Interview with Dr. Dan A. Rossignol: Hyperbaric Oxygen Therapy improves symptoms in autistic children

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Abstract

Multiple studies have found that autism is characterized by cerebral hypoperfusion which correlates with many core features including repetitive, self-stimulatory, and stereotypical behaviors, and impairments in communication, sensory perception, and social interaction. Hyperbaric oxygen therapy (HBOT) can help overcome cerebral hypoperfusion by providing more oxygen to the brain. Recent studies have shown that children with autism have neuroinflammation and gastrointestinal inflammation, and HBOT is strongly anti-inflammatory. Autistic children also have increased oxidative stress and HBOT can decrease oxidative stress through up-regulation of antioxidant enzymes and increased antioxidant production. Children with autism have a relative mitochondrial dysfunction and HBOT can increase the production of mitochondria. Autistic children appear to have impaired production of porphyrins, which are involved in heme synthesis. Impaired production of porphyrins reduces the ability to deliver oxygen and HBOT may help overcome this. Autism is a considered to be a neurodegenerative disease. HBOT has been shown to increase the production of stem cells, which may aid in reversing "irreversible" brain disorders, including autism. In our recent prospective, open label study, we found that HBOT ameliorates some symptoms in autistic children. Significant improvements were noted by parents in lethargy, communication, motivation, mannerisms, speech, sensory and cognitive awareness, and overall health. Markers of inflammation decreased, and there was no statistically significant change in oxidized glutathione levels. Further evaluation with a double-blind placebo-controlled study to verify these findings is indicated.

Keywords: hyperbaric oxygen therapy, HBOT, autism, hypoperfusion, anti-inflammatory, SPECT scan, oxidative stress, stem cells, mitochondria, glutathione

Dr. Dan Rossignol, who will soon be joining the International Child Development Resource Center (ICDRC), is a Clinical Assistant Professor at the University of Virginia Department of Family Medicine and a Defeat Autism Now! (DAN!) physician. He is the father of two children with autism, ages five and three. Dr. Rossignol and Lanier Rossignol, Dr. Rossignol's wife who is a family nurse practitioner and who is involved heavily with the research, authored the study entitled Hyperbaric Oxygen Therapy May Improve Symptoms in Autistic Children, published in Medical Hypotheses. Today we'll be talking about the study-in-progress entitled Hyperbaric Oxygen Therapy Improves Symptoms in Autistic Children, and a placebo controlled trial will begin in the next few weeks, to be sponsored by the International Hyperbarics Association. The Rossignols will also be involved with research in the future and are in the planning stages for several other research studies.

Why consider hyperbaric for autism? Why did you undertake this study, and what are the ways you think things are actually working ---the mechanisms involved in HBOT?

In doing my literature search, I came across a case report of a child who was treated in 1994 with HBOT and apparently had improvement in symptoms. The paper was called, "Little Michael's development had stopped—it was called 'childhood autism'—until hyperbaric oxygen therapy." Unfortunately, things like this happen in medicine all the time where someone notices something, maybe publishes it, but nothing really comes of it. So here we are 12 years later talking about Hyperbarics and autism.

As we know, the rates of autism have gone up over 10 fold in the last 15 years. Time magazine just published an article on autism called, "New insights into the hidden world of autism." In this article, they quote Dr. Thomas Insel, director of the National Institute of Mental Health as saying, "When my brother trained at Children's Hospital at Harvard in the 1970's, they admitted a child with autism, and the head of the hospital brought all of the residents through to see. He said, 'You've got to see this case; you'll never see it again.'" So we know the rate of autism is up, and we have some people stating that the rates really are not up, it is just "diagnostic substitution." But that is a whole different story.

Some of the new findings on the pathophysiology (or abnormal findings) of autism make me think that HBOT will help improve symptoms in autistic children. These include, but are not limited to:

1. Numerous studies demonstrate that some children with autism have diminished cerebral blood flow, especially of the temporal lobes. This decreased blood flow has been correlated with many of the autism core symptoms such as repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication, sensory perception, and social interaction. Furthermore, not only do they have decreased blood flow at baseline, but when autistic children need to pay attention to a task they do not always have the compensatory increase in blood flow like typical children and instead sometimes demonstrated decreased blood flow in some studies. HBOT can help overcome cerebral hypoperfusion by providing more oxygen to the brain.

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2. Recent studies have shown that children with autism have neuroinflammation and GI inflammation and HBOT is strongly anti-inflammatory. Children with autism have high levels of cytokines which HBOT has been shown to decrease. A study from 2002 I recently came across shows that the decrease in inflammation obtained with HBOT is due to the increased pressure provided by HBOT, not necessarily by the increased oxygen. In the study I am referring to, hyperbaric pressure (without oxygen) caused a decrease in inflammation, whereas 100% oxygen without the pressure did not decrease inflammation at all. This is very important and may be the way that hyperbarics works at 1.3 ATA and room air like in the CP study from Canada in 2001. Some people have criticized using mild hyperbarics at 1.3 ATA because they state that when compared to this pressure, you can get just as high an oxygen concentration in the blood with oxygen by face mask without a chamber. And this may be true in some cases. However, we must remember we are dealing with 2 separate components with HBOT—the oxygen and the pressure. So it appears that many of the effects of HBOT are from the increased oxygen, but we cannot dismiss the pressure effect. I think we need more studies on this as well.

3. Children with autism have increased oxidative stress and HBOT can decrease oxidative stress through up-regulation of antioxidant enzymes and increased antioxidant production. From my review of the literature, it appears that oxidative stress is not a problem until you get to higher pressures, typically over 2.0 ATA, which most people would not use in autistic children.

4. Children with autism also have a relative mitochondrial dysfunction. Only about 0.3% of the oxygen we breathe actually gets to our mitochondria. HBOT increases oxygenation to mitochondria and a paper just published in the last month or so shows that HBOT can also increase the production of mitochondria.

5. A paper in press now and presented by Dr. Nataf at Autism One shows that children with autism appear to have impaired production of porphyrins which are involved in heme synthesis. Heme is the molecule which carries oxygen in the body. Interesting, the mitochondria are involved in the synthesis of porphyrins. Impaired production of porphyrins may reduce the ability to deliver oxygen and HBOT may help overcome this.

6. Autism is a neurodegenerative disease which most people consider irreversible. Stem cells are produced in bone marrow, but are also produced in the brain. HBOT has been shown to increase the production of stem cells which may aid in reversing "irreversible" brain disorders. It is conceivable that new stem cells could replace abnormal cells in the body.

Some of these mechanisms were outlined in our original paper just published in Medical Hypotheses. Our original case series on 6 children seemed to indicate that hyperbaric therapy improved symptoms in autistic children. We undertook this larger study on 18 children as a pilot study.

The purpose of this pilot study was to establish if HBOT in autistic children is efficacious (works) and if further larger studies are indicated. It was funded by the International Hyperbarics Association, and we worked with Dr. Liz Mumper in Lynchburg, VA and Dr. Jill James. My wife Lanier was also instrumental in the study.

How many children were in this study and how were they treated?

Eighteen children, four girls and fourteen boys, with ages ranging 3 to 16 years, were enrolled in the study. Nine children were age 5 or less, and nine were over age 5.

Baseline Childhood Autism Rating Scale (CARS) scores were obtained to determine severity, which was similar in each chamber group (34.4 in the 1.5 group versus 33.8 in the 1.3 group). All patients had been previously diagnosed with Autistic Disorder (299.0) by a pediatrician or neurologist. Children with a diagnosis of PDD-NOS or Asperger's Syndrome were excluded.

Eight children had CARS above 35 which placed them in the more severe category. Ten children had CARS below 35, placing them in the mild-moderately autistic group.

Of the 18 children, 6 children were assigned to receive hyperbaric oxygen therapy at 1.5 ATA and 100% oxygen. 12 were assigned to receive hyperbaric therapy at approximately 1.3 ATA and 24% oxygen. I use the term hyperbaric therapy for these 12 children because we used less than 100% oxygen. Some people would also call this mild hyperbaric therapy or hyperbaric air therapy. Since we added a small amount of oxygen, I actually prefer to call it hyperbaric enriched air therapy, but this name is probably too long.

All current therapies (including medicines and supplements) were held constant in the trial. Children were not allowed to begin or stop any therapies.

Other characteristics of the children:

- 3/6 in 1.5 ATA Group were chelating
- 5/6 in 1.5 ATA Group were already on Methyl-B12
- 1/12 in 1.3 ATA Group were chelating
- 7/12 in 1.3 ATA Group were already on Methyl-B12
- 3/12 in 1.3 ATA Group were taking only multivitamins

So we had a variety of previous interventions in these children—ranging from very basic to more advanced.

Written informed consent was obtained from the parents and, when possible, the child. The study protocol was approved by an Institutional Review Board.

How did you measure behavioral and cognitive indicators?

Parents filled out 5 standardized forms at the beginning of the study and after every 10 treatments. Teachers also filled out 2 of the forms at the beginning and after every 20 treatments. The 5 forms we used were:

- *Childhood Autism Rating Scale* (CARS)

Gives a measure of the severity of autism.

- *Aberrant Behavior Checklist—Community (ABC-C)*

58 item checklist that assesses maladaptive behaviors in individuals with developmental disabilities using simple 4 point rating scale. Scores obtained in the following areas: irritability,

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lethargy and social withdrawal, stereotypic behavior, hyperactivity, and inappropriate speech. This is a standard scale used in many autism drug studies, like the study published in 2002 in the New England Journal of Medicine on risperidone.

- *Social Responsiveness Scale* (SRS)

SRS is a recently validated test of interpersonal behavior, communication, and stereotypical traits in autism.

- *Autism Treatment Evaluation Checklist* (ATEC)

A scoring system of verbal communication, sociability, sensory/cognitive awareness, and health/autistic behaviors published by the Autism Research Institute.

- Gastrointestinal rating scale

Assessed things such as nausea, vomiting, diarrhea, constipation, gas, bloating, abdominal pain, hard bowel movements, soft bowel movements, etc. We did this because HBOT has been shown to achieve remission of Crohn's Disease and Ulcerative Colitis not responding to conventional therapies. Furthermore, some patients with autism have mucosal inflammation of the stomach, small intestine and colon characterized by ileo-colonic lymphoid nodular hyperplasia. We wanted to see if HBOT would improve gastrointestinal symptoms in autistic children.

What about metabolic and other biomarkers?

Because of the inflammation found in the gastrointestinal tract and brain of autistic children, we wanted to measure inflammation. We measured C-reactive protein which is a pretty good measure of overall inflammation in the body. We saw improvements in C reactive protein with nearly statistical significance. 15 children had an average C-reactive protein of 0.81 and had mild improvements to about 0.58. However, three children had huge decreases from an average of about 22 to 0.2. Now 22 is very elevated. This large improvement in this subset was almost to be expected as it is those with the largest amount of inflammation who would be expected to have the biggest improvements.

With Dr. Jill James, we measured markers of oxidative stress including oxidized glutathione in the plasma. Oxidized glutathione is a good indicator of intracellular oxidative stress, and we found no significant changes in this after HBOT in both groups.

What did you find with higher-pressure hyperbaric?

At 1.5 ATA, we found statistically significant improvements (which means a p-value less that 0.05) in several of the scales including: Lethargy (ABC); Motivation (SRS); Sensory and Cognitive Awareness (ATEC); and Speech, Language and Communication (ATEC).

What did you find with mild hyperbaric?

We found statistically significant improvements in several scales as well:

Lethargy (ABC); Communication (SRS); Motivation (SRS); Mannerisms (SRS); Speech, Language and Communication (ATEC); Sensory and Cognitive Awareness (ATEC); and Health and Physical Behavior 21% (ATEC).

So we saw similar improvements in both groups. Some of the % improvements were larger in the 1.5 ATA group and some were larger in the 1.3 ATA group, depending on which test you looked at.

In which area or areas was improvement noted, and in which area or areas was the greatest improvement noted?

In both groups, the biggest improvements were in lethargy and motivation. Both group had good improvements in sensory and cognitive awareness along with speech, language and communication.

A lot of children began putting words together and some who were non-verbal began talking. One young child in the chamber, who wasn't in the study but went in with his mother and brother, gained several words (was completely non-verbal to that point). He also had no ability to bear weight but was able to stand after HBOT at 1.3 ATA.

Some things improved that we did not necessarily expect like improvements in appetite and sleep. One child who wasn't gaining weight gained significant weight after 40 sessions at 1.3 ATA. Some children had big improvements in bowel movements with some having formed stools after having diarrhea all of their life.

It can be difficult to determine why we had significant improvements in so many areas. It actually makes the study interpretation more difficult, because we would like to explain the mechanism of improvement. However, we do know from the literature, that many children with autism have cerebral hypoperfusion, and that the location of this decreased blood flow can vary in different children. So if we improve the hypoperfusion, we may see different clinical outcomes that will vary child to child. Some physicians have begun using SPECT scans to determine where the hypoperfusion is and how much is present. One day, we may be able to take the SPECT findings before HBOT and predict what improvements we think will take place. SPECT scans can also be helpful if a child is not responding to HBOT to gauge if hypoperfusion is even there.

Were there differences in gains with either high-pressure or mild hyperbaric as significantly correlated with patient age or severity of diagnosis coming into the study?

There was a trend for the children 5 and younger to have better improvements but it was not statistically significant. This was a surprise because I felt we would see big differences based upon age, and it was a factor, but not as large as I would have thought.

Severity also played a role. There was a trend for the children with initial CARS scores > 35 to have slightly more improvements than children who were milder. This does make sense as we would expect the more severe children to have more improvements to gain. However, this was a trend and was not statistically significant.

What further research is indicated by this study, and what kinds of studies are in the works?

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In the past, when I have talked to other physicians, including developmental pediatrics, they state that "autistic children get better with time." Interestingly, a paper just published in the Archives of General Psychiatry this month states that younger children with PDD tend to get worse over time and almost all are diagnosed with Autism at a later age. Improvements in children with autism is very uncommon, at least in the children in this study. So I think that finding improvements in our current study is significant.

I have tried to take a stepwise approach to HBOT and autism research. At first, I was sceptical that it would help. Then I began researching HBOT and found a wealth of information in the literature that made me think HBOT would help autistic children. So then we undertook a small case series on 6 children and published this and our hypothesis in *Medical Hypotheses*. Then we moved to this pilot study on 18 children with autism which demonstrated HBOT ameliorates some symptoms in autistic children. This study was prospective but was an open label study meaning that parents knew their children were receiving HBOT and there was no control group. However, we wanted to see if a larger study was worth undertaking by evaluating HBOT with a smaller study to start with. What we now need is a placebo controlled study to determine if the improvements occurred because of "normal development" or parental bias.

We just received IRB approval to do this prospective study. The official name is: *A Prospective, Randomized, Double-blind, Placebo Controlled Study on the Clinical Effects of Hyperbaric Therapy in Autistic Children.* This study will be sponsored by the International Hyperbarics Association and involves Dr. Liz Mumper, Dr. Cindy Schneider and Dr. Jeff Bradstreet. It will enroll 60 children, half of whom will receive hyperbaric therapy at 1.3 ATA and 24% oxygen and the other half will receive a placebo. We will have psychologists who will be blinded to the treatments (which means they will not know what the children received) administer standardized scales. The physicians will also be blinded and will also perform some standardized tests. Finally, the parents will be blinded as well. As an aside, the placebo group will receive free hyperbaric treatments after the study to help compensate for the fact they were in the placebo group.

We chose 1.3 ATA because a lot of children with autism are currently receiving this dose and we are hoping to prove that it works. As an aside, I still think it is best for children with autism to receive HBOT initially at a HBOT center and then maybe move to a home chamber eventually. The nice thing about the 1.3 chamber is the home use, making it available to many more people that otherwise could not receive it, due to cost, travel, time, etc…

How is the insurance situation coming along?

Well, obviously, HBOT is not approved for autism, but we hope to get there. Interestingly, if you take the ABC scale and look at the lethargy subset score, we saw a 49% improvement in symptoms at 1.5 ATA with a p-value of 0.008. If you look at the New England Journal of Medicine study on risperidone from 2002, there was a 56.9% improvement on the ABC irritability subscale with a p-value < 0.001. So the results we had on these 6 children with 1.5 ATA approached the percentage improvement seen with a drug approved for the use in autism. We just need to be able to reproduce these type of findings in a placebo study.

Hopefully when we finish these studies and show that hyperbaric therapy works, then insurance reimbursement will follow.

So please tell us about Dr. Dan Rossignol's, Lanier Rossignol's, and the Rossignol family's plans for the future.

Well, I just recently quit my job in a family practice up here in Virginia and am taking a "small sabbatical", although we are trying to get our house ready to sell and move, which makes a sabbatical difficult to do. I am in the process of working on several different papers for publication now. Of course, we have already talked about the upcoming study of 60 children which will take a lot of my time as well. And in the next month or two, we are going to be moving to Florida and joining Dr. Bradstreet at the International Child Development Resource Center.

My final thoughts about HBOT I would like to leave you with: there is no magic timing to HBOT. A child with autism can do it at anytime. In the pilot study, we had several children who were chelating. But the majority had never chelated and we were still seeing good improvements. I have had several parents tell me that they were told not to do HBOT until they had chelated for one year. I have no idea where this info is coming from, but even the children who were taking only a multivitamin with no other interventions (including Methyl-B12, etc) had good improvements.

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