Autistic Spectrum Disorders Report

From the National Birth Defect Registry

2009

Birth Defect Research for Children www.birthdefects.org

Summary

This report provides data about the high frequency of physical defects among children with Autistic Spectrum Disorders in an analysis of 137 Autistic Spectrum Disorders in a database of 2030 cases of birth defects in the National Birth Defect Registry. The report also includes the most frequent parental exposures and illnesses recorded for pre-conception and pregnancy.

Background:

The National Birth Defect Registry was started in 1990 by Birth Defect Research for Children (BDRC) to collect information on all kinds of birth defects both structural and functional, as well as information on the pre-conceptual and prenatal health, genetic factors and exposure histories of both parents. The Registry was designed and evaluated by an advisory board of seven prominent scientists working in fields ranging from obstetrics and genetics to epidemiology and the effects of toxic exposures on reproduction. The original questionnaire for the project was a 16-page booklet that parents filled out and mailed to BDRC. Data from the questionnaire were then manually entered into an inter-relational data base. Approximately 4,000 case reports were collected in this version of the registry.

In April of 2004, BDRC converted the registry to an on-line project so that parents could fill out the questionnaire at any convenient time of the day or night. The on-line project also made it easier to add new sections to the registry questionnaire without the cost of reprinting thousands of questionnaire booklets and mailing them to parents. The quality of data collection is more accurate as well, since the parent enters information directly into the on-line questionnaire and then BDRC staff imports the questionnaire into the main registry.

The registry is designed to identify patterns of similar birth defects that may have similar conditions or exposures in common in the parents' pregnancy or pre-conceptual history. A slide presentation http://www.birthdefects.org/NIEHS/3510.html made to the National Institute of Environmental Health Sciences explains the operation of the registry and some of the birth defect issues BDRC has worked on using registry data.

Since April of 2004, parents have completed 1853 questionnaires with case reports for 2030 children (more than one child in a family can be reported on a questionnaire) in the on-line National Birth Defect Registry. We have reports for 1095 males, 926 females and 9 cases where the gender was not entered.

Report on Autistic Spectrum Disorders in the National Birth Defect Registry

Autism is a developmental disability that significantly affects verbal and nonverbal communication and social interaction. The symptoms of autism generally become evident before age three. Autistic Spectrum Disorders (ASDs) form a continuum with autism at the most severe end of the spectrum through pervasive developmental disorder not otherwise specified (PDD-NOS), to the much milder form, Asperger's syndrome. ASDs also include two rare disorders, Rett syndrome and childhood disintegrative disorder.

ASDs have been increasing in incidence. Studies in late 1960's reported rates of ASD at 2-6 children per 10,000. A recent report by the General Accounting Office indicated that ASD has increased to a rate of between 20-60 cases per 10,000. The cause(s) of this increase are the subject of millions of dollars in new research in genetics and environmental exposures with no clear answers from either discipline.

It is unclear whether ASDs are congenital defects; i.e., present at birth or acquired developmental problems that are associated with post-natal exposures.

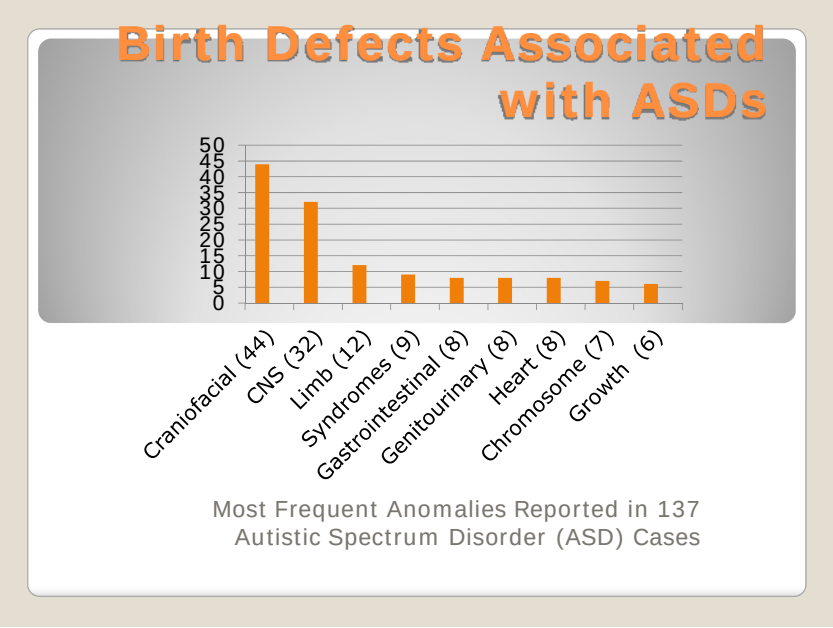
Most Frequent Birth Defects Reported by ASD Cases

Since the online version of the National Birth Defect Registry began, there have been 137 reports of Autistic Spectrum Disorders (autism, Asperger's, PDD, PDD-NOS and or Rett Syndrome). These cases were self-reported by the parents in the general public and through a special outreach to parents served by the Center for Autism and Related Disorders at the University of Central Florida (CARD). A case analysis has revealed that over 60% (82 cases*) with Autistic Spectrum Disorders (ASDs) also had structural birth defects, primarily Central Nervous System (CNS) or Craniofacial Defects. Fifty-five (40%) of the ASD cases reported associated developmental problems, but no structural birth defects.

The registry has birth defect cases recorded for 2030 children. The 137 ASD cases represent 7% of the cases in the registry. ASD rates nationally are 10% of the national rate of birth defects, so the Registry's 7% rate is close to a representative sample.

Although continued case reporting could change the ratio of ASD/birth defect cases and ASD only cases, past experience with Agent Orange and Gulf War data has shown that reporting patterns do not vary greatly with increased data collection.

Chart 1: Birth Defects Reported in 137 ASDs in the National Birth Defect Registry



*See Appendix for complete list of birth defects reported for each case.

The most frequent Central Nervous System (CNS) disorders reported were Microcephaly, Cerebral Palsy, Chiari Malformation and Absent or Thin Corpus Callosum. The number of microcephaly (small head size) cases was interesting since recent studies have suggested an increased rate of macrocephaly (large head size) in autism.

Chart 2: CNS Disorders in 137 ASD Reports in the National Birth Defect Registry

CNS Disorders in 137 ASD Reports	
Abs or Thin Corpus Callosum	3
Abs Septum Pellucidum	1
Chiari Malformation	4
Cerebral Palsy	5
Dandy Walker Malformation	1
Delayed Myelination	1
Hydrocephaly	2
Lissencephaly	1
Microcephaly	7
Periventricular Leukomalacia	1
Seizure Disorder	1
Spina Bifida	1
Syringomyelia	1

The most frequent Craniofacial Defects included Low Set Ears, Partial Hearing Loss, Abnormal Teeth and Dysmorphic or Asymmetric Facies*.

Chart 3: Craniofacial Defects in 137 ASD Cases in the National Birth Defect Registry

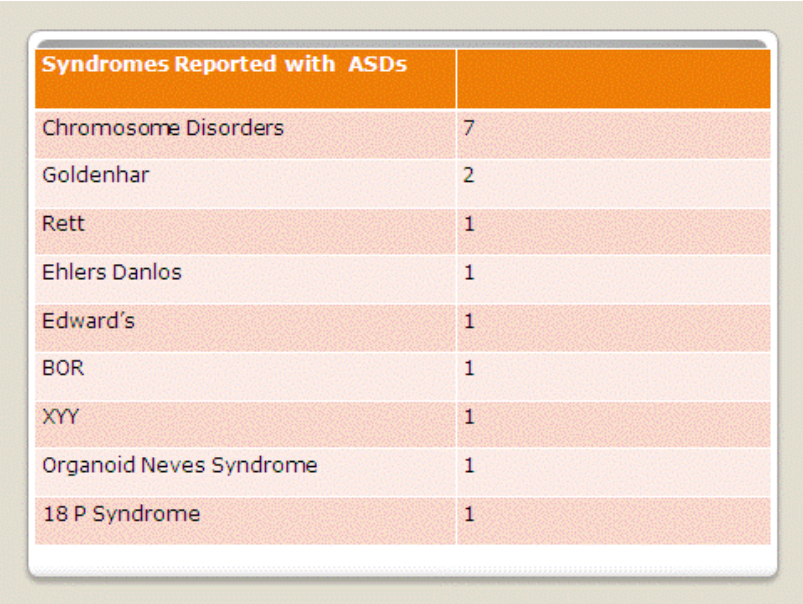
Craniofacial Defects in 137 ASD Cases	
Craniosynostosis	1
Cleft Palate and/or Lip	3
Abnormal Teeth	7
Dysmorphic or Asymmetric Face	5
Facial Nerve Paralysis	1
High Arched Palate	1
Macrocephaly	1
Macrostomia	1
Micrognatia	1
Low Set Ears	6
Partial Hearing Loss or Deaf	8
External Ear(s) Abs or Malformed	3
Septo-Optic Dysplasia	3
Anopthalmia	1
Coloboma	1

*Thalidomide exposed children with autism had impairment to the cranial nerves, upper-limb structures and ear pathways.

Syndromes and Chromosomal Disorders

Many studies have focused on discovering a specific gene or genes for autism. Seven cases of ASDs in the registry reported chromosomal disorders. There were also two cases of Goldenhar Syndrome and six other syndromes. In literature reviews, Rett Syndrome, XYY and Goldenhar Syndrome have been associated with autism.

Chart 4: Syndromes and Chromosomal Disorders Reported in 137 ASDs



Syndromes Reported with ASDs	
Chromosome Disorders	7
Goldenhar	2
Rett	1
Ehlers Danlos	1
Edward's	1
BOR	1
XYY	1
Organoid Neves Syndrome	1
18 P Syndrome	1

Most Frequent Symptoms in Different Categories of ASDs

A number of the cases in the registry had overlapping diagnoses of autism and Asperger's Syndrome or PDD. This suggests that the diagnosing physicians may be unsure about differences in specific categories of ASDs.

A spectrum or syndrome is defined by a set of similar symptoms or defects occurring together. ASD data from the registry were diagnosed separately for each category (Autism, Asperper's and PDD) because children with ASDs have similar symptoms but some disorders are reported more frequently in one category of an ASD diagnosis than another. For instance, retardation was one of the more frequently reported conditions in the Registry's cases of Autism, but not in the Asperger's and PDD cases. Frequent ear infections were reported more often for the cases of Autism and PDD. All three categories of ASDs included speech delays and speech disorders; motor skills delay; Sensory Integration Dysfunction; allergies; ADHD; OCD; language processing problems, specific learning disabilities and comprehension difficulties

Chart 5: Analysis of Most Frequent Disabilities in 88 Autism Cases

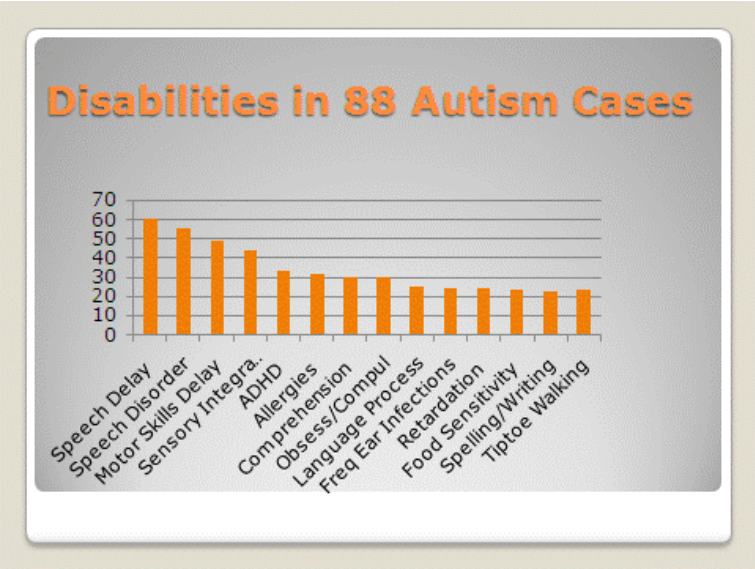


Chart 6: Analysis of Most Frequent Disabilities in 36 Asperger's Cases

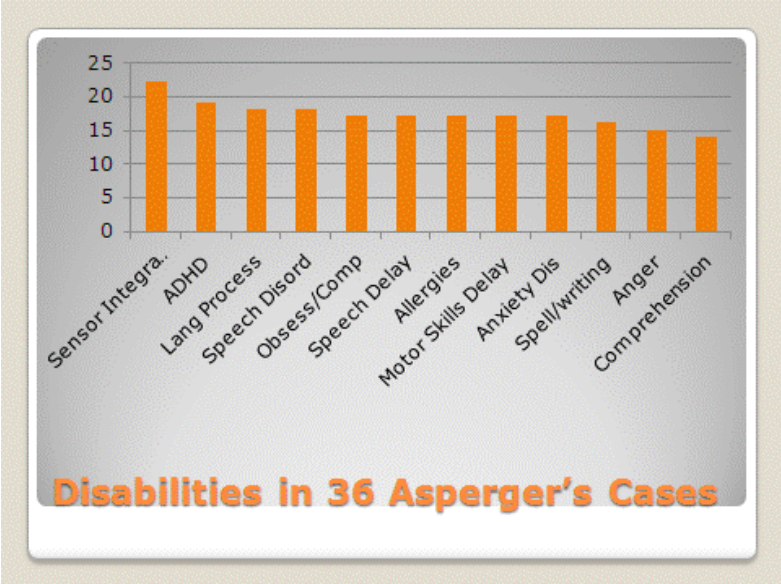
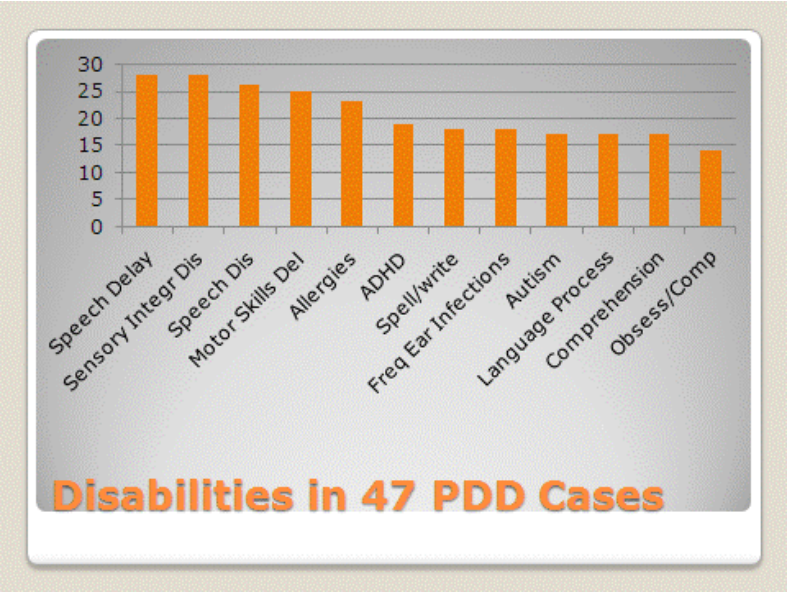


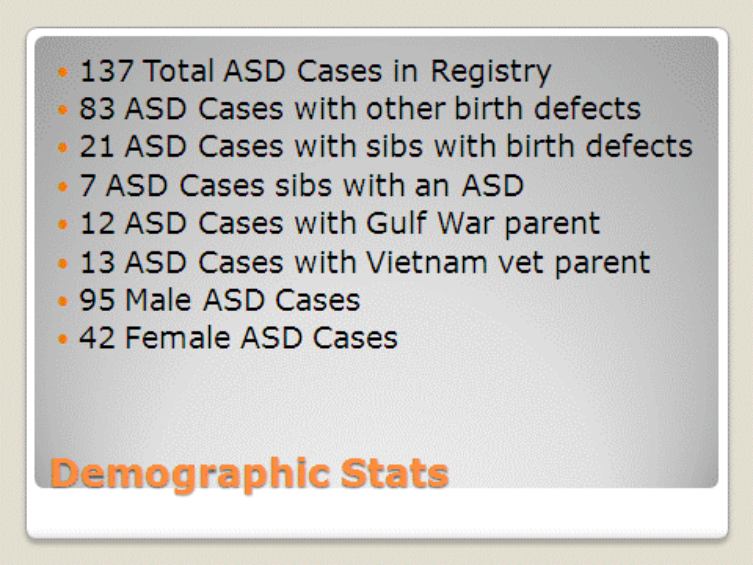
Chart 7: Analysis of Most Frequent Disabilities in 47 PDD Cases



Demographic Statistics

The 137 ASD cases in the registry represent 95 males and 42 females. National reporting systems have found 3 to 4 times more boys than girls with autism. Twenty-one families who reported a child with an ASD have other children with birth defects. Seven families of children with an ASD had two children with an ASD, in one case a set of twins. In 12 ASD cases, one parent served in the first Gulf War. In 13 ASD cases one parent was a Vietnam veteran.

Chart 8: Demographic Statistics



Racial Groupings

The breakdown of cases by racial groupings showed a preponderance of Caucasian and Hispanic cases. This distribution has been reported in other studies of ASDs.

Chart 9: Cases by Racial Groupings

Maternal Illnesses in the Pre-conceptual Year

A section in the National Birth Defect Registry collects data on maternal and paternal illnesses in the pre-conceptual year. This list was developed from symptoms reported by families exposed to environmental toxins. These symptoms are also similar to those found in Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) which may affect as many as 4 million people (CDC 2009 http://www.cdc.gov/CFS)

Chart 10: Maternal Symptoms Reported in Pre-conceptual Year

Maternal Illnesses in Pre-conceptual year – 88 autism Cases	
Mood Swings	25
Depression	23
Chronic Headaches	21
Anxiety/nervousness	18
Chronic Fatigue	17
Menstrual Problems	16
Ovarian Cysts	14
Chronic Stomach Problems	13
Sleep Disorders	12
Increase in Allergies	12
Thyroid Disorder	11
Muscle/joint pain	11
Reduced Sex Drive	10
High Blood Pressure	10
Diabetes	10
Night Sweats	9

Paternal Illnesses in the Pre-conceptual Year

Paternal exposures and illnesses may also play a part in adverse pregnancy outcomes. Although paternal histories are not reported as completely as maternal histories in the registry, the similarity of symptom reports suggests similar causes to those reported by the mothers.

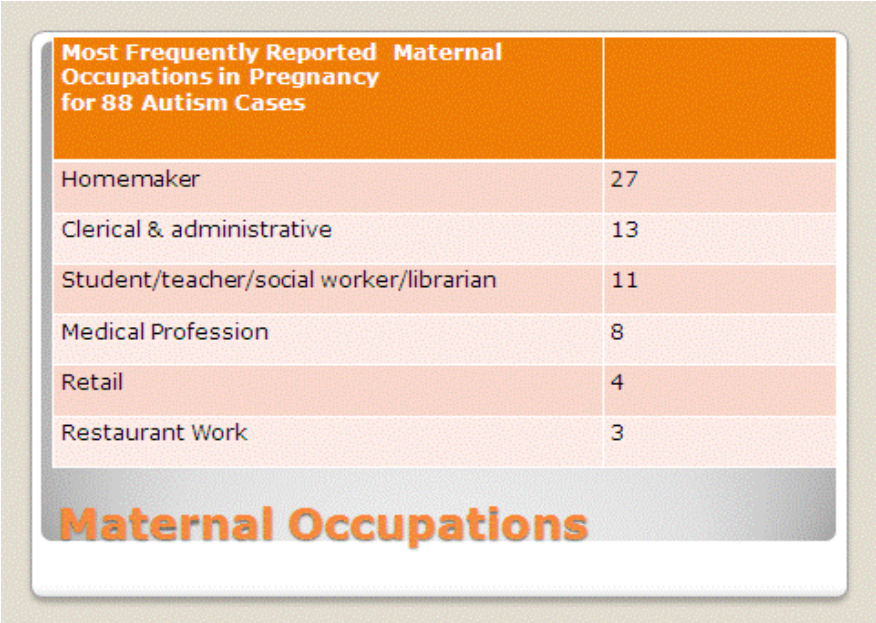
Chart 11: Paternal Symptoms Reported in Pre-conceptual Year

Paternal Illnesses Pre-conceptual Year – 88 Autism Cases	
Mood Swings	25
Sleep Disorders	13
Angry Outbursts	12
Depression	11
High Blood Pressure	9
Muscle/joint Pains	8
Anxiety/nervousness	7
Chronic Headaches	6
Reduced Sex Drive	5
Diabetes	5
Chronic Stomach Problems	5
Chronic Respiratory Problems	4
Thyroid Disorder	4
Alcohol Intolerance	3

Maternal Occupations During Pregnancy

The maternal workplace may be an important source of exposures to both illnesses and toxins. The medical and teaching professions place the prospective mother in contact with frequent illnesses and toxic exposures. Many studies of medical professionals have reported increases in birth defects and pregnancy loss. In the school setting, teachers and administrative workers have been exposed to pesticides, roof tarring and/or asbestos in many facilities. Restaurant workers may be exposed to pesticides because of health department requirements to control insects in cooking and food storage areas.

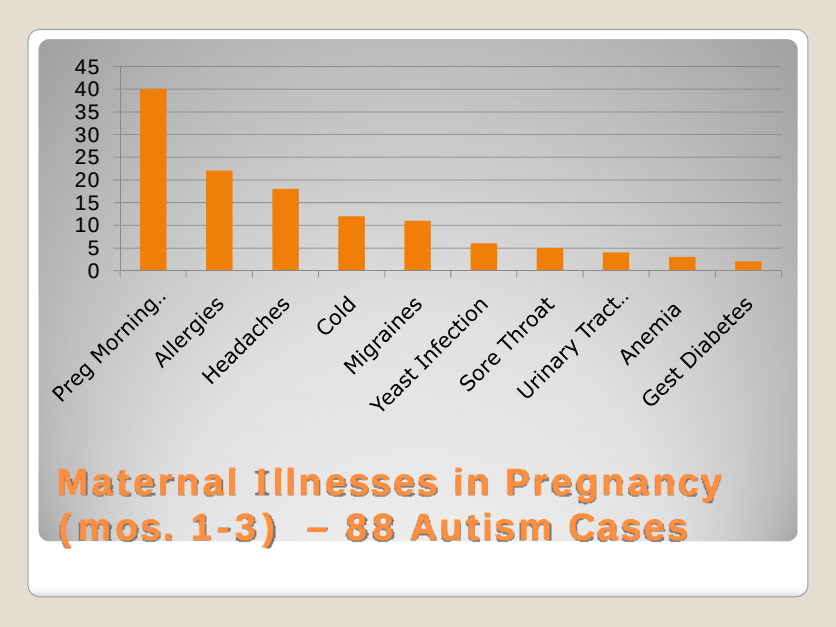
Chart 12. Maternal Occupations in 88 Autism Cases



Maternal Illnesses During Pregnancy

Maternal illness during pregnancy may expose the developing baby to viruses, bacterial infections, metabolic problems like diabetes and thyroid disorders and/or medications, X-rays and procedures used to treat maternal illnesses. Fifty-five of the 88 autism cases reported one or more maternal illnesses.

Chart 13: Most Frequent Maternal Illnesses (Mos. 1-3) 88 Autism Cases



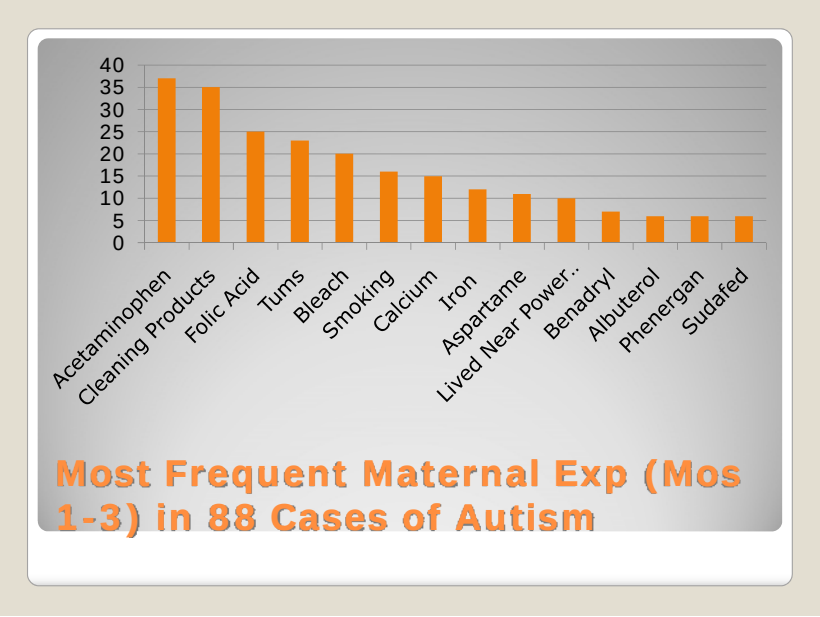
Maternal Exposures During First Trimester of Pregnancy

The most frequently reported maternal exposure in the 88 Autism cases was acetaminophen (Tylenol). The use of acetaminophen (AP) has increased in recent years. In 1978, a study in *Pediatrics* indicated that aspirin was the most frequently consumed drug in pregnancy, but reports of adverse effects on the mother and fetus began to change prescribing recommendations. Although AP is widely assumed to be safe for use in pregnancy, recent reports have found associations between childhood asthma (Shaheen, 2005) and/or gastroschisis (Adjei 2008) in children whose mothers took acetaminophen during pregnancy.

Acetaminophen (AP) is also the most frequent drug of overdose in pregnancy. It can cross the placenta and has been found in neonatal serum after birth. It can cause liver injury when a toxic metabolite of acetaminophen exceeds the binding capacity of glutathione. (Wilkes, 2005) The ability to metabolize AP begins at approximately 18 weeks and increases through 23 weeks, so a question could be raised about the consequences of exposures to AP before 18 weeks. Large doses of AP have been shown to result in increased degradation of the hepatic cytochrome P450. (Zhang, 2004) If this were to happen in utero, it could leave the baby with decreased detoxification pathways which is of interest since children with autism have been reported to have decreases in the ability to detoxify heavy metals and other toxins.

The second most frequent category of maternal exposures reported was cleaning products. Some cleaning products contain glycol ethers which are reproductive toxins, but since the Cleaning Products category does not specify which cleaning products were used it is difficult to know how many mothers may have been exposed to glycol ethers or other toxins in cleaning products.

Chart 14: Most Frequent Maternal Exposures (Mos 1-3) 88 Autism Cases



Discussion:

Sixty percent of the ASD cases in the National Birth Defect Registry are associated with structural birth defects. The analysis of 137 cases may not reflect what would be found in a larger case collection, but if this ratio remains the same with continued reporting, registry data could suggest several possibilities. 1) ASDs are part of a birth defect pattern and those cases without reports of associated birth defects should be evaluated for subtle physical anomalies; or 2) There are two types of ASDs….one that occurs as part of a birth defect sequence and the other that may have an origin that may be either pre or post-natal; or 3) ASDs without associated birth defects may be the result of an expanded definition of autism that includes children with severe ADHD, Sensory Integration Disorders and other neuro-developmental problems that were not previously classified as autism.

The pattern of illnesses reported in the Pre-conceptual year for both the mothers and the fathers of ASD cases in the registry is of interest since it could suggest a common disease process or exposures to similar environmental toxins.

The most commonly reported maternal exposures in the ASD cases were acetaminophen and cleaning products. These exposures should be studied in larger, more highly controlled studies to rule out any possibility of a contributing effect to ASDs.

Appendix:

Birth Defects Reported In 137 ASD Cases

Case #	ASD	Birth Defect	Birth Defect	Birth Defect
2073	PDD	Ab Corpus Callosum		
4872	Autism	Ab Corpus Callosum	Periventricular leukomalcia	Abnorm teeth
1321	Autism	Short Stature		Abnorm teeth
4356	Autism			Abnorm teeth
1419	Aspergers	Absent lung	Pyloric stenosis	
969	Autism	Anopthalmia	Septo-optic-dysplasia	
622	Autism	ASD/pulmonary artery	Undescended testicles	Abnorm teeth
2080	PDD	Chromosome disorder	ASD/VSD	Part hear loss
4295	Autism	Bradycardia		
1296	PDD	Chiari Malformation	Cleft lip	
3050	Aspergers	Chiari Malformation	Syringomelia	Abs Muscle
3467	Aspergers	Chiari Malformation	Pigeon Chest	
3585	Autism	Chiari Malformation	Malformed Kidney	
991	Autism	Chromosome Disorder		
1165	Autism	Chromosome Disorder	Tetralogy of Fallot	Abs kidney
2596	Autism	Chromosome Disorder		
4591	Autism	Chromosome Disorder		
5060	Autism	Chromosome Disorder	Hydrocephaly/patent ductus	CP
2951	Autism	Ear absent/malformed	Cleft palate	Macrostomia
4868	Aspergers	Cleft palate	BOR Syndrome	Ear pits
1847	Autism	Low set ears/tags	Clinodacytyly	
1478	Aspergers	Clubfoot	Absence Muscle	
2629	Aspergers	Clubfoot		
5156	Autism	Part hearing loss	Coloboma/ab kidney	Micropthalmia
2016	PDD	Cortical blindness	Dandy Walker	
2312	Autism	Cortical blindness		
3743	Autism	Cortical blindness	Hydrocephalus	
3000	Autism	CP	Stabismus	
3442	Autism	CP	Organoid Nevus Syndrome	
3700	Autism	CP	Diabetes	
4607	Autism	CP	Seizure disorder	Hypotonia
4929	Autism	Craniosynostosis		
2637	PDD	Diaphragmatic hernia		
4591	Autism	Dislocated hip	Diabetes	Abnorm teeth
2743	Autism	Chromosome Disorder	Low set ears	Und testicles
1396	Autism	Edwards Syndrome	Low set ears	Clubfoot
2113	PDD	Ehlers Danlos		
1053	Aspergers	Facial asymmetry	White matter undeveloped	
1351	Aspergers	Facial asymmetry		
2596	Autism	Deafness	Facial defects	Overgrowth

4550	PDD	Partial hearing loss	Facial nerve paralysis	Overgrowth
2460	Autism	Fragile X	Large cranium	Lg genitals
1366	Autism	Gastroschisis		
1107	Autism	Goldenhar Syndrome	External ear abs/malf	
1285	Autism	Goldenhar Syndrome	Malf hands/fingers	Low set ears
1413	Autism	Hemihypertrophy	Malf feet/toes	
3722	Autism	Hearing loss	Hernia	
3605	PDD	High arched palate	Protruding ears	Ureter defect
949	PDD	Hydrocele		
440	Autism	Hydrocephalus	Anomalous pulmonary vein	
5187	Aspergers	Hypospadias		
625	Autism	Immune deficiency		
4175	Autism	In utero growth retard		
4718	Autism	In utero growth retard	Umbilical hernia	
4972	Autism	Lamellar Ichthyosis		
828	PDD	Lissencephaly	Low set ears	Micrognatia
2312	Autism	Macrocephaly	Kyphosis	
2730	Autism	Malf feet, toes or legs		
3483	Autism	Malf feet, toes or legs		
2097	Autism	Microcephaly	Chromosome Disorder	
2772	PDD	Microcephaly	Facial asymmetry	
3419	Autism	Microcephaly	Septo-optic-dysplasia	CP
3612	Autism	Microcephaly	hydronephrosis	CP
4564	Autism	Microcephaly	Partial hearing loss	Gastroschisis
4982	Autism	Microcephaly		
5045	Autism	Microcephaly		
5078	Aspergers	Low set ears	Micrognathia	
4398	Autism	Overgrowth		
4972	Autism	Pectus excavatum		
276	Autism	Partial hearing loss	Pituitary defect	
1419	PDD	Pyloric stenosis		
1471	Autism	Rett Syndrome	Partial hearing loss	Scoliosis
5263	PDD	Septo-optic-Dysplasia	Abs septum pellucidum	
530	PDD	Severe comb immune def		
3103	Aspergers	Short toe	Skin tags	
5279	PDD	Spina bifida	Hydrocephaly	
3889	Autism	Trisomy	18P Syndrome	
639	PDD	Umbilical hernia		
3107	Autism	VSD	Thin corp callosum	Imperf anus
326	Autism	Wide set nipples	Overgrowth leg	Umbil hernia
1675	PDD	XYY Syndrome		

Definitions Birth Defects

Ab Corpus Callosum – absence of corpus callosum which is the band of tissue connecting the two hemispheres of the brain

Abs septum pellucidum – absence of the septum pellucidum, a thin membrane located at the midline of the brain.

Anomalous Pulmonary Veins - a rare congenital malformation in which all four pulmonary veins do not connect normally to the left atrium, but instead drain abnormally to the right atrium by way of an abnormal (anomalous) connection.

Anopthalmia – absence of the eye or eyes

Atrial Septal Defect (ASD) – defect or opening between the heart's two upper chambers (the atria)

BOR Syndrome -Branchiootorenal (BOR) syndrome is a genetic condition that typically disrupts the development of tissues in the neck and causes malformations of the ears and kidneys.

Bradycardia - heart beats at an abnormally slow rate

Clinodacytyly - a bending or curvature deformity of the finger which occurs in the plane of the hand typically caused by abnormal growth and development of the small bones of the finger (the phalanges)

Coloboma - a gap in part of the structures of the eye

Cortical Blindness-the total or partial loss of vision in a normal-appearing eye caused by damage to the visual area in the brain's occipital cortex

Craniosynostosis - a birth defect of the brain characterized by the premature closure of one or more of the fibrous joints between the bones of the skull (called the cranial sutures) before brain growth is complete

Dandy Walker- a congenital brain malformation involving the cerebellum (an area at the back of the brain that controls movement) and the fluid-filled spaces around it

Diaphragmatic hernia- an abnormal opening in the diaphragm, the muscle that helps you breathe. The opening allows part of the abdominal organs to move into the chest area.

Goldenhar Syndrome- abnormalities of the head and the bones of the spinal column. The abnormalities of the head can include differences with the eyes, ears, facial bones, and mouth and are usually more severe on one side.

Hydrocephaly-exessive accumulation of fluid in the brain

Hydronephrosis -distention (dilation) of the kidney with urine, caused by backward pressure on the kidney when the flow of urine is obstructed.

Hypospadias- a birth defect found in boys in which the urinary tract opening is not at the tip of the penis.

Hemihypertrophy- the enlargement of one side of the body or part of the body

Imperforate Anus - the opening to the *anus* is missing or blocked

Kyphosis- a forward curvature of the spine

Lamellar Ichthyosis – a rare inherited skin disorder

Lissencephaly -a rare, gene-linked brain malformation characterized by the absence of normal convolutions (folds) in the cerebral cortex and an abnormally small head (microcephaly).

Macrocephaly- a condition in which the head is larger than normal

Microcephaly – a condition in which the head is smaller than normal

Micrognathia - a condition where the jaw is undersized

Organoid Nevus Syndrome- a rare syndrome involving the skin, eye and brain.

18 P Syndrome - a frequent deletion *syndrome* characterized by dysmorphic features, growth deficiencies, and mental retardation

Pectus Excavatum – sunken chest wall

Periventricular leukomalcia – a white matter lesion in the brains of premature infants

Pyloric stenosis - a narrowing of the *pylorus*, the lower part of the stomach

Septo-Optic-Dysplasia- a syndrome characterized by absence of the midline part of the brain and underdevelopment of the optic nerve

Severe combined immune deficiency- a life-threatening syndrome of recurrent infections, diarrhea, dermatitis, and failure to thrive

Spina Bifida - a birth defect that involves the incomplete development of the spinal cord or its coverings

Rett Syndrome - a neurological and developmental disorder that mostly occurs in females

Umbilical hernia - an outward bulging (protrusion) of the abdominal lining or part of the abdominal organ(s) through the area around the belly button

Undescended testicles – a baby boy's testicle(s) have not moved into their proper position in the first few months of life

Ureter Defect – malformation of the tube(s) that connect the bladder to the kidney

Ventricular Septal Defect - A defect or opening between the heart's two lower chambers (the ventricles)

XYY Syndrome - an extra copy of the Y chromosome in each of a male's cells

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