Review of the Pathophysiology of Autism and Possible Benefits of Hyperbaric Oxygen Therapy (HBOT)

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HBOT and Autism Overview

At first glance, the use of hyperbaric oxygen therapy (HBOT) in autism appears out of the ordinary. That is what I first thought when I heard about the use of HBOT in autism almost 2 years ago. At the time, no studies existed on the use of HBOT in individuals with autism (there was one published case report [1]). In fact, many people who were proponents for this therapy could not give a theoretical reason why it should/could work. We began using HBOT in children with autism with a great deal of skepticism. After seeing improvements in some of these children (including our own), we decided that further study was needed. Just over 2 years later, we have finished our third study on the use of HBOT in autism. Many of the underlying pathophysiological findings in autism might be improved with HBOT and these have been reviewed in another publication [2]. HBOT in children is generally regarded as safe [3].

Cerebral Hypoperfusion and Hypoxia in Autism

To understand how or why HBOT works in children with autism, we need to review some basic, but newly described, fundamental problems found in many individuals with autism. There are now numerous studies in the medical literature [4-11] demonstrating cerebral hypoperfusion (decreased blood flow to the brain) in as many as 86% of individuals with autism [4]. In one study, this hypoperfusion typically worsened as the age of the child increased, and become "quite profound" in older children compared to younger [5]. Furthermore, this diminished blood flow typically correlates with many core autistic symptoms (see *Table 1*).

When a typical person has to focus on a task or generate speech (in other words, when the brain has to do more work), there is an increase in blood flow to the brain, supplying more blood, oxygen, and glucose (fuel) [12]. However, several studies have now demonstrated that not only do some children with autism have diminished blood flow at baseline, they also do not get an increase in blood flow when brain cells have to do more work, such as when the children have to pay attention to a task or generate a sentence [13-15]. In fact, sometimes the cerebral blood flow actually goes *down*, and this appears to be mediated, in part, by inappropriate vasoconstriction (narrowing of blood vessels) instead of vasodilatation [15]. The interesting thing about these studies demonstrating cerebral hypoperfusion in autism is that none of these studies has stopped to examine *why* the diminished blood flow exists in the first place. This cerebral hypoperfusion appears to lead to cerebral hypoxia (impaired oxygen delivery) to the brain in some individuals with autism. In fact, several studies have demonstrated a reduction in Bcl-2 and an increase in p53 in the brain of some children with autism [16, 17]. Elevated p53 is caused by hypoxia [18] and an increase in Bcl-2 normally protects from cell death provoked by hypoxia; a reduction is associated with increased damage caused by hypoxia [19].

Table 1: Selected Areas of Cerebral Hypoperfusion in Autism and Clinical Correlations

Area of Cerebral Hypoperfusion	*Clinical Correlation*
Thalamus	Repetitive, self-stimulatory, and unusual behaviors [6]
Temporal lobes	Desire for sameness and social/communication impairments [7]
Temporal lobes and amygdala	Impairments in processing facial expressions and emotions [8]
Fusiform gyrus	Difficulty recognizing familiar faces [9]
Wernicke's and Brodmann's areas	Decreased language development and auditory processing problems [5; 10]
Temporal and frontal lobes	Decreased IQ [11]

Cerebral Hypoperfusion and Neuroinflammation in Autism

The cause of cerebral hypoperfusion in individuals with autism is unknown but might be due to inflammation. Evidence published out of Johns Hopkins in 2005 demonstrates that, upon autopsy, some individuals with autism have evidence of inflammation in the brain (neuroinflammation) [20]. Also described was inflammation around blood vessels, which is consistent with vasculitis (inflamed blood vessels), and could cause the vessel wall to become stiff and inflexible. Vasculitis decreases the ability of the blood vessel to dilate and can lead to diminished blood flow. There have been several other studies in the literature confirming the presence of inflammation in the brain of some individuals with autism [21-23]. Children with autism also produce more serum autoantibodies to the brain [24], including IgG and IgM autoantibodies to brain endothelial cells and nuclei when compared to typical children [25]. Elevated serum autoantibodies to many neuron-specific antigens and cross-reactive peptides have been found in children with autism [26], including antibodies directed against cerebellar Purkinje cells [27] and neural proteins such as myelin basic protein [26, 28]. Furthermore, in one study, 49% of children with autism created serum antibodies against the caudate nucleus and 18% produced serum antibodies to the cerebral cortex [29].

Inflammation generally is associated with edema (increased swelling), can increase the space between cells [30], and might increase the amount of fluid present inside cells. Two fMRI (functional Magnetic Resonance Imaging) studies published in 2006 demonstrated that individuals with autism had more fluid inside brain cells when compared to typical children [31-32]. Furthermore, functional connectivity (the ability of one brain cell to communicate to another cell) is diminished in some children with autism when compared to typical children [33]. It is possible that inflammation present in the brain of some individuals with autism leads to diminished blood flow, impaired functional connectivity, and increased fluid inside brain cells as described in these studies.

Furthermore, elevated urinary levels of 8-isoprostane-F2α have recently been described in some individuals with autism [34]. In some studies, this isoprostane elevation has been shown to cause *in vivo* vasoconstriction and increase the aggregation (stickiness) of platelets. A more recent study also demonstrated increased urinary levels of isoprostane F2α-VI (a marker of lipid peroxidation, or oxidative stress), 2,3-dinor-thromboxane B2 (which reflects platelet activation), and 6-keto-prostaglandin F1α (a marker of endothelium activation) [35]. Therefore, the inflammation surrounding blood vessels, and the increase in the inflammatory substances leading to vasoconstriction, and increased activation of platelets and endothelium might cause the diminished cerebral blood flow found in many individuals with autism.

Treatment of this inflammation might help restore normal blood flow. In fact, many inflammatory conditions such as lupus, Kawasaki disease, Behçet's disease, encephalitis, and Sjögren's syndrome are characterized by cerebral hypoperfusion [36-42], and treatment with anti-inflammatory medication can restore normal cerebral blood flow in some of these conditions [43, 44]. In addition, review of the literature demonstrates that the use of anti-inflammatory treatments appears to improve symptoms in some children with autism [45]. In fact, treatment with corticosteroids in one child who developed an autoimmune lymphoproliferative syndrome and subsequent autism led to objective improvements in speech and developmental milestones [46]. In another child with autism, whose behavior and language regressed at 22 months of age, treatment with corticosteroids ameliorated abnormal behaviors such as hyperactivity, tantrums, impaired social interaction, echolalia, and stereotypies [47].

Gastrointestinal Inflammation in Autism

Also described in dozens of studies is the presence of inflammation in the gastrointestinal tract of some children with autism. This has been termed autistic enterocolitis or chronic ileocolonic lymphoid nodular hyperplasia (LNH). This condition is characterized by mucosal inflammation of the colon, stomach, and small intestine [48-50]. As many as 90% of children with autism with gastrointestinal symptoms (diarrhea, constipation, etc…) have evidence of ileal LNH, with 68% having moderate to severe ileal LNH [48]. Several studies have shown that some children with autism have evidence of inflammatory cells such as lymphocytes [51, 52] and eosinophils [53] inside the gastrointestinal mucosa, sometimes mimicking an autoimmune lesion [51]. Inflammatory markers in the blood are also elevated, including TNF-α, Interferon-γ (IFN-γ), and IL-6, and anti-inflammatory markers such as IL-10 are decreased

[52, 54]. Children with autism typically make significantly more serum antibodies against gliadin and casein peptides resulting in autoimmune reactions [55]. More than 25% of individuals with autism make serum IgG, IgM, and IgA antibodies against gliadin which can then cross-react with cerebellar peptides [23].

HBOT, Cerebral Hypoperfusion, and Inflammation

Since the cerebral hypoperfusion in autism is likely secondary to inflammation, HBOT might be especially helpful because it possesses potent anti-inflammatory tissue effects [56], with equivalence to diclofenac (an anti-inflammatory medication) 20 mg/kg noted in one animal study [57]. HBOT has been used in cases of vasculitis with good results [58], and with some success in disorders characterized by cerebral hypoperfusion including fetal alcohol syndrome [59], cerebral palsy [60, 61], chronic brain injury [62], closed head injury [63], and stroke [64]. HBOT also attenuated the production of proinflammatory cytokines including TNF-α [65], IL-1 [65], IL-1β [66], and IL-6 [65], and increased the production of anti-inflammatory IL-10 [67]. HBOT reduced neuroinflammation in a rat model after traumatic brain injury [68], and diminished both inflammation and pain in an animal model of inflammatory pain [69]. HBOT has been used in humans to achieve remission of Crohn's disease [70-74] and ulcerative colitis [75, 76] not responding to conventional medications, including corticosteroids and immunosuppressive drugs. Interestingly, in some studies, the decrease in inflammation with HBOT appeared to be caused by the increased pressure, not necessarily by the increased oxygen tension. In one animal study, hyperbaric pressure without additional oxygen was shown to decrease TNF-α levels [77]. In a human study, HBOT at 2 atmosphere (atm) and 100% oxygen, and hyperbaric pressure at 2 atm and 10.5% oxygen (thus supplying 21% oxygen, equal to room air oxygen levels) both showed anti-inflammatory activity by inhibiting IFN-γ release, whereas 100% oxygen at room air pressure (1 atm) actually increased IFN-γ release [78]. For these reasons, HBOT might help ameliorate the inflammation found in some individuals with autism (see *Table 2*).

Table 2: Effects of HBOT on Inflammatory Markers and Inflammation in Autism

Marker	*Classification*	*Autism Finding*	*HBOT Effect*
TNF-α	Inflammatory	↑ [52; 54]	↓ [65; 66; 77[1]]
IL-1β	Inflammatory	↑ [54]	↓ [66]
IL-6	Inflammatory	↑ [20; 54]	↓ [65]
IL-10	Anti-inflammatory	↓ [52]	↑ [67]
IFN-γ	Inflammatory	↑ [52]	↓ [78[2]]
Neuroinflammation		↑ [20-22]	↓ [65]
GI inflammation		↑ [48-50]	↓ [70; 75]

[1] Hyperbaric pressure without additional oxygen decreased TNF-α.
[2] Hyperbaric pressure without additional oxygen also decreased IFN-γ.

Clinical Studies on HBOT in Autism

In one case report, Heuser et al. treated a four year old child with autism using hyperbaric therapy at 1.3 atm and 24% oxygen and reported "striking improvement in behavior including memory and cognitive functions" after only ten sessions. The child also had marked improvement of cerebral hypoperfusion as measured by pre-hyperbaric and post-hyperbaric Single Photon Emission Computed Tomography (SPECT) scans [1]. Our previous case series suggested that hyperbaric therapy at 1.3 atm and 28% oxygen led to clinical improvements in some children with autism as measured by the Autism Treatment Evaluation Checklist (ATEC), Childhood Autism Rating Scale (CARS), and Social Responsiveness Scale (SRS) scales [79]. This low pressure HBOT was well tolerated by all 6 children with no adverse effects noted.

Recently published is a prospective open-label study on 18 children with autism who underwent 40 hyperbaric sessions of 45 minutes duration each at either 1.5 atm and 100% oxygen (6 children), or 1.3 atm and 24% oxygen (12 children) [80]. Results were calculated before and after the 40 treatments using parent-rated Aberrant Behavior Checklist-Community

(ABC-C), SRS, and ATEC. Fasting blood was drawn before and after the 40 treatments for C-reactive protein (CRP) and markers of oxidative stress.

For the 1.5 atm group, parents reported significant improvements in irritability, lethargy, hyperactivity, motivation, and sensory and cognitive awareness. For the 1.3 atm group, parents reported significant improvements in motivation, mannerisms, physical health, sensory and cognitive awareness, speech, and communication. Mean CRP improved in both groups, especially in a subgroup of children with very elevated initial CRP. There was no statistically significant change in mean plasma oxidized glutathione levels in either group after 40 treatments. Oxidized glutathione is normally expelled out of cells when oxidative stress inside the cell is high [81]. Therefore, since oxidized glutathione did not appreciably increase in the plasma, oxidative stress did not significantly worsen at either pressure in this study. Comparisons between the 2 groups in this study in clinical outcomes must be done with caution because of the small number of participants involved. Finally, HBOT at both 1.5 atm/100% oxygen and 1.3 atm/24% oxygen were both used safely in children with autism.

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