one year after the COVID-19 acute infection, and both previously defined as independent factors associated with disease severity. They could be potential biological predictors of the PCS. Positive aCL have been reported in 13.9% of COVID-19 patients (Taha et al, 2021) and more than 50% of those suffering from the severe form of the disease whereas aCL prevalence was only 1.5 % in individuals from general population (Selmi et al, 2020). At the moment, the prevalence of aCL in post-COVID remains unknown as well as the pathophysiological mechanism involved in PCS, but are suggested the possibility of 1- persistence of the virus, especially in the nervous system, 2- a post-infectious inflammatory or autoimmune reaction, or 3- microglial involvement (Matschke et al., 2020). The aCL could be associated with viral infections and may have in this context persistent pro-inflammatory effects, as recently described (Müller-Calleja et al, 2021).

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors have no conflict of interest to declare.

Authors' contribution

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EK, BF, AM: treatment, care of the patients, and sample collection. NB, JLM, RA, DB drafted the manuscript. SW, BB collected clinical and biological data. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

Ethical Approval

Informed consent was obtained from the patient's family for publication of this case report.

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Table 1: Longitudinal follow-up of biological markers

			Date					
		Normal Values	***2020/03/26***	***2020/06/17***	***2021/01/13***	***2021/02/17***	***2021/03/29***	***2021/04/07***
COVID-19	PCR SARS-CoV2		Positive Ct = 28	N.A	N.A	Negative	N.A	Negative
	Serology SARS-CoV2		N.A	N.A	N.A	Positive	Positive	Positive
	Hemocultures		Sterile	N.A	N.A	N.A	N.A	N.A
Hemogram	Red Blood Cells (T/L)	(4 - 5)	4,28	4,61	N.A	4,86	4,72	4,7
	Hemoglobin (g/dL)	(12 - 15)	11,3	12,2	N.A	12,4	12,4	12
	Platelets (G/L)	(150 - 400)	229	377	N.A	398	377	408
	WBC (G/L)	(4 - 10)	4,4	6,1	N.A	6,1	6,5	5,9
	Neutrophils (G/L)	(2 - 7,5)	2,8	2,6	N.A	2,3	3,1	2,9
	Eosinophils (G/L)	(0,1 - 0,5)	0	0,07	N.A	0,1	0,08	0,06
	Basophils (G/L)	(0 - 0,2)	0,01	0,02	N.A	0,02	0,02	0,01
	Lymphocytes (G/L)	(1 - 4)	1,4	3	N.A	3,3	3	2,6
	Monocytes (G/L)	(0,2 - 1)	0,17	0,42	N.A	0,39	0,36	0,29
	Neutrophil-to-lymphocyte ratio	(< 6,63)	2	0,87	N.A	0,7	1,03	1,12
	Platelet-to-lymphocyte ratio	(< 2,98)	1,64	1,26	N.A	1,21	1,26	1,57
	Neutrophil-to-platelet ratio	(< 2,98)	1,22	0,69	N.A	0,58	0,82	0,71
	Systemic immune-inflammation index (SII)	(< 13,87)	4,58	3,27	N.A	2,77	3,9	4,55
Haemostasis	Prothrombin Time (%)	(> 70)	110	122	112	110	122	106
	aPTT ratio	(< 1,2)	1,1	0,9	0,9	0,9	0,9	1
	D-Dimers (µg/ml)	(0 - 0,5)	N.A	0,39	0,41	0,62	N.A	0,53
	Fibrinogen (g/L)	(1,8 - 4)	6,95	5,36	5,49	5,85	N.A	5,34
Inflammatory markers	CRP (mg/L)	(0 - 5)	130	7,8	7,9	12,1	14,1	15,9
	Ferritin (µg/L)	(30 - 280)	N.A	N.A	N.A	N.A	N.A	N.A
	IL-6 (pg/mL)	(< 55)	N.A	N.A	7,76	14,82	20,63	9,82
Blood ionogram	Na (mmol/L)	(136 - 145)	136	140	139	138	138	139
	Cl (mmol/L)	(98 - 107)	99	103	101	102	99	102
	K (mmol/L)	(3,4 - 4,5)	4,16	4,72	5,24	4,64	4,13	4,73
	Ca (mmol/L)	(2,15 - 2,50)	2,17	N.A	N.A	N.A	2,49	N.A
Renal function	Creatinine (µmol/mL)	(45 - 84)	62,9	61,6	64,6	89	71	79
	GFR (CKD-EPI) (mL/min/1,74m²)	(> 90)	95	97	92	62	82	72
Liver markers	AST (UI/L)	(0 - 35)	31	N.A	N.A	21	20	18

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	ALT (UI/L)	(0 - 35)	25	N.A	N.A	28	28	24
	GGT (UI/L)	(0 - 40)	71	N.A	66	58	60	52
	Total Bilirubin (µmol/L)	(0 - 21)	4	N.A	5	5	6	7
	Alkalin Phosphatase (UI/L)	(35 - 105)	74	N.A	N.A	97	106	91
Tissue damage markers	Lactico dehydrogenase (UI/L)	(135 - 214)	303	N.A	192	N.A	194	N.A
	Creatine Kinase (UI/L)	(0 - 170)	87	N.A	N.A	N.A	120	N.A
Immunology : Conventional	Antinuclear antibodies	(< 160)	N.A	N.A	Negative	Negative	Negative	Negative
Antiphospholipid Antibodies	Anti-cardiolipin IgG (U/mL)	(< 15)	N.A	53,28	21,19	N.A	20,41	24,4
	Anti-cardiolipin IgM (U/mL)	(< 15)	N.A	0,77	0,46	N.A	2,06	1,75
	Anti-B2GP1 IgG (U/mL)	(< 8)	N.A	1,17	1,42	N.A	0	0,68
	Anti-B2GP1 IgG (U/mL)	(< 8)	N.A	1,17	1,42	N.A	0	0,68
	Anti-B2GP1 IgM (U/mL)	(< 8)	N.A	2,3	0,57	N.A	0,23	1
	Lupus Anticoagulant		N.A	Negative	Negative	Negative	N.A	Negative

N.A: non-available data

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