Editor's Choice

Clinical clues for autoimmunity and neuroinflammation in patients with autistic regression

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ABBREVIATION
ASD Autism spectrum disorder

AIM Autistic regression is a unique variant within the autism spectrum disorders (ASDs), with recent reports raising the possibility of immune aetiology. This study explores clinical clues for an association between autistic regression and autoimmunity.
METHOD Single-centre charts of children diagnosed with ASD in 2014 were reviewed. We compared the rates of: (1) familial autoimmunity in first-degree and second-degree relatives; (2) febrile illness preceding initial parental concern, as a potential precipitant of immune activation; and (3) possible non-immune precipitants such as pregnancy and postnatal complications.
RESULTS The charts of 206 children with ASD and 33 diagnosed with autistic regression variant were reviewed. The incidence of febrile illness in the 6 months prior to initial parental concern was significantly higher in the children with autistic regression compared with those with ASD (30% vs 0%; $p<0.001$). The overall prevalence of familial autoimmunity was also higher in children with autistic regression compared with those with ASD (33% vs 12%; $p<0.001$). Type 1 diabetes and autoimmune thyroiditis were both more common in families with children with autistic regression. Other non-immune risk factors did not differ between the two groups.
INTERPRETATION Our findings suggest that predisposition to autoimmunity, and immune/inflammatory activation, may be associated with autistic regression.

Autism spectrum disorder (ASD) represent an array of neurodevelopmental entities of varying severities. Diagnostic criteria include impairments in social, cognitive, and communication skills, stereotypical and repetitive behaviours, and restricted areas of interest.[1] The majority of patients present with ongoing developmental delay that begins at infancy; however, up to a third of patients demonstrate regression and loss of milestones between 18 months and 24 months of age.[2] The latter variant is known as autistic regression.

The autistic regression variant is poorly understood, and its aetiology may differ from that of ASD. In search of possible precipitants, some reports suggested early neonatal insults, prematurity, or seizures as possible culprits;[3,4] however, others have not been able to confirm such an association.[5,6] One emerging theory suggests that immune dysregulation may be involved in the pathogenesis of some cases of autistic regression.[7,8] Impetus for this theory originates in the field of psychiatry, demonstrating the presence of serum antineuronal antibodies in patients with acute psychiatric presentations.[9] With regard to autistic regression, some reports have documented development of autistic regression in the context of the autoimmune anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis.[10,11] Another case study reported on autistic language regression in the context of autoimmune proliferative syndrome; the patient responded remarkably to corticosteroid treatment.[12]

This aim of this chart review study was to further explore the relationship between autoimmunity and autistic regression. Our research questions were as follows: (1) Is the prevalence of familial autoimmunity different between patients with autistic regression and those with ASD? (2) Given the role of infectious pathogens in autoimmune activation,[13] is a preceding febrile illness more common in autistic regression compared with ASD?

A comparison of other previously suggested precipitants, including pregnancy and perinatal complications, was also performed.

METHOD

Patients

This study was conducted at the Glenrose Rehabilitation Hospital, University of Alberta. The study was approved by the University of Alberta Health Research Ethics Board, and adhered to all of the committee's recommendations. Charts of all patients diagnosed with ASD in 2014 were reviewed for possible inclusion in the study. The criteria for inclusion in the study were an ASD diagnosis made in

2014, based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria,[1] as well as medical files containing a completed parental questionnaire, administered to all new patients in our clinic prior to first visit, and a full physician assessment. Exclusion criteria included a history of any known genetic syndromes, seizure disorders, movement disorders, congenital anomalies, or a history of any acquired brain injury, resulting from trauma, stroke, or meningitis. Exclusion of children with known genetic conditions and inborn errors of metabolism was done, because some of these have a known association with regression, which may have served as a confounding factor, impeding our ability to interpret the study results.

Diagnosis of autistic regression was determined based on the Autism Diagnostic Interview-Revised criteria,[14] which stipulate onset of developmental regression prior to 3 years of age. A developmental regression must have been observed by parents in at least one of the following domains, according to Autism Diagnostic Interview-Revised: (1) speech and language development; (2) social interaction and play skills (pointing to express interest, eye contact, use of gestures such as wave 'goodbye' or blow a kiss, facial expressions used to communicate, social smiling, showing and directing attention, offering to share, ability for reciprocal conversation, imitative social play, interest, and interaction with other children); (3) fine motor skills related to purposeful hand movements (ability to hold and grip, self-feed, self-dress, and drawing); or (4) gross motor skills. The developmental milestone must have been maintained for at least 3 months, followed by loss of skill for at least 3 months.[14]

Diagnosis of ASD was determined based on DSM-V criteria.[1] Children included in the ASD group had demonstrated core, persistent deficits in their social or communication skills, and exhibited behavioural descriptors that were atypical for age since early infancy. These children were never reported as typically developing according to parental report, medical records, and health care professionals' reports.

Data collection

Following identification of charts to be included in the study, each chart was assigned a number and all names were removed. The anonymized charts were then separately reviewed by a member of the study team who was not familiar with the patients, for purposes of data extraction.

The following information was gathered from patient charts: (1) sex; (2) ASD versus autistic regression; (3) pregnancy complications (maternal hypertension, infections, teratogen exposure, gestational diabetes, or other maternal illness); (4) gestational age at birth (term or preterm); (5) mode of delivery: spontaneous vaginal delivery versus other (forceps/vacuum-assisted, or Caesarean section); and (6) immediate postnatal complications, such as oxygen requirement or neonatal intensive care unit stay. We also collected information about any preceding febrile illness in the 6-month period prior to first parental concern. The family history data collected included any known first-degree or second-degree relatives with the following autoimmune conditions: autoimmune thyroid disease (Graves or Hashimoto thyroiditis), type 1 diabetes mellitus, rheumatoid arthritis, coeliac disease, inflammatory bowel disease (Crohn disease or ulcerative colitis), and psoriasis.

What this paper adds

- Familial autoimmunity is more prevalent in autistic regression variant compared with autism spectrum disorders (ASDs).
- A higher rate of familial type 1 diabetes and autoimmune thyroid disease is seen in autistic regression variant than in ASDs.
- Incidence of febrile illness preceding symptom onset is higher in autistic regression variant than in ASDs.
- We suggest immune activation as a possible aetiology of autistic regression.

Statistical analysis

Statistical analysis of extracted anonymized data was performed by an analyst who was not a member of the study team. Analysis was done using SPSS version 20.0 (IBM, Armonk, NY, USA) and R version 3.1.3 (IBM, Stanford, CA, USA). Patients were grouped according to diagnosis (autistic regression vs ASD) and the data were summarized for each group (e.g. frequencies, percentages, and means with standard deviations [SDs]). A two-sample z-test was used to compare the incidence of various autoimmune diseases in participants' family histories. χ^2 tests were used to compare groups in terms of sex, preceding febrile illness, pregnancy complications, delivery, gestational age at birth, and the existence of postnatal complications. Normality assumption was verified for all parametric analyses.

Logistic regression models were fitted, adjusting for sex and the presence of preceding illnesses, to predict how a patient's family history of autoimmune diseases affected the odds of the patient having autistic regression rather than ASD. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported.

Causal mediation analyses were performed using the 'mediation' package in R and implementing the Baron and Kenny method,[15] to investigate whether the association between autistic regression and the odds of having a family history of autoimmune diseases was mediated by preceding febrile illnesses. The effect of the potential mediator on the estimated OR was examined by including the mediator in the logistic regression model and observing the change in the estimated OR. Then, the proportion of the total effect size mediated by the mediator was tested for statistical significance. In all statistical tests, $p<0.05$ was considered statistically significant.

RESULTS

The charts of 299 patients diagnosed with ASD in 2014 were reviewed. Of those, 37 were excluded owing to chart incompleteness and 23 patient charts were excluded owing to previously diagnosed genetic disorders or congenital

anomalies. Of the 239 patients included in the study, 206 (86.2%) had ASD and 33 (13.8%) were diagnosed with autistic regression variant. The sex ratio was similar in both groups: eight patients (24.2%) in the autistic regression group were female versus 58 (28.2%) in the ASD group (see Table I). All the children in the autistic regression group had sudden acute deterioration without fluctuations or a plateau. Regression data regarding specific domains of initial concern are provided in Table II.

The proportion of pregnancy complications, prematurity, modes of delivery other than spontaneous vaginal delivery, and postnatal complications were not significantly different between the two groups. The incidence of a preceding febrile illnesses differed significantly between the groups: the parents of 10 patients (30.3%) in the autistic regression group reported a febrile illness in the 6 months prior to first concern versus none reported (0%) in the ASD group ($p<0.001$; Table I). Testing for serum anti-NMDAR antibodies had been performed in three of the children with autistic regression, all of whom had negative results. Neuronal antibodies in the cerebrospinal fluid had not been measured for any of the patients.

Table I: Summary of patient characteristics and findings

	Autistic regression	Autism spectrum disorder	*p*
Sex			
Female	8 (24.2)	58 (28.2)	0.641
Male	25 (75.8)	148 (71.8)	
Mean (SD) age at diagnosis (mo)	37.36 (7.32)	31.58 (9.09)	<0.001
Preceding febrile illness[a]			
Yes	10 (30.3)	0 (0)	0.003
No	23 (69.7)	206 (100)	
Family history of autoimmune diseases[b]			
Thyroid disease	8 (24.2)	17 (8.3)	0.011
Type 1 diabetes	4 (12.1)	3 (1.5)	0.008
Rheumatoid arthritis	2 (6.1)	3 (1.5)	0.142
Coeliac disease	1 (3.0)	0 (0)	0.138
IBD	2 (6.1)	2 (1.0)	0.093
Psoriasis	1 (3.0)	2 (1.0)	0.361
Total prevalence of familial autoimmunity	11 (33.3)	24 (11.7)	<0.001
Mothers with autoimmunity	8 (24.2)	7 (3.4)	<0.001
Pregnancy complications[c]			
Yes	2 (6.1)	6 (2.9)	0.680
No	31 (93.9)	200 (97.1)	
Mode of delivery			
SVD	31 (93.9)	193 (93.7)	0.956
Non-SVD	2 (6.1)	13 (6.3)	
Preterm delivery			
Yes	1 (3.0)	6 (2.9)	0.970
No	32 (97.0)	200 (97.1)	
Early postnatal complications[d]			
Yes	0 (0)	10 (4.9)	0.196
None	33 (100)	196 (95.1)	

[a]In the first 6mo prior to first concern. [b]Some patients have family histories with more than one autoimmune disease. [c]Including maternal hypertension, infections, teratogen exposure, gestational diabetes, or other maternal illness. [d]Including oxygen requirement or neonatal intensive care unit stay. Data are *n* (%). SD, standard deviation; IBD, inflammatory bowel disease; SVD, spontaneous vaginal delivery.

With respect to family history, the autistic regression group had a significantly higher proportion of patients with first-degree or second-degree relatives who had an autoimmune condition (11 [33.3%] vs 24 [11.7%]; $p=0.003$). When examining the prevalence of maternal autoimmunity in particular, eight out of 33 (24.2%) children in the autistic regression group had a mother with an autoimmune condition versus seven out of 206 in the ASD group (3.4%) who had an affected mother ($p<0.001$). None of the patients in either group had any siblings with ASD.

Regarding specific conditions, patients with autistic regression had a significantly higher number of relatives with autoimmune thyroid disease (8 [24.2%] vs 17 [8.3%]; $p=0.011$) and type 1 diabetes mellitus (4 [12.1%] vs 3 [1.5%]; $p=0.008$). The proportion of familial coeliac disease (1 [3.0%] vs 0 [0%]; $p=0.138$), rheumatoid arthritis (2 [6.1%] vs 3 [1.5%]; $p=0.142$), psoriasis (1 [3.0%] vs 2 [1.0%]; $p=0.361$), and inflammatory bowel disease (2 [6.1%] vs 2 [1.0%]; $p=0.093$) did not differ significantly between the groups (Table I). Of note, seven patients in the autistic regression group and three patients in the ASD group had family members who had two autoimmune conditions.

When stratifying the family history by sex, of the 35 patients with family histories of autoimmune diseases, five (14.3%) were female and 30 (85.7%) were male; however, sex was not associated with family history of autoimmune diseases (OR 0.39, 95% CI 0.15–1.06). The sex ratio for family history of autoimmunity was similar in the two groups: nine of the 11 patients in the autistic regression group with a family history of autoimmunity were male (81.8%) versus 20 male patients out of the 24 (83.3%) in the ASD group.

The results from fitting bivariate models indicate significant associations between autistic regression and the odds of a family history of autoimmunity (OR 3.79, 95% CI 1.64–8.78) and the odds of a preceding febrile illnesses (OR 6.07, 95% CI 2.79–13.21). After adjusting for sex, autistic regression was found to be significantly associated with the odds of having a family history of autoimmunity (adjusted OR 3.78, 95% CI 1.61–8.83), as well as having a preceding febrile illness (adjusted OR 6.12, 95% CI 2.81–13.33).

Causal mediation analysis was conducted to examine whether the observed association between autistic

Table II: Summary of regression data in the autistic regression group[a]

Domain of initial concern	Number of children (%)
Speech/language skills	4 (12.1)
Social skills	21 (63.6)
Fine motor skills	3 (9.1)
Gross motor skills	0 (0)
Two or more domains initially affected	5 (15.2)

[a]Based on parental report.

regression and family history of autoimmunity was mediated by the preceding febrile illness. After adjusting for the presence of a preceding febrile illness, the estimated OR increased from 3.78 (95% CI 1.61–8.83) to 4.43 (95% CI 1.75–11.24). Hence, the indirect influence of preceding febrile illness on the association between autistic regression and a history of family autoimmunity was 2%, which was not statistically significant (p=0.840).

DISCUSSION

Autistic regression is a unique variant of ASD, postulated to involve immune dysregulation.[7,8] Our study demonstrated that children with autistic regression differ from those with ASD with respect to family history of autoimmunity – and, in particular, maternal autoimmunity – and occurrence of a febrile illness in the 6 months prior to first concern. Sex ratios, as well as complications of pregnancy, delivery, and early postnatal life, did not differ significantly between the two groups.

The possibility of immune involvement in ASD has been previously raised. Indeed, a number of studies report on altered profiles of inflammatory markers, cytokines, and immunoglobulins in the sera of patients with ASD.[16,17] Moreover, immune-mediated conditions are known to be more prevalent in people with ASD and their unaffected family members than in the general population.[18] Nevertheless, to date, no specific or consistent pattern has been established. This may be owing to the heterogeneity of ASD, suggesting the need to explore separately various subgroups within the ASD population.[7,19]

Recently, a study by Molloy et al.[19] demonstrated a link between autistic regression and familial autoimmune thyroid disease. Further, our study found an overall higher prevalence of familial autoimmunity among patients with autistic regression than in patients in the ASD group. Conditions that were significantly more prevalent in families of children with autistic regression included type 1 diabetes mellitus and autoimmune thyroid disease. Our study also found a higher prevalence of maternal autoimmunity in the autistic regression group. The notion of maternal autoimmunity as contributing to neurodevelopmental disability has been previously proposed. Dalton et al.[20] isolated neuronal autoantibodies from the serum of a mother of three children, of whom one had ASD and another had severe language delay. When injecting these antibodies in pregnant mice, the investigators reported alterations in fetal brain development, whereas the dams remained asymptomatic.[20] More recently, a large cohort study involving mothers of children with ASD demonstrated a higher prevalence of brain-reactive autoantibodies than unselected females of child-bearing age.[21] Finally, a study by Vinet et al.[22] recently found a higher incidence of ASD in children born to mothers with systemic lupus erythematosus than in those born to females without this condition. Interestingly, none of our study participants in either group had siblings affected by ASD, suggesting that even if maternal autoimmunity is a contributor, other factors may play a role in development of ASD.

The incidence of a febrile illness in the 6 months prior to first concern was significantly higher in the autistic regression group than in the ASD group. As infectious pathogens are thought to be major environmental triggers of autoimmune activation,[13] this finding may suggest an inflammatory or immune pathology underlying the development of autistic regression in some patients. Interestingly, our causal mediation analysis showed that the association between autistic regression and family history of autoimmunity was not significantly mediated by the presence of a preceding febrile illness.

When examining the role of possible non-immunological precipitants, our study found no difference between the groups with respect to pregnancy and delivery complications, neonatal need for oxygen support, or neonatal intensive care unit stay. This is in keeping with previous studies, which did not find an association between autistic regression and various obstetrical and neonatal risk factors.[5,6]

The notion of autoimmune and inflammatory pathology in autistic regression is of particular interest when considering potential immune-modulatory interventions. A number of reports have already documented improvement in various developmental parameters in patients with autistic regression following treatment with corticosteroids.[8,23] Less evidence is currently available for the use of intravenous immunoglobulin; studies in patients with ASD show improvement in autistic features in some participants treated with intravenous immunoglobulin.[24,25] However, these studies were characterized by heterogenic patient populations with respect to autism subgroup (autistic regression vs ASD). More recently, reports of three children with anti-NMDAR receptor encephalitis and autistic regression demonstrated significant symptom amelioration with intravenous immunoglobulin; however, these cases were marked by associated neurological symptomatology, including seizures and movement disorders.[10,11] It would be interesting to investigate whether the use of immune-modulatory interventions in children with autistic regression shortly after the onset of symptoms is beneficial in ameliorating autistic features, outside of the context of anti-NMDAR encephalitis.

Some limitations of our study include the small sample size of patients with autistic regression, owing to the relatively smaller proportion of this subgroup within the ASD patient population diagnosed in 2014. Another limitation is that information regarding preceding febrile illness, as well as regression of milestones, was based solely on parental recall, and not directly observed by clinicians. These limitations call for careful interpretation of the study results, as the notion of regression as a whole is still a subject of debate in the literature. Certainly, more extensive data will be needed in order to discuss the possibility of immunotherapy in the context of autistic regression. Finally, one needs to consider the possible multiple

comparisons issue; for example, when breaking down comparison of familial autoimmunity into a set of separate comparisons for each condition. However, given that the presence of one autoimmune condition may not be independent from another (as is evident by some family members with more than one autoimmune condition), performing a correction is challenging in this case. Interpretation of our analysis should therefore be done with caution.

Follow-up studies in the form of whole genome sequencing may be warranted to further elucidate whether a particular genetic factor underlies susceptibility to autistic regression.

CONCLUSION

Patients with autistic regression represent a unique subgroup within the spectrum of autistic disorders. Our study shows higher familial incidence of autoimmunity, in particular maternal autoimmunity, and increased incidence of febrile illness in autistic regression. These findings may help further define the specific features of autistic regression, suggesting possible directions for research into both pathophysiology and treatment of this intriguing entity.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th edn. Arlington, VA: American Psychiatric Publishing, 2013.
2. Thomas MS, Knowland VC, Karmiloff-Smith A. Mechanisms of developmental regression in autism and the broader phenotype: a neural network modeling approach. *Psychol Rev* 2011; **118**: 637–54.
3. Kobayashi R, Murata T. Setback phenomenon in autism and long-term prognosis. *Acta Psychiatr Scand* 1998; **98**: 296–303.
4. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry* 2013; **70**: 1231–40.
5. Luyster R, Richler J, Risi S, et al. Early regression in social communication in autism spectrum disorders: a CPEA Study. *Dev Neuropsychol* 2005; **27**: 311–36.
6. Tuchman RF, Rapin I. Regression in pervasive developmental disorders: seizures and epileptiform electroencephalogram correlates. *Pediatrics* 1997; **99**: 560–6.
7. Wasilewska J, Kaczmarski M, Stasiak-Barmuta A, Tobolczyk J, Kowalewska E. Low serum IgA and increased expression of CD23 on B lymphocytes in peripheral blood in children with regressive autism aged 3–6 years old. *Arch Med Sci* 2012; **8**: 324–31.
8. Duffy FH, Shankardass A, McAnulty GB, et al. Corticosteroid therapy in regressive autism: a retrospective study of effects on the Frequency Modulated Auditory Evoked Response (FMAER), language, and behavior. *BMC Neurol* 2014; **14**: 70.
9. Schou M, Sæther SG, Borowski K, et al. Prevalence of serum anti-neuronal autoantibodies in patients admitted to acute psychiatric care. *Psychol Med* 2016; **46**: 3303.
10. Scott O, Richer L, Forbes K, et al. Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis: an unusual cause of autistic regression in a toddler. *J Child Neurol* 2014; **29**: 691–4.
11. Hacohen Y, Wright S, Gadian J, et al. *N*-methyl-D-aspartate (NMDA) receptor antibodies encephalitis mimicking an autistic regression. *Dev Med Child Neurol* 2016; **58**: 1092–4.
12. Shenoy S, Arnold S, Chatila T. Response to steroid therapy in autism secondary to autoimmune lymphoproliferative syndrome. *J Pediatr* 2000; **136**: 682–7.
13. Ercolini AM, Miller SD. The role of infections in autoimmune disease. *Clin Exp Immunol* 2009; **155**: 1–15.
14. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994; **24**: 659–85.
15. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51**: 1173–82.
16. Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Pessah I, Van de Water J. Elevated plas-ma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. *Brain Behav Immun* 2011; **25**: 40–5.
17. Heuer L, Ashwood P, Schauer J, et al. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. *Autism Res* 2008; **1**: 275–83.
18. Atladóttir HO, Pedersen MG, Thorsen P, et al. Association of family history of autoimmune diseases and autism spectrum disorders. *Pediatrics* 2009; **124**: 687–94.
19. Molloy CA, Morrow AL, Meinzen-Derr J, et al. Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disorder: a CPEA Study. *J Autism Dev Disord* 2006; **36**: 317–24.
20. Dalton P, Deacon R, Blamire A, et al. Maternal neuronal antibodies associated with autism and a language disorder. *Ann Neurol* 2003; **53**: 533–7.
21. Brimberg L, Sadiq A, Gregersen PK, Diamond B. Brain-reactive IgG correlates with autoimmunity in mothers of a child with an autism spectrum disorder. *Mol Psychiatry* 2013; **18**: 1171–7.
22. Vinet É, Pineau CA, Clarke AE, et al. Increased risk of autism spectrum disorders in children born to women with systemic lupus erythematosus: results from a large population-based cohort. *Arthritis Rheumatol* 2015; **67**: 3201–8.
23. Stefanatos GA, Grover W, Geller E. Case study: corticosteroid treatment of language regression in pervasive developmental disorder. *J Am Acad Child Adolesc Psychiatry* 1995; **34**: 1107–11.
24. Gupta S, Aggarwal S, Heads C. Dysregulated immune system in children with autism: beneficial effects of intravenous immune globulin on autistic characteristics. *J Autism Dev Disord* 1996; **26**: 439–52.
25. Boris M. Improvement in children with autism treated with intravenous gamma globulin. *J Nutr Environ Med* 2005; **15**: 169–76.