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Preconception Blood Brain Barrier Integrity and Autism Risk at Birth: A Protocol from an Indian Population

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ABSTRACT

Autism Spectrum Disorder (ASD) is a multifactorial neurodevelopmental condition influenced by genetic, epigenetic, and environmental factors. While maternal prenatal factors have been widely studied, preconception paternal health — particularly semipermeable blood–brain barrier (BBB) integrity — remains underexplored in relation to ASD risk in offspring. This paper presents a cross sectional observational study protocol designed to assess surrogate measures of BBB permeability in Indian men prior to conception and examine their associations with semen quality, epigenetic markers, and autism birth risk. Using biochemical markers, reproductive health parameters, and follow up infant developmental screening, this research aims to elucidate whether disruptions in systemic barrier regulation may correlate with increased ASD risk.

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Introduction

The blood–brain barrier is a specialized endothelial interface maintaining central nervous system (CNS) homeostasis through tight junctions and regulated transport. Disruption of BBB integrity has been linked to inflammation and altered neurodevelopment in animal and human studies of ASD, although directly exploring this in preconception paternal health has not been comprehensively investigated [1]. ASD is known to have multifactorial etiology, with advanced paternal age and sperm epigenetic alterations shown to be associated with increased ASD risk in offspring. The mechanistic role of systemic physiological states — such as altered barrier regulation — may reflect broader systemic inflammation or oxidative stress that could influence germ line epigenetics and fetal neurodevelopment [2].

Objectives

To assess semipermeable BBB integrity markers in Indian men prior to conception. To evaluate correlations between surrogate BBB markers, seminal parameters, and hormonal/inflammatory profiles. To investigate associations between such preconception profiles and autism risk in offspring, assessed during early developmental follow up.

Methods

Study Design

A prospective cohort study enrolling Indian men planning conception ($n \approx 200$), with follow up of offspring until age 3 years for developmental outcomes, including ASD screening.

Ethics

Approved by relevant Indian institutional ethics boards; written informed consent obtained.

Inclusion Criteria

Indian men aged 25–45 planning conception within 1 year. No known neurological, reproductive, or systemic autoimmune disease.

Exclusion Criteria

History of infertility treatment or CNS pathology. Exposure to teratogenic agents.

Assessments

Semen Analysis

WHO standard semen evaluation: sperm count, motility, morphology, and DNA fragmentation.

Hormonal Profile

Serum levels of testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), and sex hormone binding globulin (SHBG) [3].

Systemic Inflammation

Markers such as C reactive protein (CRP), IL 6, and TNF α.

Surrogate BBB Integrity Markers

Measurement of circulating levels of tight junction proteins (e.g., claudin 5, occludin) and matrix metalloproteinases that influence endothelial permeability.

Epigenetic Profiling

Assessment of sperm DNA methylation patterns linked to neurodevelopmental risk, such as loci previously associated with autistic traits [4].

Infant Follow Up and ASD Screening

Developmental monitoring using validated tools (e.g., Modified Checklist for Autism in Toddlers M CHAT) at 18, 24 and 36 months. Cases of ASD will be confirmed by clinical developmental specialists using DSM 5 criteria [5].

Statistical Analysis

Primary Outcomes: Correlation between surrogate BBB markers and ASD risk in offspring.

Secondary Outcomes: Association of BBB indicators with semen quality, hormone levels, and inflammatory markers. Use multivariate regression adjusting for paternal age, BMI, lifestyle factors (smoking, alcohol), and socioeconomic status.

Discussion

Linking BBB Alterations and Autism Risk: Evidence suggests environmental and physiological factors that can disrupt barrier integrity including inflammation and oxidative stress — may contribute to neurodevelopmental alterations associated with ASD. Disrupted BBB or placental barrier during critical developmental windows has been implicated in ASD pathogenesis. Paternal Age and Epigenetics: Advanced paternal age has consistently shown associations with ASD risk in offspring, potentially mediated by sperm epigenetic changes. Potential Mechanisms:While direct mechanistic links between adult BBB status and fetal neurodevelopment are hypothetical, systemic inflammation and endothelial dysregulation may reflect shared pathways affecting germ line integrity and developmental programming.

Limitations

Surrogate peripheral markers may not perfectly represent BBB status. ASD etiology is multifactorial; paternal contributions are one piece of a complex risk profile.

Conclusion

This protocol proposes an integrated evaluation of semipermeable BBB surrogate markers, reproductive health, and autism risk, aiming to explore novel interconnections in paternal preconception health. Data from this study could inform early risk stratification and holistic reproductive counseling in Indian populations.

References

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