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Risk Factors for Autistic Regression: Results of an Ambispective Cohort Study

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Abstract

A subgroup of children diagnosed with autism experience developmental regression featured by a loss of previously acquired abilities. The pathogeny of autistic regression is unknown, although many risk factors likely exist. To better characterize autistic regression and investigate the association between autistic regression and potential influencing factors in Chinese autistic children, we conducted an ambispective study with a cohort of 170 autistic subjects. Analyses by multiple logistic regression showed significant correlations between autistic regression and febrile seizures (OR = 3.53, 95% CI = 1.17-10.65, $P = .025$), as well as with a family history of neuropsychiatric disorders (OR = 3.62, 95% CI = 1.35-9.71, $P = .011$). This study suggests that febrile seizures and family history of neuropsychiatric disorders are correlated with autistic regression.

Keywords

autistic regression, risk factors, febrile seizures, neuropsychiatric disorders

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Autism spectrum disorders are a set of heterogeneous disorders characterized by profound impairments in social reciprocity, abnormalities in communication, and the presence of nonfunctional restricted, repetitive, and stereotyped behaviors.[1] According to the latest *Diagnostic and Statistical Manual of Mental Disorders*, autistic disorder, Asperger syndrome, and pervasive developmental disorder-not otherwise specified are part of autism spectrum disorders. The prevalence of autism spectrum disorders has significantly increased in recent surveys. Current estimate of autistic disorder prevalence is about 20 out of 10 000, while that of autism spectrum disorders is in the 60 to 70 out of 10 000 range.[1-4]

Most patients with autism spectrum disorders exhibit developmental differences, as compared with normal children, since birth or early infancy. However, a substantial minority of patients develop in a normal or relatively normal fashion for the first months of life and then undergo a remarkable developmental regression characterized by loss of previously acquired abilities and sudden appearance of autistic behavioral patterns.[5-7] According to the report of parents, some children with regression showed a very abrupt change in their development and behavior, while the others showed a more gradual change. This phenomenon has been termed "autistic regression."[8] Autistic regression often appears between 12 and 24 months of age, with the mean age around 21 months and essentially prior to 3 years of age.[8-14] According to studies of caregivers' retrospective reports, regression varied within the range of 13.8% to 50%, depending on the definition of regression and the specific population studied, and individuals with autistic disorder are more likely to regress as compared with subjects within the whole spectrum of autism spectrum disorders.[12,13,15-21]

The lost previously acquired skills in autistic regression can involve language and social and/or other skills, and often consist of loss of function in more than one of the above-mentioned domains.[22] Language regression has been the most prominent indicator of autistic regression, which is more likely to attract the attention of parents.[21] Before meaningful word development, regression of babble and proto-words has also been noted.[8] Social skills that are lost during regression may include eye contact, joint attention, social peer interest, social smiling, reactivity, gestural communication (eg, pointing, nodding head, waving bye-bye), spontaneous imitation of actions, play skills, and appropriate affect.[6,23,24] After months or longer, the lost skills can be regained in some children, but not others.[12,22] In comparison with nonregressive autistic children, regression is associated with poorer prognosis, reflected as lower cognitive and adaptive outcomes in several investigations.[16,20,25]

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Autistic regression is a highly disturbing phenomenon, since it changes a normally developing child into a nonverbal, severely autistic, child. The association between risk factors including epilepsy and epileptiform EEGs and autistic regression has been widely investigated. Many studies suggest that epilepsy is highly related to regression, but some controversies remain.[17,26-31] Relatively few studies have investigated perinatal risk factors and family background. In the process of our clinical work, we discovered that several typically or relatively typically developing children exhibited autistic regression following febrile seizures. The time course and epidemiology of autistic regression and febrile seizure have some similarities, in that they are both likely to occur in children before the age of 3 years, with a peak age of onset during the second year of life, and boys were more likely to be affected than girls.[8-11,13,32] To our knowledge, no published studies specifically investigated whether febrile seizure is a risk factor for autistic regression. So we included febrile seizure as a potential risk factor for autistic regression in this study.

The 2 main aims of our study are (1) to characterize the regression in a cohort of children with regressive and nonregressive autism, including the prevalence, onset age, gender, and the type of previously acquired skills lost during regression, and (2) to examine the correlation between autistic regression and perinatal risk factors, family background, and febrile seizures.

Methods

Study Design and Target Population

This study was implemented at the Children's Hospital of Fudan University, a tertiary referral center for patients with autistic disorder and other pervasive developmental disorders, where approximately 120 to 150 patients with autistic disorder are admitted for assessment, diagnostic workups, and therapeutic interventions annually. This ambispective cohort consisted of patients who were admitted in the 2-year-5-month period from August 2007 to January 2010 and diagnosed with autistic disorder based on *DSM-IV-TR* criteria. A total of 262 children with autistic disorder were admitted during this time window. Since some of the children were too young to give a definitive diagnosis of autism spectrum disorder and the older children were relatively few in number, we only included children born within the 6-year-3-month period between January 2000 and April 2006 in our study. Only 184 patients met the above criteria. Seven patients who were not ethnically Chinese Han were excluded; 5 patients had moved elsewhere and changed the phone number such that we were not able to contact them; and 2 were reluctant to participate. Thus, 170 patients were included in the end. For all patients, a detailed medical history was taken and a complete physical examination was performed. Follow-ups were executed by members of our research group until April 2011 when all the subjects had reached the age of 5 years or older. The mean follow-up period was 2.89 ± 0.88 years. Children with autistic regression were identified as having typical or relatively typical development prior to loss of previously acquired skills for at least a period of 3 months. The study was approved by the Ethical Committee of the Children's Hospital of Fudan University.

Investigated Risk Factors

Perinatal risk factors. The perinatal factors investigated included mode of delivery, birth weight, birth length, gestational age at birth, maternal conditions during pregnancy, number of previous pregnancies and deliveries, and maternal age at time of pregnancy. The data were collected from mothers and medical records.

Family background. The family background investigated in this study included parental character, maternal education, and family history of neuropsychiatric diseases. Parental character was categorized into 3 groups: introversion, ambiversion, and extroversion (self-reported). Family history of neuropsychiatric disorders was defined as first-, second-, and third-degree relatives of probands having a reported neuropsychiatric history in schizophrenia-like psychosis, affective disorder, or other mental disorders, intellectual disability, epilepsy, etc. The information was obtained from parents and medical records.

Febrile seizures. Febrile seizure was defined as a convulsion associated with a significant rise in body temperature documented by pediatric neurologists. It was divided into 2 types: simple febrile seizures (generalized, last <15 minutes and not recurring within 24 hours) and complex febrile seizures (focal, longer than 15 minutes or recurring more than once in 24 hours). The diagnoses were made by pediatric neurologists.

Analysis and Statistical Methods

All data recorded on the case report forms were entered into Epidata 3.1 (http://www.epidata.dk) databases. The data were analyzed using SPSS statistical software V.11.5 (SPSS, Chicago, Illinois). For all variables, we gave risk ratios (RRs) and 95% confidence intervals (95% CIs) calculated by the Woolf approach. Then, a multiple logistic regression model was developed, in which the outcome (autistic regression or not) was modeled as a binary variable, and all potential factors associated with autistic regression were included as independent variables. We also tested possible correlations between variables in the multiple logistic regression model. Statistical significance was defined as a 2-tailed $P \leq .05$.

Results

Descriptive Characteristics of Regressive Individuals

Of the 170 patients diagnosed with autistic disorder, 34 patients had a definite history of regression at the end of follow-up. Thus, the prevalence of regression in this autistic group is 20%. A summary of the characteristics of all patients (sex, age at diagnosis) is given in Table 1. Autistic disorder diagnosis usually occurs between the ages of 18 and 54 months, especially 37 and 54 months of age. The male-to-female ratio of subjects in the regressive group is 16:1. Compared with the nonregressive group's male-to-female ratio of 7:1, boys were more prone to experience regression, but with no statistical significance ($P = .371$). Regression occurred in 67.6% of patients before 24 months and in 88.2% of patients before 36 months. The mean onset age was 23.8 months, and the median onset age was 20.0 months. In the regressive group, 3 of 34 (8.8%) subjects lost language (meaningful words) only, and 23 (67.6%)

Table 1. Sex and Age at Diagnosis for Regressive and Nonregressive Cases

Characteristic	Nonregressive Autism		Regressive Autism		*P* value
	No.	%	No.	%	
All	136	100	34	100	–
Sex					.371
Male	119	87.5	32	94.1	
Female	17	12.5	2	5.9	
Age at diagnosis,[a] mo					.482
18-36	48	35.3	9	26.5	
37-54	68	50.0	18	52.9	
55-72	12	8.8	6	17.6	
73-90	5	3.8	1	2.9	
91-108	3	2.2	0	0	

[a]Age when patients were diagnosed with autism.

Table 2. Characteristics of Regression

Loss of Skills	n = 34	%
Language alone	3	8.8
Meaningful words	3	–
Babble or proto-words	0	–
Social skills alone	5	14.7
Gesture communication	1	–
Eye contact, gaze aversion, joint attention	1	–
Social smiling, reactivity, social interest	2	–
Play skills	1	–
Other skills[a]	1	2.9
Language and social skills	9	26.5
Language and other skills	5	14.7
Social and other skills	2	5.9
Language, social, and other skills	9	26.5

[a]Skills that cannot be classified as language or social skills, such as learned motor skills, self-help skills, etc.

subjects lost language skill in combination with a nonlanguage skill (social skill or other skills, such as learned motor skill, self-help skills). Overall, the extent of language regression is 76.5% (26 of 34). The extent of regression in 1 domain (language, social skill, or other skills) is 26.5% (9 of 34) versus 73.5% (25 of 34) in more than 1 domain (Table 2).

Until April 2011, 7 subjects (7/34, 20.6%) in the regressive group had febrile seizures, 3 simple, 2 complex, and 2 patients first diagnosed with febrile seizure developed epilepsy. Importantly, these patients were diagnosed with autistic regression prior to the development of epilepsy. Among the 7 subjects with febrile seizures in the regressive group, 4 exhibited autistic regression after the occurrence of febrile seizures (less than 1 month), suggestive of a potential temporal association between these 2 events. In the other 3 patients, a long interval elapsed between the occurrence of febrile seizures and that of autistic regression.

Three subjects in the regressive groups had epilepsy, with 2 of the 3 patients having prior febrile seizures. Since some of the children included in our study were of a relatively young age, and therefore we could not preclude the possibility that more of the patients with febrile seizures eventually develop epilepsy, we did not include epilepsy as a variable in our analyses. We also tried to investigate the variable of "any seizure." But in the logistic regression model, there was a very high correlation between "any seizure" and "febrile seizure." As a result, the prediction of the model would not be meaningful because of inflation of the variance.

Univariate Analysis

The comparison of perinatal risk factors between the regressive and nonregressive groups is presented in Table 3. No statistically significant differences were observed between the regressive and nonregressive groups for any of the investigated perinatal factors at $\alpha = .05$.

The data with regard to maternal education, parental character, family history of neuropsychiatric disorders, and child febrile seizures are presented in Table 4. No statistically significant differences were observed for any of the above variables at $\alpha = .05$, but the variables of family history of neuropsychiatric disorders (90% CI = 1.14-5.73) and febrile seizures (90% CI = 1.02-6.12) are statistically significant with autistic regression at $\alpha = .1$.

Multiple Logistic Regression Analysis

Since the sample size is small, we only included factors that had a statistical significance of $P \leq .1$ in the univariate analysis. As presented above, the variables of febrile seizures and family history of neuropsychiatric disorders are statistically significant with regression at $\alpha = .1$, and thus were included into the binary logistic regression model. We found statistically significant correlations between autistic regression and febrile seizures ($P = .025$) as well as with family history of neuropsychiatric disorders ($P = .011$) in the final model (Table 5).

Discussion

Although regression is an important characteristic of autism, attracting growing interest, studies are relatively limited. Most previously published studies investigated the association between autistic regression and epilepsy or abnormal electroencephalography (EEG).[17,26-30] Few studies have compared perinatal risk factors and family background in children with an autistic disorder with and without a history of regression. And to our knowledge, no published studies specifically evaluated febrile seizure in subgroups of autistic children with and without regression.

In this study, we set out to examine the prevalence, characteristics, and potential risk factors associated with autistic regression in an ambispective cohort of 170 Chinese Han children with autistic disorder. The most striking finding of our study is that a family history of neuropsychiatric disorders and febrile seizures are correlated with autistic regression in a statistically significant manner in the multiple logistic regression model.

Table 3. Risk Ratios (95% Confidence Intervals) for Perinatal Risk Factors in Univariate Analysis

Variable	Nonregressive, No. (%)	Regressive, No. (%)	RR	95% CI
All	136 (100)	34 (100)	–	–
Mode of delivery				
Natural delivery	59 (43.4)	16 (47.1)	Ref	–
Cesarean section	77 (56.6)	18 (52.9)	0.89	0.42-1.89
Gestational age at birth, wk				
<37	18 (13.2)	5 (14.7)	1.14	0.39-3.36
37-40	106 (77.9)	25 (73.5)	Ref	
41-42	12 (8.8)	4 (11.8)	1.31	0.39-4.40
>42	0	0	0	0
Birth weight, g				
≤3000	22 (16.2)	7 (20.6)	1.19	0.44-3.25
3001-3500	67 (49.3)	17 (50.0)	Ref	
3501-4000	42 (30.9)	8 (23.5)	0.55	0.31-1.99
4001-4500	5 (3.7)	2 (5.9)	1.41	0.25-7.91
Birth length, cm				
≤48	27 (19.9)	6 (17.6)	0.89	0.33-2.40
49-52	98 (72.1)	25 (73.5)	Ref	–
53-56	11 (8.1)	3 (8.8)	1.05	0.27-4.07
Maternal conditions during pregnancy				
No	98 (72.1)	26 (76.5)	Ref	
Yes	38 (27.9)	8 (23.5)	0.83	0.35-1.99
No. of previous pregnancies				
0	77 (56.6)	18 (52.9)	1.05	0.46-2.41
1-2	50 (36.8)	11 (32.4)	Ref	
>2	9 (6.6)	5 (14.7)	1.98	0.55-7.08
No. of previous deliveries				
0	109 (80.1)	24 (70.6)	Ref	
1-2	24 (17.6)	8 (23.5)	1.39	0.56-3.46
>2	3 (2.2)	2 (5.9)	2.22	0.35-13.40
Maternal age, y				
≤20	1 (0.7)	1 (2.9)	2.09	0.16-45.48
21-25	26 (19.1)	10 (29.4)	1.49	0.59-3.78
26-30	60 (44.1)	14 (41.2)	Ref	
31-35	40 (29.4)	8 (23.5)	0.89	0.34-2.32
36-39	9 (6.6)	1 (2.9)	0.54	0.06-4.58

Abbreviations: RR, risk ratio; CI, confidence interval.

Previously published prevalence of regression in autism spectrum disorders range from 13.8% to 50% depending on the definition of regression and the population studied, and higher prevalence of regression were found in autistic disorder compared with pervasive developmental disorder-not otherwise specified and Asperger syndrome.[12,13,15-21] The prevalence of regression in autistic disorder in this study is 20%, which appears to be at the lower end of the spectrum. Possible reasons may include (1) a relatively strict definition of autistic regression, including normal or relatively normal development before regression, and loss of skills for at least 3 months, and (2) differences that may exist between Chinese and Western populations. Consistent with previous publications,[33] boys are more liable to have experienced regression (a male-to-female ratio of 16:1), but with no statistical significance between the regressive group and the nonregressive group ($P = .371$). Most cases of regression occurred before 24 months of age, and almost certainly before 36 months, similarly to other reports.[8,9,12,13,19] Language loss is a very common phenomenon in autistic regression (76.5% of subjects) and often occurs in combination with regression of social or other skills (67.6% of subjects), which is also in agreement with previous studies.[12,34]

Febrile seizure is the most common seizure disorder occurring during childhood. The prevalence of febrile seizures is estimated to be 2% to 5% before the age of 5 years in the developed world[35] and 6% to 9%, 8.8%, and 0.5% to 1.5% in Japan, North America, and China, respectively.[36-39] Febrile seizures are most common in children before age 3 years, with a peak age of onset during the second year of life, and boys were more likely to be affected than girls, similar in time course and epidemiology to autistic regression. In this study, the prevalence of febrile seizures in autistic regressive individuals is 20.6% (7/34), significantly higher than that in nonregressive autistic individuals (6.6%, 9/136), and both higher than in the general population. In multiple logistic regression analyses, febrile seizures were associated with a significantly increased risk of regression. We also found an interesting incidental association between the occurrence of

Table 4. Risk Ratios (95% Confidence Intervals) for Family Background and Febrile Seizures in Univariate Analysis

Variable	Nonregressive, No. (%)	Regressive, No. (%)	RR	95% CI
All	136 (100)	34 (100)	–	–
Maternal education				
Up to middle school	59 (43.3)	16 (47.1)	1.11	0.45-2.78
High school/vocational	38 (27.9)	9 (26.5)	Ref	–
Bachelor's degree or higher	39 (28.7)	9 (26.5)	0.98	0.35-2.73
Maternal character				
Introversion	46 (33.8)	8 (23.5)	0.69	0.26-1.79
Ambiversion	51 (37.5)	14 (41.2)	Ref	–
Extroversion	39 (28.7)	12 (35.3)	1.09	0.45-2.62
Paternal character				
Introversion	66 (48.5)	13 (38.2)	0.86	0.33-2.29
Ambiversion	34 (25.0)	8 (23.5)	Ref	–
Extroversion	36 (26.5)	13 (38.2)	1.39	0.51-3.78
Family history of neuropsychiatric disorders				
No	124 (91.2)	25 (73.5)	Ref	–
Yes	12 (8.8)	9 (26.5)	2.55	0.97-6.71
Depressive disorder	3	2	–	–
Schizophrenia or Schizophrenia-like disorder	3	2	–	–
Intellectual disability	5	3	–	–
Epilepsy	1	2	–	–
Febrile seizures				
No	127 (93.4)	27 (79.4)	Ref	–
Yes	9 (6.6)	7 (20.6)	2.50	0.85-7.29
Simple FS	7	3	–	–
Complex FS	1	2	–	–
Diagnosed with FS first but developed into epilepsy later	1	2	–	–
Epilepsy				
No	133 (97.8)	31 (91.2)	Ref	–
Yes	3 (2.2)	3 (8.8)	2.65	0.51-13.74

Abbreviations: RR, risk ratio; CI, confidence interval; FB, febrile seizures.

Table 5. Multiple Logistic Regression of the Statistically Significant Factors in Univariate Analysis

Variable	*B*	SE	*P*	OR	95% CI
Febrile seizures					
No	Ref	–	–	–	–
Yes	1.26	0.56	.025	3.53	1.17-10.65
Family history of neuropsychiatric disorders					
No	Ref	–	–	–	–
Yes	1.29	0.50	.011	3.62	1.35-9.71

Abbreviations: *B*, logistic regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

febrile seizure and the display of regressive behaviors in 4 children with autistic regression. It would be interesting to further examine their relationship in a larger sample size and assess whether febrile seizures may temporarily correlate with the occurrence of regression.

No significant associations were found between autistic regression and perinatal risk factors, in agreement with the findings of other authors.[40,41] Significant association was found between autistic regression and family history of neuropsychiatric disorders in the multiple logistic regression analysis. It has been reported in the literature that family history of psychiatric disorders is a risk factor for autism but to our knowledge, this is the first report of its association with autistic regression.

In this study, the small sample size was a major limitation. To narrow the age gap, we only included children with autistic disorder who were admitted in the 2-year-5-month period between August 2007 and January 2010 and born within the 6-year period between 2000 and 2006. Excluding patients not ethnically Chinese Han, and those who were not contactable or willing to participate in the study, only 170 subjects were recruited. In this group, the parents of all subjects gave informed consent to participate in this study. The limitation of the small sample size restricted us to only include factors that had a statistical significance of $P \leq .1$ in the univariate analysis in the final multiple logistic regression model. Another limitation was the definition of autistic regression. We defined autistic regression as having typical or relatively typical development prior to loss of previously acquired skills for least a period of 3 months. The data were based on retrospective parent report but not home movies, which may have resulted in recall biases and reporting biases.

In this study, a relatively low prevalence of autistic regression was observed in ethnically Chinese Han People. The factors of febrile seizures, and family history of neuropsychiatric disorders

were found to be associated with regressive autism in a cohort study of 170 subjects with autistic disorder. The conclusions as well as the limitations of the study bring some interesting possible avenues for future research and analyses, and it would also be interesting to determine if a temporal relationship exists between these factors in a larger sample.

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Author Contributions

XX designed and organized the study, as well as manuscript revising. YZ wrote the manuscript draft and participated in data collection. QX and JL were responsible for collecting the data and entering it into Epidate database. S-cL was responsible for data analysis.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

All parents or guardians participated in an informed consent process and provided written consent. The study was approved by the ethical committee of Children's Hospital of Fudan University.

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