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THE INFLUENCE OF TERATOGENS IN THE DEVELOPMENT OF MENTAL DISORDERS

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ABSTRACT

The Mental Disorders (MD) are neuropsychological disorders that are gaining greater prominence in society and have the most widespread etiology sociocultural factors. However, recent surveys indicate that teratogenic agents may also play a role in the genesis of these disorders due to changes that promote on embryonic and fetal development. Among such agents, stand out in the study: Congenital Rubella Syndrome (CRS); Congenital syphilis; alcohol; drugs such as thalidomide, valproic acid and SSRI; hypervitaminosis of retinoic acid. Another recent study line is responsible for relating the mother's exposure to psychological stress during pregnancy to the onset of mental disorders such as schizophrenia, attention deficit, hyperactivity and anxiety in their children. The aim of this paper was to investigate the origin of various MD, set the embryological basis of individuals who were exposed to teratogens and have developed various types of mental illness.

Keywords: Teratogens. Mental Disorders. Syndromes. Drugs. Environmental Factors.

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INTRODUCTION

According to the International Classification of Mental and Behavioral Disorders (ICD-10), mental disorders can be classified as a psychological manifestation that is related to some kind of functional, physiological and homeostatic disorder, due to issues such as genetic, biological and even social disorders. These deficiencies eventually affects personal relationships of the mentally ill in their various social roles, including in this classification also the global development disorders. It is worth to point out that mental disorders are not considered mentally disabled or delays, which are classified as broad intellectual and behavioral limitations, with difficulty in practical, social and conceptual skills and are originate before the age of eighteen years old. In this context, it is important to recognize the causes of the appearance of these mental disorders[1,2.]

It was observed that, because of the high socio-economic costs, such disorders responsible for causing grave and sustained disabilities were treated with due seriousness from 1996. In this year, the World Health Organization (WHO), in conjunction with researchers at Harvard University, published a study which attested that around 30 % of persons with disabilities to exercise their activities worldwide are affected by mental illness, including depression (13 %), the intake of alcohol (7.1 %), bipolar affective disorders (3.3 %), schizophrenia (4 %) and obsessive compulsive disorder (2.8 %). Besides this, in 2001, the Pan American Health Organization (PAHO) in partnership with the WHO released a report that attributed 12 % of the world's disease to the mental disorders, which corresponds to approximately 700 million people. In contrast, less than 1 % of health resources are invested for mental health, what may contribute to a greater concern on the subject[3,4].

There is a clear need, to better address them, recognize the causes of the onset of mental illness, it is worth highlighting the action of several teratogenic agents. This is because it is responsible for promoting a greater predisposition to psychiatric disorders in individuals who, even in intrauterine life, come into contact with such substances. From this, it is noteworthy that these substances cause changes in embryological development, especially in the central nervous system formation, responsible for increasing the chance of frames as autism, schizophrenia and anxiety[1 2,3,4].

It is remarkable to note that the aim of this review article is, to lay the foundation for a better understanding about the origin of various mental disorders, define the embryological basis of individuals who were exposed to teratogens and have developed various types of mental illness.

METHOD

This is a systematic review of scientific literature study. The choice of this method is to create opportunities a scientific foundation that allows, through previous studies, provide a more complete understanding of the topic of interest. The study was conducted through a literature search, which was to embasadora tool scientific papers, periodicals and materials on the Internet available in the following databases: PORTAL CAPES, SCIELO, Lilacs, PubMed and MEDLINE. The descriptors used for the search of the articles were: "teratogens" and "mental disorders". For the organization of the material, were carried out the steps and procedures of the literature search and preliminary identification, summary book report, analysis and interpretation of material, bibliography, review and final report.

RESULTS AND DISCUSSION

THE TERATOGENIC EFFECT

It is crucial to understand that any substance (physical agent, chemical agent, organism or deficiency state) can be considered teratogenic agent, so that by being present during embryonic or fetal life, produces anomalies in structural or functional conformation in the development. Among the main teratogens, are radiation, certain drugs, maternal diseases and viruses[5].

It is also noticed that because of the wide range of teratogenic agents, the mechanism of action of each one and, in consequence, the type and seriousness of defects caused vary according to several factors. These include: time of exposure to teratogen, teratogen dosage, maternal genotype, genotype and susceptibility of the embryo, enzymatic activity of the fetus, interaction between teratogens and specificity of these and can cases of mental disorders resulting from

teratogenic often be accompanied by a mental retardation frame[6].

It is also worth noticing that there is a recognized and consensual difficulty in establishing exactly the mechanism of action of many teratogenic agents in the embryo. This is because ir depends on the teratogen exposure period and the structures that were being formed in the individual. Therefore, it is emphasized that the development of diseases involving the nervous system from teratogenesis occur mainly due to changes in cellular differentiation and morphogenesis of the nervous system, which gives the 3a-16a 7 weeks of development[7].

MAIN TERATOGENS RELATED TO MENTAL DISORDERS

The teratogens act more easily during organogenesis of tissues and organs and can cause significant functional and physiological defects. In this context, the mental illness resulting from disorders caused by such agents are developed, in most cases, since the fetal period, and it depend on the tissues and / or organs under development[8].

Such deformations in structures as neural tube and neural crests can be the result of wider changes, as in the case of some congenital syndromes. However, they may be the result of minor changes, without a noticeable systemic manifestation depending on the level of exposure to the teratogenic agent, the organogenesis stage and embryo genotype in question, but there trends that exposure to the agent teratogenic favors future manifestations of mental disorders[7,8].

It is clear, therefore, that the knowledge of the action of certain teratogens as a source of mental disorders is able to prevent significantly the appearance of such disorders. From the time that pregnant women are aware of the harmful effects of chemical compounds and biological agents (such as viruses and bacteria), these can avoid exposure to such agents[7,8].

Teratogens responsible for the onset of mental disorders and gained prominence (Table 1).

One of the prominent case reports in this context that was responsible for opening doors for new studies on the neurological disorders associated with CRS is that of a male patient of 14 years of São Paulo. He was affected by congenital rubella syndrome, confirmed by serology, having developed episodes of gestural stereotypes, laughs without motivation, psychomotor agitation, apathy, refusal to eat, frequent crying, depressed mood, self-injury and insomnia. Such symptoms culminated in clinical and neurological evaluation showed that bipolar depression frame and infantile autism in a patient with Congenital Rubella Syndrome. The report confirms the thesis that the CRS has mental disorders as clinical feature, with particular emphasis on autism, which still has unknown origins, but presents a significant incidence among patients of congenital rubella syndrome.

Despite being recognized primarily by clinical features more easily identifiable as spots on the skin, cataracts and mental disability, the mental disorders frame due to Congenital Rubella Syndrome (CRS) has been gaining greater bibliographic foundation. One of the pillars of this clinical aspect of the CRS was a study that followed 243 children with CRS until the school term, with review of 205 of them when they were aged between 8 and 9 years, noting that 15 % had several behavioral changes related clinically to cases such as depression and hyperactivity and 7 % were identified with frame infantile autism[8,9,10].

An interesting aspect about the investigative line around the CRS is that the vaccine against rubella, MMR (prevents rubella, measles and mumps), was involved in the controversy that would be responsible for causing regressive mental disorders in children who underwent vaccine. This was based on the observation of 12 children who presented regression of cognitive abilities, and in 8 of them parents associated the onset of symptoms after exposure to the vaccine. 11 Further work, however, disproved this theory 12 for lack of evidence so that there was scientific support, however, this question leads many parents to stop their children vaccinated until today, which ends up being an indirect factor for increased cases of CRS and may be accompanied by clinical conditions that lead to mental disorders[11,12].

Congenital syphilis is also one of teratogêneses by most prominent infectious agents, being es-

Figure 1: Child with Congenital Sifilis

Source: RODRÍGUEZ-CERDEIRA; SILAMI-LOPES (2011).

Figure 2: Child with Fetal Alcohol Syndrome

Source: O'RAHILLY (1996).

Table 1: Main teratogens related to mental disorders Source: RIBEIRO (2015).

TERATOGENS	MENTAL IMPLICATIONS
Congenital Rubella Syndrome	Autism and Comportamental Modifications
Congenital Sifilis	Comportamental Modifications and Retard
Alcohol	Autism and Comportamental Modifications
Thalidomide	Autism, Anxiety and Insomnia
Valproic Acid	Autism
ISRS	Transitory Neurocomportamental Disturbs
Vitamin A	Neuropsychological Damage

pecially alarming because the number of cases is increasing. There was tripling of cases reported in Brazil between 2005 and 2013, from 1.9 cases per thousand live births in 2005 to 4.7 cases in 2013[13,14].

It is important to understand that the clinical picture of congenital syphilis is usually demonstrated by the most common clinical symptoms, which occurs usually by mucocutaneous bullous lesions, perioral and anal fissures and bone malformations (Figure 1)[14].

But it stands out also that congenital syphilis may be responsible for neurological damage due to *Treponema pallidum* trend breaking into the irrigation system and brain drain blood and meninges still during prenatal development.In this context, it is causing cases of mental retardation and can contribute directly to associated cases of neurological disorders, similar to what happens with the CRS, and there are reports of associated cases of cases of congenital syphilis and infantile autism[15,16].

The consumption of alcoholic beverages during pregnancy, especially in the beginning, can also result in serious abnormalities in fetal growth and morphogenesis. This fact brings about a series of physical and mental disabilities responsible for outlining symptomatology of neurological disorders that determine changes in behavior and learning, making individuals who were exposed to the teratogenic effects of alcohol during intrauterine life more likely to develop disorders such as attention deficit, for example[7].

The form of more severe impairment of fetal alcohol exposure occurs in the newborn, in a set of characteristics: short stature, low weight, facial deformities and impaired brain development; that determine fetal alcohol syndrome (FAS) - this is the main syndrome in charge of cadres of non-hereditary childhood mental retardation. Still, we see that is related to some cases of autism, having been raised by Nanson the thesis that the alcohol consumption levels are responsible for determining whether or not the evidencing of autistic characteristics of children affected by the FAS (Figure 2), although there is disagreement among scholars about this theory[17,18,19].

The teratogenic activity of thalidomide, known drug of the class of tranquilizers, is already world known and widespread. According to Moore, over 12,000 children have been victims of defects caused by thalidomide. The main feature of teratogenic action of this agent is meromelia or “seal members”, which designates the known atrophy of upper and lower limbs due to thalidomide action. Also according to Moore, the critical period for the action of thalidomide is from 20 to 36 days after fertilization[7].

The theories that the use thalidomide during pregnancy is also decisive in the appearance of neurological disorders began to gain scientific support from the dissemination of studies like the Japanese psychiatrist Koubon Imai. The doctor, in order to identify psychological and mental problems in patients with thalidomide syndrome, analyzed the electroencephalogram, intellectual / cognitive abilities and mental health of 22 participants (9 men

and 13 women), through testing applications such as Scale Wechsler Intelligence Adult and International Neuropsychiatric Interview. The results showed abnormalities encefalográficas (not necessarily on account of thalidomide), cognitive dysfunction, difficulties in processing memories most deficient in patients with syndrome thalidomide than in healthy patients. Also it showed that 40.9 % of test participants are possible mental disorders due to symptoms that refer to clinical cases of mental disorders such as anxiety, insomnia and difficulty in social interaction. The results indicate that patients victims of teratogenic action of thalidomide are more likely to develop mental disorders such as depression[20].

Another survey, sponsored by the Federal University of Rio Grande do Sul (UFRGS), pointed to the greater propensity of individuals affected by thalidomide embryopathy in developing psychological disorders, and depression and anxiety were cited by the survey. The survey was conducted after finding that the 23 analyzed Brazilians (10 men and 13 women), born between 1959-1994, the mental disorders affected in more often individuals affected by thalidomide (17.4 % and 26.1 % to men and women respectively) than in the general population, estimated at 13 % and 12 % [21].

There was also a study sponsored by the University of Göteborg in Sweden, which analyzed a population of 100 swedes affected by Thalido-

mide Syndrome. Such research, in order to relate this condition to autism, reached the diagnosis of four individuals in this population sample as autistic and recognized that the embryonic period of contact of these people with thalidomide occurred in histogenetics similar periods between 20 and 24 days after fertilization. This allowed the opening of a research line on which the neural circuits involved in the pathogenesis may be due to thalidomide. This contribution is responsible for shed light both on the causes of autism associated with embryopathy due to thalidomide, as other mental disorders, to take into account the embryonic stage where it took contact with the drug to better analyze future dysfunctions that were entailed by such an event[22].

The valproic acid is an anticonvulsant that promotes changes in the serotonergic system (SS), has action similar to thalidomide when given in periods embryonic preceding the closure of the neural tube. As shown by the experiment sponsored by the University of Tsukuba in pregnant rats exposed to valproic acid and thalidomide, before there was closure of the neural tube, there were behavioral model similar to autism in mice, due to changes in the serotonergic system and abnormalities in the differentiation and migration neurons involved in system[23], which is also disrupted in clinical conditions of other mental disorders such as bipolar disorder. Importantly, the teratogenic action of valproic acid are already widely known, and recommended the use of other anticonvulsant drugs such as phenobarbital for pregnant women[23].

This scientific line of teratogenicity of identification, due to exposure levels embryonic drug, is of great value to highlight the knowledge of the action of psychotropic agents as teratogens. This is because it is already confirmed that depression is one of the most important clinical problems during pregnancy, often estimated 10-20 %. The risks arising from the use of selective serotonin reuptake inhibitors (SSRIs) by pregnant women are widespread, since there are indications that the use of these agents, especially in the last trimester of pregnancy, is responsible for promoting neurobehavioral disorders in newborn born. Gentile concluded that an indirect effect of the drug in the autonomic parasympathetic nervous system of newborns, SSRIs may have changes in heart rhythms, changes in sleeping and tremors, which refer to transient neurological disorders[24,25].

It is also necessary to consider, in order to better understand the breadth of compounds which have teratogenic activity that can trigger mental disorders, teratogenic substances naturally found in the body. Up highlights in particular the action of vitamin A, essential for the correct development and growth of tissues and organs. It scoring the teratogenicity of this vitamin is still controversy object. On the other hand, there is already studies showing, from analysis of the diet of pregnant 22,478, the use of more than 10,000 IU daily vitamin A, especially in the first 6 weeks of embryonic development, have teratogenic potential. It can cause cranioneurais deformations 27 and yet, according to Moore, significant neuropsychological damage from intrauterine exposure to isotretinoin (derivative of vitamin A and used to treat acne), being understood that classification disorders such as hyperactivity and attention deficits[26,27].

THE ROLE OF PSYCHOLOGICAL FACTORS IN THE DETERMINATION OF MENTAL DISORDERS

At first, it is interesting to point out that stress, a natural reaction of the body generated by the perception of stimuli that disrupt homeostatic balance, leads to a systemic adaptation characterized by increased adrenaline secretion due to mobilization of the parasympathetic autonomic nervous system axis. This promotes several systemic consequences, and is already considered a typical feature of the social dynamics of the contemporary world. In this context, the physiological responses that trigger stress when driven at intervals of very short time, can end up causing a pathological framework, from compromising important hippocampal areas. So the physiological mobilization capacity for adaptation to future adverse events is lost[28].

A recent review study, led by Nicole Talge, showed evidence that a stress framework in pregnant is responsible for a wide activation via hipotalâmicapituitária-adrenal (HPA). The effect is a change in the fetal environment from the mother's stress due to changes in hormone levels of maternal cortisol, which maintain an interdependence with fetal cortisol levels. Consequently, there is, according to the article, a great-

er propensity of children to mental disorders frames display as hyperactivity, attention deficit disorder, anxiety and even schizophrenia. Ie the physiological changes resulting from stress in the mother, can act as a kind of teratogenic agent determinant of future mental disorders[29].

Also according to this line of research, it is worth highlighting a study by Asnat Walfish identifying cases of depression in pregnant women as well as being responsible for determining the onset of future mental disorders and even congenital malformations in beings so far in training. This is due precisely because changes in breast physiological environment, causing hormonal dysregulations which alter the correct dynamic gestational and therefore acts as a teratogen agent, so as drugs used to control the depression[30].

FINAL CONSIDERATIONS

It is clear the importance of understanding the etiology of neuropsychological disorders may be linked to teratogenic factors, and such extremely relevant factors so there is improvement in treatment and diagnosis of various mental disorders and development, and that one should not take into account, for this purpose, uniquely social and cultural factors.

It is also clear the need to carry forward the line of study that also points maternal psychological factors as triggers of future mental disorders in children, since psychological stress is a trademark of contemporary society. For this may be responsible, indirectly, by increasing the percentage of mental disorders in the long run, if not treated with due seriousness. Finally, it makes explicit the need for maternal knowledge on teratogenic agents, which are and the damage they can cause to the utmost care in relation to such substances.

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