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Is Autism a Neurodevelopmental Disease Due to Chronic Inflammation of the Central Nervous System (Cns)?

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Abstract

Background: Autistic Spectrum Disorders (ASD) are still regarded and treated as psychiatric disorders. A lot of research evidence supports the inflammatory basis of ASDs implicating a new basis for the diagnosis and treatment of the disease.

Methods: An extended recording of relative literature and new research findings.

Results: The genetic background of ASDs is analyzed. The inflammatory molecular basis of autism is emphasized.

Conclusions: Although autism is diagnosed based on psychiatric criteria and treated with mainly antipsychotic drugs, a multidisciplinary approach should be established taking into account new research findings, incorporating them to treatment.

Key Words: ASD, Neuroinflammation, CNS immunity, Neurotransmitters.

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1- INTRODUCTION

Autism or Autism Spectrum Disorder (ASD) is a childhood neurodevelopmental disorder that is behaviorally defined and psychiatrically diagnosed based on a spectrum of qualitative impairments in social interaction and communication, stereotyped patterns of behavior, interests, and activities (1). Despite various comorbidity syndromes, ASDs still remain under the diagnostic criteria of a psychiatric disorder (2).

The term "autistic" was used for the first time in 1911, by a Swiss Psychiatrist Eugen Bleuler, who noticed similarities of the disease with schizophrenia. The pediatrician Hans Asperger described a separate diagnosis called Asperger syndrome with symptoms of autism in 1981. In 1980 criteria the diagnosis of 'autism' was described in the Manual of Mental Disorders (DSM III), which was recently revised in DMS V (3).

As mentioned, ASD is diagnosed as a psychiatric disorder due to historical reasons, and its treatment is based on amelioration of psychiatric symptoms. However, advances in the diagnostic criteria defined more cases of ASDs without giving a reasonable answer to the etiology of the disease. The biological etiology of the disease is underestimated (4).

2- MATERIALS AND METHODS

Articles regarding the genetic basis and research articles regarding the pathophysiology of ASDs reported in Pubmed were analyzed.

3- RESULTS

A dramatic rise in the prevalence of ASD has begun since the 1990s and increasing rates reach up to 289% in different studies (2). Reports estimate the prevalence of autism in the EU up to 1:150 children in 2007 from 1:2500 children in the 1980s and according to the Autism and Developmental Disabilities Monitoring (ADDM) Network, it has rocketed to 1:68 children in 2012 in the US (4).

Scientific research first concentrated on the genetic basis of the disease. There is cumulative evidence for the involvement of genetic predisposition in the etiology of ASD. It is estimated that 400-1000 genes may be related to ASD and genome-wide associations allowed the identification of candidate genes related to the disorder (4) (Fig. 1). Siblings have a 35-40% greater risk to develop ASD. Twin studies show that the risk of developing autism is 35-40% for the 2nd sibling. Prenatal, perinatal and postnatal environmental factors could attribute up to 60% of cases (5).

First of all, single gene associations were detected in the CNTNAP2 gene (contactin-associated protein-like 2), SHANK3 (SH3 and multiple ankyrin repeat domains 3), NLGN3/4 (neuroligin 3) and variable chromosomal abnormalities such as duplication at 15q11-q13 and 16p11.2, or deletions at 16p11 loci. Mitochondrial DNA mutations and large-scale deletions were associated mainly with mitochondrial dysfunction. Other ASD candidate genes include the FOXP2 gene (forkhead box 2), IMMP2L gene (IPP2 inner mitochondrial membrane peptidase like), RELN (reelin) at 7q22-q33, GABAa receptor subunit (gamma amino- butyric acid), and UBE3A (ubiquitin- protein ligase E3A) on chromosome 15q11-13 (3).

Secondly, at the biological level, ASD is characterized by a number of documented biologic manifestations. These include redox imbalance, oxidative stress, mitochondrial dysfunction and glutathione deficiency related to the brain chronic inflammation and the neuroglia activation, overactive and dysfunctional immune system, and the presence of autoantibodies against the brain proteins as well as imbalance of the gut microbiota (8). Additionally, there is evidence to support

that viral infections and perinatal factors during critical periods of development contribute to the appearance of ASD (6).

Thirdly, regarding the structure of the brain in autism, fMRI and PET imaging of the CNS do not present major morphological abnormalities. However, measurements of head circumference revealed reduced head size at birth with subsequent increase between 1-2 months and 6-12 months. Overgrowth occurred in the areas of frontal lobe, cerebellum and limbic structures between the age of 2-4 years, a pattern followed by abnormal slowness and an arrest in brain growth (7). fMRI neuroimaging detected significant decrease in amygdala volume compared to normal control subjects, even in non-mentally retarded individuals (4). During cognitive tasks, a reduced connectivity is detected between frontal and more posterior brain regions and an arrest in frontal executive or occipito-temporal gyrus regions during memory tasks or spontaneous brain activity at rest (4).

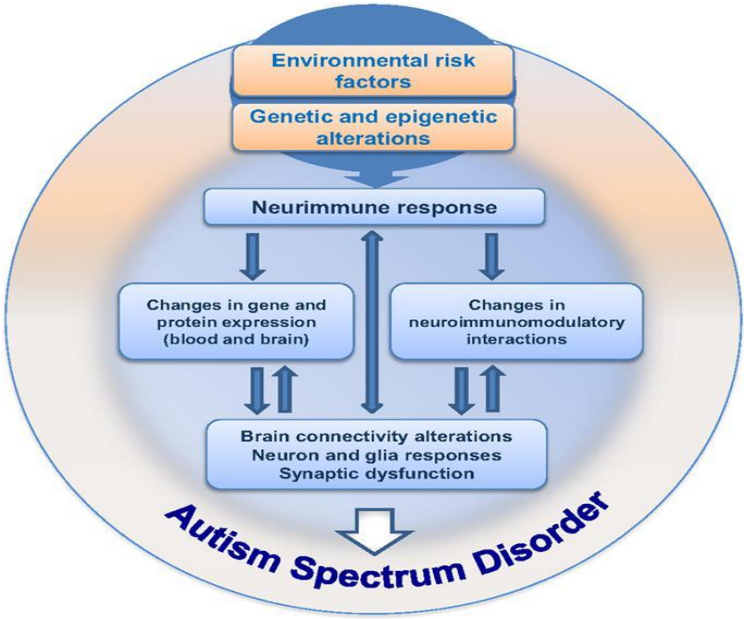

Fig. 1: New insights in the development of Autistic Disorders (3)

In more detailed analysis, cytoarchitectural organization abnormalities of the cerebral cortex, cerebellum and subcortical structures appear to be the most prominent neuropathological changes (3). An unusual pattern with packed small neurons has been described with no abnormality in the external configuration of the cerebral cortex. Additionally, loss and atrophy of Purkinje cells are described (3).

Finally, the contribution of inflammation in the development of ASDs is a newly established finding of research. The chronic inflammation as well as the triggering factors leading to the inflammation in the CNS is worth describing as they have been described in different research protocols. The responsible immune cells implicated in the inflammation of the CNS (Central Nervous System) are neuroglial cells consisting of microglia and astrocytes. Microglia cells are the resident macrophages of CNS and they act as the main cells of defense in the brain and the spinal cord. Microglia cells activate the

innate immunity response and specifically the proinflammatory response to attack infectious agents and altered proteins or cells due to injury. However, at the same time, due to the dual role of neuroglia, an anti-inflammatory phenotype could be developed that is responsible to remove debris and to repair damage. The dual role of microglia cells has beneficial and detrimental effects (8).

More specifically, in the normal healthy brain, microglia expresses the 'resting' phenotype characterized by typical morphology, a slow turnover rate and low expression of surface molecules. Even at this stage, neuroglia is not dormant and it continually supervises parenchyma through fine processes. The microglia cells could sense the changes in the microenvironment of the brain and they dynamically interact with other neural cells such as astrocytes, oligodendrocytes, and neurons. Microglia contacts synapses with appropriate receptors and it 'strips' dysfunctional ones, by removing cell debris and modulating neuronal activity. Hence, it contributes to normal functioning of the CNS and homeostasis as well as plasticity (8).

Under pathological conditions, microglia senses the external and internal 'danger signals' through diverse types of receptors and it responds rapidly displaying the 'activated phenotype' (2). Depending on inputs and feedback signals arising from the neural environment, it shifts towards a dynamic morphological, molecular and functional type responding with high accuracy to inputs and calming signals. Microglia cells are highly engaged to occupy different roles. It is interesting to mention that the signals are rather the 'on' or 'off' type and that there is not any relation to the cause of activation (8) (Fig. 2).

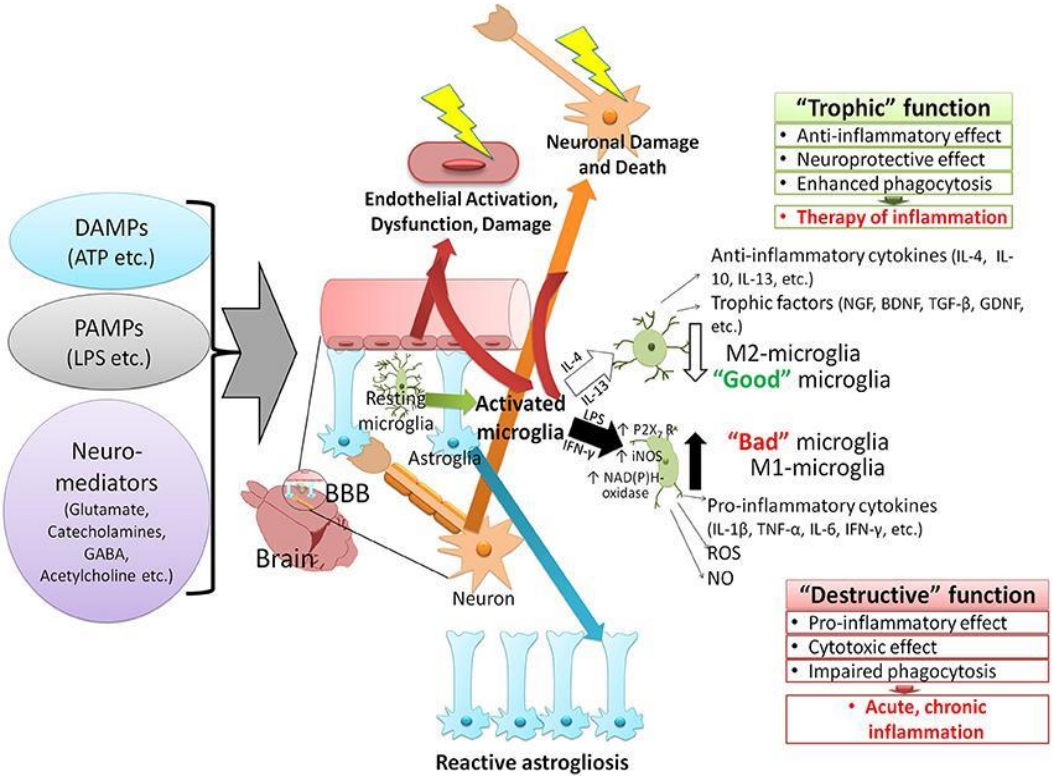

Fig. 2: Activation of neuroglia towards the pro- or anti-inflammatory phenotype (10)

In other words, microglia activation is not an 'all or none' process, but a continuous process depending on encountering stimuli. It expresses a spectrum of molecular and functional phenotypes ranging from the 'classically activated' form with a highly pro-inflammatory profile, to an 'alternative activated' type associated with a beneficial, less inflammatory and neuroprotective profile (9). Microglia activation has been implicated in many neurodegenerative diseases of different etiologies and the activation of the neuroprotective phenotype is a target for future treatments of diseases such as Alzheimer disease, Parkinson, etc (10).

In the healthy brain, apart from neuroglia, astrocytes are implicated in neurodevelopment. They facilitate neuronal survival by producing growth factors and they mediate uptake and removal of neurotransmitters from synaptic microenvironment. However, under conditions of injury, astrocytes secrete pro-inflammatory cytokines, chemokines and metalloproteinases that could magnify the immune response in the CNS leading to dysfunction (4, 11).

In general, the 'classically activated' phenotype is associated with an increased production of reactive oxygen species, through NADPH oxidase activity, proinflammatory cytokines such as tumor necrosis factor (TNF-a) and interleukin 1b and increased levels of nitric oxide. On the contrary, the 'alternative phenotype' is associated with high levels of anti-inflammatory cytokines and neutrophilic factors (8).

Post mortem biopsies from ASD patients detect a number of proinflammatory cytokines including TNF-a, IL-6, IL-1b as well as INF-g and chemokine IL-8. Additionally, neurotrophic factors are found such as TGF-1 (transforming growth factor), and MCP-1 (macrophage chemoattractant protein) implying chronic inflammation. Cytokine IL-33 functions as an alarm and it has been linked to brain inflammation (4). There are also several indirect findings that confirm the activation of microglia, including an increase of the acute phase proteins and of numerous autoantibodies directed against the brain proteins. Neurotensin (NT) and Corticotropin-Releasing Hormones (CRH) are also associated with autism indicating the implication of the stress system (12). Research has focused on the detection of inflammatory proteins which could be used as biomarkers to early identify new cases with the disease.

A new research area is trying to identify the complex and intricate pathways of interaction between the immune and nervous system. Proinflammatory cytokines, decreased total IgM and IgG antibodies, autoantibodies (e.g. increased levels of ANA in 34% of patients and ds-DNA in 25% of patients, autoantibodies against the human neuronal progenitor cells (NPCs), and predominance of the HLA-DR4) are detected. There is an Increase of inflammation indexes and the number of monocytes, which suggest chronic inflammation (13). The dysfunction of the metabolic system is confirmed by increased ROS, a decrease of antioxidant systems that reduce capacity of natural killer cells. The above pro-inflammatory profile is also detected in various psychiatric and psychological disorders including anxiety and depression; it affects different brain regions, it is related to ASD and it is known as 'sickness behavior syndrome' (14). It is, moreover, related to the 'cumulative' stress hypothesis which leads to the wear and tear of tissues recording 'the allostatic load' model, part of the maladaptive chronic disease processes (15).

Regarding the immunity of CNS, the pre-occupied notion that the brain is the structure of the body that is free from

immune cells is highly debated. This concept developed due to the fact that T cells residing in the brain and more specifically CD4+ cells are not differentiated to the Th1 or Th2 phenotype of function and this restriction is associated with a 'protective role' against the development of deleterious immune responses (3, 8).

Changes of the innate immune response, abnormalities of B and T cells, impaired lymphocyte PHA induced proliferation and the reduced capacity of natural killer cells to kill K562 cells are some of the figures of altered immunity in CNS (3, 16). Production of ROS and proinflammatory cytokines by resident CNS cells leads to impairment of Blood-Brain-Barrier integrity permitting lymphocytes and other immune cells to enter CNS leading to a deterioration of the local inflammation (8) (Fig. 3).

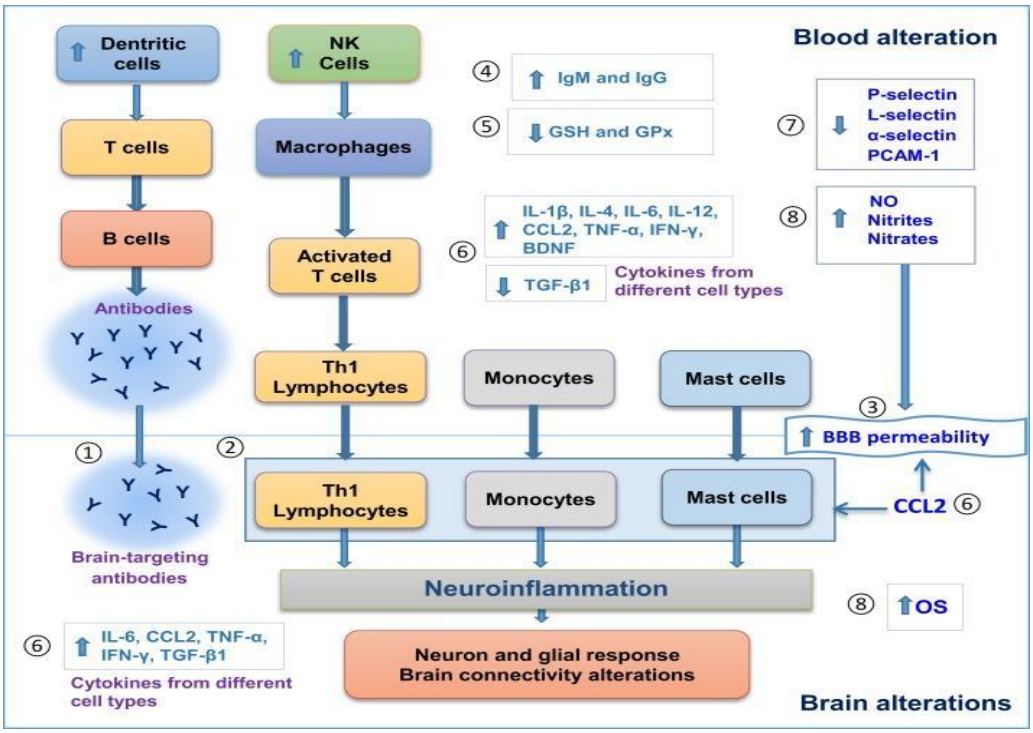

Fig. 3: Evidence of neuroimmune interactions in ASD (3)

The 'neuron-astrocyte coupling' is a metabolic state that causes extracellular lactate and H+ production, which contribute to accumulation of ROS products. (8). Stimuli could be acute like bacterial and virus infections via Pathogen-Associated Molecular Patterns (PAMPs) and Pattern Recognition Receptors (PRRS) or stroke, head injury, and hemorrhage via Danger Associated Patterns (DAMPs). Chronic inflammation is established via the same patterns, when the brain is exposed to those noxious stimuli (Fig. 4). During the rubella pandemic in 1964, there was an increase of 8-13% in autistic disorders (8).

There is a lot of discussion regarding the expression of neurotransmitters in autism. Specifically, serotonin has been detected in high levels in up to 45% of ASDs, which are responsible for social interactions and it is associated with neurogenesis, cell migration, survival, synaptogenesis, and synaptic plasticity. The dopaminergic circuit in ASD is well recognized to play an important role in

brain functioning. Antipsychotics targeting D2 receptors offer a great help to ASD patients improving stereotype movements and sociability.

Gabaminergic and glutaminergic systems are mainly involved in the presence of seizures, cognitive functions, and hyperactivity. Mutations in the cascade for the production of acetylcholine play an important role in behavioral symptoms including attention, cognitive flexibility, social interaction, and stereotyped behaviors. The histamine neurotransmitter system is also involved in ASD and it manifests a critical role in cognition, sleep and neuro psychopathic disorders including schizophrenia. Progress in understanding the dysfunction of neuronal circuits in children with ASD will improve our attitude to the appropriate treatment protocols for these children by improving functioning and ameliorating symptoms. Currently, risperidone and aripiprazole are the only drugs approved by FDA for improving behavioral symptoms of autism (4).

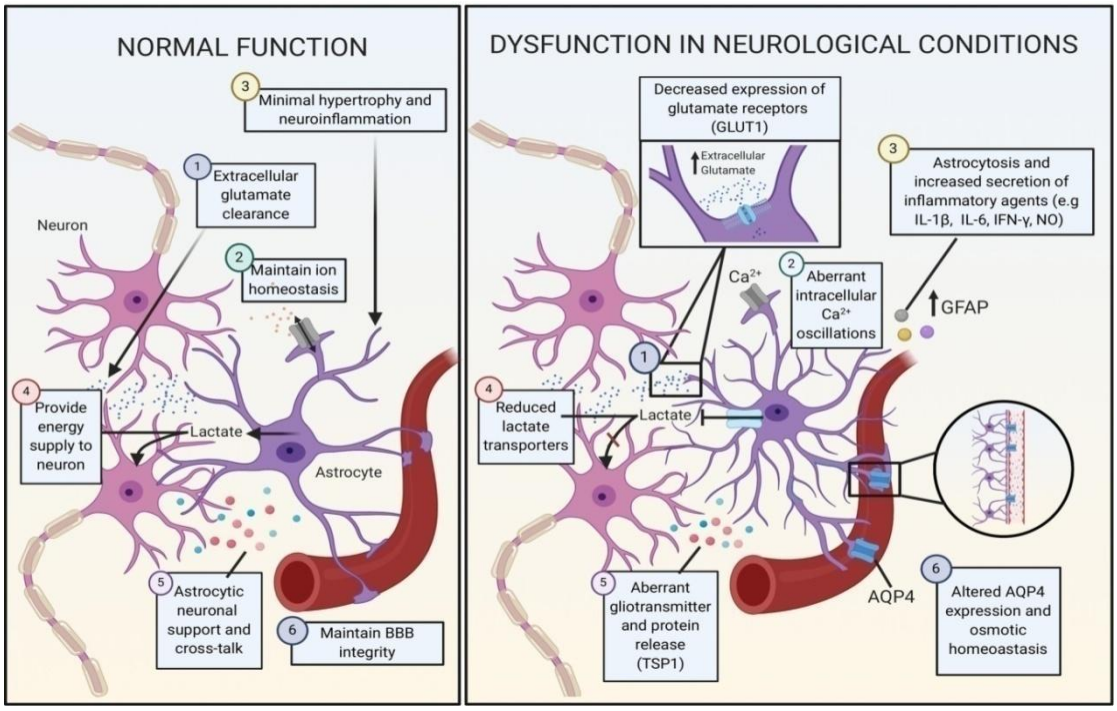

Fig. 4: The neuroinflammatory process supporting the hypothesis of neuroimmune interactions in the pathogenesis of ASD (3)

Numerous prenatal environmental exposures such as sex hormone alterations, maternal obesity, diabetes, hypertension, infections, iron deficiency, lifestyle including substance use alter the microenvironment of the fetus (12). Apart from infectious insults during pregnancy, other factors such as poor nutritional diversity could also contribute to the appearance of ASD, although investigation of the effects of vitamin D, ω-3 or folate supplementation are not conclusive (17). In the same spectrum, mitochondrial dysfunction during critical windows of life could lead to increased ROS and neuroinflammation (8) (Fig. 5).

The gut microbiota and its metabolites participate in the body physiology including the brain. Dysbiosis, microbiota alterations, have been described in autism. Clostridia species are consistently high

and it is known to produce toxins which affect neurotransmitter function. The abundance of Bacteroides and Furmicute is related to inflammation. However, treatments based on the change of microbiota microenvironment, although used for prevention, offer no benefit to the treatment of ASD (17). Dysregulated gut-brain communications, in addition to genetic heritability, could participate in the development of the disease (17).

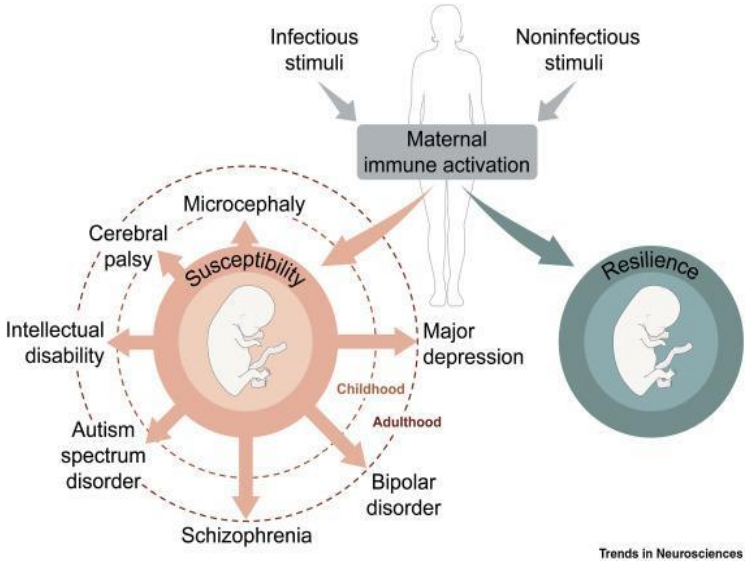

Fig. 5: Prenatal exposures and genetic factors contributing to the development of ASD (17)

In Addition to these factors, the modern environment is constantly pressed by 80.000 environmental chemicals released indoors and outdoors with approximately 1000 of them demonstrating neurotoxicity. Xenobiotic agents including pollutants, heavy metals, persistent organic pollutants, and pesticides react with diverse pathophysiological pathways including the immune, the gut-brain, and the endocrine system. They interact with genetic factors and alter the development of neuronal circuits, synapses, cell migration and connectivity. The immune response to this 'attack' is the generation of ROS and oxidative stress, which lead to chronic inflammation. Few examples to mention, are pollution particularly the traffic related, mercury and lead, industrial chemicals generate ROS, and promote chronic inflammation processes as in the case of diesel activate microglia (18) (Fig. 6).

Lifestyle and environmental chemicals interfere via epigenetic mechanisms with the expression of multiple genes. The point of 'multiple hit' and 'threshold models' integrates both genetic and environmental factors that threaten vulnerability and resilience of the complex development of the human brain (4, 19).

4- CONCLUSION

Although autism is diagnosed based on psychiatric criteria and treated with mainly antipsychotic drugs, a multidisciplinary approach should be established taking into account new research findings and incorporating them in treatment. The biological etiology of autism which includes chronic inflammation and microglia activation, neurotransmitter, and mitochondria dysfunction should be taken into consideration (2).

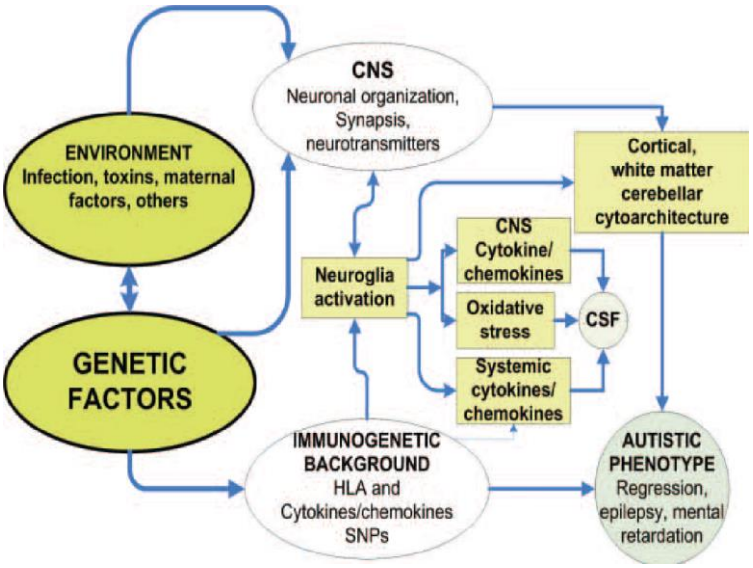

Fig. 6: Hypothetical interactions of environmental and genetic factors that influence neuroglia activation, CNS organization, and the presence of autism (7)

5- CONFLICT OF INTEREST

None.

6- FUNDING

None.

7- REFERENCES

1. Halfon N, Kuo AA. What DSM-5 could mean to children with autism and their families. JAMA pediatrics. 2013 Jul 1;167(7):608-13.

2. Kern JK, Geier DA, Sykes LK, Geier MR. Relevance of neuroinflammation and encephalitis in autism. Frontiers in Cellular Neuroscience. 2016 Jan 19;9:519.

3. Gottfried C, Bambini-Junior V, Francis F, Riesgo R, Savino W. The impact of neuroimmune alterations in autism spectrum disorder. Frontiers in psychiatry. 2015 Sep 9;6:121.

4. Shuid AN, Jayusman PA, Shuid N, Ismail J, Kamal Nor N, Naina Mohamed I. Update on atypicalities of central nervous system in autism spectrum disorder. Brain Sciences. 2020 May 20;10(5):309.

5. Eissa N, Al-Houqani M, Sadeq A, Ojha SK, Sasse A, Sadek B. Current enlightenment about etiology and pharmacological treatment of autism spectrum disorder. Frontiers in neuroscience. 2018 May 16;12:304.

6. Nevison CD. A comparison of temporal trends in United States autism prevalence to trends in suspected environmental factors. Environmental Health. 2014 Dec;13:1-6.

7. Pardo CA, Vargas DL, Zimmerman AW. Immunity, neuroglia and neuroinflammation in autism. International review of psychiatry. 2005 Jan 1;17(6):485-95.

8. Giunti D, Parodi B, Cordano C, Uccelli A, Kerlero de Rosbo N. Can we switch microglia's phenotype to foster neuroprotection? Focus on multiple sclerosis. Immunology. 2014 Mar;141(3):328-39.

9. Salter MW, Beggs S. Sublime microglia: expanding roles for the guardians of the CNS. Cell. 2014 Jul 3;158(1):15-24.

10. Wilcock DM, Griffin WS. Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis. Journal of neuroinflammation. 2013 Dec;10:1-0.

11. Wilcock DM, Griffin WS. Down's syndrome, neuroinflammation, and Alzheimer neuropathogenesis. Journal of neuroinflammation. 2013 Dec;10:1-0.

12. Bölte S, Girdler S, Marschik PB. The contribution of environmental exposure to the etiology of autism spectrum disorder. Cellular and Molecular Life Sciences. 2019 Apr 15;76:1275-97.

13. Sinmaz N, Nguyen T, Tea F, Dale RC, Brilot F. Mapping autoantigen epitopes: molecular insights into autoantibody-associated disorders of the nervous system. Journal of neuroinflammation. 2016 Dec;13:1-23.

14. O'Connor TG, Moynihan JA, Caserta MT. Annual research review: the neuroinflammation hypothesis for stress and psychopathology in children–developmental psychoneuroimmunology. Journal of Child Psychology and Psychiatry. 2014 Jun;55(6):615-31.

15. Giunti D, Parodi B, Cordano C, Uccelli A, Kerlero de Rosbo N. Can we switch microglia's phenotype to foster neuroprotection? Focus on multiple sclerosis. Immunology. 2014 Mar;141(3):328-39.

16. Theoharides TC, Asadi S, Patel AB. Focal brain inflammation and autism. Journal of neuroinflammation. 2013 Dec;10:1-7.

17. Madore C, Leyrolle Q, Lacabanne C, Benmamar-Badel A, Joffre C, Nadjar A, et al. Neuroinflammation in autism: plausible role of maternal inflammation, dietary omega 3, and microbiota. Neural plasticity. 2016;2016(1):3597209.

18. Kalkbrenner AE, Schmidt RJ, Penlesky AC. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. Current problems in pediatric and adolescent health care. 2014 Nov 1;44(10):277-318.

19. Qureshi IA, Mehler MF. Epigenetic mechanisms underlying the pathogenesis of neurogenetic diseases. Neurotherapeutics. 2014 Oct 1;11(4):708-20.