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The Influence of Agrochemicals Present in Maternal Nutrition in the Birth of Children with Autistic Spectrum Disorder

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Abstract

Both psychological and neurological changes are related to deficits in communication and social interaction in patients diagnosed with autism spectrum disorder (ASD). There is evidence that fetuses are exposed to agrochemicals because some agrochemicals have the capacity to cross the blood-brain barrier, thus affecting the fetal central nervous system. The aim of the present study is to carry out a literature review about maternal exposure to some pesticides and the possible relationship between this exposure and the development of autism spectrum disorder (ASD) in children. A search was conducted in the Science Direct, Medline, Scopus, Web of Science, and Lilacs databases. As a result, in most articles the agrochemicals analyzed in this study showed that they have some relation of the exposure of mothers and children with autism spectrum disorder. It was observed that gestational contact with pesticides as chlorpyrifos interferes with early neuromotor development, causes deficits in social behavior, and increases restrictive behavior in adulthood. It was verified too the presence of endosulfan metabolites in the umbilical cord and breast milk that could interfere in the congnitive functions of the child. Contact of chlorpyrifos, ammonium glufosinate and glyphosate with pregnant women may also interfere with normal development, with changes in communication, early reflexes and affiliative behavior. A growing body of evidence suggests the role of these agrochemicals in interference with normal neurodevelopment, autism etiology, and impairment of psychomotor and mental functions, including attention and verbal skills in children.

Keywords: *Agrochemicals, Autism Spectrum Disorder, Neurodevelopmental Disorders, Neuroinflammation.*

Introduction

Autism Spectrum Disorder (ASD) is a disorder of neurodevelopment, where it is characterized by deficits in development that lead to impairments in personal, social, academic or professional functioning. The diagnosis of ASD depends on the recognition of a set of neurological and psychological changes related to deficits in communication and social interaction and to restricted and repetitive patterns of behavior, interests or activities. The symptoms are present from the beginning of childhood bringing functional limitations or damages. The stage at which functional impairment becomes apparent will vary according to the characteristics of the individual and their environment[1]

Environmental exposures of fetuses still in intrauterine life may increase the risk of developing autism spectrum disorder[2]. There is evidence that fetuses maybe exposed to pesticides because their residues are able to cross the placental barrier and have been

found in the amniotic fluid as well as cross the blood-brain barrier and reach the fetal central nervous system[3].

Autism Spectrum Disorder involves several factors including the time period of fetal development when pregnant mothers are exposed to environmental agents that may interfere with the development of the brain of the fetus. The period from 4 to 18 weeks of gestation is considered the most susceptible to exposures of pesticides[4]

The aim of the present study is to carry out a literature review about maternal exposure to agrochemicals such as endosulfan, chlorpyrifos, glufosinate ammonium and glyphosate pesticides and the possible relationship between this exposure and the development of ASD in children.

Material and Methods

A search was conducted in the Science Direct, Medline, Scopus, Web of Science, and Lilacs databases using as descriptors "pesticides", "insecticides", "agrochemicals" and "herbicides" combined with "autistic disorder". The inclusion criteria for the selection were: original articles written in English with year of publication between 2000 to 2018, period coinciding with an increase in the number of publications related to the theme, available in full in the databases, with subject matter related to the subject studied which specifically talks about agrochemicals: chlorpyrifos, endosulfan, glufosinate ammonium and glyphosate. Articles which do not argue about chlorpyrifos, endosulfan, ammonium glufosinate and glyphosate in their content, of revision, articles in other languages, with year of publication outside the established period, as well as those whose full contents were not accessible were excluded. The research was conducted in the period from March 14, 2018 until September 21, 2018. We found 240 articles from the search in the databases that were submitted to a selection criterion as detailed in the flow chart presented in Figure 1.

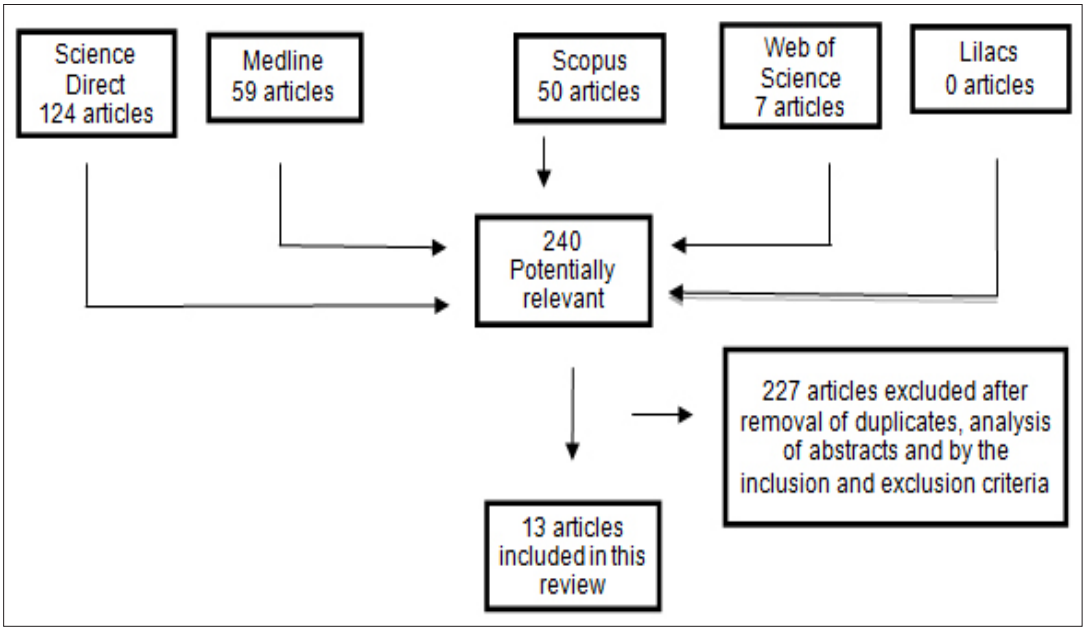

Fig 1. *Flow diagram of the review "The influence of agrochemicals present in maternal nutrition in the birth of children with autistic spectrum disorder."*

Results and Discussion

The literature review has resulted in 13 studies since 2000 showing that there may be relationships between some agrochemicals such as chlorpyrifos, endosulfan, glufosinate ammonium and glyphosate, and autistic spectrum disorder by counting these substances with mothers in the gestational period. The main data of the articles were compiled in table 1.

Table 1. *Summary of previous studies evaluating the association between ASD*

Agrochemical	Author	Species	Main Findings
Chlorpyrifos	ESKENAZI et al (2007)	Humans	- Problems in mental development in children - Delay in psychomotor development - Pre and postnatal treatment associated with invasive developmental disorder
Chlorpyrifos	LAN et al (2017)	Animals (mice)	- Delayed development of postnatal reflexes - They presented deficits in social preference tests - Demonstrated greater restrictive interest - Did not cause memory deficit - It has deleterious effects in the long term and limits the exploration of new objects
Chlorpyrifos	FELICE et al (2016)	Animals (mice)	-Affects oxidative stress and PGE2 synthesis in a model with autism
			-Worsening of autistic symptoms after exposure to chlorpyrifos
			-Delay in motor maturation
Endosulfan	CERRILO et al (2005)	Humans	-Presence of metabolites in adipose tissue, maternal milk, placental homogenate and umbilical cord blood.
			-Health risk even at low concentrations of endosulfan.
			-Carcinogenic, teratogenic and neurotoxic
Endosulfan	CASTILLO et al (2002)	Humans	-Slower escape time
			-Behavioral delas
			-They present more significant behavioral changes when administered in combination of endosulfan (ES) and methyl parathion (MP).
Endosulfan	CABALEIRO et al (2008)	Animals (rats)	-Changes in functions related to the prefrontal cortex
			-Affects development of cognitive tasks
			-Behavioral variation
			-Changes related to short-term memory and selective attention
Endosulfan	ROBERTS et al (2007)	Animals (rats)	-Children born to mothers living within 500 meters of areas using endosulfan are more likely to develop Autistic Spectrum Disorder (ASD)
			-ASD risk increased proportionally to the amount of organochlorine applied
Ammonium glufosinate	ARIS et al (2011)	Humans	-Metabolite (3-MPPA) detected in pregnant women and their fetuses
			3-MPPA appears to cross the placenta to the fetus.
Ammonium glufosinate	HERZINE et al (2016)	Animals (mice)	-Low doses induce neuroblast changes in the subventricular region
			-Perinatal exposure alters neurogenesis
			-Affects cellular migration modulation
			-Potentially contributing to neurodevelopment of behavior similar to autism
Ammonium glufosinate	LAURAGEY et al (2016)	Animals (mice)	-Mature contact with ammonium glufosinate (GLA) interferes with the development of communication.
			-It generates affiliate problems.
			-Behavioral changes that showed a similarity to changes seen in animal models of Autistic Spectrum Disorders.D28
			-The reduced expression of Pten and Peg3 - two genes implicated in autistic deficits - were observed in the brains of offspring exposed to GLA on the 15th postnatal day.
Glyphosate	NEVISON (2014)	Humans	-Some environmental toxins only correlate with increased autism.
			-Ethers, aluminum adjuvants and glyphosate herbicide have a tendency to correlate positively with increased autism

Glyphosate	DAGER et al (2007)	Humans	-Changes in the shape of the hippocampus in children with autism spectrum disorder were correlated with the degree of mental retardation and performance deficits in neuropsychological tests.
			-Although the hippocampus is an area known to be affected in autism spectrum disorder, the correlation between hippocampal alterations due to glyphosate neurotoxicity and ASD manifestations due to impairment of this brain area has not been demonstrated.
Glyphosate	CATTANI et al (2014)	Animals (rats)	-Contact with glyphosate generates neurotoxicity involving NMDA receptor activation.
			-Commitment of cholinergic transmission and astrocytic dysfunction.

Chlorpyrifos

Chlorpyrifos (CPF) is the most widely used organo phosphate for the control of insects both in agriculture and in urban communities, being the food intake one of the human exposure routes that contains residues of this pesticide[5].

Exposure to organophosphates can have several effects on brain development. High doses may cause acute neurotoxicity, which probably results from inhibition of acetylcholinesterase (AChE), producing exacerbation of cholinergic effects due to synaptic accumulation of acetylcholine and hyperstimulation of postsynaptic muscarinic and nicotinic receptors[6]. Exposure to lower doses also produces neurotoxicity, interfering with brain development, although mechanisms for this effect are not fully elucidated[7]. In toxicologically relevant doses, these compounds disrupt neuronal proliferation, differentiation, gliogenesis and apoptosis by directly interfering with the number of signaling molecules or indirectly with the morphogenetic activity of acetylcholine, which are distinct from its enzymatic activity[8].

Although chlorpyrifos acts on the central and peripheral nervous system acting through inhibition of AChE, exposure to chlorpyrifos also causes changes in catecholaminergic neurotransmission, in addition to axonal growth atrophy, suggesting that chlorpyrifos also has non-cholinergic mechanisms of action, which may involve changes in the expression and function of nuclear transcription factors[9,10]. Recent studies have shown that fetuses and young children have lower levels of detoxifying enzymes (paraoxonase or chlorpyrifosoxonase) than adults - enzymes that act to deactivate organophosphates, suggesting that children may be more vulnerable to exposure to pesticides[11].

Inflammatory imbalances were observed following prenatal exposure to organophosphates, with increased levels of IL-6 and IL-1β in the central nervous system, suggesting the participation of neuroinflammation in the neurotoxicity process of these compounds[8].

Gestational contact with chlorpyrifos interferes with early neuromotor development, causes deficits in social behavior, and increases restrictive behavior in adulthood.There was a study that showed, through behavioral tests, the occurrence of long-term behavioral deficits, repetitive behaviors and routine preference in the group that had gestational contact with chlorpyrifos in relation to the non-exposed group. The contact in different periods of gestation causes different changes in the behavior of exposed individuals[9].

In autism, the development of a typical social communication is present, as well as restrictive or repetitive behaviors and interests[1]. The alterations found in the Lan et al. (2017) study are very characteristic of autism spectrum disorder, which leads to a thought regarding gestational exposure to chlorpyrifos that may possibly lead to the development of autism[9].

However, a recent study demonstrates that inhibition of AChE through acetylcholinesterase inhibitors may induce an improvement in the autistic condition. This study demonstrates that elevation of acetylcholine (Ach) levels led to a significant improvement in cognitive rigidity, social preference and social interactions, all major symptoms in patients who have the ASD.[12]

Therefore, it may be suspected that the neurotoxicity of chlorpyrifos is not specifically related to the increase of acetylcholine, but due to other non-cholinergic mechanisms, such as the increase of inflammatory cytokines in the central nervous system, or because children have lower levels of detoxifying enzymes, thus making chlorpyrifos exposure more susceptible to toxicity. There is also the question of not being sure of the actions of an increase of acetylcholine in the period of fetal neurodevelopment, considering that the aforementioned study presents this cholinergic increase in children already born and no longer in the gestational phase. The study presented uses an acute treatment protocol with an acetylcholinesterase inhibitor, not inferring the effect of chronic exposures or with different dose ranges.

Experimentally, gestational exposure to chlorpyrifos has been shown to be related to the induction of oxidative stress, causing permanent alterations in molecular pathways that are relevant in autism spectrum disorder, as well as causing a significant delay in motor maturation and worsening of autistic characteristics in already autistic mice in adulthood [13].

Endosulfan

Organochlorine pesticides are a group of widely used chemicals with characteristics of bioaccumulation in food chains, persistence in various environments and potential toxic effects on the brain[14]. In addition, they are highly liposoluble and resistant to degradation, they have low volatility, and a slow rate of biotransformation. These characteristics that confer the effectiveness of pesticides are the same ones that led to the prohibition of the use of these substances in some countries due to their harmful effects on the environment and on the health of living beings[15].

Endosulfan is an organochlorine widely used as a broad spectrum insecticide for the control of agricultural pests, used both in non-food crops such as tobacco and cotton, as well as in food crops such as cocoa, coffee and soybeans. Although it is no longer produced in the United States, this insecticide is widely used in other countries, such as Turkey, Mexico and Brazil[16,17].

The main source of human exposure to endosulfan is food contaminated with agrotoxic waste. Exposure of the mother and child to these pesticides is a common event both in the uterus and through breastfeeding due to the high frequency of exposure of women of childbearing age[18].

The mechanism of action of endosulfan is to alter the activity of the chlorine channels, which are necessary for a healthy pre and postnatal development. Similarly, it can disrupt the balance between excitatory and inhibitory neurotransmission in the brain[19]. The action of endosulfan mainly affects the region of the prefrontal cortex, related to cognitive tasks, short-term memory, selective attention, inhibition of response, sexual behavior, behavioral variation and depression[20].

The stimulation of the central nervous system is caused by the antagonistic action of cyclodienes in ionotropic γ-aminobutyric acid (GABA) receptors, which causes a reduction in the uptake of chlorine ions. The blockade of chloro ion input by endosulfan results in partial repolarization of the neuron, generating an uncontrolled state of excitation. Endosulfan has an affinity for GABA receptors in the brain, acting as a non-competitive antagonist[21]. The GABA neurotransmitter is fundamental in the development of the brain in the gestational period, so that a change in the metabolism of GABA may play an important role in autism spectrum disorder[22].

Genetic studies continually implicate genes that regulate GABA receptor expression with ASD. These findings demonstrate that GABA systems may be one of the final paths of ASD [23,24,25].

Both endosulfan and its metabolites have been found in the umbilical cord, in breast milk and in the serum of women who gave birth through cesarean delivery, indicating that these compounds cross the placenta and expose the fetus still in the uterus and may have effects on the physical development and cognitive functions of a child[26]. Cerrillo et al. (2005) observed that the highest concentrations of endosulfanwere found in adipose tissue due to the lipid affinity of these chemicals, followed by human milk, being secreted along with other lipophilic compounds[18].

Mice exposures to endosulfanwas found to produce changes in the nervous system that persists a few days after cessation of exposure and which are accompanied by behavioral performance deficits. This exposure may have effects on the nervous system because its targets include the gabaergic and cholinergic systems, which are the main modulators of neuronal excitability in the cortex and hippocampus[17].

Glufosinate Ammonium

Glufosinate ammonium, a phosphorus-containing amino acid, is an active ingredient in nonselective herbicides and is a glutamate analog that inhibits glutamine synthetase in plants and blocks glutamine synthesis from glutamate and ammonia. The associated intracellular accumulation of ammonia causes tissue necrosis and death[27].

Thus, this herbicide interferes with glutamate homeostasis, leading to an imbalance in signaling mediated by this neurotransmitter, so that acute exposure to this pesticide has been related to memory problems, structural brain modifications and astrogliosis[28] .

Glufosinate ammonium was detected in 18% of non-pregnant women and was not detected in maternal and fetal blood, but its metabolite, 3-MPPA, was detected in 100% of blood and umbilical cord samples, in addition to 67% of samples of non-pregnant women. This demonstrates that this metabolite is more detectable than its precursor and seems to easily cross the placenta to reach the fetus[29].

Microscopic evaluation of embryonic "pools" of mice obtained from treated and untreated groups with a herbicide containing glufosinate ammonium demonstrated that doses (58 μg/kg) negatively affect the developmental capacities of *in vivo* derived embryos. At higher doses (290 to 580 μg/kg), none of the developing embryos in the maternal body were able to reach the blastocyst stage, most of them remaining in the cleavage stages (up to 16 cells). The proportion of degenerate embryos also showed elevation. This herbicideapplication at concentrations (29 μg/kg) had no significant effect on embryonic development. However, the morphological evaluation of isolated blastocysts showed that even this dose (corresponding to approximately 1/100 of the LD_{50}) can negatively affect its quality, since a decrease in the average number of cells and a significant increase in the incidence of dead cells by blastocyst[30].

Neurobehavioral tests revealed that maternal exposure to glufosinate ammonium interfered in the development of initial reflex, communication, affiliative behaviors, and preference for olfactory social cues, but emotional reactivity and emotional memory remained unchanged. These behavioral changes have shown a similarity to changes seen in animal models of autism spectrum disorder. Thus, pre and postnatal exposure to glufosinate ammonium was associated with behavioral changes during childhood, which may cause a deficiency in social interaction[31].

The hypothesis of glufosinate ammonium induced neurogenesis deficiency is enhanced by observing transcriptometric analyzes on the 15th postnatal day in brains of fetuses exposed in the prenatal period to glufosinate ammonium. In fact, exposure to gluphosinateammonium has affected the standard expression pattern of genes that regulate the cytoskeleton, which has potentially contributed to the development of autism, cell proliferation and cell migration behavior[28]

Glyphosate

Glyphosate is widely applied to genetically modified crops, including corn, soybeans, cotton, canola, beet, and alfalfa.[32]Among the ten chemical pesticides most used in Brazil in 2014, the herbicide glyphosate was the most important, corresponding to 31.45% of the total commercialized in the country, representing alone around 40% of the consumption of local agrochemicals. In the same year, the Brazilian Ministry of Health reported the highest number of reports of intoxication by glyphosate[33].

This herbicide has been associated with the induction of oxidative stress and neuroinflammation, and may affect neural cells leading to oxidative damage, neuronal cell death and neurodegenerative conditions, which are generally associated with glutamate excitotoxicity and oxidative stress[34,35] .There was a study that demonstrated that glyphosate formulations induce apoptosis and necrosis in umbilical, embryonic, and placental cells[36] .

The increasing use of glyphosate may correlate with increased ASD due to an increase coincide in the number of births of autistic children since the herbicide began to be used in the United States[32]

In study realized, Samsel and Seneff in 2013 observed that contact with glyphosate has negative impacts on body and may manifest slowly, causing inflammation that damages the cellular systems throughout the body. The herbicide interferes with the cytochrome P450 enzyme that acts synergistically with the breakdown of the biosynthesis of aromatic amino acids by the intestinal bacteria, as also the compromised transport of serum sulfate. There are also gastrointestinal disorders, depression, autism, infertility, cancer and Alzheimer's disease.[37]

Exposure to glyphosate also disrupts the synthesis of sulfate as well as the transport of sulfate from the intestine to the liver and pancreas.[38]

In the study by Cattani et al (2005) it was shown that maternal exposure to glyphosate-based herbicides leads, therefore, to glutamate excitotoxicity and energy deficit in hippocampal cells of immature rats, through mechanisms that involve the activation of cascades of kinases, as well as deregulation of glutamatergic synapses, influx of Ca^{2+}, energy deficits and oxidative damage in the hippocampus, resulting in neuronal death. Although the hippocampus is an area known to be affected in autism spectrum disorder, the authors did not demonstrate the correlation between hippocampal alterations due to glyphosate neurotoxicity and ASD manifestations resulting from impairment of this brain area.[39,40]

Final Considerations and Limitations

Endosulfan, chlorpyrifos, glufosinate ammonium and glyphosate are agrochemicals used for agricultural purposes and with the consequent presence of residues in foods and consequently in maternal nutrition. Several experimental studies have emphasized the association between neurodevelopment and neuro degenerative disorders resulting from exposure to these pesticides.

Mothers contact with residues of these pesticides, such as organochlorines and organophosphates, causes concern for neonates due to neuroinflammation generated in the gestational period and consequent interference in the neurodevelopment of these children, may induce the occurrence of autism spectrum disorder.

A growing body of evidence suggests the role of these agrochemicals in interfering with normal neurodevelopment and impairment of psychomotor and mental functions, including attention and verbal skills in children.

These agrochemicals maybe associated with the increase the risk of development of autism spectrum disorder because their metabolites are able to cross the placental barrier and have been found in amniotic fluid, umbilical cord, breast milk and placenta causing neurodegenerative disorders, problems in neurodevelopment and fetal neuroinflammation.

The number of articles published on the topic addressed in this study is still very small, making this fact one of the limiting factors of our research. The consequence of this is that there is little information involving the descriptors of the research, and these are not yet completely clarified or proven. However, in the face of a social problem involving the increase in the number of cases of births of children with ASD worldwide, this study aims to collaborate with the discussions on this subject so that we can see in the near future new perspectives in order to elucidate the causes of the increase of cases of ASD.

Conclusion

Although it can be observed in this study that there maybe some evidence of a relationship between the use of some agrochemicals and the development of autism spectrum disorders in children, it is still necessary to carry out more studies related to this subject that can prove this hypothesis and clarify better if there is a causal relation between these two variables.

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