Original Research

Can Awareness of Medical Pathophysiology in Autism Lead to Primary Care Autism Prevention Strategies?

Elizabeth Mumper, MD, FAAP*

2919 Confederate Avenue, Lynchburg, VA

Emerging research suggests that the timing of environmental factors in the presence of genetic predispositions has influenced the increase in autism spectrum disorders over the past several decades. A review of the medical literature suggests that autism may be impacted by environmental toxicants, breastfeeding duration, gut flora composition, nutritional status, acetaminophen use, vaccine practices and use of antibiotics and/or frequency of infections. The author reports her retrospective clinical research in a general pediatric practice (Advocates for Children), which shows a modest trend toward lower prevalence of autism than her previous pediatric practice or recent CDC data. Out of 294 general pediatrics patients followed since 2005 there were zero new cases of autism (p value 0.014). Given the prevalence of autism for that cohort of 1 in 50 children in the United States, it is important to consider implementing strategies in primary care practice that could potentially modify environmental factors or affect the timing of environmental triggers contributing to autism.

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INTRODUCTION

During the author's career, reported prevalence of autism increased from 1 in 5,000 (1975) to 1 in 2,500 (1985), to 1 in 500 (1995) to 1 in 250 (~2001) to 1 in 166 (~2004) to 1 in 88 (~2008) to 1 in 50 (2013); all reflected birth cohorts born earlier.[1,2] Further research into autism prevalence studies have debunked the initial contention that higher numbers could be explained away by better diagnosis and broadening of diagnostic criteria.[3-6]

Environmental Toxicants

Multiple studies confirmed that proximity to airborne pollutants is associated with higher prevalence of autism. Windham studied particulate emissions in the San Francisco Bay Area (American Lung Association grade of C for particle pollution), and found an association with mercury, cadmium, nickel, trichloroethylene, and vinyl chloride.[7] A recent UCLA study looked at the records of more than 7000 women in Los Angeles county and found that those exposed to higher estimated air pollution levels for ozone and particulate matter had a 12% to 15% greater chance of having an autistic child than women living in areas with cleaner air during their pregnancies.[8] Adjusting for sociodemographic factors and maternal smoking in 304 autism cases and 259 typically developing controls in the CHARGE study, maternal residence at time of delivery was more likely to be near a freeway for cases than controls (OR = 1.86, 95% CI).[9] Palmer used Poisson regression analysis for an ecological study examining environmentally released mercury and autism and special educations rates. Using data from the Texas Education Department and the U.S. Environmental Protection Agency (EPA) he found that for every 1000 pounds of environmentally released mercury, there was a 43% increase in the rate of special education services and a 61% increase in autism rates.[10] In a population-based case control study (CHARGE), exposure to traffic-related air pollution, nitrogen dioxide, and particulate matter during pregnancy and infancy was associated with autism. Comparing 279 children with autism to 245 controls, children with autism were more likely to live at residences with the highest quartile exposure to traffic-related air pollution during gestation (AOR 1.98, 95% CI 1.20-3.31).[11] Toxicologists and epidemiologists at UC Davis have examined shared mechanisms between autism pathophysiology and the effects of pesticide exposures, including neuroexcitability, oxidative stress, and immune dysregulation.[12]

Breastfeeding

Breastfeeding has been associated with lowered risk of type 1 diabetes, celiac disease, other inflammatory bowel disease and some childhood cancers.[13,14] A questionnaire about food introduction in 627 Swedish children with celiac disease and 1254 referents showed the risk of celiac disease was reduced in children if they were still being breast fed when gluten was introduced (OR 0.59) and further reduced if they continued to be breast fed after gluten was introduced (OR 0.36).[15] Breastfeeding has been associated with decreased risk for

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***Corresponding Author:** 2919 Confederate Avenue, Lynchburg, VA 24501. (Email: drmumper@rimlandcenter.com)

infection, allergy and autoimmunity.[16,17] Breastfeeding is protective against child obesity.[18] Fewer breastfed infants are hospitalized for respiratory disease when compared to formula-fed infants.[19]

The impact of breastfeeding on autism has not been definitively determined, however, one report using parent reported data from the Autism Internet Research Survey comparing 861 children with autism to 123 control children used logistic regression to determine that the absence of breastfeeding was associated with an increase in the odds of having autistic disorder (OR 2.48, 95% CI 1.42, 4.35). Use of formula with docosahexaenoic and arachidonic acid supplementation versus breastfeeding was associated with a significant increase in the odds of autism for all cases (OR 4.41, 95% CI 1.24, 15.7) and for autism with regression (OR 12.96, 95% CI 1.27, 132).[20] A case–control study with 102 Autism Spectrum Disorder (ASD) cases and 102 matched healthy controls showed the risk of ASD decreased in a dose–response fashion over increasing periods of exclusive breast-feeding (P for trend = 0.04) and continued breast-feeding (P for trend = 0.001).[21]

Cross-sectional data on 22,399 children from the 2003 National Survey of Children's Health was based on each mother's recall about breastfeeding and response to questions regarding level of concern about her child's development of expressive language, receptive language, fine motor skills, and gross motor skills. Multivariate analysis revealed that mothers who initiated breastfeeding were less likely than mothers of never-breastfed children to be concerned "a lot" about their child's expressive and receptive language development and fine and general motor skills. Mothers of children breastfed for 3 to 5.9 months were less likely than mothers of never-breastfed children to be concerned "a lot" about their child's language and motor skills.[22] Results should be interpreted with caution since it was based on recall; however, it was a large sample size.

Table 1. Gut biopsies in autism: patients from Advocates for Families demonstrate high percentages of abnormalities.

stomach	esophagus	ileum	cecum	ascending colon	transverse colon	descending colon	recto-sigmoid
gastritis	normal	normal	LNH	LNH	normal	normal	normal
normal	normal	normal	normal	normal	normal	normal	normal
normal	normal	LNH	LNH	LNH	normal	LNH	LNH
normal	normal	normal	normal	normal	normal	normal	normal
gastritis	erosive	LNH	LNH	LNH	LNH	LNH	LNH
normal	normal	normal	normal	normal	normal	normal	normal
normal	normal	normal	normal	normal	normal	normal	normal
gastritis	reflux	LNH	normal	normal	normal	normal	normal
normal	normal	LNH	LNH	LNH	LNH	LNH	LNH
normal	normal	normal	normal	normal	normal	normal	normal
> IEL	normal	normal	normal	normal	normal	normal	normal
normal	normal	normal	LNH	normal	normal	normal	normal
gastropathy	normal	LNH	normal	LNH	normal	LNH	normal
normal	normal	normal	normal	normal	normal	normal	normal
normal	normal	normal	normal	normal	normal	normal	normal
gastritis	reflux	normal	normal	LNH	normal	LNH	normal
normal	normal	normal	LNH	normal	normal	normal	normal
normal	reflux	normal	LNH	LNH	colitis, LNH	LNH	LNH
normal	normal	LNH	normal	normal	normal	normal	proctitis
normal	normal	LNH	LNH	LNH	LNH	LNH	LNH

LNH Lymphoid nodular hyperplasia
> IEL high number intraepithelial lymphocytes

The role of breastfeeding in prevention of inflammatory bowel disease including Crohn's disease and its role in promoting optimal development seems important with regard to children with autism. 21 of our patients with autism underwent endoscopy and colonoscopy for gastrointestinal symptoms; the community pathologist who did the histology was blinded as to whether the child had autism or not. 13 of 21 patients had evidence of significant lymphoid nodular hyperplasia or inflammation; only 7 had normal biopsies (**Table 1**). A recent study by Walker from Wake Forest examined gastrointestinal mucosal biopsies painstakingly obtained from children with autism spectrum disorders and 3

control groups (Crohn's, ulcerative colitis, and histologically normal). Comparison of differentially expressed gene expression profiles in intestinal tissue showed that children with autism have a gastrointestinal mucosal molecular profile that overlaps significantly with known inflammatory bowel disease but has distinctive features that suggest either an autism-associated inflammatory bowel disease variant or a prodromal phase of classic inflammatory bowel disease.[23]

Probiotics

"By young adulthood, humans…support one of the most complex ecosystems on the planet, with over 100 trillion bacteria in the distal gut...This consortium contains tenfold more cells than the human body, 100 times the number of genes in the human genome, and has the metabolic capacity of the human liver."[24] Gut-associated immune tissue makes up approximately 80% of immunologically active cells. Intestinal bacteria help develop protective mechanisms including improved gut barrier function, immune modulation and immune tolerance.[25]

Diet has a huge effect on gut flora. Metagenomic analysis of humanized gnotobiotic mice reveal that shifting from a plant based diet to a high fat, high sugar Western diet shifted the census of gut microflora, metabolites and gene expression in one day.[26] Genome studies have led to insights into the relationship between gut flora and metabolic expression.[27]

Many parents of children with autism report the child having gastrointestinal problems, often predominantly diarrhea or chronic constipation or alternating diarrhea and constipation. Many medical researchers have shown that children with autism have altered bowel flora compared to neurotypical controls.[28] Additionally and not surprisingly given the known interactions between the gastrointestinal and immune system, children with autism have dysregulated immune function.[29,30] Immunologic actions of probiotics that seem particularly relevant to the immune dysregulation seen in autism include their ability to inhibit pathogenic bacteria from binding and invading the gut epithelium, increasing the immunomodulatory interleukin 10 and transforming growth factor beta, as well as decreasing the inflammatory tumor necrosis factor.[31]

Probiotics in pregnancy and infancy decrease the risks of eczema, allergic rhinitis and asthma by ~50%.[32] Infants with a family history of atopic allergy had a 100% higher prevalence of atopy at two years of age than infants who received a lactobacillus probiotic.[33] A meta-analysis of probiotics for irritable bowel syndrome of 19 randomized controlled trials (1,650 patients) showed probiotics improved symptoms significantly better than placebo. The number needed to treat for benefit was 4 (95% CI 3-12.5).[34] Exciting work in fecal transplants embraces the paradigm that many diseases result, at least partially, from microbiota-related dysfunction.[35-37]

Nutritional Factors

Mothers of children with autism, when compared with mothers of typically developing children, were less likely to report having taken prenatal vitamins during the 3 months before pregnancy or the first month of pregnancy (OR 0.62 95% CI = 0.42-0.93).[38] Mean folic acid intake in the first month of pregnancy was significantly greater for mothers of typically developing children than for mothers of children with autism ($P<0.01$). Mean daily folic acid intake >600 mcg during early pregnancy was associated with decreased autism risk (OR 0.62 95% CI, $P = 0.02$). The biggest differences were for women with single nucleotide polymorphisms affecting the function of MTHFR.[39] This single nucleotide polymorphism profoundly negatively impacts the production of methylfolate and methylcobalamin. Maternal metabolic conditions during pregnancy including diabetes, hypertension and obesity are associated with increased autism spectrum disorders and developmental delays in offspring.[40]

Antibiotic Stewardship

Antibiotics are widely overused for illnesses that are actually viral.[41,42] Our experience taking extensive medical histories in more than 400 children with autism is consistent with the published literature that they have significantly more ear infections than neurotypical children and have used significantly more antibiotics.[43] A large study involving 53 general practices in the Netherlands studied improvement in symptoms by day four in children aged 6 to 24 months treated with antibiotics versus not treated. Number needed to treat was 7-8 children with acute otitis media to achieve symptom reduction in one child. They concluded that such a modest improvement does not justify the prescription of antibiotics initially, assuming close follow-up.[44]

Role of Acetaminophen

Pathophysiology in autism includes oxidative stress, neuroinflammation, mitochondrial dysfunction, and abnormalities in glutathione, a crucial detoxifier.[45] Given this biomedical complexity, potential environmental stressors like acetaminophen should command more attention. Although acetaminophen is commonly used in traditional pediatric practices, it can stress the liver and also has less well known metabolic side effects that can increase the risk for developmental and general health problems.

Waring's work on sulphation deficits in children with autism showed that children with autism, unlike age-matched controls, were much less able to form the sulphate conjugate of paracetamol, a step critical to metabolism of this medication, although other metabolic pathways were normal. She also did a small pilot study in which healthy adult volunteers vaccinated against hepatitis B took a therapeutic 1000 mg dose of acetaminophen on day 1 before vaccination on day 7 and also doses on days 8, 10 and 15 after vaccination. Subjects showed severe depression of the phase 2 conjugation reaction of sulphation, only reaching control values a week later.[46] Waring reports that raised cytokine levels in autism have secondary effects on the sulphation of a range of substrates and discusses the vital role of sulphate in the brain and gastrointestinal tract. She also reports that some children with autism have a lack of sulphotransferase activity using PAPS (3'-phosphoadenosine-5'-phosphosulphate) as a co-factor to sulphate tissue components and signal molecules

such as steroids, thyroid hormone and neurotransmitters. This subset of children may react badly to foods containing phenols, catecholamines or flavonoids.[47,48]

The work of James regarding abnormal methylation and transulfuration pathways in autism demonstrates that children with autism have lower levels of methionine, S-adenosyl methionine, homocysteine, cystathionine, cysteine, and glutathione as well as a lower redox ratio of reduced to oxidized glutathione. This metabolic profile is consistent with impaired methylation capacity and increased oxidative stress.[49] She and her colleagues also demonstrated differences in allele frequency and/or significant gene-gene interactions for reduced folate carrier, transcobalamin II, catechol-O-methyltransferase, methylenetetrahydrofolate reductase, and glutathione-S-transferase.[50] Her research also extends into the treatment realm and shows improvement in both oxidative stress and methylation markers after nutritional interventions.[51]

Glutathione is a vital intracellular anti-oxidant and important in detoxification, replenishment of gut epithelium, T cell immunity, and mitochondrial function.[52] Schultz has raised concerns about the relationship between acetaminophen and autism,[54] but others have been critical of his original paper.[55] Schultz's studies in mouse cortical neurons showed loss of mouse cortical neuron viability at 24 hours compared to controls when exposed to p-aminophenol at 1-100 micrograms per milliliter; thus, he urges caution in recommending acetaminophen to children with brain injury.[56] A review by Good took this a step further and questioned whether acetaminophen was a factor in the autism epidemic.[57]

The Vaccine Controversy

The CDC and AAP have issued statements that vaccines are not associated with the risk of autism and that there are epidemiologic studies suggesting no causal role.[58-60] Under immunization as a result of parental perceptions of vaccine safety remains a primary concern of the American Academy of Pediatrics.[61] As a result, primary care physicians are taught ways to address parents' vaccine concerns, take opportunities to vaccinate, and use recall methods to catch patients up on vaccines.[62] Despite having one of the most aggressive vaccination policies in the developed world, specifying 22 vaccine doses for a total of 12 diseases by 1 year of age,[63] the United States had higher infant mortality rates in 2009 than 33 other nations.[64]

The author has visited 12 of the countries with a lower infant mortality rate than the United States to lecture about medical problems in children with autism, mentor clinicians, and collaborate on research about patients with autism. By rank in infant mortality, they are: Sweden 2, Japan 3, Finland 6, Norway 7, Czech Republic 10, Switzerland 12, Denmark 18, Australia 23, the United Kingdom 25, New Zealand 26, Canada 28, and Italy 31. Singapore, Sweden, and Japan have infant mortality rates below 2.8; the United States' rate is 6.22. Clinicians and scientists in other countries often express surprise at the number of vaccinations recommended in the United States. In 2009, five of the 33 nations with the lowest infant mortality rates required 12 vaccine doses, the least amount, while the United States required the most vaccine doses. Using linear regression analysis of unweighted mean infant mortality rates, Miller calculated a statistically significant high correlation between increasing number of vaccine doses and increasing infant mortality rates ($r = 0.992$ p value 0.0009).[64] Correlation does not equal causation. But since the United States spends more money per capita on medical care than the rest of the industrialized world,[65] it seems prudent to examine all possible contributions to the relatively poor health of our most vulnerable citizens - children.

The controversy regarding accepting parent reports about vaccine reactions and subsequent regression remains, but it is increasingly difficult to ignore. Many histories of children with autism involve a seemingly well child developing a high fever, seizure, or neurological deterioration within 24 hours of vaccination and being told by emergency room personnel or their primary care doctors that the vaccine could not have been related to their child's symptoms. It is prudent to remember that medications and medical interventions including vaccination can cause side effects, that short term vaccine reactions are tracked, and that a federal program exists to provide compensation for children who suffer significant reactions.

Skepticism about parental reports of vaccine reactions is reminiscent of the skepticism with which some physicians regarded parents who reported their child regressed into autism, since autism was thought to be prenatal and therefore present from birth. Parents were vindicated by a study in which before and after videos were viewed and scored by blinded observers who quantified differences and confirmed the existence of regressive autism.[66]

Universal hepatitis B vaccine at birth was initially recommended in order to insure that babies whose mothers were hepatitis B positive or had unknown hepatitis B status were not missed. Hepatitis B vaccine at birth has been associated with an increased odds ratio of autism in male infants. In one study, U.S. male neonates vaccinated with hepatitis B vaccine prior to 1999 had a threefold higher risk for autism compared to boys not vaccinated as neonates. Nonwhite boys bore a greater risk. Some research has documented waning immunity and the need for booster vaccines 15 years after neonatal vaccination.[67]

There has been a protracted controversy over the role of MMR in autism.[68,69] A review of the medical literature review reveals some concerns about giving a live viral vaccine during suboptimal health. Research from Johns Hopkins demonstrated that infection of B lymphocytes with MMR vaccine induced IgE class switching.[70]

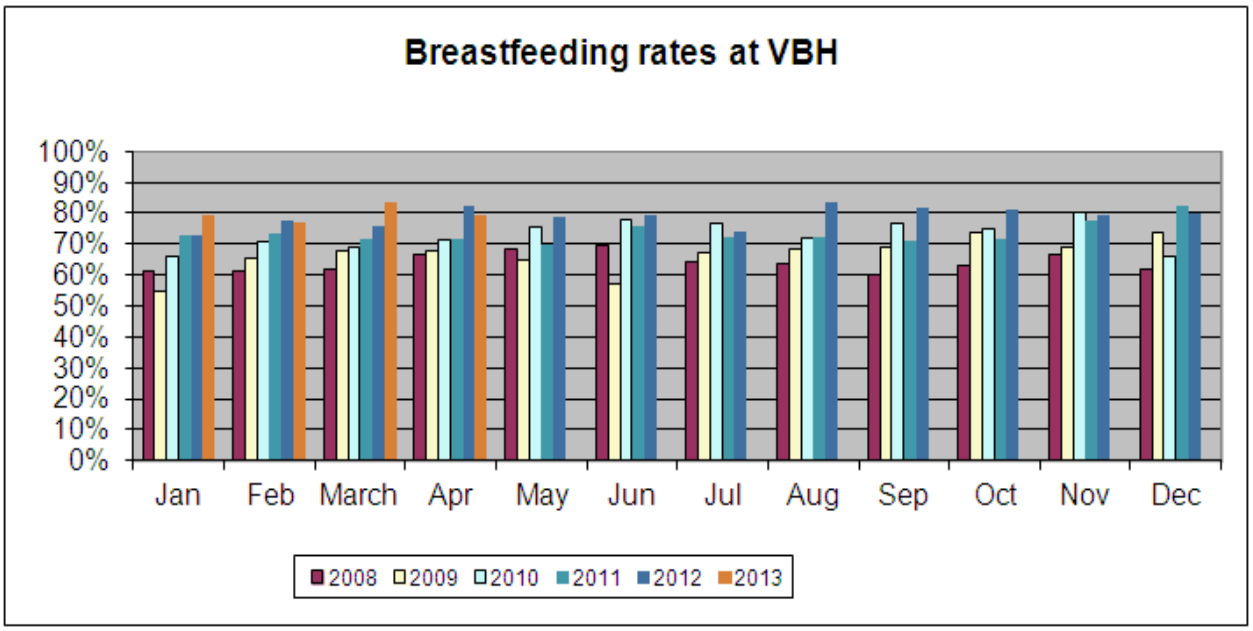

Figure 1. Local hospital rates of initiation of breastfeeding.

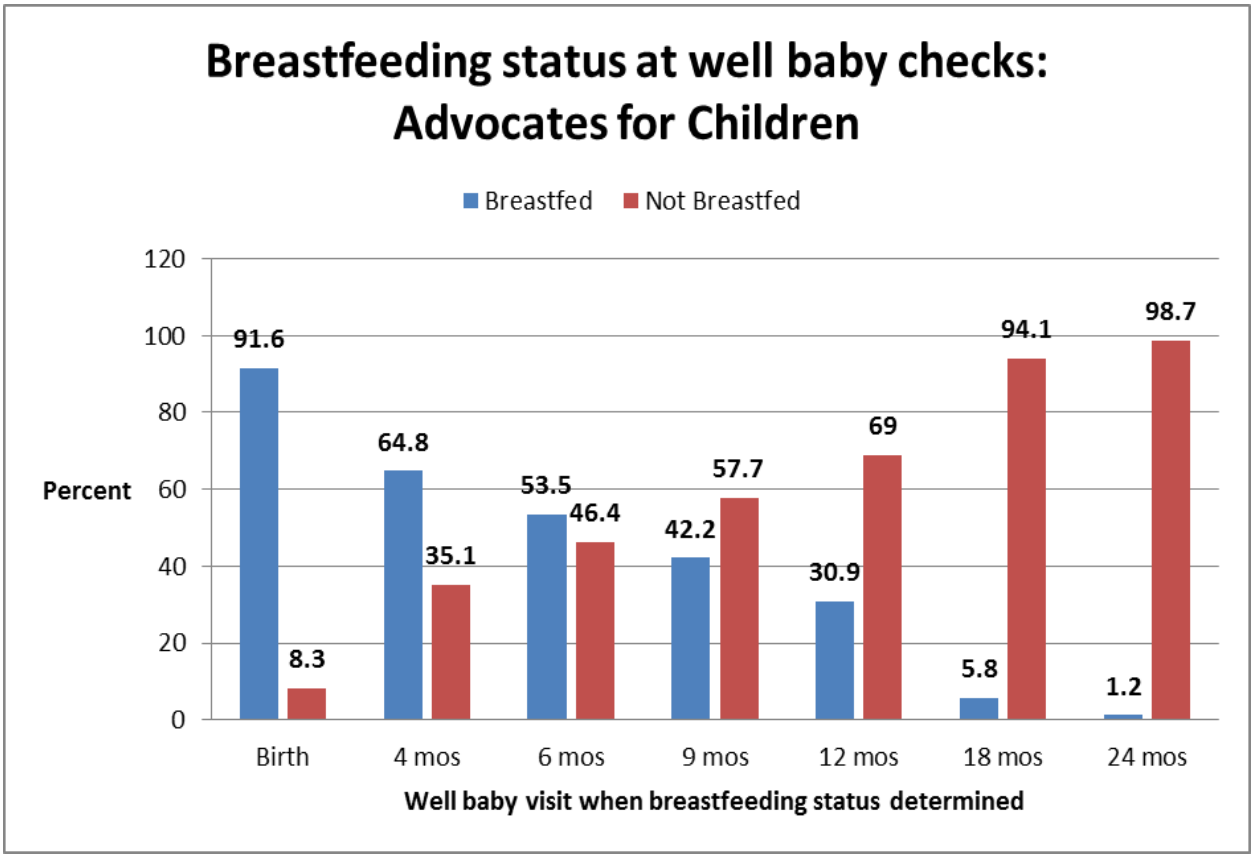

Figure 2. Advocates for Children initiation and duration of breastfeeding.

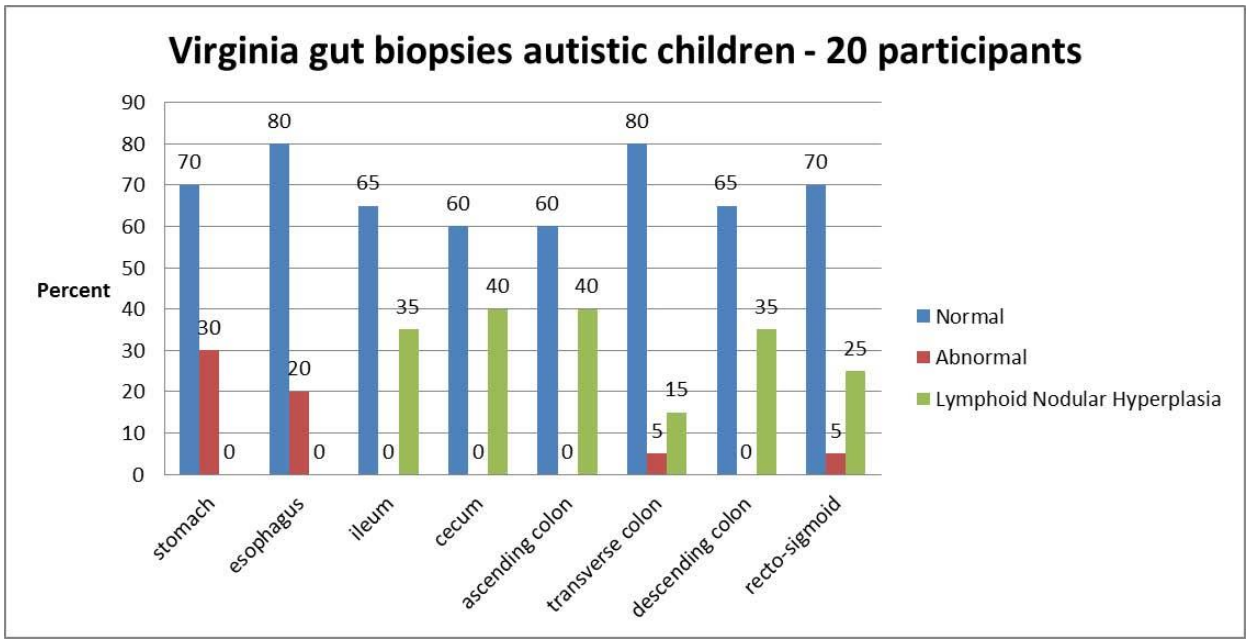

Figure 3. Gut biopsies read by pathologist blinded to autistic or neurotypical status.

METHODS

Patient Selection

Inclusion criteria were: 1**)** all general pediatric patients born in 2005 or later; 2) presented for well child care prior to 2 months of birth and 3) followed until at least the age of 2 years and 2 months. Totally 294 patients qualified for the inclusion criteria and have been selected in the current research.

Data Collection

All the patients have been treated and examined utilizing the same well child procedures. The electronic records for all infants cared for in our general pediatrics practice since July 1, 2005 who visited our office from prior to 2 months of age (usually in the first 3-5 days after birth) to at least the age of 2 years and 2 months have been reviewed and examined, since the age range would provide ample opportunity to observe symptoms of autism. Their developmental milestones in the domains of gross and fine motor, speech and language, and social behaviors at each of 11 well child visits in the first 2 years of life have been recorded. The medical record is marked for any child who does not meet milestones. No new cases of autism in our general pediatric practice since it was established in 2000 have been recorded; the current research reports on the cohort born in 2005 or after. CDC prevalence disease data and other published data have been utilized in analysis of this research.

RESULTS

In the current research, there are no new cases of autism out of the 294 cases recognized and recorded, resulting in 0% prevalence of ASD. Based on the CDC background risk of autism of 1 in 50 for the cohort born around 2005 we would expect to have about 6 new cases of autism in our practice. We calculated our statistics using a Chi-squared test with 1 degree of freedom. Using the CDC autism rate of 1 in 50 reported in 2013 (but based on surveys of eight year old children), the expected rate for our 294 patients starting in 2005 would be 5.88 children with autism. Zero new cases of autism would occur by chance 1.4% of the time (p-value 0.014, significant at 0.05).

Examination of family histories identified 6 males with an older autistic sibling and 6 females with an older autistic sibling. Based on a recurrence risk for autism of 26.2% for males with an autistic sibling and 9.1% for females with an autistic sibling[71] we would have expected 1.5 males with autism and 0.5 females (sic). Our sample size was small and we did not find statistical significance at 0.05 for no new cases of autism in siblings. For males, there was a 14.5% chance that our results are simply due to chance. For females, there was a 43.8% chance our results are simply due to chance. The significance of our clinical experience and results will be discussed in the following sections.

DISCUSSION

The author first noticed what seemed to be an increase in neurodevelopmental disorders clinically in the mid 1990's; several of her patients regressed into autism during that time. Several of those patients who developed autism in the 1990's are still followed in the practice today. One is a 15 year old male who regressed into autism with the development of chronic diarrhea and loss of language milestones temporally associated with the MMR vaccine. He has not developed much language and now has seizures. Another is a 13 year old female who was reported to have language regression which the parents thought was related to immunizations. She receives special education, occupational therapy and speech therapy and has problems with obsessive compulsive behavior and attention.

In 2000, the author established Advocates for Children to care for children in Central Virginia whose complicated neurodevelopmental and behavioral problems were difficult to address in a traditional, busy office setting. In 2004, she became Medical Director of the Autism Research Institute, which has historically been on the cutting edge of research into medical problems of children with autism, and attended more than 1500 hours of think tanks and lectures that featured emerging evidence about the anatomy, pathophysiology, immunology and biochemistry of autism spectrum disorders. She has listened carefully to the clinical histories provided by the parents of more than 500 children with autism here and abroad. Armed with a better understanding of the science of autism, she incorporated strategies into her general pediatric practice that were designed to minimize potentially modifiable risks of developing autism.

Strategies Utilized at Advocates for Children that Might Impact Autism Prevention

1) Minimizing environmental toxicant exposures

Lynchburg, Virginia, the location of the pediatric practices considered here, is one of 80 cities in the United States that received an "A" rating from the American Lung Association for its air quality, according to the local newspaper The News and Advance (May 8, 2013). Located at the foothills of the Blue Ridge Mountains Lynchburg is very densely populated with trees. In Lynchburg, there may be relatively good air quality and lack of proximity to industrial emissions, but children with autism are like "canaries in the coal mine" and show us with their neurobiological problems the impact environmental toxicants can have on a vulnerable population. We recommend strategies such as avoidance of pesticides and herbicides during pregnancy, feeding children and pregnant women a whole food diet that is as organic as possible, and using less toxic "green" cleaning products in the home in hopes of preventing some cases of neurodevelopmental disorders and in the knowledge that it seems to be safe and reasonable anticipatory guidance for all children.

2) Maximizing breastfeeding prevalence

Our practice is committed to devoting resources to increase success rates for prolonged breastfeeding. Two of our five staff members are lactation educators. Our patients initiated breastfeeding at a rate of 91.6%, a rate much higher than the rate of initiation of breastfeeding at discharge from our local hospital, which varied monthly between 55% and 80% during 2008, 2009 and 2010 increasing over time with adopting of breastfeeding support strategies **(Figure 1**). In 239 of our primary care patients surveyed, only 20 (9.13%) never breastfed, 74 (30.9%) breastfed longer than 1 year and 5% breastfed longer than 18 months (**Figure 2**).

Our clinical experience with the frequency and intractability of gastrointestinal symptoms in our patients with autism and our research data based on our blinded study of gut biopsies in children with autism have renewed our commitment to promote breastfeeding for beneficial effects on the gut and microbiome and to be interested in the potential value of probiotics for prevention.

3) Recommending probiotics

Due to the importance of gut flora in the first few years of life, our practice has a very low threshold for initiating probiotics in infancy. We recommend probiotics for any baby with the following history or clinical findings: 1) antibiotics during delivery, in the perinatal period, in infancy or toddlerhood 2) eczema, wheezing, or chronic rhinitis in the first year of life 3) chronic diarrhea or constipation 4) gut motility problems and 5) family history of allergy, asthma, eczema or autoimmunity.

4) Nutritional counseling

Our practice employs a full time nutritionist. We rarely have the opportunity to counsel pregnant mothers pre-conceptually before their first infant, but we take every opportunity once mothers are coming to our practice to recommend the following safe and reasonable strategies prior to conception and during pregnancy: 1) pre-natal vitamins containing folinic acid, ideally in the active form such as 5 methyl- tetrahydrofolate, 2) eating locally grown organic fruits, vegetables and protein as much as possible 3) avoiding processed foods, preservatives, monosodium glutamate, aspartame, nitrites and 4) avoiding mercury containing fish.

5) Antibiotic stewardship

We limit our use of antibiotics to certain bacterial illnesses and avoid over diagnosing bacterial otitis media. We diagnose otitis media when the following criteria are met: extreme erythema of the tympanic membrane associated with distortion of landmarks, a definite effusion, or poor mobility of the drum. We explain that most ear infections are viral and do not require antibiotics, educating families as to the impact of antibiotics systemically, especially on bowel flora. When we do use antibiotics, we often provide a prescription for the parent to fill in a few days after the initial visit only if the patient develops signs of high fever or toxicity.[72]

We reject the approach of using antibiotics "just to be safe" and share the potential side effects of antibiotics with patients. Even though physicians may perceive it is quicker to write for an antibiotic than to explain why the illness appears viral, we have chosen to educate families about the difference between viral and bacterial illness, the role of fever in the inflammatory response, and innate healing measures.[73,74] When we do prescribe antibiotics, we recommend broad spectrum probiotics to be taken at a time away from the antibiotic doses. We discourage parents from relying on the inadequate doses and strains of probiotics in commercial yogurt.[75]

6) Minimizing use of acetaminophen

We are cautious in our use of acetaminophen because it

has the potential to reduce glutathione stores. In other Central Virginia--based practices, acetaminophen is often recommended for the fever and irritability that is often associated with vaccinations. In our practice we specifically recommend against acetaminophen after vaccines in favor of tepid baths with evaporation to cool fevers. If this is unsuccessful, parents are advised to use ibuprofen 10 mg/kg sparingly for fussiness or fever control. We also provide patient education about the role of fever as part of the inflammatory response. We argue that "fever is your friend" informing the parent that the child may be ill or having an immunologic response to a vaccine, not an enemy who needs to be eradicated with antipyretics even at minimal elevations.

7) Allowing/implementing a modified vaccine schedule

Years of clinical experience and observation, emerging research, and thorough history taking from families with autistic children have helped shape our vaccine strategies at Advocates for Children. While these strategies differ from the United States Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) guidelines, our schedule complies with Commonwealth of Virginia requirements by kindergarten entrance.

We are concerned that epidemiology may be too blunt a tool to determine all risks for subsets of the population who may be more vulnerable to vaccine reactions due to their unique genetic predispositions and biochemistry. We are concerned about the emerging evidence about the association between autism and mitochondrial dysfunction, and what implications mitochondrial impairment might have for giving vaccines to genetically vulnerable or acutely ill children with increased oxidative stress.[76-81]

Clinical histories from our patients are considered in addition to research data. We consulted on a patient who developed seizures after a DPT vaccine, had to be airlifted to a major medical center, then regressed in language, social skills, and behavior and was diagnosed with autism. After visiting an estimated 30 specialists along the east coast, he eventually died during the night, presumably from an intractable seizure. The published accounts of a girl who experienced a devastating autistic regression after receiving multiple vaccines at once[82] and the developmentally precocious four year old child of a pediatrician who had evidence of immune dysregulation in retrospect prior to multiple vaccines on the same day followed by a regression into severe autism[83] have triggered changes in our decision making processes when confronted with children who need to catch up on vaccines.

Based on the author's best efforts at integrating the data in the medical literature with the histories of families, and trying to make informed judgments about the risks of vaccine preventable illness and benefits of immunization within the context of human imperfection, the following modified vaccine schedule was developed (**Table 2**). In addition, we only immunize when children are free of acute illness. As noted above, despite these modifications our schedule complies with Commonwealth of Virginia requirements for school entry.

In our practice, we have the advantage of knowing hepatitis B status of our mothers prenatally and can immunize infants of mothers who are hepatitis B positive selectively. Since we immunize before kindergarten instead of at birth, our patients may be less at less risk for hepatitis B than infants immunized at birth if they start sexual activity in their adolescent years without benefit of booster doses of hepatitis B vaccine.

Careful histories from parents of children with autism have often revealed some variant of the following story: a neurotypical child was given MMR vaccine at the time of acute or chronic diarrhea, or during an acute infection (usually otitis media) or after receiving antibiotics (often amoxicillin-clavulanate). Within a week, they developed gastrointestinal symptoms and experienced a behavioral regression. In approximately ten years of routinely delaying MMR vaccines from one to two years of age (with exceptions for international travel, acute exposures to active cases, and parents who prefer earlier vaccination with MMR), we are not aware of any of our patients developing measles, mumps, or rubella. However, we do benefit from herd immunity because the two large group pediatric practices and the vast majority of family practice groups in our area following the standard recommendations for vaccines.

Our practice of giving two vaccines at a time (one in each leg) has not been supported in the literature but allows us to better track local reactions to the specific vaccine and identify other reactions more specifically to the suspected vaccine. Rationales for giving multiple vaccines at once and combination vaccines include saving the baby/parent pain, better efficiency, and better compliance.[84] Our patients have expressed a willingness to return in 1 month to get the other 2 vaccines at a nursing only visit, so the primary immunization series for Hib, IPV, DTAP, or PCV is not significantly delayed.

The horrifying increase in the numbers of children with neurodevelopmental problems happened on our watch. It was frustrating for me and my colleagues to see more children with autism while the debate over whether the autism epidemic was real, whether parents could be trusted to give histories about their own children, and whether there really was a regressive sub-type of autism went on for years. There have been missed opportunities for treatment and possibly prevention.

The search for "the" autism gene(s) has evolved to the recognition that as many as a thousand or more genes may be involved in the genesis of the behavioral constellation of

symptoms we call autism. Awareness of strong family histories of autoimmunity[85-87] and evidence of autoantibodies in family members,[88-92] associations with metabolic polymorphisms affecting methylation[93-95] and transulfuration biochemistry affecting glutathione metabolism,[96] as well as other research about additional biomarkers, familial risk factors,[97,98] changes in gene expression,[99] and environmental genomics[100] have amplified our understanding so we can recommend nutritional, metabolic and immunologic interventions that can alter gene expression in at risk children and potentially alter expression of autistic symptoms.

Recent reports of children recovering from autism[101] mandate that we be open minded about the recovery expectations of those affected. Dietary interventions were associated with improvement in one child's Childhood Autism Rating Scale score from 49 to 17 representing a change from severe autism to nonautistic and accompanied by a 70 point increase in her IQ.[83] Given this information, treatment strategies should include nutrition counseling in addition to medical management.

We are aware of several other integrative pediatric practices who report a lower than expected prevalence of autism and are continuing to collect data and accumulate more patients. We look forward to collaborating with other researchers who have the statistical and data mining experience to learn more from the rich clinical documentation captured in these records.

Patients report choosing our practice for several reasons: our modified vaccine schedule, our interest in underlying medical reasons for differences in behavior and academic performance, our staff's role in patient education about nutrition and environment, our focus on individual health while being mindful of public health, our ability to support breastfeeding, and our reputation for listening carefully and spending extra time with our patients. As medicine continues to become more complex, physicians have a responsibility to address the uniqueness of the individual patient in the face of developing public health recommendations, practice guidelines, and clinical algorithms. Although epidemiological research is very important to identify effects on populations, epidemiology is often too blunt a tool to detect effects on subsets of individuals.

Limitations

Frankly, it would be difficult to quantify the individual effects of any of the strategies that were implemented, as many were phased in over time as the evidence emerged, without prospective tracking measures. It is impossible to quantify the effects of our recommendations on practices families actually followed. It is difficult to control for all confounding variables and for the role of self-selection in families who chose to enroll in a solo integrated pediatric practice versus more traditional pediatric and family medicine practices locally. The clinical experience reported was based on one clinician's practice experience and therefore the numbers are relatively small.

Our practice has changed electronic records four times in the past 13 years, so it was difficult to insure adequate data capture prior to 2005 with our current data mining techniques. Therefore, we report only a subset of our clinical experience. In addition, although the number of children in this cohort who moved away was quite small, we could not quantify that number with absolute certainty, so it is possible some of those children developed autism and we would not know. We followed our patients for at least two years and 2 months to allow for the signs and symptoms of autism to emerge before the trained eyes of the physician, autism coordinator, and nurses, but it is possible that some 2 year olds may develop autism in the years to come. After our paper went to reviewers, we referred a 16 month old child to Early Intervention for expressive language delay and suspicion of an autism spectrum disorder. His multi-disciplinary evaluation confirmed the expressive language delay, but he was not diagnosed with autism. If he had been or is diagnosed in the future, our findings would still be statistically significant, but just barely ($p = 0.042$).

Table 2. Modified vaccine schedule Advocates for Children**:**Well Child Visit and Immunization Recommendations.

1 month	**Well child visit**
2 months	**Well child visit** – HIB, Polio (IPV)
3 months	DTaP, Prevnar
4 months	**Well child visit** – HIB, IPV
5 months	DTaP, Prevnar
6 months	**Well child visit** – HIB, IPV
7 months	DTaP, Prevnar
8 months	*No visit or vaccines unless need to catch up
9 months	**Well child visit** – no vaccines
12 months	**Well child visit** – Discuss varicella with physician
15 months	**Well child visit** – HIB
18 months	**Well child visit** – DTaP, Prevnar
2 years	**Well child visit** – MMR; discuss Hep B with physician
3 years	**Well child visit**
4 years	**Well child visit**
5 years	Kindergarten Physical – DTaP, IPV, MMR, varicella (these can be given any time after age 4)

CONCLUSION

There was a trend toward lower prevalence of new cases of autism in the author's integrative medicine practice after 2005, with no new cases of autism out of 294 children (133 females and 161 males) born between July 2005 and March of 2011, and no new cases of autism out of an as yet undetermined number of children born between 2000 and 2005. This is in contrast to her traditional practice during the 1990's, in which several patients developed autism in a field of patients a less than one-quarter the volume of patients in the integrative practice.

Collaborations between epidemiologists, basic research scientists, clinicians, and parents as practiced in the Autism Research Institute model should be more widely available to clinicians in practice. We all have things to teach and learn from one another. We report our clinical experience in hopes that it will spark fruitful discussions between researchers and practicing clinicians and inspire prospective research in clinical settings to see if our hypothesis – that integrative pediatric practices might impact autism prevalence - can be confirmed or disproven.

Dr. McLemore Birdsong, a former chair of pediatrics for which an annual pediatric conference at the University of Virginia was named, repeatedly told house staff he trained: "look at the child and listen to the mama." At Advocates for Children and Advocates for Families, we have tried to do just that when caring for this generation of children in hopes that the next generation may be much less affected by autism and healthier overall.

CONFLICT OF INTEREST

None.

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