The Etiology of Autism

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ABSTRACT

A single etiology for autism or for any of the disorders on the autistic spectrum has yet to be determined. In the past, suspected causes of these disorders included parentally induced autism, brain injury/anomalies, constitutional vulnerability, and developmental aphasia, as well as deficits in the reticular activating system, and an unfortunate interplay between psychogenic and neurodevelopmental factors. Other suspected etiologies are structural cerebellar changes, genetics, viral infections, and immunological abnormalities, with various teratogens, seizures and vaccines also being investigated. Until we know the multiple etiologies of those within the Autism Spectrum; as researchers, health care providers, educators and optometrists, we must offer all within the autistic continuum the very best, most current and accessible care available based upon the latest known science.

Keywords: Aspergers syndrome, attention deficit hyperactivity disorder, autism spectrum disorders, childhood disintegrative disorder, non-verbal learning disabilities, pervasive developmental disorders-not otherwise specified (pdd-nos), Rett syndrome, semantic pragmatic communication disorder.

The topic of autism and its many potential etiologies, treatments and cures have taken hold of the public’s heart strings and imagination. The who are affected by this disorder, their care givers, politicians, and celebrities have successfully moved autism from the realm of scientific study into the living room of everyday people across the country. Oprah has presented several shows on this topic, there are dedicated blogs and you can even follow autism on Twitter. Major news magazines (US News and World Report, Time Magazine, Newsweek, Forbes) and newspapers, frequently highlight this disorder as well.

The media often questions its own accuracy and hype, however. How much does the public really understand? For that matter, how much do health care professionals know about special populations in general and autism in particular? Recent publications within the eye care field would suggest that a great deal still needs to be done in this area.

The eye and vision care professions of optometry and ophthalmology have few available resources from within their respective professions regarding the oculo-visual needs of special populations including those diagnosed with one or more of the disorders associated within the Autism Spectrum. The attitudes of eye care professionals, professional degree graduate education, and research and continuing education (continuing competence) programs are not often available and therefore do not provide these health care providers with the necessary education and state of the art information about the special needs patient and how to care for this population. There are resources accessible to the eye care professional that

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if sought out will demonstrate the numerous eye and vision care deficits, found within the special needs patient population. There are also resources on hand that specifically discuss how to examine and treat the patient with disability. But these are few and often underutilized.

The discussion of any special needs patient population should probably begin with the etiology of the disorder. This is fairly straightforward for several anomalies, but unfortunately we often only know the etiologies of but a handful of developmental disabilities. Most children and adults diagnosed with a disability will only have a generic diagnosis of “mental retardation” or “intellectual disability”. Individuals within the Autism Spectrum however, have a specific diagnosis, but no single proven specific cause for the disorder.

To make matters even more complicated when it comes to determining the etiology of autism, this disorder now encompasses multiple developmental anomalies with several levels of involvement, disability and ability as opposed to a single, relatively rare anomaly. While this makes autism more visible and therefore more likely to attract media attention, political support and research dollars; it only complicates getting to the basic underlying etiology.

The Autism Spectrum

It has been noted that the frequency of individuals demonstrating at least one of the disorders on the spectrum was 3.4/1,000 for children 3 to 10 years of age with the CDC now estimating that 2-6/1,000 (from 1 in 500 to 1 in 150) children having the disorder. Males diagnosed with ASD have a 3 to 4 times greater risk of having the disability than females. Although this rate is lower than that found for intellectual disability (9.7 per 1,000 children); it is higher than the prevalence of cerebral palsy (2.8 per 1,000 children), deafness (1.1 per 1,000 children), and severe visual impairment (0.9 per 1,000 children). The spectrum includes: Autistic Disorder, Aspergers Syndrome, Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS), Retts Syndrome, and Childhood Disintegrative Disorder. Other professionals in the field incorporate within this continuum Semantic Pragmatic Communication Disorder, Non-Verbal Learning Disabilities, High Functioning Autism (may be similar to Aspergers), Hyperlexia, and some individuals with Attention Deficit Hyperactivity Disorder.

There are several developing biomedical models for the cause of autism that suggests there are many “autisms” and that the etiology is based not on behavior but biology. The older models were genetically determined, brain based, hard wired, and treatable but not curable. The newer models being considered now note that the etiologies of autism tend to be environmentally triggered, but genetically influenced; engages both the brain and the body; involves metabolic abnormalities, and is not only treatable but suggests the possibility of recovery.

As you can imagine, discovering a single etiology for such a diverse spectrum is a monumental undertaking. Most often the scientist would investigate several areas including genetics, trauma, environmental factors, the presence of teratogens, and even psycho-social etiologies. In the recent past hundreds of potential causes of autism have been suggested. These possible causes included but have not been limited to: parentally induced autism, yeast infections, and intolerance to food substances, as well as phenolsulphertransferase (PST) deficiency, and brain injury. Other suggested etiologies included: constitutional vulnerability, developmental aphasia, deficits in the reticular activating system, and an unfortunate interplay between psychogenic and neurodevelopmental factors, as well as structural cerebellar changes. And finally others have postulated that genetics, viruses, immunological problems, vaccines, and seizures as being etiologies for this spectrum of disorders. The limited breadth of this paper cannot provide an in-depth evaluation of each of these potential etiologies, but will highlight a few of the more commonly encountered and touted causes of ASD.

Etiology Review

Parentally Induced Autism: Parentally induced autism was one of the earliest suggested etiologies for autism. Cold, unfeeling parents; especially mothers, caused their children to show the signs and symptoms associated with autism. Research into this potential etiology showed that there are autistic children born to parents who do not fit the autistic parent personality pattern, as well as parents who fit the description of the supposedly pathogenic parent who have normal, non-autistic children. It has also been noted that frequently siblings of autistic children are normal and that autistic children are unusual “from
the moment of birth” which appears to rule out the parental etiology theory.

**Yeast infections, Food Intolerance, Leaky Gut Syndrome, Gluten Free Diets:** Although several websites and various authors of non-peer reviewed publications and single case reports seem to support yeast infections, food intolerance, and leaky gut syndrome as possible etiologies for autism most research suggests no concrete food/yeast/diet associative causative factors. It is currently thought unlikely that food/digestive associated problems are etiological in nature for autism.

**Seizures, Epilepsy:** There is research to support the role of seizures/epilepsy and an association with autism. One study noted that higher rates of epilepsy associated with autism have often been reported in the literature. The prevalence of this association however may vary as much as 5% to 46% depending upon the population studied. They also noted that a critical review of the literature showed the rate in idiopathic cases with normal intelligence was still significantly above the population risk. This suggests that autism is associated with an increased risk of epilepsy. Although some authors propose that a causal relationship may exist; the debate among scientists in this area continues. It is acknowledged however; that those who have ASD and epilepsy (asd+e) and those just with ASD differ in several important ways including that the asd+e group demonstrated a greater number of females and were more likely to have received a diagnosis of ASD at a later time. These individuals also had more motor difficulties, developmental delays and problematic behaviors.

**Phenolsulphertransferase (PST) deficiency:** Phenolsulphertransferase is supposed to be critical in the process of breaking down and removing various toxins from the human body. Waring postulated that symptoms arise from an inadequate supply of usable sulfate ions, rather than from a deficiency of the metabolic enzyme itself. She has also noted that the inability to effectively metabolize certain compounds particularly phenolic amines, toxic for the CNS, could exacerbate the wide spectrum of autistic behavior but does not suggest a causative relationship.

**Brain and Brain Injury:** Since the emergent brain is more susceptible to insult than the older and more developed adult brain and that genetics and environmental factors (lead, methyl-mercury, toluene, arsenic, polychlorinated biphenyls) are known etiologies of neurodevelopmental anomalies, it has been postulated that autism may be caused by injury to the cerebral cortex. This includes disorders associated with the amygdala and may explain some of the visual behaviors associated with autism. Neurotoxicity, altered neurotransmission, false neurotransmitters and disturbed neuro-connectivity may also play a role. Other studies have noted that an increased total brain, parieto-temporal lobe, and cerebellar hemisphere volumes are often seen in autism and that the size of amygdala, hippocampus, and corpus callosum may also be abnormal.

**Reticular Activating System:** A study by Buchwald et al supports that the reticular activating system (RAS) and/or its post-synaptic thalamic targets may be dysfunctional in autism. Since autism is noted for altered states of susceptibility to stimulation and that the RAS is responsible for our state of arousal and motivation, a link between the two has been suggested. The exact causal relationship, if any, remains unknown.

As noted previously, although discussing all potential etiologies of autism is well beyond the scope of this single paper, there remain two areas that must be included in this review. These areas of discussion are usually in the media every day and have taken not only the scientific professions by storm, but have also captured the general public’s imagination as well. These two areas include vaccines and genetics.

**Vaccines:** A paper by Gerber and Offit noted that on February 28th, 1998, Andrew Wakefield who was a British gastroenterologist, (and his colleagues) published a paper in The Lancet that described 8 children whose first symptoms of autism appeared within 1 month of receiving a MMR (measles-mumps-rubella) vaccine. All of these children had gastrointestinal symptoms and signs as well as lymphoid nodular hyperplasia. Wakefield postulated that the MMR vaccine caused intestinal inflammation that led to a translocation of usually nonpermeable peptides to the bloodstream and the brain. These then went on to affect the children’s development.
Unfortunately this case series as presented in Wakefield’s paper had several problems that undermined his unwarranted conclusions. These problems included a self-referred subject cohort, a lack of control subjects, no determination of causation versus coincidental occurrence, and a poor study design (not a double blind methodology, incomplete data collection in an unsystematic fashion). Other problematic issues noted with this paper included that in some instances the gastrointestinal symptoms did not appear before the onset of autism, and MMR vaccine viruses have not been a basis of persistent intestinal irritation or failure of intestinal barrier functionality. Gerber and Offit continued their rebuttal of Wakefield’s study by stating that “putative encephalopathic peptides traveling from the intestine to the brain have never been identified”.

An extensive final report by the Immunization Safety Review Committee (ISRC) of the Board on Health Promotion and Disease Prevention Institute of Medicine56 evaluated the premise that vaccines (MMR and those containing Thimerosal) cause autism. The ISRC reviewed both published and unpublished epidemiological studies and publications of possible biologic mechanisms by which immunizations could be causative for the development of autism. The ISRC concluded that the body of evidence rejects a causal relationship between autism and the MMR vaccine. They also noted that the data reviewed supports a rejection of any causal relationship between Thimerosal containing vaccines as an etiology of autism. The Centers for Disease Control and Prevention: Immunization Safety and Autism Research Agenda57 reviewed 9 major national and international studies as well. None demonstrated a causative etiological link between autism and vaccines and/or Thimerosal. It appears that the majority of research strongly rejects MMR/Thimerosal as an etiology of autism.

The Courts, Autism and Vaccines: There have been several court cases that have also rejected the connection between MMR/Thimerosal and autism. George L. Hastings Jr. in the U.S. Court of Claims58 in Washington, DC noted that:

After studying the extensive evidence in this case for many months, I am convinced that the reports and advice given to the Cedillos by Dr. [Arthur] Krigsman and some other physicians, advising the Cedillos that there is a causal connection between Michelle’s MMR vaccination and her chronic conditions, have been very wrong. Unfortunately, the Cedillos have been misled by physicians who are guilty, in my view, of gross medical misjudgment. Nevertheless, I can understand why the Cedillos found such reports and advice to be believable under the circumstances.... However, I must decide this case not on sentiment, but by analyzing the evidence.

However, the US Vaccine Court and its application of justice and science appear somewhat mismatched. The court noted that:

The plaintiff’s

... ADEM (acute disseminated encephalomyelitis) was both caused-in-fact and proximately caused by his vaccination. It is well-understood that the vaccination at issue can cause ADEM, and the Court found, based upon a full reading and hearing of the pertinent facts in this case, that it did actually cause the ADEM. Furthermore, Bailey’s ADEM was severe enough to cause lasting, residual damage, and retarded his developmental progress, which fits under the generalized heading of Pervasive Developmental Delay, or PDD [an autism spectrum disorder]. The Court found that Bailey would not have suffered this delay but for the administration of the MMR vaccine, and that this chain of causation was... a proximate sequence of cause and effect leading inexorably from vaccination to Pervasive Developmental Delay.

Post-vaccination ADEM has been associated with several vaccines59 (rabies, diphtheria-tetanus-polio, smallpox, Japanese B encephalitis, pertussis, influenza, hepatitis B, and the Hog vaccine) not only MMR and may or may not have been the causative agent in this case even though the court ruled otherwise. A recently conducted online PubMed search showed no publications that linked autism and/or Pervasive Developmental Disorder — Not Otherwise Specified (PDD-NOS) with ADEM.

Regarding another case, Taub in her paper, Autism and the Courts: What does the recent settlement really mean?60 stated that:

Legally speaking, and despite what laypeople in the media might say or think, this settlement is not legal precedent, because it is not a conclusion by a judge, special master or jury. This means that in future cases, judges or special masters likely will not allow plaintiffs to cite this case in support of their claims.
There is however, precedent for this settlement in that the Vaccine Court has awarded compensation in another recent case where the administration of vaccines aggravated an underlying condition leading to an autism like disorder.\textsuperscript{61}

Please note that the case that resulted in compensation to the plaintiff was because the court decided that the vaccine “aggravated an underlying condition leading to an \textit{autism like disorder}”. It did not cause autism (only an \textit{autism like disorder}). It did not cause autism but \textit{aggravated} an already existing condition. It appears that both our scientific and legal communities have a great deal more to do before this issue can be settled.

\textbf{Genetics:} The topic of the role that genetics play in the development of a child with autism now seems to be reported in the media almost daily. We know that in studies of identical twins with one child being autistic, the other child has an 82\% chance of being affected. For fraternal twins that percentage was only 10\%. Genetic researchers now think that as much as 90\% of the behavioral phenotype of autism is related to inherited genes.\textsuperscript{62}

A review by Muhle et al\textsuperscript{63} of the genetics involved in autism showed that data from whole-genome screens suggested interactions of at least 10 genes in the etiology of autism. It appears that the area 7q31-q33, a speech and language region, is linked to the development of autism. In a paper in the \textit{American Journal of Human Genetics} and an accompanying editorial, it was noted that chromosome 7 is “the first widely replicated autism-predisposition gene.” This gene makes proteins called Neurexins which play an important role in the development of the mechanism by which brain cells communicate.\textsuperscript{64} Other locus anomalies that are frequently implicated as a potential cause of autism can be found at 15q11-q13, while some animal models involve the oxytocin receptor at 3p25-p26.

Other studies that support a genetic etiology show that the chances a brother or sister of someone who has autism will also be autistic are 2 to 8\%. This percentage is a great deal higher than what you would typically find in the general population. It has also been noted that autistic-like symptomology occurs more often in parents, sisters, and brothers of those with autism than in families who have no relations with ASDs.\textsuperscript{65}

Although many of these (and other) findings are beginning to show us the connection between the environment, the role of genetics, the interaction of the brain and body, and the role of metabolic abnormalities; we still have a very difficult research path in front of us before the “right” answer (more than likely several right answers) are apparent. As was noted in the blog,\textsuperscript{66} \textit{Age of Autism: Daily Web Newspaper of the Autism Epidemic, Latest Autism Gene Studies Find…Not Very Much}; healthy skepticism about this and other autism/genetics research is evident. They state that:

There’s a familiar rhythm to the most prominent autism gene hunt publications. Their authors hype their newly minted study aggressively in the media. The prestigious journals that publish them lend their imprimatur to press releases that say, “this study is a big deal.”

At this point, we do not really know which of the studies “are the big deals”. We do know that discovering the etiology of autism may someday lead to a wide variety of cures for those somewhere along the spectrum. We also know that until that time; as researchers, health care providers, educators and optometrists; we must offer all within the autism spectrum the very finest, most current and accessible care available based upon the best science known.\textsuperscript{67-69}

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**Student Awards for Excellence in Vision Therapy**

COVD is pleased to announce that the following students received the 2009 COVD Award for Excellence in Vision Therapy during graduation services this spring at their school or college of optometry.

The COVD Excellence in Vision Therapy Award is given to recognize those students who have demonstrated a strong interest and clinical skills in vision therapy. Congratulations to each of these new optometrists!

- **Jennifer Shaba** – Ferris State University, Michigan College of Optometry
- **Kelly Meehan** – Illinois College of Optometry
- **Kim Kohne** – Indiana University School of Optometry
- **Amy Camerota** – New England College of Optometry
- **Kimberly A. Brunk** – Northeastern State University Oklahoma College of Optometry
- **Rebecca J. Fleming** – Pacific University College of Optometry
- **Candace DeCock** – The Ohio State University College of Optometry
- **Grace Morano** – Salus University, Pennsylvania College of Optometry
- **Linda Luong** – Southern California College of Optometry
- **Joe Borden** – Southern College of Optometry
- **Dorothy H. Nguyen** – University of California, Berkeley
- **Whitney Barker** – University of Houston College of Optometry
- **Andrea K. Braden & David D. Ernst** – University of Missouri - St. Louis College of Optometry
- **Debbie Luk** – University of Waterloo