



Medical conditions in autism and events associated with the initial onset of autism

JK Kern^{1,2*}, DA Geier¹, LK Sykes³, KG Homme⁴, MR Geier¹

Abstract

Introduction

This study examined whether autism spectrum disorder (ASD) is associated with certain medical conditions. Certain psychiatric disorders were also examined. In addition, this study examined events prior to or associated with the onset of symptoms.

Materials and methods

The study used an online survey of developmental and medical information from parents of 83 children with a diagnosis of autism, pervasive developmental disorder (PDD), or ASD.

Results

Reportedly, in the study group of children, 74% had food allergies, 51% had constipation, 26% had diarrhoea, 17% had irritable/inflammatory bowel disease, 12% had Clostridia infection in the gut, 51% had environmental allergies, 14% had asthma, 12% had seizures, 28% had insomnia, and 23% had eczema. For co-morbid psychiatric diagnoses, 45% had attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD); 17% had obsessive compulsive disorder; and, 18% had anxiety disorder. Acute physical symptoms associated with the onset of autism were fever (24%) and rash (22%). Events associated with the onset of autism were vaccinations (54%), a series of infections (52%), a viral infection (30%), a bacterial infection (19%), an allergic reaction

(24%), and bronchitis (16%). Regression was reported in 55% of the children.

Conclusion

The findings suggest that several medical and psychiatric conditions are frequently observed in children with an ASD diagnosis. In addition, certain medical events, including vaccinations and infections, are often observed by parents to be associated with the onset of ASD.

Introduction

Autism spectrum disorder (ASD) is defined by qualitative impairments in social interaction and communication, and restricted and stereotyped patterns of behaviour, interests, and activities.¹ Although an ASD diagnosis is defined by these core features, recent investigations have described many medical and behavioural co-morbid conditions associated with ASD.² For example, children diagnosed with an ASD are more likely to have headaches/migraines, eczema, respiratory and food allergies, and physician visits, and are more likely to be taking prescription medication than children without autism.^{3,4}

For example, Gurney et al.³ compared parent-reported prevalence of health conditions and healthcare use between children with and without autism in the 2003 to 2004 United States (US) National Survey of Children's Health from more than 100,000 parents. They found that children with autism had significantly higher mean physician visits over 12 months for preventive care, nonemergency care, and hospital emergency care.

Some examples of medical conditions commonly found in are seizures, gastrointestinal symptoms, immune dysfunction (frequent infections), and autoimmune dysfunction.

For example, the reported rate of seizures in autism is 20% to 38% of patients.^{5,6} Epileptiform abnormalities on electroencephalography (EEG) are present in 10.3% to 72.4% of patients.^{5,6} Furthermore, an increased severity of autistic symptoms appears to be associated with a higher likelihood of epileptiform abnormalities.⁷

Gastrointestinal (GI) symptoms are also common. Studies have found that up to 92% of children with ASD have GI symptoms,^{8,9,10} and that GI symptoms are positively correlated with autism symptoms (i.e., the worse the GI symptoms, the worse the autism symptoms).¹¹ GI symptoms include (but are not limited to): chronic constipation and/or diarrhea,² abnormal gut flora,¹² increased intestinal permeability or "leaky gut",¹³ and GI inflammation.¹⁴ For example, Adams et al.¹¹ examined the GI status of 58 children with ASD and 39 healthy typical children of similar ages using the GI Severity Index (6-GSI) questionnaire and the Autism Treatment Evaluation Checklist (ATEC). The results showed that GI symptoms were strongly correlated with the severity of ASD.

Immune dysfunction is also reported in ASD. For example, Atladóttir et al.¹⁵ investigated the association between hospitalization for infection in the perinatal/neonatal period or childhood and a diagnosis of ASD. They conducted a population-based cohort study of all children born in Denmark from January 1, 1980, through December 31, 2002, comprising a total of 1,418,152 children. The authors found that children admitted to the hospital for any infectious disease displayed an increased rate of ASD diagnoses. Children with ASD also have higher rates and greater persistency of ear infections.^{16,17,18}

*Corresponding author
Email: jkern@dfwair.net

¹ Institute of Chronic Illnesses, Inc., Silver Spring, USA

² University of Texas Southwestern Medical Center, Dallas, USA

³ CoMeD, Inc., Silver Spring, USA

⁴ International Academy of Oral Medicine and Toxicology, ChampionsGate, USA

Studies also report autoimmunity in ASD.^{19,20} For example, a study by Classen, examined the association between prevalence of autism in children and the incidence of type 1 diabetes or type 2 diabetes in children by performing Medline and Google searches in late 2010 to find a country where there was simultaneous data on the incidence or prevalence of type 1 diabetes, type 2 diabetes and autism. The study found a statistically significant positive association between ASD and type 1 diabetes.²¹ The author indicated that the aetiologies of both epidemics are likely to be related.

Brain-specific auto-antibodies are found in autistic children. For example, a study by Mostafa and Al-Ayadhi²² examined serum levels of both anti-myelin basic protein (anti-MBP) and anti-myelin associated glycoprotein (anti-MAG), which are brain-specific auto-antibodies, in 42 autistic children in comparison to 42 healthy, matched controls. They found that 78.5% of autistic children had increased serum levels of both anti-MBP and/or anti-MAG auto-antibodies. They also found that the children with autism with allergic manifestations (bronchial asthma, atopic dermatitis and/or allergic rhinitis) had significantly higher serum levels of anti-MBP and anti-MAG auto-antibodies than those without these manifestations.

Other symptoms commonly reported in ASD include sleep issues;^{23,24} eating issues;²⁴ hyperactivity or lethargy;²⁵ self-injury, aggressiveness, and destructive behavior;²⁶ sensory processing abnormalities;^{27,28} anxiety or abnormal levels of fear;²⁹ and obsessive-compulsive (OC) behaviour.³⁰

The purpose of this study was primarily to examine medical symptoms in ASD. The study also examined some psychiatric comorbidities. In addition, the study examined whether the onset of the

Table 1: A summary of the participants.

Descriptive Information	Overall (n = 83)
Sex / Age	
Male / Female (ratio)	71 / 12 (5.9:1)
Average Age in Years (range)	7.5 (2-25)
Average Birth Year (range)	2003 (1987 - 2010)
Race (n)	
Caucasian	47.0% (39)
Asian	8.4% (7)
African American	4.8% (4)
Hispanic	39.8% (33)
Autistic Disorder Characteristics	
Average Onset in Months (range)	18.4 (0-108)
Average ATEC Score (range)	69.0 (15 - 159)
Autism (n)	53.0% (44)
ASD (n)	25.3% (21)
PDD NOS (n)	21.7% (18)
Regression (n)	55.4% (46)
Co-morbid Psychiatric Diagnoses	
ADD/ADHD (n)	44.6% (37)
OCD (n)	16.9% (14)
AD (n)	18.1% (15)

Acronyms: ASD = Autism Spectrum Disorder other than "Autism"; ADD = Attention Deficit Disorder; ADHD = Attention Deficit Hyperactivity Disorder; OCD = Obsessive-compulsive Disorder; AD = Anxiety Disorder

ASD symptoms was associated with other medical symptoms or events. For the purposes of this study, ASD includes pervasive developmental disorder (PDD) as well as autism.

Materials and methods

Ethics: IRB Approval and Consent

The study received Institutional Review Board (IRB) approval from Liberty IRB, Inc. (Deland, Florida), which has full accreditation from the

Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP). All studies complied with the American Psychological Association ethical standards in the treatment of participants and in obtaining informed consent. All parents signed a consent and Health Insurance Portability and Accountability Act (HIPAA) form and all received a copy of the signed form.

Table 2: A list of the study questions.

No	Study Question
1	At what age did your child show sign and symptoms of a developmental disorder?
2	Was the onset of symptoms and signs preceded by or associated with anything?
3	What developmental disorder(s) is your child diagnosed with?
4	If your child regressed and lost previously acquired skills, what skills were lost?
5	What medical conditions does your child have?
6	What allergies does your child have?
7	What kind of bowel problems does your child have?
8	What medications does your child take?
9	What supplements does your child take?
10	What treatments does your child receive?
11	What antivirals does your child take?
12	What vaccines has our child received?

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Table 3: Other medical conditions among the participants (n=83) and the rates of those conditions on the general population of US children.

Medical Conditions	ASD children in the study n (%)	Children in the general population % (reference)
Food allergies	61 (73.5%)	5.1% (33)
Environmental allergies	42 (50.6%)	17.4% (33)
Asthma	12 (14.5%)	10% (33)
Seizures	10 (12.0%)	0.1% (34)
Irritable/inflammatory bowel disease	14 (16.9%)	10% (35)
Constipation	42 (50.6%)	22.6% (36)
Diarrhea	22 (26.5%)	8.2% (37)
Clostridia infection in the gut	10 (12.0%)	12% (40)
Insomnia	23 (27.7%)	15-25% (38)
Eczema	19 (22.9%)	10% (39)

Study Design

The study was a cross-sectional evaluation of data collected from parents of 83 children with a diagnosis of autism, ASD, or PDD who participated in an online survey. The children in the study resided in the US and the Commonwealth of Puerto Rico (an unincorporated territory of the US that is included in US health statistics). Information about each child's formal diagnosis was obtained and the child's parents completed an Autism Treatment Evaluation Checklist (ATEC) that provides a quantifiable measure of severity.^{31,32} All information was obtained from the parents regardless of the child's age. A qualitative examination of the available information on the children was conducted.

Participants

The 83 children who participated were diagnosed with autism, ASD, or PDD. Each child had been previously diagnosed by a professional, and a medical record of proof of diagnosis was obtained. The study was designed to exclude children with foetal alcohol or a drug-based syndrome or a genetic basis for their diagnosis, such as Fragile X disorder, tuberous sclerosis, phenylketonuria (PKU), Lesch-Nyhan syndrome, or Down's syndrome. Also excluded were children of mothers with a history of maternal illicit drug use.

Table 1 summarizes the demographic information for the study participants,

including age, race, gender, and year of birth.

Description of Online Survey

The study survey, available on a website, was titled, "Autism/Immune System Medical Disease Registry." The purpose of the survey was to gather basic medical information on children with ASD, particularly medical information related to immune system function. The website described the study, the inclusion/exclusion criteria, and how to participate. Prior to their participation, no information was provided to the parents about the specific questions that would be asked.

Parents were first required to complete the basic contact information and to sign and return a consent and HIPAA form. Also, a copy of the child's formal diagnosis was required. Once these items were received, the parent was given a user name and password to enter the study website and answer the survey. Table 2 lists the twelve questions asked in the survey. The questions were based on the autism literature and anecdotal reports of medical issues of concern to parents of children with ASD. The survey provided a complete and broad range of possible answers from which the parents could choose. In addition, a text box allowed for comments or additional answers. The responses were automatically incorporated into Excel files.

The website was not affiliated with the study investigators. Parents learned about the study through social groups, Yahoo! groups and Facebook. In addition, some parents were recruited at lectures on autism given in the US and Puerto Rico by the author of the website. The survey questions were written by the author of the website, who consulted with Dr. Kern.

Autism Treatment Evaluation Checklist (ATEC)

To participate in the study, the participants' parent(s) completed an ATEC form developed by the Autism Research Institute.³¹ The ATEC is a one-page form designed to be completed by parents, teachers, or others who see the individual's behaviour on a regular basis.³¹ The ATEC consists of four subtest scales: Scale I.

Speech/Language/Communication (14 items – scores can range from 0-28), Scale II. Sociability (20 items – scores can range from 0-40), Scale III. Sensory/Cognitive Awareness (18 items – scores can range from 0-36), and Scale IV.

Health/Physical/Behaviour (25 items – scores can range from 0-75). The four subscale scores can be used to calculate a total score (total scores can range from 0-180). The scores are weighted according to the response and the corresponding subscale. The higher the subscale and total score, the more impaired the participant. This measure was used to ascertain ASD symptom severity.

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Table 4: Factors reported to be associated with onset of autism symptoms (n=83).

Preceding Events	Percent (n)	Preceding Events, Sub-category	Percent (n) for the Sub-category
Unknown	12.0% (10)	NA	NA
Viral infection	30.1% (25)	NA	NA
Bacterial infection	19.3% (16)	NA	NA
Series of infections	51.8% (43)	Ear	22.8% (19)
		GI	15.7% (13)
		Other	13.3% (11)
Fever	24.1% (20)	NA	NA
Rash	21.7% (18)	NA	NA
Allergic reaction	24.1% (20)	NA	NA
Bronchitis	15.7% (13)	NA	NA
Seizures	3.6% (3)	NA	NA
Vaccination	54.2% (45)	Multiple vaccine inoculations given at the same time	33.7% (28)
		MMR inoculation alone	13.2% (11)
		Influenza vaccine inoculation alone	2.4% (2)
		DTaP inoculation alone	1.2% (1)
		Rotavirus vaccine inoculation alone	2.4% (2)
		Hepatitis B vaccine inoculation alone	1.2% (1)

Results

Based on the information provided by the parents of the study participants, as shown in table 3, 74% had food allergies, 51% had environmental allergies, 14% had asthma, 12% had seizures, 17% had irritable/inflammatory bowel disease, 51% had constipation, 26% had diarrhoea, 12% had a Clostridia infection in the gut, 28% had insomnia, 23% had eczema. In addition, 45% had attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD); 17% had obsessive compulsive disorder (OCD); and 18% had anxiety disorder, as shown in table 1.

Further, according to the parents, 55% of the children regressed, losing previously acquired skills and abilities (Table 1). The skills most frequently reported to be lost were speech, eye contact, and socialization; and to lesser extent, fine and gross motor skills.

To the question of factors that preceded or were associated with the onset of autism (Table 4), the physical symptoms most commonly reported were fever (24%) and rash (22%). In regard to events that were noted to be associated with the onset of autism,

54% reported vaccination, 52% reported a series of infections (GI, ear, or other), 30% reported viral infection, 19% reported bacterial infection, 24% reported an allergic reaction, 16% reported bronchitis, and 12% reported "unknown".

Discussion

Many serious medical symptoms were reported by study participants. Although the sample size in this study is small and a larger sample size may more accurately reflect the conditions of the autistic population at large, most of the findings in this study are relatively consistent with other studies with large sample sizes.³ It is still interesting to note, however, the difference in the rates of problems reported by the parents of children with ASD in this study as compared to the rates in the general public.

Table 3 compares the rates of medical symptoms for the study group versus the general population in the US. For example, the reported rate for seizures in the study group is about one hundred times higher than that for the general population. The reported rate for food allergies is about fourteen times higher. The reported rates for environmental

allergies, asthma, irritable/inflammatory bowel disease, constipation, diarrhea, and eczema are also significantly higher in the study group than in the general population. Only the rates of Clostridia gut infection and insomnia are about the same in both the study group as the general population.

For the co-morbid psychiatric conditions shown in table 1, in this study group the rate of 45% for ADHD or ADD is about six times higher than the rate of 7.8% for the general population.⁴¹ Of similar magnitude, the rate of 17% for obsessive compulsive disorder (OCD) in the study group is about five to eight times higher than the rate of 2-3% for the general population.⁴² Finally, the rate of 18% for anxiety disorder in the study group is about twice the rate of 8-10% for the general population.⁴³

First, the frequent overlap with other psychiatric diagnoses has been found before. ADHD, for example, is defined by features of inattention, hyperactivity, and impulsivity; however, these three features are also among the most frequent symptoms of ASD.²⁵ Conversely, social impairments which characterize ASD are often reported in ADHD.⁴⁴ Some scientists

suggest that ADHD and ASD are a continuum, with ADHD being a milder form of ASD.^{44,45}

Finally, other studies have shown that anxiety and obsessive compulsive behaviour are found at above-average rates in children with ASD.^{2,3}

The two most frequently reported physical symptoms in this study were food allergies (74%) and environmental allergies (51%), both of which are commonly reported in autism.^{3,46,47} For example, a study by Pennesi and Klein⁸ found that 93.4% of children with ASD (N=312/334) had food allergy symptoms. In a study by Gurney et al.³, respiratory, food, and skin allergies were reported by parents more often for children with ASD than controls, with food allergies having the strongest relative difference between the groups.

The percentage of children in the current study as well as other studies⁸ that are reported to have food and environmental allergies is dramatically greater in the children with ASD as compared to children in the general population (Table 2). As mentioned above, food allergies are about 14 times more frequent in the current study group than in the general population. Environmental allergies are about three times as frequent, and eczema is about twice as frequent.

The higher rates of food allergies and environmental allergies in ASD suggest an immunological mechanism.

Theoharides¹⁹ reviewed the literature since 1995 and found that children with ASD disproportionately present with food and skin allergies that involve mast cells. Theoharides postulated that activation of brain mast cells by allergic, environmental, immune, neurohormonal, stress, and toxic triggers, especially in those areas associated with behaviour and language, can lead to focal brain allergies and subsequent focal encephalitis. To this point, the study by and Klein,⁸ mentioned earlier regarding food allergies, found that a

gluten and casein-free diet brought about improvements in ASD behaviours, physiological symptoms, and social behaviours.

GI symptoms (inflammation, constipation, and diarrhea) were reported to be higher in the study group than in the general population. As described in the Introduction, this finding is consistent with the findings in many previous studies.^{2,9,10,11}

Evidence suggests that GI disturbance in ASD is associated with abnormal sulphation chemistry. For example, Waring and O'Reilly⁴⁸ found low plasma levels of inorganic sulphate and sulphur oxidation deficiencies in children diagnosed with an ASD who also had food/chemical intolerances. They found that the ratio of plasma cysteine (a precursor of sulphate and taurine) to sulphate was much higher in children with autism compared to controls. Later, Waring and Klovvza⁴⁹ found that the abnormal sulphate chemistry in children diagnosed with an ASD involved a specific population of children whose ASD symptoms manifested with food allergies and gastrointestinal (GI) symptoms (e.g., frequent diarrhoea, bloating, etc.) after 15 months of age (most were at approximately 2 years of age). In the current study, the large numbers of children with food allergies and GI symptoms suggest that many may have abnormal sulphation chemistry⁵⁰.

Seizures, as mentioned above, were reported to be about 100 times higher in the study group than in the general population, even though the percentage in this study (12%) was somewhat lower than the reported seizure rate of 20% to 38%.^{5,6}

The finding that 55% of the children in the study regressed, losing previously acquired skills and abilities including speech, eye contact, and socialization, is consistent with previous studies. For example the reported incidence of regression in autism ranges from 15% to 62% of cases, and loss of verbal, nonverbal,

and social abilities is typically reported.^{51,52,53,54,55,56}

The finding that 54% of the parents reported that the onset of symptoms was preceded by or was associated with some vaccination is consistent with previous research.^{56,57,58} Goldberg et al.⁵⁶ for example, stated that the event mentioned by the majority of parents (67.6%) as concurrent with loss of skills was vaccination. Also consistent with the Goldberg study, other medical events such as illnesses were reported by about one-third of the parents in the present study.

Notwithstanding the reported associations between vaccination and the onset of ASD symptoms, the 2004 Consensus Report issued by the Institute of Medicine⁵⁹ as well as several studies⁶⁰ have failed to find an association between vaccination and autism. However, other independent studies have reported such an association.^{61,62,63,64,65}

Further, Majewska et al.⁶⁶ studied 91 autistic children compared to 75 age- and sex-matched healthy children and found that after vaccination the autistic children had a significantly greater prevalence of adverse reactions and abnormal development than did the controls.

One of the main findings of this study is the extent and degree of medical symptoms coexisting with ASD. This finding supports previous research that suggests this diagnosis is a disorder governed not only by psychological criteria but also by medical symptoms. The extent of the medical symptoms suggests a systemic aetiology, which would involve metabolic biomarkers and predisposing factors.

Thus, for best outcomes, ASD treatments need to address underlying medical conditions. However, the current, mainstream ASD treatments and therapies emphasize educational interventions such as applied behavioural analysis (ABA) and/or psychoactive drugs such as Risperdal. Neither of these types of treatments

addresses medical illnesses or disease pathologies. This may be the reason for the dismal findings reported in a 2011 article in Paediatrics by Al-Qabandi et al.⁶⁷ These researchers found that "There are many available therapeutic approaches to childhood autism, including educational interventions, applied behaviour analysis, structured teaching, parent-mediated intervention, speech and language therapy, social skills therapy, and pharmacologic therapy.Many therapies are available, but none has curative outcome or even well-established efficacy to change the course of the condition."

Strengths and Limitations

The study is small, involving 83 children. The small sample size may have contributed to a study bias; however, given that most of the study findings are consistent with other published parental reports, this may not be significant. Other limitations include possible variations in parental and clinical recognition and reporting, and possible recall bias (a bias affected by respondent's memory). Because it was an online survey, there is a possibility the some parents may have misunderstood or misinterpreted the questions. However, this format may also reduce any direct influence on the participants by the study personnel. Another limitation of the study is that the questions did not elicit the severity of the physical symptoms; they merely asked whether the child had the symptoms or not. Future studies should probably include a measure of severity of the symptoms.

Conclusion

The findings from this study are consistent with previous research that has reported on medical conditions in children with ASD. Although several other studies report these findings separately, this study addresses multiple medical conditions. The findings suggest that ASD is: more than a diagnosis governed by psychological criteria, but a medical condition.

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Conflict of interests

Four of the five authors have been involved in vaccine litigation as expert witnesses and consultants.

Competing interests

Four of the five authors have been involved in vaccine litigation as expert witnesses and consultants.

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