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Alzheimer's disease: Potential Therapeutic Application of Hyperbaric Oxygen Therapy

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Abstract

Hyperbaric oxygen therapy has been recently proposed as a potential treatment for Alzheimer's disease. However, only one known clinical trial has been undertaken in the case of the early-onset phase of this disease. The purpose of this article is to review and assess this novel approach. For this purpose, the disciplines and core principles of enhanced medicine are first set forth followed by a description of the various particulars of hyperbaric oxygen therapy. It is concluded that insufficient data exists at present to make any valid conclusion. Irrespective of any future findings and conclusions of like trials, the proposed approach, while helpful, would at most be palliative as it does not address the root cause of the disease.

Abbreviations

AD: Alzheimer's disease; APP: Amyloid precursor protein; ASME: American Society of Mechanical Engineers; ATA: Atmosphere absolute; BBB: Blood-brain barrier; CAA: Cerebral amyloid angiopathy; CMB: Cerebral microbleeds; COPD: Congestive-obstructive pulmonary disease; DESS: Diet, exercise, stress, sleep; EPC: Endothelial progenitor cells; ERMC: Enhance, remove, measure, communicate; FDA: (U.S.) Food & Drug Administration; HBA: Hyperbaric air; HBAT: HBA therapy; HBO: Hyperbaric oxygen; HBOT: HBO therapy; HEDIHM: Hormesis, exercise, diet, immune, hyperbaric; mental: HIF: Hypoxia-inducible factor; HPP: Hyperoxic-hypoxic paradox; MMP: Metallic metalloproteinase; NDD: Neurodegenerative diseases; NFPA: National Fire Protection Association; NFT: Neurofibrillary tangles; O: Oxidative stress; PD: Parkinson's disease; PTSD: Post- traumatic stress disorder; PVHO: Pressure vessel for human occupancy; RBC: Red blood cell; ROS: Reactive oxygen specy; VEGF: Vascular endothelial growth factor. WML: White matter lesions.

Keywords

Alzheimer's disease; enhanced medicine; hyperoxic-hypoxic paradox; hyperbaric medicine; hyperbaric oxygen therapy.

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Hyperbaric medicine is a medical treatment in which a gas is inhaled under increased barometric pressure over ambient pressure for the purpose of reducing the size of an embolism. It is practiced under two variations, hyperbaric air therapy (HBAT) in which air is inhaled and hyperbaric oxygen therapy (HBOT) in which almost pure oxygen is inhaled [more details are provided in the Sidebar]. Very recently (Efrati, 2024), an interesting volume was published on the new science of HBOT-based enhanced medicine and how it can elevate peak performance as well as repair brain injuries. Whereas the purpose of traditional medicine aims to restore the "normal state" of a patient (i.e., normal for the

patient's sex, age, and present medical condition) according to generally accepted medical guidelines, by contrast, enhanced medicine aims to attain the best state allowed by that patient's physiological and biological condition. The purpose of this article is to review and assess enhanced medicine solely with regard to memory and cognition impairments, especially in neurodegenerative diseases and including in particular Alzheimer's disease (AD). I will begin with the four principles and the six core disciplines of enhanced medicine as enunciated by Dr. Efrati.

The four principles of enhanced medicine

The first two principles (the most important ones) are concerned with physiology and biology whereas the remaining two relate to the practice of enhanced medicine:

1. "To enhance physiology and biology to the highest levels achievable from the current levels even if the latter levels are below average;
2. "To remove those bottlenecks that prevent the biology, even at the cellular level, from performing;
3. "To measure and quantify every procedure administered before and after intervention; and
4. "To maintain at all times effective communication with the patient."

The above principles are encapsulated in the acronym ERMC (where E stands for Enhance; R for Remove; M for Measure; and C for Communicate). Next, I will examine the six core disciplines of enhanced medicine.

The six core disciplines of enhanced medicine

The six core disciplines of enhanced medicine are:

1. "Hormesis: It consists in exposing the body to a controlled exposure to a stress so as to trigger the better functioning of the biology;
2. "Intermittent physical exercise: While the benefits of physical exercise are well known, the following advantages are of particular note: (a) preparing the body at the cellular level to meet a heightened physical challenge and induce resilience to the next stressor; and (b) benefiting from the immediate flow of the body's natural biochemistry, specifically the hormone osteocalcin that produces biochemical benefits in the brain;
3. "Diet, nutrition, and fasting: Here (a) the amount and quality of the food eaten are important; (b) when fasting is as important as when to eat; and (c) intermittent fasting helps autophagy (the cellular process of cleaning out the garbage and toxic elements accumulated);
4. "Immune system: Its resilience or weakness is a factor in many age-related declines of the physical and biological functions;

5. "Hyperbaric oxygen therapy (HBOT): This is described more at length in the next section. It takes advantage of the so-called "hyperoxic-hypoxic paradox" (HPP) in which, following a hypoxia producing damages to biochemical mechanisms, a rapid decline of a very high oxygen level to a normal level activates multiple repair mechanisms. Through HBOT, HPP elevates the body's biochemistry in four remarkable ways: (a) it dramatically increases the mitochondria volume; (b) it enhances the efficiency of the mitochondria's capacity to convert oxygenation to energy; (c) it accelerates the production and migration of stem cells; and (d) it generates new blood vessels where blood flow had been reduced; and
6. "Mental perception and resilience: With each stressful event encountered, resilience can either continue to build (hormesis) or slip further towards a breakdown."

The above core disciplines are embodied in the acronym HEDIHM (where H stands for Hormesis; E for Exercise; D for Diet; I for Immune; H for Hyperbaric; and M for Mental). It is now time to review HBOT, the major tool of enhanced medicine.

The hyperbaric oxygen therapy

With its core HPP component, HBOT is a powerful tool in enhanced medicine therapy.

Basic principle

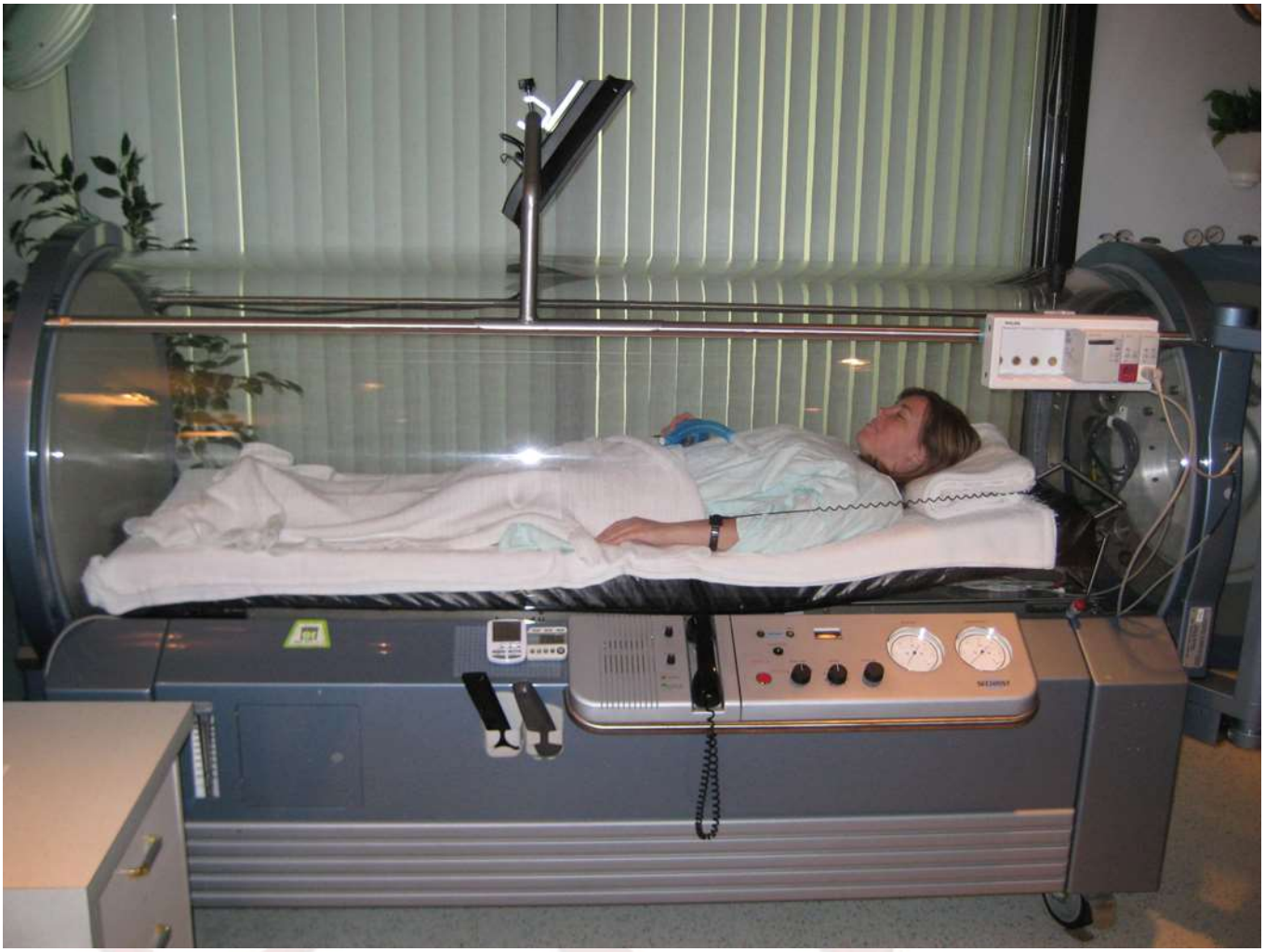
In general, oxygen is necessary to sustain life. In the blood, it can be found in two compartments: (a) dissolved in blood plasma (~ 2% of total oxygen in the blood stream); and in (b) hemoglobin - the protein in RBCs that transports oxygen (~ 10-20 [g] in every 100 [mm] of blood). The hyperbaric chamber affects only the dissolved oxygen in plasma.

Hyperbaric oxygen therapy increases oxygen delivery to the body by providing pure oxygen in an enclosed space with higher than normal air pressure. While originally developed to treat decompression sickness caused by rapid drops in water pressure in scuba diving or air pressure in air or space travel, it also treats other conditions that include serious tissue disease or wounds, trapped air bubbles in blood vessels, carbon monoxide poisoning, and tissue damage from radiation therapy.

During a typical two-hour session in the hyperbaric chamber, the arterial pressure rises to 1,520 [mm] of mercury, representing approximately 13 times the normal pressure at sea level of 120 [mm] of mercury. Meanwhile, through a mask, the patient breathes and absorbs pure oxygen at nearly 13 times more than the normal amount of oxygen breathed at sea level. The absorbed oxygen can be delivered through blood flows or within and between tissues to locations not reached by red blood cells (RBC).

While still in the chamber, the patient removes the oxygen mask at three intervals for brief periods (five minutes) when h/she breathes normal air but at twice the pressure at sea level. Oxygen concentration drops sharply during these breaks from very high to slightly high. In addition to daily gaps between sessions, these repeated fluctuations are interpreted as cellular hypoxia even though actual oxygen

levels are higher than normal (hyperoxia). The body's perceived lack of oxygen is the trigger for tissue repair and regeneration in a hyper-oxygenized environment (see Figures 1 and 2).



(Source: Wikipedia)

Figure 1: A Sechrist monoplace hyperbaric oxygen chamber, Moose Jaw Union Hospital, Saskatchewan, Canada

Molecular biology foundations

The molecular biology foundations in HBOT treatments spark higher levels of the body's conduction of the hypoxia-inducible factor (HIF), specifically the protein HIF-1 alpha.

Therapeutic principles

The therapeutic consequences of HBOT and recompression result from multiple effects:

• Clinical pressure (2.0–3.0 Bar): The therapeutic principle of HBOT lies in its ability to drastically increase the partial pressure of oxygen in body tissues. The oxygen partial pressures thus achieved are much higher than those achievable while breathing pure oxygen under normal atmospheric pressure. This effect is achieved by an increase in the oxygen transport capacity of the blood. At normal atmospheric pressure, oxygen transport is limited by the oxygen binding capacity of hemoglobin in RBCs with very little oxygen being transported by blood plasma. Because the hemoglobin of the RBCs is almost saturated with oxygen at atmospheric pressure, this route of transport cannot be exploited any further. Oxygen transport by plasma, however, is significantly increased using HBOT because of the higher solubility of oxygen as pressure increases.

(Source: Wikipedia)

Figure 2: Multiplace hyperbaric chambers, showing control panel, monitoring facilities, and different chamber sizes in Spanish facilities

• Proangiogenic stem progenitor cell mobilization: Exposure to HBOT also mobilizes stem/ progenitor cells from the bone marrow by a nitric oxide-dependent mechanism.

• Low pressure hyperoxia, stem progenitor cell mobilization and inflammatory cytokine expression: Stem cell mobilization is also invoked at relatively normal atmospheric pressure with a significantly smaller increase in oxygen concentration. There is also a significant decrease in the expression of the systemic inflammatory cytokine TNF-α in venous blood. These results suggest that hyperbaria may not be required to invoke the transcriptional responses seen at higher partial pressures of oxygen and that the effect is due solely to oxygen.

Treatments

HBOT is often a part of a broader treatment plan that includes other medical or surgical specialties. Initially, HBOT was developed as a treatment for diving

disorders involving bubbles of gas in the tissues, such as decompression sickness and gas embolism; it is still considered the definitive treatment for these conditions. The chamber treats decompression sickness and gas embolism by: (a) increasing pressure, (b) reducing the size of the gas bubbles, and (c) improving the transport of blood to downstream tissues. After elimination of the bubbles, the pressure is gradually reduced back to atmospheric levels. The treatment has been extended to many other diseases and, of special interest here, potentially to neurodegenerative diseases (NDD).

Benefits

The main benefits are:

1. Overcoming atherosclerosis: Atherosclerosis is the reduced capacity of the cardiovascular system to deliver oxygen to cells due to the narrowing passageways in the vessels as plaque deposits accumulate and constrict blood flow.
2. Inducing hypoxia followed by hyperoxia (the HPP paradox): This is one of the most powerful biochemical triggers for the regenerative cascade. This process activates biochemical mechanisms to repair whatever new damage the body senses is happening from hypoxia.
3. Extending the delivery of oxygen: Oxygen can be delivered to, and even bypass, small arteries with blockages to reach tissues and cells that RBCs cannot reach due to those blockages.
4. Sensing several organs: The healing properties of the dissolved oxygen are not limited to a specific organ. Rather, they are sensed by multiple organs, including the heart and the brain.

5. Inducing regenerative processes: Calibrating oxygen and air pressure fluctuations can induce regenerative processes to heal damaged tissues and generate healthy new tissues. Targeting oxygen and pressure-sensitive genes offers three advantages: (a) improving the chemical processes (metabolism) of mitochondria production; (b) stimulating more rapid production of stem cells and speeding their distribution where they are needed; and (c) inducing the growth of new blood vessels (angiogenesis) and better blood flow in ischemic areas.

6. Provoking a virtuous regenerative cascade: The following virtuous regenerative cascade in tissues occurs: (a) increasing levels of HIF-1; (b) heightening the activity of metallic metalloproteinases

(MMP); (c) raising levels of vascular endothelial growth factor (VEGF); (d) enhancing the proliferation of stem cells; (e) increasing the levels of factors that generate new blood vessel growth (angiogenesis), which improve the circulation to oxygen-deprived ischemic tissue; and (f) improving the circulation of certain cells, specifically the endothelial progenitor cells (EPC) that restore the lining of blood vessels after a sudden, often severe injury (acute insult).

Disadvantages

In the hands of a skilled specialist operating in a certified chamber, the HBOT treatment presents no physiological or physical danger. Nonetheless, notwithstanding its enormous advantages, HBOT therapy presents certain disadvantages, including:

1. **Protocol:** The protocol within the chamber is of a complex nature. For example, the protocol at the renown Sagol Center for Hyperbaric Medicine and Research, Shamir Medical Center, Israel, consists of the following steps:

• Inhalation in a mask of pure oxygen (100%) at twice the normal sea level pressure (2x120 mm of mercury) in four 20-minute sequences separated by 5-minute breaks after each sequence (essentially a 2-hour session).

• During those 5-minute breaks, masks come down, and patients breathe normal air (21% oxygen) at twice the normal sea level pressure.

• The initial treatment ends after about 4 weeks, 5 days/week, of repeated sessions for 3 months for a total of 60 sessions.
• Any unexpected change in the above schedule could render the treatment ineffective.

2. **Hyperbaric Center:** Generally, lack of availability of a conveniently located hyperbaric center.
3. **Costs:** Elevated cost (generally non-reimbursable by insurance or other government programs) to cover all medical and incidental expenses.
4. **Maintenance program:** Necessity for an as yet ill-defined maintenance program including (a) an identical treatment plan (as outlined above) or an appropriate variation of the same, and (b) the frequency of such a program. The number of sessions depends on the medical condition. Some conditions, such as carbon monoxide poisoning, might be treated with a few sessions. Other conditions, such as non-healing wounds, may require 40 treatment sessions or more.

Possible complications and concerns

While the treatment is often considered safe, the use of hyperbaric equipment comes with risks to the patients and to the operating personnel when improperly used. The risks are similar to some diving disorders and include:

1. **Pressure changes:** They can cause a "squeeze" or barotrauma in the tissues surrounding trapped air inside the body (such as in the lungs, behind the eardrum, inside paranasal sinuses, or trapped underneath dental fillings).

2. **Breathing high-pressure oxygen**: It may cause oxygen toxicity.

3. **Temporary blurred vision:** It can be caused by swelling of the lens, which usually resolves in 2-4 weeks.

4. **Cataracts:** They may progress following HBOT and may rarely develop de novo. The cause is not fully explained, but evidence suggests that lifetime exposure of the lens to high partial pressure oxygen may cause oxidative damage to lens proteins. This may be an end-stage of the relatively well-documented myopic shift detected in most hyperbaric patients after a course of multiple treatments. HBOT can accelerate the development of cataracts over multiple repetitive treatments, and can cause temporary relative myopia over the shorter term.

5. **Pressure effects:** Patients inside the chamber may notice discomfort inside their ears as a pressure differential develops between their middle ear and the chamber atmosphere. Continued increase of pressure without equalizing may cause ear drums to rupture, resulting in severe pain.

6. **Side effects:** Oxygen toxicity is a limitation on both maximum partial pressure of oxygen, and on length of each treatments.

Regulation and legality

The use of hyperbaric chambers for medical and therapeutic procedures is generally regulated. In some jurisdictions, it is further restricted at the subnational level. Unlicensed and fraudulent operators have been subject to prosecution.

Costs

In the U.S., HBOT is recognized by Medicare as a reimbursable treatment for 14 "approved" conditions. A

1-hour HBOT session may cost between $300 and higher in private clinics, and over $2,000 in hospitals. U.S. physicians may lawfully prescribe HBOT for "off-label" conditions such as stroke and migraine. Such patients are treated in outpatient clinics. In the U.K., most chambers are financed by the National Health Service. In Australia, HBOT is not covered by Medicare as a treatment for multiple sclerosis. China and Russia treat more than 80 maladies, conditions, and trauma with HBOT.

Personnel

Personnel usually include:

• Hyperbaric medical practitioner: A specialist in hyperbaric medicine.
• Hyperbaric nurse: A nurse responsible for administering hyperbaric oxygen therapy to patients and supervising them throughout the treatment.
• Chamber operator: A person competent to operate a hyperbaric chamber.
• Chamber attendant: A person trained in basic first aid.

Research

Research in HBOT has proceeded along several streams that will only be listed here. These include:

- **Radiation-induced hemorrhagic cystitis;**
- **Inflammatory bowel disease;**
- **Rejuvenation;**
- **Cancers of the head and neck:** local tumor control, mortality, and recurrence.
- **Stem progenitor cells (SPC):** increase in cell numbers; and
- **Inflammation:** decrease.

Potential applications to Alzheimer's disease

Over the past few decades, Alzheimer's disease (AD), once considered a rare disorder, has emerged from obscurity to become a major public health problem. AD is a chronic neurodegenerative disease that results in the loss of neurons and synapses in the cerebral cortex and certain subcortical structures, resulting in gross atrophy of the temporal lobe, parietal lobe, and parts of the frontal cortex and cingulate gyrus. It is the most common neurodegenerative disease (NDD).

AD pathology is primarily characterized by the presence of amyloid plaques and neurofibrillary tangles (NFT). Plaques are made up of small peptides, typically 39–43 amino acids in length, called amyloid beta (A-beta or Aβ). Aβ is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP appears to play roles in normal neuron growth, survival, and post-injury repair. It is cleaved into smaller fragments by enzymes such as gamma secretase and beta secretase. One of these fragments gives rise to fibrils of amyloid beta which can self-assemble into the dense extracellular amyloid plaques.

Based on a lack of treatment, it has generally been considered as an irreversible, progressive brain disease that slowly destroys memory and thinking skills, eventually even the ability to carry out the simplest tasks. It is a chronic NDD of poorly (or not) understood cause(s).

Potential etiologies

Based on identified risk factors, several theories (hypotheses) have been propounded for its cause(s).

The hypotheses can be classified as:

- Cholinergic;
- Amyloid-beta (Aβ) protein;
- Tau protein;
- Viral or fungal infection;
- Neurovascular;
- Neuroinflammation;
- Neurodevelopmental;
- Cardiovascular;
- Gum disease infection;
- Dysfunction of oligodendrocytes; and
- Other hypotheses are related to lifestyle, diet, and the environment. (For a rundown of these several hypotheses, relevant additional references have been provided at the end of this article.)

Such a wide array of hypotheses is by itself indicative of our lack of true understanding and knowledge of the disease, notwithstanding the fact that the disease has been identified since 1901, has been the subject of a considerable number of publications dealing with it (in excess of 50,000 articles according to some authors), hundreds of failed clinical trials, and billions of dollars spent worldwide. In the absence of medical breakthroughs, 152 million people are predicted to develop the illness by 2050, with a worldwide cost projected to reach $2 trillion by 2030!

Notwithstanding claims by some research clinicians, there are currently no known and accepted treatments if only to stop or reverse the progression of the disease. Some of these alleged treatments, including the advocated program DESS (Diet, Exercise, Stress, Sleep), and variations on this theme, are palliative in nature, temporarily improving symptoms, while the disease progresses unabated. One must keep in mind that these programs address risks, but risk is not causation and risk management is not treatment, … only palliation! Lacking advances in curative treatment, research has therefore been refocused on diagnosing the condition before symptoms begin. Thus, a number of biochemical tests have been developed to attempt earlier detection. Such tests include the analysis of the cerebrospinal fluid for Aβ or tau proteins and preventive vaccination. Neuroprotective agents (such as Al-108, PBT2, and TNFα receptor-blocking fusion protein etarnacept) have also been mentioned.

Further, among the more than 400 pharmaceutical treatments having been investigated or are in advanced clinical trials, putative pharmaceutical therapies attempt to treat the underlying disease pathology by reducing the levels of Aβ in the plaques (for example, by *Apomorphine*, vaccination). Such treatments also include inhibiting tau-aggregation in the neurofibrillary tangles (NFT), e.g., with *Methylthionium chloride* and *Dimebon*. However helpful, such treatments are likewise not curative.

Researchers increasingly believe that much of the damage in AD is done when naturally occurring proteins fold into the wrong shape and clump together into harmful structures (the amyloid fibrils). Once these begin forming, they can start a “chain reaction” which rapidly kills off brain cells. The primary clinical manifestation of AD is dementia, an accelerated loss of cognitive function beyond that due to normal aging. Alterations in mood and behavior often accompany the onset of dementia followed in time by memory loss, disorientation, and aphasia. In AD, the hippocampus and cerebral cortex are severely affected. Pathologically, there are two hallmarks in affected tissues (senile or neuritic plaques in blood vessels and neurons, and the occurrence of neurofibrillary tangles that accumulate in the cytoplasm of affected neurons).

Now, … what is going on?

Have we got the cause of Alzheimer's all wrong?

As known, in 1901, Dr. Alois Alzheimer first described a disorder of progressive memory loss and confusion in Frau Auguste Deter, a 46-year-old woman. After she

died on 8 April 1906, he examined her brain and saw that it was full of unusual protein clumps known as plaques. Over a century later, we now know that these plaques are full of a protein called amyloid-beta (Aβ) and are one (out of four) hallmark(s) of the disease that bears Alzheimer's name. While other features of AD have since been discovered, the theory that Aβ is the main cause of this so far incurable disease has unfortunately (and erroneously) long dominated the discourse. There are many subtle variations of the "amyloid-beta hypothesis", but generally the theory goes that Aβ accumulates in the brain, then clumps together.

Somewhere in this process, nerve cells in the brain become damaged, which leads to memory loss and other well-known symptoms of AD. So, it was thought, the approach to treating the disease should be rather straightforward – stopping the clumping would halt the disease! Unfortunately, decades of research, many failed clinical trials later, and many billions of dollars in research spending by governments and the pharmaceutical industry (Roche Holding AG, Eli Lilly and Co., Eisai Co. and others), it appears that this approach is not working. The most recent plaque-busting treatment has been Aducanumab – an antibody-based therapy designed to stick to and destroy Aβ.

Initial data suggested that the treatment did indeed clear Aβ from the brain. But the clinical trials, which involved thousands of patients, produced apparently disappointing results and were stopped by the drug company Biogen and Esai because they "… (the trials) were unlikely to meet their primary end-point upon completion". It is very hard to tell what is truly the situation without the full information (not available) from the Aducanumab trial. Some have suggested that may be the disease had progressed too far in the participants for the treatment to be effective. Perhaps, also, the small Aβ oligomers had already done their damage, setting the disease in motion before the participants were even recruited to the trial. Earlier trials with other Aβ-busting drugs had shown that, in some cases, the disease even worsened! Further, some people with large accumulations of plaques do not necessarily have symptoms of dementia.

This has led many to ask whether the amyloid hypothesis of AD should be abandoned. In reality, few neuroscientists still subscribe to the view that it is the Aβ plaques themselves that cause the symptoms of AD. Studies with mice that mimic human AD have shown that memory loss occurs "before" plaques form in the brain. Other studies have suggested that it is the smaller fragments (called "oligomers") of Aβ that are really toxic to nerve cells. And it has even been suggested that the formation of plaques is a manifestation of the brain rounding-up all these dangerous oligomers into one place for safety. I believe that we got the cause of AD all wrong and we had been side tracked for very long. Like in so many medical treatments, when we cannot find the root cause of the disease, we treat a surrogate end-point, which would be acceptable had the surrogate end-point been demonstrably shown to be uniquely correlated with the real end-point. Unfortunately, in many of those treatments, that correlation was not established. While we treat that surrogate, the disease continues along its devastating course, and so it has been with Alzheimer's. Clearing the plaques (the surrogate) did not cure AD (the real issue). It is therefore high time to think the disease anew, to identify its root cause, and to come up with a cure.

We distinguish between the "familial" AD and the "sporadic" AD. The candidate genes for familial AD are the four major loci (APP; PSI, which codes for presenilin 1; PS2, which codes for presenilin 2; and Apolipoprotein E or ApoE) and those for sporadic AD are the three common ApoE alleles (ε2, ε3, and ε4). Both familial and sporadic ApoE have been clearly and reproductively linked to AD. In order for ApoE genotype to predispose to AD, some additional genetic or environmental risk factors must be present as well. It has been reported, but not generally agreed upon, that

the relationship of ApoE- genotype and total cholesterol, as well as age and gender, indicate gene-environment interaction. There are some epidemiological reports of an association between head injury and AD. It has lastly been shown that the effect of smoking on AD risk may be dependent upon ApoE-genotype as well. Recently (Journal: Nature Structure and Molecular Biology, February 2015), researchers at the Cambridge University and the Karolinska Institute in Sweden discovered that a naturally occurring molecule found in the lungs binds to the surface of the fibrils, preventing them from sticking together. Such molecules might eventually be turned into drugs that could be given to people before symptoms appear to stop the disease from progressing. They can theoretically arrest the build-up of the deadly protein tangles, which are thought to be crucial in the progression of the disease. Thus, improving the body's natural defenses could hold AD at bay in a discovery that paves the way for new treatments. In particular, AD could be halted in its early stages, raising the prospect of "statin-like drugs" to stave off the disease. Nonetheless, further studies are needed before clinical trials could begin, which themselves would take at least a decade.

It has even been suggested that arthritis, multiple sclerosis, and even AD and Parkinson's disease (PD) could all be treatable with a single "marvel" pill. Laboratory studies suggest that a compound discarded years ago by a drug company might block the damaging inflammation caused by a host of serious diseases. Human trials are being planned with such a compound. Currently, the diagnosis of AD is subpar, and better methods need to be utilized for various aspects of clinical diagnoses. Alzheimer's has a 20% misdiagnosis rate. Notwithstanding the large sums expanded (billions of dollars), no effective treatments for AD have been found. Even within clinical trials, stable and effective AD therapeutic strategies have a 99.5% failure rate. Reasons for this failure rate include: Lack of identification of the root cause(s) of the disease, inadequate knowledge of the underlying pathophysiology, invalid target and participant selection, and inappropriate drug doses. For a more comprehensive treatment of this disease, refer to Fymat 2017-2022).

Is there a ray of hope for the therapeutic application of HBOT to AD?

Ischemia etiology and HBOT

HBOT treatments have reportedly improved conditions related to five different brain conditions (again, these are "improvements" not cures) all of which being rooted in low cerebral blood flow (ischemia):

1. Stroke;
2. Concussion;
3. Fibromyalgia;
4. Post-traumatic stress disorder (PTSD); and
5. Long COVID.

The question naturally arises therefore whether ischemia and lack of oxygen in the brain may play a crucial role in AD. Now, ischemia is a condition that occurs when a part of the body does not receive enough blood flow, which can lead to tissue damage and organ failure. This can itself originate in five ways, which can cause hypoperfusion, tissue ischemia, chronic inflammation, accelerating death of neurons, gliosis or inflammation of the cells, and cerebral atrophy or loss of brain tissue:

1. Atherosclerosis: A syndrome characterized by a chronic inflammatory response occurring in the arterial wall. It is commonly referred to as the hardening or narrowing of the arteries. During the course of the disease, atherosclerotic plaques develop in the arteries. The soft atherosclerotic plaque most often ruptures suddenly, leading to thrombus formation that quickly reduces or halts blood flow, killing the tissue supplied by the artery.

2. Arteriosclerosis: A vascular disease that causes the walls of the arteries to thicken and soften, restricting blood flow and increasing the risk of heart disease, stroke, or kidney failure.

3. Infarcts or stroke: These are acute blockages in a vessel. An infarct is a localized area of tissue that has died or is dying due to a lack of blood supply. (Infarcts can occur in the heart, brain, kidneys, or other organs).

4. White matter lesions (WML): These are abnormal areas in the brain's white matter that appear bright on MRI scans. They can indicate small vessel disease, but can also have other causes.

5. Cerebral microbleeds (MB): These are small chronic brain hemorrhages which are likely caused by structural abnormalities of the small vessels of the brain.

Whatever the cause, ischemia makes the blood-brain barrier (BBB) less effective in preventing toxic material (bacteria, viruses, etc.) from entering the brain. This will contribute to amyloidosis or building of protein fragments and plaque that may develop into cerebral amyloid angiopathy (CAA).

The biochemical links between the pathophysiology of AD and ischemia can be observed through three changes, each of which having become a new target for developing pharmaceuticals to treat AD:

1. **Damage to mitochondria;**
2. **Hypoperfusion;** and
3. **Inflammation.**

A number of interventions have been devised to reverse ischemia in cases where AD has not yet reached the full or last stage. In this latter case, neither HBOT nor any other therapeutic intervention may have any significant effect. For other cases, the issue is whether the basic Hyperoxic-Hypoxic Paradox (HPP), fundamental in HBOT, may prove effective in curtailing AD.

HHP does:

1. Bolster the normal health and functions of neurons by regenerating damaged neurons and stimulating the growth of new neurons (angiogenesis);
2. Generate new blood vessels in the brain, a crucial element to restore and improve brain perfusion;
3. Repair damage to the BBB;
4. Reduce inflammation;
5. Improve the chemical efficiencies of cell life and reduce apoptosis, or abnormal volumes of cell death;
6. Alleviate an imbalance between production and building of reactive oxygen species (ROS);
7. Dampen the oxidative stress (OS) related to toxic aspects of ROS in cells and tissues;
8. Enhance the energy-converting functions of mitochondria in neurons and glial cells; and
9. Increase levels of neurotrophins, the proteins that help neurons survive and grow, and of nitric oxide, which helps blood vessels dilate, and improve brain and exercise performance.

In summary, ischemia is a common trigger (not the root cause) of several NDDs, including AD. The narrowing or interruption of blood flows contributes to:

1. Chronic ischemia in brain tissue;
2. Accumulation of A-beta and tau proteins;
3. Inflammation of neurons with glial activation;
4. Loss of neurons;
5. Damage to the BBB; and
6. Dysfunction of mitochondria.

However, the definitive clinical trials on the application of HBOT to AD are still wanting. Dr. Efrati ands his colleagues in Israel are undertaking an ambitious study investigating the applicability of HBOT to early-onset AD with results anticipated in the forthcoming years. Notwithstanding hopefully positive results, the aim of the study is to palliate the effects of early-stage AD … not to attack the root cause of AD.

Conclusions and take-aways

• Hyperbaric medicine is a medical treatment in which a gas is inhaled under increased barometric pressure over ambient pressure for the purpose of reducing the size of an embolism. It is practiced under two variations, hyperbaric air therapy (HBAT) in which air is inhaled and hyperbaric oxygen therapy (HBOT) in which almost pure oxygen is inhaled.

• Whereas the purpose of traditional medicine aims to restore the "normal state" of a patient according to generally accepted medical guidelines, by contrast, enhanced medicine aims to attain the best state allowed by that patient's physiological and biological condition.

• Enhanced is based on four principles and encompasses six core disciplines.

• Hyperbaric oxygen therapy increases oxygen delivery to the body by providing pure oxygen in an enclosed space with higher than normal air pressure. While originally developed to treat decompression sickness, it also treats other conditions.

• The therapeutic principles of the hyperbaric oxygen therapy have been set forth along with the associated benefits, disadvantages, concerns and potential risks

• The potential etiologies (hypotheses) of Alzheimer's disease advanced so far have been dismissed as they do not address the root cause(s) of the disease. They are palliative in nature and remain helpful.

Sidebar - Hyperbaric medicine

Hyperbaric medicine is a medical treatment in which an increase in barometric pressure over ambient pressure is employed for the purpose of reducing the size of an embolism. An embolism is usually caused by illness or injury, can provoke a vascular occlusion (i.e., a partial or total blockage of blood flow in the affected vessel), and may also affect a distant part of the body. An embolism may also be caused intentionally (a procedure called "embolization") for a therapeutic reason such as to stop bleeding or to kill a cancerous tumor by stopping its blood supply.

Types of hyperbaric medicine

There are two types of hyperbaric medicine depending on the gases compressed: air or solely oxygen.

1. Hyperbaric air therapy (HBAT): It consists of compressed atmospheric air (79% nitrogen, 21% oxygen, and minor gases). It is FDA-approved for hypoxemia caused by the decreased partial pressure of oxygen resulting from high altitude by increasing the partial pressure of air (including oxygen and nitrogen) thus simulating a descent in altitude. The hyperbaric air environment is created by placing the patient in a portable hyperbaric chamber and inflating that chamber up to 1.5 atmosphere absolute (ATA).

2. Hyperbaric oxygen therapy (HBOT): It uses oxygen at greater than 99% concentration at an ambient pressure higher than atmospheric pressure for the purpose of increasing the availability of oxygen in the body. It is followed by therapeutic recompression to reduce the injurious effects of systemic gas bubbles by physically reducing their size and providing improved conditions for elimination of bubbles and excess dissolved gas. The equipment required consists of a pressure vessel for human occupancy (PVHO) and a means of a controlled atmosphere supply. Operation is

performed to a predetermined schedule by trained personnel who monitor the patient and may adjust the schedule as required. All chambers used in the U.S. fall under the jurisdiction of the FDA, the American Society of Mechanical Engineers (ASME), and the National Fire Protection Association (NFPA) (Standard 99, Health Care Facilities Code).

Medical uses of HBOT

In the U.S., the following indications cover:

• Air or gas embolism;
• Carbon monoxide poisoning;
• Carbon monoxide poisoning complicated by cyanide poisoning;
• Central renal artery occlusion;
• Clostridal myositis and myonecrosis (gas gangrene);
• Crush injury, compartment syndrome, and other acute traumatic ischemias;
• Decompression sickness;
• Diabetically-derived illness such as short-term relief of diabetic foot, diabetic retinopathy, and diabetic nephropathy;
• Enhancement of healing in selected problem wounds;
• Exceptional blood loss (anemia);
• Idiopathic sudden sensorineural hearing loss;
• Intracranial abscess;
• Mucomycosis, especially rhinocerebral disease in the setting of diabetes mellitus;
• Necrotizing soft tissue infections (necrotizing fasciitis);
• Osteomyelitis (refractory);
• Radiation injury - delayed (soft tissue and bony necrosis):
• Skin grafts and flaps (compromised); and
• Thermal burns.

• Ischemia is a common trigger (not the root cause) of several neurodegenerative diseases, including Alzheimer's.
• The definitive clinical trials on the application of hyperbaric oxygen therapy to Alzheimer's are still wanting. Notwithstanding hopefully positive results, the aim of the ongoing trial is to palliate the effects of the early-stage of the disease, not to address its root cause and, thus, will not provide a cure.
• The sidebar is a synopsis of the field of hyperbaric medicine.

However, at present, there is no reliable evidence to support its use in:

- Autism;
- Cancer;
- Diabetes' HIV/AIDS;
- Alzheimer's disease (see above section);
- Asthma;
- Bell's palsy;
- Cerebral palsy;
- Depression;
- Heart disease;
- Migraines;
- Multiple sclerosis;
- Parkinson's disease;
- Spinal cord injury;
- Sports injuries; or
- Stroke.

There is also insufficient evidence to support its use in acute traumatic or surgical wounds.

Contraindications

There are the following absolute contraindications to HBOT:

- Congestive-obstructive pulmonary disease (COPD): Can lead to pneumothorax during treatment; and

- Pneumothorax: For untreated pneumothorax

because it can progress to tension pneumothorax, especially during the decompression phase of therapy, although treatment on oxygen-based tables may avoid that progression.

The following are relative contraindications:

• Cardiovascular disease;
• Emphysema with carbon dioxide retention: Can lead to pneumothorax due to rupture of an emphysema bulla during decompression;
• High fevers:
• History of thoracic (chest) surgery: There is concern that air may be trapped in lesions that were created by surgical scarring;
• Malignant disease: There is concern because HBOT increases blood flow via angiogenesis;
• Middle ear barotrauma: An issue because of the necessity to equalize pressure in the ears; and
• Upper respiratory infections: Can result in what is termed ear or sinus squeeze; Pregnancy is not a relative contraindication to HBOT.

Risks

Hyperbaric oxygen therapy is generally a safe procedure. Most complications are mild and do not last. Serious complications are rare. The risk of complications increases with longer and repeated therapies.

Increased air pressure or the pure oxygen can result in the following:

• Ear pain.
• Middle ear injuries, including eardrum rupture and leaking fluid from the middle ear.
• Sinus pressure that can cause pain, runny nose or nose bleeds.
• Short-term changes in sight.
• Cataract formation with long courses of treatment.
• Short-term decline in lung function.
• Low blood sugar in people who have diabetes treated with insulin.

Uncommon, more-serious complications include:

• Lung collapse.
• Seizures from too much oxygen in the central nervous system.

Some people may experience anxiety while being in an enclosed space, also called claustrophobia.

Oxygen-rich environments increase the risk of fires. Certified programs that provide hyperbaric oxygen therapy must follow guidelines to prevent fires.

Preventing side effects

Steps to lessen certain side effects include the following.

• Yawning or swallowing can help relieve the pressure or feelings of fullness in the ears.
• For more-serious ear side effects and needed repeat treatments, the placement of ear tubes may be recommended.
• In case of hay fever or other nasal symptoms, a decongestant, steroid or antihistamine can prevent sinus pain or runny nose.
• For anxiety in an enclosed space, a relaxant may help.

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