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Autism, Sleep Disordered Breathing, and Intracranial Hypertension: The Circumstantial Evidence

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Abstract. The ASD/OSA hypothesis as proposed in this paper will incorporate over 90 pieces of the "autism puzzle". It is suggested that the cause of autism is four-fold, requiring that: 1) the mother has sleep disordered breathing (SDB) during her pregnancy, 2) the infant is born with sleep disordered breathing, 3) both mother and infant have polymorphisms of the methylation pathway which are then triggered by the SDB, and 4) the infant is prone to intracranial hypertension. This theory can explain many, if not most, of the pieces of information that we currently know about the biology of autism. The fact that the sleep disordered breathing (SDB) in autism and in the mothers of autistic children has not been previously noted is due to flaws in the current methods for detecting SDB. Esophageal manometry is much more sensitive for detecting SDB but is not used routinely, however it may be more accurate than the apnea hypopnea index in terms of correlation with disruptive behavior disorders. There is evidence that SDB is much more common than previously believed. Apneas are known to increase intracranial pressure, and intracranial hypertension can be caused by obstructive sleep apnea. Recent studies showing behavioral problems and special needs correlated with SDB urge further evaluation of autistic children for SDB. The ASD/OSA hypothesis suggests that autism might be primarily prevented by detecting and treating SDB in women prior to conception, and in infants shortly after birth.

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1. Introduction — Sleep Disordered Breathing

There has been a great deal of scientific investigation over recent years into possible causes for autism, and speculation regarding the increase in diagnosis seen since the early 1990s. We have learned many things which define the biology of autism and fuel the fire for those of us searching for a cure. There is the analogy of the puzzle piece for each of these items, with the hope that they can be used to construct a clear picture of cause and cure. We hold the pieces this way and that to see how they fit together. This author believes that they are beginning to show a picture that makes sense, we just need to have a particular framework to fit them into so that we can see it. Like an optical illusion, a trick of the light and the way your eyes focus can change what you see. This paper will discuss many of the pieces we have, show the reader how to focus their eyes differently, and ultimately attempt to construct at least part of the puzzle so that we can see the picture it represents.

Autism is a spectrum disorder characterized by deficits in language, social communication, and restricted and repetitive behaviors. It has been demonstrated that obstructive sleep apnea (OSA) can be an underlying factor in autism [1], and we know that up to 83% of those with autism spectrum disorders (ASD) can have significant sleep disturbance [2]. This paper will argue for the hypothesis that sleep disordered breathing (SDB) may be the underlying trigger in most cases of idiopathic autism. That this has gone unrecognized before now is likely due to the fact that the diagnostic tools used in sleep medicine lack standardization and most sleep labs do not use the methods required to detect mild sleep disordered breathing.

2. Obstructive Sleep Apnea

Obstructive sleep apnea in adults is defined as a collapse of the upper airway leading to cessation of breathing (apnea) or significant diminished breathing (hypopnea) for more than 10 seconds, with these events occurring at least 5 times per hour. This will generate the AHI, or apnea hypopnea index, and the apnea may lead to intermittent hypoxia [3]. In children, an AHI >1 is considered abnormal. Apnea in children has been defined as the absence of airflow with continued chest wall and abdominal wall movement for a duration longer than 2 breaths. Hypopnea in children has been defined as a decrease in nasal flow between 30% and 80% from baseline with a corresponding decrease in oxygen saturation of 3% and/or an arousal. Children with OSA do not always have a cortical arousal associated with obstructive events and are less likely to have fragmented sleep compared to adults. The majority of their events occur during REM sleep, and they may present with persistent obstructive hypoventilation with snoring and labored breathing rather than the pauses and gasps associated with complete airway collapse [4]. The symptoms of OSA in children can be subtle and not always recognized by parents. Children may mouth breathe and hyperextend their necks in sleep to compensate for their airway problems and this will reduce snoring [5]. Daytime symptoms of OSA may include mouth breathing, nasal obstruction, morning headache, daytime sleepiness and trouble concentrating [6].

3. Upper Airway Resistance Syndrome

Upper airway resistance syndrome (UARS), a “mild” form of SDB that many doctors are not even aware of, can actually cause more significant symptoms than OSA. UARS was first described in 1982 but the term was not coined until 1993 [7]. It occurs when a person arouses prior to complete airway collapse, due to the upper airway resistance. On polysomnogram (PSG) the AHI is less than 5, the oxygen saturation is not below 92%, and there are frequent RERAs (respiratory event related arousals) and other nonapnea/hypopnea respiratory events. The current gold standard for detecting the respiratory abnormalities in UARS is the use of esophageal manometry. This technique is available at very few locations. Nasal pressure transducers are used in most sleep labs but they lack comparable sensitivity for detecting respiratory events [8]. Newman et al. describes patients with UARS to have abnormal intrathoracic pressure measurements despite normal RDIs (respiratory disturbance indices) [9]. In children, several polygraphic patterns can be seen which may not involve apnea or hypopnea, but show abnormal effort seen on esophageal manometry, or tachypnea, as well as events which may be mistaken for central apneas. An end tidal CO₂ monitor may also miss many of these events [7]. Therefore we can see that detection of UARS can be quite difficult. Furthermore, it has been shown that somatic symptoms in SDB are inversely proportional to the AHI [10], creating a paradox in which the individuals who are least likely to be diagnosed have the worst day to day symptomatology. Individuals with UARS have a different clinical presentation than those with OSA; they tend to be thin and can be hypotensive, opposite to the typical OSA presentation. They can have orthostatic hypotension, chronic insomnia, sleep walking, sleep terrors, difficulty getting up in the morning, and they are significantly more fatigued than people with OSA. One third of patients with UARS do not snore. They may present with myalgias, headache, anxiety, depression, and diarrhea/irritable bowel syndrome. Comorbidities in UARS are nasal allergies [8], asthma, migraine and hypothyroidism [10]. Misdiagnoses in UARS are chronic fatigue syndrome, fibromyalgia, depression and ADHD/ADD (attention deficit hyperactivity disorder/attention deficit disorder) [8]. While OSA patients tend to be predominantly male, there is a much higher percentage of females with UARS [10].

In UARS, as in OSA, we see increased arousals leading to sleep fragmentation, but also there are the significant increases in negative intrathoracic pressure which can be documented by esophageal manometry as noted above. This negative intrathoracic pressure has been shown to generate elevated levels of atrial natriuretic peptide (ANP). ANP has been considered to be one of the causes for the nocturnal polyuria seen in SDB, as it leads to natriuresis and diuresis [11]. This author has previously published a complex theory which explains the majority of the somatic symptoms seen in UARS based on known actions of ANP, as ANP also causes hypotension and suppression of adrenal function, among other actions [12]. There will be a rise in intrathoracic pressure at the termination of an apnea, and this and other factors may raise arterial pressure and lead to increases in intracranial pressure (ICP). Certainly any degree of hypoventilation can increase cerebral blood flow and as a result intracranial pressure [13]. This would be more or less significant in the individual depending on other factors related to cerebrospinal fluid (CSF) drainage. It has been demonstrated that OSA can be the cause of papilledema as well as of idiopathic intracranial hypertension (IIH) [14-17]

which may be present without papilledema (IIHWOP) [18]. Despite these facts, there does not seem to be much awareness in the medical community that intracranial hypertension (IH) may be responsible for some of the symptoms seen in SDB. All of these things described above occur in sleep disordered breathing, whether it is OSA or UARS. What occurs in OSA different from UARS is complete airway collapse leading to apnea and at times hypoxia as a result. This is thought to be secondary to the development of a neuropathy in the throat that occurs after longstanding snoring causing vibrational damage to nerve centers which detect impending airway collapse [8]. To summarize, those with UARS awaken due to impending airway collapse, while those with OSA awaken due to hypoxia, the difference being in the nervous system response.

4. Sleep Study Results Can Be Inaccurate

The issue which is not well understood outside of sleep medicine is that the methods for collecting data for the sleep study have varied between centers, as have the criteria used for counting a hypopnea [19]. The 2007 American Academy of Sleep Medicine (AASM) statement has allowed the medical director of each sleep lab to choose which criteria are used, and has suggested the use of either the "recommended" or the "alternative" criteria. The recommended criteria scores a hypopnea if there is a $\geq 30\%$ reduction in nasal pressure signal excursions from baseline and associated with $\geq 4\%$ desaturation from pre-event baseline. The alternative hypopnea criteria requires $\geq 50\%$ reduction in nasal pressure signal excursions and associated $\geq 3\%$ desaturation or arousal. The 1999 hypopnea criteria, also referred to as the "Chicago" criteria, are even less strict. The Chicago criteria define two types of hypopneas: 1) those with a greater than 50% decrease in a valid measure of airflow without a requirement for associated oxygen desaturation or arousal, and 2) those with a lesser airflow reduction in association with oxygen desaturation of $>3\%$ or an arousal. A comparison study demonstrated that using criteria most like the 2007 AASM recommended criteria, an AHI cut off level of 5/hr is approximately equivalent to an AHI of 10/hr using the alternative criteria, and to an AHI of 15/hr using the Chicago criteria [20]. A recent study performed in Sao Paulo Brazil found surprising results when using alternative criteria to assess the prevalence of OSA in the general population. There was no assessment of individuals under the age of 20, however in all other age groups the prevalence of OSA in this study is much higher than that previously reported. The overall frequency of AHI >5 in men was 46.3%, and in women was 30.5%. Overall prevalence of OSA Syndrome for men in this study was 40.6%, and for women 26.1%. The prevalence increases with age, until at age 70 the risk for a woman to NOT have an AHI >5 is only 6% [21]. Previously published prevalence data from the Wisconsin Sleep Cohort Study indicated a prevalence of 24% for men and 9% for women with AHI >5 . When this is combined with an assessment of excessive daytime sleepiness, their prevalence of "Sleep Apnea Syndrome" is downgraded to 4% for men and 2% for women [22]. The syndrome essentially requires that a person have unwanted episodes of falling asleep during the day. For a person who has OSA and insomnia, they know that this requirement is illogical. Indeed, in the Sleep Heart Health Study it was found that for women, the results of the Epworth Sleepiness Scale did not correlate with their feelings of being unrested, while for men there was a correlation [23]. A common presentation of SDB in children is

ADHD [4]; these children might not be described as sleepy, despite the fact that they are sleep deprived. Therefore qualifying the prevalence data as important only in the presence of sleepiness may not be appropriate, and certainly not for children. A recent study done at Stanford showed that the 2007 AASM hypopnea criteria underscored pediatric sleep disordered breathing. The Stanford criteria diagnosed 99% of the study group with SDB, while the AASM criteria diagnosed only 19% of the study group with SDB. What is significant is that all patients diagnosed by Stanford with SDB in the study group had clinical improvements after treatment of their SDB, confirming that the Stanford criteria was correct. The Stanford criteria are complicated to explain, but are probably most similar to the Chicago criteria [19]. In conclusion, the prevalence of SDB reported depends on the hypopnea criteria used, and is therefore likely much higher than most sources report, leading to SDB being a significantly under-recognized clinical entity.

Recently (published in October 2012) the American Academy of Sleep Medicine Sleep Apnea Definitions Task Force reviewed the current rules for scoring respiratory events and revised the definition of a hypopnea in both adults and children. Now a hypopnea in adults should be scored if the peak signal excursions drop by $\geq 30\%$ of pre-event baseline for ≥ 10 seconds in association with either $\geq 3\%$ arterial oxygen desaturation or an arousal. In children a hypopnea should be scored if the peak signal excursions drop is $\geq 30\%$ of pre-event baseline for \geq the duration of 2 breaths in association with either $\geq 3\%$ oxygen desaturation or an arousal [24]. Hopefully this standardization and improvement in the sensitivity of the criteria will reduce confusion and increase the ability of all sleep centers to detect the presence of SDB, going forwards.

These changes, however, may still not be enough: a recent study published by Chervin et al. showed that quantitative esophageal pressures taken during polysomnography were able to predict disruptive behavior disorders in children as well as their response to treatment, and that both the AHI and the RERA were unable to predict the same data [25]. A prior study by the same group showed neurobehavioral improvement after adenotonsillectomy in children with ADHD who were not able to be diagnosed with SDB by their methods, suggesting that the methods used (esophageal manometry) may still be inadequate to detect SDB [26]. Therefore in practice we may have many children with behavioral problems who we are unable to properly manage because we cannot diagnose the underlying problem even if sleep studies are obtained. This ultimately leads to a failure of recognition of the true problem by the primary doctor. Given the results of Chervin's studies, we probably cannot say that autistic children do not uniformly have SDB unless we evaluate them using esophageal manometry, or perhaps even more sensitive methods that have yet to be discovered.

In light of these diagnostic problems, one thing to consider is that in an individual with risk factors predisposing to intracranial hypertension, they might end up with symptoms of IH caused by sleep hypoventilation that is below the detection level of most sleep studies. Also important to note is the fact that there have been multiple cases of optic disc edema caused by OSA (as evidenced by resolution with OSA treatment) that were NOT associated with what was considered abnormal opening pressures on lumbar puncture. In some of these patients, the ICP was elevated only during apneas [16]. Therefore, if children with autism have OSA or even mild SDB, they could be having consequences of increased ICP on their brains that are virtually impossible to detect

without invasive ICP monitoring during sleep. As well, their SDB may be undetectable by standard sleep studies. These facts might also suggest that we should be paying more attention to children whose ICPs fall in the borderline range, certainly if they have any neurological symptoms (such as autism). The association of autism and elevated ICP has been described previously in the case of mild trigonocephaly [27], which has been suggested to be an "autistic head shape" [28].

5. What Really Causes Sleep Disordered Breathing?

There actually may not be much difference between mild OSA without hypoxia, and UARS. The distinction seems to be mainly in whether or not the hypopnea criteria used are able to detect the SDB which is present. If OSA cannot be detected but SDB clearly is present, then it is called UARS. Again, this problem in diagnosis may account for the fact that the primary doctor may have little awareness of how significant a problem sleep disordered breathing is. How can we expect doctors to second guess what they are told by their local sleep labs? We can't. This is a big factor in the severe problem of underdiagnosis in SDB. Doctors may not even be fully cognizant of the true cause of SDB, because the only patients who end up being diagnosed by the sleep lab are those with obesity or adenotonsillar hypertrophy. SDB is actually primarily caused by a mainly bony narrowing of the upper airway. This is manifested as a narrow high arched palate, narrow nose, enlarged nasal turbinates, deviated septum, tongue scalloping, dental crowding, as well as overbite [8]. Guilleminault et al. demonstrated that these disproportionate craniofacial features are common in familial groups with OSA, and are a strong indicator of risk for OSA [29]. Many of the features of the human airway that allowed the development of speech actually predispose modern humans to obstructive sleep apnea [30], and there is evidence that on top of these changes the human jaw has been slowly shrinking for the last 10,000 years since the advent of agriculture and a soft cooked foods diet. The Western diet may be playing a role in a more rapid shrinkage, given the knowledge that when indigenous cultures change to a Western diet there will be an increase in dental crowding and malocclusion [31]. It has also been recently demonstrated that up to 4 months of exclusive breastfeeding can reduce the severity of SDB as measured by the AHI [32], suggesting that normal suckling forces may help to develop the size and function of the jaws. Therefore decreasing breastfeeding rates could also be accelerating the jaw shrinkage in humans. And shorter breastfeeding has been associated with higher risk of autism [33]. How ironic all this would be, if the final progression of the shrinking human jaw leads to autism and the loss of speech?

There is evidence in humans confirmed by studies in Rhesus monkeys that nasal obstruction and mouth breathing will lead to long faces and various dental malocclusive patterns depending on the chosen compensatory response of the individual (open bite, overbite, or prognathic bite). In mouth breathers the maxilla narrows and the mandible becomes retrognathic. In a study of allergic children who mouth breathed, they developed longer and more retrusive faces than a group of nasal breathing controls [34]. Therefore, because the palate is the floor of the nose, the nasal obstruction ultimately leads to more nasal narrowing as the maxilla narrows in response to mouth breathing. This long face is what has been termed abnormal vertical growth, because

the face grows down instead of forwards. If the face does not grow forwards as it should, the soft tissue and bony structures behind the face will impact on the upper airway [35]. There are genetic facial characteristics which may start this process in infancy, in the absence of environmental factors causing nasal congestion, such as the high arched palate which when seen in Marfan syndrome has been associated with increased nasal resistance [36]. This airway narrowing combined with mouth breathing in sleep predisposes to tongue collapse due to the dynamic changes of the airway in sleep. Sleep apnea begets more sleep apnea, because of the suction pressure leading to stomach contents being drawn up into the nose, ears and throat which causes inflammation and may lead to lymphoid hyperplasia, in addition to sinus, ear and pulmonary complications [3], including asthma [37]. This would explain many cases of GERD as well as the relationship between GERD and asthma; they may both be complications of SDB. There are increased reflux events in patients with OSA, and GERD will improve with CPAP therapy [38]. A simple Strep throat infection with enlargement of the tonsils may set in motion a vicious cycle, where the acid reflux initiated by the OSA from the tonsillar hypertrophy causes more nasal congestion and more sleep apnea which perpetuates the upper airway obstruction. This may explain the severe fatigue seen after a case of infectious mononucleosis; it may be simply OSA, rather than a chronic viral infection [3]. If a Strep infection can trigger OSA, then might this explain some of what is seen in PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections)? A 2012 review on PANDAS states that it is not yet clear that it is a unique and distinct clinical entity from obsessive compulsive disorder [39]. Yue et al. found that measures of obsessive compulsive symptoms were significantly higher in patients with OSA compared to controls [40].

Therefore to answer the question of what really causes sleep disordered breathing: it starts with a basic problem in human airway anatomy, which may be exacerbated by specific inherited alterations and then worsened as a result of environmental factors such as diet and nasal congestion. Mouth breathing leads to increased vertical development which further narrows the airway and perpetuates the problem into adulthood, predisposing modern humans to an epidemic of sleep disordered breathing.

6. The ASD/OSA Hypothesis

6.1. Sleep Disordered Breathing and Behavioral Consequences

Recently we have seen several studies published showing stronger data linking sleep disordered breathing in children to developmental and behavioral problems. Bohnick et al. demonstrated 40% and 60% more behavioral problems at age 4 and 7 years, respectively, in their long term outcome cohort study following children with parental reports of snoring, mouth breathing in sleep, and witnessed apnea. The behavioral problems seen were hyperactivity, anxiety, depression, and conduct disorders. Prior analysis of the data from this cohort showed a 10-21% prevalence of habitual snoring from 6 to 81 months [41]. This is greater than the previously reported OSA prevalence in children of 2-3%, and habitual snoring prevalence of 7-12% [5]. Most recently, Bohnick et al. showed that sleep disordered breathing was associated with a nearly 40% increase in the odds of having a special educational need. Children in the worst SDB symptom cluster had a 60% increase in the odds of having a special educational need.

The authors conclude that there is a need for better early screening of SDB symptoms, which they seem to imply might occur at the level of the early intervention program [42]. Perfect et al. recently showed that youth with current SDB exhibited hyperactivity, attention problems, aggressivity, lower social competency, poorer communication, and/or diminished adaptive skills [43]. Watching this data emerge, it would be a natural progression to soon see studies showing an increased incidence of sleep disordered breathing in autism. If these studies are not currently underway, this author urges major sleep centers to undertake such a project.

6.2. Airway Obstruction in Autism

We know that children with autism tend to have a history of recurrent upper respiratory infections, otitis media, and allergic rhinitis [44-47]. This would correlate with the factors seen in OSA, as described above. Jyonouchi et al. found that there is a subgroup of autistic patients who have worsening of their autistic symptoms in conjunction with frequent (usually viral) infections. They found an alteration in the toll-like receptors between two groups of autistic children [46], however the simple effect of nasal congestion on OSA may explain the worsening in the infection group. Matarazzo reports two cases of normally developing children who developed autistic symptoms following reactivation of a chronic oto-rhinolaryngologic infection. Interestingly, while the author does not make a connection to OSA, both patients had significant behavioral improvements after adenotonsillectomy [48], consistent with the idea that airway obstruction is the primary problem in autism. It has been demonstrated that pollen exposure may trigger regression in autistic children, however the authors state this was not associated with respiratory symptoms and hypothesize an effect on inflammatory cytokines which then can affect the brain [47]. Regardless, their data was collected by questionnaires and it may be that there were subtle changes in the airway that were not appreciated which may have increased SDB in these children. This observation suggests the need for further study, perhaps using a measure of nasal airflow resistance.

The nasal narrowing which initiates the facial changes described above may be environmentally caused by colds and allergies as well as dietary factors, but as suggested above these narrow facial characteristics may be congenital. We see this in the extreme in genetic syndromes like Pierre-Robin (micrognathia), Down's syndrome (maxillary hypoplasia, macroglossia), Smith-Lemli-Opitz syndrome (micrognathia), Cohen syndrome (maxillary hypoplasia and micrognathia) [49], the last 3 of which have been associated with autism [50]. Yet pediatricians know how common it is for a normal newborn to have a relative micrognathia which improves over time. Premature infants with the dolichocephaly which develops in them will have a long narrow face and a high arched palate. We know that the risk of both OSA and of autism is higher in the premature infant [6,51], and we see autistic characteristics in many children with genetic syndromes. This paper argues for a consideration that the autism in some of these genetic conditions as well as in prematurity may be a consequence of the airway problem rather than of a direct effect on the brain.

6.3. The ASD/OSA Hypothesis

Critics will argue that many children have chronic nasal congestion and not all will develop autism. Many children and adults have increased vertical development and

only a fraction have autism. And, obviously, many children and adults have OSA and do not have autism. The theory presented here is actually 4-fold. If the cause of autism were simple, we would have discovered it already; it is clearly quite complex. This author, based on observations of the scientific data, suspects that the development of autism requires the existence of potentially four factors: 1) OSA/SDB present in the mother during the pregnancy, 2) OSA/SDB present in the baby at birth, 3) polymorphisms of the methylation pathway in both mother and child, and 4) an underlying predisposition to intracranial hypertension. Without all of these present, autism may not develop. More explanation is necessary in order to understand these conclusions.

6.4. Obstructive Sleep Apnea in Pregnancy

Pregnancy is a condition which is known to increase risk for SDB. Several studies indicate that snoring and other symptoms suggestive of OSA will increase during pregnancy. A study using PSG showed that the AHI will increase as pregnancy progresses in women with OSA. Another study showed that the rate of diagnosis of OSA by PSG tripled from the first trimester to the third trimester. However, OSA is more prevalent in high-risk pregnancies, and most prevalent among high-risk hypertensive pregnancies. In one study OSA was present in 82% of women with gestational hypertension. This is not surprising given the fact that hypertension, obesity and diabetes, factors which define high risk during pregnancy are also factors which are associated with OSA [52]. A small study using CPAP (continuous positive airway pressure) to treat OSA in hypertensive pregnancy showed improvements in blood pressure control and decreased complications [53]. Pertinent to our discussion however, is a recent study which showed that the risk of having a child with autism is increased for a woman with preeclampsia [54]. With the high incidence of OSA in preeclampsia, the obvious next step would be to confirm that the risk of autism is likely associated with the presence of maternal OSA. The recent data regarding increased risk of autism with maternal obesity also supports this theory [55], given the fact that obesity is associated with OSA. Furthermore, the recent findings by Hallmayer et al. that a shared twin environment has a substantial effect on autism susceptibility [56] also supports this idea that a mother's OSA affects her unborn offspring. An interesting study from 1986 showed that in mothers with preeclampsia, their hemoglobin dissociation curves are shifted more to the left than normal pregnant women [57], indicating that their oxygen affinity is higher and the fetus will have more difficulty extracting oxygen across the placenta. If this effect on oxygen affinity is related to OSA in the preeclamptic mother, then this implies that the fetus of a mother with OSA may experience hypoxia in the absence of significant maternal oxygen de-saturation with apneas. Regardless of the cause of the shift, this may be involved in the increased incidence of autism for children of preeclamptic mothers.

Another piece of interesting data is that pregnancy induced hypertension, preeclampsia, as well as placental abruption are all associated with hyperhomocysteinemia [58]. An elevation in the homocysteine (HCys) level is a marker for problems with the methylation pathway, and has also been found to be elevated in people with OSA, independent of cardiac disease [59,60]. A study in rats showed that hypoxia will decrease the activity of CBS (cystathionine beta synthase), an enzyme necessary for HCys breakdown. Hypoxia will also decrease the activity of MAT (methionine adeno-

yltransferase), needed for production of SAME (S-adenosylmethionine) which is essential for DNA methylation [61]. This author's recent paper on atrial natriuretic peptide (ANP) suggests a mechanism for depletion of methylation intermediates via ANP induction of NOS (nitric oxide synthase), which could occur in the absence of hypoxia (therefore possibly in UARS) [12]. This data above implies that sleep disordered breathing is a trigger for methylation problems, which could be presumed to be more significant for those with polymorphisms in the methylation pathway. A recent study showed that HCys levels are significantly elevated in autistic children [62]. James et al. showed that HCys levels are elevated in mothers of autistic children, suggesting that methylation problems in the mothers may have led to epigenetic changes in their offspring [63]. OSA may actually be the explanation for Dr. Jill James' recent results discussed at the October 2011 Autism Research Institute conference. She stated that she has found that in mothers with a child with autism, their HCys levels rise abnormally during a subsequent pregnancy, from one trimester to the next [64]. Based on the data above, this suggests that these women, who already have a recurrence risk of autism of 18.7% [65], may have had a worsening of OSA during pregnancy that led to the increase in HCys. Of the known causes of HCys elevation besides OSA, the factors which might increase during pregnancy (obesity, diabetes) are intricately tied to OSA [52,64,66].

Homocysteine is a neurotoxic amino acid [67] which may have a direct excitotoxic effect on the NMDA (N-methyl-D-aspartate) receptor [68] It may enhance the excitotoxicity of environmental neurotoxins like mercury, lead, cadmium, aluminum and fluoride [62]. HCys has also been shown to have the potential to disrupt normal palatal development through increasing apoptosis, and so may be involved in the development of cleft palate [69] and perhaps in lesser structural alterations. This may be the mechanism by which maternal folate deficiency causes craniofacial anomalies; in addition, hyperhomocysteinemia due to vitamins B12 or B6 deficiency or genetic defects of MTHFR (methylene tetrahydrofolate reductase) or CBS has been associated with an increased incidence of cleft palate [69]. We have already discussed how a narrowing of the palate may cause SDB. And so we see the possibility here for how poor methylation may produce the structural problems that cause SDB, and how SDB may worsen methylation problems and lead to a cycle of worsening airway problems with each successive generation. This would overlay the other causes for human jaw shrinkage previously discussed, making things worse for those families with methylation mutations. It may be that the recent increasing incidence of autism is simply the culmination of this process reaching a critical point in terms of shrinkage of the human airway.

6.5. Methylation Problems in Autism

Again, we know that there are derangements in methylation which have been associated with autism. Abnormalities in biomarkers indicating decreased methylation capacity have been shown to be present in autistic children [70]. Oxidative protein/DNA damage and DNA hypomethylation have been found in autistic children but not in paired siblings or controls, indicating that there is epigenetic alteration in autism. The genomic instability and de novo mutations seen in autistic children but not in their parents may be explained by an oxidizing microenvironment in parental germ cells, during gestation or early post-natal development [71]. Women with MTHFR 677T and CBS polymorphisms have a higher incidence of autism in their offspring if they do not

take prenatal vitamins [72]. A gene deletion polymorphism of DHFR (dihydrofolate reductase) by itself and in combination with the MTHFR 677T mutation has been shown to be a significant risk factor for autism [73]. Mohammed et al. also showed that MTHFR C677T is a risk factor for autism [74]. Maternal DNA from autism mothers has been found to be significantly hypomethylated, and their HCys levels are significantly elevated, compared to controls. A functional polymorphism of the reduced folate carrier gene G allele was found more frequently in mothers of autistic children, but not fathers [63]. These data together imply that while methylation is impaired in autistic children, methylation is impaired in their mothers during gestation and this may be a causative factor for the development of autism, through epigenetic alteration of critical genes. There are many other genes which have been associated with autism: SHANK3, RORA, Bcl-2, MeCP2, PTEN, Reelin, Neurexins. Most if not all of these are turned on or off by the process of methylation [75-78]. Again, if OSA/SDB contributes to a methylation defect via the mechanisms described above, then SDB may serve as a trigger for the underlying genetic predisposition to methylation pathway problems, leading to more severe DNA hypomethylation and more significant epigenetic change in utero. In this scenario, the autism associated genes above may be more likely to be triggered by the methylation problem. If SDB is present in the infant, the methylation problems begun in utero will be perpetuated. Hopefully the reader will have grasped that if SDB is present in the mother, that the infant will likely also have SDB if he inherits her craniofacial structure. Under these conditions, and given the mechanism of HCys potentially narrowing the palate further, the craniofacial structure may get narrower with each successive generation. Also, the older an individual is, the higher the HCys level and the higher their risk for OSA, and the worse any existing OSA will become as they age [21,60]. This will explain the finding that autism risk is higher with advanced maternal age [51]. Putting this all together, it suggests that in the absence of OSA/SDB (at critical points in neuro-development), it might be that the underlying genetic methylation issues would not be declared, and the autism associated genes above not turned on/off. OSA/SDB may be the factor that tips the balance; the trigger that led to the autism epidemic. Furthermore, autism is only one human condition of many that has been increasing in incidence in recent years, and the shrinking human jaw and its resultant OSA may be the underlying cause for all of them.

6.6. Supine Sleep, and the Neurological Consequences of Sleep Disorders

A recent paper published in *Autism Science Digest* discusses how several illnesses in children have increased over the last 25 years. These include allergies, GERD, obesity, positional plagiocephaly and ADD/ADHD in addition to autism [79]. We know that obesity, GERD, and ADD/ADHD are associated with OSA/SDB. There is some suggestion that OSA may actually cause obesity, rather than simply obesity causing OSA [12]. It is well known that OSA may cause attention deficit problems, with up to 50% of children losing their diagnosis after tonsillectomy [26,80]. It has been reported that up to 56% of children with ADHD have an AHI >1. The data on ADHD and its response to OSA treatment should be something that autism researchers sit up and pay attention to, given how frequent the symptoms of inattention, impulsivity and hyperactivity are in autism [81], such that it has been suggested there is a pathophysiological link between the two conditions [82]. Allergies certainly may cause OSA as previously discussed and

are often seen in SDB [8]. Could the increases seen in these conditions be simply from an underlying increase in SDB?

From the above list we are left with only positional plagiocephaly, and here we have an indication for what may have triggered the increase in autism which started in the early 1990s. In 1992 we started putting our babies to sleep on their backs. Supine sleep position is known to increase airway collapse [3]. Therefore, beginning in the early 1990s, we started several generations of infants who would have more obstructive breathing events in sleep, beginning at birth. Supine sleep in infants has been associated with more short arousals, body movements and sighs, as well as a longer duration of apneas [83]. The most recent study looking at supine sleep position and development shows that infants who slept supine had slower fine and gross motor development at 6 months, something that disappeared at 18 and 36 months [84]. However, it would be interesting to look at a group of children with a developmental diagnosis and compare supine vs. prone sleep, to see if there is a pattern that emerges. Also, many children with autism are not diagnosed until after age 3, and might have been missed in this study that went only to 36 months. Finally, this study was conducted in 2004 in Taiwan, using 1783 subjects in the study group. Autism incidence in 2005 in Taiwan was only 4.4 per 10,000 [85], such that perhaps only one or two children in the study group might be expected to develop autism; this would be below the ability of this study to detect an effect of sleep position on autism. An even more recent study investigating an association between deformational plagiocephaly (DP) (a known sequelae of supine sleep [86] and perhaps a good measure of compliance with the recommended sleep position) and development showed that children with DP scored lower than those without it on all scales of the Bayley Scales of Infant and Toddler Development, Third Edition. The greatest differences were in cognition, language, and parent-reported adaptive behavior, measured at approximately 36 months. The authors suggest that there is a neuro-developmental anomaly already present in the children who develop DP which places them at risk for DP [86]. They have not imagined that in the setting of a narrowed airway, supine sleep positioning might end up contributing to the neuro-developmental anomaly.

Sleep deprivation has been documented to cause memory deficits, executive dysfunction, and a reduction in IQ when sleep in children is disrupted by sleep disordered breathing. Functional MRI testing demonstrates a hippocampal deficit in sleep deprived subjects. Sleep deprivation in adults has been shown to negatively affect recall but also assessment of emotional and situational context for memory. REM deprivation in newborn rats can remove the positive effects of environmental enrichment on problem solving, synaptic connections and size of the cerebral cortex. Sleep disordered breathing has been shown to negatively impact school performance, as well as to be related to reduced attention and increased social problems, anxiety and depression in children who snore [87]. Jan et al. states regarding long-term sleep disturbances in children: "untreated chronic sleep disorders may lead to impaired brain development, neuronal damage and permanent loss of developmental potentials" [88]. It doesn't take much of a leap to imagine that if SDB is present from birth, the effect on the brain during critical periods of neurodevelopment will likely be significant, and could very well account for some of the changes seen in autism. Preliminary work on the effect of cognitive reserve, showing that those with higher intelligence experience a protective effect

from the impact of OSA [87], may explain some of the differences seen between children with low functioning and high functioning autism. Therefore, while we have cut the incidence of SIDS (sudden infant death syndrome) in half using supine sleep, we need to consider whether we may have simply traded this problem for a much more prevalent behavioral problem: autism. Most parents would likely choose to keep their autistic child rather than lose him altogether, however there is the issue of informed consent when recommending supine sleep to new parents; they should understand not just the benefits but also the risks involved. Positional plagiocephaly may be simply the tip of the iceberg. Also, there may be sleep positions which are a compromise to reduce the risk of both SIDS and autism, such as supine sleep in a 45 degree elevated position.

6.7. Most Chronic Illness Is Increasing

The recent increase in autism, again, is not isolated, and the increase in chronic illness is not limited to children. According to the WHO report from 2005, they projected a 17% increase in chronic diseases worldwide over the subsequent 10 years. These include obesity, hypertension, heart disease, stroke, diabetes, and hypercholesterolemia [89]. What these illnesses have in common is that the risk of metabolic syndrome, hypercholesterolemia, hypertension, heart disease, stroke and diabetes are all increased by OSA [3,5]. Obesity has been causally related to OSA, yet there are metabolic pathways which indicate that OSA may be causative for obesity [12]. Asthma prevalence increased from 6.8 million in 1980 to 14.9 million in 1995 [90]. OSA is associated with asthma and chronic cough [37,38]. Childhood and adolescent depression is increasing, and presenting at younger ages [91]. SDB is a known cause of depression [8,22]. There was a 2.3-fold increase in the rate of office-based visits documenting a diagnosis of ADHD from just 1990 to 1995 [92]. We have already discussed the role of OSA in causing ADHD symptoms. On the other end of the spectrum, Alzheimer's disease is on the rise. It currently affects as many as 5.2 million Americans, and is estimated to affect 13.2 million by the year 2050 if no cure is found. We also know that 90% of Alzheimer's patients have OSA [93]. As an aside, homocysteine is known to be elevated in Alzheimer's [94]. Fibromyalgia is another illness which has increased significantly in recent years. In one study looking at data from 1999-2007, discharge diagnoses of fibromyalgia increased each year. Also, the most common primary diagnoses when fibromyalgia was the secondary diagnosis, were hypertension, disorders of lipid metabolism, heart disease, and mental disorders [95]. It is now becoming understood in sleep medicine that fibromyalgia will improve with stabilization of the upper airway in sleep [94]. All of these illnesses above, known to be associated with OSA, are increasing in incidence over the last 20-30 years: this suggests that it is the underlying problem, OSA, that is increasing in incidence and influencing the rest. This may implicate the shrinking human jaw in nearly all of chronic disease.

6.8. The Shrinking Human Jaw

The dramatic increase in chronic illness in recent history, if it is due to the shrinking human jaw, begs the question of, have we reached a critical point in the shrinkage, vs. is the human jaw shrinking more rapidly now? The critical point theory is plausible, if you consider Poiseuille's law of flow resistance. Airway resistance during laminar flow is inversely proportional to the fourth power of the internal radius of the tube the

air is flowing through [97]. This means that as the airway gets smaller, airway resistance increases dramatically with small changes. We might have reached a critical point over a short period of time.

Alternatively, we need to ask the question, what in our environment could be causing more rapid shrinkage? There are several candidates and of course there are likely many more. The advent of the microwave is one possibility: microwaving destroys vitamin B12, causing a 30-40% loss of the vitamin in foods [98]. Could the increased use of the microwave in the late 1980s have precipitated more methylation problems in mothers, with a resultant effect on fetal palatal growth and based on this theory, autism rates? Fluoridation rates increased from 23.9% of the population served in 1965 [99] to 49.4% of the population served with fluoridated water in 1975 [100]. Fluoride has been shown to retard palatal shelf growth, either completely or partially depending on concentration [101], as well as to reduce the horizontal linear measurement of the mandible in rats [102]. The production of synthetic organic chemicals, including pesticides, nearly tripled between 1960 and 1988 [103]. The organophosphate pesticide chlorpyrifos has been shown to cause cleft palate in mice, consistent with epidemiological studies in humans showing increased palatal clefting with pesticide exposure [104]. Gomes et al. showed that exposure to organophosphorous pesticides causes maxillary and mandibular hypoplasia in mice [105]. This data mirrors the finding that autism risk increases associated with maternal exposure to organochlorine pesticides [106]. Keller et al. demonstrated that certain strains of mice and also mainly males of a particular strain of mice were more susceptible than the females of that strain to a decrease in mandibular size after exposure to TCDD (2, 3, 7, 8-tetrachlorodibenzo-p-dioxin) [107]. More recently, the herbicide atrazine has been linked to choanal atresia and choanal stenosis [108], a defect that would also contribute to an airway problem. Interestingly, Roberts et al. found that the greatest risk of autism in their study occurred if there was maternal organochlorine exposure during the 8 weeks immediately after neural tube closure [106]. This happens to correspond to the embryological period during which the branchial arches and the face forms [109]. If girls' jaws started shrinking more rapidly in the 1970s secondary to exposures as discussed above, creating more SDB in them, then in the 1990s these girls would be having babies; obviously this is when autism started increasing dramatically. So by the 1990s the mothers would have more SDB, affecting their offspring whose jaws may end up being narrower than their mother's jaws given the compounding effect of the exposures plus the methylation issues. We do not see an association of autism with cleft palate, but perhaps the exposures we are discussing are just not sufficient to produce complete clefting, but only a decrease in palatal diameter of a few millimeters. Again it does not take a large decrease in airway diameter to produce a significant increase in airway resistance.

7. ASD/OSA Correlations From The Biomedical Literature

7.1. Sleep Problems in Autism

Sleep issues in autism are seen in up to 83% of cases [2]. The clinical findings in autistic sleep are resistance to bedtime, difficulty falling asleep, frequent and prolonged night-time awakenings or early morning awakenings, irregularity in sleep/wake pattern and poor sleep routines. The interesting thing is that the peak onset of sleep difficulties

in autism is the second year of life, corresponding to the peak age for autistic regression [110]. This suggests that whatever is causing the autism is related to sleep, or also has an effect on sleep. In terms of sleep architecture in autism, overall the findings are of longer sleep latency, increased arousals with decreased sleep efficiency, and decreased REM sleep. Giannotti et al. showed these measures as well as increased REM latency were worse in regressed than in non-regressed autism [110]. We know that most obstructive events in children occur during REM sleep [4], therefore we would expect to see these REM problems if the proposed hypothesis is true. We also know that SDB will produce more arousals [10] as are seen in autism. The duration of REM sleep is typically higher in early development than later in life, and it has been concluded that the primary purpose of REM sleep is the promotion of brain development [88]. Therefore anything which disrupts REM sleep in children, notably SDB, would be expected to have significant neurobehavioral consequences. Given that the longest periods of REM are in the early morning hours [3], for a child with OSA to be unable to sleep at this hour is not surprising, and may explain this finding in autism if OSA is present. Longer sleep latency is seen in insomnia, highly associated with UARS, and which will be discussed below. Prevalent symptoms in UARS which are also characteristics of insomnia, are frequent night-time awakenings and difficulty returning to sleep [8]. On a more technical level, Giannotti et al. found an increase in the cyclic alternating pattern A2 and A3 percentages in autistic subjects [110]. A similar pattern has also been identified in UARS, in that their A2 and A3 indices are increased [111]. Therefore this data on sleep is consistent with SDB in autism that has simply been missed due to methodological problems.

Williams et al. has published a table of sleep problems seen in autism. Fifty-three percent had difficulty falling asleep, 40% restless sleep, 34% frequent awakenings, 27% enuresis, 25% daytime mouth breathing, 23% excessive daytime sleepiness, 21% bruxism, and 21% snoring. They found that poor weight gain was associated with greater insomnia, which they could not explain [2]. However, UARS is associated with being thin, and with more insomnia than OSA, such that SDB would explain this association. Any snoring indicates sleep disordered breathing, but the absence of snoring does not rule it out [8], therefore 21% snoring in autistic subjects is not indicative that only 21% have SDB; the percentage with SDB is likely higher than this. Bruxism has been shown to be cured by tonsillectomy, indicating its relationship to OSA. It has been stated that OSA is the highest risk factor for tooth grinding in sleep [112]. We have already discussed the relationship of mouth breathing to OSA. In a child, enuresis may indicate nocturnal polyuria, a condition associated with OSA [11]. The other symptoms specifically regarding sleep essentially indicate that there is a very high incidence of insomnia in children with autism. Miano et al. has written a review of insomnia in autism, and reports that 1/4 of parents state that the sleep problems were present at birth [113], which is consistent with this theory that the OSA must be present from birth to create autism. They also report that fewer hours of sleep per night predicts autism scores and social skills deficits [113], which again implies that the sleep disorder is intimately related to the pathology of autism. In their discussion of insomnia in autism, Miano et al. reports the finding of elevated catecholamines found in blood, urine and CSF of autistic subjects [113]. Elevated urinary catecholamines have also been found in children with OSA [5]. Also, Miano et al. reports the abnormal melatonin secretion pattern found in

autism [113]. An abnormal melatonin secretion pattern has also been found in OSA, with some evidence that CPAP may reverse it [114]. Melatonin has shown great promise for treating the insomnia in autism [113]. Interestingly, melatonin has been shown to reduce cerebral edema in ischemic rats [115], as well as in a rat model of traumatic brain injury [116]. Melatonin will also ameliorate problems with blood-brain barrier permeability [117], and can stimulate glutathione synthesis [116]. It has been shown that improving glutathione status with antioxidants can improve sleep and apneas in OSA [118]. Therefore if mild SDB is increasing ICP in autistic children, melatonin might blunt this increase during sleep and allow fewer arousals if they are due to ICP, but it may also reduce OSA by its antioxidant properties. Clonidine is also used for insomnia in autism [113], and it has also been shown to reduce experimental brain edema [119]. Improvement in autism sleep has been shown to occur with iron supplementation [113]; certainly improving oxygen carrying capacity will reduce any arousals that might be triggered by hypoxemia.

What do we know about insomnia in (neurotypical) adults? Dr. Barry Krakow has published a study in which he showed that in adults with chronic complex insomnia, meaning that they were on long term sleeping medication, the incidence of OSA was 75%. The authors state that if more inclusive hypopnea criteria were used, that the incidence of OSA in their insomniac sample would have been much higher [120]. Dr. Krakow has also found that of 1035 treatment seeking insomnia patients, 81% had complaints that reflected a sleep breathing concern [121]. Additionally, he has shown that in a group of chronic insomniacs who were selected for the absence of classic sleep disordered breathing symptoms, the large majority of their awakenings on PSG were caused by obstructive respiratory events. These patients were unaware that they had SDB and the majority would have only met criteria for PSG based on the failure of their insomnia to remit [122]. Guilleminault et al. found that 83% of a sample of postmenopausal women with insomnia had sleep disordered breathing, usually with a low AHI [123]. Glidewell et al. recently showed that the Insomnia Severity Index provided predictive value for the diagnosis of OSA, especially for women [124].

It has been mentioned previously that somatic symptoms in sleep disordered breathing are inversely related to the AHI [10]: meaning that when you have SDB, the lower your AHI the MORE symptoms you have. And so it is not at all counter-intuitive to suggest that an autistic child with all of their symptomatology might have such mild SDB that most sleep labs cannot detect it. In the 2010 review by Miano et al. on insomnia in autism, the authors freely state that it is not possible to conclude how significant OSA might be in causing the insomnia in autism, because most autistic children do not get sleep studies. They suggest that, as is implied here, further research in this area is necessary [113]. Given how high the rates of OSA/SDB are in adults with chronic insomnia, it is not a great leap to propose that the same mechanism may be operating in autistic children.

7.2. Seizures in Autism and OSA

Epilepsy has a frequency of from 11-39% in autism, and is associated with regression and low functioning. A review showed that 60.7% of 24 hour ambulatory EEGs done in autism patients demonstrated abnormal EEG activity only during sleep [113]. This suggests that the epileptiform activity is being triggered by something occurring

only during sleep. Interestingly, the site with the highest frequency of abnormal epileptiform activity was over the left temporal lobe. The temporal lobe is the site of the amygdala, the brain region that is involved in arousal and autonomic responses to fear [125]. What is more fearful than suffocation? It has been proposed that SDB triggers neural sensitization of the amygdala and that this may be responsible for some of the pathology seen in SDB [96]. Kleinhans et al. demonstrated that autistic children showed decreased amygdala habituation that was correlated with worse social functioning; this is synonymous with amygdala hyperarousal [126]. SDB is commonly reported in epilepsy, and preliminary studies have shown that seizures in adults and children can be significantly reduced by treatment of sleep breathing disorders. A higher percentage of paroxysmal activity on EEG has been found in children with OSA syndrome, compared to children with primary snoring. Nocturnal epileptic seizures have been noted in association with UARS [127]. This is yet another area of overlap between ASD and SDB.

7.3. Male Vulnerability Explained

In experiments in mice it has been shown that stress early in pregnancy may change the expression of some genes in males but not in females, and that male offspring from stressed mothers show maladaptive behavioral-stress responsivity and anhedonia [128]. In addition, male rat hippocampal cells are more vulnerable to the effects of hypoxia than female cells, and administered estrogen has a neuroprotective effect on the male cells [129]. Exposure to intermittent hypoxia (as seen in SDB) is associated with increased apoptosis in vulnerable brain regions as well as with spatial reference memory deficits in adult and developing rats, with developing rats being more susceptible, and male rats showing greater deficits than females [130]. This data would explain male vulnerability if OSA/SDB causes autism. The finding that OSA is more frequent in boys than girls would also be consistent with this theory [6].

7.4. Facial Differences

Could it be that the difference between low and high functioning autism may be related to the presence or absence of hypoxia in SDB? Hypoxia might affect not only the severity of the methylation defect, but obviously neurological injury and repair. A recent paper showing particular facial characteristics in autism, and a difference in the face between low and high functioning autism, may correlate with this supposition. The authors conclude that facial development follows neural migration patterns [131], but in the world of sleep medicine, the face reflects the structure of the airway and the risk of SDB. Any correlation of facial structure in autism suggests that the airway is different in autism, and may play a role in causation. It may be that the face associated with low functioning autism is associated with hypoxic OSA, and the face associated with high functioning autism is associated with UARS. Further study would be required to investigate this question. Interestingly, Aldridge et al. also found a mild hypotelorism in autistic subjects [131], something that is associated with trigonocephaly which again is associated with increased ICP and autism [27]. Two prior studies have also shown differences in the face of autistic children, compared to neurotypically developing children [131]. This issue requires further investigation, as what we do know is that the overall growth of the brain has an impact on the size of the folds that make up the branchial arches, the progenitors of maxillary and mandibular structures. There

are in fact over 150 congenital syndromes associated with some type of fetal brain injury and abnormal breathing during sleep [7]. Therefore, abnormal brain development and SDB likely go hand in hand.

7.5. Oxidative Stress in Autism and OSA

Oxidative stress has been shown to be elevated in children with autism, as manifested by significant reductions in plasma cysteine, glutathione, and the ratio of reduced to oxidized glutathione [132]. Lipid peroxides and urinary isoprostanes are significantly higher in autistic children. [133]. Looking at OSA, we find that there are also lower glutathione levels and increased lipid peroxidation seen in this condition. One study showed that CPAP improved these markers, and that antioxidant supplementation led to improvements in sleep and in apneic episodes [118]. Del Ben et al. found elevated urinary isoprostane levels in OSA which were decreased with CPAP treatment [134]. Interestingly, serum nitrate levels are elevated in autism [133] and decreased in OSA [134]. A recent complex theory involving atrial natriuretic peptide as it may interact with the nitric oxide/peroxynitrite (NO/ONOO) cycle (as proposed by Dr. Martin Pall) suggests that in UARS there will be a systemic upregulation of the NO/ONOO cycle, however in OSA this will be localized only [12]. If most cases of autism involve mild OSA/UARS without significant hypoxia, this would explain the difference in nitrate levels seen between autism and (hypoxic) OSA.

7.6. Mitochondrial Dysfunction in Autism and OSA

There is evidence of mitochondrial dysfunction in autism. This can be manifested in many ways. Possibly the most classic finding is an elevated lactate level [135]. This has also been found in OSA, as a marker of tissue hypoxia [136]. Elevated AST (aspartate aminotransferase) has been seen in autistic children [135]. As well, elevated AST levels are seen in OSA as a marker of oxygen desaturation [137]. Douglas et al. has documented that the neuronal cell death that occurs from cyclic hypoxia/hypercapnia (as seen in OSA) is due to oxidant stress from mitochondrial dysfunction [138]. A recent report discussed 5 autistic patients who were found to have hyperfunction of mitochondrial complex IV, associated with abnormal electron microscopy [139]. This is striking, given the known effect of atrial natriuretic peptide on mitochondria. Increased effect of ANP leads to increased mitochondrial DNA copy number and giant mitochondria, associated with increased fat oxidation and higher oxygen consumption [140]. Again, we know that SDB is associated with increased levels of ANP [11]. The recent ANP hypothesis suggests that this will be more significant in UARS, because of the evidence that there is ANP resistance in obesity and therefore in OSA, as a result of elevated leptin levels and intermittent hypoxia. Because of the higher oxygen consumption at the cellular level, this may render the patient with UARS to suffer cellular hypoxia despite what may be considered a "normal" nocturnal oxygen desaturation. As implied above, hyperleptinemia is a consequence of intermittent hypoxia [12] and has been demonstrated in childhood OSA [5]. It should not be surprising at this point to learn that autistic children have been found to have elevated leptin levels. Ashwood et al. found that the highest leptin levels were associated with early onset autism, compared to regressive autism [141]. According to the ASD/OSA hypothesis, this could indicate that those with early onset autism have lower oxygen levels at night, and those

with regressive autism might have UARS. An effect on improved cellular oxygenation at the mitochondrial level may explain some improvements seen in autistic children using hyperbaric oxygen therapy (HBOT). There is evidence of poor oxygenation of autism brains as measured by a reduction in brain Bcl-2 and increase in brain p53, with the effects on both markers known to be induced by hypoxia [135]. Again this is more evidence that OSA might be involved in producing the hypoxia, however it might also be caused by the cerebral hypoperfusion that has been described in autism [135]. Yet, this hypoperfusion has been seen on SPECT scans not only in autism subjects [142], but also in patients with intracranial hypertension [143]. Interestingly, the maximal hypoperfusion seen in autism is in the frontal and prefrontal areas [139], which would correlate with the narrowest part of the skull as seen in trigonocephaly, again, associated with autism and increased ICP [27,28]. Finally, intracranial hypertension is another condition known to be helped by HBOT [144]. If autism is actually caused by intracranial hypertension as a consequence of SDB, then might this explain the improvement in autistic symptoms from HBOT?

7.7. Cerebellar Damage in Autism and OSA

Purkinje cell loss in the cerebellum has been the most consistent finding in post-mortem autism brains [145]. OSA patients also show neuronal loss, and experiments in rats show that intermittent hypoxia will cause dose-dependent cerebellar Purkinje and fastigial neuron damage, significantly more so than sustained hypoxia at a comparable level [146]. In addition to the hippocampus, the cerebellum is the brain region most vulnerable to hypoxic injury, with Purkinje cell damage being one of the most sensitive indicators of this [147].

7.8. Accelerated Head Growth In Autism - Could It Be Intracranial Hypertension?

A related finding in autism is of accelerated head growth during the first year of life. A larger head circumference at 15 to 25 months is associated with a greater number of symptoms of social impairment [148]. What has been suggested based on quantitative transverse relaxation time imaging is that the white matter abnormalities found in autism are due to increased tissue water content [149]. Vargas et al. demonstrated an active neuroinflammatory process in the cerebral cortex, white matter, and cerebellum of autistic patients [145]. This data suggests that the increase in head circumference may be due to enlargement of the autistic brain from neuroinflammation and brain edema. Hypoxia is known to cause neuroinflammation [150]. What is less recognized is that glutamate as well as quinolinate, both neuroexcitotoxins that stimulate the NMDA (N-methyl-D-aspartate) receptor, may cause brain edema [151-155], and that OSA is known to trigger glutamate neuroexcitotoxicity [156]. Glutamate levels are known to be elevated in autism [133]. Therefore this is another pathway for OSA to raise ICP via the mechanism of causing brain edema, which based on the above neuroimaging data is apparently found in autism. In fact, a recent MRI-DWI study has demonstrated some evidence for brain edema in OSA [157]. Going back to the head circumference findings, if increased ICP is present in infants and children with autism, this would explain an increase in head circumference during the period of growth in which the cranial sutures are open. Because fontanelles are known to attenuate pressure [158], at the time of anterior fontanel closure around 18 months of age [159] ICP would likely increase, correlat-

ing with the time of peak regression in autism. The rapid head growth in autism increases significantly between ages 2-4 years [75]. This correlates with the period in a child's life that the lymphoid tissue in their airways are at their greatest size in proportion to the rest of the airway [4], supporting a theory that SDB increases ICP to effect the head growth. A recent hypothesis paper suggests that because boys have a larger average head size, that their larger posterior fossae will allow higher peaks of pressure in the ventricles as generated by movements in the chest and abdomen, and therefore males will continue to grow larger heads, as seen in autism. The author states that the head circumference is influenced by intracranial pressure, and the pressure pulsations are transmitted from the chest and abdomen. She implies that there are higher ICPs in males, and in males with autism [158], but does not make the leap to intracranial hypertension. However, if this theory is true, it implies that if there are abnormal pressure changes in the chest as seen in SDB, this will lead to higher CSF pressure spikes and larger heads, and it suggests that abnormal ICP spikes may be common in autism. Davidovitch et al. reported on the head circumference findings in 1996, and stated that there were no signs of increased intracranial pressure or hydrocephalus in their group of autistic subjects. However, they performed imaging studies but no lumbar punctures [160], therefore their conclusion is erroneous. There is no way to rule out increased ICP without direct CSF pressure measurement. There have been no studies investigating ICP in autistic subjects. There is one study of children with hydrocephalus, indicating an increased incidence of autism in this group [161]. Certainly the data we already have, suggesting brain edema in autistic children, indicates that a study looking at ICP in autistic children is a required step in attempting to solve the puzzle.

Now, there is no known association of autism with papilledema, and autism patients do not present with symptoms that most neurologists associate with intracranial hypertension. If you look through a lens of IH, you may see things that correlate that you might otherwise not have noticed. But certainly autistic children do not present a full blown syndrome of IIH. What this paper is suggesting, is that OSA/SDB causes low level elevations of ICP that are more significant in some than others, which when combined with the effects of OSA/SDB during early development, lead to the constellation of behavioral symptoms we call autism spectrum disorder.

7.9. Immune System Effects In Autism And OSA

There have been many investigations into the immune system in autism. The pro-inflammatory cytokines TNF- α , IL-6, GM-CSF, as well as IFN- γ and IL-8 were found to be significantly increased in autism brains. Plasma elevation of TNF- α , IFN- γ and IL-6 has also been shown in autistic children compared to controls. NF- κ B is upregulated in blood and brain, and MCP-1 and TGF- β are upregulated in brains of autistic individuals [162]. Sweeten et al. found elevated plasma neopterin levels in autistic children [163]. It has been reported that there is decreased NK cell killing in autism [162] as well as decreased IgG and IgM in autistic children [164].

In OSA researchers have found decreased IgM and decreased NK cell percentage, compared to a control group without OSA [165]. In subjects with sleep disordered breathing, neopterin levels are elevated, and the degree of elevation correlates with the degree of sleep-related hypoxemia [166]. Both TNF- α and IL-6 are elevated in OSA syndrome, and TNF- α levels decrease after surgical treatment of OSA [5]. Interestingly,

increased IL-6 levels in a mother can cross the placenta and trigger seizures in the offspring [55], suggesting a role for maternal OSA in producing neonatal seizures. Tam et al. demonstrated that children with OSA have significantly elevated IFN- γ levels, and a trend toward elevated IL-8 levels, and this was present even in mild OSA. IL-8 is known to be elevated by hypoxia [167]. A polymorphism in TNF- α at the 308G position has been associated with increased daytime sleepiness in children with OSA. Also, children with OSA who harbor this allele had higher TNF- α levels than those with other alleles. (In the absence of OSA, levels did not differ between allele groups) [168]. If SDB is shown to underlie most cases of autism, there may be similar polymorphisms in autism which amplify various effects of SDB as seen here and may explain why only some children with SDB become autistic. Also, TNF α has been shown to increase blood-brain barrier (BBB) permeability and as a result to increase cerebral edema [169], therefore this is a mechanism in both autism and SDB for alteration of the BBB and production of increased ICP via the development of brain edema. This example of a polymorphism triggered by OSA is the ideal illustration of what the ASD/OSA hypothesis is based upon. The cascade of physiologic events which results from SDB may be dictated by the genetics of the individual, yet the genetics are the promoter only. The SDB is the initiator.

7.10. Looking At Biomedical Treatments Through The Lens of IH

There have been many supplements which have been shown to be helpful for autism patients, and some have quite a bit of data to support their use in autism. The most successful and best documented substance is melatonin [170], which has been discussed previously, as have clonidine and iron supplementation. As above, both melatonin and clonidine have been shown to reduce brain edema. Several studies indicate that omega 3 essential fatty acids can lead to improvement in autistic symptoms [170]. Docosahexaenoic acid (DHA) has been demonstrated in rats to reduce the effect of ischemia/reperfusion injuries, as evidenced by decreases in brain edema, blood-brain barrier (BBB) disruption, and IL-6 expression. DHA also led to elevation of the Bcl-2 expression [171]. Another popular treatment for autism is vitamin B6 and magnesium, which has been demonstrated to lead to improvements speech, social interaction, and other autistic symptoms [170]. Magnesium is known to block the NMDA receptor for glutamate [172], and it has been shown to reduce the formation of brain edema and restore BBB permeability after experimental brain injury [173]. Vitamin B6, among other effects, may lessen excitotoxicity [133] which has been suggested above to be related to the development of brain edema. Rivastigmine is an acetylcholinesterase inhibitor which has been shown to lead to improvements in autistic symptoms [170]. In mice, rivastigmine has neuroprotective effects and can reduce cerebral edema by 50% after closed head injury [174]. Pentoxifylline is known to inhibit TNF α secretion and has immunomodulatory effects, and has been shown in several uncontrolled studies to improve language and attention in autistic children [170]. Pentoxifylline has also been shown to reduce not only TNF α levels, but also BBB breakdown and brain edema following temporary focal cerebral ischemia in rats [169]. Glutamate antagonists have been used in autism, and hyperactivity, attention, and social interaction have improved with the use of Memantine [170]. Memantine can attenuate brain edema and BBB permeability after focal cerebral ischemia and reperfusion in the rat [175]. Most recently, the use of N-

acetylcysteine (NAC) in children with autism showed significant improvements on the Aberrant Behavior Checklist irritability subscale, in a randomized controlled pilot trial. The authors suggest the mechanism of action is related to modulation of glutamatergic transmission and/or antioxidation [176], however, in rats NAC administration reduces brain edema, BBB permeability and TNF α levels after traumatic brain injury [177]. Several case reports have indicated that Prednisone has led to significant improvements in autistic behaviors [170]. Steroids are a well known effective treatment for cerebral edema to reduce ICP [178]. Pioglitazone, which has anti-inflammatory properties, has led to improvements in stereotypy, hyperactivity, irritability and lethargy in one study [170]. Pioglitazone has also been shown to significantly reduce brain edema in mice after experimental ischemia, as well as to reduce serum TNF α levels [179]. Improvements in both autism and intracranial hypertension with hyperbaric oxygen therapy have been mentioned above. Here we have a conjunction of the data for multiple points. Again, we are missing the smoking gun, but what is the likelihood that all of these substances which improve brain edema lead to improvement in autism by a different mechanism, especially when we have evidence that in autism the brain is swollen? The chances are quite high that what we are treating in autism with these substances is brain edema, and more than likely, increased ICP.

7.11. Gastrointestinal Effects In Autism And OSA

It seems that gastrointestinal (GI) problems are more common in autistic children; a history of GI symptoms have been found in 70% of autistic children compared to only 28% of typically developing children in one study. In a study of autistic children referred for tertiary GI evaluation, 69% were found to have reflux esophagitis. 58% had low intestinal carbohydrate digestive enzyme activity [170]. Williams et al. has recently found that ileal transcripts encoding disaccharidases and hexose transporters were deficient in children with autism [180]. As previously stated, GERD is highly associated with OSA, and remember that GERD can potentially make OSA worse [3]. This could account for how treatment of GERD can lead to improvement in some autistic symptoms, notably treatment with famotidine led to behavioral improvements in one study [170]. There has been very little published regarding other gastrointestinal issues in sleep disordered breathing, however irritable bowel syndrome is associated with UARS [8]. One case report demonstrated a patient with diffuse abdominal pain, bloating and weight loss associated with fat malabsorption and vitamin B12 deficiency, in which these symptoms completely resolved with treatment of OSA with CPAP [181]. This overlap in GI symptoms between OSA and autism supports the ASD/OSA hypothesis.

8. Conclusions

8.1. Implications for Treatment/Prevention

If the ASD/SDB hypothesis is true, then what does this imply regarding prevention and treatment? There is definitely the suggestion in the above data that what we currently do in biomedical autism management is deal with the metabolic and physiologic consequences of SDB, and this should likely be continued. Yet, going forwards with the new information, all attempts to reverse SDB in the mother and child should be undertaken. However, as we do not know anything about when in pregnancy SDB causes

problems for the fetus, the mother will need to have pre-conceptional care for diagnosis and treatment, so that her SDB is properly managed prior to conception. It takes much too long to get a sleep study and a CPAP machine for treatment to be initiated expeditiously if the mother waits until she finds out she is pregnant; she would likely be well into the second trimester before CPAP would be started. Once babies are born, any sleep difficulties should be immediately evaluated. If an infant has difficulty sleeping supine, this should be a red flag. Nasal congestion should be treated aggressively. Sleep studies should be conducted on infants and CPAP started if necessary. Mandibular distraction is quite invasive but may be indicated in some cases [5]. As children get older, adenotonsillectomy should be considered sooner rather than later. Only 50% of children with OSA are cured by adenotonsillectomy [5], so sleep studies should be repeated after surgery to evaluate the need for further treatment. Maxillary expansion has been shown to have good results in treating pediatric sleep apnea [4]. Other functional appliance therapy methods may also prove effective: Biobloc therapy has been shown to increase posterior airway space [182]. More invasive craniofacial surgery may be indicated in advanced cases [5]. If a child is found to have borderline or elevated ICP, then measures to decrease ICP would be indicated. It may be that definitive treatment of the OSA will significantly decrease the ICP, however, treating OSA definitively can take time and can be a difficult process, such that adjunctive management of ICP would be necessary in the short term. Keeping a CPAP mask and machine on an autistic child is certainly a challenge, and may not be the best option for many families once autism has developed. Once OSA has been managed in the autistic child, improvements are sure to result, however what remains to be seen is whether autism would be reversible in this situation. If irreversible epigenetic changes occur due to the mother's OSA during pregnancy, then complete recovery may not be possible. If we lose critical periods of neurodevelopment to OSA during infancy, it may be that we cannot turn the clock back and recover what was lost. Any studies done to investigate this hypothesis must take these considerations into account. We know that the recurrence rate of autism is 18.7%, [65] therefore what may need to be done is to address OSA in mothers of known autistic children during subsequent pregnancies, and address OSA in those infants, and then evaluate the incidence of autism in that group. If this is significantly lower than the known recurrence rate of autism, this should give credence to the theories explained in this paper. Additionally, as previously suggested, studies need to be conducted to assess ICP in autistic children. If it is elevated, the effect of treatment of ICP on autistic symptoms should be determined.

For clarity, the data discussed above can be summarized in tabular form as shown in TABLES I and II.

8.2. Summary

In summary, the information outlined here presents a complex theory of autism that requires the presence of sleep disordered breathing in a mother during her pregnancy and in her infant at birth, methylation mutations in both, as well as a tendency to intracranial hypertension. This theory endeavors to compile multiple pieces of data which have heretofore not been able to be connected or explained, in regards to the pathogenesis of autism. It incorporates the required elements of heredity and interaction with environmental factors. The correlation of findings between autism and sleep

disordered breathing is so striking it is almost as if one could superimpose one data-set upon the other. As implied by the title of this paper, these are admitted correlations only, however there are so many that coalesce to explain this theory that the data call for further investigation. There may be some differences seen between adult OSA and autism, however age of onset of sleep disordered breathing and the effect on the developing brain may explain some of these. Another way of looking at this is to say that this paper takes over 90 pieces of the autism puzzle and fits them together. It has been said that autism is a systemic illness that affects the brain. Obstructive sleep apnea is an illness with systemic effects that most prominently affect the brain, fulfilling the criteria for what is seen in autism. It bears repeating that the reason this connection has not been recognized up until now, is primarily because of problems with performing and interpreting sleep studies accurately. Several recent publications in this area demand attention to this issue and a re-evaluation of how we have been assessing pediatric sleep disordered breathing. There are multiple research studies which must grow out of this paradigm in order to confirm the hypothesis that most cases of autism are caused by a combination of sleep disordered breathing and intracranial hypertension. It is this author's hope that this research will commence, and the puzzle will finally be constructed. The picture it shows will surely reveal a mother and her infant, both struggling to breathe while they sleep.

Abbreviations Use:

ADHD	Attention Deficit Hyperactivity Disorder
AHI	Apnea Hypopnea Index
ANP	Atrial Natriuretic Peptide
ASD	Autism Spectrum Disorder
BBB	Blood-Brain Barrier
CPAP	Continuous Positive Airway Pressure
CSF	Cerebrospinal Fluid
EEG	Electroencephalogram
GERD	Gastroesophageal Reflux Disease
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
HCys	Homocysteine
ICP	Intracranial Pressure
IFNγ	Interferon Gamma
Ig	Immunoglobulin
IH	Intracranial Hypertension
IIH	Idiopathic Intracranial Hypertension
IL-6	Interleukin-6
IL-8	Interleukin-8
MCP-1	Monocyte Chemoattractant Protein 1
NF-κB	Nuclear Factor Kappa B
NK cell	Natural Killer Cell
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
REM	Rapid Eye Movement
RERA	Respiratory Event Related Arousals

SDB	Sleep Disordered Breathing
TGFβ	Transforming Growth Factor Beta
TNFα	Tumor Necrosis Factor Alpha
UARS	Upper Airway Resistance Syndrome

TABLE I. Findings Common to Both Autism and Sleep Disordered Breathing.

- Breastfeeding decreases risk
- Inattention
- Impulsivity
- Hyperactivity
- Memory deficits
- Executive dysfunction
- IQ reduction
- Insomnia
- Enuresis
- Daytime mouth breathing
- Excessive daytime sleepiness
- Bruxism
- Snoring
- Elevated urinary catecholamines
- Abnormal melatonin secretion pattern
- EEG abnormalities
- More prevalent in males
- Elevated homocysteine levels
- Low glutathione levels
- Increased lipid peroxides
- Elevated urinary isoprostanes
- Elevated lactate levels
- Elevated AST levels
- Elevated leptin levels
- Cerebellar Purkinje cell loss
- Increased glutamate levels
- Elevated TNF- α
- Elevated IL-6
- Elevated IL-8
- Elevated IFN- γ
- Elevated neopterin
- Decreased IgM
- Decreased NK cell function
- Gastrointestinal problems

Table II. Findings Suggesting Elevated Intracranial Pressure (ICP) in Autism.

- Association with trigonocephaly
- Elevated brain water seen on neuroradiological studies
- Improvement with medications/supplements known to reduce brain edema:

Melatonin	Pentoxifylline
Clonidine	Docosahexaenoic acid
Magnesium	N-acetylcysteine
Rivastigmine	Steroids
Memantine	Pioglitazone
- Improvement with hyperbaric oxygen therapy (seen also in ICP)
- Cerebral hypoperfusion (seen also in ICP)
- Regressions correlate with anterior fontanel closure
- Increased head circumference/accelerated head growth

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