Diagnostik der chronischen Borreliose und Koinfektionen: Innovation in der Diagnostik

Dr. med. Armin Schwarzbach
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COLLEGE of AMERICAN PATHOLOGISTS

CERTIFICATE OF ACCREDITATION

Arminlabs
Clinical Laboratory
Augsburg, Germany
Armin Schwarzbach, MD, PhD

CAP Number: 8458129
AU-ID: 1901491

The organization named above meets all applicable standards for accreditation and is hereby accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur prior to **August 8, 2024** to maintain accreditation.

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Kathleen G. Beavis, MD, Accreditation Committee Chair

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COLLEGE of AMERICAN PATHOLOGISTS

CAP #: 8458129
AU-ID: 1901491
March 23, 2023

Armin Schwarzbach, MD, PhD
Arminlaba
Clinical Laboratory
2nd Flr
Augsburg 86154
Germany

Dear Dr. Schwarzbach:

I have completed my review of the findings from the College of American Pathologists (CAP) inspection of your laboratory conducted on August 8, 2022 by Gregory A. Gagnon, MD.

I recommend accreditation for your laboratory.

Congratulations on the excellent services that your laboratory is providing for your community and the efforts that you have made towards accreditation. We value your participation in the CAP's Accreditation Programs.

Sincerely,

C. Robert Bindeden, MD
International Regional Commissioner
CAP Accreditation Programs

DEFREC

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„Wie alles begann 2005“: Chronische Borreliose Stadium III: T-zelluläre Immunantwort

43-jährige Patientin mit seit Mai 2005

- erstmalig aufgetretene persistierende Lähmungen des linken Beines,
- 80%ige Erblindung des linken Auges,
- ausgeprägten Muskelschmerzen,
- Immer wieder Schwindel,
- deutlicher Leistungsknick bei der Arbeit mit drohender Berufsunfähigkeit

Ambulante Vorstellung in unserer Laborpraxis am 26.10.2005

Nervenwasserentnahme vorbefundlich unauffällig

(Keine Borrelien-Antikörperindices, keine IgG-Synthese!)

Mehrere Antiköper-Untersuchungen (IgM-/IgG-EIA sowie Immunoblots inklusive VlsE) wiederholt negativ

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Fallbeispiel “Wie alles began 2005”: Borrelia-EliSpot und CD57 vor Antibiose

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DIAGNOSING TICK-BORNE DISEASES

Armin Schwarzbach MD PhD
Specialist for laboratory medicine

ArminLabs GmbH - Zirbelstr.58 3rd floor, 86154 Augsburg, Germany

Patient:

Date of birth: Date of Reception: Date of Report: Barcode-ID: Physician:

Material: CPDA, Heparin, EDTA, Serum

Analysis		Result	Units	Reference Range
Borrelia burgdorferi antibodies (Westernblot)				
Borrelia-Blot-IgG-antibodies		negative		negative
Borrelia-Blot-IgM-antibodies		negative		negative

The specific Borrelia burgdorferi-IgG/IgM-antibodies are no indication for a humoral immune response against Borrelia burgdorferi. Please look at the results of the Borrelia-EliSpot and the CD57+cell-count.

CD 57 Flow Cytometry				
CD 57 + NK-cells (%)		28	%	2-77
CD 57 + NK-cells (absolute)	-	40	/ul	100-360

The CD57-cell-count indicates a chronic immune-suppressive situation, which can be caused by Borrelia burgdorferi.

Borrelia burgdorferi Elispot				
Borrelia burgdorferi Fully Antigen	+	30	SI	< 2
Borrelia b. OSP-Mix (OSPA/OSPC/DbpA)	+	5	SI	< 2
Borrelia burgdorferi LFA-1	+	8	SI	< 2

The results of the EliSpot-Tests are an indication for an actual cellular activity against Borrelia burgdorferi.

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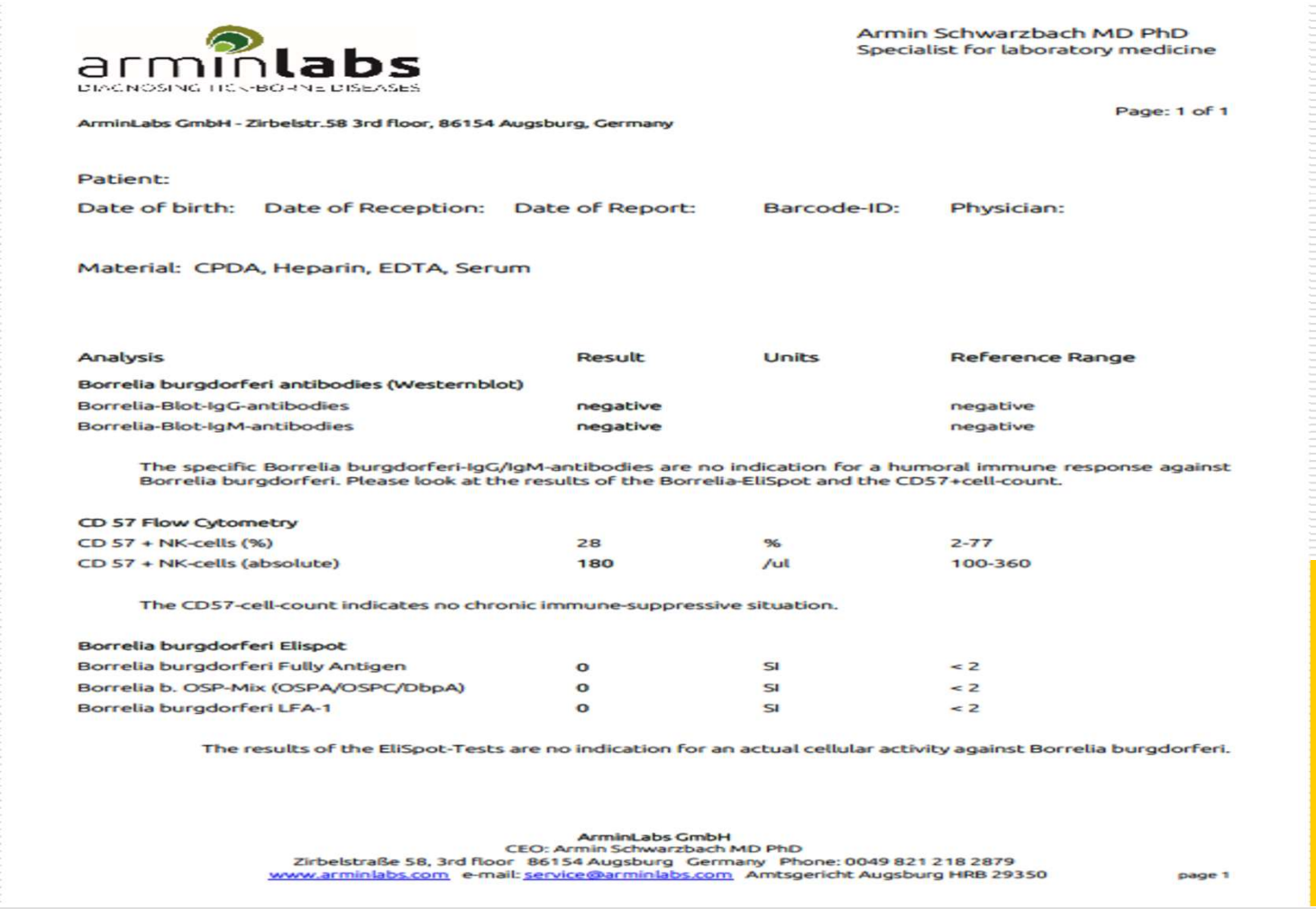
"Wie alles begann 2005": Borrelia-EliSpot nach Ceftriaxon Behandlung (8 Wochen nach Therapieende)



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DIAGNOSING TICK-BORNE DISEASES

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Specialist for laboratory medicine

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Page: 1 of 1

Patient:

Date of birth: Date of Reception: Date of Report: Barcode-ID: Physician:

Material: CPDA, Heparin, EDTA, Serum

Analysis	Result	Units	Reference Range
Borrelia burgdorferi antibodies (Westernblot)			
Borrelia-Blot-IgG-antibodies	negative		negative
Borrelia-Blot-IgM-antibodies	negative		negative

The specific Borrelia burgdorferi-IgG/IgM-antibodies are no indication for a humoral immune response against Borrelia burgdorferi. Please look at the results of the Borrelia-EliSpot and the CD57+cell-count.

CD 57 Flow Cytometry			
CD 57 + NK-cells (%)	28	%	2-77
CD 57 + NK-cells (absolute)	180	/ul	100-360

The CD57-cell-count indicates no chronic immune-suppressive situation.

Borrelia burgdorferi Elispot			
Borrelia burgdorferi Fully Antigen	0	SI	< 2
Borrelia b. OSP-Mix (OSPA/OSPC/DbpA)	0	SI	< 2
Borrelia burgdorferi LFA-1	0	SI	< 2

The results of the EliSpot-Tests are no indication for an actual cellular activity against Borrelia burgdorferi.

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page 1

8 Wochen nach Therapieende mit Ceftriaxon war die Patientin klinisch beschwerdefrei und arbeitsfähig!

Korrekte Diagnose: Chronische Neuroborreliose mit Multiple Sklerose-ähnlichen Symptomen

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Ein Zeckenbiss raubte Gabi Götz zwei Jahre ihres Lebens

Borreliose Ärzte erkannten die Krankheit bei der Frau aus Hiltenfingen lange nicht. Heute leitet die 48-Jährige eine Selbsthilfegruppe mit 15 Betroffenen

VON MONIKA SCHMICH

Hiltenfingen Gabi Götz erinnert sich nur ungern an die schlimme Zeit. Die Krankheit, so sagt sie, habe ihr zwei Jahre ihres Lebens gekostet. 2004 war die heute 48-Jährige an Borreliose erkrankt. Das Problem: Lange erkannte niemand die Krankheit. Zwei Jahre lang lebte die Frau aus Hiltenfingen mit schrecklichen Schmerzen – und kein Arzt konnte ihr helfen.

Heute versucht Gabi Götz gemeinsam mit weiteren Betroffenen, andere Menschen vor einem ähnlichen Schicksal zu bewahren. Sie hat 2006 eine Selbsthilfegruppe gegründet. „Wir waren selbst überrascht, wie viele Betroffene es in unserer Gegend gibt", erzählt sie.

Einmal im Monat treffen sich bis zu 15 Erkrankte und tauschen Informationen aus. Denn noch immer sei das Wissen über die Krankheit gering, klagt Götz. Dabei lauert die Gefahr überall – gerade jetzt in den Sommermonaten. Denn Borreliose wird durch Zecken übertragen.

Auch Gabi Götz muss eines der kleinen Tierchen gebissen haben. Doch davon habe sie nichts gemerkt, erinnert sich die Frau heute. Monate später fing ihr Leidensweg mit Schmerzen im Schultergelenk an. Auch der Nacken tat ihr weh.

> **„An ein gesellschaftliches Leben war nicht mehr zu denken."**
>
> Gabi Götz

Die Kräfte im linken Bein schwanden nach und nach, der linke Arm wurde taub. Und schließlich litt sie unter höllischen Rückenschmerzen. „Es wurde immer schlimmer", erzählt die 48-Jährige. Nach vier Wochen suchte Götz medizinische Hilfe. „Ich bin kein Mensch, der gleich zum Arzt rennt", sagt sie. „Aber ich konnte in dieser Zeit nicht mal mehr schlafen." Doch die Ärzte erkannten nicht, woran sie wirklich litt. Neurologische Tests brachten kein Ergebnis. Selbst eine Cortisontherapie, die ihr verordnet wurde, schlug fehl. „Danach war man mit dem Latein am Ende", sagt Götz.

Fast zwei Jahre lief sie von Arzt zu Arzt. Die Beschwerden wurden immer schlimmer. Gabi Götz hatte Probleme beim Sehen und beim Sprechen. Sie war „müde ohne Ende", berichtet sie. Götz verlor wegen der Krankheit schließlich sogar ihren Arbeitsplatz. „An ein gesellschaftliches Leben war nicht mehr zu denken", erzählt die Hiltenfingerin.

Zufällig lernte Gabi Götz bei einem Vortrag einen Arzt kennen, der sich auf das Thema Borreliose spezialisiert hatte. „In seinen Schilderungen über die Symptome habe ich mich wiedererkannt", sagt sie. Götz unterzog sich daraufhin einem speziellen Borreliose-Test. Das Ergebnis: sie litt tatsächlich unter der Infektionskrankheit. Ihr wurde sofort ein Antibiotikum verordnet. Die Symptome verschwanden. Auch ein Rückfall, den sie ein Jahr später erlitt, überwand sie mit einer medikamentösen Behandlung.

Sie will Betroffene für das Thema sensibilisieren

Für Gabi Götz ging damit ein langer Leidensweg zu Ende. Ein Weg, den viele andere möglicherweise noch vor sich haben. Denn noch immer bleibt die Krankheit vielfach unerkannt. „Oft werden die Symptome auf etwas Psychosomatisches geschoben", weiß Götz. Mit ihrer Selbsthilfegruppe will sie die Probleme thematisieren und auf die Gefahren hinweisen. „Denn wenn man das Wissen hat, kann man auch etwas dagegen tun", sagt Götz.

Treffen Die Selbsthilfegruppe trifft sich jeden ersten Donnerstag im Monat um 19 Uhr in Raum 124 der Leonhard-Wagner-Realschule in Schwabmünchen. Das nächste Treffen findet am 1. Juli statt.

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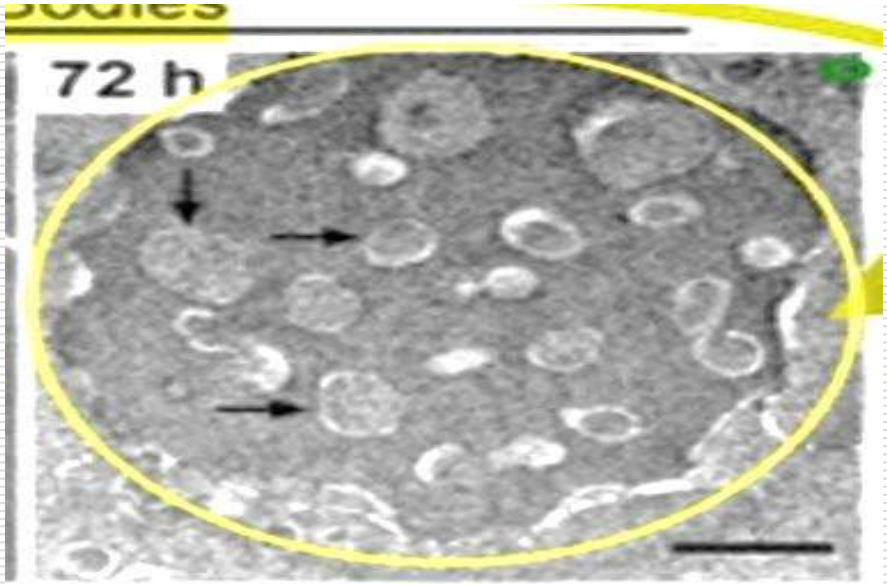
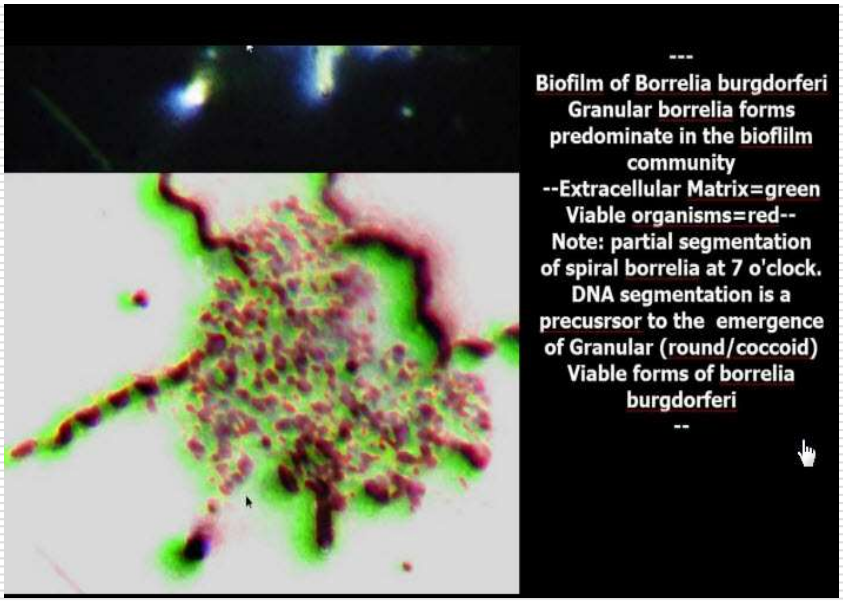
17 Jahre danach 2022:
3 I´s in Diagnostik und Therapie

Pleomorphe Formen und Biofilm-ähnliche Kolonien von Borrelia burgdorferi in vitro





...pleomorphic B. burgdorferi should be taken into consideration as being clinically relevant and influence the development of novel diagnostics and treatment protocols...

Merilainen L., Herranen A., *Schwarzbach A.*, Gilbert L. Morphological and biochemical features of B.b. pleomorphic forms, Microbiology, published online ahead of print January 6, 2015, doi: 10/mic.0.000027

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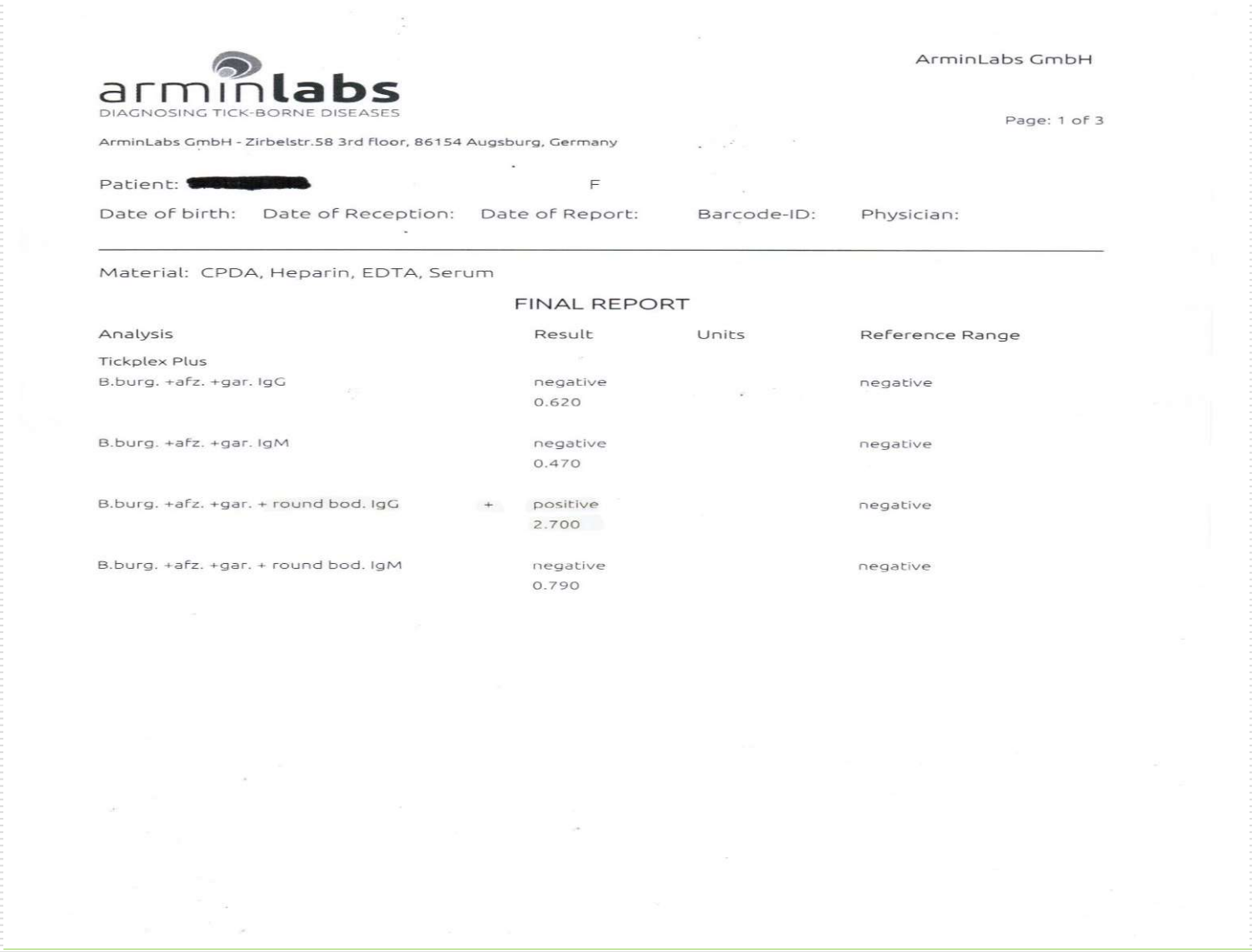
Antikörper gegen round-bodies = Persister Formen: Tickplex Basic www.tezted.com



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DIAGNOSING TICK-BORNE DISEASES

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Page: 1 of 3

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Patient: [redacted] F

Date of birth: Date of Reception: Date of Report: Barcode-ID: Physician:

Material: CPDA, Heparin, EDTA, Serum

FINAL REPORT

Analysis		Result	Units	Reference Range
Tickplex Plus				
B.burg. +afz. +gar. IgG		negative 0.620		negative
B.burg. +afz. +gar. IgM		negative 0.470		negative
B.burg. +afz. +gar. + round bod. IgG	+	positive 2.700		negative
B.burg. +afz. +gar. + round bod. IgM		negative 0.790		negative

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CD3-/CD57+ Lymphozyten

1. Subpopulation der NK-Zellen
2. Verminderung weist auf chronische Borreliose hin (Beschwerden > 1 Jahr)
3. Verminderung bei unbehandelter und nicht ausreichend therapierter Borreliose
4. Nach Therapieende einer chronischen Borreliose: Normalisierung als möglicher Ausdruck des Erfolges
5. Reflektierung eines fortgeschrittenen (chronischen) Aktivitätsgrades der Borreliose oder anderen bakteriellen Infektion wie Chlamydia/Mycoplasma pneumoniae

CD3-/CD57+T-Lymphozyten

Referenzbereiche (Mittelwert/Range)

Borreliose-Patienten: 46 /ul / 8 – 160 /ul

Gesunde: 164 /ul / 60 – 354 /ul

Quelle: J.J.Burrascano JR., MD, R. Stricker, MD, 2006 ILADS, Crowne Plaza Hotel, Center City Philadelphia

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Autismus: Verminderte CD57+ Zellen

In vivo 30: 83-90 (2016)

Decreased Numbers of CD57+CD3− Cells Identify Potential Innate Immune Differences in Patients with Autism Spectrum Disorder

DARIO SINISCALCO[1,2,3], TATJANA MIJATOVIC[4], EUGENE BOSMANS[4], ALESSANDRA CIRILLO[5], PETER KRUZLIAK[6,7], VINCENT C. LOMBARDI[8], KENNY DE MEIRLEIR[9] and NICOLA ANTONUCCI[5]

[1]*Department of Experimental Medicine, Second University of Naples, Naples, Italy;*
[2]*Centre for Autism – La Forza del Silenzio, Caserta, Italy;*
[3]*Cancellautismo – Non-profit Association for Autism Care, Florence, Italy;*
[4]*R.E.D. Laboratories, Zellik, Belgium;*
[5]*Biomedical Centre for Autism Research and Treatment, Bari, Italy;*
[6,2nd]*Department of Internal Medicine, Faculty of Medicine, Masaryk University, Brno, Czech Republic;*
[7]*Laboratory of Structural Biology and Proteomics, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic;*
[8]*Nevada Center for Biomedical Research, Reno, NV, U.S.A.;*
[9]*Himmunitas vzw, Brussels, Belgium*

Abstract. *Background/Aim: Autism spectrum disorders (ASD) are complex, and severe heterogeneous neurodevelopmental pathologies with accepted but complex immune system abnormalities. Additional knowledge regarding potential immune dysfunctions may provide a greater understanding of this malady. The aim of this study was to evaluate the CD57+CD3− mature lymphocyte subpopulation of natural killer cells as a marker of immune dysfunction in ASD. Materials and Methods: Three-color flow cytometry-based analysis of fresh peripheral blood samples from children with autism was utilized to measure CD57+CD3− lymphocytes. Results. A reduction of CD57+CD3− lymphocyte count was recorded in a significant number of patients with autism. Discussion and conclusion: We demonstrated that the number of peripheral CD57+CD3− cells in children with autism often falls below the clinically accepted normal range. This implies that a defect in the counter-regulatory functions necessary for balancing pro-inflammatory cytokines exists, thus opening the way to chronic inflammatory conditions associated with ASD.*

This article is freely accessible online.

Correspondence to: Dario Siniscalco, Department of Experimental Medicine, Second University of Naples, via S. Maria di Costantinopoli, 16 – 80138 - Napoli, Italy. Tel/Fax: +39 0815665880, e-mail: dariosin@uab.edu

Key Words: Autism, CD57+CD3− lymphocytes, HNK-1, immune dysfunction.

Autism and autism spectrum disorders (ASD) are complex and severe, heterogeneous neurodevelopmental pathologies. Their multifactorial nature suggests they originate from the interactions of several genes with environmental, lifestyle and immunological factors (1). ASD diagnostic criteria substantially changed in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (2). The revised diagnosis represents a new and hopefully more accurate depiction of these disorders.

Despite significant progress in our understanding of the associated immunobiology of autism, the pathogenesis, as well as defined molecular mechanisms, remain unclear (3). The dramatic increase in the prevalence of autism (one in 42 boys and one in 189 girls) (4) underscores the urgent need for a broader understanding of the immunological underpinnings of this disease (3, 5). The DSM-5 criteria of autism diagnosis continue to limit this disorder to the evaluation of social, communication skills, and behavioral criteria. However, others are proposing to sub-type of ASD based on a combination of socio-behavioral and biomedical criteria (6-8). Our long-lasting clinical experience points towards a multifactorial disorder combining disorders from four major sub-groups, namely immune disorders, infection, intestinal dysfunction and environmental or maternal toxicant exposure (*i.e.* valproic acid, endocrine disrupting plasticizers, ethanol, air pollution, organophosphates and heavy metals). Sufficient immunological evidence presently exists to encourage the identification of more specific biological criteria (9), thus enabling better diagnostic categorization, and in turn, leading to better management of the complex clinical picture associated with ASDs.

0258-851X/2016 $2.00+.40

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Niedrige CD57 Zellen weisen auf eine chronische Immunsuppression hin

CD3-/CD57+ Cells

5 CD3-/CD56+ Flow Cytometry					
5 T cells CD3+ (%)	**+**	**82,18 %**	**62,00 - 80,00**	[.....	*>
5 T cells CD3+ (absolute)		1225 /ul	900 - 1900	[..*.....	]
5 NK cells CD56+ CD3- (%)	**-**	**4,75 %**	**6,00 - 29,00**	<*	]
5 NK cells CD56+ CD3- (absolute)		71 /ul	60 - 700	[*.....	]
5 CD57+ NK-cells (%)		18,27 %	2,00 - 77,00	[.*.....	]
5 CD57+ NK-cells (absolute)	**-**	**13 /ul**	**100 - 360**	<*	]

The result of the CD57-cell count indicates chronic immune-suppression, which can be caused by Borrelia burgdorferi or other bacteria like Chlamydia pneumoniae or Mycoplasma pneumoniae.

Suppression = generally bacterial causes: Borrelia, Chlamydia pneumoniae, Mycoplasma

Source (partly, rest Dr. Schwarzbach): Ginger Saveley PhD, http://www.publichealthalert.org/everything-you-always-wanted-to-know-about-the-cd-57-test-but-were-too-sick-to-ask.html

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CD57+ Zahl ist bei viralen Infektionen erhöht

frontiers in Immunology

Front Immunol. 2013; 4: 422.
Published online 2013 Dec 9. doi: 10.3389/fimmu.2013.00422

Functional Significance of CD57 Expression on Human NK Cells and Relevance to Disease

Carolyn M. Nielsen,[1] Matthew J. White,[1] Martin R. Goodier,[1] and Eleanor M. Riley[1,*]

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Abstract

Go to:

Historically, human NK cells have been identified as $CD3^{-}CD56^{+}CD16^{\pm}$ lymphocytes. More recently it has been established that CD57 expression defines functionally discrete sub-populations of NK cell cells, CD57 expression has been regarded as a marker of terminal differentiation and (perhaps wron anergy and senescence. Similarly, CD57 expression seems to identify the final stages of peripheral maturation; its expression increases with age and is associated with chronic infections, particularly cytomegalovirus infection. However, $CD57^{+}$ NK cells are highly cytotoxic and their presence seem beneficial in a number of non-communicable diseases. The purpose of this article is to review our c understanding of CD57 expression as a marker of NK cell function and disease prognosis, as well as to outline areas for further research.

Keywords: CD57, NK cells, HCMV infection, ageing, chronic infection, cancer, autoimmune diseases, T cells

"Chronic viral infections such as HCMV (104), human immunodeficiency virus (HIV) (105), hepatitis C virus (106), and Epstein–Barr virus (EBV) (107) infections offer some of the clearest examples of expansion of $CD57^{+}CD8^{+}$ T cells, presumably as a result of persistent antigenic stimulation"

"Similar skewing of NK cells toward the $CD57^{+}$ phenotype is now reported in a variety of viral infections"

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856678/

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Chronische Virus Infektion: Niedrige CD3+ Zellen

CD 57 Flow Cytometry

T cells CD3 + (%)		76.58	%	62-80
T cells CD3 + (absolute)	-	659	/ul	900-1900
NK cells CD56+CD3- (%)		16.91	%	6-29
NK cells CD56+CD3- (absolute)		146	/ul	60-700

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Email: info@arminlabs.com · VATReg-No.: DE815543871 · Amtsgericht Augsburg HRB 29350

There is also one sign for a viral infection, this can be seen with the low CD3+cells, which should be looked at with CMV-Elispot, EBV-Elispot, HSV 1/2-Elispot, VZV-antibodies, Coxsackie Virus antibodies.

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Zusammenfassung NK Zellen (CD57+NK)

Erhöht bei:

1. Chronisch virale Infektionen (EBV, CMV, HSV1/2, VZV etc.)

Vermindert bei:

1. Chronisch bakterielle Infektionen (Borrelien, Chlamydia, Mykoplasma usw.)

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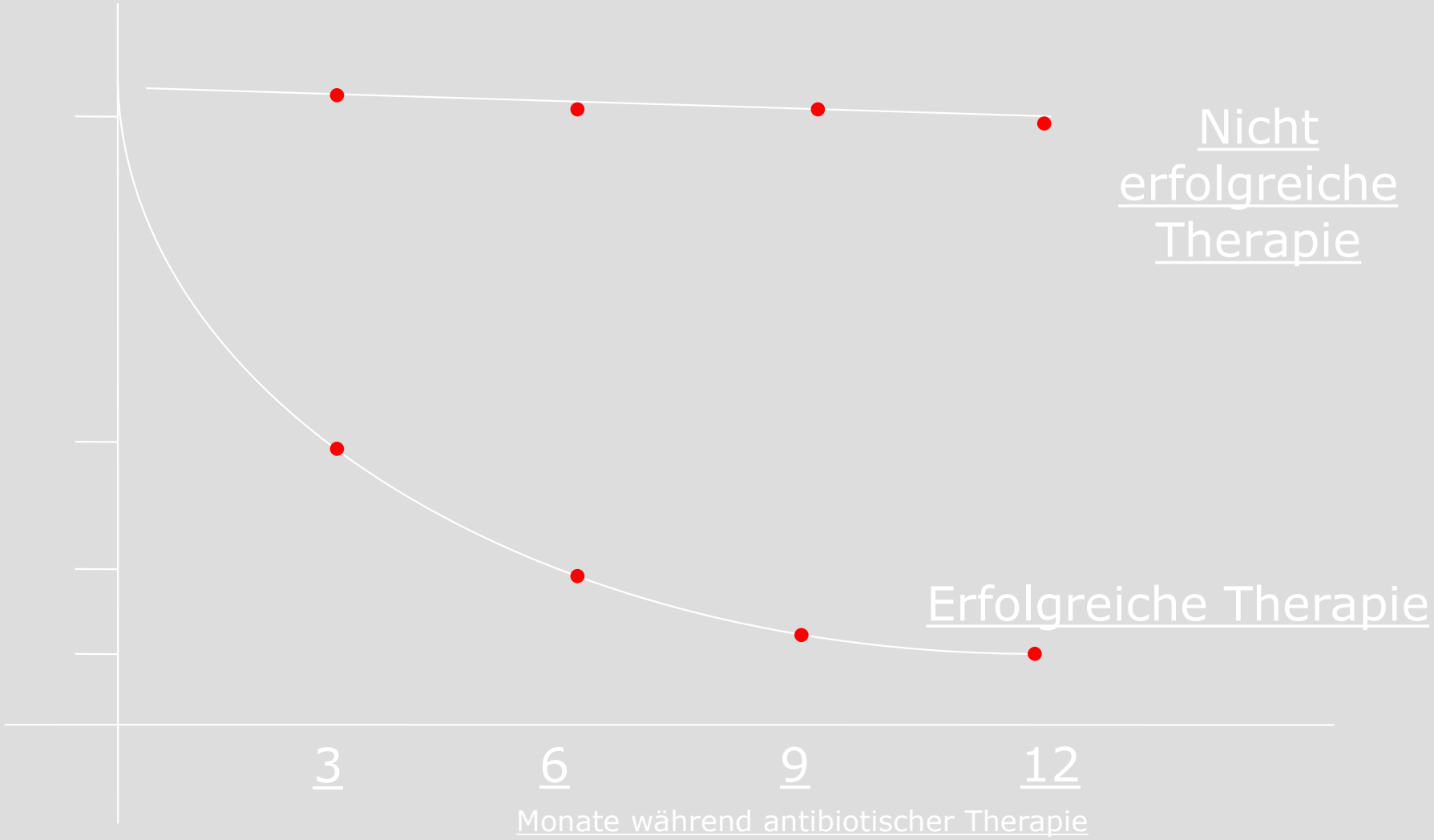
EliSpot während Antibiose: “Staging” Verlauf



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ELISPOT: Neuer T-Cell Test ein "Game Changer" bei der Lyme-Borreliose

… The sensitivity of ELISPOT is estimated at 84%, and the specificity is 94%...

… ELISPOT assays provide robust, highly reproducible data…

… ElISPOT can be retested for the acquisition of additional information in follow-up assays…

… the two assays systems (ELISPOT + CD57-cell count) compliment each other in the quest to understand T cell-mediated immunity in vivo….

Lehman PV et al.: Unique Strengths of ELISPOT for T Cell Diagnostics in: Kalyuzhny AE. Handbook of ELISPOT: Methods and Protocols, Methods in Molecular Biology, Vol. 792. 2nd Ed: Springer; 2012: 3-23

Zusammenfassung:

82-100 % Spezifität des Borrelien-Elispot

84 % Sensitivität des Borrelien-EliSpot

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Fibromyalgie
ANA Titer assoziiert mit Borrelien-EliSpot

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Current Rheumatology Reviews, XXXX, XX, 1-3 1

RESEARCH ARTICLE

Antinuclear Antibody Seropositivity in Fibromyalgia Associated with *Borrelia*-specific T Lymphocytes

Basant K. Puri[1,*], Gary S. Lee[2] and Armin Schwarzbach[3]

[1]*Faculty of Health and Well-Being, University of Winchester & C.A.R., Cambridge, UK;* [2]*Department of Psychology, University of Southampton, UK;* [3]*Department of Pathology, Arminlabs, Augsburg, Germany*

ARTICLE HISTORY

Received: July 29, 2022
Revised: December 08, 2022
Accepted: December 19, 2022

Abstract: ***Background***: Our group have recently reported that there is no evidence of an association between fibromyalgia and *Borrelia*-specific T lymphocytes. However, a small number of case reports has suggested that infection by the bacterial genus *Borrelia* may be associated with the presence of antinuclear antibodies (ANAs).

Objective: To test the hypothesis that those fibromyalgia patients who are ANA seropositive are more likely to show evidence of *Borrelia*-specific T lymphocyte reactivity than those who are seronegative.

Methods: T lymphocyte reactivity to *Borrelia burgdorferi sensu stricto* (full antigen) was assessed using the enzyme-linked immunospot and serum ANA status was assessed using immunofluorescence in 27 fibromyalgia patients fulfilling the revised diagnostic criteria of the American College of Rheumatology.

Results: The ANA seropositive and seronegative groups were matched for age, sex and ethnicity; the T lymphocyte reactivity to *Borrelia burgdorferi sensu stricto* (full antigen) in the former group (mean 5.60) was significantly higher than that in the seronegative group (mean 1.77; $p < 0.05$).

Conclusion: This novel study points to an association of ANA seropositivity in fibromyalgia with *Borrelia*-specific T lymphocytes.

Keywords: Antinuclear antibody, fibromyalgia, T lymphocytes, Borrelia, immune response, autoimmune disease, enzyme-linked immunospot.

Author Proof Personal use only

1. INTRODUCTION

Our group have recently reported that there is no evidence of an association between fibromyalgia and *Borrelia*-specific T lymphocytes [1]. However, a small number of case reports has suggested that infection by the bacterial genus *Borrelia* may be associated with the presence of antinuclear antibodies (ANAs) [2-6], although, thus far, no systematic study has been reported. We therefore hypothesised that those fibromyalgia patients who are ANA seropositive are more likely to show evidence of *Borrelia*-specific T lymphocyte reactivity than those who are seronegative.

The aim of the present study was to carry out the first assessment of this hypothesis.

2. MATERIALS AND METHODS

This was a retrospective study of our previously reported cohort of 27 fibromyalgia patients fulfilling the revised diagnostic criteria of the American College of Rheumatology [1, 7]. T lymphocyte reactivity to *Borrelia burgdorferi sensu stricto* (full antigen) was assessed using the enzyme-linked immunospot assay, as reported previously, while serum ANA status was assessed by immunofluorescence at the same time, using serum from the same venous peripheral blood samples [1]. The *Borrelia burgdorferi sensu stricto* (full antigen) consisted of the *Borrelia burgdorferi* B31 reference strain. The cut-off ratio between negative and positive values of the ANA immunofluorescence was 1:100.

Non-parametric group comparisons were carried out using the Mann-Whitney test while two-by-two contingency tables were analysed using the chi-squared test. All tests were two-tailed. Statistical analyses were carried out using R v. 4.1.1 and JASP 0.16.3 running on a 64-bit Windows 10 platform [8, 9].

3. RESULTS

Five of the patients were ANA seropositive (mean (standard error) age = 56.0 (1.9) years; all female; all white Caucasian) while the remaining 22 were ANA seronegative

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Beispiel Borrelien EliSpot Ergebnis

Armin Schwarzbach MD PhD
Specialist for laboratory medicine

arminlabs
DIAGNOSING TICK-BORNE DISEASES

ArminLabs GmbH - Zirbelstr.58 3rd floor, 86154 Augsburg, Germany

Patient:

Date of birth: Date of Reception: Date of Report: Barcode-ID: Physician:

Material: CPDA, Heparin, EDTA, Serum

FINAL REPORT

Analysis		Result	Units	Reference Range
Borrelia burgdorferi Elispot				
Borrelia burgdorferi Fully Antigen	+	15	SI	< 2
Borrelia b. OSP-Mix (OSPA/OSPC/DbpA)	+	16	SI	< 2
Borrelia burgdorferi LFA-1	+	10	SI	< 2

The results of the EliSpot-Tests are an indication for an actual cellular activity against Borrelia burgdorferi.

Explanation of antigens:

- Borrelia burgdorferi Fully Antigen: Borrelia b. B31-reference strain (Borrelia b sensu stricto)
- Borrelia burgorferi Peptide-Mix: OspA from Borrelia b. sensu stricto, Borrelia afzelii, Borrelia garinii + OspC native + DbpA recombinant
- Borrelia burgdorferi LFA-1 (Lymphocyte Function Antigen 1): Own body protein + Borrelia burgdorferi sensu stricto (shared epitope). Often associated with autoimmune diseases: collagenosis, Rheumatoid Arthritis, vasculitis. If positive or borderline positive look at: ANA, CCP-antibodies, ANCA.

(Native : cultured antigens/ Recombinant: genetic technology produced)

Report validated by

Armin Schwarzbach MD PhD

Specialist for laboratory medicine

ArminLabs GmbH
CEO: Armin Schwarzbach MD PhD
Zirbelstraße 58, 3rd floor 86154 Augsburg Germany Phone: 0049 821 218 2879
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EliSpot Test Results Compared to "Standard" Laboratory

Samples (n=31)	Standard Lab C6		
EliSpot	Positive	Negative	Total
Positive	9	17	26
Negative	1	4	5
Total	10	21	31

EliSpot versus C6	
EliSpot Positive	84%
Standard Lab Positive	32%
Ratio	38%
"Standard" Lab Missed Cases	62%

Samples (n=13)	Standard Lab Western Blot		
EliSpot	Positive	Negative	Total
Positive	2	9	11
Negative	0	2	2
Total	2	11	13

EliSpot versus WB	
EliSpot Positive	85%
Standard Lab Positive	15%
Ratio	18%
"Standard" Lab Missed Cases	82%

Samples (n=14)	Standard Lab Two-Tier test		
EliSpot	Positive	Negative	Total
Positive	2	10	12
Negative	0	2	2
Total	2	12	14

EliSpot versus Two-Tier	
EliSpot Positive	86%
Standard Lab Positive	14%
Ratio	17%
"Standard" Lab Missed Cases	83%

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Elispot reflektiert die aktuelle T-zelluläre Aktivität von Bakterien und Viren

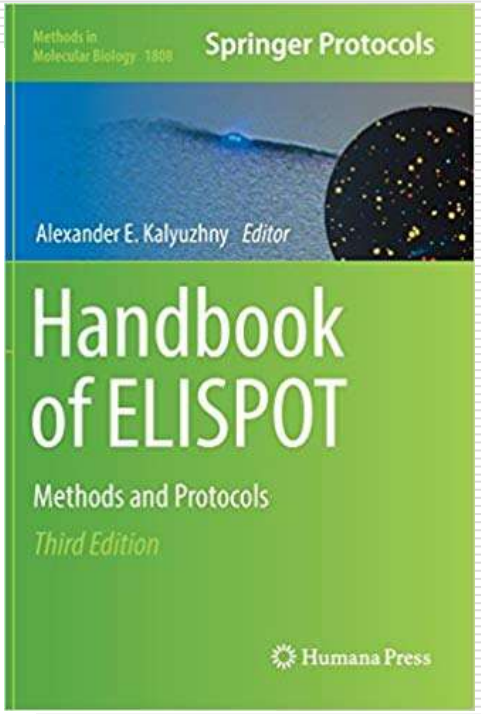
Chapter 1

Unique Strengths of ELISPOT for T Cell Diagnostics

Paul V. Lehmann and Wenji Zhang

Abstract

The T cell system plays an essential role in infections, allergic reactions, tumor and transplant rejection, as well as autoimmune diseases. It does so by the selective engagement of different antigen-specific effector cell lineages that differentially secrete cytokines and other effector molecules. These T cell subsets may or may not have cytolytic activity, can preferentially migrate to different tissues, and display variable capabilities to expand clonally. The quest of T cell immune diagnostics is to understand which specific effector function and T cell lineage is associated with a given clinical outcome, be it positive or adverse. No single assay can measure all of the relevant parameters. In this chapter, we review the unique contributions that ELISPOT assays can make toward understanding T cell-mediated immunity. ELISPOT assays have an unsurpassed sensitivity in detecting low frequency antigen-specific T cells that secrete effector molecules, including granzyme and perforin. They provide robust, highly reproducible data – even by first time users. Because
cytometry, ELISPOT is ideally su
ditions. These include defining (
establishing the fine–specificity
concentrations of the antigen in se
secretory products released by T
because T cells survive ELISPOT



"The quantification of single cell interferon-gamma (IFN-γ) release for assessing cellular immune responses using the Enzyme-linked immunospot (ELISPOT) assay is an invaluable technique in immunology."[1]

Source: 1 Sedegah M. The Ex Vivo IFN-γ Enzyme-Linked Immunospot (ELISpot) Assay Methods Mol Biol. 2015;1325:197-205; Humana Press; 3rd ed. 2018 edition (14 July 2018)

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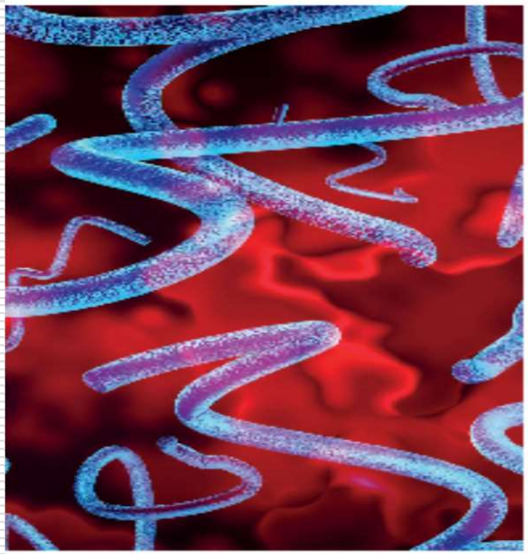
Armin Schwarzbach

Zelluläre Funktionstests in der Immunologie: LTT und EliSpot



Die Lyme-Borreliose ist in Europa und den USA die bedeutendste zeckenübertragene Infektionskrankheit mit zum Teil schwerwiegenden Verläufen. Die bisherigen serologischen Diagnoseverfahren sind begrenzt und vor allem in der Spätphase der Erkrankung nur noch wenig informativ. Eine T-Zell-Diagnostik mit dem Nachweis der Interferon-γ-Freisetzung, aber auch anderer Zytokine durch ELISPOT-Assays kann hier, ähnlich wie bereits bei der Diagnostik der Tuberkulose, eine hilfreiche Erweiterung sein.

Da die T-Zell-Antwort den dynamischen Verlauf eines Infektionsgeschehens differenzierter und präziser abbilden kann als die Bestimmung spezifischer Antikörper, kann der ELISPOT-Assay hier ein wichtiger Informationsgeber und Grundlage für eine gezielte Behandlung der Borreliose sein.

Anhand von Ergebnissen aus Routineuntersuchungen konnte gezeigt werden, dass insbesondere der Borrelien-ELISPOT der klassischen Methode des WesternBlots in Bezug auf Sensitivität und Aussagekraft deutlich überlegen ist. Im Gegensatz zur Serologie, die nur wenige dieser Kriterien erfasst, kann mit der Untersuchung der T-Zell-Reaktivität des Patienten auf Borrelienantigene in Form von Lymphozytentransformationstest (LTT) oder ELISPOT-Assays deutlich bessere Ergebnisse gewonnen werden.

Wofür also der LTT besonders eignet

Der LTT ist ein basaler Test für die Untersuchung der Proliferation, also die Vermehrung und das Wachstum, von Zellen. Hierzu werden die Zellen für drei Tage mit Mitogenen stimuliert. Mitogene sind hier polyklonale Aktivatoren, die B- und T-Zellen aktivieren. Hierbei kommen radioaktiv markierte Substanzen wie 3H-markiertes Thymidin messtechnisch zum Einsatz.

Aufgrund der hohen regulatorischen Anforderung im Umgang mit Radioaktivität und der stetig steigenden Entsorgungskosten sind radioaktiv basierte LTT aus heutiger Sicht für viele Labore nicht mehr sinnvoll und werden zunehmend durch andere Verfahren ersetzt.

Der LTT eignet sich als sogenannter Mitogen-LTT in der Diagnostik primärer Immundefekte, um eine generelle Übersicht über die Stimulierbarkeit der Lymphozyten zu erhalten sowie auch zum Nachweis einer antigen-spezifischen T-Zell-Antwort im Bereich der Typ-IV-Sensibilisierung wie zum Beispiel bei Nickel und anderen Metall- und weiteren Allergenen (z.B. Acrylate).

Wie also der ELISPOT etabliert hat

Der Enzyme-Linked Immuno SPOT (ELISPOT) Assay (entwickelt von Czerkinsky et al. 1983) ist eine sinnvolle, routinetaugliche und gut etablierte Methode zur Überwachung der Immunantworten bei Infektionen wie Tuberkulose, SARS CoV2, CMV, EBV, Borreliose, Ko-Erreger oder auch von Impfungen.

Der ELISPOT kann beschrieben werden als eine in-vitro-Konfrontation von Lymphozyten eines Patienten mit ausgewählten Antigenen von Pathogenen im Well

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Next generation EliSpot = Lyme iSpot

AUTOIMMUN DIAGNOSTIKA GMBH

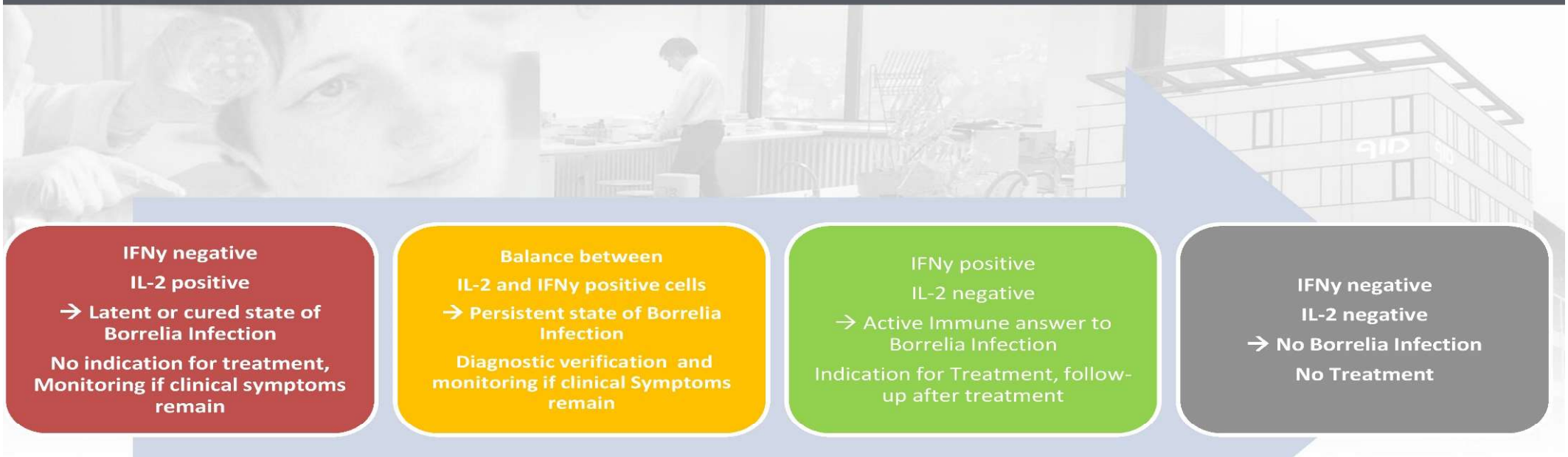
Next generation antigens for cellular immune response against Lyme coinfections in routine diagnostics

Rosemarie Preyer - Paris, ILADS May 20th 2017

Next generation EliSpot = Lyme iSpot

AUTOIMMUN DIAGNOSTIKA GMBH

Interpretation



IFNy negative
IL-2 positive
→ Latent or cured state of Borrelia Infection
No indication for treatment, Monitoring if clinical symptoms remain

Balance between
IL-2 and IFNy positive cells
→ Persistent state of Borrelia Infection
Diagnostic verification and monitoring if clinical Symptoms remain

IFNy positive
IL-2 negative
→ Active Immune answer to Borrelia Infection
Indication for Treatment, follow-up after treatment

IFNy negative
IL-2 negative
→ No Borrelia Infection
No Treatment

Beispiel: Lyme iSpot Ergebnis

Borrelia iSpot

1	**Borr.iSpot INF gamma Full Ag. +**	**5 SI**	**< 1**	**[..... *>**
1	**Borr.iSpot INF gamma OSP-Mix +**	**4 SI**	**< 1**	**[..... *>**
1	Borr.iSpot INF gamma LFA-1	1 SI	< 1	[.....*]
1	Borr.iSpot IL2 Full antigen	1 SI	< 1	[.....*]
1	Borr.iSpot IL2 OSP-Mix	1 SI	< 1	[.....*]
1	Borr.iSpot IL2 LFA-1	0 SI	< 1	[*.....]

0-1 = negative
2-3 = weak positive
> 3 = positive

The results of the EliSpot tests indicate current cellular activities against Borrelia burgdorferi.

Explanation of antigens:
Borrelia-burgdorferi Full Antigen: Borrelia burgdorferi B31 reference strain (Borrelia burgdorferi sensu stricto)
Borrelia-burgdorferi Peptide-Mix: OspA from Borrelia b. sensu stricto, Borrelia afzelii, Borrelia garinii + OspC native + DbpA recombinant.
Borrelia-burgdorferi LFA-1 (Lymphocyte Function Antigen 1) Own body protein + Borrelia burgdorferi sensu stricto (shared epitope). LFA1 can be associated with autoimmune diseases: collagenosis, Rheumatoid Arthritis, vasculitis. If positive or borderline positive look at: ANA, CCP-antibodies, ANCA.

Explanation i-Spot:
Interleukin 2 i-Spot can help to detect latent infections if results are positive or weak positive.

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Basisdiagnostik einer chronischen Borrelien-Infektion

1. Bestimmung der Borrelien-IgM- und IgG-Antikörper mittels Tickplex Basic (persister Formen)

2. Borrelien-Elispot / iSpot = aktuelle Aktivität / abgelaufene Aktivität

3. CD57+ T-Lymphozyten = chronische Aktivität

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LYME BORRELIOSE und CO-INFEKTIONEN

Borrelia burgdorferi

+ Babesien

+ Bartonellen

+ Ehrlichien

+ Rickettsien

+ Chlamydien

+ Mycoplasmen

+ Viren (EBV, CMV, HSV)

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Ehrlichiose/Anaplasmose

Erreger: Anaplasma phgocytophilum (gramnegativ, obligat intrazellulär in Granulozyten)

Übertragung: Ixodes ricinus

Wirtsspektrum: Wild-, Haus-, Nutztiere, Mensch

Klinik (Inkubationszeit: Tage bis 4 Wochen):
Grippeähnlicher Verlauf mit Fieber, „stechende, oft hinter den Augen befindliche" Kopf- und Muskelschmerzen, neurologische Beschwerden (Dauer 1 bis 60 Tage) bis hin zu letalem Ausgang, selten diffuse Hautrötungen auch der Handflächen und Fußsohlen, 2 aktuelle Fälle einer systemischen Sarkoidose (M. Boeck)!

Risikofaktoren: alte Menschen, schwere Grunderkrankungen, Immunsuppression

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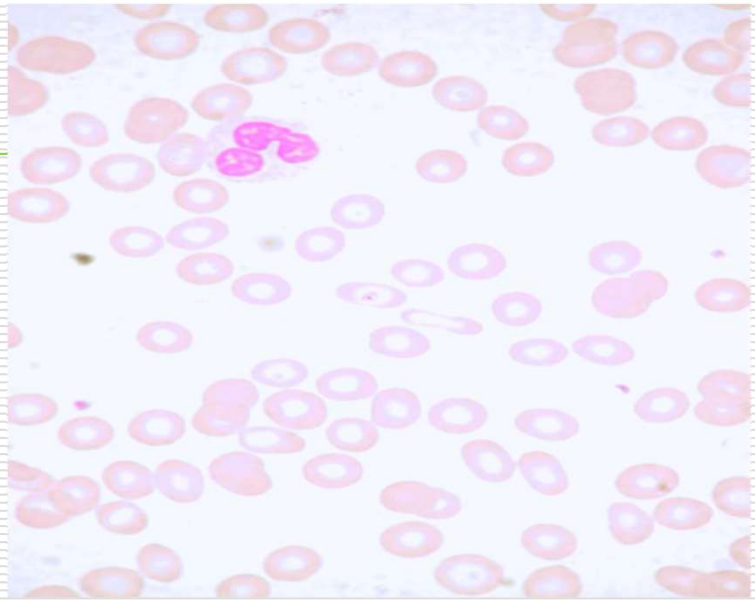
Babesiose



Erreger: Babesia microti, Babesia divergens

Übertragung: Ixodes ricinus, Bluttrans-fusionen

Wirtsspektrum: Wild-, Haus-, Nutztiere, Mensch

Klinik (Inkubationszeit 5 Tage – 9 Wochen):
Schwitzen, Nackensteifigkeit, Übelkeit, Erbrechen, Appetitlosigkeit, Müdigkeit, Schwächegefühl, permanente Erschöpfung noch verstärkt bei Anstrengungen, hämolytische Anämie, Hämoglobinurie, Fieber bis 40°C, Schüttelfrost, selten Hepatosplenomegalie, Muskelschmerzen, „schraubstockartige" Kopfschmerzen, Schwindel, Gerinnungsstörungen (Hyperkoagulopathien), Bauchschmerzen, emotionale Labilität, „Stumpfsinnigkeit", Nierenversagen, Dyspnoe Influenza-ähnliche Symptome bis lebensbedrohlich !

Risikofaktoren: Splenektomie, HIV, Immunsuppression, Organtransplantation, alte Menschen

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Bartonellose (Katzenkratzfieber)

Erreger: Bartonella henselae (gram-negativ, fakultativ intrazellulär in Endothelzellen/Erythrozyten) und/oder BLO = Bartonella like organisms

Übertragung: Katzen-Kratzwunden, Ixodes ricinus

Klinik (Inkubationszeit 3 – 38 Tage): Kopfschmerzen (80%), Müdigkeit (100%), Muskelzittern, Muskelzuckungen und Muskelkrämpfe, Schüttelfrost, morgendliches Fieber (30%, in Schüben bis zu 6 Wochen, sonst 1-3 Wochen), Lymphknotenschwellungen, Arthralgie (häufig), Myalgie, Schlaflosigkeit, Depressionen, Wutausbrüche, Verwirrtheit, Konzentrations- und Aufmerksamkeitsstörungen, Schwindel, Ängstlichkeit, Ruhelosigkeit, Gastritis, Darmbeschwerden, schmerzhafte Fußsohlen (besonders morgens!), sukutane Hautknoten an den Extremitäten, Haut-Striae

Schwere Verläufe: Endokarditis, Retinitis, Epileptische Anfälle, aseptische Meningitis, Hepatosplenomegalie

Risikofaktoren: Immunsuppression

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Rickettsiosen

Erreger: Rickettsia conori, R. rickettsii, R. helvetica, R. slovaca, R. prowazekii (nicht gram-färbbar, obligat intrazellulär in Endothelzellen)

Übertragung/Wirtsspektrum: Nagetiere, Hunde, Mensch, Ixodes ricinus

Klinik (Inkubationszeit 5 - 7 Tage):
Fieber, Lymphadenitis, Exanthem (roseolär bis makulopapulös)

Komplikationen (ca. 13%): Peri-/Myocarditis, Niereninsuffizienz, Pneumonie, Enzephalitis, gastrointestinale Blutungen, Anämie, Hepatitis, Myalgie

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EliSpot (zelluläre Analytik) ist verfügbar:

- **Borrelia burgdorferi**
- **Ehrlichia/Anaplasma**
- **Rickettsia**
- **Bartonella**
- **Babesia**
- Borrelia miyamotoi
- **Chlamydia pneumoniae**
- Chlamydia trachomatis
- Mycoplasma pneumoniae
- Yersinia enterocolitica
- **Epstein Barr Virus (EBV)**
- **Cytomegalovirus (CMV)**
- Herpes Simplex Virus 1 / 2
- Varicella Zoster Virus (VZV)
- **HHV-6**, HHV-7

Auch:
Candida
Aspergillus niger

Und auch:

Corona Virus iSpot
Aktuelle Infektion?
Zelluläre Immunität?

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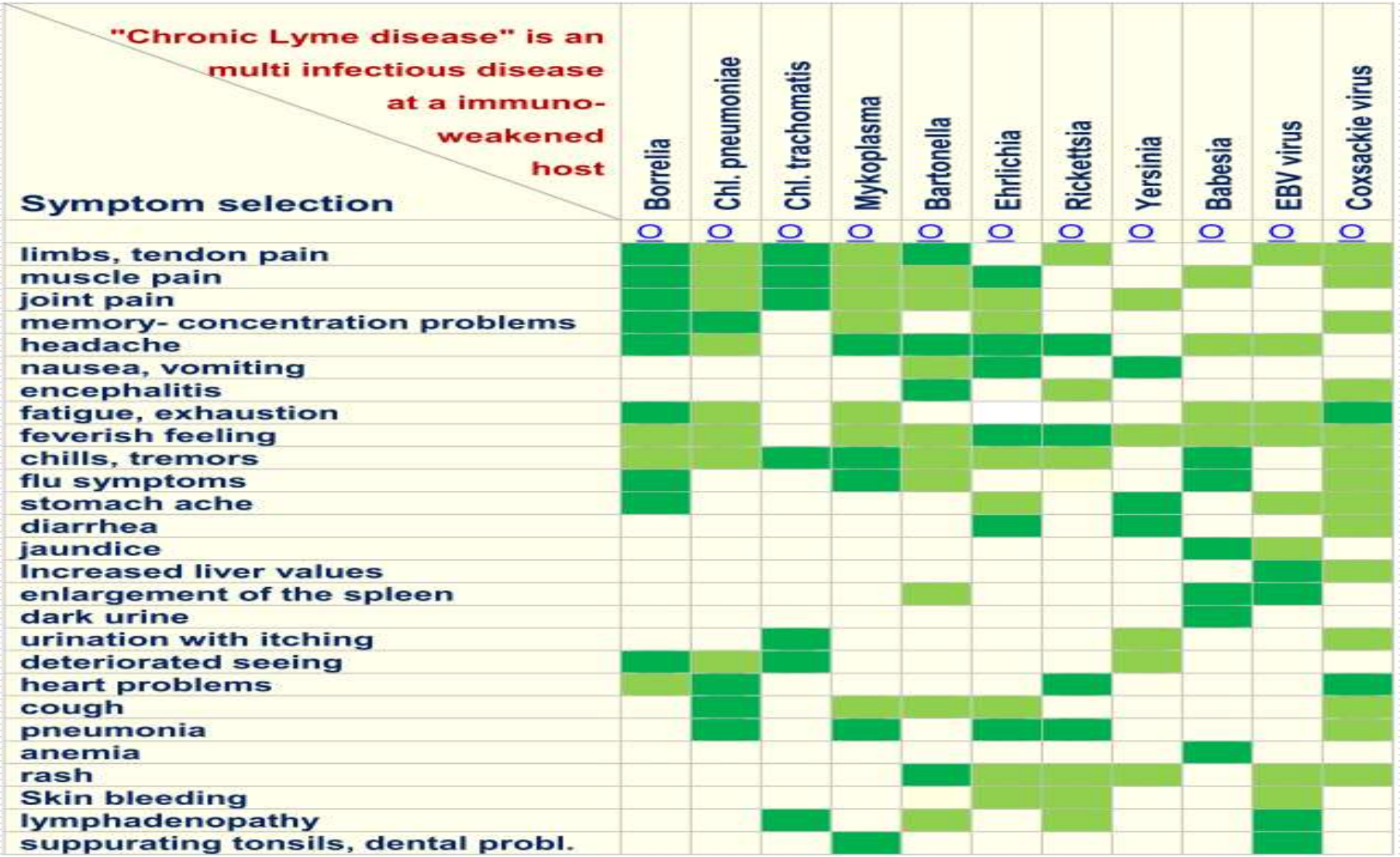
MULTIPLE SYMPTOME = MULTIPLE INFEKTIONEN ?



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Infektions-Checkliste für Patienten von Dr. Schwarzbach entwickelt: www.arminlabs.com

B.C.
Name, First name

15th Oct. 2010
Date

►	**Symptoms - Please tick the appropriate symptoms** (to be filled in by the patient)	X	**Score-Points** (to be filled in by the physician)	**Ranking**
01	Stomach-ache	X	Ehrlichia: **5**	**4**
02	Anaemia		Babesia: **5**	**4**
03	Diarhoea		Rickettsia: **5**	**4**
04	Fever or feverish feeling	X	Bartonella: **6**	**3**
05	Lack of concentration, memory disturbance, forgetfulness	X	Chl.pneumoniae: **8**	**1**
06	Encephalitis (Inflammation of the brain)		Chl.trachomatis: **3**	**6**
07	Yellowish colour of the skin (Jaundice)	X	Yersinia: **4**	**5**
08	Painful joints	X	Mykoplasma: **7**	**2**
09	General aches and pains	X	Coxsackie-Virus: **7**	**2**
10	Flu-like symptoms	X	EBV: **6**	**3**
11	Rash			
12	Petechiae			
13	Heart-problems	X		
14	Cough			
15	Headache	X		
16	Impaired liver function/ liver parameters			
17	Pneumonia			
18	Swollen or inflamed lymph nodes			
19	Tonsilitis			
20	Enlargement of the spleen (Splenomegaly)			
21	Fatigue / exhaustion	X		
22	Muscle pain	X		
23	Shivering	X		
24	Blurred vision			
25	Nausea, vomiting	X		
26	Dark urine	X		
27	Painful or ichty urinating			

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Pathologische Laborergebnisse Patientenbeispiel

		Results	Unit	Reference range
Borrelia burgdorferi Elispot				
Borrelia burgd. Fully Antigen	+	**4**	SI	< 2
Borrelia OSP-Mix (OSPA/OSPC/DbpA)	+	**3**	SI	< 2
Borrelia LFA-1		1	SI	< 2
CD 57 Flow Cytometry				
CD 57 positive NK-cells	-	**37**	/µl	100-360
Yersinia antibodies				
Yersinia-IgG-antibodies (EIA)	+	**1.9**	Ratio	<0.8=neg.; >1.1=pos.
Yersinia-IgA-antibodies (EIA)	+	**8.6**	Ratio	<0.8=neg.; >1.1=pos.
Yersinia Elispot				
Yersinia-Elispot	+	**20**	SI	< 2
Chlamydia pneumoniae antibodies				
Chlam.pneum.-IgG-antibodies (ELISA)	+	**1.2**	Ratio	<0.8=neg.;>1.1=pos.
Chlam.pneum.-IgA-antibodies (ELISA)	+	**3.5**	Ratio	<0.8=neg.;>1.1=pos.
Chlamydia pneumoniae Elispot				
Chlamydia pneumoniae-Elispot LTT	+	**18**	SI	< 2

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Pathologische Laborergebnisse Patientenbeispiel

		Results	Unit	Reference range
Mycoplasma pneumoniae antibodies				
Mycoplasma pneumoniae-IgG (EIA)	+	**1.1**	Ratio	< 0.8 = neg.; >1.1 = pos.
Mycoplasma pneumoniae IgA (EIA)	+	**2.0**	Ratio	< 0.8 = neg.; >1.1 = pos.
Coxsackie-Virus antibodies				
Coxsackie-Virus-IgG Type B1 (IFT)	+	**1:400**	Titer	< 1:100
Coxsackie-Virus-IgA Type B1 (IFT)	+	**1:100**	Titer	< 1:10
Rickettsia antibodies				
Rickettsia rickettsii IgG-antibodies	+	**1:256**	Titer	< 1:64
Rickettsia typhi IgG-antibodies		< 1:64	Titer	< 1:64
Epstein-Barr-Virus antibodies				
EBV-CA-IgG-antibodies (EIA)	+	**7.1**	Ratio	< 0.8=neg; >1.1=pos
EBV-Early antigen-antibodies (EIA)	+	**4.2**	Ratio	< 0.8=neg; >1.1=pos
EBV-CA-IgM-antibodies (EIA)		0.4	Ratio	< 0.8=neg; >1.1=pos
Epstein-Barr-Virus Elispot				
EBV-Elispot-LTT (lytic)	+	**17**	SI	< 2
EBV-Elispot-LTT (latent)	+	**8**	SI	< 2

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Zusammenfassung

- **!!! Alle Patienten haben MULTIPLE Infektionen !!!**
- **!!! Jeder Patient hat ein INDIVIDUELLES ERREGERPROFIL !!!**
- Alle genannten Erreger sind intrazellulär
- Reaktivierungen von Bakterien und weiteren…
- Opportunistischen Infektionen (Viren, Candida, Protozoen=Prof. Auer) ?
- Dominanz einer einzelnen Infektion ?
- Biofilme ?
- Persister Formen / Zysten/Pleomorphe Formen/Aberrante Formen ?

Auf jeden Fall 3 I´s diagnostizieren und therapieren:

- **Infektion + Immundysfunktion + Inflammation**

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Long Covid / Post Vac
Opportunisten mit Reaktivierungen von Bakterien und Viren

Dr. med. Armin Schwarzbach
Facharzt für Laboratoriumsmedizin

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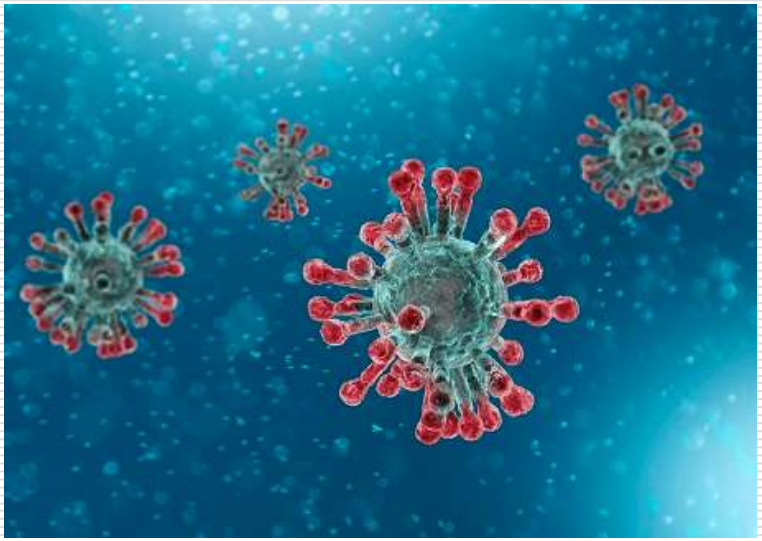
www.arminlabs.com



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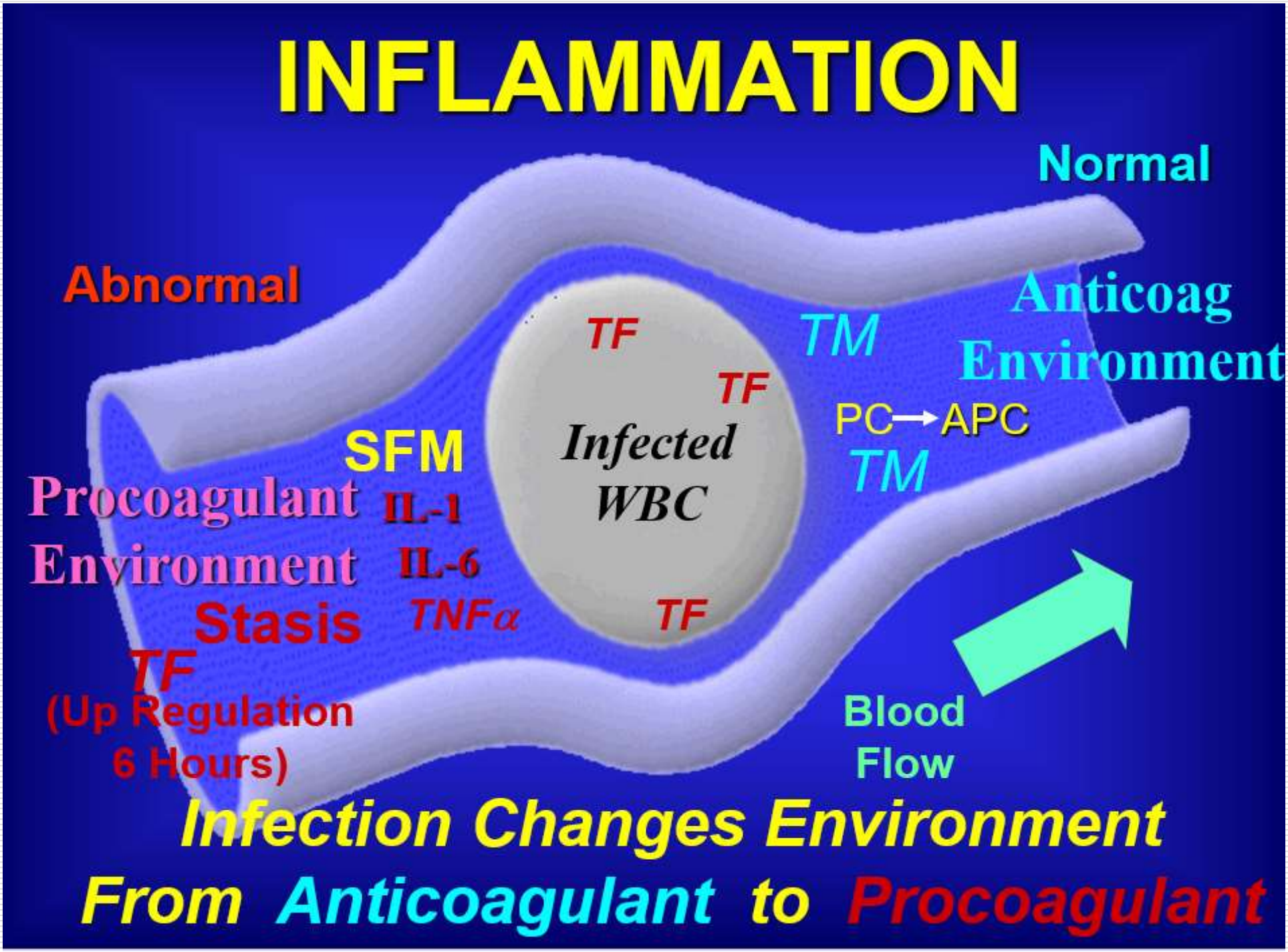
3 I´s in Diagnostik und Therapie



Source: David Berg Coagulation 202 Proteins and Coagulation Pathways, from The Role of Hypercoagulation and Biofilms in Chronic Illness Conference (2011)

S1 Segment infiziert Monozyten, die als Virus Reservoir dienen

These monocytes able to acquire such a proinflammatory phenotype can also act as a viral protein reservoir. "**The significance of these cells as a viral protein reservoir in PASC* is supported by our data reporting the presence of S1 protein within nonclassical monocytes**."

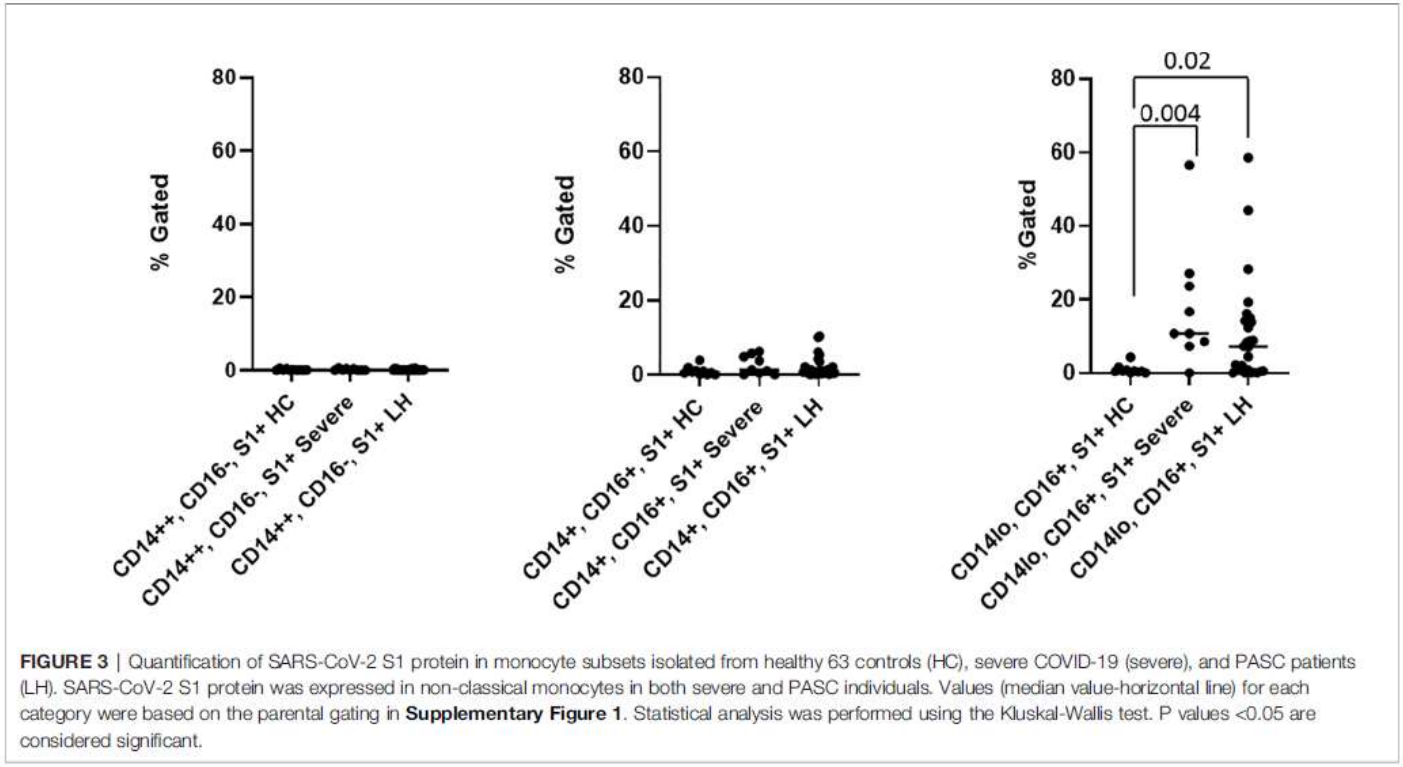


FIGURE 3 | Quantification of SARS-CoV-2 S1 protein in monocyte subsets isolated from healthy 63 controls (HC), severe COVID-19 (severe), and PASC patients (LH). SARS-CoV-2 S1 protein was expressed in non-classical monocytes in both severe and PASC individuals. Values (median value-horizontal line) for each category were based on the parental gating in **Supplementary Figure 1**. Statistical analysis was performed using the Kluskal-Wallis test. P values <0.05 are considered significant.

***PASC = post-acute sequelae of COVID-19**

Source: https://pubmed.ncbi.nlm.nih.gov/35082777/

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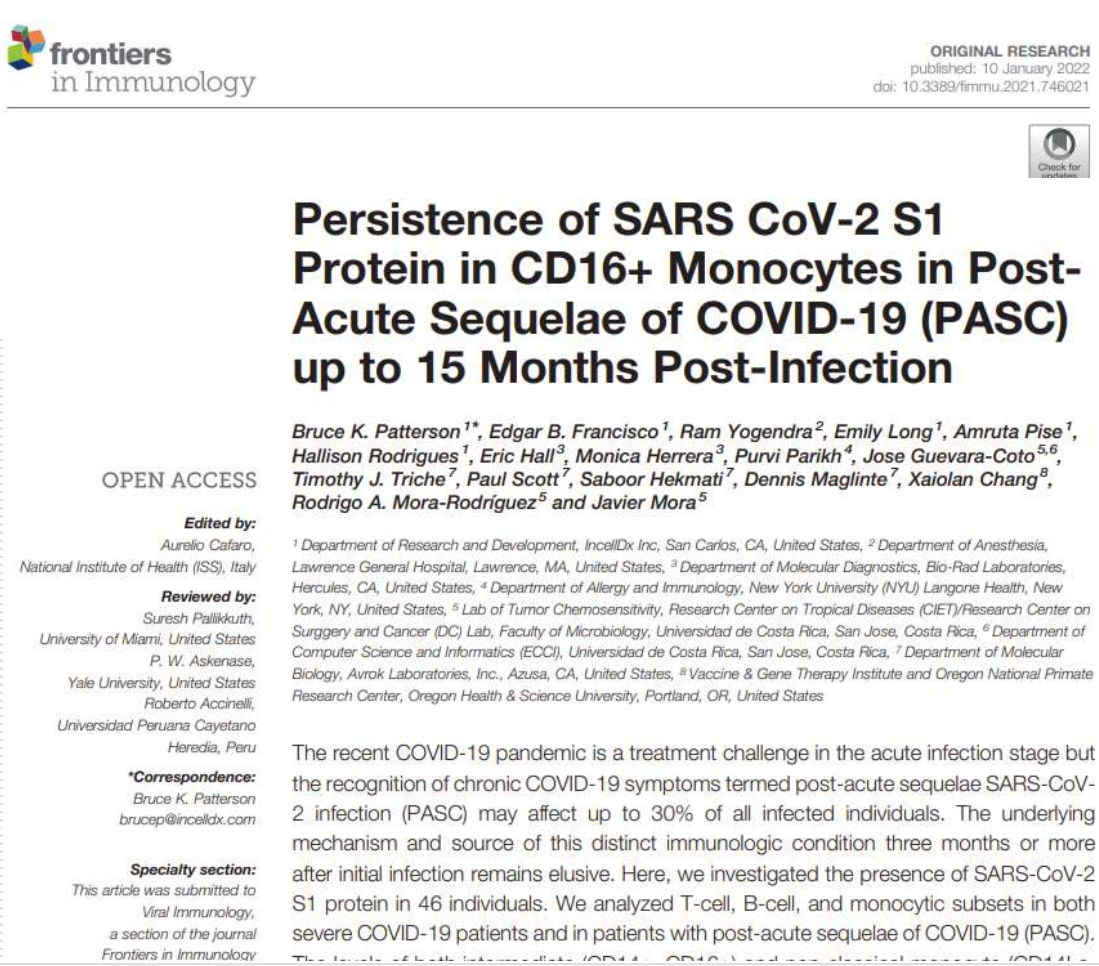
S1 protein bei Post-COVID Patienten bis zu 15 Monaten nach Infektion nachweisbar



frontiers in Immunology

ORIGINAL RESEARCH
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Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection

Bruce K. Patterson[1], Edgar B. Francisco[1], Ram Yogendra[2], Emily Long[1], Amruta Pise[1], Hallison Rodrigues[1], Eric Hall[3], Monica Herrera[3], Purvi Parikh[4], Jose Guevara-Coto[5,6], Timothy J. Triche[7], Paul Scott[7], Saboor Hekmati[7], Dennis Maglinte[7], Xaiolan Chang[8], Rodrigo A. Mora-Rodríguez[5] and Javier Mora[5]*

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The recent COVID-19 pandemic is a treatment challenge in the acute infection stage but the recognition of chronic COVID-19 symptoms termed post-acute sequelae SARS-CoV-2 infection (PASC) may affect up to 30% of all infected individuals. The underlying mechanism and source of this distinct immunologic condition three months or more after initial infection remains elusive. Here, we investigated the presence of SARS-CoV-2 S1 protein in 46 individuals. We analyzed T-cell, B-cell, and monocytic subsets in both severe COVID-19 patients and in patients with post-acute sequelae of COVID-19 (PASC).

"This means the body has literally been sprayed with the virus and it spends 15 months, in a sense, trying to clean out the spike protein from our tissues. **No wonder people have Long-COVID syndrome."**
Board-certified internist and cardiologist Dr. Peter McCullough, https://www.facebook.com/watch/?v=1149250505479349, minute 6.18

Source: Patterson BK, Francisco EB, Yogendra R, Long E, Pise A, Rodrigues H, Hall E, Herrera M, Parikh P, Guevara-Coto J, Triche TJ, Scott P, Hekmati S, Maglinte D, Chang X, Mora-Rodríguez RA, Mora J. Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection. Front Immunol. 2022 Jan 10;12:746021.

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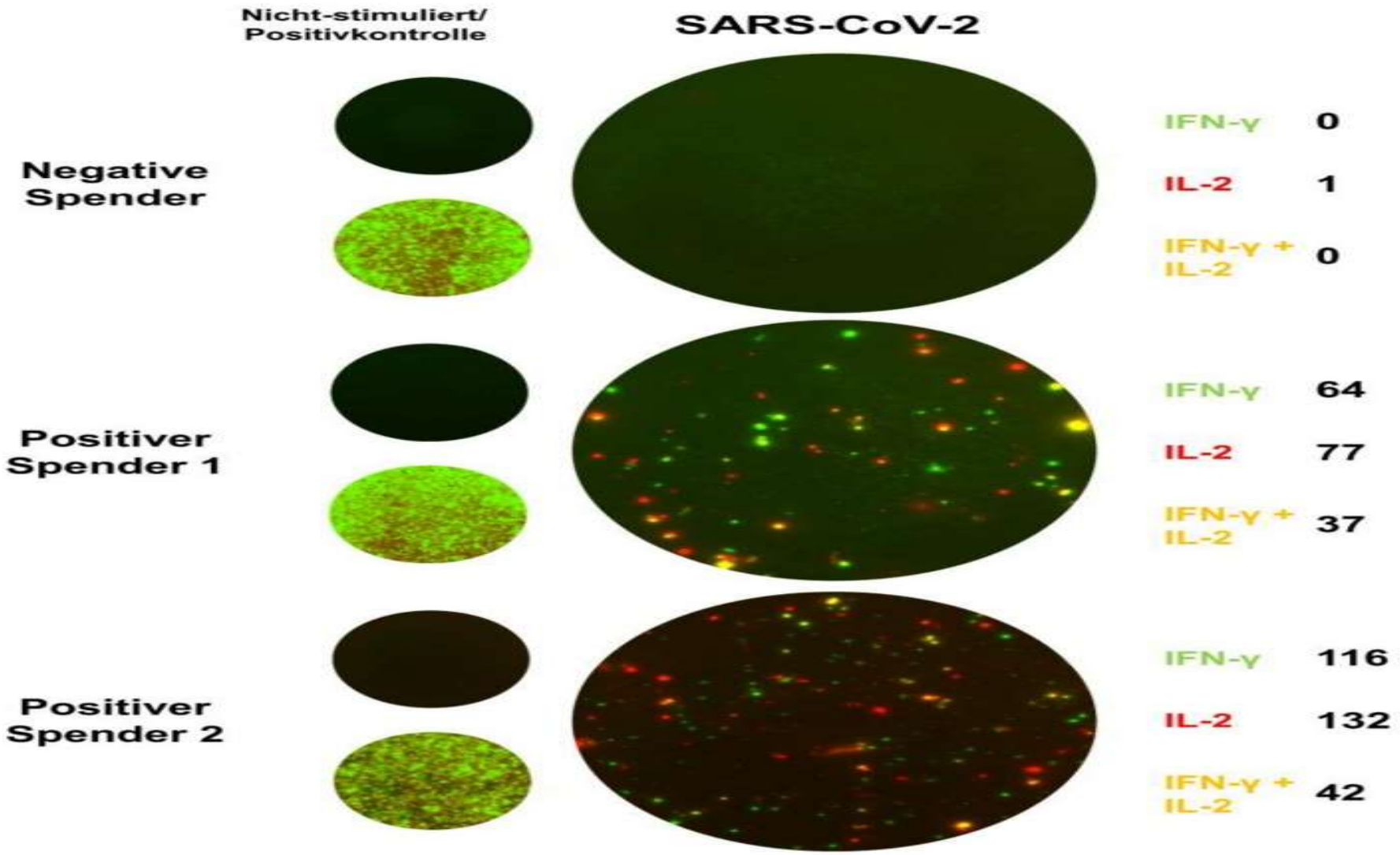
Zelluläre Analytik mittels Covid iSpot: Interferon Gamma vs. Interleukin 2



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Beispiel Covid iSpot: Interleukin 2 ohne Interferon Gamma nach SARS CoV 2 Infektion oder Impfung

Untersuchung	Ergebnis	Einheit	Normbereich	Grafik
SARS-CoV-2 iSpot *				
1 SARS-CoV-2 iSpot				
1 Sars-CoV-2 iSpot INF gamma	1	SI		
1 Pan Corona iSpot INF gamma	2	SI		

SI = Stimulations Index

< 5 = negativ
5-6 = grenzwertig
ab 7 = positiv

1 Sars-CoV-2 iSpot IL2	7	SI		
1 Pan Corona iSpot IL2	1	SI		

SI = Stimulations Index

< 2 = negativ
2-3 = grenzwertig
ab 4 = positiv

Mittels CoV-iSpot Hinweis auf eine zelluläre Immunantwort gegen SARS-CoV-2 (SARS-CoV-2-Peptid-Mix).

Erläuterungen CoV-iSpot:
Ein alleiniger Nachweis von Interferon Gamma (IFN-G) aktivierten T-Zellen weist auf eine aktive Immunreaktion im Rahmen einer SARS-CoV-2-Infektion oder nach Impfung hin. Eine nahezu gleiche Anzahl an IFN-G und IL-2 (Interleukin-2) produzierenden Zellen spricht für eine persistierende Infektion SARS-CoV-2 oder z.n. Impfung. Kein Nachweis von IFN-G-produzierenden Effektor Zellen bei gleichzeitig positivem Nachweis von IL-2-produzierenden Memory-Zellen spricht für eine abgelaufene SARS-CoV-2-Infektion oder Impfung.

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Direktnachweis mittels RT-PCR dar.
Antikörper-Testungen dienen der Abgrenzung gegenüber Infektionen mit anderen Erregern.
Literaturhinweise finden Sie unter: www.arminlabs.com/corona

SARS-CoV-2 iSpot

1	SARS-CoV-2 iSpot	
1	Sars-CoV-2 iSpot INF gamma	8 SI
1	Pan Corona iSpot INF gamma	8 SI

< 5 = negativ
5-6 = grenzwertig
ab 7 = positiv

1	Sars-CoV-2 iSpot IL2	10 SI
1	Pan Corona iSpot IL2	1 SI

< 2 = negativ
2-3 = grenzwertig
ab 4 = positiv

Mittels CoV-iSpot Hinweis auf eine zelluläre Immunantwort gegen SARS-CoV-2 (SARS-CoV-2-Peptid-Mix).

Mittels CoV-iSpot Hinweis auf eine zelluläre Immunantwort gegen weitere Coronaviridae inkludierend SARS-CoV-2 (PAN-Corona-Peptid-Mix).

Erläuterungen CoV-iSpot:
Ein alleiniger Nachweis von Interferon Gamma (IFN-G) aktivierten T-Zellen weist auf eine aktive Immunreaktion im Rahmen einer SARS-CoV-2-Infektion hin.
Eine nahezu gleiche Anzahl an IFN-G und IL-2 (Interleukin-2) produzierenden Zellen spricht für eine persistierende Infektion mit SARS-CoV-2.
Kein Nachweis von IFN-G-produzierenden Effektor Zellen bei gleichzeitig positivem Nachweis von IL-2-produzierenden Memory-Zellen spricht für eine abgelaufene SARS-CoV-2-Infektion.
Der alleinige positive Nachweis von IL-2-aktivierten T-Zellen weist auf ein Vorhandensein von Gedächtniszellen als Hinweis auf eine zurückliegende Infektion mit

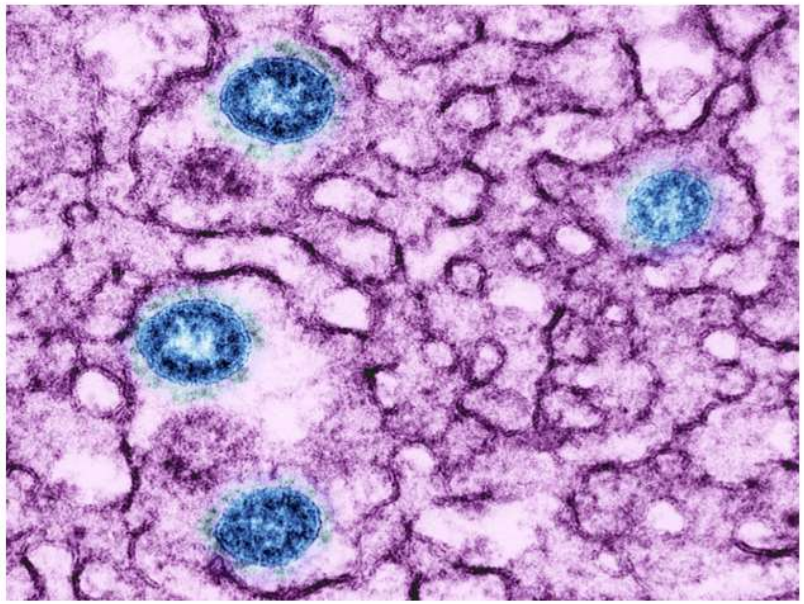
Studie Aug. 2022 untersucht die Verbindung zwischen Long Covid und Herpes Viren

NEWS | 25 August 2022

Could long COVID be linked to herpes viruses? Early data offer a hint

Low cortisol levels and herpes-virus reactivation are associated with prolonged COVID-19 symptoms, preliminary research suggests.

Emily Waltz



Particles of the SARS-CoV-2 virus (blue) inside an infected cell. Credit: NIH/SPL

"Most strikingly, the study found that in the long-COVID group, **levels of cortisol**, a stress hormone that has a role in regulating inflammation, blood sugar levels and sleep cycles, **were about 50% lower than in healthy participants**. The authors also found hints that in people with long COVID, **Epstein–Barr virus**, which can cause mononucleosis, and **varicella-zoster virus**, which causes chickenpox and shingles, might recently have been '**reactivated**'. **Both** of these viruses are in the herpes family, persist indefinitely in the body after infection and **can start to multiply again after a period of quiescence.**

Source: https://www.nature.com/articles/d41586-022-02296-5#:~:text=Low%20cortisol%20levels%20and%20herpes,19%20symptoms%2C%20preliminary%20research%20suggests.&text=Researchers%20looking%20for%20biological%20drivers,of%20a%20stress%20hormone1.

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Epstein Barr Virus (EBV)

Virus: Epstein Barr Virus (obligate intrazelluläre), Doppelstrang DNS virus, gehört zur Herpesvirus-Gruppe, "Mononukleose"

Übertragung: "kissing disease", Speichel, aus gleichem Glas trinken, Zahnbürste, Blut, sexuell, Bluttransfusion, Organtransplantation

Symptome (Inkbationszeit mehrere Wochen): **Fatique**, Fieber, Grippe-ähnliche Symptome, Übelkeit, Appetitlosigkeit, Lymphknotenschwellungen, Hautrötung, Rachenentzündung, Schwächegefühle, Muskelentzündung

Komplikationen: Milzvergrösserung, Leberschwellung, Non-Hodgkin Lymphome, **Multiple Sklerose (neurotrop), CFS (Chronic Fatigue Syndrom)/Mitochondropathie, Colitis/Leaky Gut, Nahrungsmittelunverträglichkeiten**

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"Long COVID Symptome vermutlich durch Epstein-Barr Virus Reaktivierung"

› Pathogens. 2021 Jun 17;10(6):763. doi: 10.3390/pathogens10060763.

Investigation of Long COVID Prevalence and Its Relationship to Epstein–Barr Virus Reactivation

Jeffrey E Gold [1], Ramazan A Okyay [2], Warren E Licht [3], David J Hurley [4]

Affiliations + expand

PMID: 34204243 PMCID: PMC8233978 DOI: 10.3390/pathogens10060763

Free PMC article

Abstract

Coronavirus disease 2019 (COVID-19) patients sometimes experience long-term symptoms following resolution of acute disease, including fatigue, brain fog, and rashes. Collectively these have become known as long COVID. Our aim was to first determine long COVID prevalence in 185 randomly surveyed COVID-19 patients and, subsequently, to determine if there was an association between occurrence of long COVID symptoms and reactivation of Epstein-Barr virus (EBV) in 68 COVID-19 patients recruited from those surveyed. We found the prevalence of long COVID symptoms to be 30.3% (56/185), which included 4 initially asymptomatic COVID-19 patients who later developed long COVID symptoms. Next, we found that 66.7% (20/30) of long COVID subjects versus 10% (2/20) of control subjects in our primary study group were positive for EBV reactivation based on positive titers for EBV early antigen-diffuse (EA-D) IgG or EBV viral capsid antigen (VCA) IgM. The difference was significant ($p < 0.001$, Fisher's exact test). A similar ratio was observed in a secondary group of 18 subjects 21-90 days after testing positive for COVID-19, indicating reactivation may occur soon after or concurrently with COVID-19 infection. These findings suggest that many long COVID symptoms may not be a direct result of the SARS-CoV-2 virus but may be the result of COVID-19 inflammation-induced EBV reactivation.

We found that **66.7% (20/30) of long-term long COVID subjects versus 10% (2/20) of long-term control subjects were positive** for EBV reactivation

"We found similar rates of EBV reactivation in those who had long COVID symptoms for months, as in those with long COVID symptoms that began just weeks after testing positive for COVID-19," said coauthor David J. Hurley, PhD, a professor and molecular microbiologist at the University of Georgia. "**This indicated to us that EBV reactivation likely occurs simultaneously or soon after COVID-19 infection**."

Source: https://pubmed.ncbi.nlm.nih.gov/34204243/; https://www.news-medical.net/news/20210623/Epstein-Barr-virus-reactivation-may-be-the-cause-of-long-COVID-symptoms.aspx; https://world.org/EBV/

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Epstein-Barr virus (EBV)-Reaktivierung aufgrund Inflammation nach Coronavirus-Infektionen kann die Ursache von Long Covid sein

pathogens

MDPI

Article

Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation

Jeffrey E. Gold [1,*], Ramazan A. Okyay [2], Warren E. Licht [3] and David J. Hurley [4]

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3 Warren Alpert Medical School of Brown University, Providence, RI 02903, USA; warren.licht@brownphysicians.org
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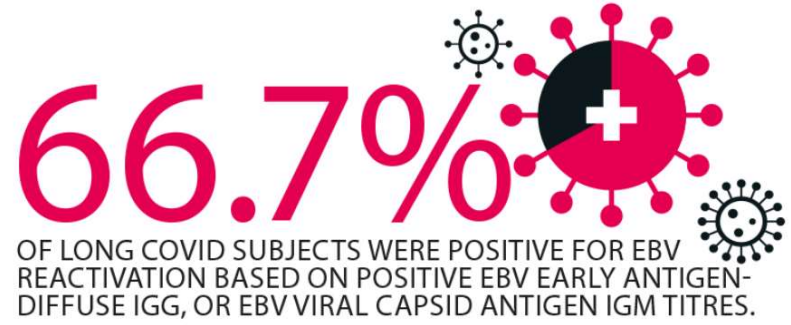
* Correspondence: jeff_gold@world.org

Abstract: Coronavirus disease 2019 (COVID-19) patients sometimes experience long-term symptoms following resolution of acute disease, including fatigue, brain fog, and rashes. Collectively these have become known as long COVID. Our aim was to first determine long COVID prevalence in 185 randomly surveyed COVID-19 patients and, subsequently, to determine if there was an association between occurrence of long COVID symptoms and reactivation of Epstein–Barr virus (EBV) in 68 COVID-19 patients recruited from those surveyed. We found the prevalence of long COVID symptoms to be 30.3% (56/185), which included 4 initially asymptomatic COVID-19 patients who later developed long COVID symptoms. Next, we found that 66.7% (20/30) of long COVID subjects versus 10% (2/20) of control subjects in our primary study group were positive for EBV reactivation based on positive titers for EBV early antigen-diffuse (EA-D) IgG or EBV viral capsid antigen (VCA) IgM. The difference was significant ($p < 0.001$, Fisher's exact test). A similar ratio was observed in a secondary group of 1
may occur soon afte
long COVID sympto
COVID-19 inflamma

check for updates

Citation: Gold, J.E.; Okyay, R.A.; Licht, W.E.; Hurley, D.J. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. *Pathogens* **2021**, *10*, 763. https://doi.org/10.3390/



Lead study author Jeffrey E Gold said: "We ran EBV antibody tests on recovered COVID-19 patients, comparing EBV reactivation rates of those with long COVID symptoms to those without long COVID symptoms. The majority of those with long COVID symptoms were positive for EBV reactivation, yet only 10% of controls indicated reactivation.

… In a subset of 68 COVID-19 patients randomly selected from those surveyed, 66.7% of long COVID subjects versus 10% of controls were positive for EBV reactivation based on positive **EBV early antigen**-diffuse **IgG**, or **EBV viral capsid antigen IgM** titres."

Source: https://thebiomedicalscientist.net/news/long-covid-linked-epstein-barr-virus, https://www.mdpi.com/2076-0817/10/6/763

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Studie Juli 2022: Der Einfluss einer EBV-Reaktivierung auf die Entwicklung von Long COVID

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CSH Cold Spring Harbor Laboratory BMJ Yale

Impact of Pre-Existing Chronic Viral Infection and Reactivation on the Development of Long COVID

Michael J. Peluso, Tyler-Marie Deveau, Sadie E. Munter, Dylan Ryder, Amanda Buck, Gabriele Beck-Engeser, Fay Chan, Scott Lu, Sarah A. Goldberg, Rebecca Hoh, Viva Tai, Leonel Torres, Nikita S. Iyer, Monika Deswal, Lynn H. Ngo, Melissa Buitrago, Antonio Rodriguez, Jessica Y. Chen, Brandon C. Yee, Ahmed Chenna, John W. Winslow, Christos J. Petropoulos, Amelia N. Deitchman, Joanna Hellmuth, Matthew A. Spinelli, Matthew S. Durstenfeld, Priscilla Y. Hsue, J. Daniel Kelly, Jeffrey N. Martin, Steven G. Deeks, Peter W. Hunt, Timothy J. Henrich

doi: https://doi.org/10.1101/2022.06.21.22276660

In a cohort of 280 adults with prior SARS-CoV-2 infection, we observed that LC symptoms such as fatigue and neurocognitive dysfunction at a median of 4 months following initial diagnosis were independently associated with serological evidence of recent EBV reactivation

ABSTRACT

The presence and reactivation of chronic viral infections such as Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human immunodeficiency virus (HIV) have been proposed as potential contributors to Long COVID (LC), but studies in well-characterized post-acute cohorts of individuals with COVID-19 over a longer time course consistent with current case definitions of LC are limited. In a cohort of 280 adults with prior SARS-CoV-2 infection, we observed that LC symptoms such as fatigue and neurocognitive dysfunction at a median of 4 months following initial diagnosis were independently associated with serological evidence of recent EBV reactivation (early antigen-D [EA-D] IgG positivity) or high nuclear antigen IgG levels, but not with ongoing EBV viremia. Evidence of EBV reactivation (EA-D IgG) was most strongly associated with fatigue (OR 2.12). Underlying HIV infection was also independently associated with neurocognitive LC (OR 2.5). Interestingly, participants who had serologic evidence of prior CMV infection were less likely to develop neurocognitive LC (OR 0.52) and tended to have less severe (>5 symptoms reported) LC (OR 0.44). Overall, these findings suggest differential effects of chronic viral co-infections on the likelihood of developing LC and predicted distinct syndromic patterns. Further assessment during the acute phase of COVID-19 is warranted.

SUMMARY The authors found that Long COVID symptoms in a post-acute cohort were associated with serological evidence of recent EBV reactivation and pre-existing HIV infection when adjusted for participant factors, sample timing, comorbid conditions and prior hospitalization, whereas underlying CMV infection was associated with a decreased risk of Long COVID.

Source: https://www.medrxiv.org/content/10.1101/2022.06.21.22276660v1

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"Antikörper gegen SARS-CoV-2 Antigene und Herpesviridae lytische Antigene sind bei Patienten mit Long COVID erhöht"

› medRxiv. 2022 Aug 10;2022.08.09.22278592. doi: 10.1101/2022.08.09.22278592. Preprint

Distinguishing features of Long COVID identified through immune profiling

Jon Klein, Jamie Wood, Jillian Jaycox, Peiwen Lu, Rahul M Dhodapkar, Jeff R Gehlhausen, Alexandra Tabachnikova, Laura Tabacof, Amyn A Malik, Kathy Kamath, Kerrie Greene, Valter Silva Monteiro, Mario Peña-Hernandez, Tianyang Mao, Bornali Bhattacharjee, Takehiro Takahashi, Carolina Lucas, Julio Silva, Dayna Mccarthy, Erica Breyman, Jenna Tosto-Mancuso, Yile Dai, Emily Perotti, Koray Akduman, Tiffany J Tzeng, Lan Xu, Inci Yildirim, Harlan M Krumholz, John Shon, Ruslan Medzhitov, Saad B Omer, David van Dijk, Aaron M Ring, David Putrino, Akiko Iwasaki

PMID: 35982667 PMCID: PMC9387160 DOI: 10.1101/2022.08.09.22278592
Free PMC article

Abstract

SARS-CoV-2 infection can result in the development of a constellation of persistent sequelae following acute disease called post-acute sequelae of COVID-19 (PASC) or Long COVID [1-3]. Individuals diagnosed with Long COVID frequently report unremitting fatigue, post-exertional malaise, and a variety of cognitive and autonomic dysfunctions [1-3]; however, the basic biological mechanisms responsible for these debilitating symptoms are unclear. Here, 215 individuals were included in an exploratory, cross-sectional study to perform multi-dimensional immune phenotyping in conjunction with machine learning methods to identify key immunological features distinguishing Long COVID. Marked differences were noted in specific circulating myeloid and lymphocyte populations relative to matched control groups, as well as evidence of elevated humoral responses directed against SARS-CoV-2 among participants with Long COVID. Further, unexpected increases were observed in antibody responses directed against non-SARS-CoV-2 viral pathogens, particularly Epstein-Barr virus. Analysis of circulating immune mediators and various hormones also revealed pronounced differences, with levels of cortisol being uniformly lower among participants with Long COVID relative to matched control groups. Integration of immune phenotyping data into unbiased machine learning models identified significant distinguishing features critical in accurate classification of Long COVID, with decreased levels of cortisol being the most significant individual predictor. These findings will help guide additional studies into the pathobiology of Long COVID and may aid in the future development of objective biomarkers for Long COVID.

Extensive immune profiling: "The multi-dimensional immune profiling of Long COVID participants also revealed **elevated humoral immune responses to non-SARS-CoV-2 viral antigens, particularly EBV**."

Source: https://pubmed.ncbi.nlm.nih.gov/35982667/; https://www.nature.com/articles/d41586-022-02296-5#:~:text=Low%20cortisol%20levels%20and%20herpes,19%20symptoms%2C%20preliminary%20research%20suggests.&text=Researchers%20looking%20for%20biological%20drivers,of%20a%20stress%20hormone1.

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Beispiel Laborbericht: Sehr hoher Wert EBV lytisches Antigen bei einem Patienten mit Long COVID

EBV EliSpot (lytic+latent)

1 EBV EliSpot (lytic)	**!**	**657 SI**	
0-1	= negative		
2-3	= weak positive		
> 3	= positive		
1 EBV EliSpot (latent)	**!**	**65 SI**	
0-1	= negative		
2-3	= weak positive		
> 3	= positive		

The result of the EliSpot test indicates current celluar activity against Epstein-Barr-Virus (EBV).

Explanation of EBV antigens:
EBV-lytic antigen: sign for replication of infectious EBV virions
EBV-latent antigen: sign for EBV latency with no production of infectious EBV virions

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EBV-Early Antigen als Marker einer EBV-Reaktivierung mittels Microarray bei Long Covid

Viral capsid antigen (VCA), early antigen (EA), & Epstein-Barr Nuclear Antigen (EBNA)

Epstein-Barr-Virus Immuno-Array			
EBV VCA p18 IgG	+	positive	negative
EBV VCA p23 IgG	+	positive	negative
EBV EA p54 IgG		negative	negative
EBV EA p138	+	positive	negative
EBV EBNA-1 IgG	+	positive	negative
EBV VCA p18 IgM		negative	negative
EBV VCA p23 IgM		negative	negative
EBV EA p54 IgM	+	positive	negative
EBV EA p138 IgM		negative	negative

The specific EBV-IgG/IgM-, EBV-Early Antigen-antibodies and EBV-EBNA-antibodies indicate humoral immune response against Epstein Barr Virus (former or reactivated or EBV-infection in convalescence?).

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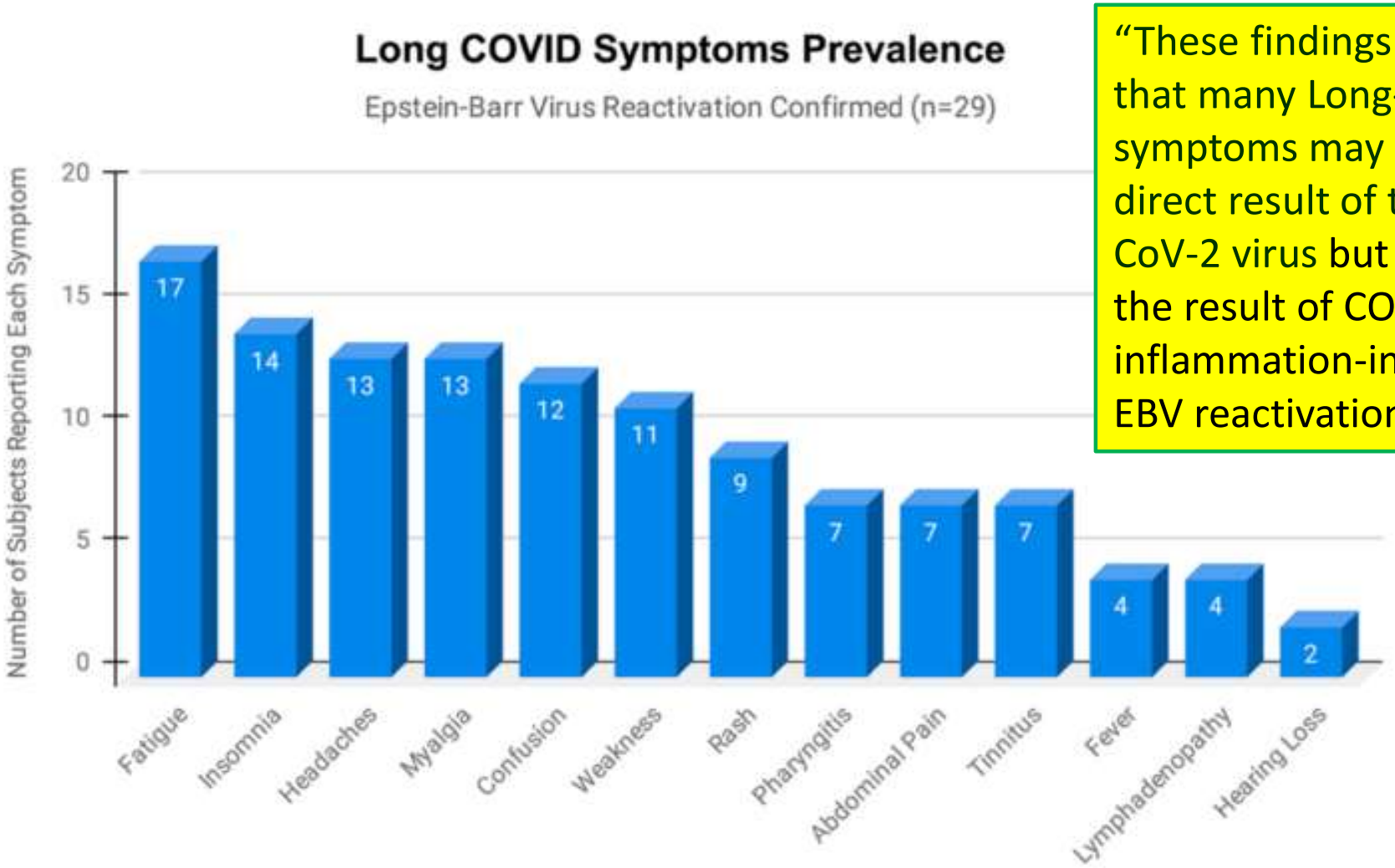
Long COVID Symptome korrelieren mit ursächlich Inflammation-induzierter EBV-Reaktivierung



"These findings suggest that many Long-COVID symptoms may not be a direct result of the SARS-CoV-2 virus but may be the result of COVID-19 inflammation-induced EBV reactivation."

Source: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8233978/

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Aber auch: EBV-Infektionen erhöhen das Risiko einer potentiellen Infektion mit SARS-CoV-2

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology®

VIRUS-CELL INTERACTIONS

Epstein-Barr Virus Lytic Replication Induces ACE2 Expression and Enhances SARS-CoV-2 Pseudotyped Virus Entry in Epithelial Cells

Dinesh Verma,[a] Trenton Mel Church,[a] Sankar Swaminathan[a,b]

[a]Division of Infectious Diseases, Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA
[b]Division of Microbiology and Immunology, Department of Pathology, University of Utah School of Medicine, Salt Lake City, Utah, USA

ABSTRACT Understanding factors that affect the infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is central to combatting coronavirus disease 2019 (COVID-19). The virus surface spike protein of SARS-CoV-2 mediates viral entry into cells by binding to the ACE2 receptor on epithelial cells and promoting fusion. We found that Epstein-Barr virus (EBV) induces ACE2 expression when it enters the lytic replicative cycle in epithelial cells. By using vesicular stomatitis virus (VSV) particles pseudotyped with the SARS-CoV-2 spike protein, we showed that lytic EBV replication enhances ACE2-dependent SARS-CoV-2 pseudovirus entry. We found that the ACE2 promoter contains response elements for Zta, an EBV transcriptional activator that is essential for EBV entry into the lytic cycle of replication. Zta preferentially acts on methylated promoters, allowing it to reactivate epigenetically silenced EBV promoters from latency. By using promoter assays, we showed that Zta directly activates methylated ACE2 promoters. Infection of normal oral keratinocytes with EBV leads to lytic replication in some of the infected cells, induces ACE2 expression, and enhances SARS-CoV-2 pseudovirus entry. These data suggest that subclinical EBV replication and lytic gene expression in epithelial cells, which is ubiquitous in the human population, may enhance the efficiency and extent of SARS-CoV-2 infection of epithelial cells by transcriptionally activating ACE2 and increasing its cell surface expression.

IMPORTANCE SARS-CoV-2, the coronavirus responsible for COVID-19, has caused a pandemic leading to millions of infections and deaths worldwide. Identifying the factors governing susceptibility to SARS-CoV-2 is important in order to develop strategies to prevent SARS-CoV-2 infection. We show that Epstein-Barr virus, which infects

"Epstein-Barr virus, which infects and persists in 90% of adult humans, **increases susceptibility of epithelial cells to infection by SARS-CoV-2**. EBV, when it reactivates from latency or infects epithelial cells, increases expression of ACE2, the cellular receptor for SARS-CoV-2, enhancing infection by SARS-CoV-2. Inhibiting EBV replication with antivirals may therefore decrease susceptibility to SARS-CoV-2 infection.

Source: https://journals.asm.org/doi/pdf/10.1128/JVI.00192-21/

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Verschiedene Aspekte sprechen für eine EBV-Reaktivierung in Long COVID

- **Eine EBV Infektion kann reaktiviert sein bei SARS-CoV-2/COVID[1]**
- **Eine chronische EBV Infektion kann verstärkt werden durch SARS-CoV-2/COVID[2]**
- **EBV-Infektionen, ob dominierend oder chronisch oder reaktiviert, können die Wahrscheinlichkeit erhöhen einer Infektion mit COVID[3]**
- **Immunsuppression spielt eine Rolle: "**Recent studies suggest the possible interaction between SARS-CoV-2 and EBV. .. One possible mechanism involves a decrease in CD8+ cells which are the primary cells responsible for immunity against EBV infection … A correlation between reduced $CD8^+$ T cells and NK counts, EBV DNA levels and COVID-19 severity was observed."
- **Medikamente gegen COVID können zu einer EBV Reaktivierung führen[5]:** "Drugs used in the treatment of COVID-19 may also play a major role in altering immune responses by means of regulating intracellular signaling pathways, thus prompting the reactivation process of EBV. The use of high-dose corticosteroids has been stated as a risk factor for herpes virus reactivation"[5]

Source: 1. https://pubmed.ncbi.nlm.nih.gov/34204243/; 2. https://pubmed.ncbi.nlm.nih.gov/35872097/; *3. https://journals.asm.org/doi/pdf/10.1128/JVI.00192-21/; 4. https://pubmed.ncbi.nlm.nih.gov/35505635/; 5. https://pubmed.ncbi.nlm.nih.gov/35505635/*

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Epstein Barr Virus, Cytomegalie-Virus und Anfälligkeit für Multiple Sklerose

Eine multiethnische Studie

1. Annette Langer-Gould, MD, Dr, Jun Wu, MD, MS, Robyn Lucas, Dr, Jessica Smith, MPH, Edlin Gonzales, MA, Lilyana Amezcua, MD, MS, Samantha Haraszti, MS, Lie Hong Chen, DrPH, Hong Quach, BA, Judith A. James, MD, Lisa F. Barcellos, Dr und Anny H. Xiang, Dr

ABSTRAKT

Ziel: Feststellung, ob die Seropositivität des Epstein-Barr-Virus (EBV) oder des Cytomegalievirus (CMV) mit Multipler Sklerose (MS) bei Schwarzen und Hispanics assoziiert ist und inwieweit Maßnahmen der Hygienehypothese oder des Stillens diese Ergebnisse erklären könnten. EBV und CMV wurden mit dem MS-Risiko bei Weißen in Verbindung gebracht, und der Zeitpunkt und die Häufigkeit beider Viren variieren durch Faktoren, die in die Hygienehypothese einbezogen sind.

Methoden: Die Fälle von MS oder ihrer Vorläufer, das klinisch isolierte Syndrom (CIS) und die entsprechenden Kontrollen (Schwarze, 111 Fälle/128 Kontrollen; Hispanics, 173/187; Weiße, 235/256) wurden aus den Mitgliedern der Kaiser Permanente Southern California rekrutiert. Logistische Regressionsmodelle berücksichtigten den HLA-DRB1*1501-Status, das Rauchen, den sozioökonomischen Status, Alter, Geschlecht, genetische Abstammung und das Geburtsland.

Ergebnisse: Die Seropositivität von Epstein-Barr-Kernantigen-1 (EBNA-1) war unabhängig mit einer erhöhten Wahrscheinlichkeit von MS / CIS in allen drei rassischen / ethnischen Gruppen assoziiert (p <0,001 für Schwarz und Weiß, p = 0,02 für Hispanics). Im Gegensatz dazu war die CMV-Seropositivität bei Hispanics (p = 0,004) mit einem geringeren MS / CIS-Risiko verbunden, nicht jedoch bei Schwarzen (p = 0,95) oder Weißen (p = 0,96). Die Geburt in einem Land mit niedrigem / mittlerem Einkommen war mit einem geringeren MS-Risiko bei Hispanics verbunden (p = 0,02), jedoch nicht nach Berücksichtigung der EBNA-1-Seropositivität. Die Berücksichtigung des Stillens verringerte die Assoziation zwischen CMV und MS bei Hispanics nicht.

Schlussfolgerungen: Die Übereinstimmung der EBNA-1-Seropositivität mit MS über die verschiedenen rassischen/ethnischen Gruppen und zwischen den Studien weist auf eine starke biologische Verbindung zwischen EBV-Infektion und MS-Risiko hin. Der Zusammenhang zwischen früherer CMV-Infektion und MS-Risiko stützt die breitere Hygienehypothese, aber die Inkonsistenz dieses Zusammenhangs zwischen Rassen / ethnischen Gruppen impliziert nicht kausale Zusammenhänge.

•Eingegangen am 10. November 2016.
•Angenommen in der endgültigen Form am 30. Juni 2017.

Epstein Barr Virus und Multiple Sklerose

Signal Transduction and Targeted Therapy www.nature.com/sigtrans

RESEARCH HIGHLIGHT OPEN

Epstein-Barr virus infection: the leading cause of multiple sclerosis

Ruirui He[1,2], Yanyun Du[1,2]✉ and Chenhui Wang[1,2]✉

Signal Transduction and Targeted Therapy (2022)7:239 ; https://doi.org/10.1038/s41392-022-01100-0

In a recent study published in *Science*, Bjornevik and colleagues demonstrated Epstein-Barr virus (EBV) infection is a trigger for multiple sclerosis (MS) in a longitudinal analysis of more than 10 million US military individuals who were on active duty.[1]

MS is an autoimmune disease that originates in the central nervous system characterized by inflammatory demyelinating lesions. There is no consensus on the etiology of MS. However, we all know that MS is a multifactorial disease which can be influenced by genetic and environmental factors. Genetic factors associated with MS risk are mainly major histocompatibility class II (MHC II) alleles (e.g., HLA-DRB1*15:01, the earliest identified and most dominant risk factor in MS) and MHC I alleles (e.g., HLA-A*02 and HLA B*44, decreasing MS susceptibility). Additionally, more than 200 genetic loci have been identified to be associated with the risk of MS,[2] but only a few specific genes or biological mechanisms of the identified genetic loci have been studied. Specific environmental exposures including ultraviolet radiation/vitamin D deficiency, cigarette smoking, diet, and viral infections have influence on the incidence of MS. Viral infection is one of the crucial environmental factors and most researches have focused on EBV, a highly B cell-tropic human herpesvirus, which infects about 95% of individuals worldwide. Significantly elevated risk of MS after EBV infection compared with EBV seronegative individuals supports a link between EBV infection and MS.[3] In addition, anti-EBNAs antibody elevated in blood of MS patients, which can be detected years before MS onset.[4] Although the hypothesis that EBV causes MS has been studied for many years, clear causality remains inconclusive.

In this study, Bjornevik et al. gave direct evidence that EBV infection is a critical contributor of MS based on a large cohort of more than 10 million young adults in the US military. Among this large population, 955 individuals of them were diagnosed with MS during their active duty. In a 20 year collaboration with US military between 1993 and 2013, the authors collected up to three serum samples for each MS case before the date of disease onset (Fig. 1). At the same time, each MS case was matched to two individuals without MS who were randomly selected but with the same sex, age, race/ethnicity, kinds of military service, and the collection dates of blood samples (Fig. 1). Removing serum samples insufficient for EBV serology, they got a reasonable sum of samples from 801 cases of MS and 1566 matched controls that could be used to assess EBV infection status and 35 MS cases were identified as EBV-negative at the baseline (Fig. 1).[1] In order to clarify the relation of EBV infection and MS onset, EBV status of the 35 MS cases and 107 corresponding controls were analyzed during the follow-up. A significantly higher seroconversion (97% rate contrasts with the 57% rate of seroconversion in the third serum samples) was found in the individuals who developed MS.[1] However, seroconversion rates for cytomegalovirus (CMV), the negative control virus, were comparative between the population who had MS symptoms later and others who did not have.[1] Moreover, by comparing EBV seroconversion and EBV-positive rates versus EBV-negative rates, the authors found that risk ratio for MS were 32.4 and 26.5, respectively.[1] Collectively, these data confirmed that EBV infection happens before MS onset and further revealed the significant association of EBV infection and higher risk of MS.

Serum neurofilament light chain (sNfL) is a sensitive biomarker of neurodegeneration, and may be also a biomarker of initiation time of MS process . To further clarify the temporal correlation between EBV infection and MS, Bjornevik et al. detected concentrations of sNfL at different time points of EBV infection in serum samples from 25 MS cases and 79 controls (Fig. 1).[1] They found that sNfL levels significantly increased in MS cases than in controls only after EBV infection compared with before EBV infection. Thus, the results further indicated that EBV infection happens earlier than sNfL elevation before MS onset.

There is also a question that whether immune disorder in the preclinical phase of MS were able to increase susceptibility more generally to virus infection and further aggravate the disease. The authors randomly selected 30 cases of MS and 30 matched controls with two serum samples, collecting before and after the onset of symptoms (Fig. 1).[1] Moreover, the VirScan data of serum samples showed similar antibody response of MS patients and controls to viral peptides at two time points, except for EBV.[1] This finding thus argues against the possibility that a second hit from other viruses may have important influence on MS etiology and further supports that EBV infection is specifically associated with MS risk.

MS includes three clinical stages: a pre-clinical stage detected only by MRI; a relapsing-remitting (RR) stage characterized by a marked relapse and remission course; and a progressive stage usually evolving from the relapsing stage. EBV likely involves in the entire clinical course of MS, and may play different roles in MS different stages. With the understanding of the immune

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Epstein Barr Virus und Multiple Sklerose

JEM Journal of Experimental Medicine

BRIEF DEFINITIVE REPORT

Broader Epstein–Barr virus–specific T cell receptor repertoire in patients with multiple sclerosis

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Epstein–Barr virus (EBV) infection precedes multiple sclerosis (MS) pathology and cross-reactive antibodies might link EBV infection to CNS autoimmunity. As an altered anti-EBV T cell reaction was suggested in MS, we queried peripheral blood T cell receptor β chain (TCRβ) repertoires of 1,395 MS patients, 887 controls, and 35 monozygotic, MS-discordant twin pairs for multimer-confirmed, viral antigen–specific TCRβ sequences. We detected more MHC-I–restricted EBV-specific TCRβ sequences in MS patients. Differences in genetics or upbringing could be excluded by validation in monozygotic twin pairs discordant for MS. Anti–VLA-4 treatment amplified this observation, while interferon β– or anti-CD20 treatment did not modulate EBV-specific T cell occurrence. In healthy individuals, EBV-specific CD8⁺ T cells were of an effector-memory phenotype in peripheral blood and cerebrospinal fluid. In MS patients, cerebrospinal fluid also contained EBV-specific central-memory CD8⁺ T cells, suggesting recent priming. Therefore, MS is not only preceded by EBV infection, but also associated with broader EBV-specific TCR repertoires, consistent with an ongoing anti-EBV immune reaction in MS.

Introduction

EBV seroconversion has been shown in large epidemiological studies to precede clinical signs of multiple sclerosis (MS; Bjornevik et al., 2022; Levin et al., 2010), confirming that EBV infection is necessary but not sufficient for disease initiation and associated central nervous system (CNS) damage. Additionally, antibody cross-reactivity was detected between a latent viral epitope of Epstein-Barr nuclear antigen-1 (EBNA-1) and a CNS autoantigen (GlialCAM) in a subset of patients as a humoral component of—and potential link to—MS pathology (Aloisi and Salvetti, 2022; Lanz et al., 2022). While relapsing-remitting MS (RRMS) is specifically characterized by the presence of B- and plasma cells in the cerebrospinal fluid (CSF; Gross et al., 2021), T cells and macrophages dominate CNS immune cell infiltrates in MS (Kuhlmann et al., 2008) and relapses are associated with influx of T cells (Schneider-Hohendorf et al., 2021). This hints at recurrent antigen drainage from the CNS into the periphery and subsequent recruitment of peripheral cytotoxic as well as T helper cells (Bar-Or et al., 2021). It has been suggested previously that peripheral T cells show increased cytokine response to latent EBNA-1 epitopes (Lunemann et al., 2006) with presumed cross-reactivity to myelin (Lunemann et al., 2008). However, it has also been discussed that the anti-EBV T cell response in MS patients targets lytic components, indicating ongoing EBV activity (Angelini et al., 2013; Lassmann et al., 2011) and/or insufficient EBV control (Cencioni et al., 2017; Pender et al., 2009).

Results and discussion

Quantification of EBV-specific, MHC-I–restricted TCRβ sequences in HLA-A*02–positive MS patients and healthy controls

In light of the finding that EBV infection precedes the development of MS and that some MS patients showed cross-reactive

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*T. Schneider-Hohendorf, L.A. Gerdes, B. Pignolet, R. Liblau, H. Wiendl, and N. Schwab contributed equally to this paper. Correspondence to Nicholas Schwab: nicholas.schwab@ukmuenster.de.

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Diagnostik Epstein Barr Virus (EBV)

Epstein Barr Virus IgG/IgM Antikörper

Epstein Barr Virus Anti-EBNA Antikörper

Epstein Barr Virus Early Antigen Antikörper (Chronisch oder Reaktivierung) mittels **Microarray**

Epstein Barr Virus Elispot

- EBV **lytisches Antigen**: Zeichen der Replikation
- EBV latentes Antigen: Zeichen der Latenz

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Cytomegalie-Virus (CMV)

Virus: Cytomegalie-Virus (obligat intrazellulär), Doppelstrang DNS Virus, gehört zur Herpes Virusgruppe

Übertragung: Körperflüssigkeiten (Urin, Speichel, Brustmilch, sexuell), Bluttransfusion, Organtransplantation

Symptome (Inkubationszeit mehrere Wochen: **Fatigue**, Fieber, grippe-ähnliche Symptome, Lymphknotenschwellungen, Halsentzündungen, Milzvergrösserung

Komplikationen: Übertragung während Geburt mit Hörverlust, Sehverlust, Krampfanfällen, mentale Probleme, Koordinationsstörungen; bei Immunsuppression: Hepatitis, Colitis, Retinitis, Pneumonie, Ösophagitis, Polyradikulopathie, transverse Myelitis, Subakute Enzephalitis; Arterielle Hypertonie, Arteriosklerose, Aorten-Aneurysma; Non-Hodgkin Lymphome, **CFS (Chronic Fatigue Syndrom)/Mitochondropathie, Colitis/Leaky Gut, Nahrungsmittelunverträglichkeiten**

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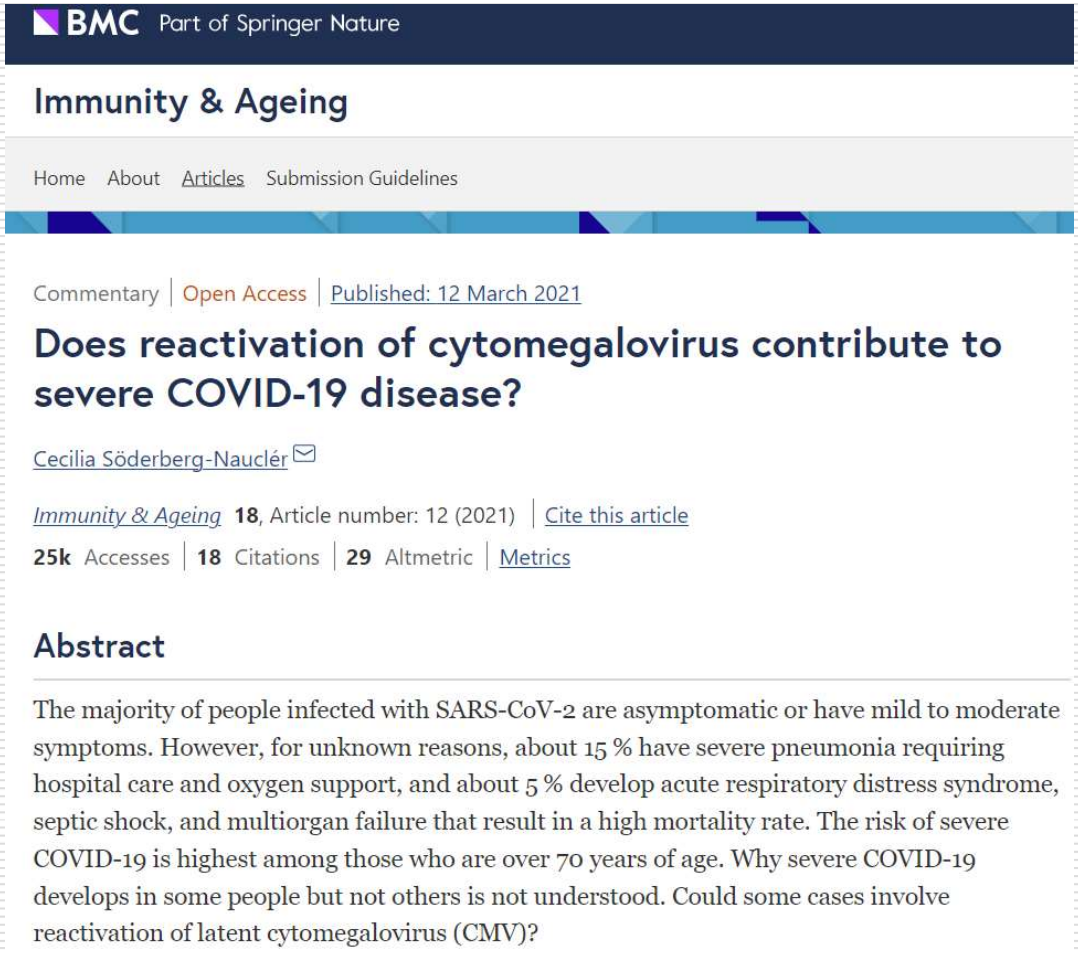
"CMV Reaktivierung und Virus-induzierte Immundysfunktion als Antreiber unterschätzt"[1]



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Does reactivation of cytomegalovirus contribute to severe COVID-19 disease?

Cecilia Söderberg-Naucler

Immunity & Ageing **18**, Article number: 12 (2021) | Cite this article

25k Accesses | **18** Citations | **29** Altmetric | Metrics

Abstract

The majority of people infected with SARS-CoV-2 are asymptomatic or have mild to moderate symptoms. However, for unknown reasons, about 15 % have severe pneumonia requiring hospital care and oxygen support, and about 5 % develop acute respiratory distress syndrome, septic shock, and multiorgan failure that result in a high mortality rate. The risk of severe COVID-19 is highest among those who are over 70 years of age. Why severe COVID-19 develops in some people but not others is not understood. Could some cases involve reactivation of latent cytomegalovirus (CMV)?

"CMV reactivation and virus induced immune dysfunction may be under-estimated as a driver of immuno-pathogenesis in patients with severe COVID-19."[1]

"… diagnosing CMV in COVID-19 patients could be well worth the effort." [1]

"Intriguingly, severe acute respiratory syndrome coronavirus 2 and cytomegalovirus may potentiate each other, since they share some innate immune pathways."[2]

Source: 1. *Söderberg-Naucler, C. Does reactivation of cytomegalovirus contribute to severe COVID-19 disease?. Immun Ageing* ***18,*** *12 (2021). https://doi.org/10.1186/s12979-021-00218-z*; 2. *https://pubmed.ncbi.nlm.nih.gov/35101103/*

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Das Cytomegalie-Virus beeinflusst das Gerinnungssystem

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Review Article

Effects of human cytomegalovirus infection on the coagulation system

Alessandro Squizzato, Victor E. A. Gerdes, Harry R. Büller
Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Summary
Pathophysiological mechanisms of acute vascular thrombosis are not fully understood. It has been suggested that different infectious pathogens are responsible agents of thrombotic disorders. The infection hypothesis is supported by an increasing number of reports on the interaction between acute infection and coagulation. Cytomegalovirus (CMV) is supposed to play an important role in apparently unprovoked thrombosis. We reviewed all human *in vitro* and *in vivo* studies on the influence of human CMV infection on the coagulation system, as well as all case reports of acute thrombosis during acute human CMV infection. In the published literature there is mounting evidence that human CMV may play a role i
finitive conclusions, however, cann
vitro studies are convincing and offe

Keywords
Infection / bacterial, viral, hypercoagulability, inflammatory mediators, endothelial cells

Thromb Haemost 2005; 93: 403-

"Immer mehr Beweise dafür, dass CMV eine kausale Rolle bei thrombotischen Erkrankungen spielen kann"

Introduction

Acute vascular thrombosis represents a major socioeconomic challenge for its heavy burden on mortality and morbidity. Acute vascular thrombosis also represents a scientific challenge since

CMV: relevant biologica features

CMV, or Human Herpes Virus 5, is a double-stranded enveloped

Source: Squizzato A, Gerdes VEA, Büller HR. Effects of human cytomegalovirus infection on the coagulation system. Thromb Haemost. 2005;93:403–410;

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Beispiel CMV Laborwerte: Long COVID

Mai 2019, vor Covid 19
Infektion April 2020

```
  CMV EliSpot

1 CMV EliSpot                    !         13 SI


  0-1    = negative
  2-3    = weak positive
  > 3    = positive

  The result of the EliSpot test indicates current cellular
  activity against Cytomegalo-Virus.
```

Septemer 2020, Long COVID

```
  CMV EliSpot

1 CMV Lytisch                    !        279 SI
     0-1    = negative
     2-3    = weak positive
     > 3    = positive

1 CMV Latent                     !         79 SI
     0-1    = negative
     2-3    = weak positive
     > 3    = positive

     The result of the EliSpot test indicates current cellular
     activity against Cytomegalo-Virus.

     Explanation of CMV antigens:
     CMV-lytic antigen: sign for replication of infectious CMV
     virions
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Diagnostik für CMV

CMV IgG/IgM Antikörper

Cytomegalie Virus CMV Elispot

- CMV **lytisches Antigen**: Zeichen der Replikation
- CMV latentes Antigen: Zeichen der Latenz

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Herpes Simplex Virus 1/2 (HSV 1/2)

Virus: Herpes Simplex Virus (Human Herpes Virus HHV 1/2) (obligat intrazellulär), Doppelstrang DNS Virus

Übertragung: Speichel, Getränke teilen, sexuell übertragbar

Symptome (Inkubationszeit 2-20 Tage): Herpes-Bläschen der Haut oder Schleimhäute von Mund, Lippen, Genitalien, Anus, grippe-ähnliche Symptome (Fieber, Muskelschmerzen, Lymphknotenschwellungen, Probleme Wasserlassen, Herpes Keratitis (Schmerzen, Lichtempfindlichkeit, Lichtblitze), **Fatigue (CFS)/Mitochondropathie**

Komplikationen: Multiple Sklerose (neurovirulent), Sehverlust, Enzephalitis, latente Infektion; Reaktivierung durch Organtransplantation oder HIV-Infektionen: Enzephalitis, Pneumonie, Knochenmarksuppression

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Herpes Simplex Virus 1 Reaktivierungem in Covid 19

microorganisms

MDPI

Article

Herpes Simplex Virus Re-Activation in Patients with SARS-CoV-2 Pneumonia: A Prospective, Observational Study

Erica Franceschini [1,*], Alessandro Cozzi-Lepri [2], Antonella Santoro [1], Erica Bacca [3], Guido Lancellotti [3], Marianna Menozzi [1], William Gennari [4], Marianna Meschiari [1], Andrea Bedini [1], Gabriella Orlando [1], Cinzia Puzzolante [1], Margherita Digaetano [1], Jovana Milic [3], Mauro Codeluppi [5], Monica Pecorari [4], Federica Carli [1], Gianluca Cuomo [1], Gaetano Alfano [6], Luca Corradi [1], Roberto Tonelli [7], Nicola De Maria [8], Stefano Busani [9], Emanuela Biagioni [9], Irene Coloretti [9], Giovanni Guaraldi [3], Mario Sarti [4], Mario Luppi [10], Enrico Clini [7], Massimo Girardis [9], Inge C. Gyssens [11,12] and Cristina Mussini [1,3,*]

"Conclusions: our study shows a high incidence of HSV-1 re-activation both virologically and clinically in patients with SARS-CoV-2 severe pneumonia"

Our study has some strengths: it is the first study that analyzed the incidence and clinical implications of HSV-1 re-activation in patients with SARS-CoV-2 pneumonia; second it has strong clinical and therapeutic implications for COVID-19 patients, especially in the present and future waves of hospitalized patients most of whom are treated with steroids, which is now considered the SOC.

In conclusion, our study shows a high incidence of both virological and clinical HSV-1 re-activation in patients with SARS-CoV-2 severe/critical pneumonia. Data show an association between this risk and treatment with steroids, which could not be explained by age, previous IMV, and level of inflammation at hospital admission. Further studies are needed, especially a randomized controlled trial, to confirm the utility of acyclovir prophylaxis in COVID-19 patients with severe pneumonia admitted to the hospital.

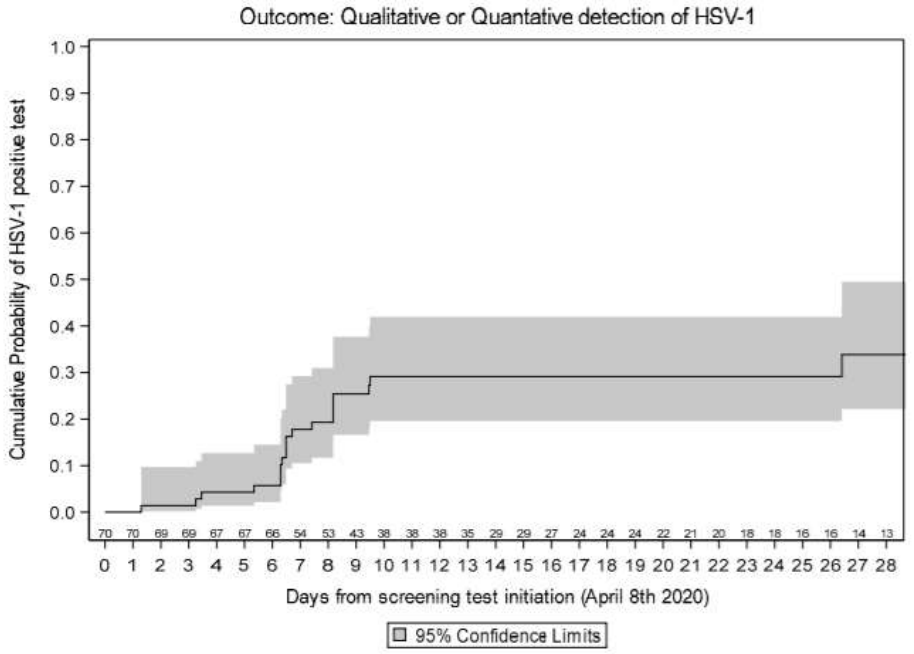

Figure 1. Kaplan–Meier estimates of HSV re-activation.

Source: *https://www.msd-animal-health.ie/species/dogs/ticks/*

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Diagnostik Herpes Simplex Virus 1/2

Herpes Simplex Virus 1/2 – IgG/**IgA**/IgM **Antikörper**
(Halbwertszeit lokalständiger IgA-Antikörper: 2 Wochen)

Herpes Simplex Virus 1 / 2 - Elispot

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Varicella Zoster Virus 1/2 (VZV)

Virus: Varizella Zoster Virus (Humanes Herpes Virus HHV 3) (obligat intrazellulär), Doppelstrang DNS Virus

Übertraung: aerogen, Kontakt mit Bläschenhinhalt

Symptome (Inkubationszeit 10-21 Tage): "Windpocken" bei jungen Patienten, "Herpes Zoster" bei Erwachsenen: Bläschen der Haut, Fieber, Müdigkeit, Appetitlosigkeit, Kopfschmerzen, **Fatigue/CFS (Chronic Fatigue Syndrom)/Mitochondropathie**

Komplikationen: Enzephalitis, Pneumonie, Bronchitis, 10-20% Reaktivierung aus Nerven-Ganglien (Herpes Zoster), Post Herpes Zoster Neuralgie, Mollaret´s Meningitis, Zoster multiplex, "Ramsay Hunt syndrome"

Inflammation of arteries (new study Journal of the American college of Cardiology, Vol. 70, Issue 2, July 2017, "Herpes Zoster increases risk of stroke and myocardial infarction" 23.233 Patienten nach Herpes Zoster hohes Risiko für Schlaganfälle (35%) and Herzinfarkte (59%)

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COVID-19 kann eine Reaktivierung von VZV auslösen

COVID-19 can potentially cause reactivation of VZV and subsequently have an additive effect in neurologic complications

CASE

COVID-19 Associated With Concomitant Varicella Zoster Viral Encephalitis

Pavan Patel, DO, Anishee Undavia, MD, Rabia Choudry, MD, Yan Zhang, MD, and Aparna M. Prabhu, MD, MRCP

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Neurology: Clinical Practice April 2021 vol. 11 no. 2 e219-e221 doi:10.1212/CPJ.0000000000000902

Coronavirus disease 2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Patients can be asymptomatic or symptomatic with severity determined by age and comorbid conditions. Common early symptoms are fever, cough, dyspnea, myalgia, headache, and diarrhea. In addition to respiratory complications, other systems involved include genitourinary, gastrointestinal, and cardiac.[1]

Neurologic complications such as encephalopathy were initially presumed to be because of multisystem involvement. Retrospective studies of patients with COVID-19 demonstrated multiple neurologic complications affecting central and peripheral nervous systems including dizziness, headache, hypogeusia, hyposmia, ischemic/hemorrhage stroke, and Guillain-Barre syndrome.[2] There was a single case report of hemorrhagic necrotizing encephalopathy reported in COVID-19, with imaging features of enhancement of bilateral thalami and medial temporal lobes.[3] To our knowledge, there have been no cases reported of coinfection with another virus during active COVID-19 infection resulting in neurologic manifestations.

PRACTICAL IMPLICATIONS

COVID-19 can potentially cause reactivation of VZV and subsequently have an additive effect in neurologic complications.

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Varizella Zoster Virus Reaktivierung nach Covid Infektion oder Impfung

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Original article

Varicella-Zoster virus reactivation following severe acute respiratory syndrome coronavirus 2 vaccination or infection: New insights

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ABSTRACT

Introduction: Varicella zoster virus (VZV) reactivation has been reported following vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but the real extent remains unknown.
Methods: We conducted a systematic review to summarize evidence of VZV reactivation or infection following SARS-CoV-2 vaccination. Episodes after coronavirus disease-2019 (COVID-19) were also identified. Related articles were identified in PubMed and EMBASE databases till December 31, 2021 using the terms "varicella zoster" and "COVID-19". PROSPERO Register Number: CRD42021289399.
Results: The search revealed 314 articles, of which 55 met the inclusion criteria. VZV manifestations were documented in 179 (82.1%) subjects following SARS-CoV-2 vaccination and in 39 (17.9%) patients with COVID-19. Among the vaccinated, median (IQR) age was 56.5 (42–70) years, and 56.8% were female. Twenty-one (16.8%) were immunosuppressed. The median (IQR) latency time after vaccination was 6 (3–10) days, and 84.4% received mRNA vaccines. VZV reactivation occurred following a first dose (68.2%), a second dose (12.8%) or a booster (0.6%). The most important VZV manifestation was dermatome herpes zoster rash, which accounted for 86.4% of events in vaccinated subjects. Twenty patients (11.3%) presented serious VZV events after vaccination, with *Herpes Zoster ophthalmicus* (5.6%) and post-herpetic neuralgia (3.4%) predominating. No VZV

"COVID-19 can potentially cause reactivation of VZV and subsequently have an additive effect in neurologic complications"[2]

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Source: *1. https://pubmed.ncbi.nlm.nih.gov/35931613/; 2. https://cp.neurology.org/content/neurclinpract/11/2/e219.full.pdf; https://www.rheumatologyadvisor.com/home/general-rheumatology/herpes-zoster-reactivation-covid19-vaccination-autoimmune-inflammatory-rheumatic/*

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Diagnostik Varizella Zoster Virus (VZV)

Varizella Zoster Virus (VZV) – IgG/**IgA**/IgM **Antikörper**
(Halbwertszeit lokalständiger IgA-Antikörper: 2 Wochen)

Varizella Zoster Virus (VZV) - Elispot

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Humanes Herpes Virus 6 (HHV6)

Virus: Humanes Herpes Virus 6 (obligat intrazellulär), Doppelstrang DNS virus, gehört zur Herpes Virus Gruppe

Übertragung: Speichel, Latenz in Speicheldrüsen und des hämatopetischen/blutbildenden Systems

Symptome: Exanthema subitum (Roseola infantum, sixth disease) mit hohem Fieber und Hautausschlag

Complikationen: **Kofaktor in Chronic Fatique Syndrom (CFS)/Mitochondropathie, Multiple Sclerose (neurovirulent),** Hashimoto, Tumoren (Kaposi Sarkom), Temporallappen-Epilepsie, Neuritis optici, Leber Dysfunktion, Fibromyalgia, AIDS, Tumoren,

Reaktivierung durch Organtransplantation: Enzephalitis, Pneumoniae, Knochenmarkdepression

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Humanes Herpes Virus 6 (HHV6): Multiple Sklerose

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Multiple sclerosis linked to variant of common herpes virus

NEUROSCIENCE NEWS (HTTPS://NEUROSCIENCENEWS.COM/AUTHOR/NEUROSCIENCENEW/) × NOVEMBER 26, 2019

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Wie lange reichen 1 Million € im Ruhest
50-54 55-
60-64 65-
70-74 75
GRÜNERFISHER INVESTMENTS

Summary: *Researchers link the Human Herpes Virus 6A to the development of multiple sclerosis.*

Source: *Karolinska Institute*

Researchers at Karolinska Institutet have developed a new method to separate between two different types of a common herpes virus (HHV-6) that has been linked to multiple sclerosis. By analyzing antibodies in the blood against the most divergent proteins of herpesvirus 6A and 6B, the researchers were able to show that MS-patients carry the herpesvirus 6A to a greater extent than healthy individuals. The findings, published in *Frontiers in Immunology*, point to a role for HHV-6A in the development of MS.

Multiple sclerosis, MS, is an autoimmune disease that affects the central nervous system. The cause of the disease is unclear, but one plausible explanation is a virus tricks the immune system to attack the body's own tissue. Human Herpesvirus 6 (HHV-6) has previously been associated with MS, but in those studies, it wasn't possible to distinguish between 6A and 6B. Through virus isolation from ill individuals, researchers have been able to show that HHV-6B can cause mild conditions such as roseola in children, but it has been unclear if HHV-6A is the cause of any disease.

According to estimates, as many as 80 percent of all children are infected with the HHV-6 virus before 2 years of age, and many also carry protection in the form of antibodies against this particular virus for the rest of their lives. But since it hasn't been possible to tell the two variants apart post-infection, it has been difficult to say whether HHV-6A or B is a risk factor for MS.

In this study, however, the researchers were able to distinguish between the A and B virus by analyzing antibodies in the blood against the proteins–immediate early protein 1A and 1B (IE1A and IE1B)–that diverge the most between the two viruses.

"This is a big breakthrough for both the MS and herpes virus research," says Anna Fogdell-Hahn, associate professor at the Department of Clinical Neuroscience at Karolinska Institutet and one of the study's senior authors. "For one, it supports the theory that HHV-6A could be a contributing factor to the development of MS. On top of that, we are now able, with this new method, to find out how common these two different types of HHV-6 are, something we haven't been able to do previously."

The researchers compared antibody levels in blood samples of some 8,700 MS-patients against more than 7,200 healthy people whose gender, date of birth, date of blood sample and other factors matched those with MS. They concluded that people with MS had a 55 percent higher risk of carrying antibodies against the HHV-6A protein than the control group. In a sub-group of almost 500 people, whose blood samples were drawn before the onset of the disease, the risk of developing MS in the future was more than doubled if they had a 6A viral infection. The younger the people were when the virus was first discovered in the blood, the higher the risk was of developing MS in the future. HHV-6B, on the other hand, was not positively associated with MS. Instead MS-patients had lower levels of antibodies toward IE1B than those without MS.

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HHV 6 und Covid 19

JOURNAL OF
MEDICAL VIROLOGY

SHORT COMMUNICATION | Free Access

Presence and clinical impact of human herpesvirus-6 infection in patients with moderate to critical coronavirus disease-19

Katia Lino, Lilian S. Alves, Jessica V. Raposo, Thalia Medeiros, Cintia F. Souza, Andrea A. da Silva, Vanessa S. de Paula, Jorge R. Almeida

First published: 14 October 2021 | https://doi.org/10.1002/jmv.27392

4 DISCUSSION

As a pilot study, we investigated the active infection of HHV-6 using nasopharyngeal samples from patients infected with SARS-CoV-2 with moderate to critically ill hospitalized, we found an impressive frequency of 21.7% of HHV-6. A recent study performed in blood samples found 22% of HHV-6 infection among COVID-19 patients in an intensive care unit.[19] All 13 positive cases of HHV-6 were identified as HHV-6B species.

In addition, our aim was also to assess the role of some clinical risk comorbidities and in-hospital outcomes, including mortality, and we were able to demonstrate a significant relationship only with prior therapeutic immunosuppression (as we can see in SLE and kidney transplant patients, for example). Besides, trying to create some relation with cutaneous or neurological manifestations, we realized that this information was very poorly described in medical records and we discuss this.

A very important issue is that herpesvirus reactivation has been reported to be very common in critically ill patients even before the COVID-19 pandemic,[19-21] as well as in cancer, autoimmune diseases, and organ transplantation.[1, 22] Guidelines exist in this setting

"As a pilot study, we investigated the active infection of HHV-6 using nasopharyngeal samples from patients infected with SARS-CoV-2 with moderate to critically ill hospitalized, we found an impressive frequency of 21.7% of HHV-6. A recent study performed in blood samples found 22% of HHV-6 infection among COVID-19 patients in an intensive care unit."

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August 2022: Reaktivierungen von HHV6 und EBV

Viruses. 2022 Aug 25;14(9):1872. doi: 10.3390/v14091872.

Epstein-Barr Virus and Human Herpesvirus-6 Reactivation in Acute COVID-19 Patients

Bailey Brooks [1 2], Christina Tancredi [2], Yufeng Song [2], Alemu Tekewe Mogus [2], Meei-Li W Huang [3], Haiying Zhu [3], Tuan L Phan [4 5], Harrison Zhu [5 6], Alexandra Kadl [7 8], Judith Woodfolk [7 9], Keith R Jerome [3 10], Steven L Zeichner [2 9]

Affiliations + expand

PMID: 36146679 PMCID: PMC9504756 DOI: 10.3390/v14091872

Free PMC article

Abstract

Beyond their pulmonary disease, many COVID-19 patients experience a complex constellation of characteristics, including hyperinflammatory responses, autoimmune disorders, and coagulopathies. However, the pathogenesis of these aspects of COVID-19 is obscure. More than 90% of people are latently infected with the lymphotropic herpesviruses Epstein-Barr Virus (EBV) and/or Human Herpesvirus-6 (HHV-6). Some of the inflammatory features of COVID-19 resemble clinical syndromes seen during EBV and HHV-6 infection, and these latent viruses can be reactivated by inflammatory mediators. We hypothesized that EBV and HHV-6 reactivation might be a common feature of early COVID-19, particularly in patients with more inflammation. We tested for EBV and HHV-6 reactivation in 67 patients acutely hospitalized with COVID-19 using previously validated quantitative PCR assays on the plasma. In our cohort, we found that 15/67 (22.4%) patients had detectable EBV and 3/67 (4.5%) had detectable HHV-6. This frequency of activation is somewhat more than the frequency reported for some healthy cohorts, such as blood donors and other healthy control cohorts. There was no association between EBV or HHV-6 and markers indicative of more inflammatory disease. We conclude that EBV and HHV-6 activation at about day 7 of hospitalization occurred in a modest fraction of our cohort of COVID-19 patients and was not associated with high levels of inflammation. In the modest fraction of patients, EBV and HHV-6 reactivation could contribute to some features of acute disease and pre-disposition to post-acute sequelae in a subset of patients.

Cohort of 67: "**We found that 15/67 (22.4%) patients had detectable EBV and 3/67 (4.5%) had detectable HHV-6**"

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Es ist bekannt, dass HHV-6 die Hyperkoagulation antreibt…

Hypercoaguable State Associated with Active Human Herpesvirus6 (HHV-6) Viremia in Patients with Chronic Fatigue Syndrome

Article *in* Journal of Chronic Fatigue Syndrome 8(3):111-116 · September 2001 *with* 6 Reads

DOI: 10.1300/J092v08n03_10

Cite this publication

Objectives: A subset of patients with Chronic Fatigue Syndrome (CFS) hav
analyze the incidence of a hypercoaguable state and assess hereditary hyp
viremia. Methods: Thirty patients diagnosed with CFS that had at least one
studied. A hypercoaguable panel was obtained to assess activation of coag
of coagulation. Hereditary thrombosis risk panels were also performed whi
Results: Twenty-four of thirty (80%) patients had a hypercoaguable state, t
hereditary abnormality. Conclusions: CFS patients with active HHV-6 infect
Hereditary thrombosis risk factors are very prevalent in these patients. The
hypercoaguable state associated with active HHV-6 infection may be a sign

"Schlussfolgerungen: CFS-Patienten mit aktiver HHV-6-Infektion (Virämie) haben eine Aktivierung der Gerinnung und sind hyperkoagulierbar. …Der hyperkoagulierbare Zustand in Verbindung mit einer aktiven HHV-6-Infektion kann ein bedeutender Faktor für die auftretenden Symptome bei CFS-Patienten sein".

… sowie Epstein-Barr-Virus

"Eine Möglichkeit, wie das HHV-6- und das Epstein-Barr-Virus Krankheiten verursachen können, ist eine leichte Verdickung des Blutes, ein Zustand, der "Hyperkoagulation" genannt wird. Die Hyperkoagulation bewirkt zwei Dinge für das Virus. Erstens: Wenn das Blut dicker ist, ist es für unser Immunsystem schwieriger, diese Viren zu unterdrücken. Viren gedeihen in dickerem Blut. **Zweitens verhindert dickeres Blut die maximale Zufuhr von Sauerstoff und Nährstoffen** auf zellulärer Ebene. ”

Quelle: 1. Brewer, Joseph & Berg, David. (2001). Hyperkoaguierbarer Zustand im Zusammenhang mit aktiver humaner Herpesvirus6 (HHV-6) -Virämie bei Patienten mit chronischem Müdigkeitssyndrom. Journal of Chronic Fatigue Syndrome. 8. 111-116; 2. http://www.medicalinsider.com/viruses.html

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Diagnostik Humanes Herpes Virus 6

HHV6-IgG/IgM-Antikörper

HHV6 EliSpot

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Coxsackie Virus

Virus: Coxsackie Virus (obligat intrazellulär), gehört zur Gruppe Picornaviridae/ Enteroviren, Einzelstrang RNA Virus Gruppe A und Gruppe B

Übertragung: fäkal-oral, Tröpfchen, Körperflüssigkeiten, Gebrauchsgegenstände, Spielsachen, Windeln

Symptome: Gruppe: Herpangina, Akut Hämorrhagische Konjunktivitis, HFM (Hand-Fuss-Mund-Krankheit), Gruppe B: Myokarditis, Perikarditis, Pleurodynie, Hepatitis; Gruppe A und B: Fieber, Hautausschlag, Rachitis, Diarrhö, Husten, **fatigue**, Konjunktivitis, Appetitlosigkeit, Kopfschmerzen, Nachtschweiss, aseptische Meningitis

Komplikationen: **Neurovirulent:** ALS, Demenz, ZNS Symptome ähnlich wie Poliomyelitis, Systemische neonatale Erkrankung, IDDM (insulin-abhängiger Diabetes mellitus), Gruppe A: generalisierte Myositis mit schlaffen Lähmungen, Gruppe B: fokale Muskelerkrankung, neuronale Degeneration mit spastischer Paralyse

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Coxsackie Virus: Fortsetzung klinische Symptome

Komplikationen: Multiple Sklerose (neurotrop), **CFS (Chronic Fatigue Syndrom)/Mitochondropathie, Colitis/Leaky Gut, Nahrungsmittelunverträglichkeiten**

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Coxsackie Virus

frontiers in Molecular Neuroscience

MINI REVIEW
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Enteroviral Infection: The Forgotten Link to Amyotrophic Lateral Sclerosis?

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease that primarily attacks motor neurons in the brain and spinal cord, leading to progressive paralysis and ultimately death. Currently there is no effective therapy. The majority of ALS cases are sporadic, with no known family history; unfortunately the etiology remains largely unknown. Contribution of Enteroviruses (EVs), a family of positive-stranded RNA viruses including poliovirus, coxsackievirus, echovirus, enterovirus-A71 and enterovirus-D68, to the development of ALS has been suspected as they can target motor neurons, and patients with prior poliomyelitis show a higher risk of motor neuron disease. Multiple efforts have been made to detect enteroviral genome in ALS patient tissues over the past two decades; however the clinical data are controversial and a causal relationship has not yet been established. Recent evidence from *in vitro* and animal studies suggests that enterovirus-induced pathology remarkably resembles the cellular and molecular phenotype of ALS, indicating a possible link between enteroviral infection and ALS pathogenesis. In this review, we summarize the nature of enteroviral infection, including route of infection, cells targeted, and viral persistence within the central nervous system (CNS). We review the molecular mechanisms underlying viral infection and highlight the similarity between viral pathogenesis and the molecular and pathological features of ALS, and finally, discuss the potential role of enteroviral infection in frontotemporal dementia (FTD), a disease that shares common clinical, genetic, and pathological features with ALS, and the significance of anti-viral therapy as an option for the treatment of ALS.

Keywords: amyotrophic lateral sclerosis, enterovirus, TDP-43 pathology, nucleocytoplasmic trafficking, RNA metabolism, autophagy, neuroinflammation

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease marked by progressive degeneration of both upper and lower motor neurons, resulting in paralysis and eventual death within 3–5 years after diagnosis (Brown and Al-Chalabi, 2017; Hardiman et al., 2017; van Es et al., 2017). Despite primarily a motor neuron disease, nearly 50% of ALS patients show cognitive/behavioral impairments, suggesting an involvement of non-motor systems in ALS pathogenesis (Hardiman et al., 2017). The overall prevalence of ALS in Europe and North America is estimated at ~3–5 cases per 100,000 people and increases with age (Brown and Al-Chalabi, 2017).

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Coxsackie-Virus und Myokarditis/Pericarditis als Koinfektion mit COVID-19

Fulminant myocarditis as an early presentation of SARS-CoV-2

Tamara Naneishvili,[✉1] Arsalan Khalil,[1] Ryan O'Leary,[2] and Neeraj Prasad[1]

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Abstract

Myocarditis is well known to be caused by viral infections s
herpes virus 6 and parvovirus B19. However, during the current emerging outbreak of SARS-CoV-2, there have been few case reports describing myocarditis as a possible presentation. In our case re-

"**Myocarditis** is well known to be caused by viral infections such as **Coxsackie virus group B**, human herpes virus 6 and parvovirus B19."[1]

"Both types of **[Coxsackie]**viruses (A and B) can cause meningitis, myocarditis, and pericarditis"[2]

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Public Health Emergency COVID-19 Initiative

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COVID-19 AND COXSACKIE B COINFECTION: A RARE CASE OF ACUTE PERICARDITIS

AMANDA ENG, NIKISHA PANDYA, and RATTAN PATEL

… this is the first case presenting **pericarditis caused by COVID 19 and Coxsackieviruses B (CV-B) coinfection**.

Source: 1. https://pubmed.ncbi.nlm.nih.gov/32928810/; 2. https://www.medicinenet.com/coxsackie_virus/article.htm; https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8503119/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8330013/pdf/IETT_0_1952985.pdf

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frontiers in Medicine

REVIEW
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Association of Viral Infections With Oral Cavity Lesions: Role of SARS-CoV-2 Infection

Giusy Rita Maria La Rosa[1], Massimo Libra[2], Rocco De Pasquale[1], Sebastiano Ferlito[1] and Eugenio Pedullà[1]*

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Different viral agents, such as herpesviruses, human papillomavirus, and Coxsackie virus, are responsible for primary oral lesions, while other viruses, such as human immunodeficiency virus, affect the oral cavity due to immune system weakness. Interestingly, it has been reported that coronavirus disease 2019 (COVID-19) patients can show cutaneous manifestations, including the oral cavity. However, the association between oral injuries and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still unclear. This narrative review aimed to summarize the available literature and provide an overview of oral lesions associated with COVID-19. An online literature search was conducted to select relevant studies published up to November 2020. The results of 17 studies showed variability in oral lesions associated with COVID-19, including ulcerations, aphthous-like lesions, and macules. The tongue, lips, and palate were the most frequent anatomical locations. According to current knowledge, the etiopathogenesis of multiple COVID-19-associated lesions seems to be multifactorial. The appearance of such lesions could be related to the direct or indirect action of SARS-CoV-2 ower the oral mucosa cells, coinfections, immunity impairment, and adverse drug reactions. Nevertheless, COVID-19-associated oral lesions may be underreported, mainly due to lockdown periods and the lack of mandatory dispositive protection. Consequently, further research is necessary to determine the diagnostic and pathological significance of oral manifestations of COVID-19. All medical doctors, dentists, and dermatologists are encouraged to perform an accurate and thorough oral examination of all suspected and confirmed COVID-19 cases to recognize the disease's possible early manifestations.

Keywords: COVID-19, novel coronavirus, oral health, oral lesions, oral mucosa, SARS-CoV-2, viral infection

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INTRODUCTION

The oral cavity is particularly susceptible to viral infections because of its conformation, particularly its soft tissue and salivary glands. Several viruses, including herpes simplex virus (HSV) and human papillomavirus (HPV), are associated with oral disease-causing primary lesions. Furthermore, oral mucosa can be affected by the secondary pathological processes of a bacterial or fungal nature due to viral immunosuppression, such as the human immunodeficiency virus (HIV).

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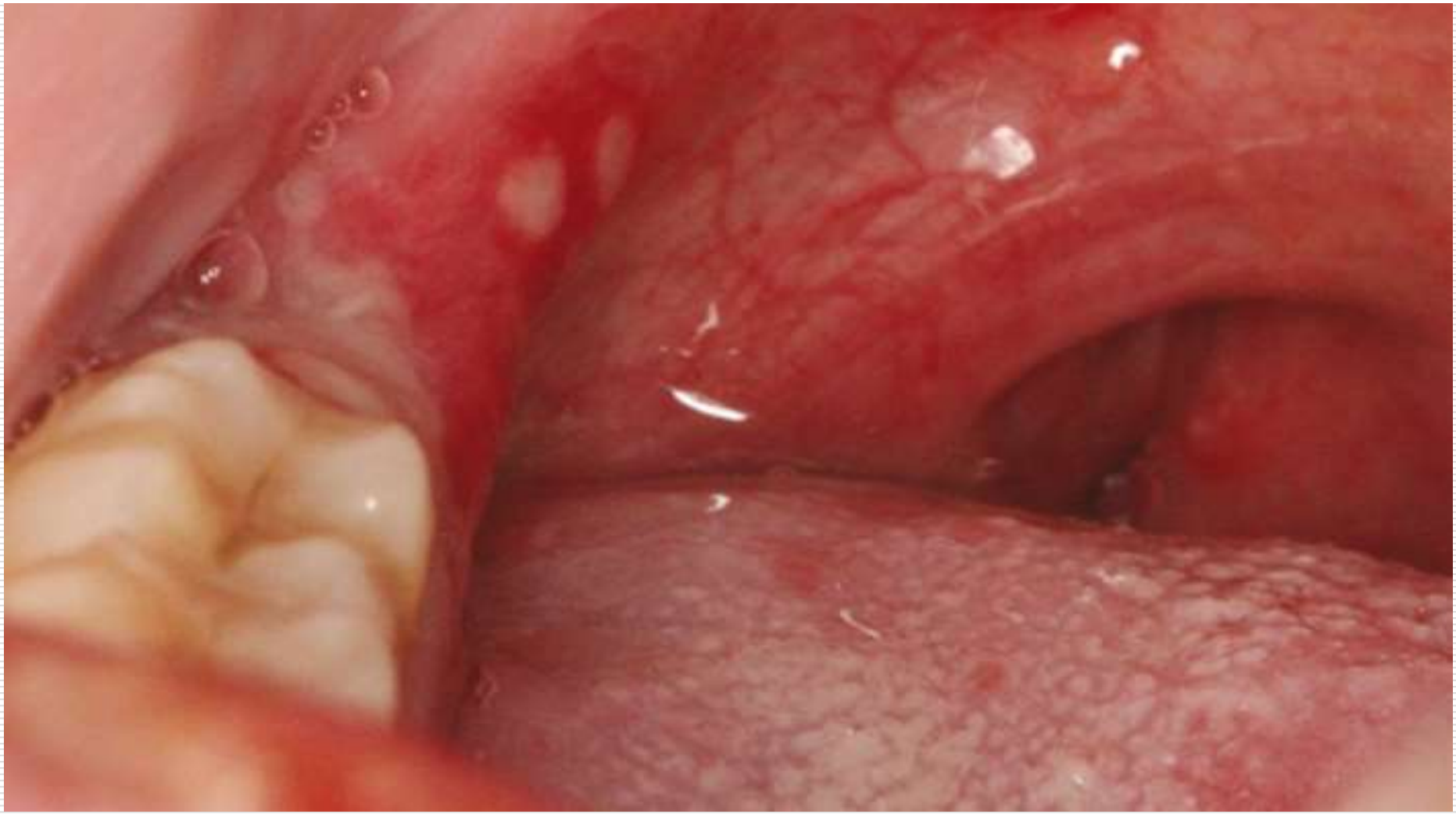
Herpangina / Aphten !



Copyright: Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic features of common oral ulcerative lesions: An updated decision tree. Int J Dent 2016. Available at: https://www.hindawi.com/journals/ijd/2016/7278925/. Copyright © 2016 The Authors (Accessed on March 6, 2020). Reproduced under the terms of the Creative Commons Attribution License 4.0.

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Diagnostik Coxsackie Virus

Coxsackie Virus Typ A7/B1 – IgG/**IgA Antikörper**

(Halbwertszeit lokalständiger IgA Antikörper: 2 Wochen)

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Eine Exposition auf Borreliose kann das Risiko einer schweren Covid 19 Infektion erhöhen

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Correlation between COVID-19 severity and previous exposure of patients to *Borrelia* spp.

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Predictors for the risk of severe COVID-19 are crucial for patient care and control of the disease. Other infectious diseases as potential comorbidities in SARS-CoV-2 infection are still poorly understood. Here we identify association between the course of COVID-19 and Lyme disease (borreliosis), caused by *Borrelia burgdorferi* transmitted to humans by ticks. Exposure to *Borrelia* was identified by multi-antigenic (19 antigens) serological testing of patients: severe COVID-19 (hospitalized), asymptomatic to mild COVID-19 (home treated or not aware of being infected), and not infected with SARS-CoV-2. Increased levels of *Borrelia*-specific IgGs strongly correlated with COVID-19 severity and risk of hospitalization. This suggests that a history of tick bites and related infections may contribute to the risks in COVID-19. Though mechanisms of this link is not clear yet, screening for antibodies targeting *Borrelia* may help accurately assess the odds of hospitalization for SARS-CoV-2 infected patients, supporting efforts for efficient control of COVID-19.

Borreliosis, also known as Lyme disease, is a zoonosis caused by the bacterium *Borrelia burgdorferi* transmitted to humans by ticks. A characteristic symptom of infection is the skin rash called erythema migrans, which however occurs in only 60–80% of infected persons, with a delay of 3–30 days after the tick bite. Other typical symptoms are non-specific, including fever, mild headaches, muscular-articular pain, and fatigue. Thus, a considerable number of cases of *Borrelia* infection can be overlooked, while if left untreated, infection can spread to joints, the heart, and the nervous system[1,2]. Subjective symptoms may persist or recur for at least six months after a patient was infected, even after antimicrobial treatment[3,4]. So-called 'chronic Lyme disease', sometimes with severe manifestations, remains controversial, lacking clearly recognized or demonstrated significance for a patient's health[5].

The diagnostics of *Borrelia* infection is challenging, primarily due to the multitude of bacterial strains that may cause the infection. In Eurasia, *Borrelia burgdorferi* sensu lato includes various spirochete species: *B. burgdorferi* sensu stricto (s.s.), *B. afzelii*, *B. garinii*, *B. bavariensis*, *B. japonica*, *B. lusitaniae*, *B. sinica*, *B. spielmanii*, *B. tanukii*, *B. turdi*, *B. valaisiana*, *B. yangtze*, *B. bissettii*, and *B. carolinensis*. Within the area of this study (Central Europe), the predominant species as the causative agents of borreliosis are *Borrelia afzelii* and *Borrelia garinii*, less frequently *Borrelia burgdorferi* s.s.[6–8]. *B. spielmanii* has also been found in an animal reservoir, postulated as an appropriate antigenic component in diagnostic tests in Europe[8,9].

Serological testing of patients' sera with antigens representing pathogenic species of *Borrelia* is the major approach in diagnostics[10], even though seropositivity alone is not sufficient for a diagnosis of active borreliosis, since antibodies may persist for long after treatment of the disease and they can be detected even in individuals after a successful treatment [3,4]. Proper interpretation of a patient's clinical status is difficult due to different life strategies of *B. burgdorferi*; these are related to their antigenic variability, which is in turn linked to adaptation to different environmental conditions, their intracellular residence, and their hiding in immunologically privileged areas[11,12]. Presence of antibodies targeting multiple antigens of Borrelia, however, indicates that an individual has been infected, without a clear indication of whether the infection has been eradicated or it is still active. Thus, serological testing remains the major tool available for epidemiological studies[10].

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Hohe Koinfektions-Rate bei COVID-19: Bakterien wie Chlamydia/Mycoplasma pneumoniae

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Researchers report 21% COVID-19 co-infection rate

Filed Under: COVID-19

Mary Van Beusekom | News Writer | CIDRAP News | Apr 16, 2020 Share Tweet LinkedIn Email Print & PDF

A research letter published yesterday in *JAMA* found that rates of COVID-19 co-infections with other respiratory pathogens are 21%, higher than previously thought, suggesting that identification of another pathogen may not rule out the presence of the novel coronavirus.

Also, a letter yesterday in the *Annals of Internal Medicine* detailing survey results on 272 primary care physicians in Lombardy, Italy, who cared for about 400,000 COVID-19 patients found that 40% had symptoms suggestive of the disease, and most had to buy their own personal protective equipment (PPE) and educate themselves on coronavirus management.

Mohammed Haneefa Nizamudeen / iStock

Co-infection rate higher than thought

Early in the pandemic, reports from China indicated that co-infection of COVID-19 and other respiratory pathogens was uncommon, suggesting that patients who tested positive for other pathogens could be assumed to not have the novel coronavirus.

Some sites tested the specimens for COVID-19 as well as influenza A and B, respiratory syncytial virus (RSV), non–COVID-19 coronaviruses, adenovirus, parainfluenza 1 through 4, human metapneumovirus, rhinovirus/enterovirus, *Chlamydia pneumoniae,* and *Myco plasma pneumoniae.*

Source: https://www.cidrap.umn.edu/news-perspective/2020/04/researchers-report-21-covid-19-co-infection-rate; https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30494-8/fulltext

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Chlamydia pneumoniae und Mycoplasma als Koinfektion mit SARS CoV 2

Comment > J Infect. 2021 Apr;82(4):e4-e7. doi: 10.1016/j.jinf.2021.01.009. Epub 2021 Jan 19.

Co-infection of chlamydia pneumoniae and mycoplasma pneumoniae with SARS-CoV-2 is associated with more severe features

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PMID: 33482238 PMCID: PMC7816623 DOI: 10.1016/j.jinf.2021.01.009

Free PMC article

Here, we present a retrospective study with the aim to evaluate the prevalence of co-infections with atypical pathogens in SARS-CoV-2 infected patients compared to non-infected patients.

We included 721 hospitalized patients who underwent testing for SARS-CoV-2, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophyla* over a two months period between 6 March 2020 and 12 May 2020 to the Spedali Civili's Hospital, Montichiari's Hospital and Gardone Val-Trompia's Hospital, Brescia, Italy. A real time reverse polymerase chain reaction was used to detect SARS-CoV-2. Chemiluminescence immunoassays and immunoenzymatic assays were used to detect IgM antibodies for *Mycoplasma pneumoniae* and IgM/IgA/IgG for *Chlamydia pneumoniae* in the serum of patients. Legionella diagnosis was made by urinary antigen testing.

Definition of pneumonia or severe pneumonia was done according to the WHO guidelines and included clinical signs of pneumonia (fever, cough, dyspnea, fast breathing).

Categorical variables are the number (percentage), and continuous variables are the median (interquartile range [IQR]). Categorical data were compared by using the χ^2 test or the Fisher exact test, as appropriate. The data in different groups were compared with the ANOVA or independent *t*-test for normally distributed variables.

Logistic regression was used in order to perform univariate and multivariate analysis for determination of risk factors [odds ratios (ORs) and 95% CIs] associated with the presence of *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* infection in SARS-CoV-2 positive patients after adjusting for confounders.

"Out of 721 subjects, 443 individuals were infected with SARS-CoV-2 and 278 subjects were negative. All individuals were negative for Legionella antigen. **Of the 443 patients with a SARS-CoV-2 infection, 242 individuals had an antibody positivity against Mycoplasma and/or Chlamydia**, while of the 278 negative for SARS-CoV-2, only 97 showed Mycoplasma and/or Chlamydia pneumoniae antibody positivity ($p < 0.0001$)."

Source: https://pubmed.ncbi.nlm.nih.gov/33482238/

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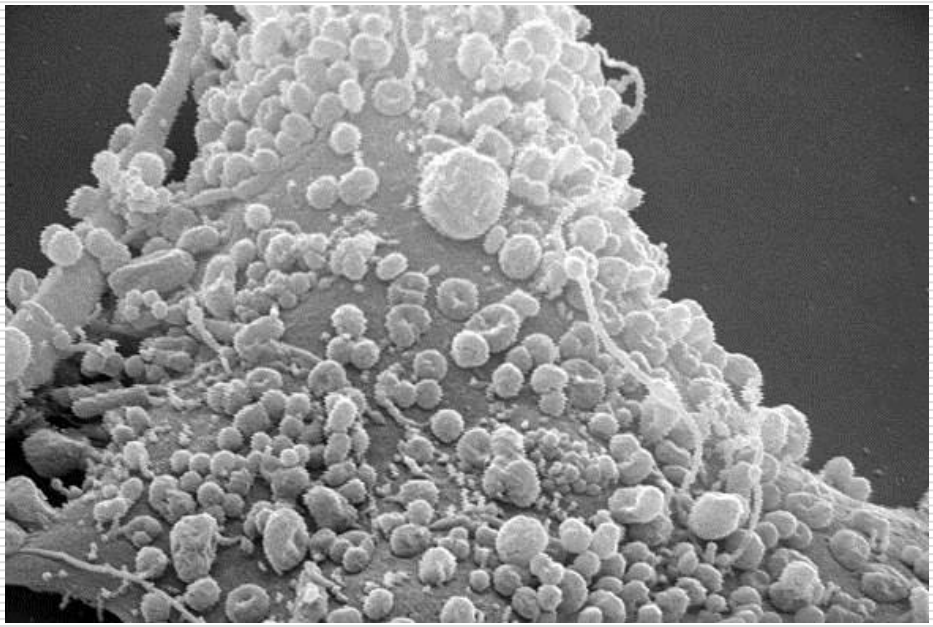
Mycoplasma in ~70% of CFS Patienten in Professor Garth Nicolson's Studien

Mycoplasmas are the stealthiest of all stealth microbes. They are the smallest free-living organisms on the planet (150 – 250 nm), and lack a cell wall. No. 1 coinfection in Lyme patients – ~ 70%. As far back as 2002, Professor Garth Nicolson found that 70% of a cohort of ME patients were infected with at least one strain of Mycoplasma.
They generally prefer low-oxygen environments, and stimulate reactive oxygen species (ROS), which cause damage to cell membranes – membrane potential is lost.



Mycoplasma on the surface of a fibroblast

Source: Nicolson GL et al. Chronic Fatigue Syndrome Patients Subsequently Diagnosed with Lyme Disease Borrelia burgdorferi: Evidence for Mycoplasma Species Coinfections. Journal of Chronic Fatigue Syndrome, Volume 14, 2007 - Issue 4

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Chlamydia pneumoniae lebt in den Membranen der Mukosa als Reservoir für chronische Infektionen

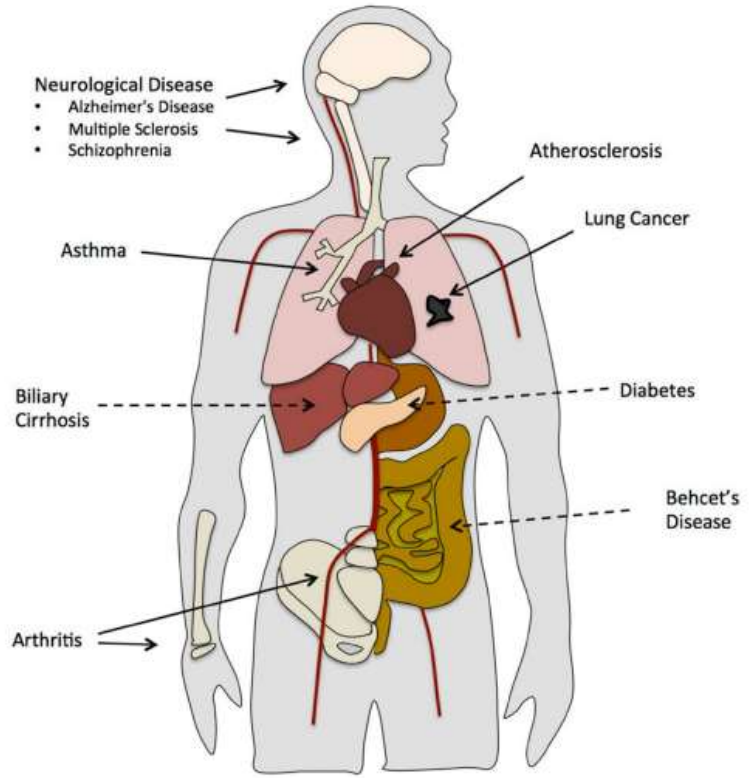

FIG. 1:
C. pneumoniae infection and inflammatory disease. In addition to pneumonia, *C. pneumoniae* infection may contribute to a range of inflammatory diseases including asthma and lung cancer. Dissemination of *C. pneumoniae* from the lung throughout the body can possibly lead to atherosclerosis, arthritis, and neurological diseases. Some evidence suggests that *C. pneumoniae* may also be associated with biliary cirrhosis, diabetes, and Bechet's disease.

1

"Chlamydia pneumoniae has long been found to be a clinically relevant coinfection … **causes arthritis** but **also affects the nervous system and the heart**, which renders the differential diagnosis difficult…[2]

Specifically, C. pneumoniae has been demonstrated to elicit ROS overproduction by upregulating NOX and cyclooxygenase (COX-2) and downregulating antioxidant enzyme systems, such as catalase, SOD-1, and thioredoxin-1 [65]. There is also evidence that C. pneumoniae-induced oxidative stress may contribute to **endothelial dysfunction** by decreasing eNOS expression and, hence, nitric oxide synthesis in endothelial cells [66,67]. …
C. pneumoniae is able to survive in monocytes/macrophages, considered as **a reservoir of chronic infection**.[3]

Source: 1. https://pubmed.ncbi.nlm.nih.gov/30687565/; 2. Berghoff W. Chronic Lyme Disease and Co-infections: Differential Diagnosis. Open Neurol J. 2012; 6: 158–178. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3565243/table/T3/; Kashyap S, Sarkar, M. Mycoplasma pneumonia: Clinical features and management. Lung India. 2010 Apr-Jun; 27(2): 75–85; 3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8301438/pdf/biomedicines-09-00723.pdf

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Chlamydia pneumoniae: Oxidativer Stress, Inflammation in Verbindung mit kardiovaskulären Erkrankungen bei SARS CoV 2

Review > Biomedicines. 2021 Jun 24;9(7):723. doi: 10.3390/biomedicines9070723.

Oxidative Stress and Inflammation in SARS-CoV-2- and *Chlamydia pneumoniae*-Associated Cardiovascular Diseases

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Free PMC article

Abstract

Throughout the years, a growing number of studies have provided evidence that oxidative stress and inflammation may be involved in the pathogenesis of infectious agent-related cardiovascular diseases. Amongst the numerous respiratory pathogens, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus responsible for the global ongoing pandemic, and *Chlamydia pneumoniae*, a widely known intracellular obligate bacteria, seem to have an essential role in promoting reactive oxygen species and cytokine production. The present review highlights the common oxidative and inflammatory molecular pathways underlying the cardiovascular diseases associated with SARS-CoV-2 or *C. pneumoniae* infections. The main therapeutic and preventive approaches using natural antioxidant compounds will be also discussed.

Amongst the numerous respiratory pathogens, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus responsible for the global ongoing pandemic, and *Chlamydia pneumoniae*, a widely known intracellular obligate bacteria, seem to have an essential role in promoting reactive oxygen species and cytokine production.

"Particularly important are the molecular studies that have **highlighted oxidative stress and inflammation** as the most likely pathogenic mechanisms by which C. pneumoniae may contribute to the early as well as late stages of the atherosclerotic process by **promoting endothelial dysfunction, foam cell formation, platelet activation, and thrombus formation**."[2]

Source: https://pubmed.ncbi.nlm.nih.gov/34202515; 2. https://pubmed.ncbi.nlm.nih.gov/30687565/;

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"Chlamydia pneumoniae fördert endotheliale Dysfunktion, Plättchen-Aktivierung, Thromsub-Formation während und nach Covid 19

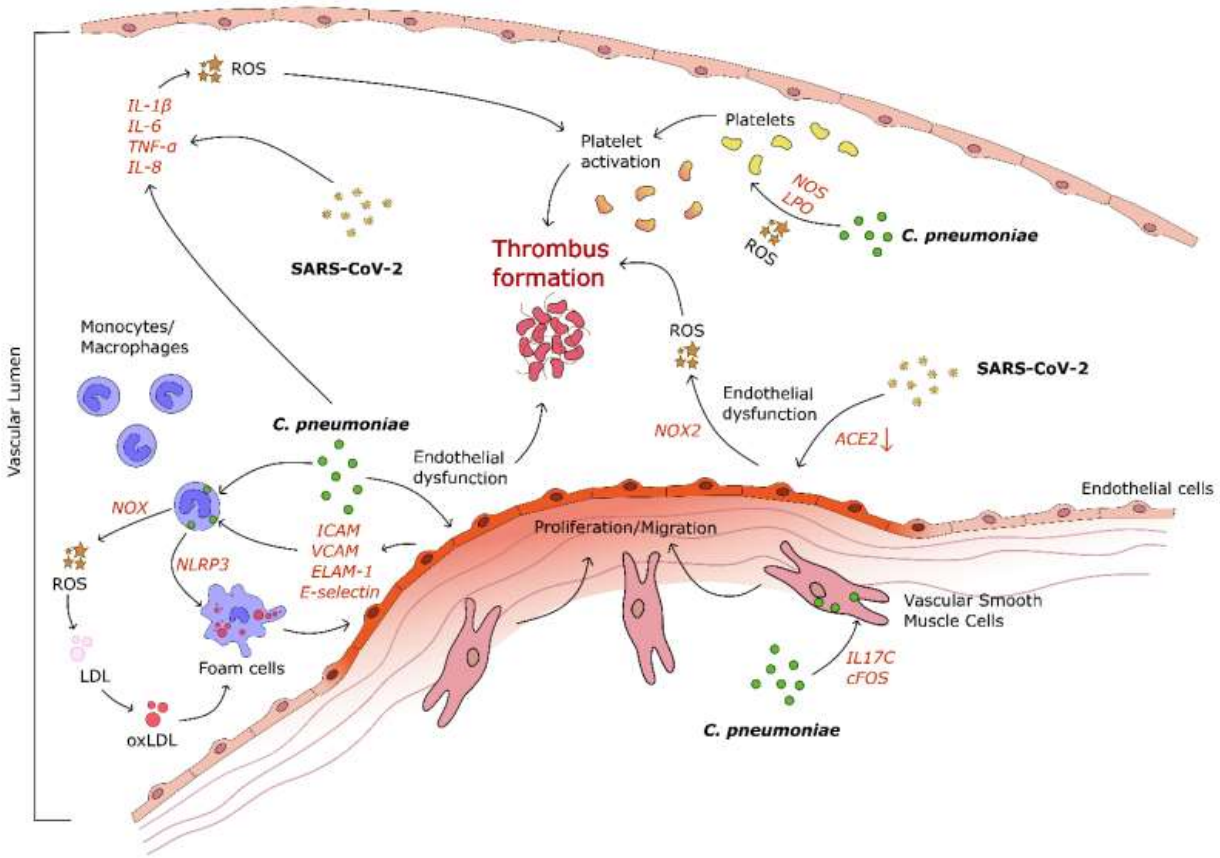

Figure 1. Cellular and molecular pathways involved in SARS-CoV-2- and *C. pneumoniae* -mediated vascular diseases. SARS-CoV-2 contributes to increased inflammation, endothelial dysfunction, and, ultimately, thrombus formation. *C. pneumoniae* induces inflammatory cytokine production, endothelial dysfunction, foam cell formation, vascular smooth muscle cell (VSMC) migration, and proliferation to intima, leading to thrombus formation. ACE-2, angiotensin converting enzyme-2; ROS, reactive oxygen species; NOX-2, nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase-2; IL, interleukin; TNFα, tumor necrosis factor; NOS, nitric oxide synthase; LOS, lipoxygenase; LDL, low-density lipoprotein; NLRP-3, nod-like receptor family pyrin domain-containing 3; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; ELAM-1, endothelial-leukocyte adhesion molecule-1. The red arrow indicates decrease in marker's levels.

SARS-CoV-2 contributes to increased inflammation, endothelial dysfunction, and, ultimately, thrombus formation. C. pneumoniae induces inflammatory cytokine production, endothelial dysfunction, foam cell formation, vascular smooth muscle cell (VSMC) migration, and proliferation to intima, leading to thrombus formation

Source: https://pubmed.ncbi.nlm.nih.gov/34202515

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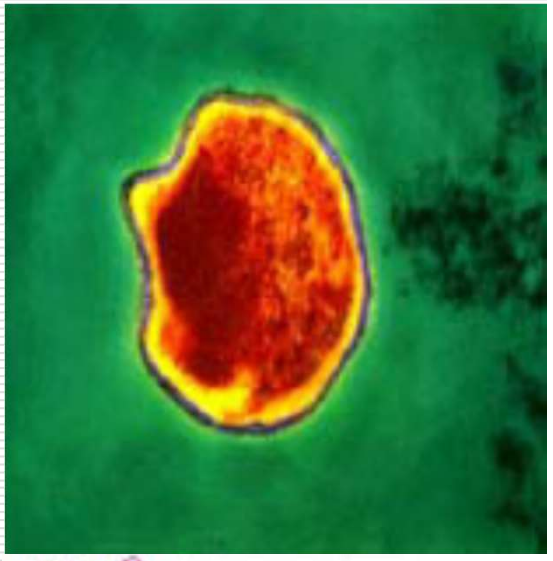
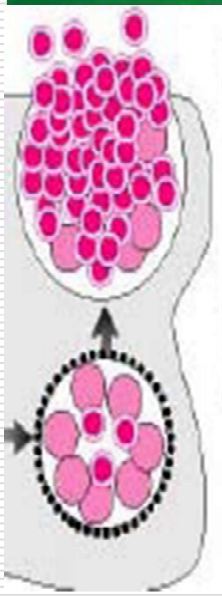
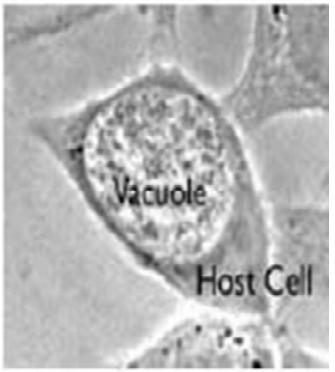
Chlamydia pneumoniae-Infektion

Erreger: Chlamydophila pneumoniae (gram-negativ, intrazellulär)
Übertragung: Tröpfcheninfektion (aerogen), Mensch-zu-Mensch, Zecken ?
Prävalenz: 50-100% der Erwachsenen
Klinik : Reinfektionen/Chronizität
Husten, Halsschmerzen, Heiserkeit, Sinusitiden, atypische Pneumonie, Meningoenzephalitis, Bronchiolitis obliterans, Myocarditis, Guillain-Barre-Syndrom
Postinfektiös(4-6 Wochen): Arthritis,Tendovaginits
Assoziationen: u.a. Morbus Alzheimer, Multiple Sklerose, Fibromyalgie, chronisches Müdigkeits-Syndrom (CFS), Prostataprobleme, Myokardinfarkte, Apoplektischer Insult, Arteriosklerose, Asthma, COPD, Arthralgien, Erythema nodosum
Risikofaktoren: Immunsuppression







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Chlamydia pneumoniae: Diagnostik

Chlamydia pneumoniae EliSpot (aktuelle Aktivität)

Antikörper auf Chlamydia pneumoniae-IgA und Chlamydia pneumoniae-IgG:

Halbwertszeit lokalständiger IgA-Antikörper:

2 Wochen

Aktuelle Studie bei AIS (Acute Ischemic Strokes): 60.8 %

"Chlamydia pneumoniae seropositivity in adults with acute ischemic stroke: A case-control study", NK Rai et al., Official Journal of Indian Academy of Neurology, 14, 2011 p. 93-97)

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Einige Antikörpertests zeigen den IgA-Status als Hinweis auf eine floride Infektion

Am J Kidney Dis. 1988 Nov;12(5):384-7.

The IgA mucosal immune system.

Lamm ME[1].

Author information

"IgA ist quantitativ das wichtigste der Immunglobuline und hat eine höhere Syntheserate als alle anderen Immunglobuline zusammen, wenn sowohl sekretorisches als auch zirkulierendes IgA berücksichtigt werden."

Abstract

This report reviews the immunophysiology of the mucosal immune system, the principal antibody of which is a special form of IgA, termed secretory IgA. This IgA is produced locally by mucosal plasma cells that are descended from precursors initially stimulated in organized, mucosal lymphoid organs designed for antigen sampling. After the initial triggering, the precursor cells pass via regional lymph nodes, lymph, and blood to disseminate widely among mucosal sites. After secretion from a local plasma cell, IgA binds to an epithelial cell surface receptor and the complex passes through the epithelial cell into the secretions where it serves as a nonphlogistic immunologic barrier to inhibit uptake of antigens. The production of IgA is facilitated by particular regulatory T cells. At the same time, the synthesis of other classes of antibody, such as the phlogistic IgG, is dampened. This differential regulation of individual antibody classes after exposure to mucosal antigen plus the interrelatedness of the various mucous membranes of the body have important implications for host defense, pathogenesis of a variety of diseases including IgA nephropathy, and strategies of immunization.

PMID: 3055963

"Die wichtigsten Antikörper, die auf den Schleimhäuten gefunden werden, sind sekretorische IgA, die hauptsächlich funktionieren, indem sie Mikroorganismen binden und dadurch ihren Kontakt mit dem Wirtsgewebe verhindern. "

Quelle: 1. mukosale Immunität, Stephen P. James, in Encyclopedia of Immunology (Zweite Ausgabe), 1998, https://www.sciencedirect.com/topics/neuroscience/immunoglobulin-a; 2. Hanson, L., Andersson, B., Carlsson, B. et al. Infection (1985) 13(Suppl 2): S166.

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Laborbeispiel:
IgA Antikörper können Indikator für floride Infektionen mit Chlamydia pneumoniae, HSV1/2, VZV, Coxsackie, Echovirus - und auch Anti-SARS-CoV-2 (Covid 19) sein

Chlamydia pneum. IgG-/IgA-AB

4 Chlam.pneum. IgG-AB (ELISA) positive negative
! 1,525 Ratio

Ratio < 0,8 = negative
Ratio 0,8 - 1,1 = weak
Ratio >= 1,1 = positive

4 Chlam.pneum. IgA-AB (ELISA) positive negative
! 1,628 Ratio

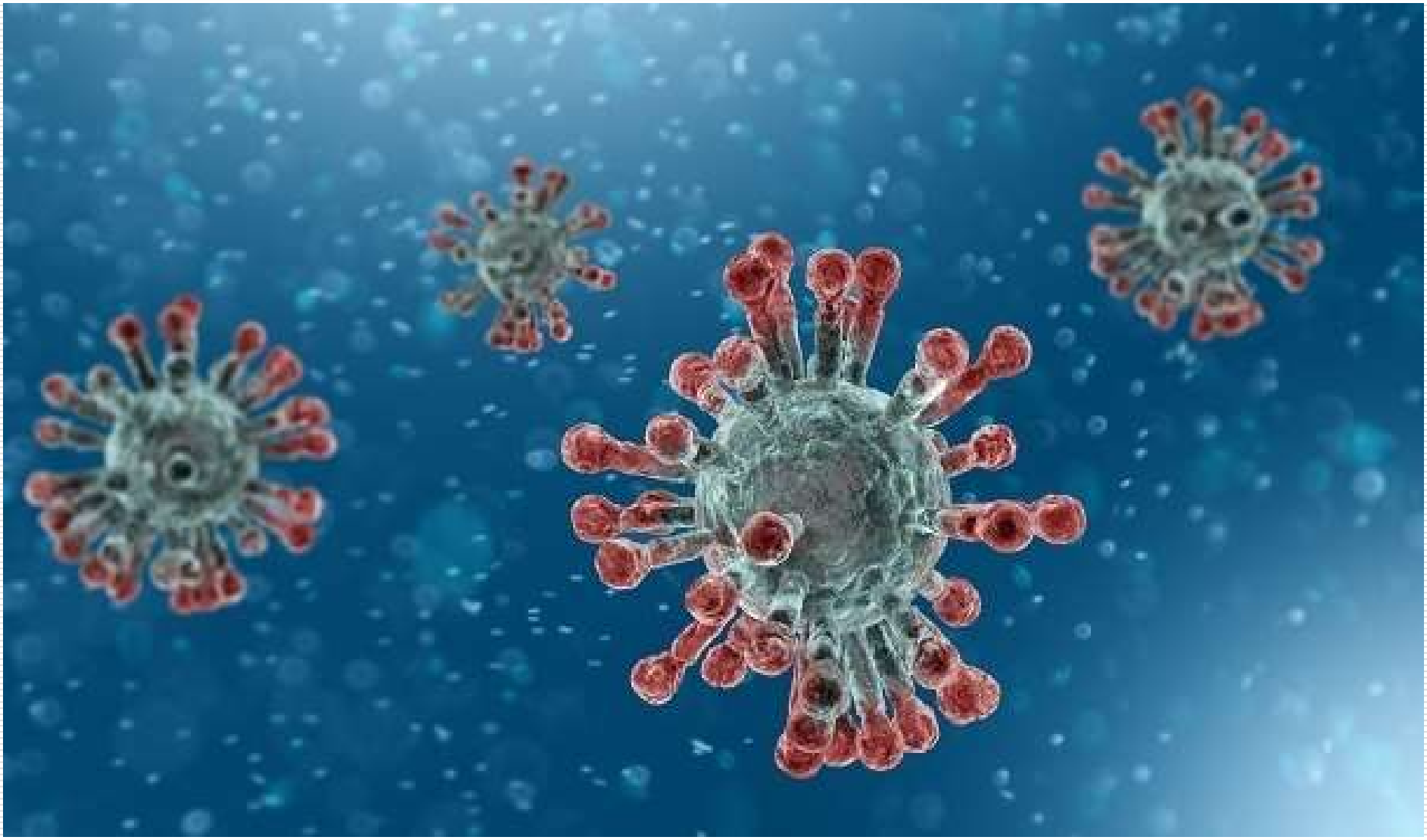
Ratio < 0,8 = negative
Ratio 0,8 - 1,1 = weak
Ratio >= 1,1 = positive

Coxsackie IgG-/IgA-antibodies

3	Coxsackie-Virus IgG A7 (IFT)	+	1:100	< 1:100	[.....	*>
3	Coxsackie-Virus IgG B1 (IFT)	+	1:1000	< 1:100	[.....	*>
3	Coxsackie-Virus IgA A7 (IFT)		<1:10	< 1:10	[....*...	]
3	Coxsackie-Virus IgA B1 (IFT)	+	1:100	< 1:10	[.....	*>

The specific Coxsackie-Virus Type B1-IgG-/IgA-antibodies indicate current humoral immune response against Coxsackie-Virus Type B1.
The specific Coxsackie-Virus Type A7-IgG-antibodies indicate humoral immune-response against Coxsackie-Virus Type A7.
The test system is highly specific for Coxsackie Virus antibodies. Other Enterovirus antibodies (f.e. Echovirus antibodies) are not detectable.

Corona Symptom Checkliste Opportunistische Infektionen: www.arminlabs.com



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DIAGNOSING TICK-BORNE DISEASES

ArminLabs GmbH
Zirbelstr. 58
86154 Augsburg
Deutschland

Post Covid Koinfections Checkliste

Name, Vorname ..... Datum (TT/MM/JJJJ) .....

	Ihre aktuellen und früheren Symptome Bitte klicken Sie auf die Kästchen neben den Symptomen, unter denen Sie leiden	X
1	Magenbeschwerden, Darmprobleme	☒
2	Blutarmut	☐
3	Schubweise Durchfälle, Darmkrämpfe/Schmerzen	☒
4	Fieber oder fiebriges Gefühl	☐
5	Konzentrationsschwäche, Gedächtnisverlust, Vergesslichkeit	☐
6	Enzephalitis/Entzündung des Gehirns	☒
7	Gelbliche Farbe der Haut/Augen	☐
8	Schmerzhafte Gelenke oder geschwollene Gelenke	☒
9	Allgemeine Schmerzen, Sehnenprobleme	☐
10	Grippeähnliche Symptome	☐
11	Rötung(en), Striemen, Hautausschläge (Exantheme)	☒
12	Kleine rote/violette Flecken auf der Haut	☐
13	Herzprobleme, Gefühl von Herzrhythmusstörungen	☐
14	Husten, Schleimbildung, "Lufthunger"	☐
15	Kopfschmerzen, Schwindelgefühl	☒
16	Gestörte Leberfunktion/ Leberlaborwerte	☐
17	Lungenentzündung, Bronchitis	☐
18	Geschwollene Lymphknoten	☐
19	Vergrößerung der Milz	☒
20	Allgemeine Müdigkeit / Erschöpfung, zeitweises oder chronisches Erschöpfungssyndrom	☒
21	Muskelschmerzen, Muskelschwäche	☐
22	Frösteln, Schüttelfrost	☒
23	Verschwommenes, nebliges, trübes, flackerndes, doppeltes Sehen	☒
24	Übelkeit, Erbrechen	☒
25	Dunkler Urin	☐
26	Juckreiz oder Schmerzen beim Urinieren	☒
27	Kribbeln, Taubheit, "brennende" Wahrnehmungen	☒
28	Nackenschmerzen, Nackensteifigkeit	☐
29	Schulterschmerzen	☐

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30	Rückenschmerzen, Beckenschmerzen	☐
31	Schlaflosigkeit	☐
32	Nachtschweiß, manchmal zwischen 2 und 4 Uhr morgens	☐
33	Halsschmerzen, Rachenschmerzen	☒
34	Tinnitus, Hörverlust	☐
35	Trockene Haut	☐
36	Bindehautentzündung, allgemeine Entzündungen in den Augen	☐
37	Panikattacken, Depression, Psychose, Stimmungsschwankungen	☐
38	Krampfanfälle, Zittern	☐
39	Sinusitis	☒

Im Folgenden finden Sie die Anzahl der Symptome für alle Infektionen, auf die wir testen, sowie die Rangfolge, in der Sie auf auf einzelne Infektionen getestet werden sollten

Ranking der Infektionen	Symptomanzahl	Test-Ranking
Chlamydia pneumoniae	9	2
Chlamydia trachomatis	3	9
Mycoplasma pneumoniae	9	3
Yersinia	7	5
Campylobacter	6	6
H. pylori	4	8
HSV 1/2	5	7
EBV	8	4
CMV	7	5
VZV	5	7
HHV 6	6	6
Parvovirus	7	5
Coxsackie-Virus	11	1
Echovirus	9	3
Candida	10	2
Aspergillus	7	5
Parasiten	10	2

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Zusammenfassung

- **Sind opportunistische/reaktivierte Infektionen aktiv und die Ursache?**
- **Sämtliche Viren sind neurovirulent, kardiotrop, enterotrop, bedingen CFS (Mitochodropathie)**
- **Alle genannten Erreger sind intrazellulär**
- **Dominanz einer einzelnen Infektion ?**
- **Die meisten Symptome sind NICHT spezifisch für eine einzelne Infektion !**
- **Sämtliche Patienten haben MULTIPLE Infektionen !**
- **Jeder Patient hat ein INDIVIDUELLES ERREGERPROFIL !**

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3 I´s in Diagnostik und Therapie

INTERNATIONALE KONFERENZ ZU CHRONISCHEN PATHOLOGIEN

» 15.-17. September 2023
» Hybrider akademischer Kongress
» Austausch der neuesten Ideen und Perspektiven im Bereich chronischer Erkrankungen
» Rathaus Gilching [bei München], Rathausplatz 1, 82205 Gilching u.a. mit Dietrich Klinghardt und zahlreichen europäischen und kanadischen Referenten und Wissenschaftlern in Deutsch und Englisch

5te Internationale Konferenz zu chronischen Pathologien 2023 (chronic-pathologies.com)
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Herzlichen Dank für Ihre Aufmerksamkeit!

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