Maternal immune activation during pregnancy is associated with more difficulties in socio-adaptive behaviors in autism spectrum disorders.

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Abstract

Background

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterised by deficits in social communication or interaction and repetitive behaviours. Maternal immune activation (MIA) during the mid-pregnancy is a known risk factor for ASD. Although reported in 15% of affected individuals, little is known about the specificity of their clinical profiles. Adaptive skills represent a holistic approach to a person's competencies and reflect specifically in autism, their strengths and difficulties.

Methods

In this study, we hypothesised that individual with ASD with a history of MIA (MIA⁺) could be more severely socio-adaptively impaired than those without MIA during pregnancy (MIA⁻). To answer this question, we considered two independent cohorts of individuals with ASD (PARIS study and FACE ASD) screened for pregnancy history, and used a supervised and unsupervised statistical approach.

Results

We included 295 mother-child dyads with 14% of them with MIA⁺. We found that ASD-MIA⁺ individuals displayed more severe maladaptive behaviors, specifically in their socialization abilities. MIA⁺ directly influenced individual's socio-adaptive skills, independent of other covariates, including ASD severity. Interestingly, MIA⁺ may affected persistently the socio-adaptive behavioral trajectories of individuals with ASD.

Limitations

The current study has a retrospective design with possible recall bias regarding the MIA event and, even if pooled from two cohorts, has a relatively small population. In addition, we were limited by the number of covariables available potentially impacted socio-adaptive behaviors. Larger prospective study with additional dimensions related to ASD is needed to confirm our results.

Conclusions

Specific pathophysiological pathways may explain these clinical peculiarities of ASD- MIA⁺ individuals, and may open the way to new perspectives in deciphering the phenotypic complexity of autism and for the development of specific immunomodulatory strategies.
Background

Autism spectrum disorders (ASD) are heterogeneous childhood-onset neurodevelopmental disorders characterised by social communication impairment or interaction and repetitive or stereotyped behaviours. Its incidence is 1 in 50 to 1 in 100 birth, affecting 52 million people worldwide [1]. The etiopathogenesis of ASD results from the close intertwining of genetic predispositions and environmental risk factors. Among the known environmental insults, maternal immune activation during the mid-pregnancy (MIA) - either due to maternal autoimmune diseases or to infections - is associated with an increased risk of ASD in the offspring [2]. In accordance with epidemiological evidences, well replicated preclinical studies show that this association is mediated by a direct action of maternal immune mediators (i.e. cytokines) on fetal cortical neurons, disrupting normal neurodevelopment and leading to autism-like behaviours in the pups [3]. Years of intensive research have made it possible to divide the common and heterogeneous autism spectrum into rarer but etiopathogenically homogeneous entities, based mainly on common genetic variants [4]. This approach allows to identify and better understand common pathophysiological pathways and thus the emergence of potential targeted therapies. Nonetheless, few studies have attempted to characterise ASD subgroup according to common pathogenic environmental factors. Despite a history of MIA being frequent, approximatively reported in 15% of ASD individuals, there is surprisingly little data on their specific clinical profiles.

Clinical studies often use symptom scales to assess the clinical characteristics of individuals and the severity of the disorder, which do not reflect their adaptability to the environment. According to the American Association on Intellectual and Developmental Disorders (AAIDD), adaptive behaviour is «the collection of conceptual, social, and practical skills that all people learn in order to function in their daily lives» [5]. Adaptive skills thus represent a higher concept of functioning, taking into account all dimensions of a person in his/her environment [6]. The level of autonomy and adaptation of children with neurodevelopmental disorders is frequently assessed with the second edition of the Vineland Adaptive Behavior Scale (VABS) [6] [7] which measures adaptive behaviors from three main areas: communication, daily living skills and socialization. As an exploratory study, we decided to use the VABS to explore the impact of MIA on the phenotype of individuals with ASD.

We hypothesised that MIA+ individuals would display more severe socio-maladaptive behaviors than MIA− ASD. To perform this study, we considered two independent cohorts of individuals with ASD (PARIS study and FACE ASD) screened for pregnancy history, and used a supervised and unsupervised statistical algorithms to decipher the interactions between MIA and adaptive behaviors in autism.

Methods

Participants

We included in our study children with ASD enrolled in the PARIS study, conducted by the Excellence Centre for Autism & Neuro-developmental Disorders (InovAND - Robert Debré Hospital, Paris, France)
between March 2017 to April 2021. This study was approved by the local ethics committee (2021-27 No. IDRCB: 2021-A00489-32). Prior to inclusion, informed consent was obtained from a parent and/or legal guardian. We also enrolled ASD individuals from an independent sample from eight Expert Centers for ASD (Créteil, Bordeaux, Grenoble, Versailles, Marseille, Caen, Strasbourg, Lyon) coordinated by Fondation FondaMental. The relevant Ethical Review Board (CPP- Est IV) approved the appraisal protocol on 18 June 2019. All participants gave their informed consent. All methods in both studies was performed in accordance with relevant guidelines/regulations and have been performed in accordance with the Declaration of Helsinki.

Considering the frequency of the MIA event (12–15%) and the number of individual per sample, we pooled all individuals to increase the power analysis of the study.

The diagnosis of ASD was performed according to DSM-5 criteria [8] by summing up the information from the Autism Diagnostic Interview-Revised [9], the Autism Diagnostic Observation Schedule – 2nd edition (ADOS-2) [10] and clinical records of individuals. All participants were screened with a parental semi-structured interview for pre- and peri-natal history. We focused on any history of MIA during pregnancy. Based on this information, children were then split either into MIA (MIA+) or in non-MIA (MIA-) sub-groups. We considered mothers with a significant history of an MIA-related event when they were: (i) with an autoimmune disease as listed by the American Autoimmune Related Diseases Association [11] and (ii) with a viral or bacterial infection during pregnancy with a fever over 38.5°C for more than 24 hours. Mothers with an infection resulting from a pathogen with a well-documented direct brain cytopathic effect (such as cytomegalovirus infection) were excluded.

Statistical analysis

Before each analysis, the normality of the distribution of the variables was tested with a Shapiro-Wilk test. For continuous variables Student’s t-tests or Wilcoxon tests were used accordingly. For categorical variables, the Fisher test was used. Only linear models with a normal distribution of residuals were used. In order to test the predictions, we performed a hierarchical regression analysis. Hierarchical regression is a type of regression model in which predictors are added to or removed from the regression model in steps and/or blocks of variables. It allows for the analysis of the variance explained in a dependent variable by more than one predictor variable. Hierarchical regression analysis are in supplementary materials. The final models of multivariate analysis (also found in supplementary materials) were all adjusted on sex and ASD scales (SRS T-score / ADOS total score). Unsupervised classification trees were generated using R package “Party” [12]. The relevance of the groups identified by the classification trees were then tested using ANOVA with post-hoc Tukey for multiple comparisons of means. Then, we performed supervised classification methods using the R package “mlr3”. [13] In sum, we split the sample in 2 groups, 80% of the individuals for training and the remaining for validation. As the MIA+ individuals were under-represented, we used an oversampling method with a 3.5 ratio. The sample characteristics before and after oversampling are in Supplementary Fig. 1. For classification, we used both a logistic regression classification learner and a linear discriminant analysis classification learner. The learning
parameters used by the model were then evaluated using the package R package «iml» [14] with three components: feature effects, Shapley values and feature importance. Lastly, to better understand the direct and indirect effects within this model, we used path analysis with R package «lavaan» [15]. Statistical analysis was performed using R studio version 4.2.1.

Results

General characteristics

We finally considered 295 mother-child dyads in our study, with a history of MIA reported in 14% of mothers (n = 40) (MIA⁺). Dyads without a history of MIA (n = 255, 86%) were used as a comparison group (MIA⁻).

The prenatal history and birth parameters are provided in Table 1.
Table 1

Prenatal and birth parameters of the population studies. MIA: Maternal immune activation

<table>
<thead>
<tr>
<th></th>
<th>MIA – n = 255 (86%)</th>
<th>MIA + n = 40 (14%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prenatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes / No (%)</td>
<td>15/240 (6/94)</td>
<td>4/39 (10/90)</td>
<td>0,3</td>
</tr>
<tr>
<td>Threatened preterm delivery (TPD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure (HBP)</td>
<td>8/247 (3/97)</td>
<td>2/38 (5/95)</td>
<td>0,6</td>
</tr>
<tr>
<td>Placenta Praevia</td>
<td>2/253 (0,8/98,2)</td>
<td>2/38 (5/95)</td>
<td>0,9</td>
</tr>
<tr>
<td>Premature rupture of membranes (PROM)</td>
<td>0/255 (0/255)</td>
<td>3/37 (7,5/92,5)</td>
<td>0,002</td>
</tr>
<tr>
<td>Materno-foetal infection (MFI)</td>
<td>2/253 (0,8/98,2)</td>
<td>3/37 (7,5/92,5)</td>
<td>0,02</td>
</tr>
<tr>
<td>Sex ratio M/F</td>
<td>211/43 (83/17)</td>
<td>35/4 (90/10)</td>
<td>0,35</td>
</tr>
<tr>
<td><strong>Birth parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (IQR)</td>
<td>50 (3)</td>
<td>50 (4)</td>
<td>0,25</td>
</tr>
<tr>
<td>Height(cm)</td>
<td>3370 (1015)</td>
<td>3420 (545)</td>
<td>0,96</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>35 (1,5)</td>
<td>35 (3)</td>
<td>0,19</td>
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<tr>
<td>APGAR 1 minute</td>
<td>10 (0)</td>
<td>10 (1)</td>
<td>0,052</td>
</tr>
<tr>
<td>APGAR 5 minutes</td>
<td>10 (0)</td>
<td>10(0)</td>
<td>0,08</td>
</tr>
</tbody>
</table>

We observed that mothers with MIA during pregnancy had more history of premature rupture of membranes (PROM) (p-value=0.002) and maternofetal infection (MFI) (p-value =0.02) than those without MIA. ASD-MIA+ individuals did not differ from those without a history of MIA in term of symptoms severity estimated with the SRS T-score (p-value=0.6) or ADOS total score (p-value =0.4). Univariate analysis did not reveal any difference in any of the three sub-domain of the VABS: communication (p-value=0.3), ssocialisation (p-value=0.2), daily living skills (DLS) (p-value=0.4) domains (Table 2).
Table 2


<table>
<thead>
<tr>
<th></th>
<th>MIA – N = 255 (86%)</th>
<th>MIA + N = 40 (14%)</th>
<th>p-value Wilcox test</th>
</tr>
</thead>
<tbody>
<tr>
<td>median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS (T-score)</td>
<td>73 (16)</td>
<td>76 (16,5)</td>
<td>0,6</td>
</tr>
<tr>
<td>ADOS (total score)</td>
<td>18 (8)</td>
<td>16 (10)</td>
<td>0,4</td>
</tr>
<tr>
<td>VABS - Communication subdomain score</td>
<td>67 (36)</td>
<td>64 (38)</td>
<td>0,3</td>
</tr>
<tr>
<td>VABS - Socialisation subdomain score</td>
<td>64 (35)</td>
<td>57 (36)</td>
<td>0,2</td>
</tr>
<tr>
<td>VABS - Daily Living Skills subdomain score</td>
<td>69 (25)</td>
<td>66 (19)</td>
<td>0,4</td>
</tr>
</tbody>
</table>

More severe impact on adaptive behaviors related to socialization is associated with MIA during pregnancy

Previous studies found a more severe social impairment in MIA+ children [16]. We found, that SRS T-score and ADOS total score were correlated with the three sub-scores of VABS (Fig. 1A). Accordingly, in adjusted analysis, we observed that more severe socio-maladaptive behaviors in ASD individuals was associated with a MIA during pregnancy (p-value = 0.006) (Details of the hierarchical regression analysis are in supplementary Table 1 and Table 2). To confirm this association, we used a non-supervised classification tree isolating three groups of individuals (Fig. 1B): (i) A MIA low-probability group (VABS - Socialisation > 55 and ADOS total score > 15) with 1% of MIA+; (ii) a medium-probability group (VABS - Socialisation > 55 and ADOS total score = < 15) with 11% of MIA+; and (iii) a high-probability group (VABS - Socialisation = < 55) with 17% of MIA+. Significant differences between the high-probability group and the low-probability group were observed (p-value = 0.002).

Finally, we further validated our results by applying a supervised classification algorithm with two distinct predictive models. Applying logistic regression classification, we discriminated MIA+ individuals with an accuracy of 70%, a sensitivity of 84%, a specificity of 27% and an area under the curve (AUC) of 72%. In accordance with our initial hypothesis, the most robust parameter to classify children was the VABS - Socialisation score followed by ADOS total score (Fig. 1C and Supplementary Fig. 2A and 2B). Linear discriminant analysis classification (LDA) reported similar results with an accuracy of 72%, a sensitivity of 84%, a specificity of 33% and AUC of 66%. Of note, the VABS - Socialisation score was also the most important parameter allowing classification, but in LDA, both ADOS total score and SRS T-score were pertinent to classify children (Fig. 1D). Considering the communication domain, we observed that more severe score was also associated with a history of MIA (p-value = 0.045) (details of the multiple linear
regression results in supplementary Table 3). We next used a non-supervised classification tree also isolating three groups of individuals (Fig. 1E): (i) A MIA low-probability group (VABS - communication > 66) with 10% of MIA⁺; (ii) a medium-probability group (VABS – Communication = < 66 and ADOS total score > 19 ) with 12% of MIA⁺; and (iii) a high-probability group (VABS - Communication = < 66 and ADOS total score < 19)) with 18% of MIA⁺. No significant differences was found between groups (p-value < 0.08). Thus, we considered that the communication domain of the VABS was not associated with MIA. Lastly, no association was observed between DLS and MIA (p-value = 0.2) (supplementary Table 4).

In sum, we found that, in ASD children, more severe adaptive behaviours in socialisation were associated with a higher probability of a history of MIA during pregnancy.

**MIA may directly affected the socio-maladaptive behaviors in autism**

We observed that MIA was associated with more pregnancy complications also known to increase independently the risk for ASD (Table 1) [17]. Pregnancy complications and more severe ASD symptomatology were correlated with more adaptive behaviours later on (Supplementary Fig. 3). Adjusting for these potential factors and corroborating our previous results, we investigated whether a history of MIA was associated with poorer adaptive behavior and if so, the mediator of this association.

Using adjustment models, we found no any association between the history of MIA and communication (p-value = 0.15) or DLS (p-value = 0.63) sub-domain but a significant association with poorer socio-adaptive behaviours (p-value = 0.03) (supplementary Tables 5, 6 and 7). Unsupervised analysis with a linear model regression learner confirmed this association (mean absolute error = 20.2; mean qsquare error = 562.7; root mean square error = 23.7, R-square = 0.16) (Fig. 2A).

According to feature importance, MIA appeared to predict the intensity of communication deficit, just after the intensity of the global autistic symptom severity itself (Fig. 2B and Supplementary Fig. 4). Finally, we explored whether there was a causal link between the MIA and the impairment intensity of socio-adaptive skills. We used structural equation modelling and applied a path analysis to our dataset. We found, with a good model performance (Fig. 2C), that MIA influenced directly the socio-adaptive skills of children, independently of pregnancy complications or global severity of autism symptoms (Fig. 2C).

**Discussion**

Using multiple and complementary statistical approaches, we found that ASD individuals with a history of MIA during pregnancy displayed poorer socio-adaptive skills. For individual with a VABS socialization subdomain score < 55, almost 20% of children had a history of MIA, compared to 1–10% for those with a VABS socialization subdomain score > 55. Social-adaptive skills are a central node of autism symptomatology. Compared to healthy children, ASD children, no matter the MIA status, have specifically more difficulties in adaptive social behaviors with the others adaptive domains being less impacted [18]. Our results were consistent with the literature since one exploratory study reported more severe
symptoms of social impairment - assessed with the SRS- in ASD-MIA+ individuals [16]. One limitation is that we did not assess all the clinical variables that potentially influence socio-adaptive behaviour. Intelligence quotient, for example, was not integrated, whereas there were significant entanglements between IQ and adaptive functioning [19]. This limitation must be contrasted with a previous study finding MIA not to be associated with decreased cognitive functions [20]. Future studies should integrate all the dimensions of ASD children and frequent comorbidity, such as ID or ADHD, in order to decipher the socio-adaptive abnormalities in ASD children [21].

We also observed that MIA directly influenced the socio-adaptive behaviors of ASD individuals. The effect of MIA appeared not mediated by the increase in the severity of autistic symptoms. This hypothesis mirrored findings in children with neurodevelopmental disorders (excluding ASD), in whom a history of AIM was associated, in a dose-response effect, with more externalizing and internalizing problems [22]. In mice, MIA directly triggers autistic-like symptoms through an effect on neuronal cytokine receptors in the cerebral cortex [3]. However, MIA also induced epigenetic changes of major transcriptional factors in the offspring that are independent of the onset of ASD core symptoms [23]. This effect is mediated by the maternal microbiota and leads to a long-term immune imbalance in the offspring, characterised by a peripheral increase in the Th17 lymphocyte subtype (Th17) [24]. Th17 are major pro-inflammatory lymphocytes and are in a constant and dynamic equilibrium with its anti-inflammatory counterpart regulatory T lymphocytes (Tregs) [25, 26]. Interestingly, ASD individuals displayed a peripheral increase in Th17 and a decrease in Tregs, which was more pronounced in those with a history of MIA [27].

Interestingly, a recent study on mice demonstrate that specific stimulation of Tregs in ASD pups from MIA mothers reverse autistic-like symptoms [28]. Overall, this suggests that the epigenetically mediated peripheral immune imbalance induced by MIA may participate in the socio-maladaptive behaviors in ASD and could be targeted by specific immunomodulatory strategies.

**Limitations**

One of the main limitation of our study was intrinsic to its retrospective design, which leads to a possible recall bias regarding the MIA event during pregnancy. To overcome this problem, we used a strict definition of MIA, but this will not replace a prospective study to confirm our results. Even if we pooled two cohorts, the population remains relatively small and to better decipher the influence of MIA, many clinical and biological factors need to be studied on larger cohorts to obtain the necessary statistical power. Nevertheless, all our results were validated by different and complementary statistical approaches with good model performance highlighting the robustness of our data.

Finally, one additional limitation of our study was the limited number of covariables which potentially impacted socio-adaptive behaviors, that we included in the analysis. Intelligence quotient, for example, was not integrated, whereas there were significant entanglements between IQ and adaptive functioning [19]. Future studies should integrate additional dimensions related to ASD, such as intellectual developmental disorder or Attention Deficit / Hyperactive Disorder, to further decipher the impact of MIA on socio-adaptive impairment in ASD [21].
Conclusions

MIA may affect at long term the socio-adaptive behavioral trajectories of individuals with ASD. Specific pathophysiological pathways may explain these clinical peculiarities of ASD- MIA\(^+\) individuals, and may open the way to new perspectives in deciphering the phenotypic complexity of autism and the development of targeted immunotherapy strategies.

Abbreviations

ADOS: Autism Diagnostic Observation Schedule 2\(^{nd}\) edition

ASD: autism spectrum disorders

MIA: maternal immune activation

SRS: Social Responsiveness Scale 2nd edition

VABS: Vineland Adaptive Behavior Scales 2\(^{nd}\) edition

Declarations

Ethics approval: As part of the PARIS study, this study was approved by the local ethics committee of Robert Debré Hospital (2021-27 N° IDRCB: 2021-A00489-32). Informed consents were obtained from patients or a parent and/or legal guardian before enrollment in the study. All methods in both studies was performed in accordance with relevant guidelines/regulations and have been performed in accordance with the Declaration of Helsinki.

Availability of data and materials: The PARIS dataset and the code used during the current study are available from the corresponding author upon request. Due to ethical and legal restrictions, data involving clinical participants of the FACE-ASD cohort cannot be made publicly available. All relevant data are available upon request to the Fondation FondaMental for researchers who meet the criteria for access to confidential data.

Competing interests: The authors declare that they have no competing interests

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Authors' contribution: PE and AM contributed to data collection. PE, HP and NT analysed and interpreted the data. PE wrote the first version of the article and revised it after its revisions by co-authors. VV, EH, AAm, AAn, PA, JMB, SB, OB, MB, AC, NC, RC, DDF, CD, MG, FGB, FG, AK, ML, AL, FL, CL, EM, NR, CMS, MS, EZ, participated in the inclusion of children and in the revision of the article and approved its final version,
and all agreed to be accountable for all aspects of the work. MR, DK and RD supervised this conception of this study

References


Figures

More severe impact on adaptative behaviors related to socialization is associated with maternal immune activation during pregnancy.

A) Correlogram of the different subdomain of the Vineland II with clinical parameters. B) Classification decision tree of the risk of maternal immune activation during pregnancy depending on Vineland II – Socialisation sub-score and ADOS total score on the autistic offspring. C) Feature importance for the supervised analysis. Feature importance computes the importance of features by calculating the increase in the model prediction error after permuting the feature. D) Feature importance for the supervised linear discriminant analysis. E) Classification decision tree of the risk of maternal immune activation during pregnancy depending on Vineland II – Communication sub-score and ADOS total score on the autistic offspring.

Figure 2

Maternal immune activation may directly affected the socio-maladaptive behaviors in autism children.

A) Linear model regression representation of the unsupervised analysis on socialization sub score B) Feature Importance of the linear regression model. C) Path analysis on the influence of MIA on socialization sub score.


Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplFigure1.pptx
- SupplFigure1d1.pptx
- SupplFigure2.pptx
- SupplFigure3.pptx
- SupplFigure4.pptx
- SupplementarymaterialSR.docx