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Hyperbaric oxygen therapy might improve certain pathophysiological findings in autism

Daniel A. Rossignol *

University of Virginia, Department of Family Medicine, P.O. Box 800729, Charlottesville, VA 22908, USA

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Summary Autism is a neurodevelopmental disorder currently affecting as many as 1 out of 166 children in the United States. Numerous studies of autistic individuals have revealed evidence of cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification of toxins, dysbiosis, and impaired production of porphyrins. Many of these findings have been correlated with core autistic symptoms. For example, cerebral hypoperfusion in autistic children has been correlated with repetitive, self-stimulatory and stereotypical behaviors, and impairments in communication, sensory perception, and social interaction. Hyperbaric oxygen therapy (HBOT) might be able to improve each of these problems in autistic individuals. Specifically, HBOT has been used with clinical success in several cerebral hypoperfusion conditions and can compensate for decreased blood flow by increasing the oxygen content of plasma and body tissues. HBOT has been reported to possess strong anti-inflammatory properties and has been shown to improve immune function. There is evidence that oxidative stress can be reduced with HBOT through the upregulation of antioxidant enzymes. HBOT can also increase the function and production of mitochondria and improve neurotransmitter abnormalities. In addition, HBOT upregulates enzymes that can help with detoxification problems specifically found in autistic children. Dysbiosis is common in autistic children and HBOT can improve this. Impaired production of porphyrins in autistic children might affect the production of heme, and HBOT might help overcome the effects of this problem. Finally, HBOT has been shown to mobilize stem cells from the bone marrow to the systemic circulation. Recent studies in humans have shown that stem cells can enter the brain and form new neurons, astrocytes, and microglia. It is expected that amelioration of these underlying pathophysiological problems through the use of HBOT will lead to improvements in autistic symptoms. Several studies on the use of HBOT in autistic children are currently underway and early results are promising.

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Abbreviations: HBOT, hyperbaric oxygen therapy; PDD, pervasive developmental disorder; SPECT, single photon emission computed tomography; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; HIF-1 α , hypoxia-inducible factor-1 α ; VEGF, vascular endothelial growth factor; IL, interleukin; PMN, polymorphonuclear neutrophil; MCP-1, macrophage chemoattractant protein-1; CSF, cerebral spinal fluid; GFAP, glial fibrillary acidic protein; BDNF, brain derived neurotrophic factor; LNH, lymphoid nodular hyperplasia; TNF- α , tumor necrosis factor- α ; IFN, interferon; atm, atmosphere; COX-2, cyclooxygenase-2; SOD, superoxide dismutase; HSP, heat shock protein; SSRI, selective serotonin reuptake inhibitors; CP, cerebral palsy.

* Tel.: +1 321 953 0278.

E-mail address: dross7@hotmail.com.

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Background

Autism is a neurodevelopmental disorder currently affecting as many as 1 out of 166 children in the United States [1] and as many as 1 in 86 in certain areas of England [2]. Over 1.5 million children and adults in the United States alone are affected with some form of autism [3]. Autism is characterized by impairments in social interaction, difficulty with communication, and restrictive and repetitive behaviors [4]. Traditionally, autism has been considered a highly genetic disorder, yet the identification of a specific genetic cause has been elusive despite numerous studies [5–7]. One recent study has demonstrated that many children with autism typically have worsening of core autistic clinical features with increasing age [8]. Moreover, young children diagnosed with Pervasive Developmental Disorder (PDD) tend to get worse clinically over time, and almost all are diagnosed with autism at a later age [9]. According to these two studies, improvements in core autistic features are uncommon. Therefore, any treatment that can improve autistic symptoms demands additional study and implementation.

Hypothesis

Recent analysis has furthered our understanding of the underlying pathophysiology of autism that was not apparent even several years ago. Novel clinical findings in autism have lately been described, including cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification enzymes, dysbiosis, and impaired production of porphyrins. Many of these findings have been correlated with core autistic symptoms. Hyperbaric oxygen therapy (HBOT) might be able to improve each of these problems and has been shown to mobilize stem cells from the bone marrow to the systemic circulation. Recent human studies have demonstrated that stem cells can enter the brain and form new neurons, astrocytes, and microglia. It is expected that amelioration of these underlying pathophysiological problems through the use of HBOT will lead to improvements in autistic symptoms.

Review of the pathophysiology of autism and possible benefits of HBOT

Cerebral hypoperfusion in autism

Numerous independent single photon emission computed tomography (SPECT) and positron emis-

sion tomography (PET) research studies have demonstrated hypoperfusion to several areas of the autistic brain, most notably the temporal lobes [10–23]. In one study, this hypoperfusion typically worsened as the age of the autistic child increased, and become “quite profound” in older children compared to younger [11]. The maximal decrease in blood flow in autistic children compared to control children was approximately 8% in another study [18]. This cerebral hypoperfusion has been correlated with many of the core clinical features associated with autism (see Table 1). Repetitive, self-stimulatory, and unusual behaviors including resistance to changes in routine and environment have been correlated with decreased blood flow to the thalamus [13]. “Obsessive desire for sameness” and “impairments in communication and social interaction” have been correlated with decreased blood flow to the temporal lobes [15]. Impairments in processing facial expressions and emotions have been correlated with decreased blood flow to the temporal lobes and amygdala [24]. Diminished blood flow to the fusiform gyrus has been correlated with difficulty in recognizing familiar faces [25]. Decreased language development [11] and auditory processing [17] have been correlated with decreased blood flow to Wernicke’s and Brodmann’s area. Finally, hypoperfusion of the temporal and frontal lobes has been correlated with decreased IQ in autistic individuals [20].

In addition, not only do autistic individuals have decreased blood flow at baseline, but when autistic children attend to a task, they often do not have a compensatory increase in blood flow like typical

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 [13]
Temporal lobes	Desire for sameness and social/communication impairments [15]
Temporal lobes and amygdala	Impairments in processing facial expressions/emotions [24]
Fusiform gyrus	Difficulty recognizing familiar faces [25]
Wernicke’s and Brodmann’s areas	Decreased language development and auditory processing problems [11,17]
Temporal and frontal lobes	Decreased IQ [20]

children, and instead sometimes demonstrate decreased blood flow. Neurotypical children have an increase in cerebral blood flow as measured by functional magnetic resonance imaging (fMRI) when performing a task that requires attention or sensory input; autistic children typically lack this increase in blood flow [26]. Control children also have an increase in cerebral blood flow when listening to tones and generating sentences; whereas autistic children typically have a decrease in cerebral blood flow [27]. Upon an auditory stimulation, "normal" children have a drop in the left middle cerebral artery resistance index as measured by transcranial doppler ultrasound (which means blood flow increases); while autistic children have an increase in resistance index, which causes blood flow to decrease [28]. These findings might indicate that the brain metabolic rate and function are diminished in autistic children because blood flow is tightly coupled with these two parameters [29,30].

The cause of this cerebral hypoperfusion in autistic individuals is unknown but might be due to inflammation. One recent study on autopsy brain samples from autistic individuals described accumulation of perivascular macrophages and microglia [31], which could be consistent with vasculitis. This accumulation could cause stiffening of the vessel wall and decrease the size of the lumen, leading to decreased cerebral blood flow. Furthermore, elevated urinary levels of 8-isoprostane-F₂ α have recently been described in some autistic individuals [32]. In some studies, this isoprostane elevation has been shown to cause *in vivo* vasoconstriction and increase the aggregation of platelets [33]. A more recent study on autistic individuals also demonstrated increased urinary levels of isoprostane F₂ α -VI (a marker of lipid peroxidation), 2,3-dinor-thromboxane B₂ (which reflects platelet activation), and 6-keto-prostaglandin F₁ α (a marker of endothelium activation) [34]. These elevated markers indicate that some autistic children have increased platelet aggregation, endothelium activation, and vasoconstriction. This is important because vasoconstriction can cause decreased blood flow to the brain, which could result in relative hypoxia. Hypoxia has been shown to activate brain microglia which in turn produce inflammatory mediators, such as Tumor Necrosis Factor- α (TNF- α) and Interleukin-1 (IL-1) [35]. 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].

Unfortunately, a vicious cycle could ensue as increased inflammation could lead to increased cerebral hypoperfusion (see Fig. 1). This, in turn, can lead to hypoxia. Hypoxia causes an increase in hypoxia-inducible factor-1 α (HIF-1 α), which in turn causes an increase in inflammation, including redness and swelling of tissues, and the attraction of lymphocytes [45]. HIF-1 α is essential for inflammation mediated by myeloid cells [46]. In fact, in one study, rats that were null for HIF-1 α demonstrated almost complete inhibition of the inflammatory response [47]. HIF-1 α is also responsible for angiogenesis that is secondary to hypoxia [47,48]. In addition, HIF-1 α induces Vascular Endothelial Growth Factor (VEGF), which increases the permeability of blood vessels [45] and causes tissue edema. This edema can lead to increased interstitial space between cells [49] and cause an increase in the distance that oxygen must diffuse from the blood vessel to the cells and can thus lead to cellular hypoxia [50]. Chronic inflammation is commonly associated with the infiltration of polymorphonuclear neutrophils (PMN's) and other immune cells, along with the cytokines that are released by these cells. This causes an increase in local oxygen usage due to the resultant oxygen requirements of these new cells. Yet, at the same time, inflammation causes reduced oxygen extraction by normal cells [51]. For instance, in one study, elevated markers of inflammation (including IL-6, TNF receptors 1 and 2, and high-sensitivity C-reactive protein) were correlated with decreased maximum oxygen uptake at peak exercise (VO₂max) in patients with known or suspected coronary artery disease [52]. Therefore, inflammation prevents maximal uptake of oxygen by cells. Inflammation also increases oxidative stress and can cause neutrophils to become more adherent and attach to vessel walls [53]. This infiltration and increased adherence of inflammatory cells can contribute to brain injury by decreasing microvascular blood flow, causing thrombosis, and increasing the production of free radicals [54].

HBOT and cerebral hypoperfusion

HBOT can overcome the effects of cerebral hypoperfusion (see Table 2) by providing more oxygen to the brain [55,56], and by causing angiogenesis of new blood vessels over time by increasing VEGF levels [57]. Furthermore, if cerebral hypoperfusion is causing hypoxia that is also driving inflammation through the induction of HIF-1 α , the oxygen

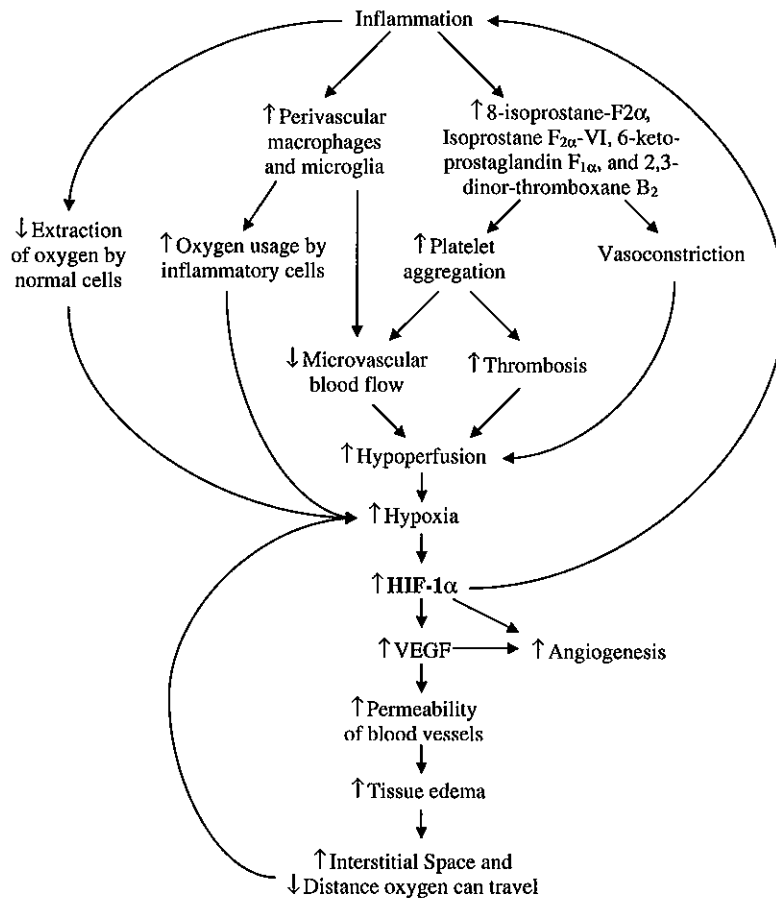


Figure 1 Proposed cycle of inflammation and resultant cerebral hypoperfusion in autism.

delivered by HBOT can improve hypoxia, and thus downregulate HIF-1 α . Hypoxia can lead to apoptosis [58] regulated by HIF-1 α [59]. HBOT has been

shown to inhibit the expression of HIF-1 α and its target genes [60], and prevent apoptosis [61] by inhibiting proapoptotic BNIP-1 [60] and by increasing

Table 2 Proposed mechanisms of Inflammatory-induced cerebral hypoperfusion found in autism and HBOT effects

Autism inflammatory finding	Mechanism of hypoperfusion	HBOT effect
↑ 8-Isoprostane-F 2α [32] and isoprostane F 2α -VI [34]	Vasoconstriction causes decreased blood flow which leads to decreased delivery of oxygen [33]	Increases the amount of oxygen in plasma and thus increases delivery of oxygen to cells [55,56]
↑ 2,3-dinor-thromboxane B $_2$ [34]	Increased aggregation of platelets	No effect on platelet aggregation [77] ^a
↑ 6-keto-prostaglandin F 1α [34]	Endothelial activation	Decreases aggregation of PMN's to endothelium [66]
Cerebral infiltration of perivascular macrophages and microglia [31]	Vasculitis-like condition	Decreases PMN infiltration in injured areas [54]
Cerebral infiltration of perivascular macrophages and microglia [31]	Increased oxygen usage by inflammatory cells and reduced oxygen extraction by normal cells [51]	Increases oxygen in plasma and thus increases delivery of oxygen to cells [55,56]

^a In this study, platelet aggregation decreased slightly after one hyperbaric treatment, but returned to normal with repeated HBOT.

the expression of Bcl-2, an inhibitor of apoptosis [62]. Interestingly, Bcl-2 levels in the brains of some autistic people are diminished [63].

Since the cerebral hypoperfusion in autism is likely secondary to inflammation, HBOT might be especially helpful because it possesses strong anti-inflammatory properties as will be discussed in detail shortly. Inflammation is often accompanied by PMN infiltration which can decrease microvascular blood flow; however, HBOT has been shown to decrease the infiltration of PMN's after an ischemic injury to the brain [54,64,65]. In addition, HBOT inhibits neutrophil attachment to blood vessel walls [66], reduces leukocyte adherence [67], and increases the distance that oxygen can travel in the interstitial space [68]. HBOT has also been used in cases of vasculitis with good results [69], and with success in disorders characterized by cerebral hypoperfusion including fetal alcohol syndrome [70], cerebral palsy [71,72], autism [73], chronic brain injury [74], closed head injury [75], and stroke [76].

Neuroinflammation in autism

Several recent studies have revealed that children with autism have evidence of neuroinflammation [31,78,79]. Marked activation of microglia and astroglia with elevations in IL-6 and macrophage chemoattractant protein-1 (MCP-1) were found in autistic brain samples upon autopsy, along with increased proinflammatory cytokines in the cerebral spinal fluid (CSF) of living autistic children [31]. Activated microglia have been shown to release inflammatory mediators such as IL-1 and TNF- α , and have been implicated as the primary cell type that controls inflammation-mediated neuronal injury [35]. A cell-mediated immune response to brain tissue in autistic individuals has also been described [80]. In addition, some autistic children have increased glial fibrillary acidic protein (GFAP) in brain samples [79] and the CSF [81], which is also indicative of inflammation and reactive injury. Autoantibodies to neuron-axon filament protein and GFAP were also increased in the plasma of autistic individuals compared to control individuals [82]. Autistic children make more serum autoantibodies to the brain [83], including IgG and IgM autoantibodies to brain epithelial cells and nuclei when compared to typical children [84]. Elevated serum autoantibodies to many neuron-specific antigens and cross-reactive peptides have been found in autistic children [85], including antibodies directed against cerebellar Purkinje cells [86], and other neural proteins (see Table 3) such as myelin basic

Table 3 Evidence of neuroinflammation in autism

A. Elevated markers of neuroinflammation
Activation of microglia and astroglia [31]
Brain IL-6 [31]
Brain MCP-1 [31]
Brain GFAP [79]
CSF GFAP [81]
B. Elevated serum antibodies to brain proteins
Neuron-axon filament protein [82]
GFAP [82]
Brain epithelial cells and nuclei [84,83]
Myelin basic protein [85,87]
Myelin associated glycoprotein [85]
Ganglioside [85]
Sulfatide [85]
Chondroitin sulfate [85]
Myelin oligodendrocyte glycoprotein [85]
a,h-crystallin [85]
Neurofilament proteins [85]
Tubulin [85]
Cerebellar Purkinje cells [86]
Caudate nucleus [89]
Cerebral cortex [89]
BDNF [90]

protein [85,87,88]. Furthermore, 49% of autistic children in one study created serum antibodies against the caudate nucleus, and 18% produced serum antibodies to the cerebral cortex [89]. Another recent study demonstrated that autistic children, when compared to control children, developed serum autoantibodies to brain derived neurotrophic factor (BDNF) and had higher levels of serum BDNF. This is important because an elevation of BDNF predicts abnormalities in intellect and social development [90]. Finally, maternal neuronal antibodies might play a role in the development of autism in some children [91].

Gastrointestinal inflammation in autism

In addition, some patients with autism have chronic ileocolonic lymphoid nodular hyperplasia (LNH) and enterocolitis characterized by mucosal inflammation of the colon, stomach, and small intestine [92–94]. These findings might represent a "new variant inflammatory bowel disease" [93], and have been described as a "panenteric IBD-like disease" [95]. As many as 90% of autistic children with gastrointestinal symptoms have evidence of ileal LNH, with 68% having moderate to severe ileal LNH [92]. In one study, the gastrointestinal mucosa was shown to have increased lymphocytic infiltration and density, crypt cell

proliferation, and epithelial IgG deposits mimicking an autoimmune lesion [96]. Another study demonstrated that the gastrointestinal mucosa in autistic individuals had evidence of increased lymphocytes and proinflammatory cytokines including TNF- α and Interferon- γ (IFN- γ), and less of the anti-inflammatory cytokine IL-10, which is counter-regulatory [97]. Some autistic children also had evidence of an eosinophilic infiltrate of the gastrointestinal mucosa [98]. Autistic children typically make significantly more serum antibodies against gliadin and casein peptides resulting in autoimmune reactions [99]. More than 25% of autistic individuals make serum IgG, IgM, and IgA antibodies against gliadin, which can cross-react with cerebellar peptides [86]. Furthermore, when compared to typical children, autistic children produce more proinflammatory cytokines, including TNF- α , IL-1 β , and IL-6 [100]. One study has shown that the genetic loci for autism have a propensity to cluster with recognized loci for inflammatory diseases [101].

Interestingly, children on a gluten and/or casein free diet produced less TNF- α in the colonic mucosa [97], and had less evidence of eosinophilic infiltration of the mucosa [98]. In addition, the use of anti-inflammatory treatments might improve autistic symptomology [102]. In fact, treatment with corticosteroids of one child who developed an autoimmune lymphoproliferative syndrome and subsequent autism led to objective improvements in speech and developmental milestones [103]. In another child with PDD, 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 [104].

HBOT and inflammation

HBOT has potent anti-inflammatory tissue effects [57] as revealed by several recent animal studies [105,106], with equivalence to diclofenac 20 mg/kg noted in one study [107]. HBOT has been shown to attenuate the production of proinflammatory cytokines including TNF- α [108–111], IL-1 [108,112], IL-1 β [110,111], and IL-6 [108], and increase the production of anti-inflammatory IL-10 [113]. HBOT has also been shown to reduce neuroinflammation in a rat model after traumatic brain injury [65]. HBOT also reduced both inflammation and pain in an animal model of inflammatory pain [114], decreased the symptoms of advanced arthritis in rats [115], and attenuated the inflammatory response in the peritoneal cavity caused by in-

jected meconium [116]. HBOT has been used in animal studies to improve colitis [105,117–119], and has been used in humans to achieve remission of Crohn's disease [120–124] and ulcerative colitis [125,126] not responding to conventional medications, including corticosteroids. 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 [127]. In another 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) both showed anti-inflammatory activity by inhibiting IFN- γ release, whereas 100% oxygen at room air pressure (1 atm) actually increased IFN- γ release [128].

The anti-inflammatory effect of HBOT might occur through the relief of hypoxia and the down-regulation of HIF-1 α [47,60]. HBOT also decreases Prostaglandin E₂ production [112] which decreases inflammation because prostaglandins increase inflammation, pain, and edema [57]. In one study, HBOT decreased cyclooxygenase-2 (COX-2) enzyme expression after transient cerebral ischemia [129]. The COX-2 enzyme is responsible for increased prostaglandin production, leading to increased inflammation. Blockade of the COX-2 enzyme has been shown to decrease inflammation and cytokine levels including IL-6 [130]. For these reasons, HBOT might help ameliorate the inflammation found in autism (see Table 4).

Immune function in autism

There is mounting evidence of immune dysregulation in autistic individuals (see Table 5), and new research is revealing the link between the immune system and the nervous system [131]. An increased number of autoimmune diseases exist in autistic families compared to control families [132,133] with as much as a 6–8 fold increased incidence [134]. Some researchers believe that autistic children might have "an underlying autoimmune disorder" [135] and that a "genetic relationship" exists between autism and immune dysregulation [101]. Two early studies revealed that 38% of autistic children had no detectible Rubella titers despite vaccination [136], and 60% produced abnormal serum antibodies to measles hemagglutinin protein when compared to control children [87]. Autistic individuals also make more serum antibodies to Heat

Table 4 Effects of HBOT on inflammatory markers and inflammation in autism

Marker	Classification	Autism finding	HBOT effect
TNF- α	Inflammatory	\uparrow [100,97]	\downarrow [111,108,110,109], [127] ^a
IL-1 β	Inflammatory	\uparrow [100]	\downarrow [111,110]
IL-6	Inflammatory	\uparrow [100,31]	\downarrow [108]
IL-10	Anti-inflammatory	\downarrow [97]	\uparrow [113]
IFN- γ	Inflammatory	\uparrow [97]	\downarrow [128] ^b
Neuroinflammation		\uparrow [31,78,79]	\downarrow [65]
Gastrointestinal inflammation		\uparrow [92-94]	\downarrow [120,125]

^a Hyperbaric pressure without additional oxygen decreased TNF- α .

^b Hyperbaric pressure without additional oxygen also decreased IFN- γ .

Shock Protein-90 (HSP-90) [137], which could cause HSP-90 levels to be lower. HSP-90 is a signal transducer which regulates development and cell differentiation. In one study, decreased levels of HSP-90 allowed natural genetic abnormalities hidden in fruit fly populations to suddenly appear [138]. Attempts to improve the underlying immune deficiency in autistic individuals with intravenous

immune globulin have shown promising results [139-141].

In addition, several studies have reported abnormalities in T-lymphocytes, including a decreased number of CD4⁺ cells [142] in approximately 35% of autistic individuals [139]. This has led to an altered ratio of CD4/CD8 cells with a reduced number of T-helper cells (CD4⁺CD8⁻) and an increased number of suppressor T-cells (CD4⁻CD8⁺) in some autistic individuals [143]. One study demonstrated that treatment with naltrexone increased the number of T-helper inducers and reduced the number of T-cytotoxic suppressors, resulting in a normalization of the CD4/CD8 ratio and improvement of symptoms in over half of the autistic children studied [144]. CD4⁺ cells are divided into Th1 and Th2 subsets. Th1 cells produce IL-2 and IFN- γ and are involved in T-cell proliferation, activation of macrophages, and cell-mediated immunity including phagocytosis of intracellular pathogens like viruses. Th2 cells are part of the adaptive immune system and produce IL-4, IL-5, IL-6, IL-10, and IL-13. IL-4 is involved in the B-cell production of IgE. IL-5 stimulates the production of eosinophils, and IL-6 is involved in the production of immunoglobulins. IL-1 and IL-6 are proinflammatory cytokines, and IL-10 inhibits Th1 cytokine production and thus down-regulates the inflammatory response [145]. Skewing toward Th2 is often seen in allergic responses [146]. Interestingly, a history of allergies in the mother during pregnancy led to a greater than 2-fold elevated risk of autism [147], and children with autism tend to have more food allergies than control children [148].

Some earlier studies demonstrated activation of the Th1 system in autistic children with increased production of IL-12 and interferon when compared to control children [149,150]. Autistic individuals make more IFN- γ and IL-1 receptor antagonist, which can cause a Th1 skewing [151]. Autistic children also have increased markers of cell-mediated

Table 5 Evidence of immunological abnormalities in autism

A. Non-neuronal serum antibodies produced in autistic individuals	
HSP-90 [137]	
Glutadin [99]	
Casein [99]	
Milk butyrophilin [85]	
<i>Chlamydia pneumoniae</i> [85]	
Streptococcal M protein [85]	
Measles hemagglutinin protein [87]	
B. Cellular, immunoglobulin, and cytokine abnormalities	
\uparrow Serum IgG2 and IgG4 [135]	
\downarrow Responsiveness of lymphocytes [155]	
\downarrow Natural killer cells [156]	
\downarrow Number of total CD4 ⁺ cells [143,142]	
\downarrow Number of T-helper cells (CD4 ⁺ CD8 ⁻) [143]	
\uparrow Number of suppressor T-cells (CD4 ⁻ CD8 ⁺) [143]	
Imbalance of CD4 ⁺ and CD8 ⁺ cells [153]	
\uparrow IFN- γ [149]	
\uparrow Markers of cell-mediated immunity (urinary neopterin and biopterin) [152]	
\uparrow IL-4 [154]	
\uparrow IL-5 [154]	
\uparrow IL-12 [149]	
\uparrow IL-13 [154]	
\downarrow IL-10 [97]	
\uparrow Serum IgE [139,148]	
\downarrow Serum IgA [139]	

immunity, a Th-1 function, including elevated urinary neopterin and biopterin [152]. Finally, a cell-mediated immune response to brain tissues in autistic individuals has also been described [80].

More recent studies indicate that autistic children exhibit a shift from Th1 to Th2 T-cell type [135,140], as evidenced by an increased production of IgE [139,148] and IL-4 producing CD4⁺ T-cells, and lower levels of IL-2 producing CD4⁺ T-cells compared to control children [153]. Furthermore, about one-third of autistic children in one study demonstrated IgG subclass deficiency not confined to the 4 subclasses of IgG [139]. Approximately 5% of autistic individuals have IgA deficiency, which is normally present in 1 in 700–1000 people, and about 30–40% have low serum IgA levels [139]. In spite of these deficiencies, a new study suggests that autism is characterized by a heightened immune system. This is evidenced by an increased activation of both the Th1 and Th2 arms with Th2 predominance as indicated by increased IL-4, IL-5 and IL-13 when compared to control individuals, without a compensatory increase in IL-10 [154].

Shifting from a Th1 to a Th2 T-cell type might enhance susceptibility to chronic viral infections in some autistic individuals [135]. In fact, depressed responsiveness of lymphocytes was found in one study on autistic children [155], and another study demonstrated a 40% decrease in the number of natural killer cells when compared to control children [156]. Therefore, autistic individuals might have "enhanced susceptibility to infections resulting in chronic viral infections" [135].

HBOT and immune function

HBOT might be useful in some autoimmune diseases [157], and has shown promise in rheumatic diseases, including lupus and scleroderma [158], and rheumatoid arthritis [159]. HBOT has been used in animal models to completely suppress autoimmune encephalomyelitis by blocking mononuclear infiltration and demyelination of the CNS [160], and acted as an immunosuppressive agent to delay skin allograft rejection [161]. HBOT has been shown to suppress immune responses such as proteinuria, facial erythema, and lymphadenopathy in an autoimmune mouse model [162]. In addition, one animal study showed increased survival and decreased proteinuria, anti-dsDNA antibody titers, and immune-complex deposition in lupus-prone autoimmune mice treated with HBOT [163]. HBOT improved symptoms in patients with atopic dermatitis and also decreased IgE immunoglobulin and complement levels [164]. In patients with mul-

iple sclerosis, HBOT produced a significant increase in total and helper T-lymphocyte numbers and serum IgA levels [165]. Two other studies demonstrated an increase in lymphocyte count, with variable subset population increases depending on which organ (spleen, thymus, or blood) was examined and how much oxygen was given with HBOT [166,167]. HBOT has also been shown to increase IL-10, the anti-inflammatory interleukin [113], and induce the production of HSP-90 [168]. Interestingly, some of the immunomodulatory effects of HBOT might be due to the increased pressure, not necessarily the increased oxygen tension [169]. Even low hyperbaric pressures, without additional oxygen, can affect the immune system. One study demonstrated that hyperbaric pressure at just 20 mmHg (approximately 1.03 atm) can have an effect on the immune system [127]. Based upon these reasons, HBOT might help improve the immune dysregulation found in autistic individuals (see Table 6).

Oxidative stress in autism

Autistic children have evidence of increased oxidative stress including lower serum glutathione levels [170,171]. Some autistic children have increased red blood cell nitric oxide, which is a known free radical and toxic to the brain [172]. Of note, HIF-1 α increases the production of nitric oxide [45]. Lower serum antioxidant enzyme, antioxidant nutrient, and glutathione levels, as well as higher pro-oxidants have been found in multiple studies of autistic children [173]. Autistic children have evidence of increased lipid peroxidation [34,174], including increased malondialdehyde which is a marker of oxidative stress and lipid peroxidation [175]. Decreased activities of certain antioxidant enzymes have also been described in autistic individuals including superoxide dismutase (SOD)

Table 6 Effects of HBOT on immune dysregulation in autism

Marker	Autism finding	HBOT effect
HSP-90	↓? (due to increased antibodies to HSP-90) [137]	↑ [168]
Serum IgA	↓ [139]	↑ [165]
Serum IgE	↑ [148,139]	↓ [164]
Lymphocytic activity	↓ [155]	↑ [166]
T-helper cells	↓ [143]	↑ [165]

[176], glutathione peroxidase [176], and catalase [174]. Some autistic children also have decreased activity of paraoxonase, an antioxidant enzyme that prevents lipid oxidation and also detoxifies organophosphates in humans [177]. The gene for Heat Shock Protein 70 (HSP-70), which protects against oxidative stress, was downregulated in multiple cases of autism [178]. Antioxidants such as ceruloplasmin [175] and zinc [179] tend to be lower in autistic patients, and the ratio of copper to zinc is abnormal in many autistic children [180]. Furthermore, in one study, treatment with antioxidants was shown to raise the levels of reduced glutathione in the serum of autistic children and appeared to improve symptoms [170]. In another study, the use of antioxidants improved behavior in some autistic children [181].

HBOT and oxidative stress

Concerns have been previously raised that HBOT might increase oxidative stress through the production of reactive oxygen species [182]. This is a relevant concern because of the increased oxidative stress just described in autistic children. However, oxidative stress from HBOT appears to be less of a concern at pressures under 2.0 atm [183] which are often used clinically. Oxidative stress is caused by an imbalance of oxidants and antioxidants. With long-term and repeated administration, HBOT below 2.0 atm can actually decrease oxidative stress [184–186] by reducing lipid peroxidation [187], and increasing the activity of antioxidant enzymes including SOD [185,188], glutathione peroxidase [118], catalase [189], paraoxonase [190], and heme-oxygenase-1 [191–193]. HBOT has also been shown to increase HSP-70, which protects against oxidative stress [194,195]. One recent animal study

has demonstrated that HBOT can suppress oxidative stress in brain tissues after a stroke [196]. HBOT also increases zinc, decreases copper [185], and increases ceruloplasmin levels [197]. Thus, HBOT might help improve the oxidative stress found in some autistic individuals (see Table 7).

Mitochondrial dysfunction in autism

Lombard hypothesized that autism might be caused by mitochondrial dysfunction [199]. Several recent case reports supporting this concept have been published including two autistic children with hypotonia, lactic acidosis and abnormal mitochondrial enzyme assays on muscle biopsy [200], an autistic child with developmental regression and mitochondrial dysfunction [201], and an autistic child with mitochondrial dysfunction [202]. A larger case series of 12 children with hypotonia, epilepsy, and autism also found mitochondrial dysfunction [203]. Another study on 100 children with autism suggested mild mitochondrial dysfunction as evidenced by reduced carnitine and pyruvate levels and increased ammonia and alanine levels [204]. Further research reveals that mitochondrial point mutations might be the cause of autism in some people [205]. An association between autism and the mitochondrial aspartate/glutamate carrier SLC25A12 gene polymorphism was recently described [206] and confirmed [207]. A mitochondrial A3243G mutation has also been associated with autism [208], and both autosomal recessive and maternally inherited mitochondrial defects can cause autism [209]. Some of the more common blood abnormalities associated with mitochondrial dysfunction include elevated aspartate aminotransferase, creatine kinase, and fasting lactic acid. In one study of 120 autistic children, 7.2%

Table 7 Effects of HBOT on measures of oxidative stress in autism

Measure	Classification	Autism finding	HBOT effect
Glutathione peroxidase	Antioxidant enzyme	↓ [176]	↑ [118]
Superoxide dismutase	Antioxidant enzyme	↓ [176]	↑ [118,188,185]
Heme-oxygenase-1	Antioxidant enzyme	?	↑ [191–193]
Catalase	Antioxidant enzyme	↓ [174]	↑ [189]
Paraoxonase	Antioxidant enzyme; organophosphate detoxification	↓ [177,198]	↑ [190]
HSP-70	Cellular protection against oxidative stress	↓ [178]	↑ [194,195]
Malondialdehyde	Marker of oxidative stress and lipid peroxidation	↑ [175]	↓ [118,185]
Ceruloplasmin	Antioxidant	↓ [175]	↑ [197]
Glutathione	Antioxidant	↓ [170]	↑ [185]
Zinc	Antioxidant	↓ [179]	↑ [185]
Copper	Metal	↑ [180]	↓ [185]

had a "definite mitochondrial respiratory chain disorder", and plasma lactate levels were elevated in 20% of the children [210]. In another study of 159 autistic children, compared to 94 control children, autistic children had higher aspartate aminotransferase levels ($p = 0.00005$), and 47% had elevated creatine kinase levels, which might be consistent with relative mitochondrial dysfunction [201]. Recently, mitochondrial abnormalities were discovered in a mouse model of Rett Syndrome [211], a disorder classified as a PDD.

HBOT and mitochondrial dysfunction

Hypoxia can impair mitochondrial function [212]. Since only approximately 0.3% of inhaled oxygen is ultimately delivered to the mitochondria [213], increasing the oxygen delivery to dysfunctional mitochondria by HBOT might aid in improving function [214,215]. In a mouse model with an intrinsic impairment of mitochondrial complex IV, HBOT at 2 atm "significantly ameliorate[d] mitochondrial dysfunction" and delayed the onset of motor neuron disease when compared to control mice [215]. In animals studies, HBOT increased the amount of work done by mitochondria [216], improved mitochondrial function after brain injury [214], and was shown to "protect mitochondria from deterioration" when compared to normal oxygen and pressure [217]. HBOT also has been shown to increase sperm motility by augmenting mitochondrial oxidative phosphorylation in fructolysis-inhibited sperm cells [218]. HBOT also prevented apoptosis and improved neurological recovery after cerebral ischemia by opening mitochondrial ATP-sensitive potassium channels [61]. Finally, HBOT has recently been shown to activate mitochondrial DNA transcription and replication, and increase the biogenesis of mitochondria in the brains of animals [219]. For these reasons, HBOT might improve the relative mitochondrial dysfunction found in some autistic individuals.

Neurotransmitter abnormalities in autism

Early childhood is typified by an increased production of serotonin when compared to adulthood; however, one study showed that autistic children synthesized less serotonin during childhood when compared to control children [220]. Another study demonstrated lower levels of serotonin in both autistic children and their mothers [221]. Plasma

levels of tryptophan, which is the precursor to serotonin, are lower in autistic children compared to control children, and are suggestive of a serotonergic abnormality [222]. In addition, tryptophan uptake by brain cells as seen on PET scan was less in autistic children compared to control children [220], and tryptophan depletion can cause a significant increase in autistic behaviors such as "whirling, flapping, pacing, banging and hitting self, rocking, and toe walking" [223]. Antibodies against cerebral serotonin receptors, which preclude the binding of serotonin, are more common in autistic individuals when compared to control individuals [224,225]. Selective serotonin reuptake inhibitors (SSRI's) have been shown to be beneficial for obsessive and repetitive behaviors [226]. In some studies, SSRI's including fluoxetine [227], fluvoxamine [226], and escitalopram [228] have shown benefit for autism.

In addition, some autistic children have evidence of dopamine overactivity, including higher CSF levels of homovanillic acid, the main metabolite of dopamine [229]. Treatment of autistic children with dopamine agonists has led to worsening of aggression, hyperactivity, and stereotypies [230]. Dopamine antagonists such as pimozide [231] and bromocriptine [232] have shown improvements in some autistic children.

HBOT and neurotransmitter abnormalities

HBOT has also been shown to reduce the uptake of serotonin by pulmonary endothelial cells [233,234], and thus might function like an SSRI. In one study, HBOT demonstrated "antidepressant-like activity" similar to that seen with some SSRI antidepressants like fluoxetine [235]. In another study on patients with cluster headaches, HBOT improved pain and was shown to act through serotonergic pathways [236]. Furthermore, in an animal model, HBOT was shown to decrease the release of dopamine after cerebral injury [237]. In another animal study, 90% oxygen at room air pressure (1 atm) decreased extracellular dopamine levels in the brain [238]. Therefore, HBOT might improve the neurotransmitter imbalances found in some autistic individuals.

Toxin exposure in autism and HBOT

Recent data has shown that organophosphate poisoning can cause atypical autism [239]. Paraoxonase

is the enzyme responsible for organophosphate detoxification in humans. In North America, autism has been associated with variants in the paraoxonase gene which can decrease the activity of this enzyme by 50 percent [177]. This was recently confirmed in another study that demonstrated reduced activity of paraoxonase in some autistic children [198].

HBOT has been shown to increase the activity of paraoxonase [190], and to prevent a decrease in paraoxonase activity normally seen with a high cholesterol diet [187]. Thus, HBOT might lead to an improved ability to excrete organophosphates in some autistic children by upregulating paraoxonase activity.

Dysbiosis in autism

Significant alterations in intestinal flora, with increased amounts of *Clostridia* bacteria [240–242], and overgrowth of other abnormal bacteria [241], exist in some autistic children when compared to control children. In fact, one author has hypothesized that *Clostridia* infection in the gut might cause autistic-like symptoms [243]. Furthermore, treatment of these abnormal gut bacteria with antibiotics has led to improvements of autistic symptoms as measured by a clinical psychologist blinded to the treatment status [244]. Some autistic children also have overgrowth of yeast, viruses, and parasites in the gut [245].

HBOT and dysbiosis

HBOT has been shown to decrease the amount of abnormal bacteria in the gut and therefore can function as an antibiotic [246]. In animal studies, HBOT decreased intestinal bacterial colony counts after bacteria overgrowth in the distal ileum associated with bile duct ligation [247]. HBOT is also bactericidal against many bacteria [248], including *Pseudomonas* [249,250], *Salmonella* and *Proteus* [249], *Staphylococcus* [251], *Mycobacterium tuberculosis* [248], and anaerobic bacteria such as *Clostridia* [252]. In addition, the killing of bacteria by phagocytic leukocytes is dependent upon oxygen [253], and HBOT has been shown to improve leukocyte phagocytic killing of *Staphylococcus aureus* in animals [254]. HBOT has also been shown to inhibit the growth of some yeast [255] and to possess virucidal activity against some enveloped viruses [256]. HBOT also appears to have an antiviral effect against HIV [257]. In an animal model, HBOT improved symptoms in a virus-induced leukemia com-

pared to a control group [258]. HBOT can also kill parasites, including *Leishmania amazonensis* [259]. Thus HBOT might lead to an improvement in the dysbiosis found in some autistic children by reducing counts of abnormal pathogens.

Porphyryn production in autism and HBOT

Children with autism might have impaired production of some porphyrins [260] which are involved in the synthesis of heme, which carries oxygen in the body. Therefore, the ability to deliver oxygen on hemoglobin could be compromised in some autistic children [261], and HBOT might help overcome this by increasing the amount of oxygen dissolved in plasma.

Stem cells and HBOT

Recently, HBOT at 2.0 atm was shown to mobilize stem/progenitor cells from the bone marrow of humans into the systemic circulation. Elevations were found in the number of colony-forming cells as demonstrated by an increase in the number of CD34⁺ cells by 8-fold after 20 HBOT sessions [262]. Since stem cells are also produced in the brain, this gives rise to the possibility of neurogenesis [263], which might aid in reversing chronic neurodegenerative disorders. Furthermore, in two human case reports, female bone-marrow-transplant patients received cells from male donors. On autopsy of these females, staining for the male Y-chromosome in their brains demonstrated that male donor stem cells from the bone marrow had crossed into the brain and formed new neurons, astrocytes, and microglia [264,265].

Additional HBOT and future study considerations

HBOT pressure considerations

Previous studies have shown improvements of symptoms in children with autism and cerebral palsy (CP) at hyperbaric pressures of 1.3 atm with or without additional oxygen [72,73,266]. The use of HBOT in children appears generally safe, even at pressures up to 2.0 atm for 2 h per day for 40 sessions [267]. Many of the potential benefits of HBOT as described above were found in studies at higher hyperbaric pressures. Further study is neces-

sary to determine if these benefits also hold true at the lower hyperbaric pressures (1.3–1.5 atm) commonly being utilized for autistic individuals and to establish the optimal hyperbaric pressure for autism and related disorders.

HBOT oxygen concentration considerations

As described above, in one study, the decrease in inflammation with HBOT appeared to be caused by the increased pressure, not necessarily by the increased oxygen tension. In this human study, both HBOT and hyperbaric pressure demonstrated anti-inflammatory activity by inhibiting IFN- γ release, whereas 100% oxygen at room air pressure (1 atm) actually increased IFN- γ release [128]. Further study is needed to verify this finding, to determine if this phenomenon equally applies to the other noted benefits of HBOT, to better understand the mechanisms of action of HBOT, and to determine the optimal oxygen concentration for use in autistic individuals.

HBOT session count considerations

The number of HBOT sessions needed to produce full clinical improvements 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 and metabolism was more profound during the last 35 HBOT sessions when compared to the first 35 [74]. In another study of children with CP using HBOT at 1.7 atm, serial functional measurements after 40 and 80 HBOT sessions showed continuing objective improvements including a decrease in the total time of custodial care and improved gross motor function. At the end of 80 treatments, children in the study were continuing to improve, and the authors noted that the optimal number of treatments could not be determined as it appeared that further HBOT sessions would yield additional improvements [268]. Further study is needed to clarify the optimal number of HBOT sessions for autistic individuals.

Pathophysiology as a primary acceptance criterion for HBOT

HBOT has been used by the Navy since 1943 for air embolism and decompression sickness, two indica-

tions that are widely accepted. However, no prospective, double-blind, placebo-controlled trials have been performed on these 2 indications; rather, the use of HBOT is justified based upon the underlying pathophysiology of these 2 conditions and the mechanism of action of HBOT [68]. The use of HBOT for autism is considered "off-label" [269]. However, examining the pathophysiology of autism continues to indicate that HBOT might be effective for treating autism [270]. Several studies on the use of HBOT in autism are currently underway and early results are promising. It is hoped that a clearer understanding of the potential benefits of HBOT in treating the common symptoms of autism will spur other researchers to investigate the use of HBOT in autistic individuals.

Conclusions

Numerous studies of autistic individuals have revealed evidence of cerebral hypoperfusion, neuroinflammation and gastrointestinal inflammation, immune dysregulation, oxidative stress, relative mitochondrial dysfunction, neurotransmitter abnormalities, impaired detoxification of toxins, dysbiosis, and impaired production of porphyrins. HBOT has been shown to increase oxygen delivery to hypoperfused or hypoxic tissues, decrease inflammation and oxidative stress, and increase the production of mitochondria and the number of circulating stem cells. HBOT might also improve the immune dysfunction, neurotransmitter abnormalities, and dysbiosis specifically found in autistic individuals. Further studies are necessary to test this hypothesis and are currently underway. The possible effects of HBOT on autism are summarized in Table 8.

Table 8 Summary of the proposed HBOT effects on the pathophysiology found in autism

Problem	Autism finding	HBOT effect
Cerebral perfusion	↓	↑
Neuroinflammation	↑	↓
Gastrointestinal inflammation	↑	↓
Immune dysregulation	↑	↓
Oxidative stress	↑	↓
Mitochondrial function	↓	↑
Neurotransmitter abnormalities	↑	↓
Detoxification enzyme function	↓	↑
Dysbiosis	↑	↓
Porphyrin production	↓	↑
Circulating stem cells		↑

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