INJ INTERNATIONAL NEUROUROLOGY JOURNAL

Unraveling the Tapestry: Linkages between Maternal Metabolic Conditions and Neurodevelopmental Disorders in Progeny, Delving into the Intricate Threads of Obstetric and Neonatal Complications

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Abstract

Studies have shown that if a mother contracts a viral or bacterial infection during the early stages of pregnancy, there is a significantly higher likelihood that her unborn child would have a neurodevelopmental disorder (NDD) such as schizophrenia, autism, or ADHD. However, there is limited knowledge regarding the impact of immunological activity during early life on the development of brain systems. It is believed that the mother's immune response may interfere with crucial brain activities necessary for the normal development of the fetus and newborn, leading to distinct behaviors observed in individuals with neurodevelopmental disorders (NDD). Maternal immune activation (MIA) in rodent models has yielded valuable knowledge regarding the brain abnormalities that arise as a consequence of MIA. This review begins by doing a comprehensive examination of human epidemiological data. Its primary objective is to investigate the correlation between various types of maternal immune activation (MIA) and the occurrence of developmental abnormalities in kids that are not related to household environments. Subsequently, we will examine prevalent rodent MIA models and assess their concordance with human data. The study also considers additional variables that influence the likelihood of neurodevelopmental disorders (NDDs) in individuals with MIA. It suggests that future research should incorporate these aspects for further analysis. The elements that influence the diversity in neurological and behavioral responses to MIA include the offspring's sex, the timing of the immunological challenge, genetics, parental age, the gut microbiome, prenatal stress, and placental buffering.

Introduction

According to Abdallah et al. (2012), the occurrence of neurodevelopmental disorders (NDDs) in the United States is 13.87%, which represents an increase of around 9.5% compared to the preceding decade. This information is based on statistics from the Centers for Disease Control and Prevention. The main factor behind this rise is the advancements achieved in diagnostic abilities. Albani et al. (2014) note that the occurrence of NDDs is generally similar around the globe, but variations exist due to socioeconomic factors, levels of awareness, and diagnostic methods in different nations. Key epidemiological parameters associated with NDDs encompass the age of onset, symptomatology, gender-specific prevalence rates, and the risk factors linked to these disorders.

Zawadzka et al. (2021) found that genetic factors establish an initial risk for various non-communicable diseases (NDDs), which is then influenced by additional factors including prenatal infections leading to maternal immune activation (MIA). This immune activation then alters the risk for certain NDDs. MIA is distinguished by increased levels of immune-related chemicals, such as cytokines and chemokines, and is typically investigated in relation to maternal exposure to immunogens during pregnancy. Rat models are extensively utilized in the field of animal testing to simulate Maternal Immune Activation (MIA). This is achieved either direct infection or stimulation of the immune system. The purpose is to investigate how immune activation during pregnancy impacts brain alterations related to non-disruptive disorders. Albani et al. (2014) study states that research on the correlation between immunological activation and brain development in the context of neurodevelopmental disorders (NDDs) is currently ongoing.

This review has three main objectives: (1) to assess the epidemiological evidence that supports the connection between maternal immune activation (MIA) and the increased risk of neurodevelopmental disorders (NDDs); (2) to provide a brief overview of the commonly used rodent models of MIA and their relevance to the study of NDDs in humans; and (3) to explore additional factors in rodent research that should be taken into account, including the timing and severity of infection, gender-based variations in susceptibility and symptoms of NDDs, and individual variations in response to MIA. The primary objective of this study is to examine the epidemiological correlation between maternal immune activation (MIA) and neurodevelopmental disorders (NDDs) in order to identify crucial elements that should be incorporated in the design of future studies involving both humans and rodents. Employing this approach will enable scientists to accurately determine the immunological and neurological roots of NDDs, thereby facilitating the development of tailored drugs and treatment approaches.

Neurodevelopmental Disorders

The term "neurodevelopmental disorders" (NDDs), introduced in the DSM-5, encompasses a variety of conditions that hinder development in areas such as language, physical skills, social interaction, and learning. The occurrence of these disorders is often linked to medical, environmental, or genetic factors that occur early in childhood (Morris-Rosendahl & Crocq, 2020). Notable neurodevelopmental disorders (NDDs) include intellectual disability (ID), autism spectrum disorder (ASD), attention deficit/hyperactivity disorder (ADHD), and communication difficulties. The frequency of these disorders in boys and girls aged 3-17 in the United States varies, exhibiting significant discrepancies (Yang et al., 2022). Although not classified as a Neurodevelopmental Disorder (NDD) in the DSM-5, schizophrenia is believed to arise from disruptions in the developmental process. The onset of symptoms often occurs during the latter stages of adolescence.

Individuals with various Neurodevelopmental Disorders (NDDs) may have a combination of symptoms such as cognitive and learning difficulties, social behavior abnormalities, disrupted sleep patterns, and metabolic or gastrointestinal problems. However, the manifestation of these symptoms is contingent upon the specific ailment and the individual. Learning difficulties and sleep disturbances vary among conditions such as Autism Spectrum Disorder (ASD), schizophrenia, and Attention Deficit Hyperactivity Disorder (ADHD).

The extent to which the underlying neurobiology in different neurodevelopmental disorders (NDDs) contributes to the overlapping symptoms remains unclear. These symptoms might arise from particular neurobiological abnormalities associated with illnesses or from general neurobiological processes, such as imbalances in the brain's excitatory/inhibitory balance. Maternal immune activation (MIA) is believed to have a significant impact on the development of numerous neurodevelopmental disorders (NDDs), perhaps leading to symptoms that resemble illness-like behavior. The National Institutes of Mental Health (NIMH) implemented the Research Domain Criteria (RDoC) framework as a reaction to the diverse and interconnected nature of symptoms. This paradigm emphasizes a multidimensional approach to study, focusing on specific elements of diseases rather than the disorders as a whole. This methodology, which considers many risk factors and patterns of symptom manifestation, can assist us in understanding the variations in neurodevelopmental disorders from one case to another.

The study acknowledges the influence of several genetic and environmental variables, including sex, parental age, stress, diet, and pregnancy complications, in predicting the likelihood of neurodevelopmental disorders (NDD). The subsequent sections of the study will go into a comprehensive analysis of the epidemiological data that supports the recognition of MIA as a significant risk factor for various neurodevelopmental disorders (NDDs).

Maternal Immune Activation And Neurodevelopmental Disorder Risk

It has been established by Zablotsky et al. (2019) that brain development and subsequent behavior in later stages of life can be negatively impacted by environmental variables and viruses. In infants, maternal immune activation (MIA) increases the risk of neurodevelopmental disorders (NDDs), according to epidemiological studies. It is critical to recognize that maternal immune activation (MIA) encompasses any disruption of the immune system that takes place in animals or humans during pregnancy. According to research conducted on animals, the initial fortnight of neonatal development in mice is analogous to the third trimester of human fetal growth (Vorstman et al., 2017). The critical processes of immunogenesis, apoptosis, and synaptogenesis, which are observed in rodents during the third trimester of human brain development, occur subsequent to birth (Wang et al., 2017).

Cohort and case-control studies are methodologies that are utilized to examine the prevalence of neurodevelopmental disorders (NDD) and maternal immune activation (MIA) in human subjects (Sarfraz et al., 2023). Cohort studies involve the identification of subjects who have undergone a designated period of exposure to an infectious agent. Following that, the likelihood of them developing a specific malady is assessed through either retrospective or prospective methods. Case-control studies involve the identification of individuals who are afflicted with a specific malady, followed by an examination of any potential risk factors or exposure variables. These investigations corroborate infection rates through the utilization of self-report, serology, or medical data. The observational nature of these studies on humans complicates the task of establishing a direct correlation between symptoms of NDD and MIA. This emphasizes the critical nature of conducting basic biomedical research and employing animal models in order to identify the precise molecular, cellular, or neural circuit modifications that are responsible for the development of Neurodevelopmental Disorders (NDD) and Maternal Immune Activation (MIA). On the contrary, the most persuasive evidence linking maternal immune activation (MIA) to neurodevelopmental disorders (NDDs) comes from epidemiological studies examining the effects of pathogens and environmental stressors, specifically viral and bacterial infections during pregnancy (Ahmed et al., 2023).

Epidemiological Disease Type, Severity, Fever Response, and Therapeutic

Researchers have shown that infants whose mothers had infections when they were pregnant are more likely to suffer from neurodevelopmental disorders (NDDs) such schizophrenia and autism spectrum disorder (ASD). Viruses like rubella and influenza, as well as bacteria like urinary and vaginal infections, can cause these neurodevelopmental disorders (NDDs) in pregnant women. Parasitic illnesses, especially Toxoplasmosis gondii, have been linked to schizophrenia.

Children whose mothers contracted rubella during the first trimester of pregnancy were at a higher risk of autism spectrum disorder (ASD), a finding that came to light during the 1960s rubella epidemic in the US. Prenatal exposure to excessive levels of vitamin A and liver failure are two possible causes of this correlation. There is mounting evidence that prenatal rubella exposure increases the risk of nonaffective psychosis and schizophrenia in young adults.

Bacterial infections in the second and third trimesters of pregnancy are significantly associated with the development of ASD and ADHD in children, according to studies. Furthermore, in situations when psychosis runs in the family, there is a strong correlation between bacterial infections in the mother and an elevated risk of schizophrenia in children.

Although there is a lack of clear evidence, it has been suggested that pregnant women with influenza are more likely to develop schizophrenia. There is mounting evidence linking influenza infection during pregnancy, especially in the second trimester, to an increased risk of schizophrenia, according to a number of studies. However, other studies have failed to find an association between influenza during pregnancy and ASD, thus the link is far from proven.

The risk of neurodevelopmental disorders (NDDs) and autism spectrum disorder (ASD) in children is increased in correlation with maternal fever, making a high body temperature during pregnancy a serious concern, according to research. This risk can be lowered by using antipyretics throughout pregnancy.

Consideration of the severity and duration of diseases and feverish responses during pregnancy is of the utmost importance. A greater risk of developing Autism Spectrum Disorder (ASD) has been associated with longer durations of fever and more severe diseases. Accordingly, the probability of a diagnosis of autism spectrum disorder (ASD) or schizophrenia is significantly affected by the severity of the fever response and the degree of infection experienced during pregnancy. When assessing the risk of neurodevelopmental disorders (NDDs) in children, it is crucial to include the type, timing, and severity of maternal infections during pregnancy. This is highlighted by these findings.

Expression of cytokines and chemokines throughout pregnancy

Numerous studies support Dr. Paul Patterson's hypothesis that the maternal immune response and the cytokines it secretes into circulation may increase children's risk of neurodevelopmental disorders (NDDs) from influenza or other infections, rather than direct fetal infection. Human epidemiological research confirms this idea after decades. Research in California, USA, found a correlation between elevated cytokine (IL-4, IL-5), interferon (IFN)-γ, and interleukin (IL)-4 levels in maternal serum during mid-pregnancy and increased risk of autism spectrum disorder (ASD) in offspring after adjusting for maternal characteristics and gestational age at specimen

collection. A Danish research found higher levels of TNF-α and TNF-β in amniotic fluid of people diagnosed with autism spectrum disorder (ASD). Autism spectrum disorder (ASD) was also linked to higher IL-4, IL-10, and MCP-1 levels after 1993, when autism diagnostic criteria were reevaluated.

According to Sullivan et al. (2015), high levels of pro-inflammatory cytokines such TNF-α, IL-1β, and IL-6 in maternal blood samples at or before birth in Philadelphia, USA, were linked to mental illnesses in adult offspring. The association was strongest in early pregnancy samples. Research in Rhode Island found a link between elevated TNF-α and IL-8 levels in parturition samples, particularly in cases of maternal infection in the third trimester, and increased risk of psychosis in offspring (Buka et al., 2001).

These data imply that infections activate several cytokines and chemokines. Chemokines and cytokines can cross the placental barrier or trigger cytokine synthesis. Thus, they may affect prenatal brain development. This inflammatory response may impede brain development, increasing NDD risk (Hsiao and Patterson, 2012).

Neurogenesis involves synapse pruning and maturation by the immune system and microglia. Early-life immune activation, especially maternal immunological activation (MIA), may hinder the above processes (Sawangchai et al., 2022). Microglia number and function, synapse maturation, neural circuit reconfiguration, and behavioral disorders may ensue. These disturbances may also affect postnatal neurodevelopmental processes including synaptic connections and brain circuits that start certain behaviors.

Thus, rat models of MIA and NDD show how the immune system impairs molecular and brain processes during key development. For further assessments of MIA's neurobiological effects on NDDs, see Bergdolt and Dunaevsky (2019), Knuesel et al. (2014), and Estes and McAllister (2016). Some of these models study how maternal illness or immune challenge cytokines affect offspring brains and behavior.

Pregnancy immune system: Cytokines without infection

Although rigorous immune system management is necessary, immune activation must be strong enough to prevent or eradicate illness. Genetics and illnesses affect immune system function. COVID-19, also known as severe acute respiratory syndrome coronavirus 2, affects people differently. Strong immune responses, high cytokine production, and little symptoms enhance the risk of severe respiratory distress (Cummings et al., 2020). Women with hypersensitive immune systems that raise cytokine and T-cell counts are more likely to develop autoimmune disorders (Klein and Schwarz, 2018). Klein, Flanagan (2016). The immune system is vulnerable to several factors that might affect the developing fetus' risk of non-communicable disease (NDD) during pregnancy and sickness.

When studying MIA and NDDs, developmental neuroimmunologists may neglect a crucial immune system shift during pregnancy. Immunosuppression protects non-self fetuses from mother's immune system throughout pregnancy. Thus, even a little disturbance in pregnancy's immunosuppressive effects might lead to an early termination. In late pregnancy, immunological changes may cause more severe infections, yet many women see a temporary improvement in autoimmune illnesses. Rodent models show immunosuppression throughout pregnancy. Compared to lactating or unbred female rats, pregnant rats show a reduced fever response to low concentrations of lipopolysaccharide (LPS) (25 μg/kg) at 96 and 24 hours before and after parturition. Most expecting rodent mothers were hypothermic and had no temperature within 24 hours before delivery, which caused 80% of them to die between 3–15 hours of birth (Martin et al., 1995). In a study by Sherer et al. (2017), mice treated to LPS (100 μg/kg) at E11 (mid-gestation) showed a 12%, 20%, and 30% reduction in IL-1β, IL-6, and IFN-γ splenic output compared to non-pregnant females. By E22, the day before birth, the mother's spleen produces almost no cytokines in response to the same LPS dose, demonstrating pregnancy's significant immunosuppression (Sherer et al., 2017). The placenta and fetal brain show a 4-5-fold rise in IL-1β and IL-6 after LPS-induced MIA at E11, although this decreases by E22, the day before birth (Sherer et al., 2017). To be healthy during pregnancy, immune system activity must reduce significantly.

A healthy pregnancy exposes the fetus to few immune molecules, yet dysregulated cytokine production can occur even without sickness. High prenatal cytokine exposure may enhance NDD risk and severity. Human studies have linked elevated cytokine expression in maternal serum and/or amniotic fluid to non-diagnostic problems in offspring, even without infection. Under certain conditions, latent inflammatory diseases, immune function changes, stress-induced immunological activation, or minor adjustments to pregnancy-associated immunosuppression may increase cytokine production and the risk of NDD. Future basic and epidemiological studies should consider this.

Immune-activated rodent models for neurodevelopmental disorders

Research conducted on humans cannot definitively establish a causal relationship between risk factors and NDD. The difficulty in comprehending the development of the disorder arises from the constraints on the information obtained after death and the inability of existing neuroimaging technology to accurately evaluate the structural and functional abnormalities in the brain at the cellular or molecular scale. Hence, in order to investigate the impact of immunological activity and the immune system on neurodevelopment, it is necessary to utilize animal models.

Researchers utilize mice models to mimic a disease by altering a genetic risk factor. NDD-specific models may overlook specific symptoms and the complexity of the disorder (Vigli et al., 2020). Contemporary animal models investigate the common phenotypic characteristics of several disorders, rather than focusing on just one. This technique aligns with Section 2 of the NIMH RDoC initiative. The presence of overlapping symptoms between NDD and other disorders suggests potential neurological similarities (Conradt et al., 2021; Auerbach, 2022). Animal models often utilize MIA alone to study the correlation between immune system disturbances, which are a risk factor for neurodevelopmental disorders (NDDs), and impairments in cognition, social interaction, and sleep. In order to comprehend the effects of MIA on brain systems, particularly the inflammatory response in both the mother's body and fetal compartments, as well as the resulting repercussions connected to neurodevelopmental disorders (NDD) in children, it is imperative to utilize rodent models.

Additionally, it is understood that neurodevelopmental disorders (NDDs) can arise as a result of both environmental and genetic factors. In order to investigate issues related to neurodevelopmental disorders (NDD), scientists are combining several factors that induce inflammation, such as genetic mutations, immunological challenges, nutritional alterations, social stresses, etc., through the utilization of "two-hit" and "multi-hit" neurodevelopmental models. Utilizing genetic models of "specific disorders" that integrate NDD risk variables might enhance our comprehension of the interplay between biology and environment in the development of such illness. Harvey and Boksa (2012) state that a risk factor can lead to many neurodevelopmental disorders (NDDs) either by having features (such as dosage, timing, immunogenic target, etc.) that contribute to diverse NDD phenotypes, or by interacting with other susceptibility factors to produce different NDDs. It is important to examine this aspect while evaluating the fundamental biology of MIA research models and their conclusions. The following section will discuss the suitability of academics' MIA models for analyzing data on human epidemiology.

Inflammation and stress during pregnancy

Extensive research has shown a link between stress experienced during pregnancy and various non-verbal developmental disorders (NDDs) including schizophrenia, autism, and ADHD (Ronald et al., 2011; Diz-Chaves et al., 2012, 2013; Chan et al., 2018; Minakova and Warner, 2018; Makris et al., 2022). Recent study has utilized the term "changes in inflammatory biomarkers in the mother's bloodstream," which might potentially heighten the likelihood of different neurodevelopmental disorders (NDDs), to describe this connection. Miller et al. (2017) revealed that socioeconomic hardship is a stressor that is linked to increased immunological activation and hindered development of placental tissue, as shown by transcriptional markers. Immune cells may generate counterinflammatory-promoting cytokines in response to this stress, as stated by Miller et al. (2017). Stress-induced alterations in the mother's baseline cortisol levels may potentially impact the likelihood of neural tube abnormalities (NDDs) in the developing brain. These changes might lead to consistently high or increasing concentrations of pro-inflammatory cytokines (Van den Bergh et al., 2005).

Animal models of prenatal stress and maternal immune activation (MIA) have shown similar amounts of pro-inflammatory cytokine production, including IL-6, and activation of microglial cells. Rats born to mothers who experienced prenatal stress had increased amounts of cytokines in the hippocampus and a higher overall number of immunoreactive microglial cells, in comparison to unstressed rats. As a result, this caused a stronger inflammatory reaction to lipopolysaccharide (LPS) in the offspring (Diz-Chaves et al., 2012). Additional evidence has surfaced that confirms a link between changes in the hypothalamic-pituitary-adrenal (HPA) axis during pregnancy and the development of anxiety-like behavior, cognitive impairments, and depressive symptoms in the offspring of stressed rodents and non-human primates (Weinstock, 2005; Weinstock, 2008). Gestational stress and elevated corticosterone levels in both the mother and the newborn can lead to an increase in the activity of corticotropin-releasing hormone (CRH) in the amygdala. The disturbance in the feedback modulation of the HPA axis can continue throughout adulthood (Van den Bergh et al., 2005; Weinstock, 2005; Weinstock, 2008). Prolonged maternal stress during pregnancy, along with increased levels of cortisol and CRH, might potentially hinder the developing brain's ability to handle future stresses, immune system problems, or maternal immune activation (MIA).

The presence of unforeseen pressures in animal models is frequently disregarded or unreported, despite its potential to worsen the neurological and behavioral outcomes for both the mother and her children in conjunction with MIA. In addition to what has been discussed, several factors such as environmental stress caused by construction, levels of background noise, accommodation, administration of substances, assessment of behavior, and circumstances of housing may often impact an experiment. Researchers must prioritize minimizing the impact of external pressures when conducting their work. However, if this is not achievable, they should meticulously record and provide detailed explanations of these aspects in their findings.

Instigator or protector: the placenta?

The placenta shields the baby from pathogens while providing nutrition and oxygen. Larger immunogenic molecules and most infectious agents are blocked from passing through the placenta, although there is some evidence that the placenta actively transfers immune molecules from the mother to the developing foetus through the circulation (Robbins and Bakardjiev, 2012). Regrettably, not much is known about the placenta entry of cytokines linked to MIA. Nonetheless, it's crucial to comprehend how the placenta transfers cytokines during MIA.

Research conducted several decades ago revealed that concordant monozygotic twins for schizophrenia had an increased chance of monochorionic deliveries (Davis et al., 1995). Benirschke (1990) proposes a four-layer separating membrane, one for each twin, in conjoined twin pregnancies. In this configuration, the two fetuses can circulate together. In that case, the mother could expose the twins to additional chemicals and cytokines. Maternal blood is able to cover the epithelial layer of placental cells during uterine implantation thanks to interactions between maternal immune and endothelial cells and extravillous fetal cells.

It's possible that syncytiotrophoblasts will shield the placenta from infection. When there are active innate immune receptors, they can also start cytokine reactions. Because they are hemochorial, rat and human placental buffers function similarly. The trophoblast epithelium of the rat placenta is immediately submerged in maternal blood, much like in humans, according to research by Furukawa et al. (2019). This occurs in the decidua, the human uterine implantation site, since it has a single dividing layer (syncytiotrophoblasts). But the three layers in this rat could suggest that the fetal-maternal exchange mechanisms are different in the two species. Uterine natural killer (NK) cells in certain placenta regions aid in the fetus's ability to adapt and adjust during pregnancy in both species. Poly I:C MIA in rats has been shown to boost placental maternally-derived IL-6 protein (Hsiao and Patterson, 2011). This causes the placenta to release acute phase immune genes, some of which enter the fetal blood, and activates the JAK/STAT3 pathway. IL-6 is produced during pregnancy in both the mother and the child (Zaretsky et al., 2004). It is still unclear how MIA stimulates fetal immune cells. According to certain studies, LPS and other immunogenic substances are unable to pass through the placental barrier (Ashdown et al., 2006; Ning, 2008). Additionally, the placenta may trigger an immune reaction. Rats' placental barriers and their capacity to transfer immunological substances from the mother's circulation hence require more investigation.

According to early research, there was a lower incidence of concordance for multiple NDDs in dichorionic monozygotic twins (Davis et al., 1995). Since every mouse pup has a distinct placenta, their reactions to MIA may vary. Placentas are able to transmit hormones since mother's blood passes through them. Blood travels caudally to distally, or from the cervix to the ovaries, in pregnant rats. After the cervical end fetus, fetuses at various uterine regions get maternal blood flow. In animals with repeated pregnancies, Ryan and Vandenbergh (2002) demonstrated that the mother's intrauterine position impacts fetal growth. According to Ryan and Vandenbergh's (2002) research, the morphological, physiological, and behavioral characteristics of female fetuses born after male fetuses were masculinized. Hormone imbalances and anomalies in the endocrine system are involved. A male fetus's amniotic fluid and the mother's circulation allow testosterone to distribute to its intrauterine neighbors. Depending on the position of the uterus, this transmission route may expose fetuses to MIA-associated substances at varying rates. This also holds true for immune substances such as cytokines. Caudal babies in MIA models receive maternal blood flow first and may be more exposed to immunological components circulating in the pregnant dam.

The placenta's influence on fetal response and the inflammatory consequences of MIA require further investigation. Researchers should take into account the differences between human and rodent pregnancies before extrapolating their findings to human NDDs or rat MIA models. This includes the number of fetuses, the properties of the placental barrier, and the transmission or production of cytokines and immunogens.

Conclusion

During Maternal Immune Activation (MIA), there are a number of potential factors that could influence fetal development and the progression of neurodevelopmental disorders. This concludes the examination at hand. According to our research, it is not mandatory for all studies to incorporate each of these criteria in their investigations. It is crucial to take into account these factors when analyzing and interpreting the findings of critical research studies concerning the impact of MIA on NDDs. In an effort to standardize animal models of maternal immune activation (MIA), increase transparency regarding the variation of parameters across laboratories, and improve the reproducibility of results across labs, Kentner et al. (2019) have formulated a set of reporting standards for MIA. While there might be some divergence in the research pertaining to the factors we have taken into account, this divergence is comparable to what is observed in the behavioral symptoms and risk factors associated with NDDs in humans. Further research is required to fully understand the comprehensive effects of these factors, their interaction with perinatal immune activation (specifically the intensity and duration of the MIA response), and their contributions to the development of the neurological and behavioral characteristics associated with NDDs.

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