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Prenatal, perinatal and neonatal risk factors for autism - study in Poland

Research Article

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Abstract: The results of conducted research studies suggest that heredity and early fetal and neonatal development play a causal role in autism. The objective was to determine a relationship between pre-, peri-, and neonatal factors and autism. The relationship between genders and individual risk factors for autism was also examined. A case-control study was conducted among 288 children (96 cases with childhood or atypical autism and 192 controls individually matched to cases by the year of birth, sex, and general practitioners). Data on autism diagnosis and other medical conditions were acquired from physicians. All other information on potential autism risk factors were collected from mothers. Autism risk was significantly higher when mothers were taking medications (OR=2.72, 95%CI: 1.47-5.04) and smoked during pregnancy (OR=3.32, 95%CI: 1.12-9.82). It was also significantly associated with neonatal dyspnea (OR=3.20, 95%CI: 1.29-8.01) and congenital anomalies (OR=7.17, 95%CI: 2.23-23.1). In gender analysis only congenital anomalies were significantly associated with autism for girls but all of mentioned factors stayed independent risk factors for boys.

Keywords: *Autism • Prenatal • Perinatal • Neonatal • Risk factors*

1. Introduction

The results of conducted research studies suggest that heredity and early fetal and neonatal development play a causal role in autism. The etiology of autism remains unknown, but twin and family studies indicate that genetic factors play a substantial role [1,2]. The role of genetics in the risk of autism is supported by the higher recurrence rate in siblings of children with autism than siblings of typically developing children. However, studies of monozygotic twins show that only 60% of twin pairs are concordant for autism and approximately 90% for a broader spectrum of cognitive abnormalities [3]. These findings point to the presence of non-heritable risk factors for autism. This observation has also been supported by the studies, that revealed the association between autism and prenatal, perinatal and neonatal conditions, like advanced parental age, low birth weight, low Apgar score, low weight for gestational age, gestational age at birth less than 37 weeks, cesarean section, and congenital malformations [4-8]. Some of them indicate the role of vaccines as risk factors for autism and others for pervasive developmental disorders. The results of studies did not confirm the association between the MMR vaccination and autism diagnosis [9].

The objective of this study was to find out whether there was a relationship in the observed study cohort between prenatal, perinatal and neonatal factors and autism. Considering the difference in the autism incidence rates between boys and girls [10] we also examined the relationship between genders and individual risk factors for autism.

2. Materials and methods

2.1 Study population

The study was conducted at the beginning of 2007 in the population of children, aged 2-15 years, from the Malopolska Voivodship. At the end of 2006 there were 533 917 children in this age group living in this area. Children diagnosed with Autism were identified using medical records from a psychiatric outpatient clinic for children, a single institution in the voivodship where the

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autism diagnoses are established. The sample population included children aged 2-15 years, diagnosed with childhood or atypical autism (ICD-10: F84.0 and F84.1). Every diagnosis was made by a Child Psychiatrist. Cases with uncertain diagnosis of autism, secondary to diseases or trauma, such as epilepsy or infantile cerebral palsy were excluded. We intentionally excluded, from the study, autistic children with genetic syndromes, like tuberous sclerosis complex, Fragile X syndrome, and Down syndrome, and no such cases were found in the analyzed group. No diagnosis was made before 1996, when the ICD Tenth Revision came into use in Poland. All autistic children from the region that fulfilled the inclusion criteria were invited to the study by General Practitioners. About 90% of parents gave their consent to participate. Two individually matched controls were selected for each affected child, by the year of birth, gender, and outpatients' clinic. The first two children, who visited the GP after the autistic child visit, and met entry criteria served as controls.

The study has received the approval of the Jagiellonian University Ethical Committee.

2.2 Autism diagnosis and medical data

The information on the date of autism diagnosis, vaccination history and other medical data on gestational age, delivery, infants birth characteristics and history of neonatal and perinatal infant's health were extracted from the physician's records. Prolonged delivery was defined as lasting more than 20 hours, while precipitated delivery as lasting less than 3 hours. Birth defects, such as congenital malformations, jaundice, convulsion and infections in the neonatal period (up to 4 weeks after delivery) were recorded. Dyspnea was defined as difficulty in breathing which often required oxygen therapy.

2.3 Questionnaire to the parents of affected children and controls

Parents were interviewed by trained nurses using a standardized questionnaire and provided information about potentially pathologic factors that were not available from the medical files. These included taking medication during pregnancy, diseases and medical symptoms during pregnancy, active and passive smoking during pregnancy, parental and family characteristics, as well as socioeconomic status. Parental wealth was categorized by three thresholds of taxes used in Poland at that time.

2.4 Data analysis

Differences between the study and control groups for the parental age, education, maternal symptoms and diseases during pregnancy, medications taken during pregnancy, gestational time, socioeconomic status, active and passive smoking during pregnancy, perinatal injury, birth weight, Apgar score, and neonatal diseases were analyzed, using χ^2 test for categorical variables and Fisher exact test (in case of low numbers). For continuous variables, Mann-Whitney test was applied. The odds ratios for autism diagnosis were calculated using conditional logistic regression. The factors associated with autism in univariate analysis were carried forward into multivariate model. The final multivariable model included only statistically significant variables.

3. Results

A study population consisted of 96 cases and 192 controls with a mean age 7.5 +/- 2.6 years, 81.2% boys and 19.8% girls.

3.1 Prenatal factors

There was a significant association between advanced paternal age and risk of autism. Offspring of men >35 years of age were more likely to develop autism compared with offspring of younger men. No relationship was observed between advanced maternal age and the risk of autism. Parental education and socioeconomic status did not influence the risk of disease, as well. Cases had significantly lower gestational age compared to controls (Table 1).

Table 1. Prenatal characteristics of cases and controls.

		Cases (n = 96)		Controls (n = 192)		p
		N	%	N	%	
Maternal education	Elementary/ vocational school	27	*28.4*	39	*20.4*	ns
	High school	39	*41.1*	84	*44.0*	
	University	29	*30.5*	68	*35.6*	
Paternal education	Elementary/ vocational school	47	*48.9*	68	*36.6*	ns
	High school	28	*29.2*	71	*38.1*	
	University	21	*21.9*	47	*25.3*	
Level of income	Low income	54	*59.7*	114	*56.8*	ns
	Medium	5	*3.7*	7	*5.3*	
	High	1	*1.0*	2	*1.0*	
	No information	35	*35.6*	68	*35.8*	
Maternal age at delivery >35 years		12	*12.9*	14	*7.3*	ns
Paternal age at delivery >35 years		22	*23.7*	26	*13.9*	0.045
Gestation	Singleton	94	*97.9*	186	*96.9*	ns
	Multiple	2	*2.1*	6	*3.1*	
Birth order	1	40	*41.7*	91	*47.4*	ns
	2-3	46	*47.9*	84	*43.8*	
	≥4	10	*10.4*	17	*8.8*	
Gestational age <37 weeks		13	*13.5*	15	*7.8*	ns

3.2 Perinatal factors

The frequency of maternal gestational diseases was higher in the cases than in the controls. Statistically significant differences were found for vaginitis, uterine bleeding, Rh sensitivity, and taking medications during pregnancy. The medications taken during pregnancy were divided into four groups of antihypertensive drugs, antibiotics, tocolytics, and others. The analysis revealed statistically significant difference between cases and controls for antibiotics only. Maternal infectious diseases and hypertension during pregnancy showed a borderline association with autism. Other maternal diseases and symptoms included in the analysis revealed no relationship with autism. Both active and passive smoking were significantly associated with autism in the univariate analysis. Children with autism were more likely to have a breech or other abnormal fetal presentation. The meconium-stained amniotic fluid and perinatal injury were significantly associated with autism. The mode of delivery did not reveal any relationship with the risk of autism (Table 2).

3.3 Neonatal factors

Congenital malformations, neonatal infections, dyspnea, oxygen ventilation, and lower Apgar scores were significantly associated with autism. No association was found between the risk of autism and birth weight, convulsions and jaundice in the neonatal period (Table 3).

Table 3. Neonatal characteristics of cases and controls.

		Cases (n = 96)		Controls (n = 192)		p
		N	%	N	%	
Birth weight <2500g		9	*9.4*	8	*4.2*	ns
Apgar score at 5 minutes	3, 4	1	*1.0*	1	*0.5*	0,036*
	5, 6	1	*1.0*	2	*1.0*	
	7, 8	15	*15.6*	17	*8.8*	
	9, 10	79	*82.4*	172	*89.7*	
Congenital malformations		14	*14.6*	4	*2.1*	<0.001
Dyspnea		16	*18.8*	16	*8.3*	0.012
Oxygen ventilation required		15	*15.6*	14	*7.3*	0.037
Jaundice		28	*29.2*	69	*35.9*	ns
Convulsions		4	*4.2*	2	*1.0*	ns
Infection		21	*21.9*	17	*8.8*	0.003

**Apgar score as continuous variables*

3.4 Multivariate analysis

In the multivariate analysis only a few prenatal and neonatal factors showed significant association with autism (Table 4). Of these, congenital malformations revealed the strongest association with the disease OR=7.17 (95%CI: 2.23-23.1). Maternal active and passive smoking during pregnancy had consistent results, increasing the risk of developing autism: OR=3.32 (95%CI: 1.12-9.82) and OR=2.57 (95%CI: 1.23-5.36), respectively, as did taking medications during pregnancy: OR=2.72 (95%CI: 1.47-5.04) and neonatal dyspnea, which tripled the risk: OR= 3.20 (95%CI: 1.29-8.01).

Table 2. Perinatal characteristics of cases and controls.

		Cases (n = 96)		Controls (n = 192)		p
		N	%	N	%	
Maternal symptoms and diseases during pregnancy	Vaginitis	24	*25.0*	24	*12.5*	0.011
	Uterine bleeding	14	*14.6*	12	*6.3*	0.028
	Infectious diseases	6	*6.2*	4	*2.1*	0.089
	Fever	10	*10.4*	12	*6.2*	ns
	Diabetes	4	*4.2*	5	*2.6*	ns
	Preeclampsia	5	*5.3*	5	*2.6*	ns
	Chronic hypertension	13	*13.5*	14	*7.3*	0.091
	Edema	16	*16.7*	44	*22.9*	ns
	Rh sensitivity (disease)	3	*3.1*	0	-	0.037
	Accidental injury	1	*1.0*	4	*2.1*	ns
Medications during pregnancy		47	*48.9*	68	*36.6*	ns
	Antihypertensive	8	*8.3*	16	*8.3*	ns
	Antibiotics	16	*16.7*	4	*2.1*	<0.001
	Tocolytics	12	*12.5*	20	*10.4*	ns
	Others	8	*8.3*	10	*5.4*	ns
Smoking during pregnancy	Active	*12*	*12.5*	*9*	*4.7*	0.028
	Passive	*29*	*30.2*	*30*	*15.6*	0.005
Delivery conditions	Breech and other abnormal fetal presentation	11	*11.5*	13	*6.8*	ns
	Induced delivery	20	*20.8*	44	*22.9*	ns
	Prolonged delivery	4	*4.2*	4	*2.1*	ns
	Precipitated delivery	12	*12.5*	21	*10.9*	ns
	Instrumental delivery	1	*1.0*	0	-	ns
	Caesarian delivery	21	*24.0*	53	*27.9*	ns
	Meconium-stained amniotic fluid	15	*15.6*	16	*8.3*	0.070
	Perinatal injury	13	*13.5*	9	*4.7*	0.016

Table 4. Multivariable model of relative risk of autism (conditional logistic regression).

	OR*	95% CI	p
Taking medication in pregnancy	2.72	1.47 - 5.04	0.001
Active tobacco smoking in pregnancy	3.32	1.12 - 9.82	0.030
Passive tobacco smoking in pregnancy	2.57	1.23 - 5.36	0.012
Congenital malformation	7.17	2.23 - 23.1	0.001
Neonatal dyspnea	3.20	1.29 - 8.01	0.013

**Odds ratio*

3.5 Gender analysis

Multivariate analyses performed separately for boys revealed statistically significant differences for congenital malformations (OR= 4.77; 95%CI: 1.22-18.70), active smoking (OR= 3.17; 95%CI: 1.60-6.27), taking medications during pregnancy (OR= 4.79; 95%CI: 1.40-16.35), and neonatal dyspnea (OR= 4.19; 95%CI: 1.51-11.64).

The population of girls was rather small and a statistically significant association with autism was found only for congenital anomalies. The odds ratio was high (11.01) but with a wide confidence interval (95%CI: 1.11-109.3).

4. Discussion

This case-control study has been conducted to investigate prenatal, perinatal and neonatal factors for autism in Poland. The main strengths of this study are that in both cases and controls derived from the general population, all autism diagnoses were confirmed by a Child Psychologist, data used in the study are relatively complete as they derive from two sources, parental questionnaire and physician's records, medical data deriving directly from physician's records have eliminated the potential recall bias, and finally, that our findings are consistent with the observations of other authors.

High risk of autism associated with congenital malformations has been reported by many authors. There is strong evidence that autism is associated with physical anomalies [11,12]. The hypothesis about the association between autism and congenital malformations relates to disturbances during early organogenesis. During this stage, high interactivity among body parts renders the organism highly susceptible to pervasive effects of developmental disturbances. Specifically, because of this high interactivity, a change in one part of the body affects other body parts. Consequently, a single mutation or environmental factor can have many different effects during early organogenesis. Congenital malformations, well documented among autistic children, can be caused by genetic factors, chromosomal changes, drugs, chemicals or infections. Malformations in children with autism, particularly the elevated rate of craniofacial anomalies, have been interpreted as the result of initiating injury around the time of neural tube closure. This suggests an injury between days 20 and 24, and abnormal development very early in gestation. Growth aberrations and congenital malformations could be the result of similar factors at critical embryonic stages, could increase susceptibility to injury, or could decrease the embryo's ability to recover from an insult [13].

In many syndromes the co-occurrence of several anomalies including autism suggests that pleiotropic effects play a role in the development of genetic syndromes, such as tuberous sclerosis complex, Fragile X syndrome, and Down syndrome [14,15]. In our study there were no autistic children with the above mentioned genetic syndromes, but congenital malformations have been revealed in 14% of cases and only in 2% of controls, much more frequently than in other studies. In multivariate analysis the risk of autism was 7 times higher for children with congenital malformations. This result is significantly higher in comparison to the findings of previously published studies [16,17]. Differences in the results could be related to various malformation definitions and accuracy of diagnosis. Our study group was rather small, which may account for the higher accumulation of abnormalities among cases compared to other study populations.

These conditions cannot be considered as causal risk factors of autism. They may act as surrogates of fetal exposure to environmental factors causing the novo mutations or disturbances during early organogenesis. Future studies on autism and congenital malformations could help to explain the causes and pathogenesis of autism. In practice the association between autism and congenital anomalies can be useful in autism diagnosis in affected children.

In our study we found a strong association between taking medications during pregnancy and autism. Among the four groups of drugs used by mothers, only antibiotics have shown a significant difference between cases and controls. Antibiotics could be the factors which can induce a specific mutations but indirectly they reflect a severity of maternal infections regardless of causes [18,19]. Pregnant women are not treated by antibiotics without important indications. Vaginitis and other infectious diseases in pregnancy were associated with autism in univariate analysis. One limitation of our study is the lack of information about the etiology of maternal infections. Most of them were diagnosed and treated empirically, without confirmation by laboratory findings. Antibiotic therapy as indirect information about infections does not allow us to consider the effects of specific infectious diseases with respect to the risk of autism. Furthermore, we had no possibility to investigate the effect of subclinical infections, as well as many infectious diseases treated without the use of antibiotics.

Maternal infection during pregnancy is a risk factor for schizophrenia and some evidence supports its role in autism [20,21]. Research has suggested that prenatal viral infection might deregulate the fetal immune system. Additionally, consequences of maternal

infection on fetal neurodevelopment may be mediated by circulating cytokines induced by the immunogens [22,23]. Several studies and case reports have associated autism with various congenital viral infections in the first trimester and bacterial infections during entire pregnancy [24]. Maternal infection is related also to fetal oxygen deprivation as a risk factor for abnormal development [25].

Several investigators have hypothesized that certain perinatal conditions which can lead to prolonged or acute oxygen deprivation to the fetus may be an important risk factor for neuropsychological disturbances. Some indirect evidence also supports an association between hypoxia and hypoxia related conditions with autism [26,27]. According to a univariate analysis performed in our study, smoking during pregnancy, uterine bleeding, and pregnancy-induced hypertension were revealed as factors significantly associated with autism. In multivariate analysis only active and environmental tobacco smoking significantly increased the risk of autism. Tobacco smoke includes polycyclic aromatic hydrocarbons, metals and other chemicals compounds with known harmful health effects, which may cause mutagenic changes in at least two ways. First, they contribute to oxidative stress, leading to DNA damage by free radicals. Second, they tend to inhibit the DNA repair system, thereby leading to the accumulation of mutations [28-30]. Furthermore, tobacco smoke causing fetal hypoxia affects fetal brain development [27]. Our findings were consistent with the observations of other authors, who found the maternal and environmental tobacco smoking as a significant risk factor for autism [14,31], although there were studies that did not confirm this observation [23].

Newborn dyspnea with assisted ventilation was the last neonatal factor in our study that was independently associated with autism. In a univariate analysis we revealed other factors related to hypoxia that occurred more frequently in cases than controls. The presence of these factors supports the significance of oxidative stress as a potential risk factor for autism. Most of the hypotheses listed above about prenatal and perinatal risk factors for autism have been related to hypoxia regardless of causes [32,33]. Hypoxia is dangerous for the neonatal central nervous system by triggering multiple biochemical cascades involving excitatory amino acids, calcium, proinflammatory cytokines, and bioactive lipids. Hypoxia impairing neuronal water-regulatory mechanisms and disrupting the blood-brain barrier may lead to cerebral edema and neuronal necrosis [4,34].

Autism affects more boys than girls. The overall ratio of boys to girls with autism is 4:1 [35], which corresponds to our findings. Due to the small study sample we could not draw definite conclusions with regard to the distribution of risk factors for gender groups. We observed more risk factors for autism in boys than in girls. It could be due to the small number of autistic girls. Another possible explanation for this difference is the role of androgens and estrogens. One of the mechanisms behind the effect of testosterone is an increase of calcium levels by the depletion of intracellular calcium. On the contrary, estrogen acts as a neuroprotective agent by raising intracellular calcium levels and by anti-oxidant properties. Estradiol is thought to influence various brain functions by acting on receptors on the neuronal membrane surface. Through these mechanisms estrogens protect neurons from harmful influence of many factors [36-38].

In conclusion, the results of our study are consistent with the findings of other authors and support the role of several prenatal, perinatal and neonatal risk factors for autism. The results suggest that taking medications, smoking in pregnancy, neonatal dyspnea and congenital anomalies are independently associated with autism risk. In gender analyses only congenital anomalies were significantly associated with autism for girls but all of the mentioned factors stayed independent risk factors for boys. The future study should examine the interaction of autism susceptibility genes with nonheritable risk factors related to gender. It could help researchers to understand the significant difference in autism prevalence between boys and girls. Finding the associations between autism and some prenatal, perinatal and neonatal factors would be useful in making diagnosis of autism in affected children. In particular, children with congenital anomalies should be subjected to extensive medical testing to allow early diagnosis, because it increases the effectiveness of intervention.

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