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J. Perinat. Med.
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Prenatal and perinatal risk factors for autism

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1 Introduction

Autism and the other pervasive developmental disorders have an infant and childhood onset and often result in severe lifelong impairments. Mental retardation and epilepsy are common comorbid conditions. Most persons with autism or pervasive developmental disorder require care throughout their life span. Institutionalization is a frequent outcome.

The etiology of these disorders is incompletely understood. There is a substantial genetic contribution to these disorders. The recurrence risk of autism in siblings of autistic probands is 2 to 5% [5, 13, 36, 31]. This represents about a fifty-fold increase in risk over the general population where the population prevalence is 1 in 2,500 or 0.04% [13, 31]. In families with multiple cases of autism the recurrence risk is about 8% which is over 200 times the general population risk [32]. The average concordance risk from several twin studies is 3 to 9% for dizygotic twins and 64 to 81% for monozygotic twins [5, 35, 37, 31]. The monozygotic/dizygotic twin concordance ratio is 25 [31]. While genetic disorders are commonly comorbid with autism no genetic disorder is uniformly associated with autism, and similar cases of autism occur in children with and without genetic disorders. Given the variability in autism, even in groups of children who have the same genetic disorder, it seems likely that environmental factors play an important role in the development of these disorders and may influence severity. Pleiotropy (the variable expression of a single gene disorder) may explain some of the variance in phenotypes. However, the genetic mechanism in autism is unknown.

Several environmental factors increasing risk for autism have been described in the past. Among these has been congenital rubella [12] and cytomegalovirus infection [24, 13]. Earlier studies have examined the role of prenatal and perinatal events as risk factors for autism. This work has not produced a consistent set of risk factors (for reviews see Nelson [29] and Tsai [38], and Gillberg [18]). Research in this area has been complicated by the use of variable case definitions for autism and the pervasive developmental disorders and use of divergent risk factors that are not directly comparable. Other problems involved differing study methodologies, small sample sizes and the use of variable information sources such as interviews with the families of autistic patients [16, 23]. Some studies do not list the data sources [22, 20]. As a consequence, there is no current consensus about the role of prenatal and perinatal risk factors in autism. If prenatal or perinatal risk factors that are in a causal chain influencing either the severity of or the risk of developing autism could be identified, this data could have important implications in prevention and treatment. These risk factors and the temporal unfolding of risk would both be appropriate to target as starting points to initiate interventions that may decrease both the severity and prevalence of the disorder.

Environmental risk factors occurring during the prenatal and perinatal periods of development have been found to be etiologically important determinants of developmental disorders [33]. The roles of prenatal exposure to maternal smoking in attention deficit hyperactivity disorder [27] or conduct disorder [39] and prenatal alcohol exposure and the resulting fetal alcohol syndrome [11, 4] are examples. Some children with fetal alcohol syndrome also have autism [28].

A limited review of previously published studies relevant to autism is presented in table I [7, 14, 15, 16, 17, 18, 21, 22, 23, 26, 30]. We have included only studies that compared cases and controls. We were especially interested in studies, which had utilized birth certificate data. Gillberg and Gillberg [18] developed an optimality score for pre and perinatal risk factors and used 25 cases of autism and 25 controls to demonstrate that the cases had decreased optimality scores. However, as the table demonstrates, no consistent pattern of findings is apparent across the studies. Studies using birth certificate data as the primary source of data could not be found.

We have demonstrated an alternative strategy for pursuing the potential relationship between prenatal and perinatal risk factors and developmental disorders [11]. This strategy combines a statewide diagnostic registry linked with data from birth certificate files. This methodology was derived from previous studies of risk factors for infant mortality and has been very useful in the identification of possible environmental risk factors [8, 10].

This methodology provides three distinct advances in research in developmental disorders. The first is a low cost strategy to control for interview or data extraction bias. The birth certificate data are collected by persons having no connection with the research project (or even knowledge of the project). The second is that birth certificate data provides access to a very large and usually a very complete data set. The third is that this type of data provides access to a very large number of potential controls that can be matched on a variety of factors. These include year and month of birth, the county of birth, and sex and race matching.

Birth certificate data should become even more useful in the future since the revision of the United States Standard Certificate of Live Birth revision in 1989. In this version many new items were added, including a switch to a check box format from open-ended questions. The new birth certificate data may also be used to develop national files of linked birth and death certificates [25]. This would represent an important advance in large-scale studies developmental disabilities.

The initial studies linking a diagnostic registry of patients with developmental disabilities and their birth certificate data was conducted with a registry of patients with fetal alcohol syndrome [11] and sudden infant death syndrome [8]. Names of the children from a diagnostic registry and their birth dates were forwarded to the State Health

Table I. A review of previously published studies of prenatal, perinatal and neonatal data in persons with autism and pervasive developmental disorders

Case-Control Studies

Variables	Levy	Deykin	Lobascher	Deb	Mason-Brothers	Finegan	Lord	Bryson	Cryan	Piven	Gillberg
Maternal Age				–	–	–		–	–	–	+
Maternal Education									–		+
Maternal Weight Gain		+									–
Gestation Length			+	–	–	–	+	+	–	–	+
Birth-weight		+		–	+	+		–			–
Apgar 1	–			–	–	+		–			+
Apgar 5					–			+			+
Meconium Staining	–			–	–	–		+		–	–

(–) = negative finding (+) = positive finding (blank) = not addressed in given study

Department. Individual birth certificate data was extracted and entered into a file, and a series of controls were identified. Birth certificate data for the controls was obtained from the same computerized birth certificate registry. We have now utilized this methodology to compare children with a diagnosis of autism or pervasive developmental disorder in North Dakota with controls to determine if we could identify prenatal or perinatal risk factors.

2 Method

Since 1980 we have maintained an autism registry at our clinic. Since the publication of the DSM-III in 1980, the data base has been expanded to include cases of autism, pervasive developmental disorders and autistic disorder as subsequent versions of the DSM have been developed. In the current registry the term autism would encompass patients meeting criteria in one of the three versions of the Diagnostic and Statistical Manual (DSM-III, DSM-III-R and DSM-IV) (American Psychiatric Association, 1980, 1987, 1994) [1, 2, 3].

In 1984 and 1985 we conducted a statewide prevalence study of autism and pervasive developmental disorders [9]. We contacted all physicians who were known to see children with developmental disabilities, all special education directors, all residential care facilities, parent support groups, clinical psychologists, and the state's comprehensive evaluation center. This study identified 59 cases of autism in North Dakota children. A recently completed 12-year follow-up of this data identified only one additional case of autism meeting the 1986 study inclusion criteria who had not been identified in the initial survey. These 60 cases and 84 additional patients were from the North Dakota Autism and Pervasive Developmental Disorder Registry. The registry lists all children and adults who had been seen since 1980 at the state's comprehensive evaluation center or who had been seen by JK. This produced a final list of 144 patients.

The project was approved by the Institutional Review Board of the University of North Dakota. We then forwarded a list of these patients, including their first names, last names, middle initials, dates of birth, sex, and no other information to the North Dakota Health Department. The Health Department then identified all patients who had North Dakota birth certificates.

We then selected five controls for each case from the computerized North Dakota birth certificate registry maintained by the North Dakota Health Department since the mid 1970's. Computer access to all birth records facilitates access and decreases costs for research, especially when selecting multiple controls and when using matching. The number of controls was selected to maximize the power of the study. Since it is expensive and time consuming to obtain additional cases of autism or PDD, adding multiple controls from a computerized data base is an inexpensive strategy to increase the power of the study to detect differences. Since the ability to increase power drops off rapidly above five controls per case, we used five controls per case [34]. The controls were matched by sex, the year of birth and month of birth. Matching for sex was considered important since males have autism three to five times more frequently than females. This sex difference has been identified in nearly all studies of autism. Matching on the year of birth was used to control for differences in obstetrical and neonatal medical practice over the wide age span of these subjects. Matching on month of birth was used to control for effects of month of birth or season of birth, which occurs in many developmental disabilities.

Since the cases and controls were matched, they were linked during the analysis (each case and the five matched controls) using the method described by Schilleschman [34]. The analysis was completed using the Number Cruncher Statistical System [19].

3 Results

We forwarded a list of 144 patients with autism to the Health Department, and they were able to identify 78 (54 %) with North Dakota birth certificates. The most common reason for not locating a birth certificate was a birth occurring in another state. We did examine the adoption files and used several other strategies to maximize the number of matches. In order to maximize confidentiality, the controls were not identified to us by name. The birth certificate data was obtained from three versions of the US standard certificate of live

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trol study of 78 cases of autism and controls we identified seven vari- of which are categorical, six con- wo that are in both groups. We used control for the effects of year of anges in medical care, and season of sults of the univariate analysis iden- significant variables in this study

autism and five controls per case using

t	d.f.	p
2.137	466	0.033
2.545	292	0.011
2.070	292	0.039
−0.935	466	0.350
2.810	466	0.005
−2.907	466	0.004
1.040	466	0.299
2.213	466	0.027
−1.267	466	0.206
1.535	292	0.126

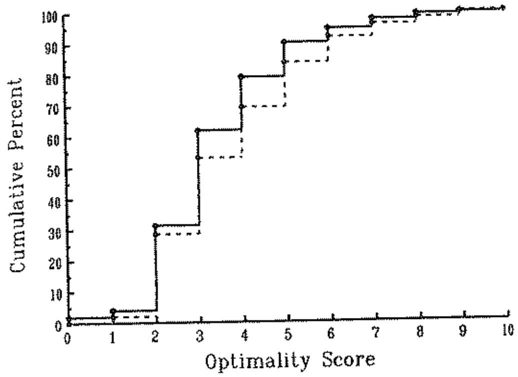

Figure 1. Cumulative percent of reduced optimality in cases and controls. Cases = dashed line, controls = solid lines.

which were: birth weight, apgar score at one and five minutes, mother's education, father's age, the trimester prenatal care started, and terminations of a prior pregnancy. Three additional variables, mother's race, apgar 5 and gestation of less than 36 weeks, approached significance at the .05 level.

We then used stepwise conditional logistic regression analysis to control for confounding from other significant variables and produced two final models, which were comprised of four and five variables (table IV). In the five variable model birth weight in grams was a risk factor (OR = 1.01), suggesting that for each gram reduction in birth weight, the risk of autism increased by a very small amount compared to the matched controls. For each year of difference in parents' education between the cases and controls (lower education was the risk factor for autism), the risk of autism increased 25%. Each month prenatal care was delayed increased the risk of autism 29%. Having had a previous termination of pregnancy increased the risk of autism 236% compared to controls who did not have a termination of pregnancy. We identified one variable (father's age) which was associated with risk reduction. A one-year decrease in the age of the father decreased the risk of autism by 6% compared to the controls. When viewed as a composite of risk the model was highly significant but produced a model, which was a poor fit with the data in this sample. Eliminating birthweight decreased the model chi-square but produced a substantial improvement in goodness of fit (table IV).

The prevalence of low birth weight babies in our sample was high (11/78 or 14%) in the cases

Table IV. Logistic regression of significant variables from 78 cases of autism and five controls per case. The final two models consisted of four or five variables

Variable	Model 1		Model 2	
	Coeff	O. R.	Coeff	O. R.
Intercept	−1.693		−.450	
Mother's Education	.217	1.24	.239	1.27
Father's Age	−.067	.94	−.063	.94
Other Terminations	1.213	3.36	1.027	2.79
Month Prenatal Care Began	.261	1.30	.258	1.29
Birth Weight	.000483	1.00		
Model parameters				
Chi-Square	36.616		31.083	
p-value	.0001		.0001	
Hosmer-Lemeshow				
Chi-Square	15.993		3.673	
p-value	.042		.885	

compared to 7% in the controls producing an odds ratio of 2.4 for autism in low birth weight infants compared to matched controls. However, this data does not indicate if low birth weight is a cause or consequence of autism. The issues of the relationship between prenatal and perinatal variables and autism is complex and has been discussed elsewhere [6]. The direction of the association between low birth weight and autism will require further study.

None of the variables which emerged as risk factors in this study appear to be either necessary or sufficient for the development of autism. This was the same conclusion reached by Bolton [6] in a study of obstetric risk factors for autism. However, this study does offer strong support for viewing these risk factors as important in cases of autism. As a result we are unwilling to dismiss them as consequences of the disorder without further study. If after replication studies consistent potential risk factors are identified further studies should be designed to elucidate if these risk factors act as additive liabilities of risk for the development of autism or are markers of complicated pregnancies resulting from the genetic influences that resulted in autism in that person. This effort will likely require both a large sample and a sophisticated design since the risk factors in this study are complex constructs and cannot be clearly categorized as environmental or genetic or as cause or consequence of autism. Like most factors influencing human behavior they probably represent an expression of an interaction of these influences.

This study may have limited clinical implications. First, the results may alert clinicians to specific signs that may be useful in developing a clinical history in patients presenting for evaluation. Second, the cluster of variables identified here may be useful as part of a screening tool for autism. Thirdly, clinicians may benefit from adding the birth certificate to the clinical record of patients with autism. Fourthly, clinicians may be able to utilize this data to discuss the role of pregnancy as a factor in the development of autism with parents. This would likely be reassuring to parents, especially mothers, of children with autism.

The methodology presented here has several important limitations that need to be considered. There are limitations in both the quality and completeness of the data from the birth certificates. In North Dakota the quality of data for both alcohol use and smoking is poor. When we examined the birth certificate data for a population of children with a diagnosis of fetal alcohol syndrome in North Dakota the birth certificate data identified only 6% as having been alcohol exposed. This was much different from the data on prenatal alcohol exposure we obtained from the mothers or other sources during our evaluations of these children. Due to the poor quality and missing data in this area we excluded alcohol exposure and maternal smoking as variables in this study.

The next issue is the quality of the data for cases in the registry. Since most registries span decades the inclusion and exclusion criteria change. In most cases the registry data will encompass several versions of diagnostic nomenclatures. This occurred in our study which spanned three versions of the Diagnostic and Statistical Manual of Mental Disorders. Several other issues can also be concerns. Will the registry include autism and profound mental retardation? Will cases of autism occurring in severely abused and neglected children be included? Will children with genetic disorders and autism be listed on the registry?

In this study we have demonstrated a registry birth certificate linkage model as a strategy to identify potential risk factors for childhood mental illness. The data developed from this model also has both clinical and public health implications. A replication of this study would be very valuable in determining the prevalence of these risk factors among persons with autism in other clinical settings.

Abstract

Aim: To identify pre- and perinatal risk factors for autism.

Method: Case control study. We matched names of patients from North Dakota who met DSM criteria for autism, a pervasive developmental disorder, and autistic disorder with their birth certificates. Five matched controls were selected for each case.

Results: Univariate analysis of the 78 cases and 390 controls identified seven risk factors. Logistic modeling to control for confounding produced a five variable

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model. The model parameters were $\chi^2 = 36.6$ and $p < 0.001$. The five variables in the model were decreased birth weight, low maternal education, later start of prenatal care, and having a previous termination of pregnancy. Increasing father's age was associated with increased risk of autism.

Conclusion: This methodology may provide an inexpensive method for clinics and public health providers to identify risk factors and to identify maternal characteristics of patients with mental illness and developmental disorders.

Keywords: Autism, case control, pervasive developmental disorder, prenatal care, risk factors.

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Received September 13, 1999. Accepted September 19, 1999.

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