Ozone Therapy Global Journal vol. 12, nº 1. pp. 19-39, 2022
Official Journal of Aepromo (Spanish Association of Medical Professionals in Ozone Therapy). Madrid, Spain
Publicación Oficial de Aepromo (Asociación Española de Profesionales Médicos en Ozonoterapia). Madrid, España
ISSN: 2174-3215

Case Report

Ozonised Saline Solution in treating Post-EBV-Fatigue Syndrome. Case Report and review of the literature

Daan De Coninck, GP
Huis voor integrale gezondheid, Brugge (8310), Belgium

Keywords

EBV, ozone therapy, ozonised saline solution, post-viral fatigue syndrome, fatigue.

Abstract

Context: Currently, there is no effective antiviral therapy recommended for Chronic-Epstein-Barr-Virus Syndrome or for Post-Epstein-Bar-Virus Fatigue Syndrome
Aims: To assess the efficacity of ozonised saline solution(O3SS) used as a complementary therapy in adults who suffer from -Epstein-Bar-Virus Fatigue Syndrome or from Chronic-Epstein-Barr-Virus Syndrome
Methods: Ten adult patients with chronic fatigue symptoms since their EBV-infection (>6 months) were included in this observational case study. Prior to initiating, and two weeks after treatment the Fatigue Severity Scale and lab values to monitor the changes in EBV-VAC-IgG, EBV-VAC-NA, EBV-EA, EBV IgM, Th1 , Th2, CD4 and CD8 were obtained. Patients were treated with O3SS, six sessions at a rate of three sessions a week then four sessions at a rate of two sessions a week (ten sessions in total). No control group was included. Secondary endpoints assessed included the fatigue score of participants and laboratory examinations.
Results: O3SS treatment demonstrated a significant ($p<0.01$) tendency to improve Fatigue Severity Scale and improve laboratory examination results. No side effects were noted during the duration of the study.
Conclusion It would be interesting to have further investigation to know which patients belong to the 20% EBV-EA positive patients who are healthy and more investigation is needed to learn to evaluate the subjective improvements in the lab values, probably by EBV PCR testing or examining the frequencies of CD8+ T-cells specific for EBV latent and Lytic Ags in healthy virus carriers could be interesting..
.

Suggestion on how to quote this paper:
Daan De Coninck, GP (2022). Ozonised Saline Solution in treating Post-EBV-Fatigue Syndrome. Case Report and review of the literature. *Ozone Therapy Global Journal* Vol. 12, nº 1, pp 19-39

Autho mail Daan De Coninck, GP, Huis voor integrale gezondheid, Brugge (8310), Belgium. E-mail: mdaan@drdeconinck.bea
Telephone number: 00(32)50717873

Introduction

Schwartz et al. (2021) noted a significant effect of Ozonised Saline Solution (O3SS) Therapy on the outcome of 25 hospitalised Covid-19 patients with pneumonia. *'Patients with Covid-19 with mild to severe symptoms who received intravenous O3SS treatment experienced no side effects. The main results of O3SS treatment were a tendency to improve clinical symptoms without side effects. None of the patients treated died.'*

This interesting article made me wonder if the same O3SS therapy could work for patients with status post-EBV-infection who subsequently develop Chronic Fatigue Syndrome?
' Infectious triggers are suggested to contribute to development of ME/CFS through disruption of not only the immune response, but also mitochondrial functioning and other cellular processes.' Noor et al.(2021) Rasa et al. (2018)

As there aren't that many therapy strategies for this indication besides anti-viral drugs as for example interferon-alpha Roliński et al. (2007) and methylprednisolone Tynell et al. (1996), probably O3SS could help this patients. The EBV belongs to the human herpes viruses. Infection of the lymphoid tissue of the oropharynx gives two kinds of reactions: the lytic infection (infection of new B-cells) and the latent form (immortalization of the B-cell). Kerr et al. (2019) The human herpesviruses (EBV and others) are most studied human pathogens in association with Chronic Fatigue Syndrome. Roizman et al.(1981) Viruses such as Epstein-Barr virus (EBV) can decrease mitochondrial DNA replication through direct protein interactions and promote the replication of viral DNA replication. This can partly explain the altered or diminisched energy metabolism.

Rasa et al.(2018) Some infected patients are mostly asymptomatic. Some patients, mainly adolescents and young adults, suffer from infectious mononucleosis. In adulthood, 90% to 95% have EBV-antibodies. Hal et al. (2011) Most infected B cells are cleared by the immune system. Latently infected B cells produce no viral particles and a limited gene expression persists. There can be periodic reactivation and shedding of viruses and this can be asymptomatic. Nowalk et al. (2016) Recently was observed that covid-19 infection can lead to an EBV reactivation. EBV with environmental and/or genetic factors can result in malignancy. Gold et al. (2021)

There is little literature on the treatment of Post-EBV-Fatigue Syndrome on Pubmed (((post)AND(EBV)AND(fatigue)AND(syndrome)AND(treatment). The relation with chronic fatigue syndrome is not proven, but patients can have prolonged (> 6 months) fatigue complaints. Roizman et al. (1981) The chronic active EBV infection is a rare disease, often seen in patients with specific T-cel dysfunctions. Histologic evidence of major organ involvement is often seen. Elevated EBV DNA , RNA or proteins are found in the affected tissues. There is extremely high serum EBV viral load, Yuichi Sakamoto et al.(2012)

The EBV-specific antibody against structural viral proteins of the nucleocapsid: anti-VCA antibody, IgG is usually present on the initial blood examination drawn at patient presentation with symptoms. EBV IgM AB is sensitive and specific for infectious mononucleosis. EBV Early Antigens are expressed by the virus against proteins early in the lytic cycle. The EBV-VAC-NA (nuclear antibody) are expressed during latent infections against nuclear proteins of the EBV by the B cells Rühl et al.(2020). The IgG antibodies against EBNA-1 are detectable from the fifth week on. A positive anti-EBNA-1 IgG result excludes a primary EBV infection because it takes five weeks after primo infection to see the EBV-VAC-NA in the blood, Nowalk et al. (2016).

Negative EBNA-1 AB result indicates a primary EBV infection or a secondary negative (immunosuppression) or 5% of patients do not form anti-EBNA-1 after overcoming the infection, Nowalk et al. (2016). EBV-EA antibodies detection is often a sign of active infection but 20% of healthy people may have these antibodies for years. EBV-EA antibody reactivity is possible in all phases: early infection phase, past infection phase and reactivation phase, Nowalk et al. (2016). EA-IgG is not helpful to discriminate between acute and past infection and do not confirm any stage-specific diagnosis, Nowalk et al. (2016).

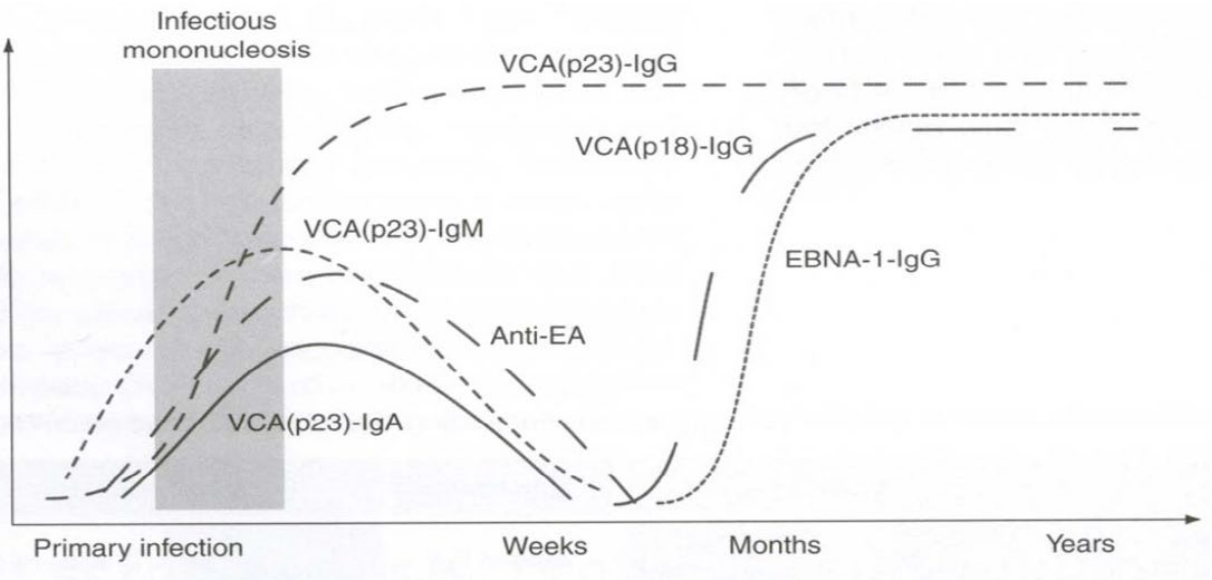


Figure 1. Serology evolution of EBV-infection

Legend:

EBV-VCA-IgM : Epstein-Barr Virus –Viral Capsid Antigen-Immune Globuline M

EBV-VCA-IgG : Epstein-Barr Virus-Viral Capsid Antigen-Immune Globuline G

EBNA-1-IgG : Epstein-Barr Nuclear Antigen-1-Immune Globuline G

Anti-EA : Anti-Epstein-Barr Virus Early Antigen

VCA IgG	VCA IgM	EBNA-1 IgG	INTERPRETATION
+	-	+	Past infection
+	-	-	Relative recent infection or past infection, follow-up serum indicated
+	+	-	Acute infection
+	+	+	EBV reactivation or false positive IgM
-	+	-	Early acute EBV infection or false positive IgM follow-up serum
-	-	-	EBV sensitive
-	-	+	Not plausible

Figure 2. Pathway to discriminate between acute and past infection accorting to Nowalk et al. (2016)

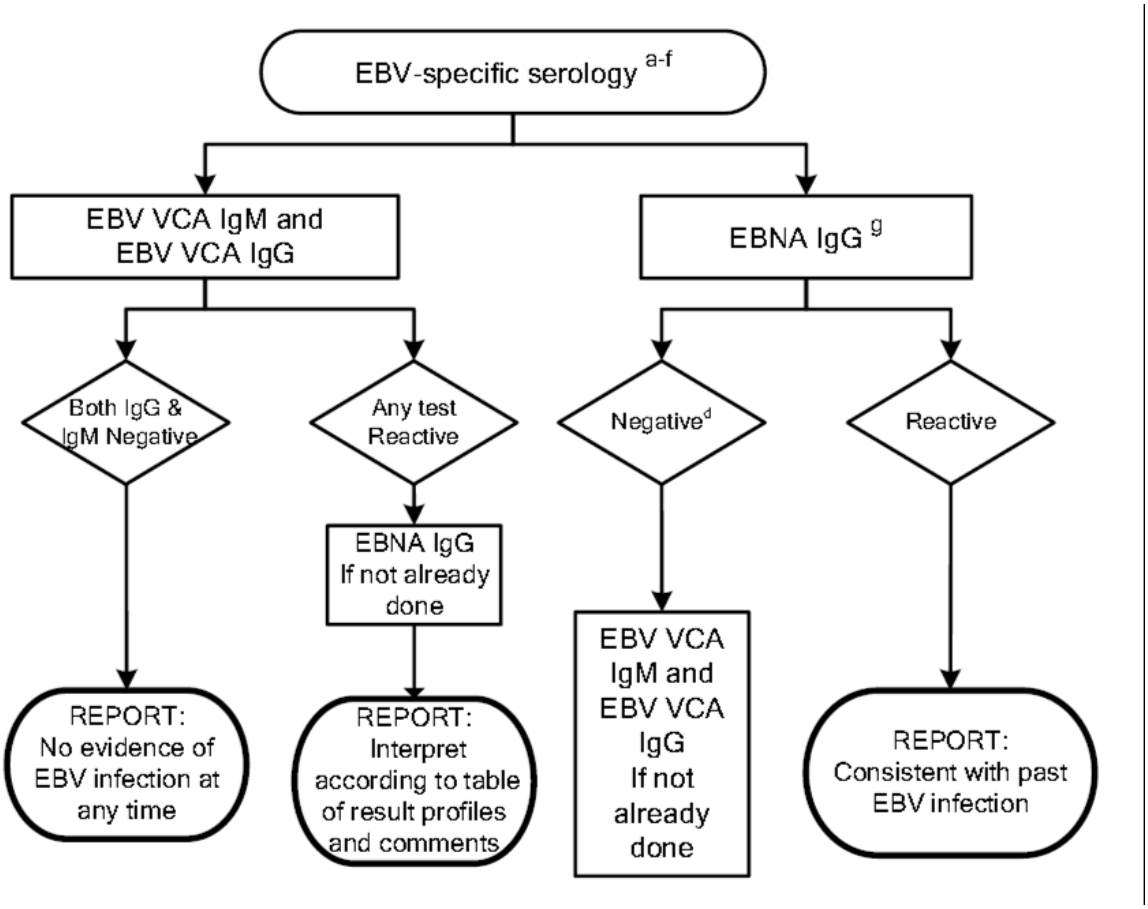


Figure 3. Standards for microbiology investigations Jenson (2011)

Because cytotoxic CD8 T cells are predominantly involved in the **killing of virus infected cells** and CD4 T cell help is required for CD8 T cell priming, maintenance of CD8 T cell memory and prevention of exhaustion, it is likely that both class I- and class II-restricted antigen presentation is involved in EBV control.
It is observed in studies that the CD4:CD8 ratio (normally >1 in healthy, immucompetent persons) becomes inverse during infectious mononucleosis, i.e. less than 1. This is due to the strong response of CD8 cells during acute Epstein barr infection. CD4 cells are said to remain relatively stable during this time. The prolonged activation of CD8 cells can last upto 3-6 months after acute infection according to some studies, meaning that the inverse ratio is also likely to remain for this time, before returning to normal, Tan et al. (1999).

Interleukin-2 (IL-2) increases circulating CD4(+) lymphocytes in patients and helps reducing EBV DNA in cells and plasma. Burighel et al. (2006).

Low dose of ozone is produced by a mixture of oxygen and ozone in a carrier of pure oxygen. Medical ozone therapies are effective in treating a range of human pathologies that have a physiological basis for inflammatory deregulation (oxidative stress). Correctly dosed and timed treatments can induce endogenous oxidative preconditioning which is essential in restoring the Th1:Th2 balance Leon et al. (1988). Potentially, ozone may improve symptoms of Post-EBV-Fatigue Syndrome, acting as an inducer of immune adaptation, a modulator of pro-inflammatory cytokines, and improving tissue oxygenation which is favourable during immunity and healingprocesses, Martinez-Sanchez et al. (2020). The results of covid-19 treatment , by Schwartz et al. (2021) suggest favourable recovery of patients, with stabilization of biochemical indeces and reduced the need for oxygen support with no noted side effects.

Material and methods

The application of O3SS was carried out following the principles of good clinical practice of the international Conference on Harmonisation (Battershill and Fielder, 1998). All patients were informed of the objectives and risks of participation, and gave written consent.

Design and site

Site

These patients were treated ambulatory at the private surgery of doctor Daan De Coninck. This surgery has all source documents recorded in an electronic medical registration system. Routine clinical analyses can be obtained locally and laboratory examinations are obtaine from Medical Laboratory Medina, Dendermonde, Belgium.

Participants

Ambulatory patients with clinical suspicion of Post-EBV-Fatigue Syndrome: male or female aged 18 to 70 at the time of registration; within two weeks of the onset; who have not participated in other clinical studies within the past three months; willing and able to sign informed consent for participation in the O3SS application. Patients were recruited before laboratory confirmation of EBV by EBV-VAC-IgG, EBV-VAC-NA, EBV-EA, EBV IgM, Th1 , Th2, CD4 and CD8.

Exclusion criteria included: participants who were pregnant, lactating or planning to become pregnant during the trial; patients with G-6PD (Favism) defect; patients with a history of uncontrolled hyperthyroidism, an unstable period of severe cardiovascular disease; patients who have used and received an immunosuppressant continuously; patients with significant renal or hepatic impairment or with scheduled elective surgery.

This is an observational case study focused on the efficacity of O3SS treatment in Post-EBV-Fatigue patients. Therefore, a control group was not included.

Procedures and technical information

The participants gave their score on the Fatigue Severity Scale before onset of therapy and 2 weeks after ending the O3SS therapy.

For each participant a blood laboratory analysis was performed before the onset of the therapy and 2 weeks after the O3SS therapy: EBV-VAC-IgG, EBV-VAC-NA, EBV-EA, EBV IgM, Th1 , Th2, CD4, CD8 and IL-2.

The patients were treated by O3SS. 6 times at a rate of 3 sessions a week then 4 sessions at a rate of 2 sessions a week.

O3SS consist of bubbling and saturating 250 ml of sterile physiological solution (0,9%) with an O2/O3 mixture for 10 min continuous bubbling using the infusion set, the solution was administered via i.v. through the basilic or cephalic vein for 15 to 30 min.
Ozonation (bubbling) was stopped when about 50 mL of liquid remained in the bottle (ISCO3, 2020).
Patients under 80 kg received O3SS of 1 ug/Nml. Patients above 80 kg received O3SS of 2 ug/Nml.
The ozone concentration was measured by a spectrophotometer integrated into the ozone generator. The concentration of ozone in saline during the continuous bubbling flow has been calculated as ¼ of the bubbling concentration Yoldi et al. (2019). Under these ozonisation conditions, it was demonstrated that no H2O2 or HOCl appeared at the appropriate concentration (H2O2 not exceeding 0.0004% , Maslennikov et al. (2008) HOCl concentrations are less than 0.001 g/mL, Peretiagyn et al. (2006). The decomposition processes of ozone in aqueous solutions of 0.9% NaCl are not accompanied by the formation of products other than oxygen, Razumovskii et al. (2010).

The ozone was generated by a class IIb CE medical device (Ozonette, Sedecal, Spain).
The container that administered the solution was disposable, made of medical-grade materials, free of phthalates and fully ozone compatible. It has been classified by Bexozone (Bexen Medical, Spain) as a class IIb medical device. Physiological saline solution (0,9% NaCl) from Baxter was used.

The student t-test was the statistical tool for assessing the data.
The standard measure of the amount of IL-2 in this case study is the International Unit (IU).
The measurement of the EBV-VAC-NA is an index. The optimal result is between 0-0.9 index
The IL2 and the EBNA results were put in box plots.

The Fatigue Severity scale is a subjective tool to measure ones feeling of overall abnormal tiredness. It is pointed out by the patient on a visual scale from 0 tot 10. Zero meaning a total lack of energy and ten full of energy.
The FIT results was put in a bar chart.

The p-value < 0.050 is statistically significant.
The p-value <0.050 is not statistically significant.

Results or outcomes

All data presentation:

EBV IgG_1	EBV IgG_2	EBV IgM_1	EBV IgM_2	EBV EA_1	EBV EA_2
269	302	0.43	0.43	7.5	6.6
1098	1125			5.0	5.0
551	539	0.38	0.36	7.2	7.1
801	782	0.28	0.23	5.0	5.0
2570	2632	0.39	0.32	5.0	5.0
3811	3457	0.21	0.21	5.0	5.0
2320	2364	0.27	0.28	10.1	9.6
449	380	0.32	0.24	9.5	10.0

EBV EBNA_1	EBV EBNA_2	T4_1	T4_2	T8_1	T8_2
95	99	523	805	215	266
136	159	788	1001	199	219
60	62	542	235	239	86
133	141	1027	1318	207	276
		825	617	346	279
13	16	522	435	329	295
0	0	548	551	349	417
		269	278	107	103
197	213	1443	1313	188	221
189	194	532	580	348	305

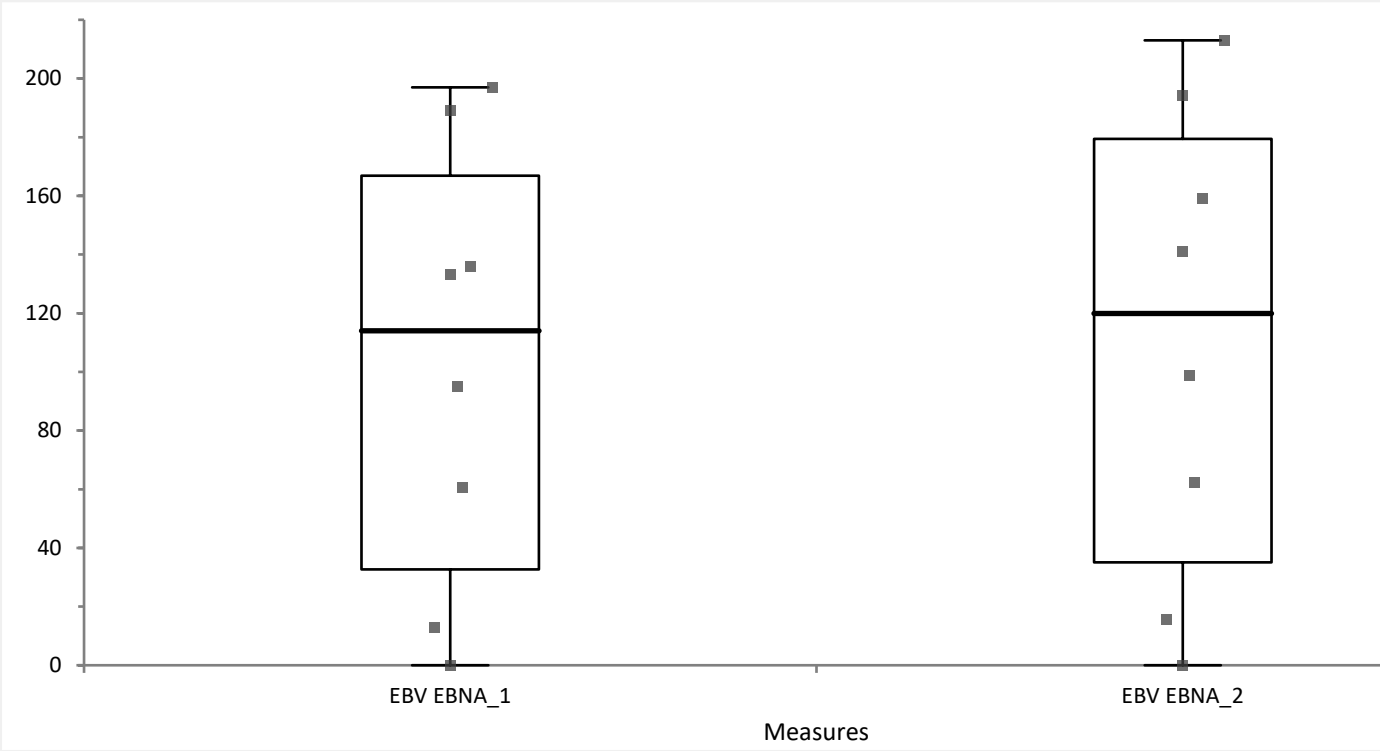
SIL2R_1	SIL2R_2	FIT_1	FIT_2
328	387	0.0	5.5
326	336	3.0	10.0
291	298	4.0	7.0
233	287	4.0	10.0
153	185	6.0	9.0
245	230	2.0	5.0
226	263	2.0	8.0
395	426	0.0	8.0
159	158	5.0	10.0
227	210	3.0	8.0

Legend:
FIT_1: Fatigue Severity Scale by onset
FIT_2: Fatigue Severity Scale after O3SS therapy
SIL2R_1: Serum Interleukin 2 by onset
SIL2R_2: Serum Interleukin 2 after O3SS therapy
T4_1: Helper CD4(+) T cells by onset
T4_2: Helper CD4(+) T cells after O3SS therapy
T8_1: Cytotoxic CD8(+) T cells by onset
T8_2: Cytotoxic CD8(+) T cells after O3SS therapy

Laboratory results

From all the data collected from the laboratory, only the IL2 and the EBNA data showed a statistically significantly difference.
As described in the normal evolution of a EBV infection, The EBV-VAC-IgM (slightly decreased), the EBV-VAC-EA and the EBV-VAC-IgG didn't change much under the influence of 10 O3SS sessions.
The EBV-VAC-NA on the contrary was decreasing slightly (p-value 0.0311) (figure 4.)
CD4 and CD8 didn't changed o lot by O3SS therapy either. The CD8- and CD4 T cells increased slightly. The CD4:CD8 ratio has turned back to >1 six months after the infectious mononucleosis fase (less than 1)
The IL-2 results improved (p-value 0.0461) after O3SS therapy (figure 5.).

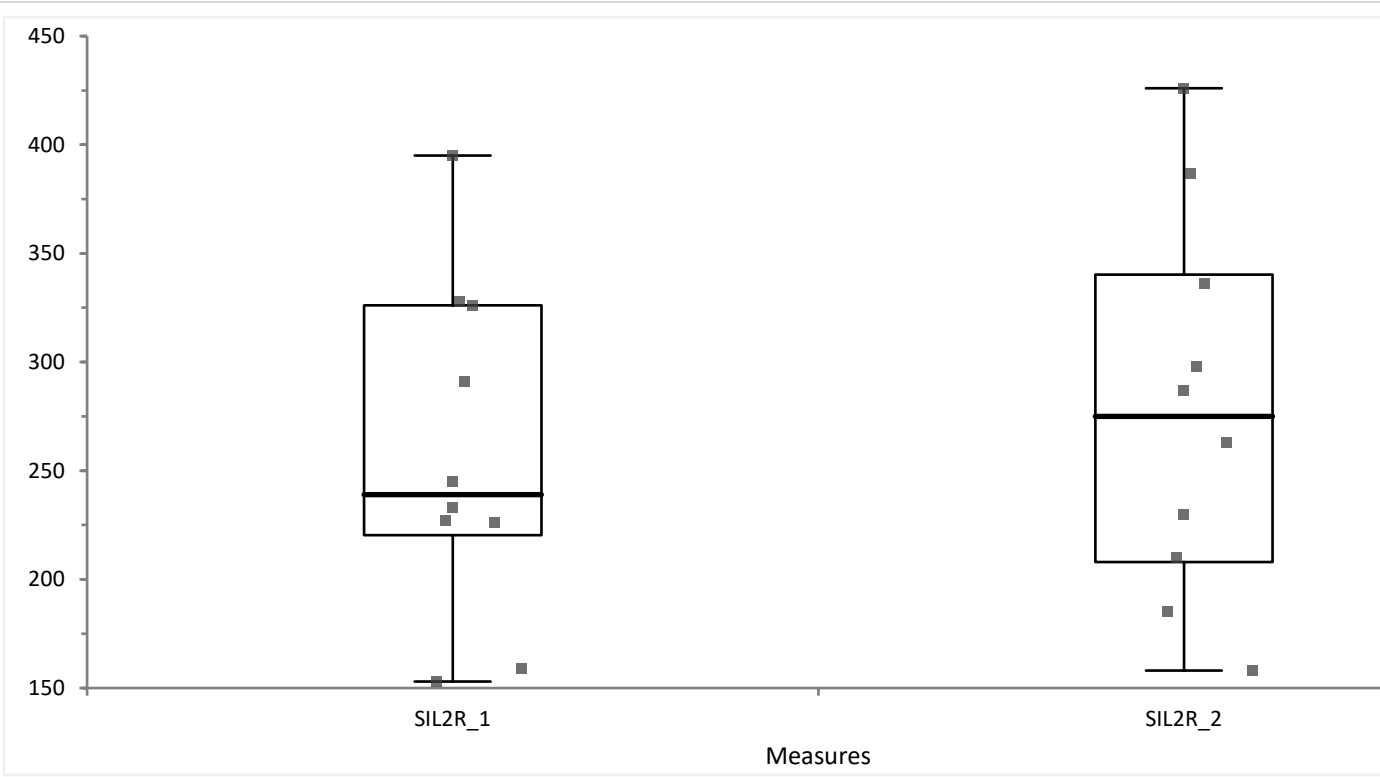
Figure 4. Compare Pairs EBV EBVNA-1, EBV EBNA-2 (plot box)



p-value 0.0311

Y-ax: index measured in laboratory

Figure 5. Compare Pairs: SIL2R_1, SIL2R_2 (plot box)



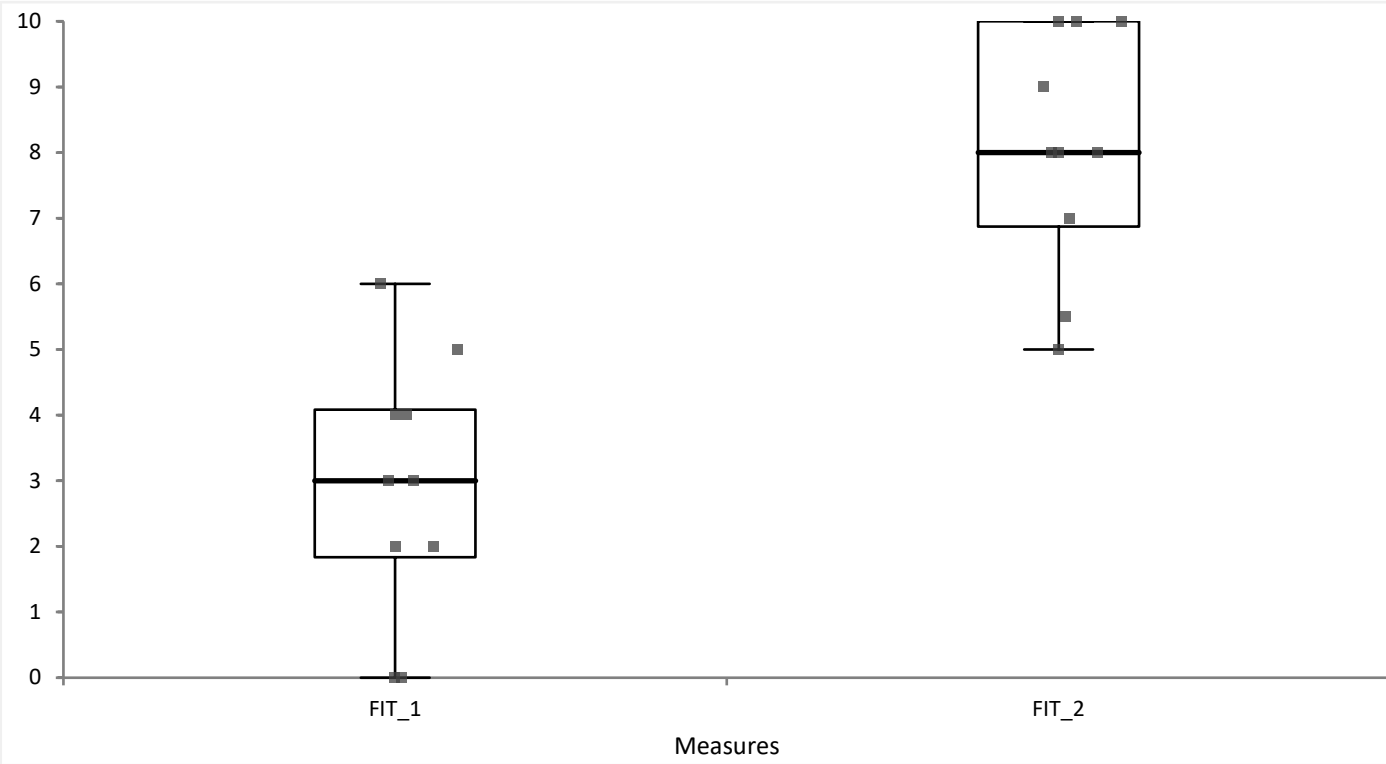
p-value 0.0461

Y-ax: IL-2 U/ml

Clinical outcomes

The FIT-score before and after treatment gave the most important statistical significant p-value.

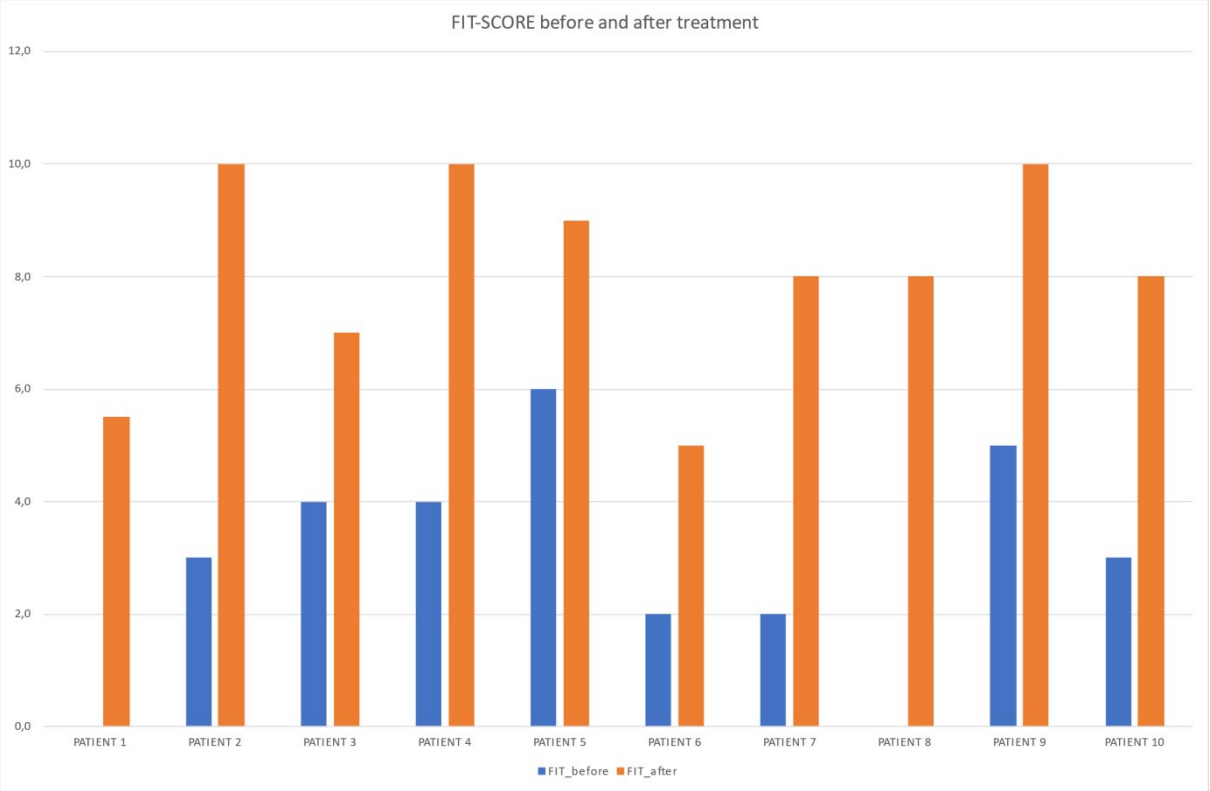
Figure 6. Compare Pairs : FIT-1, FIT-2 (box plot)



p-value <0.0001

Y-ax: Fatigue Severity Scale score on a scale from 0 (exhausted) to 10 (fit)

Figure 7. Fatigue Severity Score bar chart



Bleu bar: energy level by onset

Orange bar: energy level after O3SS therapy

Discussion

To determine scientifically whether O3SS therapy could be seen as a complementary tool in patient therapy, this case study assessed the influence of O3SS therapy in Post-EBV-Fatigue Syndrome patients on Fatigue Severity Scale and on changes of lab values: EBV-VAC-IgG, EBV-VAC-NA, EBV-EA, EBV IgM, Th1 , Th2, CD4 and CD8 .
As described in the normal evolution of a EBV infection, The EBV-VAC-IgM slightly decreased. Further investigation is necessary to determine if this is a sign of recovery of Post-EBV-Fatigue Syndrome

The EBV-VAC-NA on the contrary decreased slightly (p-value 0.0311) (figure 4.). It is still unclear if this change could be an indication of 'healing'.
CD4 and CD8 have not changed significantly by O3SS therapy either. The CD8- and CD4 T cells increased slightly. This could mean that CD8 T cells are not killing viruses in the post-EBV-Fatigue –Fase and CD4 T cells do not have to help them unless there is a viral reactivation . Further investigation on this is necessary.
The IL-2 results improved (p-value 0.0461) after O3SS therapy. Probably this helps decrease the EBV DNA intracellularly and in plasma (nicoletta Burighel et al).

The Fatigue Severity Scale results (figure 7.) confirmed that O3SS therapy has an influence on Post-EBV- Fatigue Syndrome. However the underlying mechanisms are not fully reflected in the laboratory findings.

The small number of participants and the heterogeneity of the participant group is a limitation of this Case Study
It would have been nice to have had a group of Th1:Th2 imbalance, a group of CD4:CD8 imbalance and a group of positive EBV PCR test.

PCR testing of the EBV (which was not done in this case study) is more sensitive than antibody testing for EBV.
Periodic reactivation of the dormant EBV may occur and may cause severe complications in patients suffering from a compromised immune system. Some people remain capable of transmitting the virus throughout their lives.
For these situations, a PCR test is helpful in identifying whether the virus is present in the immune system and to monitor O3SS treatment for EBV (Yuichi Sakamoto et al).

Conclusion

Post-EBV-Fatigue Syndrome is a serious health problem with poor results using the standard treatment (prednisolone and anti-viral agents). It is interesting to observe that O3SS therapy provokes statistically significant changes on the Fatigue Severity Scale and on the laboratory results such as IL-2 and EBV-VAC-NA. These findings motivate for further and more precise case studies over a longer period of time to determine whether the positive changes are temporary or long-term and how O3SS helps in Post-EBV-Fatigue-Syndrome.

The EBV PCR test should be taken into account in subsequent case studies to evaluate whether the O3SS therapy decreases the EBV DNA and to reveal the mechanisms of it (Yuichi Sakamoto et al).

The CD8:CD4 T cell balance also needs more investigation to determine reactivation and suppression of the EBV (Tan LC et al). More investigation is needed about the role of EBV-EA and how to exclude the 20% healthy people who have had these antibodies for years , Nowalk et al. (2016).

Conflict of interest: none

References

Ayako Arai*Advances in the Study of Chronic Active Epstein-Barr Virus Infection: Clinical Features Under the 2016 WHO Classification and Mechanisms of Development , Tohoku J Exp Med 2012 Aug;227(4):307-11.

Burighel N et al. Differential dynamics of Epstein-Barr virus in individuals infected with human immunodeficiency virus-1 receiving intermittent interleukin-2 and antiretroviral therapy Haematologica. 2006 Feb;91(2):244-7.

Cohen JI, Kimura Chronic Active Epstein-Barr Virus Disease Front Immunol.2017 Dec 22;8:1867.

Fugl[1] Anders and Christen Lykkegaard Andersen[1,2] Epstein-Barr virus and its association with disease - a review of relevance to general practice Curr Opin Pediatr.2000 JUN;12(3):263-8

Fujiwara Shigeyoshi[1], Hiroshi Kimura, Ken-ichi Imadome, Ayako Arai, Eiichi Kodama, Tomohiro Morio, Norio Shimizu, Hiroshi Wakiguchi Current research on chronic active Epstein-Barr virus infection in Japan Pediatr Investig J Clin Pathol.2021 Sept 22;5(3):188-194

Gold J, Okyav R, Licht W, Hurley D Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation Pathogens.2021 Jun 17;10(6):763.

Jenson Hal B, MD Epstein-Barr Virus Pediatr Rev(2011)32(9):375-384 ,

Jenson Hal B, MD Acute complications of Epstein-Barr virus infectious mononucleosis 2021 Aug;27(8):682.e1-682.e12.

Kerr Jonathan R, 2019 Oct; 72(100):651-658.Doi: 10.1136/jclin-path-2019-205822.Epub 2019 Jul 17. Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors , jclinpath-2019-205822 Full text linksCite

Kerr Jonathan R [1] Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors Clinical characteristics and effectiveness of antiviral agents in hospitalized children with infectious mononucleosis in China: A multicenter retrospective study jclinpath-2019-205822. Epub 2019 Jul 17.

Kidd P. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. Altern Med Rev. 2003 Aug;8(3):223-46.

Lu Meng-Chen Lu[1], Jing Zhao[2], Yu-Ting Liu[2], Tian Liu[2], Meng-Min Tao[2], Qi-Dong You[1], Zheng-Yu Jiang[3] , Antioxidants (Basel). 2020 May 6;9(5):389. doi: 10.3390/antiox9050389. CPUY192018, a potent inhibitor of the Keap1-Nrf2 protein-protein interaction, alleviates renal inflammation in mice by restricting oxidative stress and NF-κB activation

Martinez-Sanchez G, Schwartz A, Donna VD. Potential Cytoprotective Activity of Ozone Therapy in SARS-CoV-2/COVID-19 Antioxidants (Basel).2020 May 6;9(5):389.

Marzolini Maria A V [1], Andrew J Wilson[2], Emilie Sanchez[3], Ben Carpenter[2], Ronjon Chakraverty[2], Rachael Hough[2], Panos Kottaridis[2], Emma C Morris[2], Kirsty J Thomson[2], Natural History of Epstein-Barr Virus Replication and Viral Load Dynamics after Alemtuzumab-Based Allogeneic Stem Cell Transplantation BMC Infect Dis.2018 Apr 20;18(1):190 Int J Clin Exp Pathol

Anesth Pain Med. 2021
Miller CL, Burkhardt AL, Lee JH, et al. Integral membrane protein 2 of Epstein-Barr virus regulates reactivation from latency through dominant negative effects on protein-tyrosine kinases. Immunity 1995;2:155-166

Moghaddam A, Rosenzweig M, Lee-Parritz D, Annis B, Johnson RP, Wang F. An animal model for acute and persistent Epstein-Barr virus infection. Science 1997;276:2030-2033

Nazir Noor, Ivan Urits, Arielle Degueure, Lauren Rando, Vijay Kata, Elyse M. Cornett, Alan D. Kaye, Farnad Imani, Mahnaz Narimani-Zamanabadi, Giustino Varrassi, and Omar Viswanath A Comprehensive Update of the Current Understanding of Chronic Fatigue Syndrome Anesth Pain Med. 2021 Jun 26;11(3):e113629

Niedobitek G, Agathanggelou A, Herbst H, Whitehead L, Wright DH, Young LS. Epstein-Barr virus (EBV) infection in infectious mononucleosis: virus latency, replication and phenotype of EBV-infected cells.J Pathol 1997;182:151-9.

Nowalk Andrew, Michael Green Epstein-Barr Virus Infection Microbiol Spectr. 2016 June;4(3). Doi: 10.1128/microbiolspec.DMIH2-0011-2015

Ramazan A. Okyay, Warren E Licht, David J Hurley Affiliations expand PMID: 34204243 PMCID: PMC8233978 DOI: 10.3390/pathogens10060763 Investigation of Long Covid Prevalence and Its relationship to Epstein-Barr Virus Reactivation, 2021 Jun 17; 10(6):763.Doi: 10.3390/pathogens10060763 Pathogens

Roizman B, Carmichael LE, Deinhardt F, de The G, Nahmias AJ, Plowright W, Rapp F, Sheldrick P, Takahashi M, Wolf K. Herpesviridae. Definition, provisional nomenclature, and taxonomy. The Herpesvirus Study Group, the International Committee on Taxonomy of Viruses. Intervirology; 1981;16:201-217. Doi: 10.1159/000149269 (PubMed) (CrossRef) (Google Scholar)

Roliński[1,2], Ewelina Grywalska[3,4], Aleksandra Pyzik[1,2], Michał Dzik[1,2], Violetta Opoka-Winiarska[5], Agata Surdacka[1,2], Maciej Maj[1], Franciszek Burdan[2], Michał Pirożyński[6], Piotr Grabarczyk[7], Elżbieta Starosławska[2] J Virol Methods Real-time quantitative PCR for assessment of antiviral drug effects against Epstein-Barr virus replication and EBV late mRNA expression J Virol Methods. 2007 Jul;143(1):38-44

Rolinski et al. J Virol Methods.2007 Jul;143(1):38-44 Interferon alpha as antiviral therapy in chronic active Epstein-Barr virus disease with interstitial pneumonia - case report

Rühl Julia,[1] Carol S. Leung,[2] and Christian Münz[1,] Vaccination against the Epstein–Barr virus , Cell Mol Life Sci. 2020; 77(21): 4315–4324.Published online 2020 May 4. doi: 10.1007/s00018-020-03538-3

Sagai M, Bocci V Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress? Med Gas Res. 2011 Dec 20;1:29.

Santa Rasa, Zaiga Nora-Krukle, Nina Henning, Eva Eliassen, Evelina Shikova, Thomas Harrer, Carmen Scheibenbogen, Modra Murovska, BHUPESH k; Prusty, and the European Network on ME/CFS Chronic viral infections in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) J Transl Med. 2018 Oct 1;16(1):268

Sausen Daniel G. 1, Maimoona S. Bhutta 1, Elisa S. Gallo 2, Harel Dahari 3 and Ronen Borenstein 1,3,*
Stress-Induced Epstein-Barr Virus Reactivation Biomolecules. 2021 Sep 18;11(9):1380.

Schwartz Adriana, Gregorio Martinez-Sanchez, Alejandra M ; de Lucia, Sergio M. Viana, Alina M. Constantas Complementary application of the ozonized saline solution in mild and severe patients with pneumonia COVID-19: A non-randomized pilot study 2021 Journal of Pharmacy & Pharmacognosy Research, 9 (2) 126*142, 2021 ISSN 0719-4250

Straus SE. The chronic mononucleosis syndrome. J Infect Dis 1988;157:405-412
Published online 2019 Feb 5. doi: 10.3389/fped.2019.00014, Front Pediatr. 2019; 7: 14

Tan LC, Gudgeon N, Annels NE, et al. A re-evaluation of the frequency of CD8+ T cells specific for EBV in healthy virus carriers. J Immunol 1999;162:1827-1835
BMC Fam Pract. 2019; 20: 62.Published online 2019 May 14

Tierney RJ, Steven N, Young LS, Rickinson AB. Epstein-Barr virus latency in blood mononuclear cells: analysis of viral gene transcription during primary infection and in the carrier state. J Virol 1994;68:7374-7385

Tynell E[1], E Aurelius, A Brandell, I Julander, M Wood, Q Y Yao, A Rickinson, B Akerlund, J Andersson Tynell E, Aurelius E, Brandell A, et al. Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study. J Infect Dis 1996;174:324-331

Wang Ren-Chingg[1], Sheng-Tsung Chang[2], Yen-Chuan Hsieh[3], Wan-Ting Huang[4], Jeng-Dong Hsu[5], Chih-En Tseng[6], Ming-Chung Wang[7], Wei-Shou Hwang[8], John Wang[1], Shih-Sung Chuang[9] Spectrum of Epstein-Barr virus-associated T-cell lymphoproliferative disorder in adolescents and young adults in Taiwan
Pediatr Int.2014 Apr;56(2):159-66.

Yao QY, Rickinson AB, Epstein MA. A re-examination of the Epstein-Barr virus carrier state in healthy seropositive individuals. Int J Cancer 1985;35:35-42

Yuichi Sakamoto[1], Yasushi Mariya, Kohmei Kubo, Quantification of Epstein-Barr virus DNA is helpful for evaluation of chronic active Epstein-Barr virus infection Tohoku J Exp Med. 2012 Aug;227(4):307-11. DOI: 10.1620/tjem.227.307.