Interview with Dr. Dan A. Rossignol: Hyperbaric oxygen therapy may improve symptoms in autistic children in *Medical Hypotheses*

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Abstract

Hyperbaric oxygen therapy involves inhaling 100% oxygen at greater than one atmosphere absolute (ATA) in a pressurized chamber. The air we breathe at sea level is defined as 1 ATA. Many of the clinical uses of hyperbaric oxygen therapy (HBOT) have been at pressures above 1.5 ATA. However, recently, some researchers have been using lower pressures of hyperbaric oxygen therapy with good results in some conditions. Therefore, some people use the term mild hyperbarics or low pressure hyperbarics when they talk about using hyperbaric oxygen therapy at 1.5 ATA or less. HBOT increases the amount of oxygen that is carried in the plasma. One of the properties of HBOT is an anti-inflammatory effect.

Multiple studies have revealed that autism is a neurodegenerative disease characterized by cerebral hypoperfusion, neuro and GI inflammation, and increased oxidative stress. HBOT causes increased oxygen perfusion, has potent anti-inflammatory effects, reduces oxidative stress and increases the production of stem cells. Hypoperfusion refers to decreased blood flow. In the case of autism, numerous studies have shown decreased blood flow to the brain, especially to the temporal regions of the brain. This hypoperfusion correlates with many core autism symptoms.

A case report is mentioned wherein Heuser treated a four-year old autistic child using lower pressure HBOT at 1.3 ATA (and 24% oxygen) and reported "striking improvement in behavior including memory and cognitive functions" after only ten sessions. Furthermore, the child had improvement of cerebral hypoperfusion as measured by pre-HBOT and post-HBOT SPECT scans. Dr. Rossignol also speaks about the results of his study entitled *Hyperbaric oxygen therapy may improve symptoms in autistic children* in *Medical Hypotheses*. The interesting finding from this case series was that the younger children had more significant improvements in clinical outcome scores than the older children.

Keywords: hyperbaric oxygen therapy, HBOT, autism, hypoperfusion, anti-inflammatory, SPECT scan.

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Dr. Rossignol, thank you for joining us today.

What is hyperbaric oxygen therapy?

Hyperbaric oxygen therapy involves inhaling 100% oxygen at greater than one atmosphere absolute (ATA) in a pressurized chamber. The air we breathe at sea level is defined as 1 ATA. Many of the clinical uses of hyperbaric oxygen therapy have been at pressures above 1.5 ATA. However, recently, some researchers have been using lower pressures of hyperbaric oxygen therapy with good results in some conditions. Therefore, some people use the term mild hyperbarics or low pressure hyperbarics when they talk about using hyperbaric oxygen therapy at 1.5 ATA or less. [The abbreviation conventionally used for hyperbaric oxygen therapy is HBOT.]

What does it do?

HBOT increases the amount of oxygen that is carried in the plasma. Typically, hemoglobin which circulates in the blood stream carries almost all of the oxygen in our body to tissues. Only 0.3% of oxygen is dissolved in the plasma which is the fluid in our blood vessels not counting the red cells, white cells and platelets. Hemoglobin is normally 97% saturated or full of oxygen. However, with HBOT, the amount of oxygen that is dissolved into the plasma can increase many fold. In fact, some animal studies have shown that HBOT can keep an animal alive without circulating red blood cells. There is an old paper called "Life without blood" that studied this in a pig. Therefore, in conditions where hypoxia (or decreased amount of oxygen) is present, such as with decreased blood flow, we would expect HBOT to help overcome this problem.

Interestingly, HBOT causes vasoconstriction of blood vessels which actually causes decreased blood flow. However, because it increases the amount of oxygen in plasma so much, the overall result is increased oxygen delivery to tissue. Because it causes decreased blood flow, HBOT decreases swelling, including swelling in the brain, after injury or ischemia.

One of the properties of HBOT that is rarely discussed is the anti-inflammatory effect of HBOT. Several animal studies have revealed that HBOT has potent anti-inflammatory tissue effects with equivalence to diclofenac 20 mg/kg noted in one study using HBOT at 2.4 ATA and 100% oxygen. Diclofenac is a NSAID or non-steroidal anti-inflammatory drug like Motrin. It is 10 times as potent or strong as Motrin. So in this study it would be like taking 200 mg/kg of Motrin, or in a 70 kg aver-

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age adult, 14,000 mg of Motrin. Now of course this was an animal study so it is hard to extrapolate like this, but it does demonstrate the strong anti-inflammatory characteristics of HBOT. HBOT has also been shown to decrease markers of inflammation including IL-1, IL-6 and TNF-α in humans.

So we get decreased blood flow, increased oxygenation, decreased swelling and decreased inflammation, all from one treatment. If a drug did this, a pharmaceutical company would make quite a bit of money.

Is it safe?

There have been numerous studies in adults and children which have established the safety of HBOT. The use of HBOT in children appears generally safe, even at pressures of 2.0 ATA for 2 hours per day for up to 40 sessions. The most common side effect of HBOT is middle ear barotrauma where the ear drum gets irritated, bleeds or even ruptures. This occurs in approximately 2% of patients. The incidence of this is decreased with pseudoephedrine treatment before HBOT. Less common side effects in descending order include sinus squeeze which is a sharp pain in the sinus, serous otitis which is fluid build-up behind the eardrum, claustrophobia, and reversible myopia which is nearsightedness. Seizures may occur infrequently in about 1-3 out of 10,000 patients. Higher pressures especially over 2-3 ATA have a higher incidence of side effects. We need to remember that oxygen is a drug. And just like any drug, it has beneficial effects at a certain dose, but too high of a dose can increase side effects.

What is it about HBOT's effect that makes it a logical treatment for physiological characteristics of autism?

Multiple studies have revealed that autism is a neurodegenerative disease characterized by cerebral hypoperfusion, neuro and GI inflammation, and increased oxidative stress. HBOT causes increased oxygen perfusion, has potent anti-inflammatory effects, reduces oxidative stress and increases the production of stem cells.

What is hypoperfusion?

Hypoperfusion refers to decreased blood flow. In the case of autism, numerous studies have shown decreased blood flow to the brain, especially to the temporal regions of the brain.

I want to point out that I think that it's notable that this hypoperfusion is there but that a parent may receive a normal MRI test result for their child.

How is hypoperfusion relevant to autism? And do clinical symptoms match the imaging studies – just a brief overview; we will go into this part more in-depth soon.

Hypoperfusion is not often talked about but has been studied extensively in autism. One study showed that typical children, when they have to pay attention to certain tasks, have increased blood flow to the brain, whereas autistic children do not demonstrate this increased blood flow. Another study showed that typical children when they listen to a tone or generate a sentence have increased blood flow to the brain while autistic children have the opposite—decreased blood flow. One ultrasound study showed that when typical children receive an auditory stimulus, their cerebral arteries dilate and they have more blood flow to the brain, while autistic children have constriction of the same arteries and decreased blood flow to the brain. There are also numerous studies demonstrating that this decreased blood flow in autistic children is directly correlated to many of the core symptoms of autism.

What is a SPECT scan?

SPECT stands for Single Photon Emission Computed Tomography. It is used to create three-dimensional images of your internal organs that reveal both anatomy and function. It starts with a radionuclide that is injected intravenously. Tissues absorb the radionuclide as it is circulated in the blood. As a camera rotates around the patient, it picks ups photons from the radionuclide particles. This information is transferred to a computer that converts the data onto film. The images are vertical and/or horizontal cross-sections of the body part and can be rendered into a 3-D format. This allows for tracing of blood flow in the brain. Tracing blood flow allows us to observe the brain's actual metabolic process and its activities. By using a brain SPECT imaging scan to examine those areas of the brain that have too much or too little blood flow, we can determine which areas of the brain are and are not functioning properly. X-rays, MRI and CT scans typically show only structural brain abnormalities such as tumors and lesions, not function or metabolism.

Are studies of brain tissue from other scientific disciplines consistent with your study findings with regard to HBOT?

The cause of this cerebral hypoperfusion is autistic individuals is unknown. However, recent studies have shown that astrocytes may regulate cerebral blood flow. Astrocytes can directly cause blood vessel constriction or dilatation. Neurons, astrocytes, and vascular cells compose a functional unit that maintains proper blood flow and oxygenation for the brain. Increased brain activity normally causes increased cerebral blood flow thus delivering increased oxygen. However, a recent study found evidence of neuroinflammation and astrocyte inflammation in autism. It is possible that astrocyte inflammation may affect the control of blood flow regulated by astrocytes and lead to the hypoperfusion seen in some autistic children. It must be noted that this is a personal opinion of mine and this has not been definitely proven as the cause of cerebral hypoperfusion in autism.

What does inflammation have to do with blood flow?

Inflammation is a known cause of decreased blood flow and several inflammatory conditions have associated cerebral hypoperfusion including lupus, Sjögren's syndrome, Behçet's disease, viral encephalitis, and acute Kawasaki disease. One SPECT study of 27 children with echovirus meningitis demonstrated decreased cerebral blood flow in 74% of the children and two recent SPECT studies revealed impaired cerebral per-

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fusion in 81% of patients with Sjögren's syndrome. In one SPECT study of patients with systemic lupus erythematosus, 59% had evidence of cerebral hypoperfusion. Furthermore, treatment of the inflammation found in lupus with iloprost and methylprednisolone normalized cerebral blood flow on follow-up SPECT scans.

How does this offer theoretical hope for children with autism?

It is conceivable that the cerebral hypoperfusion found in autistic children may be triggered by neuroinflammation and therefore may be reversible with anti-inflammatory modalities. In fact, some researchers and DAN physicians are seeing improvements in autism symptoms with anti-inflammatory agents including IV-IG and Actos.

Which zones of the autistic brain are affected by decreased blood flow, and which symptoms correlate to each zone?

There have been dozens of studies showing relative decreased blood flow to the brain in autistic children. Decreased perfusion of the temporal lobes is a consistent finding in many studies of autistic children with one study demonstrating that 76% of autistic children have decreased blood flow to the temporal areas when compared to typical children. Two larger controlled studies (21-23 autistic children) using SPECT and PET scans confirmed significant bitemporal hypoperfusion. In both of these studies, the control group was mentally retarded; therefore, the hypoperfusion could not be attributed to mental retardation alone. Another SPECT study of 31 autistic children, 16 of whom had epilepsy, also demonstrated reduction of cerebral blood flow to the temporal lobes. Of note, cerebral blood flow was not different between those with and without epilepsy, suggesting that epilepsy itself was not associated with hypoperfusion in these individuals. A more recent PET study of 11 autistic children revealed diminished blood flow to the left temporal area, including Wernicke's area (which is involved in language comprehension) and Brodmann's area 21 (involved in auditory processing and language), when compared to age-matched mentally retarded children.

Interestingly, an association between temporal lobe abnormalities and the subsequent development of secondary autism has been described in tuberous sclerosis, infantile spasms, herpes simplex encephalitis, and an acute encephalopathic illness in children.

I said earlier that this hypoperfusion correlates with many core autism symptoms. Decreased blood flow to the temporal lobes has also been correlated with an "Obsessive desire for sameness" and "impairments in communication and social interaction" and also with decreased IQ. Decreased blood flow to the temporal lobes and amygdala has been correlated with impairments in processing facial expressions and emotions and trouble recognizing familiar faces. Decreased blood flow to the thalamus has been correlated with repetitive, self-stimulatory, and unusual behaviors including resistance to changes in routine and environment.

Does hypoperfusion worsen with age, and can this be prevented?

In one study, hypoperfusion of the prefrontal and left temporal areas worsened and became "quite profound" as the age of the autistic child increased. This diminished perfusion was correlated with decreased language development. The authors concluded that hypoperfusion "subsequently prevents development of true verbal fluency and development in the temporal and frontal areas associated with speech and communication."

What further research is needed with regard to hypoperfusion or neuroinflammation?

As we have discussed, hypoperfusion of the temporal and other brain regions has been correlated with many of the clinical findings associated with autism including self-stimulatory behaviors and impairments in communication, sensory perception, and social interaction. This diminished blood flow may be mediated by neuroinflammation. Further studies on the effects of inflammation on blood flow in the autistic brain are needed, especially studies involving the temporal lobes where hypoperfusion is common. We also need to study whether or not anti-inflammatory treatments help reverse this hypoperfusion in autistic children.

What is the problem with cerebral hypoperfusion? How does oxygen delivered by HBOT reverse hypoxia in brain tissues caused by hypoperfusion?

Cerebral hypoperfusion causes hypoxia (or decreased oxygen), which triggers electrical failure in brain cells. Worsening hypoxia then eventually results in ion pump failure, which ultimately leads to cell death. Studies have shown that the oxygen delivered by HBOT can reverse hypoxia in brain tissues caused by hypoperfusion.

How can hyperbaric oxygen therapy salvage some brain cells, and can it do this well after an insult involving hypoxia?

As I said, with hypoxia you first get cellular electrical failure and then ion pump failure which causes cell death. However, cells that have electrical failure but retain ion pump ability have been described as "idling" because they remain alive but non-functional. SPECT studies have confirmed the presence of these "idling cells," which surround areas of focal ischemia (or decreased blood flow) and comprise what is termed the "ischemic penumbra." Restoration of oxygenation, sometimes even years after the ischemic insult, can salvage these cells, which may explain why the acute findings of a stroke are poor predictors of ultimate clinical outcomes.

Do we have SPECT scans that bear this out?

Neubauer has studied this phenomenon extensively. In one patient with an ischemic brain injury from a near drowning episode 12 years earlier, he demonstrated that 80 sessions of HBOT at 1.5 ATA increased oxygenation to the ischemic penumbra on SPECT scans and significantly improved cognitive and motor function. Another study of three patients with brain injuries showed areas of what he called "dormant" neurons in the ischemic penumbra on SPECT scans prior to the com-

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mencement of HBOT at 1.5 ATA. All three patients had improvement in the oxygenation of these areas as seen on post-HBOT SPECT scans, which was correlated with clinical improvement.

So did this correlate with clinical improvement and post-HBOT SPECT scan images -- both?

Right -- that's exactly right. He was able to show that not only did they get better clinically, but they had increased oxygenation and perfusion to their brain on SPECT scans.

What kinds of disorders involving cerebral hypoperfusion other than autism have benefited from HBOT?

HBOT has been used with clinical effectiveness in other cerebral hypoperfusion disorders including lupus and traumatic midbrain syndrome, and may be beneficial in acute ischemic stroke, and acute myocardial infarction (or heart attack). In addition, HBOT has been used in several studies on children with cerebral palsy (CP). Some children with CP due to perinatal asphyxia have focal areas of cerebral hypoperfusion on SPECT scans. Significant clinical improvements were found in one study of children with CP after 20 sessions of HBOT at 95% oxygen and 1.75 ATA.

Some other studies using HBOT in cerebral hypoperfusion disorders have been performed at lower pressures (1.5 ATA or less). Stoller recently reported on one pediatric case of fetal alcohol syndrome, which is considered "irreversible and incurable" and is characterized by cerebral hypoperfusion on SPECT studies. Using HBOT at 1.5 ATA, the child had statistically significant improvements in verbal, memory, reaction time, impulse control, and visual motor scores.

Now what about autism?

Interestingly, a case report appeared in a journal called *Hyperbaric Oxygen Report* in 1994 about a child name Michael who had autism and received HBOT. The title of the report was: *"Little Michael's development had stopped—it was called childhood autism—until hyperbaric oxygen therapy."* This is typical of some things in medicine—someone may notice an improvement with a new therapy, but this may go unnoticed by others for many years. In this case we are 12 years out from this case report. In another case, Heuser treated a four-year old autistic child using lower pressure HBOT at 1.3 ATA (and 24% oxygen) and reported "striking improvement in behavior including memory and cognitive functions" after only ten sessions. Furthermore, the child had improvement of cerebral hypoperfusion as measured by pre-HBOT and post-HBOT SPECT scans.

So some "irreversible" and permanent neurological conditions can have clinical improvements with HBOT?

Studies have shown improvements in: Cerebral Palsy, Fetal Alcohol Syndrome, Amyotrophic Lateral Sclerosis also called Lou Gehrig's disease, multiple sclerosis, Complex Regional Pain Syndrome, Ischemic Brain Injury, Traumatic Midbrain Syndrome and stroke. These conditions, in most cases, are considered "irreversible" and permanent.

Is it possible that the increased oxygen delivered by hyperbaric could overcome any hypoxia caused by hypoperfusion and improve symptoms for children with autism?

In one study of cerebral blood flow in autistic children compared to non-autistic children, the amount of perfusion to the brain in autistic children was approximately 5-8% less than typical children when measured by PET Scan. It is unknown if this hypoperfusion leads to hypoxia in autistic children although SPECT scans performed on autistic children (including the case report by Heuser) do show evidence of relative hypoxia. Follow-up SPECT scans in autistic children after HBOT also show evidence of increased oxygenation to the brain. It is certainly plausible that the increased oxygen delivery by HBOT could overcome any hypoxia caused by hypoperfusion and thus lead to improvements in the symptoms of autistic children.

What evidence of neuroinflammation is there in autism, especially in the brain?

Recent studies reveal that autism is characterized by neuroinflammation. The study by Vargas on autopsy brain samples from autistic patients demonstrated an active neuroinflammatory process in the middle frontal gyrus, anterior cingulate gyrus, and cerebellar hemispheres including increased microglial and astroglial activation and increased proinflammatory cytokines. Furthermore, cerebrospinal fluid obtained from living autistic patients also "showed a prominent proinflammatory profile." Previous studies of autistic children have shown circulating serum autoantibodies to brain elements including neuron-axon filament protein and glial fibrillary acidic protein, the caudate nucleus, cerebral cortex and cerebellum, and neuron-specific antigens including myelin basic protein.

But inflammation in autistic children is not limited to the brain. When compared to typical children, autistic children make significantly more serum antibodies against gliadin and casein peptides—which is the basis of the gluten and casein free diet, produce more pro-inflammatory cytokines, and have an imbalance of CD4+ and CD8+ cells. Furthermore, some patients with autism have mucosal inflammation of the stomach, small intestine and colon characterized by ileo-colonic lymphoid nodular hyperplasia. In these children, the gastrointestinal mucosa has evidence of proinflammatory cytokines, increased lymphocytic density, and epithelial IgG deposits mimicking an autoimmune lesion.

Does HBOT have anti-inflammatory tissue effects?

Several animal studies have revealed that HBOT has potent anti-inflammatory tissue effects with equivalence to diclofenac 20 mg/kg noted in one study using HBOT at 2.4 ATA and 100% oxygen. HBOT has also been shown to decrease the symptoms of advanced arthritis in rats and attenuates the inflammatory response in the peritoneal cavity caused by injected meconium. In addition, one animal study using HBOT at 2.5 ATA showed increased survival and decreased proteinuria, anti-

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dsDNA antibody titers, and immune-complex deposition in lupus-prone autoimmune mice. HBOT has also been shown to decrease markers of inflammation including IL-1, IL-6 and TNF-α in humans.

Does HBOT help gut issues such as colitis and yeast?

HBOT has been used in animal studies to improve colitis. Interestingly, thirty sessions of HBOT at 2.0 ATA has been used in humans to achieve remission of ulcerative colitis not responding to conventional therapies. HBOT has also been used extensively and successfully in patients with Crohn's disease not responding to medical therapy. I think there is more evidence that HBOT works for Crohn's disease than for many other so-called "approved" conditions. This may be relevant in autistic children given the higher prevalence of gastrointestinal mucosal inflammation described above. HBOT may help with yeast but this is something that needs further study to clarify.

What is oxidative stress, and what evidence of this is there in autism?

Oxidative stress is mainly due to what are called free radicals. Free radicals are highly reactive, unstable molecules that have an unpaired electron in their outer shell. They react with various cellular components including DNA, proteins, lipids and fatty acids and cause DNA damage, mitochondrial malfunction, cell membrane damage and eventually cell death. Free radicals are formed during a variety of biochemical reactions and cellular functions (such as mitochondria metabolism). The steady-state formation of free radicals (which are also called pro-oxidants) is normally balanced by a similar rate of consumption by antioxidants. Oxidative stress results from an imbalance between formation and neutralization of pro-oxidants. Various pathologic processes disrupt this balance by increasing the formation of free radicals in proportion to the available antioxidants (thus, oxidative stress). Examples of increased free radical formation are immune cell activation, inflammation, ischemia, infection, cancer and so on. Free radical formation and the effect of these toxic molecules on cell function (which can result in cell death) are collectively called "oxidative stress."

Antioxidants are molecules or compounds that act as free radical scavengers. Most antioxidants are electron donors and react with the free radicals to form innocuous end products such as water. These antioxidants bind and inactivate the free radicals. Thus, antioxidants protect against oxidative stress and prevent damage to cells. By definition, oxidative stress results when free radical formation is unbalanced in proportion to the protective antioxidants. There are many examples of antioxidants:

Intracellular enzymes: superoxide dismutase (SOD), glutathione peroxidase

Endogenous molecules or molecules normally found in the body: glutathione (GSH), sulfhydryl groups, alpha-lipoic acid, Coenzyme Q10

Essential nutrients: vitamin C, vitamin E, selenium, N-acetyl cysteine (NAC)

Dietary compounds: such as bioflavonoids

All cells have intracellular antioxidants (such as superoxide dismutase and glutathione) which are very important in protecting all cells from oxidative stress at all times. Glutathione is very important as an intracellular antioxidant. GSH has been found to be low in many disease states indicating oxidative stress and inadequate antioxidant activity to "keep up" with the free radicals.

Recent studies have shown that autistic children have evidence of increased oxidative stress including lower serum glutathione levels. One study demonstrated that autistic children had increased red blood cell nitric oxide, which is a known reactive free radical and is toxic to the brain. Jill James recently showed that total serum glutathione levels were 46% lower and oxidized (or the bad form of) glutathione was 72% higher in autistic children when compared to neurotypical controls. This led to decreased antioxidant ability in these autistic children. Lower serum antioxidant enzyme, antioxidant nutrient, and glutathione levels, as well as higher pro-oxidants have been found in multiple studies of autistic children. Furthermore, treatment with anti-oxidants has been shown to raise the levels of reduced glutathione in the serum of autistic children and appears to improve symptoms.

Does HBOT have any effect on this?

Multiple studies have shown neutral effects on oxidative stress with HBOT use. In one study on horse platelets, measures of oxidative stress were not increased after HBOT; in fact, a rise in the antioxidant enzyme superoxide dismutase (SOD) was found 24 hours after HBOT without a fall in glutathione levels. In another study on dogs, following 18 minutes of complete cerebral ischemia, HBOT at 2.0 ATA reduced brain damage without increasing oxidative stress. Furthermore, in a rat model of reperfusion, HBOT extended skin flap life without evidence of oxidative stress.

In addition, numerous studies have shown improvements in oxidative stress with HBOT including increased production of antioxidants and antioxidant enzymes and decreased markers of oxidative stress such as malondialdehyde. An improvement in the survival rate of skin flaps and an increase in SOD levels were found in one study when rats were exposed to hyperbaric oxygen at 2.0 ATA. In another study, HBOT at 2.5 ATA induced the production of antioxidants and decreased malondialdehyde levels in rats. Furthermore, in a study of rats with pancreatitis, HBOT at 2.5 ATA decreased oxidative stress markers including malondialdehyde, and increased the levels of the antioxidant enzymes glutathione peroxidase and SOD. HBOT has also been shown to acutely raise the levels of reduced glutathione in the plasma and lymphocytes of some humans after just one treatment session at 2.5 ATA. Finally, ischemia-reperfusion injuries usually cause oxidative stress through decreases in glutathione levels and activities of catalase and SOD. However, in one rat study of ischemia, pretreatment with 1-3 doses of HBOT caused an increase in liver glutathione and SOD levels and protected against liver injury; control animals not receiving HBOT actually had drops in glutathione and antioxidant enzyme levels and had liver damage associated with this.

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Also, one recent study that has not yet been published found no evidence of increased oxidative stress with mild HBOT at 1.3 ATA.

Are there any situations in which HBOT might detrimentally increase oxidative stress?

Concerns have been raised that HBOT may cause increased oxidative stress through the production of reactive oxygen species. This concern is controversial as studies have shown mixed results. Contrary to the studies just discussed, several animal studies using HBOT at 2.5 ATA or greater have found evidence of increased oxidative stress. However, this appears to occur at the higher pressures (2.5 ATA or greater). Support for this higher pressure effect was found in one study, which demonstrated that HBOT at 2.0 ATA increased SOD levels whereas HBOT at 3.0 ATA caused SOD levels to decrease, presumably because the SOD had to neutralize more free radicals at the 3.0 ATA pressure. Thus, from an oxidative stress and SOD production standpoint, there might be an optimal HBOT pressure, which falls somewhere below 2.5 ATA.

Should patients use antioxidants and therapies to raise glutathione levels and before beginning HBOT?

In most conditions, if you are using 2 ATA or less, this is probably not necessary. However, we know that autistic children have lower glutathione level, on average 46% lower than typical children. So raising glutathione levels in autistic children is one of the mainstays of the DAN! Protocol and should be helpful. There is evidence that HBOT may also raise glutathione levels as well. Given the theoretical risk of increased oxidative stress with HBOT, antioxidants are probably helpful.

Might a combination of antioxidants and HBOT help reduce oxidative stress in children with autism and, therefore, help with symptoms?

Many antioxidants, including alpha-Lipoic acid, melatonin, N-Acetyl-Cysteine, Vitamin E, riboflavin, selenium, and glutathione have been shown to reduce oxidative stress associated with HBOT at very high pressures (above 2.5 ATA). In fact, in one animal study using HBOT at 4 ATA, melatonin was shown to completely prevent any oxidative stress with HBOT. We also know that the Autism Research Institute lists melatonin as the #4 overall parent-rated effective treatment for autism symptoms. It appears that HBOT at less that 2 ATA decreases oxidative stress, whereas above 2.5 ATA it may in some cases increase oxidative stress. Therefore, starting antioxidants before HBOT (especially melatonin) is probably a good thing.

Should patients have used chelation prior to or use chelation concurrently with HBOT?

This is a very good question and I don't think anyone knows for sure. There are certainly a lot of opinions out there. In our case series and our current study, we have several children who have or are chelating, but it is too early to tell if these children are having better outcomes. I think we need more study on this subject before I can honestly comment on this.

How might HBOT help with stem cell therapy, were stem cell therapy ever to become a viable treatment?* (*Editorial note: Some researchers feel that stem cell therapy is a viable therapy now. An alternate way of phrasing this would be "more widely used.")

The recent study by Thom that is in press demonstrated that the number of stem cells circulating in the human body doubled after just one treatment with HBOT at 2.0 ATA for 2 hours and went up 8-fold after 20 treatments. Some researchers have begun injecting stem cells into the brains of people with neurological disorders in the hopes of causing regrowth of certain brain tissue. Two disadvantages to this approach are the invasiveness and the fact that you may receive another person's stem cells. We also know that stem cells are located in the brain including the hippocampus and periventricular subependymal zone, and I think there is an exciting possibility that permanent brain conditions may one day be helped or even reversed with stem cells. The fact that HBOT can increase one's own stem cell production is extremely exciting and promising.

In your opinion, do most cases of autism involve brain injury?

If you look at some of these studies we have discussed, the autistic brain certainly appears injured, as evidenced by inflammation and decreased blood flow. The cause of this injury is not completely understood but may involve toxins, especially heavy metals such as mercury. Further study is desperately needed in this area.

Let's talk about your retrospective study: What kind of HBOT did you use pressure, oxygen concentration, equipment? (for example: chamber, concentrator, mask/hood)

Most HBOT researchers would call what we used in this case series hyperbaric air treatment. We used a portable 1.3 ATA chamber and an oxygen concentrator. The oxygen concentrator puts out 90-93% oxygen at a flow rate of 10 liters per minute. We took this oxygen and fed it into a blower which mixed room air and the oxygen to give a final chamber oxygen concentration of approximately 28% compared to room air which is 21%. So we gave 30% more pressure than room air (1.3 vs. 1.0 ATA) and about 25% more oxygen. If you calculate the partial pressure of oxygen in the chamber, it would be 277 mm Hg with our setup versus 160 mm Hg in normal room air. This is almost double. We did not have the children wear a mask (which would have raised the partial pressure of oxygen to 891 mm Hg if worn properly) because we wanted all of the children to receive the same treatment and we were concerned that some would not wear the mask. I also felt that based on the Collet trial from Canada, which saw a large benefit in CP using 1.3 ATA and room air, that we did not need to go for the higher oxygen partial pressures to see benefits.

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What were the patients' ages and levels of affect of autism?

The age range was 2-7. Three had CARS score below 30 (which technically is below the cutoff for a diagnosis of autism, but these children had received many of the DAN! protocols over the years and had already had a lot of improvements) and 3 were in the moderate to severe category.

All had regressed?

I think all but one had regressed.

Were the children taking anti-oxidants?

All of the children were following standard DAN! protocol and so were already taking multiple antioxidants.

Was HBOT the only therapy added or deleted?

HBOT was added to the regimen but parents were allowed to make other changes. This was not a prospective study but rather a retrospective analysis. Scales were filled out before and after treatment by the parents and then reviewed at a later date. Even though some parents did add other treatments from time to time during the study, none of the parents reported their child as undergoing developmental spurts of similar or greater magnitude in the recent past as was seen with HBOT.

Which pre- and post-assessments were used?

We used three scales: ATEC (Autism Treatment Evaluation Checklist), CARS (Childhood Autism Rating Scale) and SRS (Social Responsiveness Scale).. ATEC is a scoring system of verbal communication, sociability, sensory/cognitive awareness, and health/autistic behaviors published by the Autism Research Institute. CARS is a widely used scale for screening and diagnosing autism and has been shown to correlate very well with the DSM-IV criteria for autism diagnosis. SRS is a recently validated test of interpersonal behavior, communication, and stereotypical traits in autism.

What were the results? And what were the most notable findings of your study?

ATEC improved 22.1 % overall with a p value of 0.0538.
CARS improved 12.1 % overall (p = 0.0178)
SRS improved 22.1% overall (p = 0.0518).

I think the most notable finding was that the 3 youngest (less than age 5) improved more dramatically than the 3 oldest:
ATEC 31.6% vs. 8.8%
CARS 18.0% vs. 5.6%
SRS 28.9% vs. 13.0%
It must be noted that these results in the younger children compared to the older children were not statistically significant due to the small sample size.

Might higher pressure and 100% oxygen have had an even greater positive effect?

Maybe and probably. In this case series, the chamber was augmented with only 28% oxygen instead of 100% oxygen. Anecdotal reports from other DAN physicians seem to indicate that some children have more improvement more quickly with higher pressure and 100% oxygen. Every child is different and some seem to respond quickly to lower pressure and oxygen levels and some appear to need higher pressures and oxygen levels. I think it makes sense to use to the lowest amount of oxygen and pressure that gets the job done. Where this is for each patient may be tricky to discover initially. Certainly, further studies on this are needed.

Is there any trend becoming evident insofar as optimal number of treatments, degree of pressure, optimal age, or some permutation of these factors?

The number of HBOT sessions needed to produce full clinical improvements from cerebral hypoperfusion or ischemia is unclear. In one study combining the use of SPECT and HBOT, an average of 70 treatments was needed to show a significant increase in cerebral blood oxygenation and metabolism in patients with chronic neurological disorders including CP, stroke, and traumatic brain injury. Of note, the rate of improvement in cerebral blood oxygenation was more profound during the last 35 treatments compared to the first 35. In addition, reports from some HBOT researchers indicate that younger patients tend to have improvements more quickly than older patients, as also seen in our small case series. Therefore, older patients may need more treatments.

Why would younger children improve more readily?

As I said, the interesting finding from this case series was that the younger children had more significant improvements in clinical outcome scores than the older children. This is congruent with reports from some HBOT researchers indicating that younger patients tend to have improvements more quickly than older patients. The younger children in this case series may have had less overall hypoperfusion to surmount because decreased cerebral blood flow to areas associated with communication has been shown to worsen with increasing age in autistic children as we discussed earlier. It is likely that the older children in this case series need more than 40 HBOT sessions to show further improvements, especially since some HBOT researchers have noted that 50-80 HBOT sessions are typically needed to show significant clinical gains.

So what would be the procedure to do 50-80 hours of HBOT? Do different pressures or masks & hoods and different concentration of oxygen require you to take breaks at different points in treatment? How many hours per day? Days per week? Weeks to take a break? And so on…

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Most researchers recommend 40 treatments over 8 weeks which is 5 treatments per week with the weekends off. As far as I am aware, there is no magic to this number but it was rather chosen for convenience as a lot of people have to travel out of town to do treatments. Most then recommend a break of 1-2 months before another 40 treatments. Some people will do 2

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treatments per day, and most recommend a 4 hour break in between. However, if a child is tolerating HBOT and improving, the treating physician may decide to continue for 80 treatments without taking a prolonged break.

Is there evidence to suggest that improvements seen with HBOT may persist after treatment is discontinued?

If we look at the Collet study using HBOT on CP we see dramatic improvements in the children. Prior to starting HBOT, all standard therapies were discontinued. Most of the improvements seen in these children continued for three months after treatment and some of the children from the study began walking, speaking, and sitting for the first times in their lives. The literature on HBOT seems to indicate that some improvements continue for months after treatment and may even be permanent. More research is needed on this.

Does HBOT work better for certain subsets of the autistic population? What kinds of clinical gains are seen with autistic patients, and does the initial level of affect of the patient, or the type of metabolic or toxicologic issues a child has, or type of HBOT used matter?

It seems to work across the board. However, younger children seem to do better more quickly as we just discussed, which is true of many of the treatments in autism. Many of the gains that we see are in the health category (i.e. as listed on ATEC) including sleeping better, improvement of GI problems, etc… Furthermore, many have had increased speech and interaction. Our youngest child went from one word utterances to speaking in sentences after about 40 HBOT treatments at 1.3 ATA. Our oldest son had mild improvements with about 100 treatments at 1.3 ATA and 28% oxygen but now is starting to put together words at 1.5 ATA and 100% after only a few treatments. The other day, he said, "Open the gate please" and I almost fell on the floor. Again, I think every child will respond differently and it may take some trial and error to find which pressure and oxygen level will be best for each child. I certainly wish we had done higher pressure and oxygen with our older child sooner. However, this is why parents need to work with an experienced physician when starting HBOT to work through these issues.

What further research is needed insofar as gauging the safety and efficacy of hyperbaric oxygen therapy vis-à-vis autism?

Safety: the safety of HBOT had been established in children in numerous studies and I can't see any issues with this as long as the pressure is kept below 2.0 ATA.

Efficacy: We need some more studies on using HBOT in autism. Currently we are performing a prospective study on 18 children with autism. True efficacy will ultimately be proven with a placebo controlled study which is currently in the planning phase.

Well Dr. Rossignol, do you have any closing remarks or take home message that you would like to leave with people?

I think that, in summary, and the thing that excites me so much about hyperbaric oxygen therapy, is the anti-inflammatory effects, which I think is going to help a lot of conditions, not just autism, and also the increased stem cell effect that we can see with hyperbaric. Certainly, it seems like a lot of people talk about increase in oxygenation to the brain as being the mechanism of improvement with autism. I think it goes well beyond that. With more studies and more research, I think we will be able to figure out what is the true mechanism with hyperbaric. I am certainly very excited about it. I really look forward to doing more studies and more research on this. I just hope that this therapy will become available to as many people as possible.

One of the reasons we wanted to study the 1.3 ATA chambers is because this is something that is available at home. We hope that if it does work and is proven, we can begin to have insurance reimburse for hyperbaric and this is one of our goals, as well.

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