ORIGINAL ARTICLE

Social impairments in autism spectrum disorder are related to maternal immune history profile

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Maternal immune activation has been highlighted as a factor that might increase the risk and severity of autism spectrum disorder (ASD) in children. Preclinical animal evidence shows that immune activation in mothers during pregnancy causes ASD-like behavioural traits in offspring. To this point, there has been no investigation of whether immune system activation in human mothers during pregnancy is associated with more severe symptoms in children with ASD. In this study, data from an existing ASD cohort (N = 220) were analysed to investigate whether immune conditions in the mother were associated with greater severity of autism-related symptoms. Results showed that children whose mothers reported a history of immune activation (allergies and asthma) had significantly higher scores on the Social Responsiveness Scale (SRS; P = 0.016), suggesting more severe social impairment symptoms in these children. This increasing severity of social impairment symptoms was further shown on the SRS cognition (P = 0.007) and mannerisms (P = 0.002) subscales. While immune history was associated with an increase in the severity of social impairment symptoms, history of autoimmune conditions in the mother did not have any effect in this cohort. To the best of our knowledge, this study is the first to show an association between immune activation history in the mother and increased ASD symptom severity in children with ASD. These findings support the idea of an immune system-mediated subtype in ASD, where the immune history of the mother may be an important factor.

INTRODUCTION

Autism spectrum disorder (ASD) represents a group of neurodevelopmental disorders characterised by impairment in reciprocal social interaction and communication, along with restricted and repetitive behaviours and interests. In 2010, a worldwide prevalence of ASD was estimated at 1 in 132 individuals,[1] but more recently the US Centers for Disease Control and Prevention indicated a prevalence of 1 in 68.[2] Autism is associated with substantial physical and mental health problems across the lifespan[3,4] which places a large financial, social and personal burden on individuals, families and society.[5] There are no single known causes of ASD; it is believed to be caused by a complicated interplay between genetic, epigenetic and environmental factors.[6] Similarly, the clinical presentation, developmental course and treatment outcomes of ASD are heterogeneous,[7,8] posing challenges for diagnosis and treatment.

In recent years, research has developed to suggest the immune system plays an important role in the pathophysiology of ASD.[9–12] Maternal immune activation (MIA), resulting from either genetic or environmental causes, has been highlighted as a factor that can increase the risk of ASD.[13–16] MIA is broadly defined as an active immune response during pregnancy. MIA can be considered from two perspectives: externally triggered or autoimmune. MIA in response to infections, particularly when associated with fever or hospitalisation, has been shown to increase the risk of delivering a child with ASD.[17–19] Similar findings have also been reported for asthma and severe allergies during pregnancy, which are also externally triggered.[20] Maternal history of autoimmune disorders has also been associated with increased incidence in the diagnosis of ASD,[15,21,22] providing further support for the notion that maternal immune response, especially during gestation, is an important factor in the aetiology of ASD.

External immune insults and autoimmune conditions can both produce an immune response in the mother, mediated by cytokines, chemokines, inflammatory cells and antibodies, resulting in an altered immune system environment for the fetus. Preclinical animal models have already shown that immune activation during pregnancy causes ASD-like phenotypes in offspring, which supports the MIA hypothesis,[14,23,24] although the molecular mechanisms through which MIA increases the risk of ASD are still largely unknown.

It has been suggested that prenatal exposure to cytokines and chemokines may alter the expression of genes associated with the development and regulation of the central nervous system and immune system.[25,26] Additionally, MIA may compromise the ability of the placenta to regulate the maternal–fetal immune interface, causing an increase in fetal cytokine levels and disrupting the development of the fetal central nervous system and immune system.[25,27,28] Many studies have shown that a proportion of individuals with ASD have elevated levels of pro-inflammatory cytokines and chemokines, which aid in the recruitment of inflammatory cells, while anti-inflammatory cytokine levels are reduced.[29,30] This state of chronic inflammation has also been correlated with an increase in ASD symptom severity,[29,31,32] indicating a possible link between the immune system and the observed ASD phenotype.

Furthermore, some mothers of children with ASD show antibody reactivity to fetal proteins, raising the possibility that

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these antibodies interfere with development of the fetus and contribute to ASD symptoms.[33–35] Although a family history of autoimmune disease has been associated with an increased risk of ASD,[15,22] it is not yet clear whether autoimmune disease in the mother is related to the generation of these detrimental antibodies in the mother or to ASD symptom severity in the child.

Considered together, the developing research suggests the potential of an immune-mediated subtype in ASD that may be driven by alterations in cytokine, chemokine or antibody levels in the mother and/or child. In many cases, these immune system aberrations are a result of MIA, which may be externally triggered or due to an autoimmune disease. This raises the possibility that a history of MIA in mothers of children with ASD may be related to increased severity of ASD symptoms. To our knowledge, no study has examined whether MIA is associated with poorer outcomes for children with ASD. In this study, we use an existing ASD cohort with collected data from parents about immune history. We aim to test whether having an immune or autoimmune-driven MIA is associated with increased severity of ASD symptoms for the child.

MATERIALS AND METHODS

The cohort used for this study were participants in the Western Australian Autism Biological Registry (WAABR), located at the Telethon Kids Institute in Perth, Western Australia.[36] Ethics approval for the WAABR was granted by the Human Ethics Committee at Princess Margaret Hospital for Children in Perth, Western Australia. Participants were recruited between the period of January 2011 and September 2014 through newspaper advertisements and flyers, distributed among local clinicians and service providers. The study included participants with a DSM-IV clinical diagnosis of Autistic Disorder (autism), Asperger's Syndrome or Pervasive Developmental Disorder-Not Otherwise Specified (PDDNOS). Informed consent to be a part of the WAABR was provided by the primary caregiver of the participant.

ASD phenotype

The Autism Diagnostic Observation Schedule-Generic (ADOS-G) was administered to each participant by research accredited professionals. The ADOS-G is a standardised, semistructured assessment which uses simple activities and questions that are designed to prompt and observe the communicative, social and stereotyped behaviours which are relevant to the diagnosis of ASD.[37] For each participant, the ADOS-G raw scores and total scores were converted to the updated ADOS-2 calibrated severity score, as this score is less influenced by child characteristics.[38–40] The ADOS calibrated severity scores are based on a scale on 1–10, where 1 represents minimal evidence of ASD-related symptoms and 10 denotes a high severity of symptoms. A primary caregiver also completed the Social Responsiveness Scale (SRS), which is a 65-item rating scale that measures social interaction, language, and repetitive/restricted behaviours and interests in the child.[41] The SRS provides a total score, as well as separate scores for five subscales: awareness, cognition, communication, motivation and mannerisms. Higher SRS scores indicate heightened severity of ASD-related social impairment.

Demographics and maternal medical history

A primary caregiver completed a family history questionnaire, which included participant demographics such as age, gender, head circumference, height and weight. It also included a section addressing the medical history of the biological mother, where details regarding any diagnosed illnesses or chronic conditions were reported, along with age of any diagnosis.

RESULTS

Data were analysed from 220 children in the registry who completed the ADOS assessment and whose primary caregiver completed the family history questionnaire and SRS assessment. The SRS total scores (T scores; M = 88.06, Mdn = 88, s.d. = 15.25) and ADOS calibrated severity scores (M = 5.96, Mdn = 6, s.d. = 2.45) were used as measures of ASD symptom severity. Demographics of the child with ASD and the biological mother are provided in Table 1. The children were separated into categories based on maternal medical history. Children whose mothers reported a history of chronic immune activation were placed in the immune category. Allergies and asthma were the only reported chronic immune conditions in this cohort. Children whose mothers reported a diagnosis of any autoimmune conditions were grouped together in the autoimmune category. In this cohort, the reported autoimmune conditions included type 1 diabetes (N = 7), optic neuritis (N = 1), rheumatoid arthritis (N = 4), coeliac disease (N = 1), eczema/psoriasis (N = 2), sarcoidosis (N = 1), systemic lupus erythematosus (N = 1) and thyroid problems (N = 16), with three mothers reporting more than one autoimmune condition. As there were eight children whose mother reported both immune history (asthma or allergies) and autoimmune history (previous list), these two groups were analysed separately against the non-immune history category.

After checking the data for normality, T-tests were run to compare each medical history category against the demographic variables. Results showed that there we no significant differences in the demographics between mothers with an immune activation history (allergies or asthma) and those without. However, mothers with a history of autoimmune activation were older in age than those without (t(216) = 3.53, P = 0.001).

We then conducted multivariate ANOVAs for each category to examine the relationship between MIA history and outcome measures of the SRS and ADOS. There was no significant influence of autoimmune history on SRS total scores or ADOS calibrated severity scores (F(2, 202) = 2.36, P = 0.09), even when mother's age was included as a covariate. No further analysis was conducted regarding the influence of autoimmune history. For the immune history category (allergies or asthma), a one-way multivariate ANOVA examining the effect of immune status on both SRS total scores and ADOS calibrated severity scores revealed a significant effect (F(2, 202) = 3.27, P = 0.041). Follow-up ANOVAs revealed a significant influence of immune status on SRS total scores (F(1, 207) = 5.88, P = 0.016), meaning that children of mothers with a history of immune activation showed higher SRS total scores (Figure 1). Subscale analysis of the SRS showed that a history of immune activation was associated with higher SRS scores, particularly on the cognition (P = 0.007) and mannerisms (P = 0.002) treatment subscales (Figure 1). There was, however,

| Table 1. Participant demographics						
Mother's medical history	N (diagnosed prior to pregnancy)	Child's age (s.d.)	Child's gender (% male)	Child's head circumference (cm)	Child's BMI (s.d.)	Mother's age (s.d.)
Immune	49 (46)	9.00 (4.53)	73	54.31 (3.18)	18.93 (5.73)	30.14 (5.17)
Autoimmune	30 (16)	8.03 (4.43)	83	53.66 (3.41)	17.64 (3.23)	34.00 (5.50)
Non-immune	149	7.89 (4.89)	82	53.67 (2.50)	17.91 (4.27)	30.50 (5.25)
Abbreviation: BMI, body mass index.						
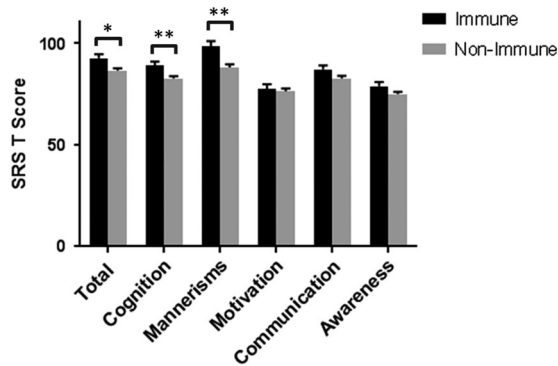
Figure 1. Mean (+s.e.m.) Social Responsiveness Scale (SRS) T scores of the immune and non-immune categories. Children whose mothers were in the immune category show higher SRS total scores ($P = 0.016$), specifically on cognition ($P = 0.007$) and mannerisms ($P = 0.002$) subscales, but not on awareness, communication or motivation.

no influence of immune status on ADOS calibrated severity scores ($F(1,212) = 0.10$, $P > 0.05$). All of these analyses remained similarly significant when the three mothers who were not diagnosed with an immune condition until after pregnancy were removed.

DISCUSSION

We believe this is the first study that has explored the relationship between maternal immune history and severity of autism symptoms in a well-characterised cohort of children with ASD. Specifically, we examined whether a history of immune activation in mothers of children with autism, driven by either an immune condition (allergies or asthma) or autoimmune condition, would be associated with an increase in severity of ASD symptoms in the child. Results showed that a positive immune history (allergies or asthma) was associated with increased severity of social symptoms in child. A history of autoimmune conditions in the mother did not influence autism symptom severity in this cohort, although we cannot rule out that this was due to a large number of mothers being diagnosed with autoimmune problems post-pregnancy. Our results provide further support of a relationship between a history of immune activation in the mother and caregiver rated severity of ASD-related symptoms in the child.

Preclinical animal models have shown that immune activation during pregnancy results in offspring displaying autism like symptoms, such as abnormal communication, decreased sociability and repetitive/restricted behaviours.[14] These models have demonstrated that the type, severity and timing of the immune insult can influence the observed ASD-like phenotype[24] and that MIA can lead to permanent immune dysregulation in offspring.[23] In humans, it has been shown that MIA increases the risk of children being born with ASD.[13–15,17–19,22] For instance, asthma and allergies during pregnancy have been associated with a twofold elevated risk of ASD.[20] Our results build upon the existing literature by showing an association between MIA (caused by asthma and allergies) and ASD symptom severity in children with ASD. Children of mothers who reported a history of immune activation had significantly higher SRS total scores, meaning that they show more severe caregiver reported social deficits. Specifically, they had higher scores on the cognition and mannerisms subscales, suggesting that they have more difficulty understanding social situations and display more restricted behaviours or unusual interests. Interestingly, this association of maternal immune history was not seen on the ADOS calibrated severity scores. The ADOS is, however, primarily a diagnostic

measure that has poor capacity for differentiating both severity and change.[42,43]

Our study extends the MIA hypothesis and indicates that MIA may contribute to increasing the severity of autism symptoms in the child. This may be caused by prenatal exposure to cytokines, chemokines or antibodies which interfere with the development and regulation of the fetal central nervous system.[25,27,44] Furthermore, immune activation in the mother may have been associated with immune system dysregulation in the child,[23] leading heightened inflammation to increase ASD symptom severity.[29,31,32] Immune profiles of the mothers and children in the immune category now need to be examined in order to determine whether maternal immune history and increased symptom severity are correlated with elevated levels of pro-inflammatory cytokines in the mother and/or child. We also note that the scope of the MIA hypothesis may include all types of maternal immune responses, including infections and fevers,[17–20] asthma and allergies,[20] as well as autoimmune diseases.[15,21,22] The interplay between these various immune responses, in terms of type, timing and molecular pathways, may be a crucial part of characterising the immune system-mediated subtype in ASD.

This study was conducted retrospectively in an existing cohort and relied on accurate caregiver report in terms of the SRS and medical history of the mother. The ADOS provided a measure of observed ASD symptom severity, but the influence of maternal immune history was not significant on this outcome measure. While the sample size of the immune and non-immune categories was large, the autoimmune category was much smaller. Within the autoimmune category, only 16 mothers were diagnosed prior to pregnancy and it remains unclear how many of these who reported thyroid problems were specifically related to autoimmunity. It is possible that the 14 mothers who were diagnosed post-pregnancy and possible thyroid cases that were not autoimmune conditions influenced the nonsignificant result in this category. This study needs to be repeated in a larger cohort with equal numbers in each category and more objective immune activation details and records regarding specific medical conditions. Future prospective studies collectively examining externally triggered immune activation and autoimmune conditions are now required to shed further light on the nature of the relationship between immune history and symptom severity.

In conclusion, this study is the first to show a relationship between immune history in the mother and increased severity of social symptoms in children with ASD. While we were not able to determine a causative relationship, this study suggests that children with ASD who are born to mothers with an immune activation history (in this case, asthma or allergies) present with more severe social deficits than those born to mothers without an immune history. Findings support the role of an immune system-mediated subtype in ASD, which may be driven by MIA and changes in levels immune markers. Identification of such a subtype in ASD will enable more streamlined diagnosis and management in clinical environments. It supports investigation of biomarkers in this subgroup and presents novel targets for immune-modulating pharmacotherapies. Further studies, using a prospective, longitudinal approach and larger cohorts are needed to elucidate the interplay between MIA, immune profiles and ASD symptom severity to further understand the role of mother's immune history status in ASD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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