ARTICLE

Association of Hospitalization for Infection in Childhood With Diagnosis of Autism Spectrum Disorders

A Danish Cohort Study

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Objective: To investigate the association between hospitalization for infection in the perinatal/neonatal period or childhood and the diagnosis of autism spectrum disorders (ASDs).

Design: A population-based cohort study.

Setting: Denmark.

Participants: All children born in Denmark from January 1, 1980, through December 31, 2002, comprising a total of 1 418 152 children.

Exposure: Infection requiring hospitalization.

Main Outcome Measure: The adjusted hazard ratio (HR) for ASDs among children hospitalized for infection compared with other children.

Results: A total of 7379 children were diagnosed as having ASDs. Children admitted to the hospital for any infectious disease displayed an increased rate of ASD diagnoses (HR, 1.38 [95% confidence interval, 1.31-1.45]). This association was found to be similar for infectious diseases of bacterial and viral origin. Furthermore, children admitted to the hospital for noninfectious disease also displayed an increased rate of ASD diagnoses (HR, 1.76 [95% confidence interval, 1.68-1.86]), and admissions for infection increased the rate of mental retardation (2.18 [2.06-2.31]).

Conclusions: The association between hospitalization for infection and ASDs observed in this study does not suggest causality because a general association is observed across different infection groups. Also, the association is not specific for infection or for ASDs. We discuss a number of noncausal explanatory models.

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AUTISM SPECTRUM DISORDERS (ASDs) are childhood neurodevelopmental disorders characterized by impairments in social interactions and communication and a stereotyped, repetitive repertoire of interests and activities.[1]

Studies of immunological function in children with ASDs reveal functional deviations in cellular and humoral immunity compared with the immune responses of typically developing children.[2,3] Findings include decreased response to T-cell mitogens,[2] reduced activity of natural killer cells,[4,5] imbalance in helper T-cell type,[6,7] and altered cytokine levels.[2,7]

The following theory of neuroautoimmunity has been proposed: ASDs may be caused by autoimmunity to the brain, possibly triggered by a viral infection such as measles virus.[7] This hypothesis is supported by a positive correlation among brain autoantibodies, viral serology findings, and elevated proinflammatory cytokine levels.[7-10]

A study by Rosen et al[11] is the only epidemiological study to investigate the association between infections and the subsequent diagnosis of ASDs. The authors found that infection diagnoses in the first 2 years of life were recorded slightly less often for children with ASDs than for a control group of children (95.0% vs 97.5%).

Congenital infections such as cytomegalovirus and the rubella virus have been suggested to be associated with the diagnosis of ASDs in the offspring.[12-14] In support of this theory, Rosen et al[11] found that, in the first 30 days of life, the frequency of having an infection was slightly higher among children later diagnosed as having autism (22.6% vs 18.7%).

Ours is a population-based cohort study in which we have investigated the association between admission to the hospital for perinatal/neonatal or child-

hood infection and the later diagnosis of ASDs or infantile autism.

METHODS

STUDY POPULATION

The study cohort includes all children born in Denmark from January 1, 1980, through December 31, 2002, identified in the Danish Medical Birth Registry,[15] comprising a total of 1 418 152 children. Data on death came from the Danish Register of Causes of Death.[16] All live-born children in Denmark are assigned a personal identification number.[17] The identification number was used as a key to individual information in all national registers to ensure accurate linkage of information.

DIAGNOSTIC SYSTEM

The *International Classification of Diseases, Eighth Revision* (*ICD-8*)[18] was used as a diagnostic instrument by physicians in Denmark from 1969 through 1993. In 1994, the *ICD-8* was replaced by the *10th Revision* (*ICD-10*),[1] which is still used.

OUTCOME DATA

Diagnoses of ASDs were found in the Danish Psychiatric Central Register.[19] The psychiatric register includes information on all inpatient admissions to psychiatric hospitals and psychiatric wards in general hospitals in Denmark since 1969 and all outpatient contact since 1995. All registered diagnoses are made by psychiatrists. Children who are suspected of having ASDs are referred by general practitioners or school psychologists to a child psychiatric ward where they receive diagnosis and treatment. Outcome was defined in the following ways: (1) all ASD diagnoses (*ICD-10* codes F84.0, F84.1, F84.5, F84.8, and F84.9 and *ICD-8* codes 299.00, 299.01, 299.02, and 299.03) and (2) all diagnoses representing infantile autism (*ICD-10* code F84.0 and *ICD-8* code 299.00).

EXPOSURE DATA

Diagnoses of infectious diseases were obtained from the Danish National Hospital Register.[20] The hospital register was initiated in 1977 and includes detailed information on all hospital admissions in the entire country. We included only the primary diagnosis of patients registered as admitted to the hospital. In this study, we included only infectious diseases diagnosed before the date of the first contact with a child psychiatric ward that led to the diagnosis of ASDs in the child. We analyzed the infection data in several categories. General infection categories included (1) all perinatal and/or neonatal infections, defined as all infections in the child registered from birth until 28 days of age, and (2) all childhood infections, defined as all infections registered after 28 days of age and until the end of follow-up. Furthermore, we divided childhood infections into microorganism- and organ-specific categories (**Table 1**). We estimated hazard ratios (HRs) for subgroups if at least 5 subjects with a diagnosis of ASD had been exposed.

ANALYTIC APPROACH

We used HRs from Cox proportional hazards regression to estimate the association between hospitalization for infection and a later diagnosis of ASDs. The age of the child was used as the time variable. The HR may be interpreted as a relative risk because ASD is a rare disease. Survival analyses methods adjust for any difference in follow-up time; follow-up time ended at the first date of the reported ASD diagnosis, at death, or on December 31, 2006. The proportional hazards assump-

Table 1. *ICD-8* and *ICD-10* Diagnostic Codes of Infectious Disease Categories

Infection Category	*ICD-8* Codes	*ICD-10* Codes
General infection[a]		
Perinatal/neonatal infection[b]	All below	P23, P35-P39, and all below
Childhood infection[c]	000-136, 780.21, 788.89, and all below	A00-B99, R50.9, R56.0, and all below
Microorganism-specific childhood infection[a]		
Viral infection	008.8-008.9, 040-079, 381.00, 470-474, and 480	A08, A80-A99, B00-B34, B97, G02.0, G05.1, H67.1, J10-J12, J17.1, J20.3-J20.7, J21.0, and M01.4-M01.5
Bacterial infection	000-005, 008.0-008.3, 010-039, 320-324, 381.01, 390-391, 481-482, 501, 508.00-508.03, 510, 513, 540-542, 590, 595, 599.00, 599.06, 680-686, and 710	A00-A05, A15-A49, B95-B96, G00, G01, G04.2, G05.0, G06-G09, H66, H67.0, I00-I01, J13-J15, J17.0, J20.0-J20.2, J36, J39.0-J39.1, J85-J86, K35-K37, L00-L08, M00, M01.0-M01.3, N10-N12, N30, N34.0, and N39.0
Fungal infection	110-117	B35-B49
Human herpesvirus	052, 053, 054, 057.19, 075, 079.50, 079.51, and 079.59	B00, B01, B02, B08.2, B25, and B27
Influenza	470-474	J10-J11
Organ-specific childhood infection[a]		
CNS infection	013, 027.01, 036, 040-045, 052.01, 053.02, 054.03, 055.01, 056.01, 062-066, 072.02, 075.01, 079.29, and 320-324	A17, A32.1, A39, A80-A89, B00.3, B00.4, B01.0, B01.1, B02.0, B02.1, B05.0, B05.1, B06.0, B26.1, B26.2, B37.5, B58.2, and G00-G09
Infectious enteritis	001-009	A01-A09
Skin infection	680-686	L00-L08
Urinary tract infection	590, 595, 599.00, and 599.06	N10-N12, N30, N34.0, and N39.0
Septicemia	038	A40 and A41
Appendicitis	540-542	K35-K37
Respiratory infection	032-034, 460-474, 480-486, 491.01, 501, 503, 506, 508.00-508.05, 510-511, and 513	A36-A38, J00-J22, J32, J36-J37, J39.0-J39.1, and J85-J86
Otitis media	381-382	H65-H67

Abbreviations: CNS, central nervous system; *ICD-8, International Classification of Diseases, Eighth Revision*; *ICD-10, International Statistical Classification of Diseases, 10th Revision*.

[a] Disease groups within the category are mutually exclusive.

[b] Includes only infectious diagnoses registered from birth until 28 days of age.

[c] Includes diagnoses from 28 days of age until the end of follow-up.

Table 2. Characteristics of All Children Born in Denmark From January 1, 1980, Through December 31, 2002

Characteristic	No. (%) of Children[a] Not Hospitalized for Infection (n=1 063 159)	Hospitalized for Infection (n=354 993)
Autism spectrum disorders	5184 (0.5)	2195 (0.6)
Infantile autism	1406 (0.1)	586 (0.2)
Sex		
Male	530 717 (49.9)	197 376 (55.6)
Female	532 442 (50.1)	157 617 (44.4)
Gestational age, wk		
<28	2360 (0.2)	863 (0.2)
28-31	5479 (0.5)	3515 (1.0)
32-36	45 174 (4.2)	21 735 (6.1)
≥37	989 774 (93.1)	321 570 (90.6)
Missing	20 372 (1.9)	7310 (2.1)
Birth weight, g		
<2500	49 288 (4.6)	24 370 (6.9)
2500-2999	127 119 (12.0)	49 356 (13.9)
3000-3499	345 098 (32.5)	116 379 (32.8)
≥3500	535 936 (50.4)	163 048 (45.9)
Missing	5718 (0.5)	1840 (0.5)
Mother's age, y		
<20	25 426 (2.4)	12 724 (3.6)
21-25	207 623 (19.5)	83 269 (23.5)
26-30	415 989 (39.1)	136 342 (38.4)
31-34	297 730 (28.0)	88 811 (25.0)
≥35	116 391 (10.9)	33 847 (9.5)
Father's age, y		
<25	108 618 (10.2)	47 460 (13.4)
26-30	331 753 (31.2)	115 008 (32.4)
31-35	352 371 (33.1)	110 412 (31.1)
≥35	259 924 (24.4)	79 067 (22.3)
Missing	10 493 (1.0)	3046 (0.9)
Parity		
First child	477 427 (44.9)	160 448 (45.2)
≥2 children	574 390 (54.0)	190 903 (53.8)
Missing	11 342 (1.1)	3642 (1.0)
Parental psychiatric disorder		
Yes	27 786 (2.6)	12 224 (3.4)
No	1 035 373 (97.4)	342 769 (96.6)
Year of birth		
1980-1982	115 727 (10.9)	47 311 (13.3)
1983-1985	111 541 (10.5)	44 829 (12.6)
1986-1988	122 512 (11.5)	47 865 (13.5)
1989-1991	139 543 (13.1)	49 589 (14.0)
1992-1994	160 087 (15.1)	44 675 (12.6)
1995-1997	156 840 (14.8)	48 325 (13.6)
1998-2000	154 165 (14.5)	45 585 (12.8)
2001-2002	102 744 (9.7)	26 814 (7.6)
Congenital malformation		
Yes	38 738 (3.6)	22 198 (6.3)
No	1 024 421 (96.4)	332 795 (93.7)

[a] Percentages have been rounded and may not total 100.

tion was evaluated for all variables by comparing estimated log–minus–log survivor curves over the different categories of variables investigated. All HRs were adjusted for birth weight, gestational age, sex of the child, maternal and paternal ages at the birth of the child, parity, congenital malformation (*ICD-8* codes 740-759 and *ICD-10* codes Q00-Q99), and a dichotomous variable indicating whether either parent had a history

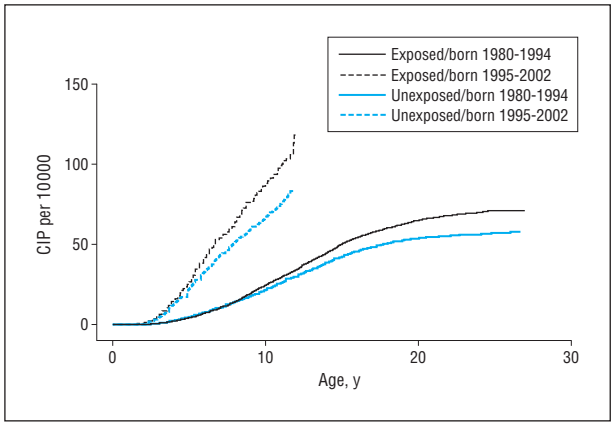

Figure. Cumulative incidence proportion (CIP) for autism spectrum disorders among children born from January 1, 1980, through December 31, 2002, in Denmark. The study population was divided by the year of birth and exposure status.

of psychiatric diagnosis before the birth of the child (*ICD-8* codes 310-315 and *ICD-10* code F7). Admission to the hospital for an infectious disease and congenital malformation were treated as time-dependent variables[21]; other covariates were categorical (categories are listed in **Table 2**). Only 4% of observations were excluded from analyses because of missing variables (Table 2). To adjust for changes in HRs over calendar time, all analyses were made in strata specific for the year of birth in specific groups listed in Table 2. To check for residual confounding, we also analyzed data using spline variables instead of categorical variables,[22] but this did not change the results. To account for the lack of independence of children within the same family, we used a robust (Huber-White) variance estimator that allowed for clustering of outcomes within a family.

PRIMARY ANALYSES

Our primary analyses concerned whether admission to the hospital for a neonatal/perinatal infection or various childhood infections was associated with a subsequent diagnosis of ASD or infantile autism.

SECONDARY ANALYSES

In secondary analyses, we investigated whether the rate of ASDs/infantile autism diagnoses increased with the number of hospital admissions for any infection. If less than 7 days passed between an individual's registered discharge from the hospital and a subsequent admission, the 2 hospitalizations were considered as 1 infection incident.

Furthermore, we investigated whether the effect between childhood infection and ASDs was modified by (1) age at admission to the hospital (29 days to 17 months, 18 to 35 months, 36 months to 6 years, and >6 years), (2) gestational age (<37 and ≥37 weeks), (3) birth weight (<2500 and ≥2500 g), (4) year of birth (1980-1994 and 1995-2002), or (5) the sex of the child.

It was relevant to investigate whether the association was specific for ASDs; therefore we studied the association between any childhood infection and a later diagnosis of mental retardation (*ICD-8* codes 310-315 and *ICD-10* code F7), adjusting for the same variables as in the main analysis. Also, it was relevant to investigate whether the association was specific for hospitalization for infection; therefore, we studied the association between hospitalization for a noninfectious somatic disease and ASDs, adjusting for the same variables as in the main analysis. In this analysis, the exposure measure included all inpatient hospitalizations in childhood (admissions

Table 3. Adjusted HRs for ASDs Among Children Hospitalized for Infection Compared With Children Not Hospitalized for the Particular Infection

Infection Category[a]	No. Exposed With Outcome	HR (95% CI)[b]			*P* Value for Interaction by Sex
		All	Boys	Girls	
General infection[c]					
Perinatal/neonatal infection[d]	135	1.16 (0.97-1.39)	1.08 (0.89-1.33)	1.54 (1.03-2.32)	.12
Childhood infection[e]	2195	1.38 (1.31-1.45)	1.31 (1.24-1.39)	1.68 (1.49-1.90)	<.001
Microorganism-specific childhood infection[c]					
Viral infection	577	1.47 (1.34-1.60)	1.40 (1.27-1.54)	1.82 (1.49-2.23)	.004
Bacterial infection	520	1.31 (1.20-1.44)	1.28 (1.16-1.42)	1.44 (1.18-1.76)	.049
Fungal infection	13	3.37 (1.91-5.96)	3.96 (2.18-7.20)	NE	NE
Human herpesvirus	73	1.49 (1.17-1.89)	1.45 (1.11-1.90)	1.62 (0.95-2.74)	.47
Influenza	20	1.51 (0.97-2.34)	1.07 (0.61-1.89)	3.91 (1.95-7.86)	.003
Organ-specific childhood infection[c]					
CNS infection	59	1.48 (1.33-1.93)	1.33 (0.98-1.80)	2.33 (1.35-4.01)	.03
Infectious enteritis	370	1.36 (1.22-1.51)	1.26 (1.11-1.42)	1.86 (1.48-2.33)	.001
Skin infection	55	0.98 (0.75-1.29)	0.96 (0.71-1.29)	1.09 (0.55-2.15)	.63
Urinary tract infection	56	1.14 (0.87-1.49)	1.13 (0.82-1.58)	1.10 (0.70-1.74)	.76
Septicemia	17	1.30 (0.80-2.13)	1.36 (0.80-2.29)	NE	NE
Appendicitis	73	1.03 (0.81-1.30)	0.99 (0.75-1.29)	1.22 (0.75-1.97)	.13
Respiratory infection	1246	1.30 (1.22-1.39)	1.23 (1.15-1.32)	1.70 (1.47-1.98)	<.001
Otitis media	359	1.71 (1.53-1.91)	1.61 (1.43-1.82)	2.22 (1.73-2.84)	.002

Abbreviations: ASDs, autism spectrum disorders; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; NE, not estimated.
[a] Children may be counted in different disease groups if they had more than 1 infectious disease admission (eg, an admission for CNS infection and an admission for otitis media). Not all infectious diagnoses were specified by microorganism, resulting in a relatively low number of microorganism-specific admissions.
[b] Adjusted for maternal age, paternal age, gestational age, birth weight, parity, sex, congenital malformation, and the parents' psychiatric condition. Data were analyzed in strata by year of birth.
[c] Disease groups are mutually exclusive within the category.
[d] Includes only infectious diagnoses registered from birth until 28 days of age.
[e] Includes diagnoses made from 28 days of age until the end of follow-up.

after 28 days of age) (*ICD-8* codes 140-999 and *ICD-10* codes C00-T98), excluding inpatient admissions for infectious diagnoses (Table 1), psychiatric diagnoses (*ICD-8* codes 290-299 and *ICD-10* codes F00-F99), and all congenital malformations (*ICD-8* codes 740-759 and *ICD-10* codes Q00-Q99). We performed statistical analyses using Stata statistical software.[23]

VALIDATION

To assess diagnostic accuracy for infection, we examined the medical records of 20 children with meningitis, 20 with urinary tract infections, and 20 with pneumonia.

To look for evidence that ASD symptoms might have been noted during the admission for infection, we reviewed a random selection of 100 medical records of admissions for infections among children later diagnosed as having ASDs.

The study was approved by the Danish Data Protection Agency and the Danish National Board of Health.

RESULTS

A total of 7379 children were diagnosed as having ASDs, of whom 1992 were diagnosed as having infantile autism. Participant characteristics by exposure status show that those admitted to the hospital for infection were more likely to be boys, have younger parents, have had a preterm birth, have a low birth weight, be diagnosed as having congenital malformations, and have parents with a psychiatric diagnosis (Table 2). As expected, children born in 1995 and thereafter had a higher cumulative incidence of ASD diagnoses compared with children born before 1995 (**Figure**). The mean follow-up time was 14.8 years, and 13 452 children died during follow-up. The mean age at ASD diagnosis was 8.9 years for all ASDs and 6.6 years for infantile autism.

PRIMARY ANALYSES

Children hospitalized with a childhood infection were more likely to be later diagnosed as having ASDs compared with children who were never hospitalized for such an infection (HR, 1.38 [95% confidence interval (CI), 1.31-1.45]). Perinatal/neonatal infection gave only a minor rise in the rate of ASDs (HR, 1.16 [95% CI, 0.97-1.39]). The same pattern of association was observed for infantile autism. Almost all microorganism- and organ-specific childhood infections displayed an association with ASDs and infantile autism (**Table 3** and **Table 4**).

SECONDARY ANALYSES

The HR between infection and ASDs increased with the number of admissions for childhood infection from 1.25 for 1 infection to 1.49 for 2 infections and 2.03 for 3 or more infections ($P<.001$ from a test of trend) (**Table 5**). A similar pattern of association was observed between the number of admissions for infection and infantile autism (Table 5).

Age at the time of infection did not modify the association between hospitalization for childhood infection and ASDs (29 days to 17 months: HR, 1.38 [95% CI, 1.29-1.47]; 18 to 35 months: HR, 1.38 [95% CI, 1.25-1.52]; 36 months to 6 years: HR, 1.45 [95% CI, 1.29-1.63]; and

Table 4. Adjusted HRs for Infantile Autism Among Children Hospitalized for Infection Compared With Children Not Hospitalized for the Particular Infection

Infection Category[a]	No. Exposed With Outcome	HR (95% CI)[b]			*P* Value for Interaction by Sex
		All	Boys	Girls	
General infection[c]					
Perinatal/neonatal infection[d]	46	1.33 (0.98-1.82)	1.18 (0.83-1.69)	2.13 (1.13-4.00)	.11
Childhood infection[e]	586	1.46 (1.32-1.61)	1.38 (1.24-1.54)	1.86 (1.48-2.32)	.005
Microorganism-specific childhood infection[c]					
Viral infection	177	1.55 (1.32-1.82)	1.48 (1.24-1.78)	1.87 (1.30-2.68)	.14
Bacterial infection	132	1.42 (1.18-1.70)	1.28 (1.04-1.58)	2.00 (1.41-2.84)	.01
Human herpesvirus	19	1.74 (1.09-2.76)	1.66 (0.98-2.81)	NE	NE
Influenza	6	1.91 (0.85-4.26)	NE	NE	NE
Organ-specific childhood infection[c]					
CNS infection	17	2.09 (1.28-3.42)	1.71 (0.95-3.10)	4.05 (1.68-9.74)	.06
Infectious enteritis	97	1.38 (1.12-1.70)	1.36 (1.08-1.72)	1.44 (0.89-2.35)	.69
Skin infection	10	0.74 (0.40-1.39)	0.81 (0.42-1.56)	NE	NE
Urinary tract infection	10	0.80 (0.43-1.48)	NE	1.43 (0.63-3.24)	NE
Appendicitis	7	0.68 (0.32-1.43)	0.72 (0.32-1.61)	NE	NE
Respiratory infection	329	1.32 (1.33-1.69)	1.23 (1.07-1.41)	1.80 (1.38-2.36)	.003
Otitis media	121	2.41 (2.00-2.90)	2.24 (1.82-2.77)	3.23 (2.16-4.82)	.03

Abbreviations: See Table 3.
[a] Children may be counted in different disease groups if they had more than 1 infectious disease admission (eg, an admission for CNS infection and an admission for otitis media). Not all infectious diagnoses were specified by microorganism, resulting in a relatively low number of microorganism-specific admissions.
[b] Adjusted for maternal age, paternal age, gestational age, birth weight, parity, sex, congenital malformation, and the parents' psychiatric condition. Data were analyzed in strata by year of birth.
[c] Disease groups within the category are mutually exclusive.
[d] Includes only infectious diagnoses registered from birth until 28 days of age.
[e] Includes diagnoses made from 28 days of age until the end of follow-up.

Table 5. Adjusted HRs of ASDs Among Children Hospitalized for Any Infection Compared With Children Not Hospitalized for Infection[a]

	No. of Admissions, HR (95% CI)[b]		
	1	2	≥3
ASDs			
All	1.25 (1.18-1.33)	1.49 (1.35-1.65)	2.03 (1.81-2.29)
Boys	1.22 (1.14-1.30)	1.36 (1.21-1.52)	1.89 (1.65-2.15)
Girls	1.41 (1.22-1.63)	2.25 (1.80-2.81)	2.88 (2.21-3.76)
Infantile autism			
All	1.25 (1.11-1.41)	1.75 (1.46-2.11)	2.20 (1.76-2.75)
Boys	1.25 (1.10-1.42)	1.48 (1.19-1.83)	1.92 (1.48-2.49)
Girls	1.25 (0.93-1.67)	3.34 (2.33-4.79)	3.83 (2.46-5.99)

Abbreviations: See Table 3.
[a] For all comparisons by the number of admissions, $P<.001$ for test of trend.
[b] Adjusted for maternal age, paternal age, gestational age, birth weight, parity, sex, congenital malformation, and the parents' psychiatric condition. Data were analyzed in strata by year of birth.

>6 years: HR, 1.24 [95% CI, 1.06-1.45]; $P=.46$ from a test of interaction). Birth weight (<2500 g: HR, 1.51 [95% CI, 1.27-1.81]; ≥2500 g: HR, 1.37 [95% CI, 1.30-1.45]; $P=.48$ from a test of interaction), gestational age (<37 weeks: HR, 1.41 [95% CI, 1.18-1.68]; ≥37 weeks: HR, 1.38 [95% CI, 1.30-1.45]; $P=.98$ from a test of interaction), and year of birth (1980-1994: HR, 1.42 [95% CI, 1.33-1.51]; 1995-2002: HR, 1.31 [95% CI, 1.20-1.43]; $P=.14$ from a test of interaction) did not modify the association between admission to the hospital for childhood infection and ASDs. However, stratification by sex revealed a generally larger HR of ASDs/infantile autism for girls compared with boys after hospitalization for infection (Tables 3 and 4).

Children hospitalized for a childhood infection were more likely to be later diagnosed as having mental retardation compared with children who were never hospitalized for infection (all children: HR, 2.18 [95% CI, 2.06-2.31]; boys: HR, 2.03 [95% CI, 1.90-2.18]; and girls: HR, 2.49 [95% CI, 2.26-2.46]). Hospitalization for a noninfectious somatic cause was also found to be associated with a diagnosis of ASDs (all children: HR, 1.76 [95% CI, 1.68-1.86]; boys: HR, 1.64 [95% CI, 1.55-1.73]; and girls: HR, 2.49 [95% CI, 2.20-2.81]). There was a substantial overlap between children admitted to the hospital for infection and children admitted for a noninfectious disease: a total of 507 764 children were admitted for a noninfectious disease, of whom

174 727 children were also admitted for an infectious disease.

VALIDATION

According to our review of medical records of admissions for infectious disease, 18 of the 20 meningitis diagnoses (90%) were affirmed by cerebrospinal fluid culture, 16 of the 20 pneumonia diagnoses (80%) were affirmed using radiographs and/or sputum culture, and 19 of the 20 urinary tract infections (95%) were affirmed using urine culture.

A review of medical records describing the hospital admissions for infections among 100 children later diagnosed as having ASDs revealed that medical professionals commented on undiagnosed developmental difficulties in only 3 cases. Seven children had already been referred for further examinations because of developmental deficiencies; that is, no specific concerns for the development of the child were noted for 90% of the children. However, eighteen of those 90 children were, at the time of the infection, being followed up in different neonatal or pediatric outpatient clinics for a variety of comorbid somatic conditions such as epilepsy, neurofibromatosis, asthma, perinatal asphyxia, hemophilia, and failure to thrive.

COMMENT

This study suggests that admission to the hospital for various childhood infections is associated with diagnoses of ASDs, as well as infantile autism specifically. Generally, a stronger association was found between infection and the diagnosis of ASDs if the child had multiple separate admissions for infection. Almost all observed associations were found to be modified by sex, with a stronger association for girls compared with boys. Moreover, noninfectious somatic hospital admissions were associated with ASDs, and admission for infection was also associated with mental retardation.

LIMITATIONS

Most infectious diseases never require hospitalization; we were unable to investigate the effect of subclinical infections as well as the many infections treated by general practitioners. Rosen et al[11] observed a slightly lower risk of overall infections in the first 2 years of life. They found that upper respiratory infections were significantly less frequently diagnosed and genitourinary tract infections were more frequently diagnosed in children later diagnosed as having autism compared with controls. These results are the opposite of our present results. This could be because Rosen et al[11] acquired exposure information from the Kaiser Permanente clinical database, which includes diagnoses from primary care, in contrast to the present study, which only includes infections requiring admission to the hospital.

We are potentially missing some diagnoses of ASDs made before 1995; children only seen in the outpatient clinic from 1980 to 1994 and with no contact with a psychiatric ward after 1994 are not registered as having ASDs. However, this misclassification is most likely nondifferentiated.

The time of the first presentation of symptoms of autism is most often unclear.[24] The time of autism diagnosis depends on factors such as diagnostic practice and parental vigilance to the first symptoms of autism,[25] but in all cases symptom debut necessarily occurs some time before the registration of the diagnosis; therefore, it is always a limitation to use register-based data to investigate causality. Indeed, our small review of medical records for children later diagnosed as having autism demonstrated that 7% of the children had already been referred for a psychiatric examination because of developmental difficulties at the time of the infection.

DATA QUALITY

The quality of infantile autism diagnoses found in the Danish Psychiatric Central Registry has been validated by Lauritsen et al[26]; after evaluating 499 medical records of children diagnosed as having infantile autism using *ICD-10* codes, 94% met the criteria for a correct diagnosis. The completeness of ASDs diagnoses in the Danish register is assumed to be good; the prevalence of ASDs for 9-year-old children is reported to be 5.1 per 1000,[27] an estimate similar to the American prevalence of 4.2 per 1000 for 8-year-old children living in metropolitan Atlanta.[28]

A small review of 60 medical records provided some evidence supporting the validity of the infection diagnoses.

The registration of mental retardation is known to be incomplete in the national registries because the diagnosis of mental retardation often is secondary to a primary diagnosis; therefore, the results concerning mental retardation can only be used to put an additional perspective on the results concerning ASDs.

CAUSAL RELATIONSHIP

We observed the same pattern of association between many different infectious categories and the diagnosis of ASDs/infantile autism. This indicates that the present findings are not a result of a causal relationship. Also, a stronger association was found between hospitalization for noninfectious diseases and ASDs and between hospitalization for infection and mental retardation compared with admission for infection and ASDs. Moreover, our study does not suggest perinatal/neonatal infection to be a major risk factor for ASDs.

Laboratory studies have suggested that specific viruses, such as the measles virus or the human herpesvirus, trigger the development of ASDs.[10] In our study, hospitalization for human herpesvirus displayed the same pattern of association with ASDs as hospitalization for other infections. Because of an effective vaccination program, almost no children in Denmark are exposed to measles; therefore, it was not possible to investigate this association specifically. Our study is not capable of making a definite conclusion about the relationship between specific microorganisms and ASDs.

NONCAUSAL EXPLANATIONS OF THE FINDINGS

The following explanatory models are based on the notion that ASDs and infantile autism are present from birth

or shortly after birth but are not diagnosed until later in childhood.

Increased Susceptibility to Infection

Certain children with ASDs may be more susceptible to infection compared with children meeting normal developmental milestones, before the ASD diagnoses are recognized and registered. The dose-response relationship between infection and ASDs suggests that children with developmental problems more often have repeated infections compared with children without these problems. Also, the association was stable throughout all ages. The theory of increased susceptibility to infection is furthermore supported by previous studies reporting that children with ASDs have frequent episodes of otitis media and respiratory infection.[29-32]

Comorbidity to Somatic Diagnoses

Our results indicate that a pattern of increased childhood illness overall may characterize children with ASDs; this is in concordance with reports that children with ASDs have a higher prevalence of different medical conditions.[33-38] A somatic disease co-occurring with ASDs could hypothetically increase the child's risk of infection. In support of this theory, we found that approximately half of the children admitted to the hospital for a childhood infection had also been admitted for a childhood noninfectious disease.

Parental Concern

Children with ASDs often have prodromal symptoms such as failure to thrive,[39] gastrointestinal tract problems,[40,41] and self-stimulatory behavior[42] before the recognition of ASDs. These symptoms could increase the anxiety and awareness of parents and physicians, lowering the threshold for hospitalization for infection as well as these symptoms, in some cases predisposing the children to infection. Furthermore, these symptoms could hinder the children from being successfully treated with oral medication and thus lead to a hospitalization. This argument is strengthened by the fact that admission for infection was also associated with mental retardation.

Medical Attention

Admission to the hospital—regardless of the cause of the admission—might direct the attention of medical professionals to developmental problems of the child, leading to referral to a child psychiatric ward and diagnosis of ASD/infantile autism. A recent study[43] found that children who were admitted for acute care at a pediatric hospital had a high prevalence of developmental disorders. Many of the developmental problems had not been identified before the hospitalization. In accordance with these results, we found that hospitalization in general was associated with diagnosis of ASDs. However, our review of 100 randomly chosen medical records describing the admission for infections of children who were later diagnosed as having ASDs showed that medical professionals recorded developmental difficulties in only 3% of the cases. It is possible that an informal conversation between medical professionals and parents occurred without being noted in the medical record. A dialogue making the parents more attentive to specific signs of ASDs may thereby indirectly lead to a diagnosis of ASD.

This study suggests that hospitalization for childhood infection is associated with the diagnosis of ASDs and infantile autism. A causal relationship between admission to a hospital for infection and ASDs seems unlikely because the same pattern of association was observed for a wide range of infections and also because the association observed was not specific to admission for infection or for the diagnosis of ASDs. The results are more likely explained through a combination of noncausal factors.

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