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Post Viral Fatigue Syndrome effectively treated with Hyperbaric Oxygen Therapy.

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Abstract

In this case study we will present the case of a 27-year-old patient that requested Hyperbaric Oxygen treatment (HBOT) to improve his cognitive performance. After a couple of years of poor general wellbeing, brain fog and fatigue the patient underwent approximately 20 hours of HBOT at the end of which he reported a significant improvement in his mental performance, vitality and social functioning. The effect of HBOT therapy has been validated through EEG test and retest scans that show an overall improvement of both the P300 measures and the EEG spectrum analysis. Subjective data on his perceived health was obtained by SF-36 pre and post treatment which revealed significant improvements in the majority of the markers. These changes of qEEG metrics and quality of life measures suggest that HBOT could be an effective treatment for general cognitive impairment, and we therefore suggest further research should be warranted and more data collected.

Keywords: HBOT, hyperbaric oxygen, EEG spectrum analysis, SF-36, cognitive impairment

Introduction

Viral encephalopathy caused by an Epstein-barr virus infection (EBV) affect mostly children and usually resolve naturally. When it affects adults, the most frequent symptoms are fever, trouble thinking, lack of focus and concentration and is usually diagnosed through blood tests and MRI scans. The easiest way to transmit EBV is through kissing between an uninfected and an EBV-seropositive person. Incubation period is between 30 and 50 days, and is generally accompanied by extreme fatigue, which is maximal in the first couple of weeks [6] and if continues past 3 months is considered to be chronic post-viral fatigue syndrome.

In most cases recovery is complete and should not cause complications. EBV can resemble other conditions such as HIV infection and Cytomegalovirus (CMV) which can also cause a mononucleosis syndrome. 60 to 90% of adults have CMV infection (resulting in lifelong latent infection). Congenital CMV infection may be asymptomatic or may cause abortion, stillbirth, or postnatal death. Complications include extensive hepatic and central nervous system (CNS) damage. CMV mononucleosis can be differentiated from infectious (EBV) mononucleosis by the usual lack of pharyngitis, a negative heterophile antibody test, and through CMV serologic testing. CMV is cured with induction therapy and resolves in about 3 weeks [6].

Hyperbaric oxygen therapy (HBOT) is a medical treatment that uses oxygen as a drug by diving patients in a pressure vessel and regulating the atmospheres at a greater than ambient pressure. First military and medical studies on HBOT are dated as far as the 1930s, however the very first rudimentary steps in hyperbaric were in the 1660's. When used for wound healing; it is thought that hyperbaric increases tissue oxygen tension and improves collagen synthesis, creates new blood vessels, and helps with resistance to bacteria in the wounds [4]. Harch has done research that shows hyperbaric oxygen therapy exerts its wound-healing effects by the expression and suppression of individual genes [12]. Harch reports that the dominant gene actions are the upregulation of trophic and anti-inflammatory genes and down-regulation of pro-inflammatory and apoptotic genes [12.] The combination of genes affected

depends on the different combinations of pressure used by the HBOT, thus protocols need to be created for optimal outcomes.

There are many layers of which hyperbaric assists in the healing process. At the cellular level, it alleviates oxidative stress and increases levels of nitric oxide through improvement of mitochondrial function. HBOT also reduces inflammatory reactions allowing tissue to heal at a more rapid rate. Hyperbaric oxygen therapy is also neuroprotective after traumatic injury, possibly through inhibition of the TLR4/NF-κB signaling pathway [21]. In the realm of cancer treatments, it is found that HBOT can increase the cystostatic effects of certain chemotherapy agents which may render them more effective [26].

Research has been extensive on HBOT utilized for multiple clinical indications such as decompression sickness, non-healing wound ulcers, osteomyelitis, carbon monoxide poisoning, and acute thermal burn injuries [4]. There are different protocols for each indication and frequently the ATM is set at 2.0-3.0 with 60-90-minute treatments for 20-40 treatment sessions [18]. There can be adverse events associated with HBOT and more frequently it is related to the use of higher pressures. These adverse events can include barotrauma to the ears and sinuses, myopia, even seizures and congestive heart disease exacerbation [18]. There are a few contraindications that patients are screened for prior to initiating HBOT and these include but are not limited to: untreated pneumothorax, seizure disorder, hyperthyroidism, CHF, pulmonary disease and severe claustrophobia [18]. Oxygen is a vasoconstrictor and HBOT can increase cardiac afterload, patients with an ejection fraction of less than 30% they may not be a candidate for HBOT therapy [18].

Recent interest has advanced on the use of HBOT as an adjunctive treatment for mild TBI patients. Results are controversial [10] despite the high interest, scientific opinion diverge on the effectiveness of such regimen and a reliable and conclusive study is yet to be published. There is though compelling evidence that suggest that such practice is beneficial to improve impaired brain functioning [10]; HBOT is postulated to help with brain function by improving oxygenation which would then stimulate local trophism via endogenous stem cell mobilization and reduction in chronic inflammation which is likely to be affecting the central nervous system during these viral illnesses [18]. Stem cells are crucial in healing; they are circulating throughout the body continuously. Hyperbaric oxygen can mobilize the stem cells as it

increases the synthesis of nitric oxide in the bone marrow. This synthesis then triggers enzymes that mediate the stem cell release. In a research study by Thom, et al; it was found that the CD34+ cells (also known as hematopoietic stem cells) in peripheral circulation doubled in response to a single HBOT session at 2.0 ATA for 2 hours and that over the course of 20 treatments the circulating CD34+ cells increased eightfold [28].

The amount of atmospheric pressure needed for positive results in a study can be disease specific. In research conducted by Harch, they concluded that in mild traumatic brain injury patients a 40-hour program over the course of 8-10 weeks at a pressure of 1.5 ATM with 60 minutes treatments resulted in significant improvement in post-concussive symptoms in cognitive variables as well as behavioral and emotional variables [13]. These improvements were sustained three months post last treatment session; this suggests that HBOT is a disease-modifying therapy for mTBI [13]. This study also evaluated the dose-response to HBOT determining the most appropriate ATM and length of treatment protocol for superior results to the patient. This factor is very important when researching protocols to utilize for specific diseases. There are very few validated studies on viral encephalopathies as the primary indication for hyperbaric oxygen therapy; there is a plethora of information and studies on traumatic brain injury, wound healing and even cancer modulation [2,8,10, 13, 26]. However, the symptoms of viral encephalopathy can and do overlap with the symptoms of a mild traumatic brain injury including cognitive and behavioral/emotional symptoms.

Here we illustrate a case study of a 27-year-old male that underwent hyperbaric oxygen treatment (HBOT) after being diagnosed with EBV and CMV as well as likely presentation of post-viral fatigue syndrome. HBOT treatments might be the cause of significant improvement in his cognitive performance and we therefore believe that future research on HBOT is warranted and could lead to interesting positive results on other patients.

Background Information

A 27-year-old male was taken into care after presenting troubles focusing, thinking and concentrating, symptoms that affected his daily activities and working performance. He requested hyperbaric oxygen therapy (HBOT) treatments for generalized health benefit including issues with fatigue and declined cognitive ability. He had complaints of above

symptoms as well as headaches, intermittent low-grade fever, mild balance problems, irritability, sadness and overall feeling more emotional since 2016. He has a positive history for Hashimoto thyroiditis with most recent ultrasound in July 2018 to be within normal limits and without nodules or abnormalities but lab value of TSH <0.02 on April 2019. He is under medical treatment for this condition.

Historically, his initial case of mononucleosis was diagnosed in June 2016. Additionally, he was found to have positive Cytomegaly virus (CMV) diagnosed on September 2017 where West nile virus, CBC, CMP and monospot were also checked and all negative at that visit. He has intermittently been on and off of antibiotics and antivirals for a number of acute conditions such as sinusitis, mycoplasma, ear infections. He was found to have intermittently high abnormal liver enzymes in 2017 AST of 61 (normal range 0-41) and ALT 186 (normal range 0-45) with a negative hepatitis panel. This elevation resolved by May 2018 where the AST normalized at 14 and the ALT at 23. During that time, he was seen by Gastroenterology specialty and the elevated liver enzymes resolved without intervention and thought to be due to toxic effects of one of his supplements. In an urgent care visit on February 2018 he completed lab work for a Strep screen, influenza antigens, mycoplasma pneumoniae, mononucleosis, CBC, CMP, and HIV – all of which were negative and/or within normal limits aside from a BUN/creatine ration which as 25 (normal 10-24). He had undergone an MRI scan in 2018 at Mayo clinic and a consultation with an infectious disease specialist. Most recently he was found to have increased systemic C. albicans on July 2019. This information is important as EBV, CMV, viral hepatitis or HIV can have similar presentations but very different outcomes. What was found is that he had an initial EBV infection with a subsequent CMV infection.

He presented to our clinic on December 2019, seeking out HBOT treatments for general health benefits. At that time, he reported that he had also undergone 15+ ozone treatments at a clinic in a larger city. He underwent a baseline cognitive Impact test on 1/20/2020 which revealed a symptom score of 39 and a cognitive efficiency index of 0.37. Impact is designed to simultaneously measure speed and accuracy of the patient's response to questions. The cognitive efficiency index looks at both. Between December 2019 and March 2020, he completed twenty-two hours of HBOT and four infusions of Intravenous nutrients of a modified Myer's cocktail. On 6/17/2020 he completed the WAVi test. At that visit he was tested with an electroencephalogram (EEG) and evoked potentials were taken as a baseline

reading of his cognitive performance. EEG measures the electrical signal of the brain via electrodes placed on the scalp and it has been widely used as a clinical tool and for research to understand brain response to various stimuli.

The WAVi EEG test was recorded in a quite space, sampled at 250 Hz and bandpass filtered between 0.5-30 Hz. The electrodes were placed on the scalp according to the international 10-20 system using caps with 19 tin electrodes. The reference electrodes are placed at the earlobes. The test administrators were instructed to keep the electrode impedances below 20kOhm for EEG locations and below 10kOhm for the ground-to-ear locations where possible. These targets are well below the 1 GOhm input impedance of the WAVi amplifiers, are practical regarding preparation time and produce sufficient yield (Kappenman, 2010). A continuous 4 minute 2-tone audio oddball eyes- closed P300 protocol was used to acquire both background and evoked EEG data. Here, 200 common tones (1000 Hz) and 40 rare tones (2777 Hz) were delivered in random order over the span of 4 minutes, creating a 0.95s interstimulus interval with a 50 ms tone length. The tones were delivered using SkullcandyTM over the ear headphones, at 65 dB.

The markers investigated in this case study were the P300 wave (both Voltage and Latency) and the EEG spectra which are the most examined metrics for EEG event-related potentials (ERP); the voltage (amplitude) of the P300 signal is a widely used measure of cognitive efficiency in decision making process. P300 voltage, measure in uV, represents the strength of the cortical signal received when a stimulus has been presented and registered and therefore greater attention produces larger P300 signals. Target ranges vary by age (Ferreri, 2017) but in the case of a 27-year-old, a healthy brain should sit in the range of 9-22 uV. This measure has been shown to alter with age, cognitive impairment, the appearance of neurological conditions (MS, fibromyalgia, autism etc..), concussion, and a wide variety of acute conditions that affect cognition [1, 14, 17].

On the other hand, P300 voltage can improve with improvements in heart health (such as lower blood pressure), nutrition, and lifestyle [11]. Another widely used and studied measure of cognitive performance is the latency (speed) of the P300 which is defined as the time it takes for the cortex to register an external stimulus after it has been presented, therefore it's the delay from when the rare tone is presented to brains feedback. Again, the speed of the P300 depends on age [9] and for a 27-year-old healthy patient, the P300 latency should lie between 246 and

320 ms. This measure of speed has been shown to decline with age, cognitive impairment, in the presence of neurological conditions. a wide variety of chronic conditions that affect cognition [9, 14]. Similar to the P300 voltage, P300 speed can increase with better heart heath, cardio exercise, meditation, among others [11].

Another important aspect of EEG is the spectrum, which is now considered to by one of the primary methods in neuroscience. A lot of information related to cognitive state and human behavior can be obtained by performing the Fourier transform of the raw EEG signal and looking at distinct frequency bands of the brain. In order of decreasing speed, the main brain frequencies of EEG waves are; delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-35 Hz) and gamma (35 HZ) waves and each wave has its own characteristics.

The alpha frequency (AF), generally between 8 and 12 Hz, is the dominant frequency of the human electroencephalogram (EEG) spectrum when in a relaxed state such as the oddball experiment done in this case study. Measured during relaxed wakefulness, the power of the alpha rhythm is typically strongest in the eyes-closed condition. AF can provide information on central nervous system functioning as well as the status of mental health and cognitive functioning. Significant correlations between AF and a large variety of cognitive measures have been observed, perhaps suggesting links between AF and speed of information processing, the timing of neural inhibition, or the gating of information in the brain [9].

Clear changes in the alpha rhythm are seen as the human brain ages, including AF slowing, reduction in alpha power, and a shift in the posterior-to-anterior direction. Slowing of the EEG has also been found to indicate central nervous system (CNS) pathology, in particular slowing of AF has been observed repeatedly in patients with dementia [17].

Results

Patient reported that after his treatment cycle and at a follow up post WAVi testing that his general wellness had dramatically improved. He reports significant improvement in short term memory and a marked increase in physical and emotional energy. He reported that he has not felt this good in four years. He did go on to complete 16 more hours, to date, and 2 more modified Myers infusions. There were some pauses in treatment during the COVID-19

pandemic; however, he remains consistent in his treatment plans. There is subjective and objective data confirming improvement in cognitive performance. This opens the opportunity for additional studies on this subject matter.

Two baseline scans were taken on the same day, 2/8/2020; these scans show no evident P300s in the parietal and occipital area, an in range P300 latency of around 300 ms and a low but in norm P300 voltage of around 9.3 uV. Both baselines done in February are consistent with the outcomes; the second scan done the same day shows a lower yield (i.e., more artifact), but there are clear P300s in F3 and F4. It must be mentioned that the condition of the patient, both environmental and physical, has evidently not changed in the short time between the two scans, but there is a clear variance between them, which can be explained only through some attentional shift. Consecutive scans are then relevant, especially in case studies which involve a single patient, as they give us an idea of the intrasession variance that can show up in such sensitive reading tools.

A second set of consecutive scans were done on June 17, 2020. P300 readings in the central channels indicate a P300 magnitude of 15.8 uV which is greater than the intrasession variance between baseline scans (+- 2uV) (Clayton, 2020) and therefore it would suggest improvement following the HBOT. Scans also seem to suggest an improvement in the P300 latency that is now around 240 ms, therefore making the brain reaction time extremely fast.

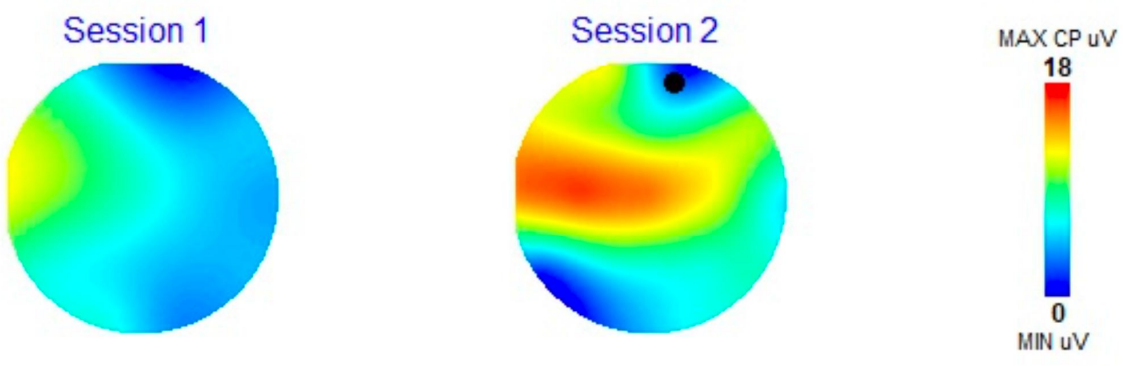

Fig.1: P300 voltage maps. Session 1 indicates the pre-scan while session 2 refers to the scan done post HBOT treatment. The black dot indicates a low yield in that location, and it is therefore not reliable, but the rest of the topography shows a significant increase in P300 voltage.

Improvement in brain performance, consistent with resolved symptoms, between pre- and post-scans is illustrated in both Figure 1, which compares voltage maps of the two scans, and Figure 2, that illustrates the central-parietal (CP) average in February and in June 2020. In Figure 1 the second topographic map manifests a wider area of the brain with higher P300 voltage. In Figure 2, we compare CP P300 average quantity in response to the rare tones in pre- and post-scans. In the retest scan, the P300 voltage average of the CP areas is not only higher but it presents a clearer P300 waveform, which was not so evident in the scan dated February.

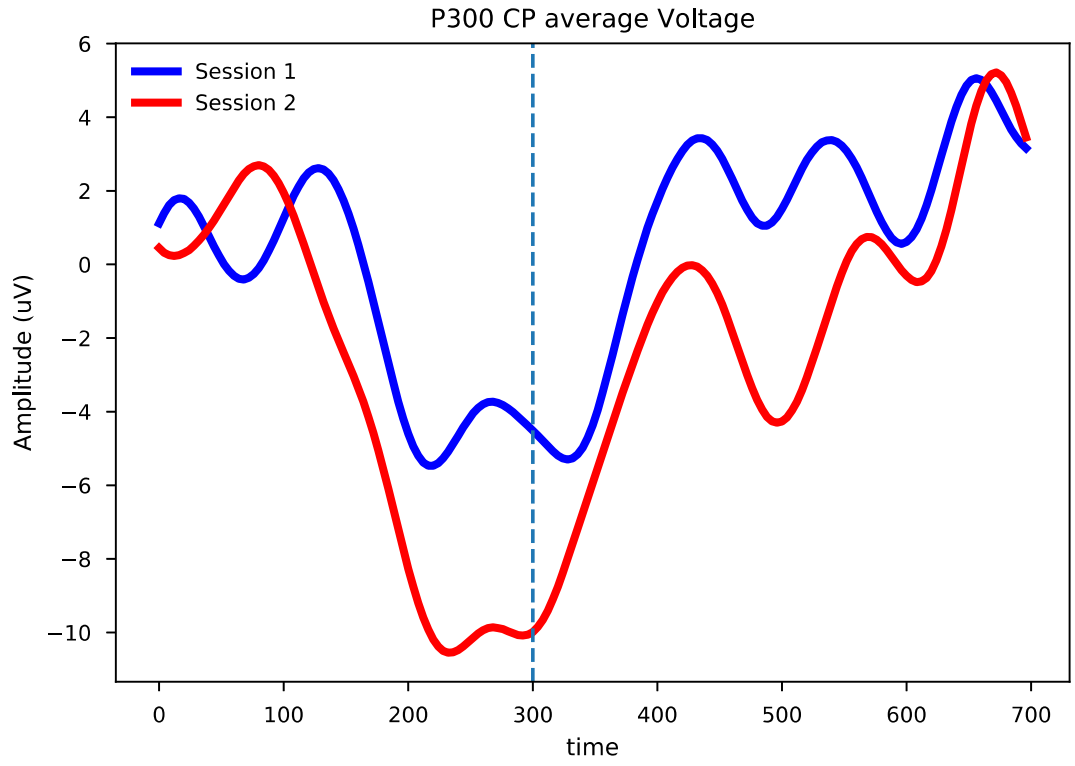

Fig.2: Central parietal average of the P300 waveform for the first session, dated February 2020 and the second session done after HBOT and recordings of improved symptoms.

The spectrum analysis of the baseline scan dated February 2020, indicates that there is a higher magnitude in the occipital area, characteristic of healthy patients, and there are good values of alpha peak frequencies (~10 Hz). An uncommon feature of the spectra is the presence of a second peak in the theta band in the central-parietal region. To explain this phenomenon, which is a pathology that appears in trauma patients, further research is warranted.

Retest scans done in June 2020, do not present double peaks as seen in baseline scans; peaks recorded are sharper and present higher magnitudes in all locations. Even in this case, higher alpha peaks in the occipital area as seen in healthy patients. This behavior is illustrated in

Figure 3, where we compare pre- (blue) and post-scans (red) spectrums of the CZ channel location.

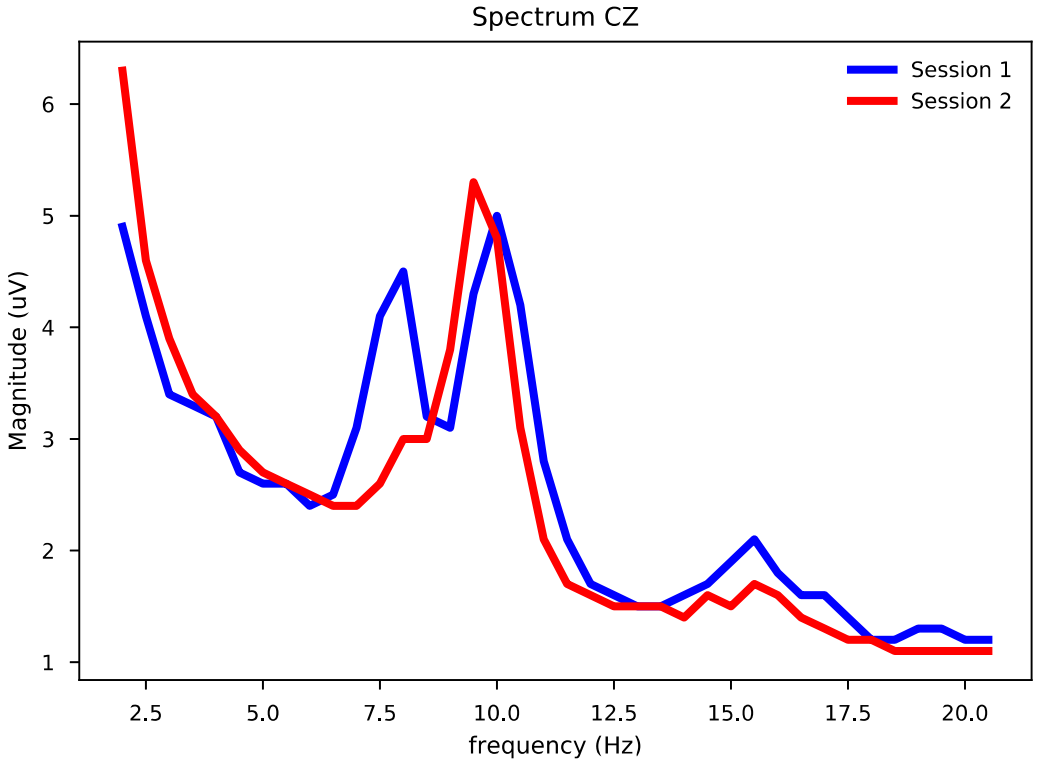

Fig.3: Comparison of spectra for the pre-scan (blue) and the post-scan (red). The double peak resolves and spectra behavior resembles normal spectra brain activity.

Note that the second set of WAVi EEG scans were repeated after around 20h of Hyperbaric oxygen treatment (HBOT). In the chamber, oxygen tension increases using pressure which forces oxygen to flow into the brain faster and deeper. This technique is used for recovery from injuries, thinking difficulties, stroke, wound healing. A fascinating article by Tal, et al., in Israel published in 2015 looked at how HBOT can induce neuroplasticity through angiogenesis. They enrolled 10 TBI patients to their study, pre-tested their brain perfusion MRI's and computerized cognitive test then put them through a protocol of HBOT for 60 sessions over 12 weeks. Post treatment they tested the patients again with MRI's and cognitive tests and the analysis revealed significantly increased cerebral blood flow and cerebral blood volume (Tal, et al, 2015). Within the cognitive testing they noted improvement in global cognitive scores with increases in motor skills, information processing speed and visual spatial processing. What is interesting is that their patient population was in old traumatic brain injuries occurring on average 7-13 years before the intervention. This concludes that HBOT may actually improve perfusion to chronic damaged brain tissue. Boussi-Gross, et al, studied 56 mTBI

patients 1-5 years post their injury in a HBOT trial of 40 – one-hour long treatment sessions at 1.5 ATM over 8 weeks [2]. As of note, this is the same treatment protocol used by Harch [13]. Boussi-Gross, et al determined that even at the chronic stage of mTBI, HBOT can significantly repair impaired brain functions and improve the quality of life for the patients; objectively, improvement in brain functions were seen on the brain SPECT images [2]. This improvement can be related to the fact that HBOT initiated a vascular repair mechanism to improve the cerebral vascular flow [4, 18].

Additional quality of life measures was taken in additional to the objective measures discussed previously. The RAND SF-36 or 36-Item Short Form Survey Instrument was developed at RAND by Ware during the Medical Outcomes Study (MOS) as a measurement of broad health concepts. This questionnaire that is broad and generalized to ensure it is relevant across a multitude of age, disease and treatment groups [30]. The original study was a 4-year longitudinal and observational study of the variations in practice styles and the health outcomes for chronically ill patients [30]. The SF-36v1 was originally developed in 1990 and version 2 was developed in 1998 with some verbiage changes. The SF-36 is the most frequently used Health Survey instrument used in clinical trials [30]. It is a 36-question patient-rated health survey that is used to evaluate the functional health and well-being of the patient. This survey is separated into 8 individual scales that can evaluate domain specific functioning of the patient. These 8 dimensions include: vitality, physical functioning, physical and emotion limitations, social functioning, bodily pain, general and mental health [30]. Interpretations of the results indicate a higher score equating to a "better perceived health" the patient has in that category. This patient filled out the SF-36 questionnaire pre and post treatment. His pre-treatment overall score was 1745 and post treatment overall score was 2820 this is an improvement of 29.9% in the overall score. He improved or stayed stable in 7 out of 8 subsections. The only subsection that he declined in was the pain section due to an acute extremity concern at the time of the survey. Most notable improvements include his social functioning status which improved 100%, his vitality improved by 65%, and finally his global general health status improved by 40%. See below table for average breakdown scores. Higher scores indicate better health status, and a mean score of 50 has been articulated as a normative value for all scales [30].

Table 1: Average score of each SF-36 domain of Pre-treatment of HBOT and Post-treatment of HBOT SF-36

	Pre-Treatment SF-36 average Score	Post-Treatment SF-36 average Score
Physical Functioning	95	100
Physical Limitations	0	50
Emotional Limitations	100	100
Energy/Fatigue/Vitality	10	75
Emotional well-being	60	76
Social Functioning	0	100
Pain	100	32.5
General Health	25	65
Overall Score	1745	2820

Conclusion

We have seen that both P300 amplitude and latency improve after HBOT. Alpha peak magnitude also increases in all channels and in June, after HBOT, there is no sign of a second peak in the alpha frequency range. Another change we see in the scans after HBOT is in the alpha symmetry, the ratio between F3 and F4 channel magnitude reading, where first time scans done in February give a off-target value of 0.6, which research has shown to indicate possible stress, anxiety or mood disorder [14] as reported by the patient when first visiting the clinic. Retest scans instead reported an in-norm value of 1.1 in accordance with better cognitive performance as experienced by the patient. We also see subjective improvement in the SF-36 survey in multiple domains of health. Taking into account that these findings are based on a n=1 study and that they are therefore limited in statistical significance, we believe that initial inquiry of the data suggests that the F3/F4 ratio returns to norm target values after HBOT.

We can conclude that by investigating these test/retest scans, there seems to be supporting evidence that HBOT can be a promising treatment for general cognitive decline improvement; there is significant growth in both latency and amplitude of the P300 and the voltage map topographies indicate an overall increase of electrical activity, consistent with the patient reporting an improved overall wellbeing utilizing the SF-36. As treatments are individualized

to patient needs this can be a barrier in creating protocols for future patients; however, having similar guidelines in place can help direct patient care for superior outcomes.

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