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Unraveling the Complexities of Autism Spectrum Disorder: A Deep Dive into Genetic and Environmental Factors

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Abstract

Autism Spectrum Disorder (ASD) is a neurological condition that affects behaviour, social interaction, and communication, with symptoms varying across individuals due to its spectrum. The prevalence of autism has increased significantly worldwide, and early diagnosis and intervention have become crucial for better outcomes. Both genetic and environmental factors contribute to ASD, with over 200 susceptibility genes identified. However, the presence of genes does not cause autism by themselves but increase the risk for the disorder in the presence of other environmental causes related to events before or during birth. Maternal viral infections such as cytomegalovirus, zika, influenza, and rubella viruses during pregnancy can directly damage the foetal brain, alter brain development, and trigger inflammation, all of which have been linked to the risk of acquiring ASD during pregnancy. Here we examine existing literature on intricate relationships between ASD, viral infections and the environment, with the hope of elucidating potential links, mechanisms, and implications of viral infections in the development and manifestation of ASD and public health initiatives. While the exact mechanisms are not fully understood, direct viral infection, cytokine storm, and maternal immune responses appear to be implicated and further research, interventions, surveillance, and health screening is necessitated to address this complex and heterogeneous disorder. Infants whose mothers have had viral infections with inflammation need long term follow up so as to signs of autism so as to reduce the burden of this condition.

Keywords: autism, ASD, genetics, maternal viral infection, fetal brain damage, cytokine storm, cytomegalovirus, influenza virus, zika virus

Introduction

A neurological condition known as Autism Spectrum Disorder (ASD) impairs behavior, social interaction and communication [DSM-5, 2013]. It is a spectrum disorder, affecting various people to varying degrees [Newwschaffer CJ et al 2007]. Some common symptoms include having trouble with social communication, engaging in repetitive behaviors, and having minimal interests or activities [Hodges H et al, 2020]. Research has suggested a combination of genetic and environmental factors as the exact cause of autism is unknown and the impact on affected individuals and their families are life-changing. Early intervention can improve

results, and diagnosis is based on observation of behavior and developmental history. The estimated prevalence of autism has risen significantly since the 1990s, and it is now considered as the most recurrent neurodevelopmental disorder affecting children (Gillberg, C & Wing, L 1999)]. Worldwide, it is projected that the number of children with autism will surpass the combined total of children affected by cancer, juvenile diabetes, and pediatric AIDS [Center N 2011]. The prevalence rate recorded in 2010 was 1 in 132 children with approximately 52 million cases of autism reported globally [Baxter AJ etal 2015]. Estimation of prevalence of autism among 8-year-old children by The Autism and Developmental Disabilities Monitoring Network, USA, increased from 1 in 150 in 2000 to 1 in 54 in 2014 [Christensen DL et al 2019].

In Malaysia, the prevalence of Autism Spectrum Disorder (ASD) among school-age children has increased from 6.34 per 1,000 children in 2018 to 9.29 per 1,000 children in 2022. This translates to a significant rise in the number of children diagnosed with autism in recent years. While specific 2024 statistics are not readily available, the trend indicates a continued increase in diagnosed cases, placing a growing demand on autism intervention and support services. The prevalence of ASD among Malaysian school-aged children has been steadily increasing, with the highest number of autistic students enrolled in primary schools. The rising numbers of children with autism are putting a strain on available services and intervention programs. Increased awareness among Malaysian parents and improved diagnostic practices have contributed to the rise in diagnosed cases. Studies have shown that male children are more likely to be diagnosed with ASD than female children. While the median age at diagnosis is around 48 months, early diagnosis (under 36 months) is associated with factors like increased severity of social communication impairments and intellectual disability. Socioeconomic status can influence the age at which children are diagnosed, with children from higher socioeconomic backgrounds potentially being diagnosed earlier. Organizations like The National Autism Society of Malaysia (NASOM) are working to meet the needs of this growing population, but the demand for services is significant. According to Centre for Disease Control (CDC) in United States, the incidence of autism is at 1 in 68 children. That would mean that approximately 9000 children in Malaysia are born with autism every year. In a few short years the kids will be looking for autism intervention programs and that is likely to increase every year by the same number. This will be a challenge for education services authorities to meet the needs of this growing group of Malaysians with autism. All the NGOs combined today do not handle more than 1500

children. Hence we need to at least double and triple our resources in the country to develop facilities and programs to cater for this anticipated increase in demand for services.

Although the causal mechanism of ASD is not well understood, it is known that both genetic and environmental factors play a significant role [Newwschaffer CJ et al 2007]. Autism has been linked to environmental exposures throughout the crucial stages of early neurodevelopment, including prenatal maternal illness and inflammation as well as perinatal and postnatal exposures to different chemicals [Ornoy A et al 2016]. Genetic background may also contribute to an individual's susceptibility to infection [Meltzer A & Van de Water J 2017]. The association between autism and congenital rubella infections was identified over 50 years ago, and since then, other infections such as measles, mumps, polyomaviruses, cytomegalovirus, and influenza have been linked to the incidence of autism [Shuid AN et al 2021]. Prenatal or early postnatal infections have been shown to cause neurological and behavioral abnormalities in the offspring, including traits resembling autism and schizophrenia, according to animal studies [Patterson PH. 2011]. For instance, pregnant mice with respiratory human influenza virus infections exhibit behavioral and pharmacological abnormalities as a result of maternal antiviral immune responses that interfere with fetal brain development [Patterson PH 2002]. Studies have suggested that immune dysregulation and autoimmunity may influence the development of autism. The immune system may attack the brain cells or interfere with the normal functioning of the brain through cytokine dysregulation and antibodies, which can lead to changes in behavior and communication [Ornoy A et al 2016]. It has been hypothesized that viral infections may contribute to the development of ASD by directly infecting the central nervous system (CNS), triggering diseases in the CNS through infections elsewhere in the body, or altering immune responses in mothers or offspring. While some studies have not reported an association, a significant body of evidence, including human and animal studies, suggests a potential link between viral infections and the risk of autism.

Genetics and the environment

There is no one cause for autism and research indicates influences not only from genes, but also non-genetic and environment. More than 200 susceptibility genes have been identified to be associated with autism. For almost every chromosome, cytogenetic abnormalities have been identified. What has been suggested is that small mutations or a combination of these may have a role in causing autism. These different combinations could cause certain behaviours. However, the presence of genes does not cause autism by themselves but

increases the risk for the disorder. Environmental causes related to events before or during birth have been suggested to influence the chances of developing autism [London EA 2000] such as exposure to pollution or pesticides, diabetic condition of mother, birth before 36 weeks, breech complications, fetal distress, and limited amounts of oxygen to the baby's brain. Infections too are said to increase a child's likelihood of having autism [Chess S. 1971]. It has also been suggested that the autism is also linked to mitochondrial function [Chugani DC. et al 1999]. The crucial aspect that is affected is the brain and the communicative channels used by our nerve cells or neurons.

It has been shown by Rodier (2000) that a genetic component was indisputable with monozygotic identical twins where, if one is autistic, the other twin had a 90% probability of being autistic [Rodier PM. 2000]. However with fraternal (dizygotic) twins other twin's probability of being autistic was only 2–3% [Defrancesco L. 2016]. Investigating the phenotypes that included communication and social disorders the concordance increased from 60–92% in monozygotic twins and 0–10% in dizygotic pairs implying a role for multiple genes. Epigenetic factors and exposure to environmental modifiers have been suggested to contribute to variable expression of autism-related traits. Recent meta-analysis [Tick B. et al 2016; Bai D. 2019] yielded a high median heritability of 64% -9% and 80.8% - 86.8% of heritability. These twin studies provide strong evidence of a mainly genetic contribution to autism and negligible shared environmental effects. Whole genome analysis of families suggests that there are at least 10 genes implicated as causation of autism [Caglayan AO. 2010]. Of these HOXA1 was the only one that is autosomally inherited. Other genes implicated include DbetaH (DBH) in families of autistic children that have a low level of serum dopamine β-hydroxylase, which catalyses the conversion of dopamine to norepinephrine [Robinson EB et al 2016], NLGN3, NLGN4, NRXN1, MeCP2, and HOXA1 [Caglayan AO. 2010], Fragile X gene [Farzin et al 2006], SHANK2 synaptic scaffolding gene [Berkel S et al 2010], FMR-1 gene [Vincent JB et al 1999], and Reelin gene [Fatemi SH. 2002]. However, the above genes alone or in combination account for only ~1–2% of the cases implicating other factors causing mutations or alteration of gene expression, with the end result being autism.

Environmental exposures during early foetal development during pregnancy has been recently suggested [London EA 2000]. A mother's genetic background, through passive gene-environment correlation, influences environmental exposures associated with autism risks, such as medical conditions or behaviors in pregnancy (e.g. dietary intake of folic acid) [Rutter

M. 2015]. Another factor is maternal age or delayed paternity being linked to a higher risk of spontaneous or de novo rare variants though this is not a primary factor. It must be emphasized that where the environmental exposure on phenotype is modified by the background genotype or genetic liability, currently confirmatory evidence is still lacking. The different manifestations in different individuals with autism is hypothesized to be due to contributory effect of inflammation of the brain caused by a defective placenta, an immature blood brain barrier, the immune response of the mother to a viral or bacterial infection, a premature birth, encephalitis in the child after birth, or a toxic environment. Despite the progress in the understanding of genetics of autism and the environmental influence, clinically it exhibits heterogeneity.

Maternal viral infection

ASD and other neurological abnormalities in the offspring have been linked to maternal viral infection during pregnancy. During pregnancy viruses may spread via the placenta and infect the growing foetus causing direct damage or alter the foetal brain, resulting in neurological abnormalities that can lead to ASD [Elgueta D. et al 2022]. One mechanism is by disrupting the normal development of brain cells, infecting and killing developing neurons and reducing the number of neurons in the brain [Fatemi SH. et al 2002], which can affect the formation of neural circuits leading to neurological abnormalities that can lead to the progression of ASD [Wake H. et al 2002]. Viral infection also triggers inflammatory responses in the mother's body, and in the foetal brain [Cordeiro CN. et al 2015] disrupting the normal development of the brain and contribute to the risk of ASD [Wong CT et al 2015]. The mother's immune system responds by producing inflammatory molecules [Wake H. et al 2002], which can cross the placenta and enter the foetal circulation, causing damage by activating microglia, disrupting neuronal migration, triggering apoptosis, and causing excitotoxicity [Hagberg H. 2012]. Development of neural circuits may be interrupted via these mechanisms and may later lead to the development of neurological disorders such as ASD.

The maternal immune system also produces antibodies against the virus, which can also target the foetal brain cells, resulting in neurological abnormalities that can contribute to the development of ASD [Ashwood P. et al 2006]. During pregnancy, maternal immune cells are activated, produce cytokines, cross the placenta and affect foetal immune cells and brain development, leading to neuroinflammation and changes in neural connectivity [Zawadzka A. et al 2021]. However, occasionally, this immune response can be dysregulated, causing excessive production of cytokines, which being pro-inflammatory in nature can cause

neuroinflammation, excitotoxicity, and oxidative stress, which can damage growing neurons and impair typical brain development [Fischer R. & Maier O. 2015]. The production of immune cells, cytokines, and antibodies is part of this immunological response [Garcia-Flores V. et al 2022] and occasionally affects the growing foetus [Falahi S. et al 2023], either protecting the developing brain or harm it, depending on the type and timing of the immune response. Figure 1 summarizes the multiple pathways affecting brain development in the growing fetus. Ultimately, not all maternal viral infections during pregnancy lead to ASD, and the exact mechanism through which maternal viral infection contributes to the development of ASD is not fully understood.

Cytomegalovirus (CMV), a double-stranded DNA virus belongs to the family Herpesviridae and genus Herpes virus [Auriti C. et al 2021]. Just 10% of babies with congenital CMV infection show clinical symptoms, while 15% to 20% of infants who appear to be asymptomatic go on to acquire long-term consequences like sensorineural hearing loss, neurodevelopmental abnormalities, ocular issues, brain neoplasms, and ASD [Lazarini F. et al 2018]. CMV infection during pregnancy can damage the foetal brain by triggering an inflammatory response, disrupting the formation and migration of neurons, and causing altered gene responses in brain development. The severity of the damage depends on the timing of the infection during pregnancy, with earlier infections generally associated with more severe damage. The virus infects the cytotrophoblasts in the placenta, passes vertically from mother to fetus, disrupts the integrity and development of the placenta and alters regulation of gene expression to intercept placental cell self-renewal, migration, and differentiation [Maidji E. et al 2002]. CMV replicates and infects microglia in a manner similar to ZIKV [Schut RL. et al 1994]. Foetal macrophages that have been infected by CMV in animal models preferentially infiltrate the foetal brain's choroid plexus, ventricular, and subventricular regions, where they cause inflammatory response by secreting TNF-a, IL-1b, and IL-6 [Cloarec R. et al 2018]. CMV is known to have a particular tropism for neural progenitor cells and has been shown to infect foetal brain cells, leading to cellular damage and inflammation [Krstanovic F. et al 2021; Zengler KE. & Kukens JR. 2021]. Studies have shown significant findings in association with infection of CMV and ASD, where mothers seropositive for CMV had children with ASD symptoms compared to seronegative mothers [Slawinski BL. et al 2018; Lin CH. et al 2021]. Magnetic resonance imaging (MRI) showed abnormality of the cerebral white matter in congenital CMV infection proving the causality of ASD symptoms [Uematsu M. et al 2016]. Recently, studies in a group of Egyptian autistics

children revealed a 97.8% positive results for childhood CMV infection [Hassan ZR. et al 2023].

Influenza A, a single-stranded RNA virus of the family Orthomyxoviridae [Shim JM. Et al 2017] is a seasonal virus accounting for 3-5 million serious cases, with pregnant women being especially vulnerable to problems after infection. Cognitive problems, schizophrenia, bipolar disorder, and delayed psychomotor growth in the first few months of life are all symptoms of a virus in children whose mothers were infected [Mistra RS & Nayak JL 2019]. Several studies (medical data & case reports) suggest that pregnant women with influenza were at risk of having offsprings with ASD, with one study indicating a two-fold increased risk of autism after self-reported gestational influenza virus infection [Atladottir HO et al 2012], and a threefold increase in risk if the mother had febrile epistaxis. In a case control study it was determined that 8% of mothers who had influenza during pregnancy or were exposed to it gave birth to autistic children, [Shuid AN et al 2021]. In Norway, the Autism Birth Cohort has been collecting data and samples from both parents and the children and this data reported that mothers infected with influenza had a higher risk of having children with increased ASD risk [Mahic M. et al 2017].

Zika virus (ZIKV) is a single-stranded RNA virus from the Flaviviridae family has been extensively studied for its impact on brain development [Baud D. et al. 2017]. In pregnant mothers, ZIKV infection results in microcephaly in offspring, which is supported by the presence of the virus's genome in cerebrospinal fluid and antibodies in neonates [Shi T-C. et al. 2018] while animal studies have shown reduced brain volume, disorganized cortex neuronal layers, and apoptosis in the hippocampus and cortex [Sherer ML. et al 2018]. Additionally, the neural precursor cell (NPC) biology is disrupted, as they are susceptible apoptosis, pyroptosis, and autophagy, leading to microcephaly in the offspring [Starr JM. et al. 2019]. During the Zika virus outbreak in Rio de Janeiro between 2015-2016, 216 infants were born with a prematurity rate of 13% with eight of the infants having microcephaly [Mlakar J. et al. 2016; Jash SM & Sharma S. 2022].

Rubella virus, a single-stranded RNA virus of the Togaviridae family [Frey TK. 1997], is highly contagious and spreads through respiratory droplets causing mild illness known as rubella, or German measles in children and adults [Gershon AA. 2000]. However, rubella infection during pregnancy can have serious consequences for the developing foetus, including congenital rubella syndrome (CRS) [Gershon AA. 2000]. A variety of birth abnormalities, including cataracts, deafness, heart defects, and intellectual incapacity, can be

brought on by CRS [Auriti C. et al. 2021]. Antibodies produced by the mother can cross the placenta and enter the foetal bloodstream which may protect the foetus from infection or cause ASD [Hutton J. 2016]. The exact mechanism by which this occurs is not well understood, but it is thought that the immune response causes inflammation and damage to brain cells [Ashwood P. et al 2006]. The severity of the immune response may be influenced by factors such as the timing of infection during pregnancy, the strain of the virus, and the mother's immune status. One study found that of the 36 children with autism, 9 had mothers who had rubella during pregnancy [Chess S. 1971; Chess S. 1977], while another reported that almost 20% of mothers whose pregnancy was affected by rubella gave birth to children with autism [Deykin EY & MacMahon, B. 1979]. In yet another investigation maternal rubella infection in the first trimester was linked to a 20% higher risk of autism in the offspring [Christensen D. & Zubler J. 2020]. In a 2015 study, 1.8 million Danish children born between 1996 and 2012 showed 17% were more likely to be diagnosed with autism whose mothers had a proven rubella infection during the first trimester [Man KK. et al. 2015]. In 2020, data from over 20,000 mother-child pairs in Norway indicated that maternal rubella infection during pregnancy was associated with a 34% increased risk of autism and a 23% increased risk of developmental delay [Fitzgerald E. et al 2020]. These studies provide some evidence for a link between rubella infection during pregnancy and autism, more research is needed to fully understand the relationship.

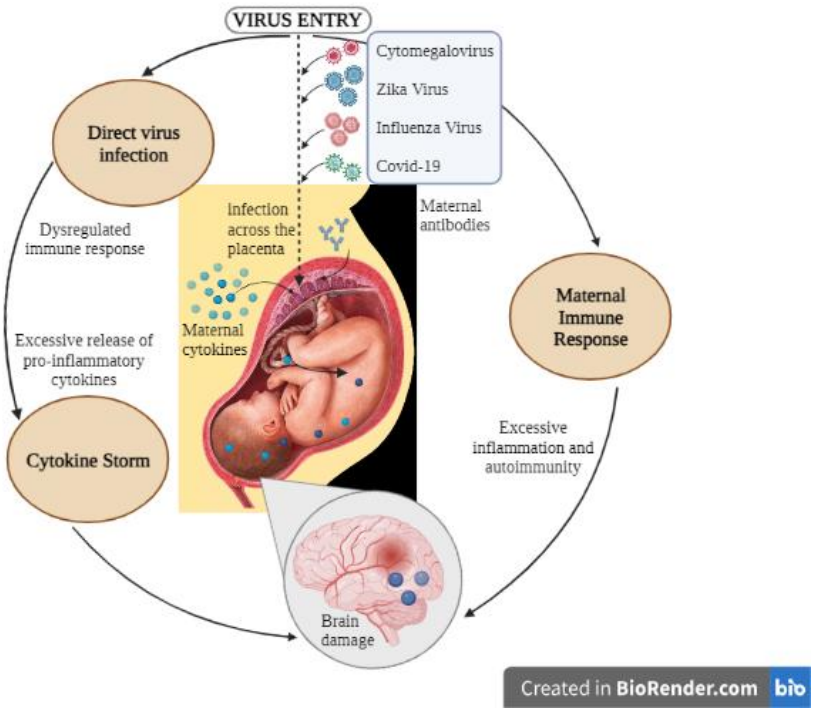

Figure 1: Viral infection leading to multiple pathways which damages the brain of growing fetus.

Foetal brain damage caused by viral infection.

Through a variety of methods, including direct infection, cytokine storm, and maternal immune responses, viral infection harms the developing brain directly impeding development and maturation of neurons, [Rouse BT. & Sehrawat S. 2010]. The inflammatory response to the virus can lead oxidative stress, neuroinflammation, and excitotoxicity [Almutairi MM. et al 2021]. Hypoxia, which can result from placental insufficiency, can further exacerbate brain injury by reducing oxygen and nutrient delivery to the developing brain [Wang B. et al 2021].

Several studies have provided evidence for the mechanism of direct viral infections causing foetal brain damage. For example, studies have shown that the Zika virus can infect and kill neural stem cells and cause microcephaly, [Li, H. et al 2016:]. In addition, cytomegalovirus (CMV) can infect the developing brain leading to a range of neurological disorders, including microcephaly, hearing loss, and intellectual disability [Zhang L. et al 2021]. Animal studies have also provided evidence for the mechanism of fetal brain damage, showing that viral infections during pregnancy can lead to brain injury, inflammation, and behavioural abnormalities in offspring [Depino AM 2018].

When a virus enters the body, it is detected by the immune system through pattern recognition receptors (PRRs) located on the surface of immune cells. PRRs recognize specific viral molecules called pathogen-associated molecular patterns (PAMPs), which are not present in normal human cells. Once PRRs recognize PAMPs, they trigger a series of signalling events that activate the immune cells to mount a defence against the virus. This leads to the activation and proliferation of T cells and B cells. Infection-related increases in maternal levels of IL-6, IL-1b, TNF-a, and IFN-b can harm the placenta. Because of the potential for intrauterine fetal growth restriction brought on by hypoxia, the placenta's overexpression of the hypoxic-inducible factor-1a (HIF-1a) gene can be used to detect the condition [Liong S. et al 2020]. In pregnant women the expression of human leukocyte antigen DRB14, can cause fetal neuroinflammation due to the production of proinflammatory cytokines [Brown AS & Begg MD. 2004]. Magnetic resonance imaging has shown that the offspring of infected mothers have smaller intracranial volumes than those of uninfected mothers, and less gray and white matter, particularly in the cerebral cortex. Animal studies also confirm that viral infection during pregnancy can induce immune responses in the fetus, leading to changes in critical signaling proteins and pathways involved in neurodevelopment [Liong S. et al 2020]. Viruses and cytokines cause an imbalance between the maintenance and differentiation of

neural precursor cells (NPC), resulting in neurodevelopmental disorders or cortical defects. ZIKV can infect NPCs, astrocytes, and microglia in the foetal central nervous system, but it is toxic only to NPCs, while microglia allows the virus to replicate without dying and can serve as a viral reservoir in the foetal brain. Microglia induce the secretion of pro-inflammatory cytokines that contribute to neuroinflammation with long-term effects].

Public Health Perspectives

A public health approach to autism spectrum disorder (ASD) focuses on reducing health disparities and improving the overall well-being of individuals with ASD and their families. This involves addressing social determinants of health, promoting early detection and intervention, ensuring access to appropriate healthcare and support services, and tackling stigma and discrimination. These include early diagnosis and intervention which are crucial for improving long-term outcomes for individuals with ASD. Public health efforts can focus on increasing awareness among parents and healthcare providers, developing and implementing screening tools, and ensuring access to evidence-based interventions. It is important to address factors contributing to these adverse health outcomes as evidence from childhood studies suggests the involvement of diet and/or nutritional problems, social impairment, sedentary behaviours, emotional problems, and avoidance behaviours.[8,9] Barriers to appropriate and timely health care and support are some factors affecting as issues that are intrinsic to the nature of autism (sensory impairment, being unable to experience pain; communication difficulties; health literacy; anxiety; avoidance behaviours or lack of routine; inertia; neglect; and social isolation),[15] require reasonable adjustments that take into account the patient's specific needs and these are not met.[15] Many experience difficulties as health professionals do not particularly address the needs of this group and this represents a significant burden to society. What is needed is autism friendly practices with there being increased awareness among professionals and clear information, towards the needs of autism individuals in a holistic manner.[10] This may require developing collaborative ways of working with other bodies in order to overcome these barriers. Sometimes individuals with autism may not welcome this approach because of potential negative stigma and hence alternative forms of health care and support would overcome obstacles. Early intervention in optimal settings and rehabilitation programs offers the best hope for children while flexible health care settings would encourage adult autistics to seek help. It has been reported that significant improvements in speech, rates of developmental progress and intellectual performance

(Dawson and Osterling 1997; Rogers 1996, 1998). Some have progressed towards achieving Masters and PhDs.

Health disparities, such as higher rates of co-occurring physical and mental health conditions, difficulty accessing healthcare services should be the focus of Public health initiatives and these can be addressed by improving access to culturally competent and accessible healthcare, addressing social determinants of health, and promoting health equity. Many of them face social isolation and exclusion due to communication differences, sensory sensitivities, and lack of understanding from others. Hence promoting social inclusion, participation through education, awareness campaigns, and creating supportive environments in schools, workplaces, and communities needs attention . Research plays a critical role in informing the development and implementation of effective public health interventions, with policies and programs supporting ASD individuals and their families including advocating for increased funding for research, training, and support services with inclusiveness in practices. Another aspect is their mental health as ASD are at higher risk for mental health conditions such as anxiety, depression, and obsessive-compulsive disorder, and this would promote mental health and well-being, thus reducing stigma associated with mental health conditions. By providing resources and support to families is also needed to improve the lives of individuals with ASD and their families.

Prevention measures, current interventions, and future directions

As there is no specific reason for the occurrence of Autism, exposure to air pollution, drugs, alcohol, viruses and vaccines during pregnancy are some of the ways to prevent autism. Others include treatment for the second child after the first autistic child is born, changing lifestyle, regular intake of folic acid and reducing mercury based dental fillings. Throughout the lifespan, training and education, management of comorbidities and social and vocational support needs to be carried out. To increase resilience in the first 2-3 years of life, altering the developmental cascade prior to birth may alleviate the emergence of autism symptomatology. From then on to adulthood attempts at prevention strategies is to preserve adaptation and wellbeing of the autistic individual and these may enable prevention of disruptive behaviours, depression, and other transition difficulties [Bonnet-Brilhault FF. et al 2018].

It has been stated [Francis K. et al 2021] that genes represent the baseline susceptibility and translation into a neuro-atypical phenotype results due to a toxic environmental load in the critical time window [Herbert M & Weintraub K. 2012]. Parental age, assisted reproductive

technology [Shimada T. et al 2012], maternal hypothyroidism [Getahun D. et al 2018) and maternal smoking during pregnancy [Hartman JD. & Craig BM. 2018] as well as second-hand smoke, revealed a positive correlation with ASD [von Ehrenstein OS. et al 2021]]. Hence a prior risk assessment would provide some indications together with indicators such as elevated glucose, triglycerides, cholesterol, leptin and proinflammatory immune markers, immune reactions to vaccines, maternal obesity and gestational diabetes, [Mawson AR & Croft AM. 2019] or maternal autoimmune conditions [Fox-Edmiston E. & Van de Water J. 2015]. Apart from these, several medications have been suggested to be avoided such as serotonin-reuptake inhibitors—SSRIs [Jiamg C-C et al 2022], antiepileptics such as valproate [Christensen J. et al 2013] and anti-asthmatic β−2 adrenergic receptor agonists [Gidaya NB. et al 2016]. Vitamins, folic acid, and minerals supplementation given intensely during the new pregnancy is said to play a protective role. Vitamin D, iron and omega-3 [Lyall K. et al 2017] have been implicated to have a positive role in brain development and functioning [Mazahery H. et al 2016]. Another intervention that is hypothesized is enrichment of the environment and enhancement of parent-child interaction. This is an attempt to guide behavioral and brain development towards more normal pathways [Dawson. G. 2008] as early as possible through video feedback. These interventions should be continuous throughout to adult life and needs to be comprehensive and coordinated, so as to maximize potential, minimizing barriers, and optimizing the person-environment fit [Lai MC. et al 2020] which would then enable autistics to exist in society on par with other individuals with dignity. It must be emphasized that prevention is still being actively researched and but needs to be prioritized.

This review provided information focused on understanding the role of genetics and maternal viral infections towards ASD. While this information is valuable for advancing our understanding of ASD, there are both limitations and merits to consider when translating this protocol into clinical practice. ASD is a complex and heterogeneous disorder, as such the protocol may not encompass the full spectrum of variables contributing to ASD. The understanding of the precise mechanisms linking genetic factors, maternal viral infections, and ASD is incomplete. Translating the protocol into clinical practice may be premature until a more comprehensive understanding is achieved. However, the protocol will allow for early identification and intervention by deciphering genetic and environmental factors contributing to ASD. The protocol provides a foundation for further clinical implementation which can contribute to data collection and the refinement of understanding, facilitating the development of more targeted interventions. The outcome of the research will be able to create great

potential for translation into clinical practices including genetic counseling, prenatal screening, and personalized interventions.

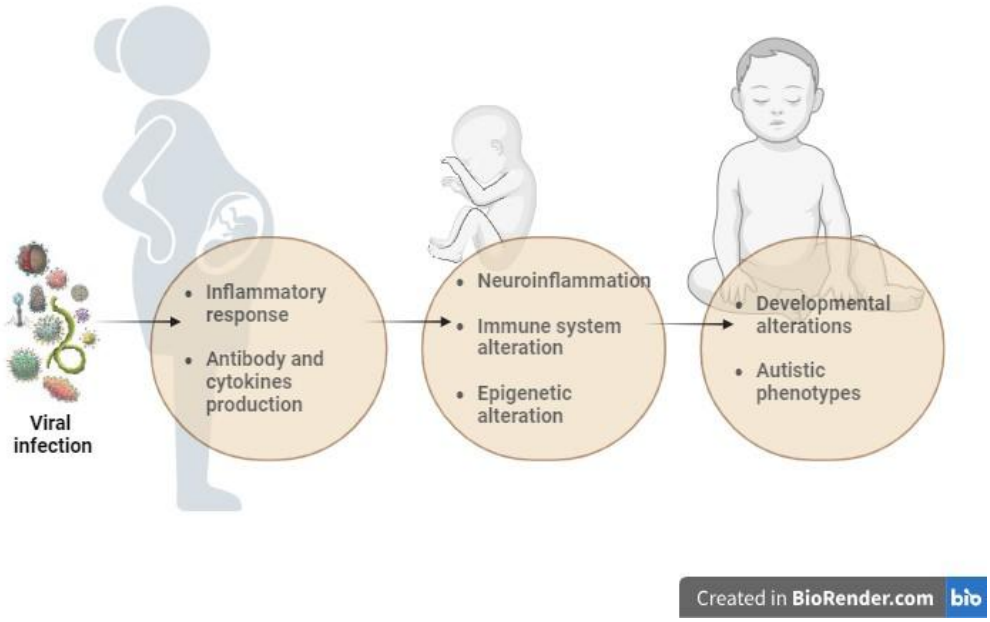

Figure 2: Possible pathogenic mechanism of autism by viral infections

Conclusion

Autism is a neurodevelopmental dysfunction that has both genetic and environmental causes. Figure 2 summarizes the possible pathogenic mechanism of autism by viral infections as one of the environmental factors leading to genetic alterations. There are still several aspects beyond our control. Early identification is critical to the well-being of children and their families. It is recommended that continued surveillance and health screening tests be conducted regularly in both families and their children affected. This may enable early intervention towards strategic treatment plans for the child and his or her parents. With increasing prevalence rates, autism has become a very significant threat to future generations. This review has explored the multifaceted interaction between autism spectrum disorder (ASD) and viral infections, shedding light on the intricate interplay between genetic predispositions and environmental factors. Further research in unravelling the specific pathways and contributing factors involved in the relationship between ASD and viral infections is needed.

Author contributions:

All authors were involved in preparation and writing of the manuscript. Each provided excerpts and comments to all others. All authors contributed to the article and approved the submitted version.

Conflict of interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be constructed as a potential conflict of interest.

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