Common mechanistic factors of infection-associated chronic illnesses:

immune dysregulation - autoimmunity (18`)

Carmen Scheibenbogen
Institut für Medizinische Immunologie, Charité, Berlin

CHARITÉ

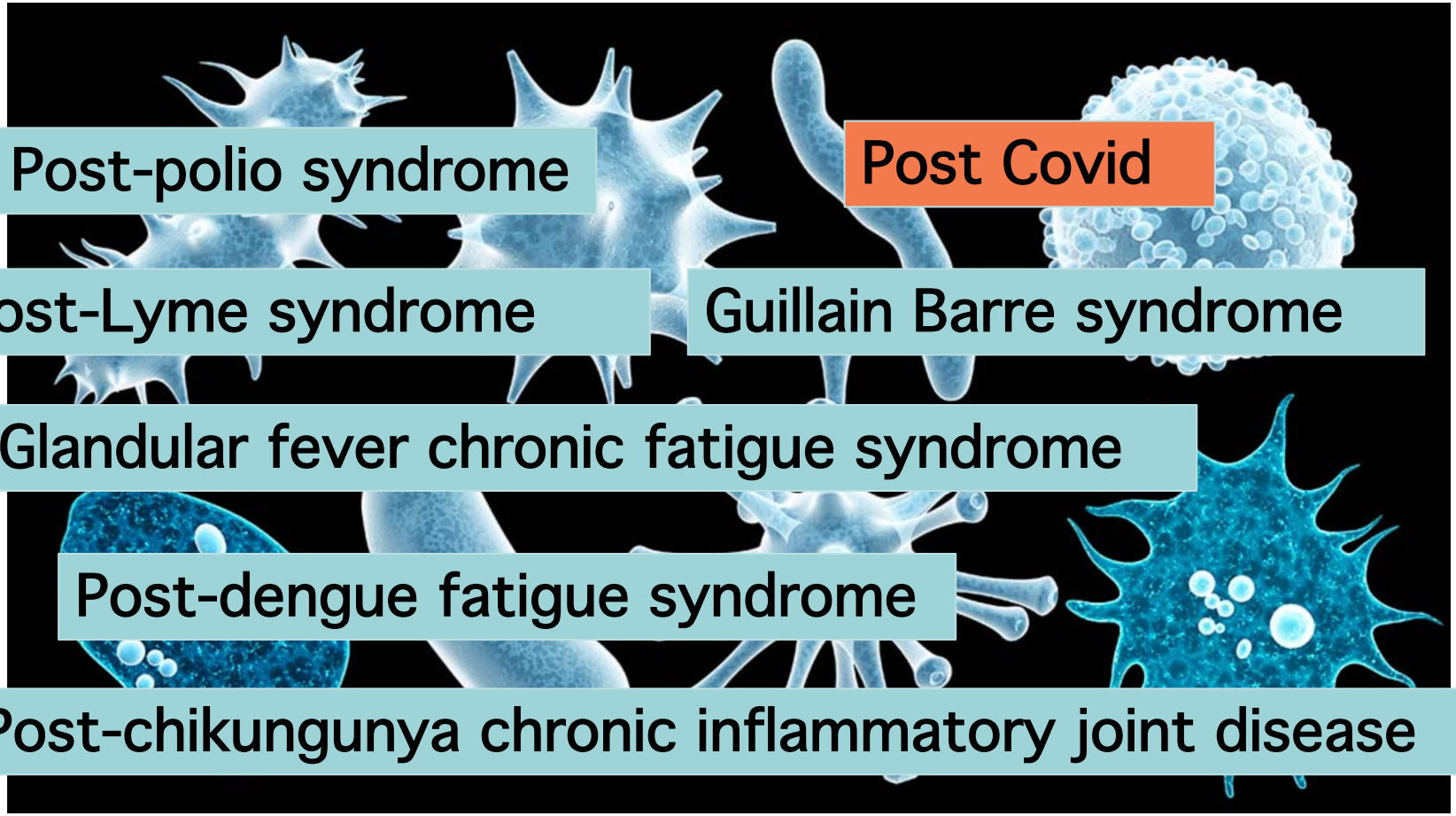
Immundefekt Ambulanz
für Erwachsene

Foto: pilli/stock.adobe.com

- **Post Covid Syndrome and ME/CFS**
- **Evidence for autoimmunity**

Disclosures
Support for clinical trials: Bayer, Fresenius und Miltenyi
Honoraria for lectures: Fresenius, AstraZeneca, BMS, Roche, Bayer, Novartis
Consultation: Roche, Celltrend, Bayer

„Long Viruses/Bacteria“ - Post infectious syndromes (PIS)



The Atlantic

HEALTH

Long COVID Could Be a 'Mass Deterioration Event'

A tidal wave of chronic illness could leave millions of people incrementally worse off.

By Benjamin Mazer

Spectrum of Post COVID conditions
(WHO definition symptoms >3 month and impairement in daily activities)

„classical diseases“
cardiovascular
diabetes mellitus
autoimmune diseases
and many others

Post COVID Syndroms:
- fatigue/exertion intolerance/PEM
- cognitiv, pain, orthostatic symptoms a.o.

ME/CFS CCC

ME/CFS IOM

PoTS orthostatic hypotonia

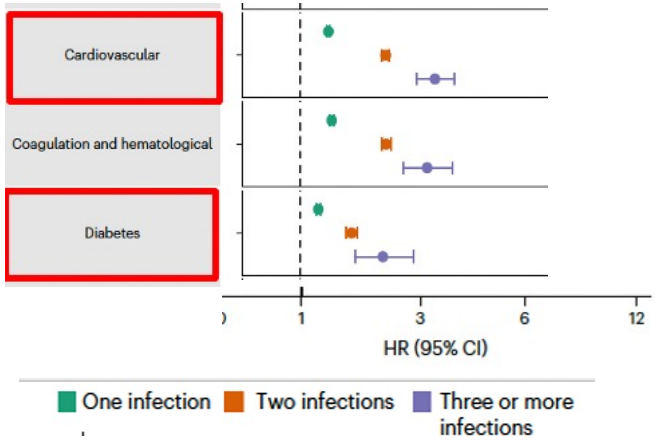
nature medicine

Article

Al-Aly Z et al 2022

https://doi.org/10.1038/s41591-0

Acute and postacute sequelae associated with SARS-CoV-2 reinfection



nature communications

Article

https://doi.org/10.1038/s41467-022-32507-6

A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity

Received: 31 May 2021

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C. Kedor[1,13], H. Freitag[1,13], L. Meyer-Arndt[2,3,4], K. Wittke[1], L. G. Hanitsch[1], T. Zoller[5], F. Steinbeis[5], M. Haffke[1], G. Rudolf[1], B. Heidecker[6], T. Bobbert[7], J. Spranger[7], H. D. Volk[1,8], C. Skurk[6], F. Konietschke[9], F. Paul[2,3,4], U. Behrends[10,11,12], J. Bellmann-Strobl[1,2,3,4,13] & C. Scheibenbogen[1,13]

ME/CFS as part of Post COVID syndroms

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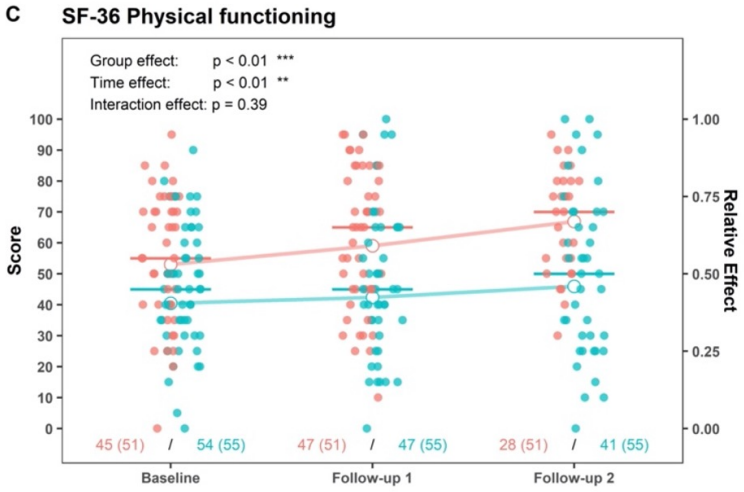
- at least moderate **fatigue** + **exertional intolerance**
- at 6 months
- no evidence for other disease
- not hospitalized
- **ME/CFS in 50% of patients** **(Can Consensus Criteria)**

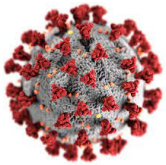
follow- up - 18 months:



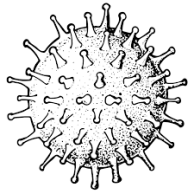
Legler F et al, medRxiv, 2023

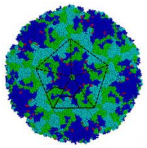
ME/CFS (ICD G93.3)

Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

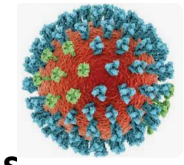


EBV





Enterovirus



Influenza

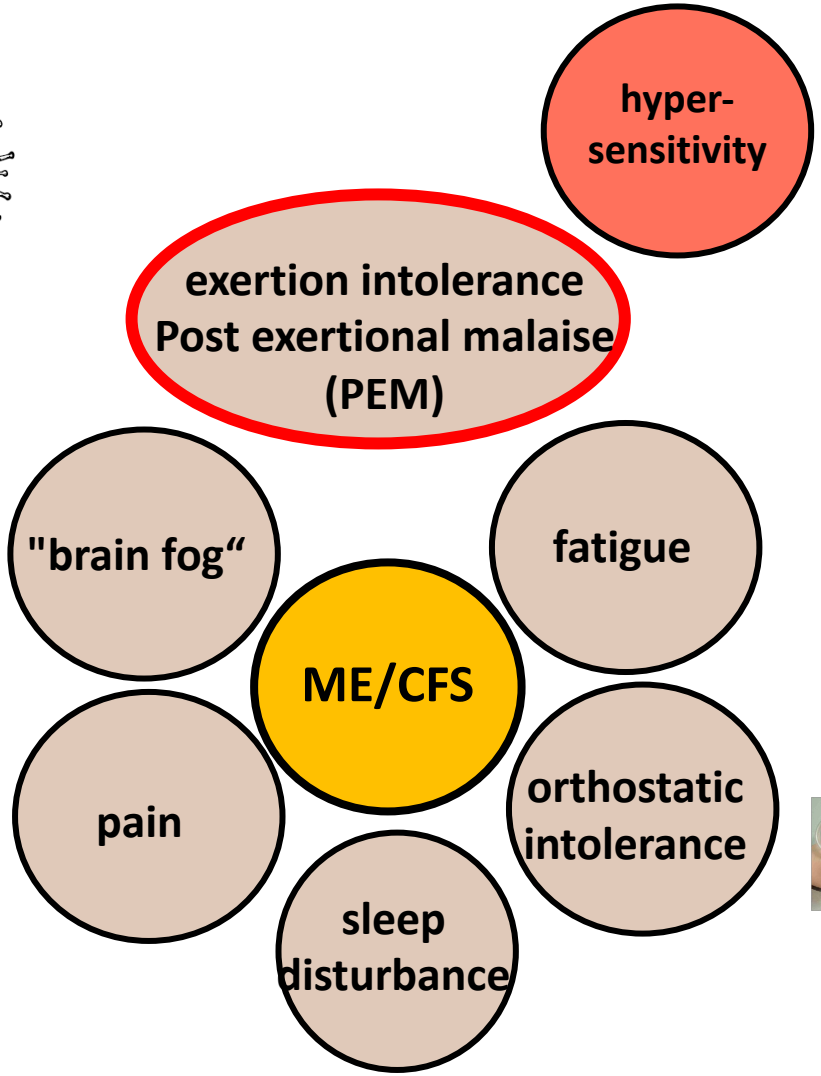


photo: DGME/CFS

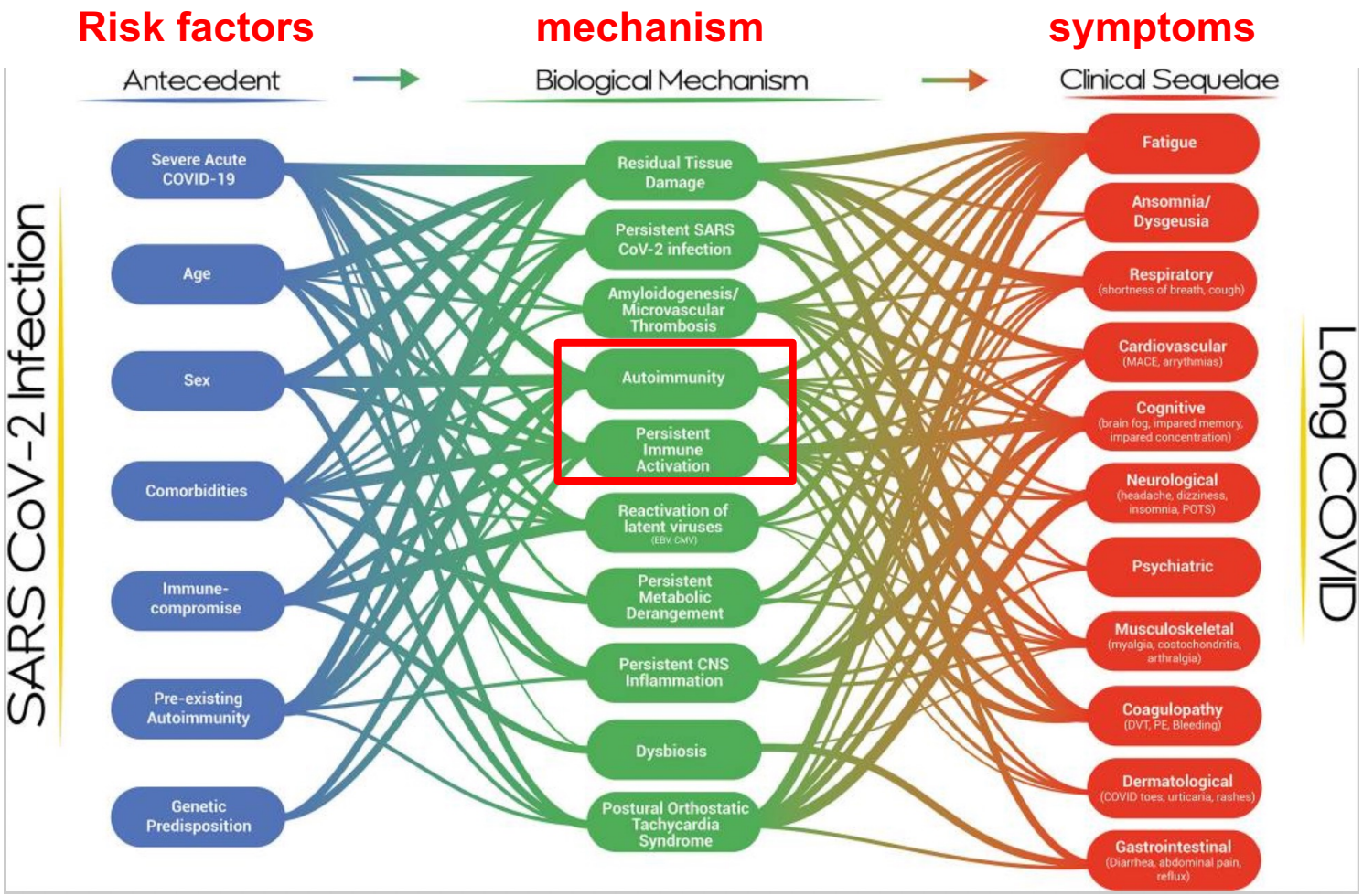
EndoPAT

Bateman Horne Center
RESEARCH | CLINICAL CARE | EDUCATION

Foto: pilli/stock.adobe.com

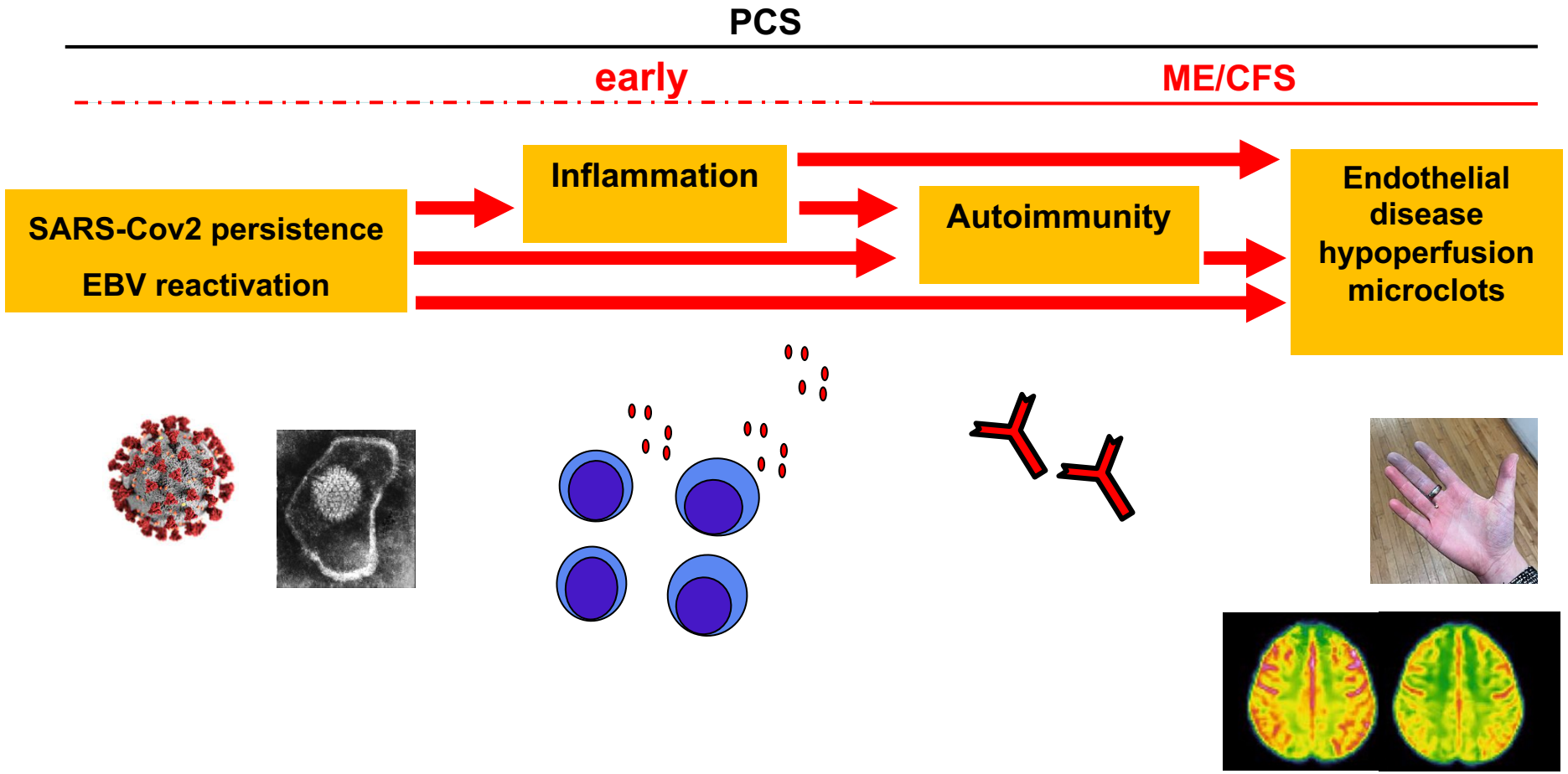
- Post Covid Syndrome and ME/CFS
- **Evidence for autoimmunity**

Systems-level visualization of the complexity of Long COVID and its pathogenesis



Perumal et al. Long COVID: a review and proposed visualization of the complexity of long COVID. Front Imm 2023

Mechanism of Post COVID Syndroms and MECFS



- Ahamed J, Lawrence J. Long COVID endotheliopathy: hypothesized mechanisms and potential therapeutic approaches. J Clin Invest, 2022
- Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol. 2023

ME/CFS – Post Covid Syndrome
- evidence for autoimmunity (AI)

	post inf ME/CFS	PCS subset
Family history of AID	review: Sotzny F 2018	
Comorbidity of AID	review: Sotzny F 2018	review: Sharma C, 2023
Potential auto (mimicry) sequences	EBV Sepulveda N, 2022	Spike Nunez-Castilla 22
EBV as (co-) trigger	yes	yes Su et al 2022
AI genetic risk factors	various Hajdarevic R, 2022	
AI immune risk factors	Igl/MBL def Gunther S 2016	MBL def Kedor C, 2022
Autoantibodies correlating with symptom severity	GPCR Fujii H, 2020, Kimura Y 2023 Sotzny F 2022	ANA Son K, 2023 RAS proteins/rec. CNS Franke C 2022
Alterations in memory B cells/ B cell receptor skewing	Sato W, 2021 Milimojevic M, 2020	Castleman MJ 2022 Woodruff MC, 2022
Efficacy of AAB targeting	IVIG, IA, endoxan, CD20/38 depletion Fluge O, 2021	IVIG, IA

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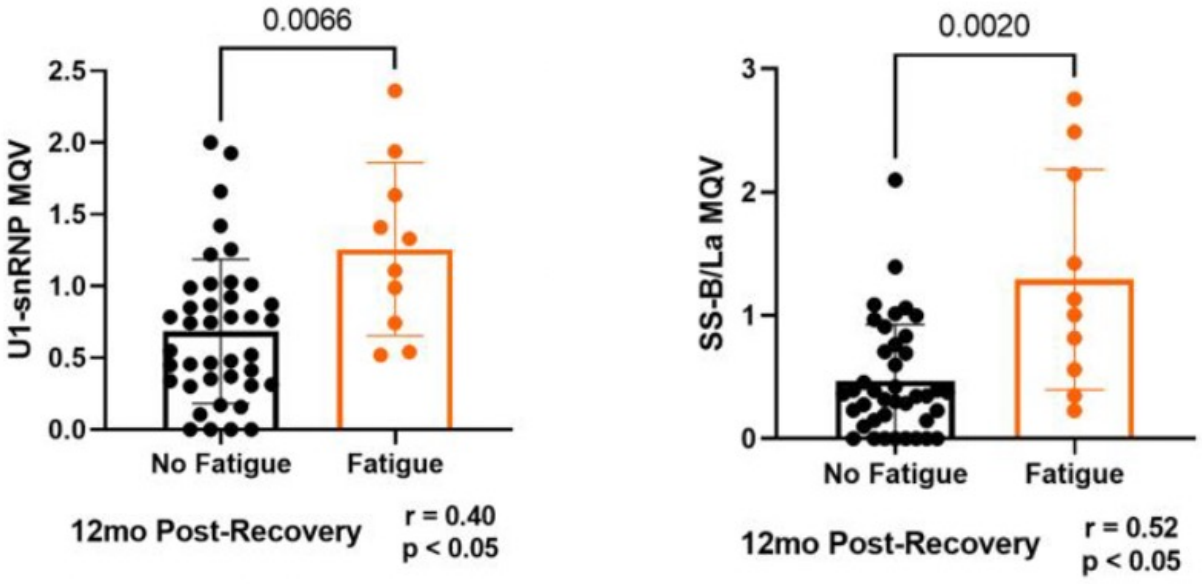
Circulating anti-nuclear autoantibodies in COVID-19 survivors predict long-COVID symptoms

Son K, Jamil R, Chowdhury A, *et al*. *Eur Respir J* 2022



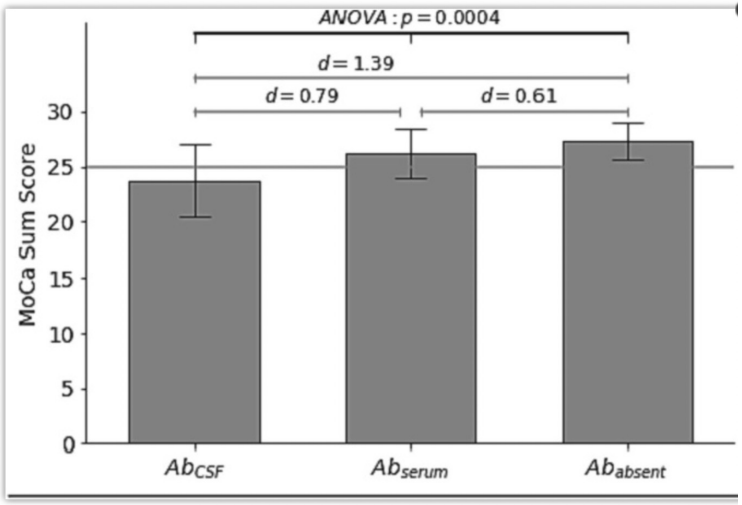
n= 106, median age 57, months 3 - 12

> Brain Behav Immun. 2023 Jan 16;109:139-143. doi: 10.1016/j.bbi.2023.01.006.
Online ahead of print.

Association of cerebrospinal fluid brain-binding autoantibodies with cognitive impairment in post-COVID-19 syndrome

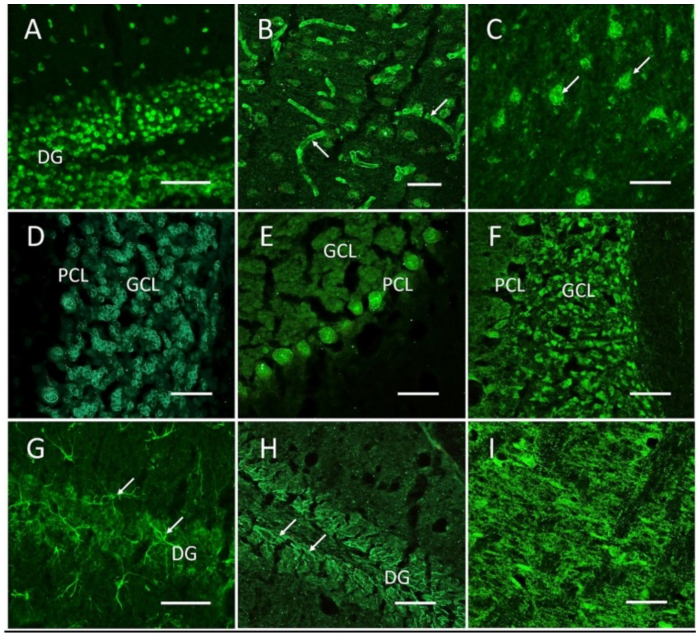
Christiana Franke [1], Fabian Boesl [2], Yasemin Goereci [3], Ameli Gerhard [2], Finja Schweitzer [3], Maria Schroeder [2], Helle Foverskov-Rasmussen [4], Josephine Heine [2], Anneke Quitschau [2], Farid I Kandil [5], Ann-Katrin Schild [6], Carsten Finke [2], Heinrich J Audebert [2], Matthias Endres [7], Clemens Warnke [3], Harald Prüss [4]

Fig. 2



Open in a separate window

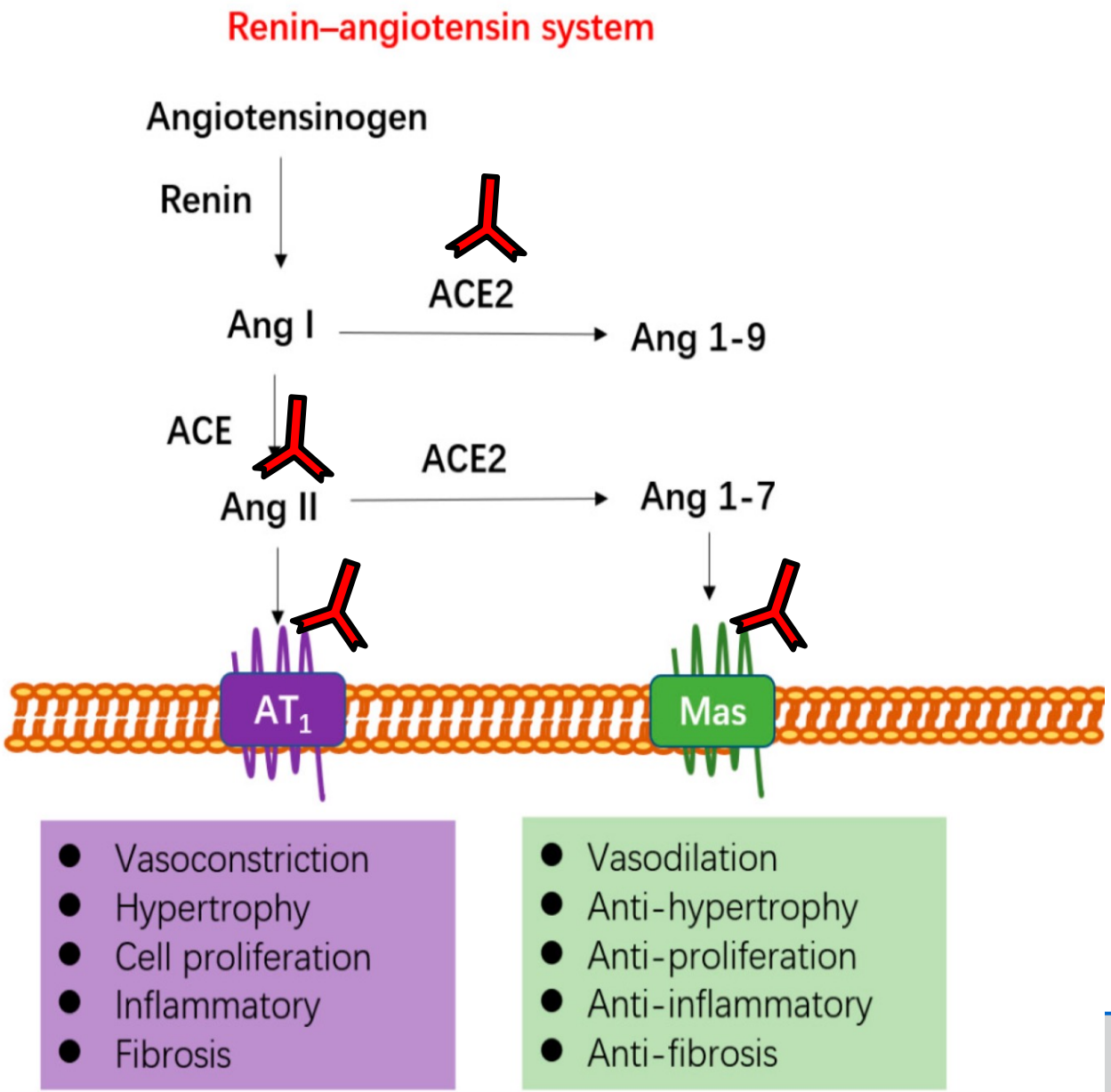
Results of the cognitive screening for PCS patient groups with any anti-neuronal autoantibodies found in CSF (left) or in serum only (middle) or antibody-negative patients (right).



CSF of patients with neurocognitive disorders in post-COVID-19 syndrome frequently shows autoreactivity on unfixed mouse brain sections. Representative images of indirect immunofluorescence using undiluted CSF with incubation overnight at 4 °C demonstrate autoantibody binding following nine major patterns including anti-nuclear antibodies (A, from patient #8), vessel endothelium (B), large neurons (C, from patient #2), perinuclear rim pattern (D, from patient #13), Purkinje neurons (E, from patient #12), cerebellar granule cells (F, from patient #5), astrocytic proteins (G, from patient #7), axon initial segments (H, from patient #10) and neuropil of basal ganglia (I, from patient #5) or hippocampus.

n= 50, median 250 days post Covid

Autoantibodies against RAS in COVID

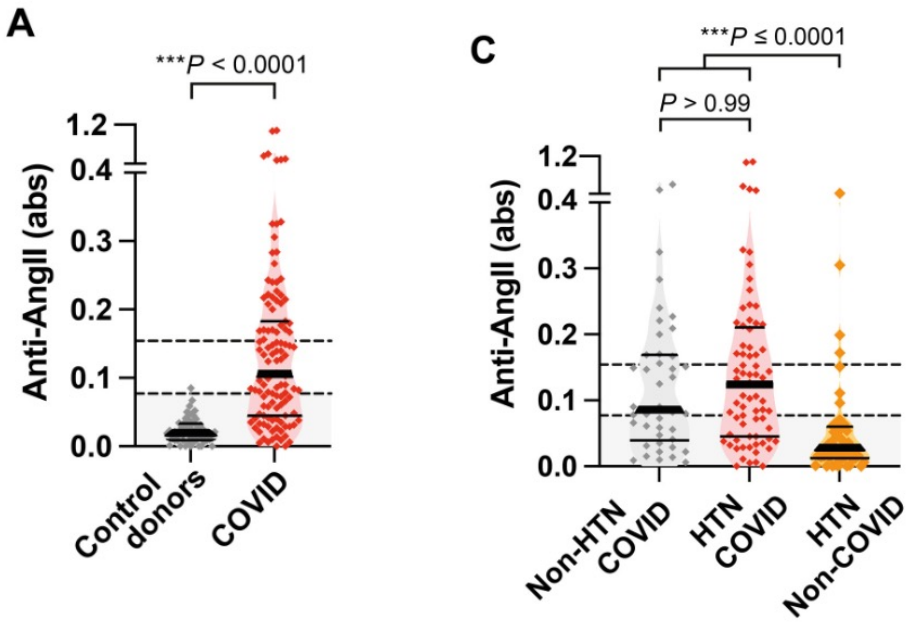


L. Casciola-Rosen, 2020
A.I. Rodriguez-Perez, 2021
Arthur JM, 2021
Cabral-Marquez, O, 2022
Briquez PS, 2022

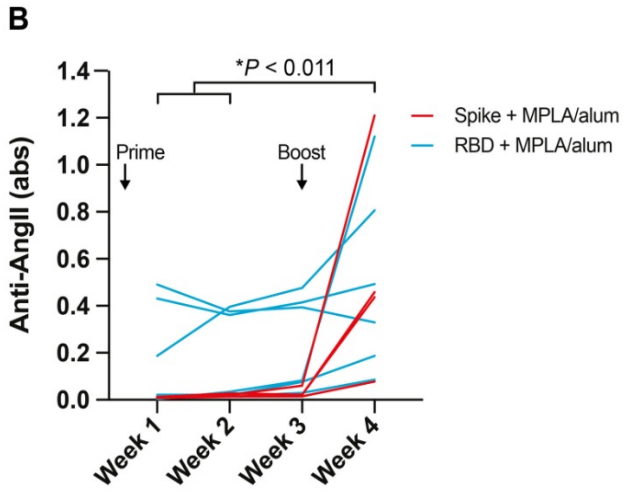
Severe COVID-19 induces autoantibodies against angiotensin II that correlate with blood pressure dysregulation and disease severity

PRISCILLA S. BRIQUEZ, SHERIN J. ROUHANI, JOVIAN YU, ATHALIA R. PYZER, JONATHAN TRUJILLO, HALEY L. DUGAN, CHRISTOPHER T. STAMPER, SIRIRUK CHANGROB, ANNE I. SPERLING, [...], AND MELODY A. SWARTZ +3 authors Authors Info & Affiliations

SCIENCE ADVANCES • 7 Oct 2022 • Vol 8, Issue 40 • DOI: 10.1126/sciadv.abn3777

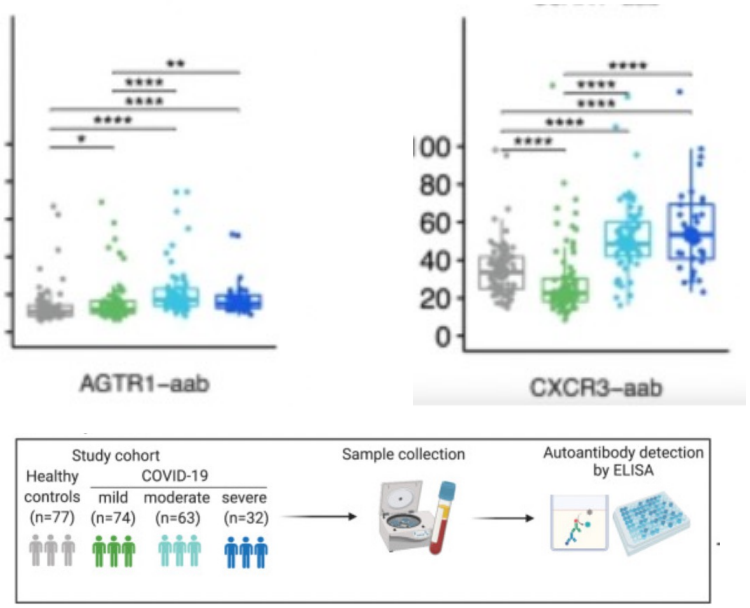


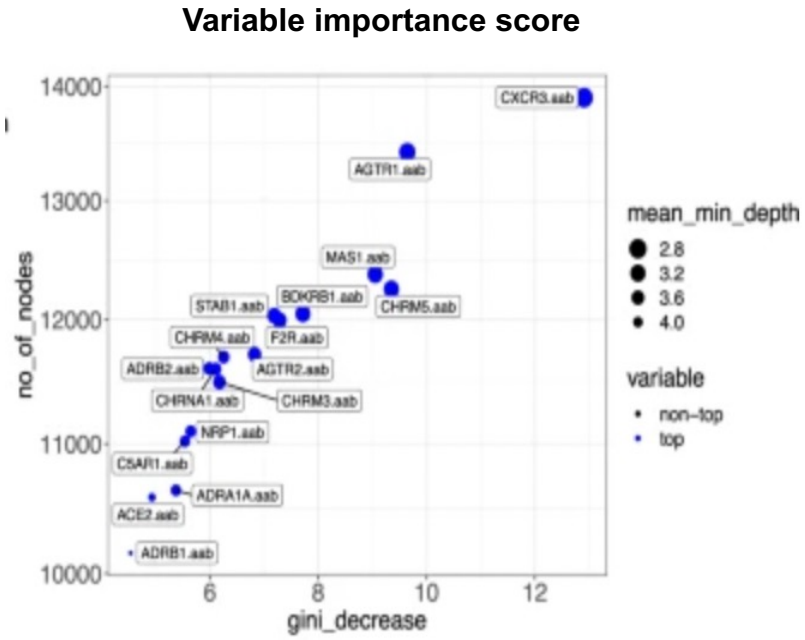
vaccinated mice



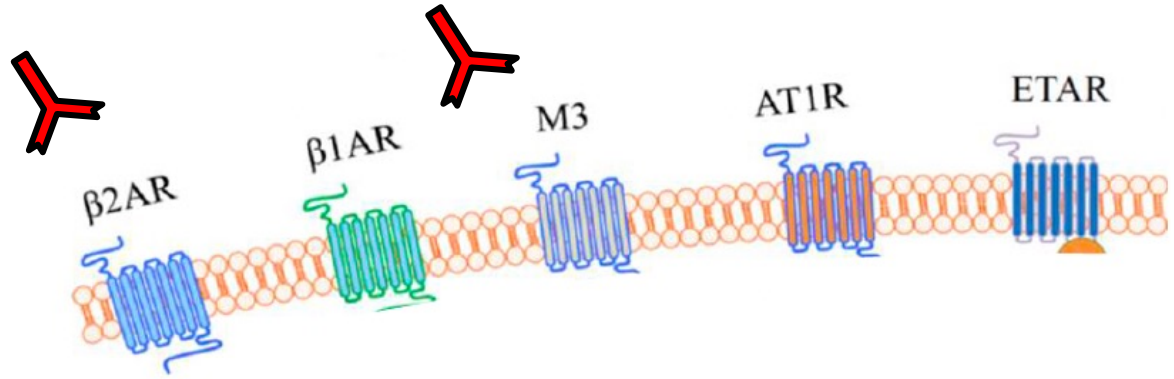
Autoantibodies targeting GPCRs and RAS-related molecules associate with COVID-19 severity. Cabral-Marques O, et al. Nat Commun. 2022

AGTR1 and CXCR3 AAB strongest association with disease severity





GPCR Autoantibodies



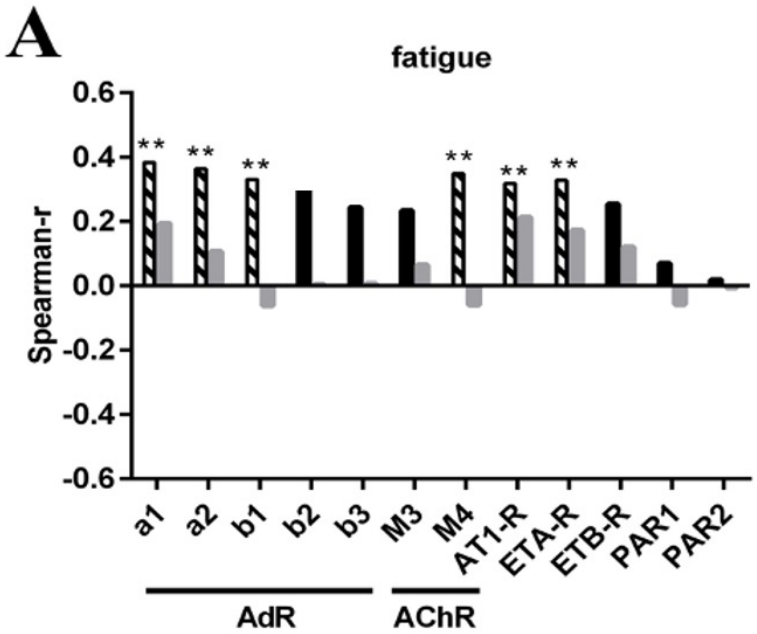
- **natural autoantibodies (1)**
- **correlation of AAB levels to GPCR with symptom severity in various diseases (1)**
- **ß adrenergic and muscarinic receptor antibody levels correlate with symptom severity and CNS alterations (MRI) in ME/CFS (2-4)**
- **ß2 adrenergic receptor antibody function is impaired in ME/CFS (5)**

1. Cabral-Marques O, et al. Autoantibodies targeting G protein-coupled receptors: An evolving history in autoimmunity. Report of the 4th international symposium. Autoimmun Rev. 2023
2. Freitag H, et al. Autoantibodies to Vasoregulative GPCR correlate with Symptom Severity, Autonomic Dysfunction and Disability in ME/CFS. J Clin Med. 2021
3. Fujii H, Sato W, Kimura Y, et al. Altered structural brain networks related to adrenergic/muscarinic receptor autoantibodies in chronic fatigue syndrome. J Neuroimaging. 2020
4. Kimura Y et al. Free water corrected diffusion and adrenergic/muscarinc antibodies in ME/CFS, J Neuroimgaging 2023
5. Hartwig J,et al. IgG stimulated β2 adrenergic receptor activation is attenuated in patients with ME/CFS. Brain Behav Immun Health. 2020

Correlation of GPCR antibody levels with symptom severity in postinfectious (non-COVID) and post COVID ME/CFS

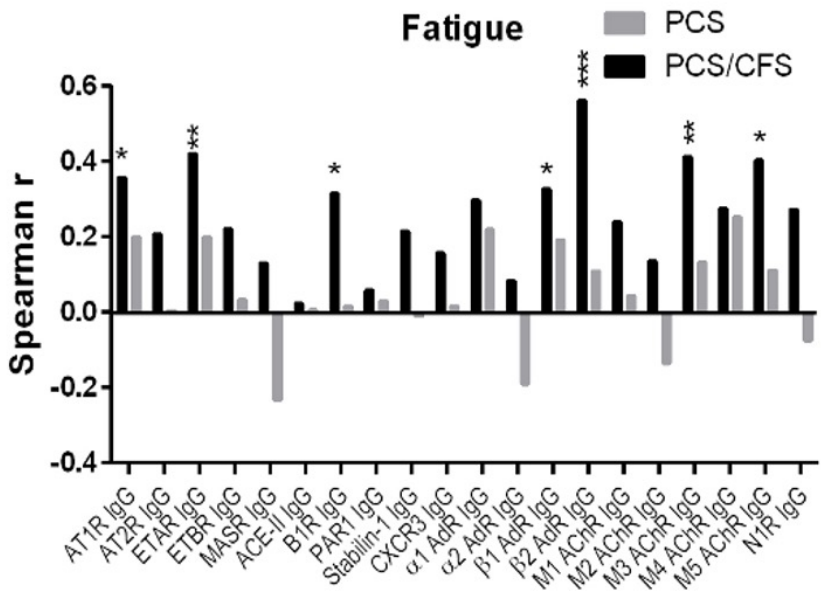
- **Postinf ME/CFS (black/striped)**
- Non-postinf ME/CFS (grey)

- **Post COVID ME/CFS month 6 – 9**
- Post COVID non-ME/CFS



n= 86/39, median age 43, 4 years disease duration

*Freitag H. et al. JCM 2021

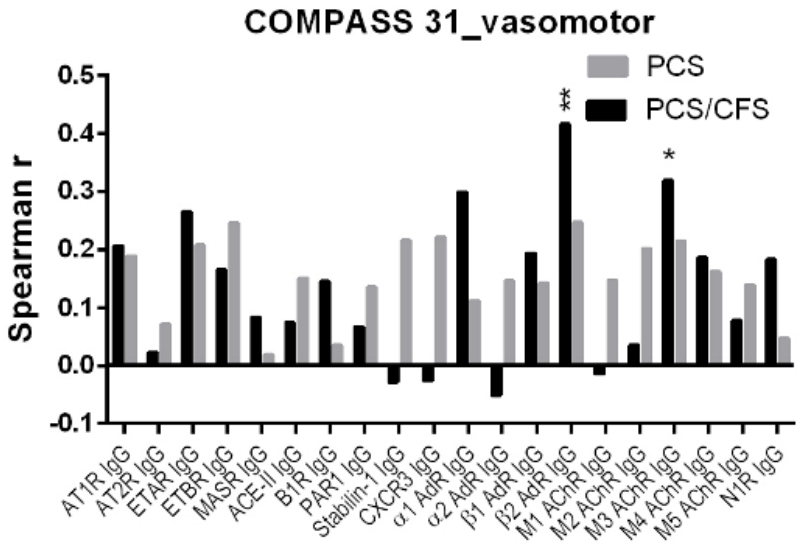


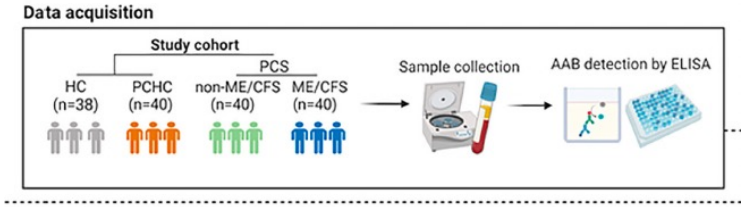
n= 2x40, median age 43, 7 months diseae duration

Sotzny F. et al. Frontiers Immunology, 2022

Correlation of GPCR autoantibodies with Raynaud syndrome in Post Covid ME/CFS

Correlation of ß2R, M3 AchR with Raynaud symptoms in Post COVID ME/CFS but not non-ME/CFS PCS





- Black post COVID ME/CFS

Sotzny F, et al Autoantibodies targeting GPCRs and RAS-related molecules are dysregulated in PCS and correlate with symptom severity, Frontiers Immunology, 2022

ME/CFS – Post Covid Syndrome
- evidence for autoimmunity (AI)

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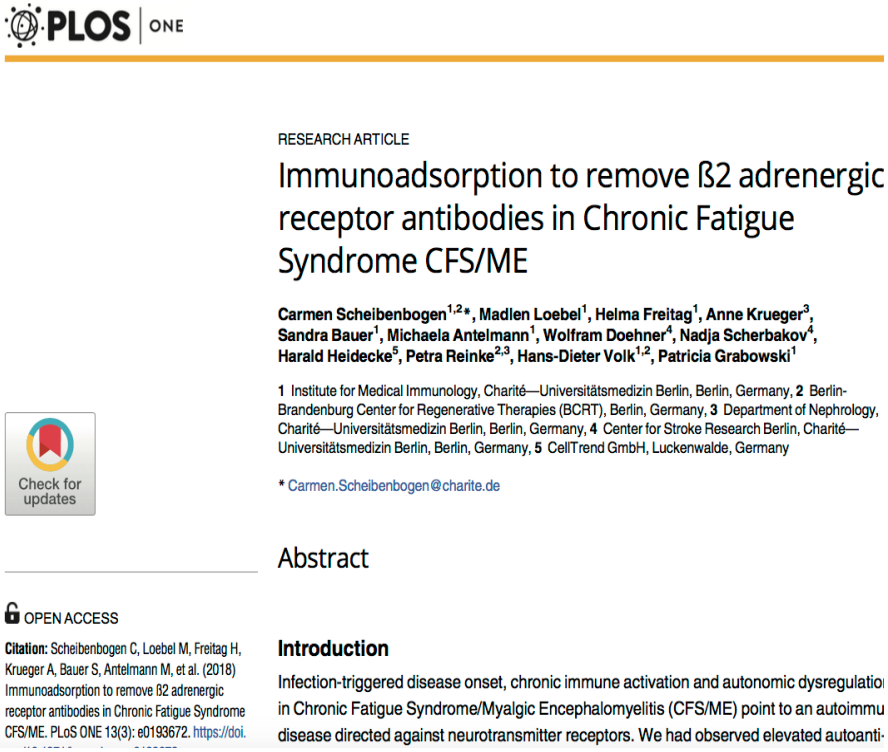
First evidence for efficacy of immunoadsorption in postinfectious ME/CFS



PLOS ONE

RESEARCH ARTICLE

Immunoadsorption to remove ß2 adrenergic receptor antibodies in Chronic Fatigue Syndrome CFS/ME

Carmen Scheibenbogen[1,2]*, Madlen Loebel[1], Helma Freitag[1], Anne Krueger[3], Sandra Bauer[1], Michaela Antelmann[1], Wolfram Doehner[4], Nadja Scherbakov[4], Harald Heidecke[5], Petra Reinke[2,3], Hans-Dieter Volk[1,2], Patricia Grabowski[1]

1 Institute for Medical Immunology, Charité—Universitätsmedizin Berlin, Berlin, Germany, 2 Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Berlin, Germany, 3 Department of Nephrology, Charité—Universitätsmedizin Berlin, Berlin, Germany, 4 Center for Stroke Research Berlin, Charité—Universitätsmedizin Berlin, Berlin, Germany, 5 CellTrend GmbH, Luckenwalde, Germany

* Carmen.Scheibenbogen@charite.de

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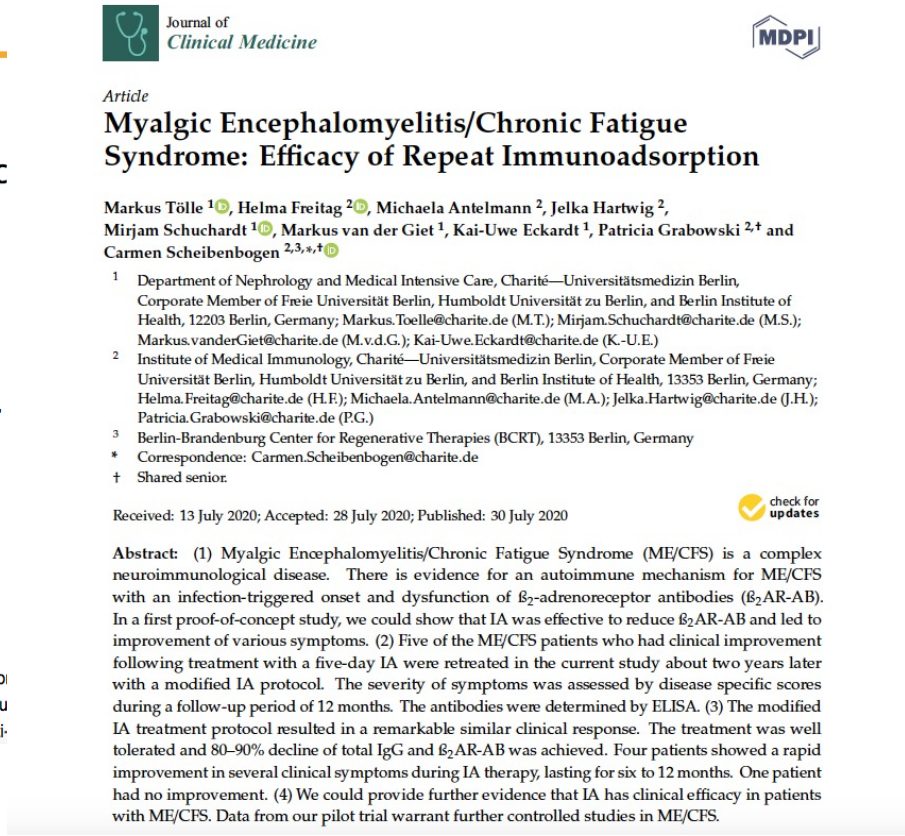
OPEN ACCESS

Citation: Scheibenbogen C, Loebel M, Freitag H, Krueger A, Bauer S, Antelmann M, et al. (2018) Immunoadsorption to remove ß2 adrenergic receptor antibodies in Chronic Fatigue Syndrome CFS/ME. PLoS ONE 13(3): e0193672. https://doi.

Abstract

Introduction

Infection-triggered disease onset, chronic immune activation and autonomic dysregulatio in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) point to an autoimmu disease directed against neurotransmitter receptors. We had observed elevated autoanti-



Journal of Clinical Medicine

MDPI

Article

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Efficacy of Repeat Immunoadsorption

Markus Tölle [1], Helma Freitag [2], Michaela Antelmann [2], Jelka Hartwig [2], Mirjam Schuchardt [1], Markus van der Giet [1], Kai-Uwe Eckardt [1], Patricia Grabowski [2,†] and Carmen Scheibenbogen [2,3,*,†]

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2 Institute of Medical Immunology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health, 13353 Berlin, Germany; Helma.Freitag@charite.de (H.F.); Michaela.Antelmann@charite.de (M.A.); Jelka.Hartwig@charite.de (J.H.); Patricia.Grabowski@charite.de (P.G.)

3 Berlin-Brandenburg Center for Regenerative Therapies (BCRT), 13353 Berlin, Germany

* Correspondence: Carmen.Scheibenbogen@charite.de

† Shared senior.

Received: 13 July 2020; Accepted: 28 July 2020; Published: 30 July 2020

check for updates

Abstract: (1) Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex neuroimmunological disease. There is evidence for an autoimmune mechanism for ME/CFS with an infection-triggered onset and dysfunction of ß$_2$-adrenoreceptor antibodies (ß$_2$AR-AB). In a first proof-of-concept study, we could show that IA was effective to reduce ß$_2$AR-AB and led to improvement of various symptoms. (2) Five of the ME/CFS patients who had clinical improvement following treatment with a five-day IA were retreated in the current study about two years later with a modified IA protocol. The severity of symptoms was assessed by disease specific scores during a follow-up period of 12 months. The antibodies were determined by ELISA. (3) The modified IA treatment protocol resulted in a remarkable similar clinical response. The treatment was well tolerated and 80–90% decline of total IgG and ß$_2$AR-AB was achieved. Four patients showed a rapid improvement in several clinical symptoms during IA therapy, lasting for six to 12 months. One patient had no improvement. (4) We could provide further evidence that IA has clinical efficacy in patients with ME/CFS. Data from our pilot trial warrant further controlled studies in ME/CFS.

Repeat Immunoadsorption in PC ME/CFS

Beobachtungsstudie zur wiederholten Immunadsorption bei Post-COVID-ME/CFS-Patienten mit erhöhten ß2-Adrenorezeptor-Autoantikörpern

NKSG Nationale Klinische Studiengruppe MECFS PCS

Bundesministerium für Bildung und Forschung

Primary endpoint:
SF-36 PF* ≥ 10 points at week 4

PF* = physical function

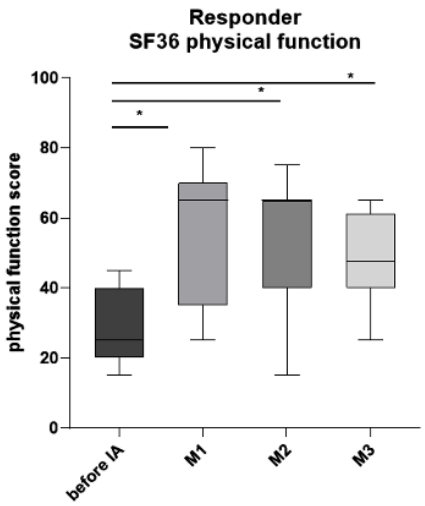
IA1 → **IA2** **IA3**

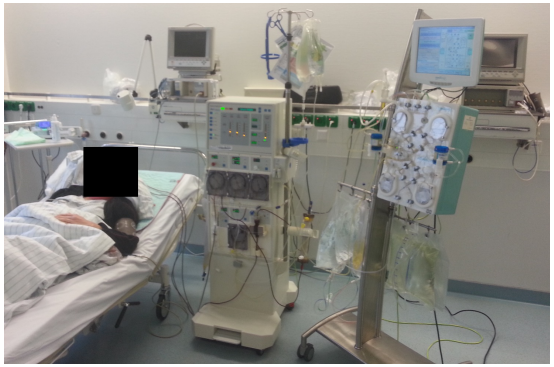
responder = repeat IA

Interim 4/23: n= 7/10 responder

Inclusion criteria

- Age 18-65
- Post COVID **ME/CFS** Canadian Consensus Criteria (CCC)
- **elevated ß2** adrenergic receptor autoantibodies
- Immunoadsorption with TheraSorb® for 5 days





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Fighting Post-COVID and ME/CFS – development of curative therapies

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ME/CFS Conference 2023

Understand, Diagnose, Treat

2nd International Meeting
of the CFC – Charité Fatigue Center

11 May, 9 am – 12 May 2023, 2 pm
Charité - Universitätsmedizin Berlin, Germany

Charité Fatigue Center (CFC)
Institute of Medical Immunology

Understanding

Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) as part of the Post-COVID Syndrome Spectrum – Endothelial Dysfunction and Biomarker – Post-Exertional Malaise (PEM) – Epidemiology – Immune Signature – Autoantibodies – EBV Mimicry – Mitochondrial Dysfunction & Herpesviruses

Diagnosis

State of the Art – Autonomic Dysfunction – Breathing and Muscular Dysfunction – Brain Fog & Neurocognitive Assessment – Sleep Disturbance – Hypermobility

Treatment

State of the Art – Multiprofessional Inpatient Treatment – Treating Orthostatic Intolerance – Medical Care Situation & Stigma – Psychological Support – B and Plasma Cell Targeting – Immunoadsorption – Neuromodulation – Late breaking

Selection of speakers and chairs

Uta Behrends, Technical University of Munich, Germany
Andreas Goebel, University of Liverpool, United Kingdom
Bettina Hohberger, University of Erlangen–Nuremberg, Germany
Leonard Jason, DePaul University, Chicago, USA
Anthony Komaroff, Harvard Medical School, Boston, USA
Eliana Lacerda, London School of Hygiene and Tropical Medicine, United Kingdom
Luis Nacul, British Columbia Women's Hospital, Vancouver, Canada
Bhupesh Prusty, University of Würzburg, Germany
Peter Rowe, Johns Hopkins, Baltimore, USA
Carmen Scheibenbogen, Charité Berlin, Germany
Nuno Sepúlveda, Warsaw University of Technology, Poland
Yehuda Shoenfeld, Sheba University, Tel Aviv, Israel
Francisco Westermaier, FH Joanneum University of Applied Sciences, Graz, Austria

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Registration and more information

www.medpoint-gmbh.de/me-cfs-conference-2023
Online participation via live stream
Submission of abstracts for poster presentations (limit one A4 page) until 6 April 2023
martina.seifert@charite.de

Organisation

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Summary

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- **A subset of PCS has ME/CFS**
- **Evidence for a role of autoantibodies in PCS and ME/CFS**
- **Treatment studies targeting AAB are warranted**

NKSG Nationale Klinische Studiengruppe MECFS PCS

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Immundefekt Ambulanz für Erwachsene

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Bundesministerium für Gesundheit

DFG Deutsche Forschungsgemeinschaft

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Lost Voices Stiftung
Hilfe für Menschen mit ME / CFS

Solve ME/CFS Initiative

Fatigatio e.V.
Bundesverband Chronisches Erschöpfungssyndrom (CFS/CFIDS/ME)

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- Über das Centrum
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Das Fatigue Centrum der Charité — Universitätsmedizin Berlin

Fatigue ist ein häufiges Symptom in der Bevölkerung und ärztlichen Praxis. Fatigue tritt bei unterschiedlichen Erkrankungen auf und kann so stark ausgeprägt sein, dass Patienten schwer krank sind. Die Ursachen von Fatigue sind vielfältig und nicht gut verstanden und oft nicht einfach zu klären. Fatigue, die im Zusammenhang mit chronischen Erkrankungen auftritt, bessert sich oft durch die Behandlung der Erkrankung selbst.

Das Chronische Fatigue Syndrom (CFS) ist davon abzugrenzen als eine eigenständige komplexe Erkrankung. Typischerweise kommt es bei CFS Infekt zu schwerer Erschöpfung die stets mit ausgeprägten körperlichen und kognitiven Symptomen einhergeht. Charakteristisch für oft erst am Folgetag einer Anstrengung auftretende Verschlechterung, die sog. postexertionelle Fatigue oder Malaise, die tage- oder enlang anhalten kann.

henschluss von Ärzten und Wissenschaftlern, die sich mit Fatigue beschäftigen, haben wir es uns zur Aufgabe gemacht, Patienten und stellung bei der Diagnostik und Therapie zu geben. Für Ärzte bieten wir Fortbildungsveranstaltungen an und stellen Informationsmaterial d Patienten zur Verfügung.

Im interdisziplinären Verbund versuchen wir die Ursachen der Fatigue zu erforschen, diagnostisch durchzuführen.

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