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ORIGINAL PAPERS

Autism and agression: the possible relevance of zebrafih studies

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Abstract
Autism spectrum disorder (ASD) is a complex neurodevelopment disease with multifactorial causes, which is charaterized by a dramatic loss of the communication, social interaction and the repetition of actions. In this mini-review we did focus on the agression part of the autistic pathology, and how this can be replicated in zebrafish experimental studies.

Keywords: autism, multifactorial causes; zebrafish; aggressivity; mirror reflection test; valproic acid.

Introduction- general aspects regarding the autistic spectrum disorder

1. Autism spectrum disorder (ASD)

1.1 History of disorder

Spectrum history originated in the early 20th century, when Eugen Bleuler described the case of a "disintegrating psychosis", attributing it to the "autism" nomenclature derived from the greek of : "autós" witch means: "self".(Sharma et al, 2018) Later, in the middle of the century, they were discovered and classified: Infantile autism by Leo Kanner in 1943 and highly functional autism by Hans Asperger at one year difference in 1944. In line with the details of the pathology described, connections were made to old works describing the same subject: in 1809 the study by John Haslan, in 1879 a similar case to the Asperger syndrome. (McPartland et al, 2012) One of the most popular similar cases was presented in 1798 by Victor de Aveyron dubbed the "French wild boy". A number of theories have been developed on the causes of the disease, leading to the conclusion of multi-factorial origin. (McPartland et al, 2012)(Wolff et al, 2004)

1.2. ASD prevalence

Worldwide, according to the "Global Burden of Deseases, Injuries and risk factors study" carried out in 2016, about 1% of the population; 6,2 million souls are covered by the diagnostic mark. Boys are affected in a higher number than girls, with a classic diagnostic ratio of 4:1. (Johnson et al, 2020) (Roullet et al,2013) In Romania, according to the "prelevance published by the National Center for Health assessment and promotion" in 2019, there were 408,13 cases until 2017. (insp.gov.ro)

1.3. Disturbance and diagnosis

Autism spectrum disorder is a complex neurodevelopment disease with multifactorial causes. The conditions that occur in the patient's behavior are contained under the wide range of disorders that hinder the plans: professional (school; service); social and in private life. He main areas affected at ASD level are those involved in the delivery of the communication, social interaction and the repetition of actions. The patient cannot start and maintain a dialog. He cannot accomplish this penuthal action as he has deficiencies in expressing himself: his feelings; his thoughts and his ideas. Thus, social interaction tends to fail. (DSM-V)

Non-verbal communication is poorly developed and tends to be non-existent. The body language (gestational; mimica) is not integrated into the dialog, but not reported to the interlocutor by the patient. Visual contact is completely missing. (DSM-V)

The repetitivness of the actions and their stereotypical integration into the day-to-day routine is observed in ASD. These are seen in the actions: disorganized walk; spontaneous mouvements, random sound production; preference for certain foods; toys or home-made objects. In addition, exaggerated attention is given to certain stimuli: visual (light/dark); olfactory; obsession for movement of persons or objects (rotation). Associated with pathology are elements of intellectual flaws; language; motors; aggressiveness toward person's spread; anxiety and even depression. (DSM-V)

1.5.1. Multi-factorial nature of ASD:

Risk factors belong to both the genetic and environmental factors.

1.5.1 Genetic factors

About 800-858 genes have been identified and linked to described pathology. (Genovese et al, 2020), 62% of the 858 TSA-risk genes were placed in the Sears database ("Simons Foundation for the Autism Research Initiative"). Of these 20% are carcinogenic, speculating on a possible treatment method for ASD with chemotherapy drugs. (Genovese et al, 2020) (Sakai et al, 2018)(Pensado-López et al, 2020)

Rett syndrome; fragile X-chromosome syndrome; tuberous sclerosis Complexe are pathologies which have hereditary transmission only and are associated with the symptom of ASD. (Kozol, 2018)

Chromosomal malformations meet in pathology are: dublications: 15q11-q13 (of maternal origin); deletas: 16p11.2 (also associated with Schizophrenia pathology and intellectual deficit) (Genovese et al, 2020) deletions and dublessings at the level of chromosome 16p11.2 (in 0,8 % of cases) are performed at the level of 21 genes. Two of the genes present: Doc2a and fam57ba generating hyperactivity; (Sakai et al, 2018) public acquisitions at 7q11.23 level registered at 0,2% of cases; 1q21.1 shows both delets and dublations in the 0,2% diagnosed patients. (Vicari et al, 2019)

1.5.2. The factors favoring the emergence of ASD include several aspects of family history. Diseases such as: diabetes; obesity; hypertension or mental (schizophrenia) present in the family. Age of parents and their way of life: nutrition; shortcomings in the intake of vitamins and mineral salts (iron; copper; zinc) from the body; alcohol consumption; nicotine and hormonal disadjustments, especially sexosteroids. (Bolte et al, 2019)

Details of time of birth (prenatal birth; by cesarean operation; below average weight). (Sharma et al, 2018) fetal contact with chemicals leads to ASD symptoms. Similarly, infections (viral, bacterial) occurring during pregnancy increase the risk of ASD. (Sharma et al, 2018) Theratogenic chemical compounds: valproic acid; talidomide used in the treatment of epilepsy; depression are also risks factor. Their effect is accentuated in the first quarter, when the sensitivity of both mother and fetus is increased to environmental factors. (Kozol, 2016) (Nicolini and Fahnestock, 2017)

1.5.3. The chemical pollutants have also been associated with the development of TSA pathology. This category includes: herbicides; pesticides; organic pollutants: persistent (furans; dioxins) and non-persistent. (Bolte et al, 2019) (Chen et al, 2020) heavy metals such as mercury; aluminum, silver (Sulaiman et al, 2020) (Dalmieda and Kruse, 2019) (Gorini and colab, 2014)

2. Anatomy and physiology of ASD

2.1. At the anatomical level, the central nervous system of the ASD diagnosed person shows pathological changes that differ on a case-by-case basis. From a topographical point of view, ASD's pathological causes are located at this level. The dysfunctions are genetic and neurological. Multiple lesions in patients are present in the encephalon lobes: Frontal (mid- and lower frontal), temporal (upper) and cerebellum. (Postema et al, 2017) Post-mortem studies on the affected brain have completed the list of causes of neurological disorders (low number, volume or poor consistency), the composition of the white substance and the gray substance respectively. (Postema et al, 2017) weak synaptic relationship of

dendrate and cerebral vascularation complete the list of possible causes of cerebral nature. (Ecker et al, 2017).

The most obvious dysfunction is the excessive increase in the encephalon (macrocephales) and the brain in patients between the age of 2-5. (Ecker et al, 2017) (Donovan et al, 2017) This growth begins around the age of 6-12 months, becoming observable around the age of 2 years (Varghessi et al, 2017) The early period of organization, reorganization and growth of the brain in general leads to poor connection between brain regions, in particular frontal and occipital areas. The measurements of the brain regions are affected and the aging path is atypical. (Ecker et al, 2017) Morphological and functional changes were analyzed in the neuroneal layers of the cortical regions: such as the decrease in the expansion of neurones (the pre-frontal cortex) and smaller purple neurones in size. Unaltered structures such as glial cells were observed. (Varghese et al, 2017)

At the cerebellum level the incomplete development of the central verb is observed; the volume of the small gray substance and the dysfunction of Purkinje cells. (Donovan et al, 2017) along with the cerebral changes there are disfunctions of the plocomotor system; memory; ability to set as for other pathologies such as ADHD (Disorder of lack of attention and hyperactivity) .(Bruchhage et al, 2018)

The presence of Purkinje cells in the case of ASD disorders is a subject in full debate because parameters (number, volume) have lower values than the neurotypical example. The result is derived from a degradation of neurones in the post-natal period. Their location in atypical layers such as the granular layer was attached to possible causes of the disturbance. (Varghese et al, 2017) it has also been observed that Purkinje cell parameters are lower than for neuro-typical cerebellum, with a major loss in lateral and vermis hemisphere.(Bruchhage et al, 2018)

2.2. Physiological aspects

The physiological events contained in the ASD are based on morphological and structural changes. Thus, the origin is at the level of the cortical and subcortical levels, including changes in the sinapses, the links they coordinate and the modification of the feed-back response that will be transmitted at the level of the body. (Lord et al, 2018) (Varghese et al, 2017)

In the frontal cortex is the origin of executive processes of type: decision-making, memory operation, learning. (Donnovan et al, 2017) These changes influence the power of executive decisions of the frontal cortex that will be observed in the stereotypical behavior. (Postema et al, 2019) also, the cells of minecolumns have wide spaces between them at the level of the primary auditory area. (Donovan et al, 2017) Altered structures at the level of the preffrontal cortex affect social and communicative functions such as the expression of words, phrases, empathy; memory and function of activation and execution of actions. The ability to interact and analyze faces is biologically degraded due to problems

with fusiform girus. The breakdown of the face at the level of the sympathetic connections between the structure and the cortical layers where the faces are analyzed and individualized. (Varghese et al, 2017)

The neural connections altered by the high-quantity presence and high density of von Economo neurones at the level of the previously ringed and pre-insular cortex, in both emotional processes and self-awareness and love (Varghese et al, 2017)

2.3. The limbic system. The importance of neurotransmitters and the limbic system in the development of ASD. The relationship between the amygdala and the brain

Among the components of the limbic system most interesting for ASD are : hippocampus and amygdala. Hippocampus (*cornu ammonis*) has two components located in the two temporal lobes. (Wright, 2020) It presented changes in neuroneal structures involving morphology and anatomy, in particular at the level of pyramid neurones with higher neuroneal body density and weakly branched dendrite. (Ecker et al, 2017) The hippocampus has direct links to several regions of the brain such as tonsil, talamus and to which it sends several signals.

In amygdala are changes of neurones in: low number, size and neurotypical values, above average density depending on the age of the diagnosed person. (Ecker et al, 2017) (Postema et al, 2017)

Neurotransmitters are an important index of TSA from the early stages of development of the nervous system that can be corrected with medicines before they become apparent. (Eissa et al, 2018) these (dopamine ; serotonin; gamma-aminobutyric; glutamate) participate actively in the symptom.(Eissa et al, 2018)

The increased level of serotonin is related to the aggressiveness of the diagnosis, being higher for diagnosed children. (Abdellatif et al, 2018) the brain of neurotypical children shows a decline in serotonin syntheses at puberty, while in children with autism the level remains high. the unadjusted level amplifies social isolation, the solitude being not felt. Has implications in stimulating repetitive behavior. (Eissa et al,2018)

In the same way, hypersecretion of dopamine influences both social behavior and stereotypical behavior. Deficiencies occur in the algorithm of event review, planning and achievement of a goal; lack of attention but also awareness of motivation and reward States.(Eissa et al, 2018) GABA receptors play an important role in the anatomical and functional manifestations of TSA.(Horder et al, 2018) (Eissa et al, 2018)the inhibitor neurotransmitter is found in several segments of the nervous system. GABA receivers are different in children from adults. Alters at the receptors interrupt inhibiting and exciter processes leading to disadjustments in the information processing and communication of the information. GABA receptors influence brain development processes such as sinapnea aging and cell death; as well as motor functions, auditorials, visual,

typical spectrum behavior. (Chen et al, 2020) In ASD, GABA produces a number of changes in postnatal and prenatal periods. Postnatal this contributes to the phenomenon of excessive head growth by developing more rapidly glutamate-dependant sinapes, encouraging the emergence of spectrum behavior characteristics (cognitive deficiencies, hyperactivity, motor functions, auditory, visual) (Chen et al, 2020) (Eissa et al, 2018)

3. Manifestations

The manifestations of the disease are prenatal and postnatal. They are obtained because of genetic baggage or environmental factors. (Ecker et al, 2017) (Bruchhage et al, 2018) (Postema et al, 2019) the body has symptoms predominantly manifested in several patients with the same diagnosis. Neuroneal swings in the cerebellum represent the origin of repetitive and stereotypical behavior in the disease such as: Swing walk (need to shake); difficulties at stability level; postural weak; rotation of objects; obsessive touch of face; blow in objects; movement and rotation of arms; difficulty in speech and expression. (Bruchhage et al, 2018). (Hong et al, 2016) (Moss et al, 2017) (Gerber et al,2008)

4. Treatment

4.1. The purpose of the medication is to reduce behavioral disorders such as hyperactivity; irritability; stereotypical actions; that is to say, to cause adverse reactions: weight gain; damage to metabolic markers (Sarkar et al, 2019) (Jobski et al, 2017) diagnosed children face irritability, aggressive behavior to themselves, bipolar and anxiety States. (Howes et al, 2018) some examples of the substances used for calming hyperactivity and aggressiveness are: Isprazole; risperidone; chlozapine; fluvoxamine; valproic acid; memantine; methylfenidate. Substances act on neurotypical behavior, also inducing adverse reactions such as: Insomnia; loss of weight; vomiting states; dry mouth sensation. (Eissaet al, 2018) the most used in treating corydiality symptoms are antisyhotics: ispipprazole beneficial in reducing irritability and risperidone which improves aggressive episodes and irritability. The associated adverse conditions are sedation status; increase in appetite with effects in overweight; anxiety.(Lamy et al, 2020) (Howes et al, 2018) (Lord et al, 2018)

1.4. Recovery activities

Recovery activities are intended to correct or implement a patient behavior pattern. They are of various kinds and are intended to develop both instinctive and social behavior. Some forms of intervention are: SBT (Social behavior Therapy) (Sharma et al, 2018); ABA (applied behavior analysis); NDBI (natural Development behavioral interventions); JASPER (Joint attention, Symbolic play,

engagement, and Regulation), but also other forms developed over time. (Lord et al, 2018)

2. Zebrafish

2.1. The biology of the săecies and taxonomic classification

Danio rerio belongs to the species *Danio rerio*, genus *Danio*, subfamily *Danionidae*, family *Cyprinidae*, order *Cypriniformes, Actinopterigi* Class, over-lance pisces, *Gnathostomata*, *Vertebrata*. (Ion et al, 2003) (fishbase.se) the genus comprises about 44 of *Danio rerio* species. (Spence et al, 2008)

The tropical species was first described by Hamilton in 1822, used in scientific research in 1981 by Streisinger and his collaborators in a study on the biology and development stages of the species. (Gerlai, 2011) *Danio rerio* comprises territories of: India (Bangladesh; Nepal; Myanmar) (fishbase.se) and Pakistan. (Parinchy and Postlethait, 2020) the species prefers clear, shallow, stagnant waters with slow flow such as rivers and canals. (Spence et al, 2008) (Engeszer and colab, 2007)

Zebra fish may be used for neurological disease studies as an embryo, larval or adult model. The animal model is obtained by exposing zebra fish to various factors influencing the appearance of pathology. These cyprinidae offer a model used in neurobiology and pharmacological studies. Zebra fish is a model of embryonic, larval and adult study to understand brain performance in different diseases and how to proceed with appropriate treatment.(Kalueff and colab, 2014)

The replication is due to the homology of parts of the mammalian-fish brain: Telencefal (mammal)-amigdal (fish); tonsil (mammal; fish); cerebellum (mammal; fish); hypocampus (mammal)- ventral nucleus(fish); dorso-lateral (mammal; fish); dorsal-lateral (mammal; fish) tele; Hypothalamo-hypophysio-suprarenal (mammal) axis hypothalmo-hypophysio-interrenal axis in fish; neuroendocrine systems that produce cortisol as the hormone of exposure in stress situations; GABA neurones; oligodenocytes and astrocytes. (Rea et al, 2020) (Geng and Peterson, 2019) (Meshalkina et al, 2017) (Sakai et al, 2018) (Kozol, 2016) (Tropepe and Sive, 2003) Thus, cognitive pathologies can be studied, such as: Attention deficit hyperactivity disorder (ADHD) (Sroubek et al, 2013) (Meshalkima, 2017); Fragile X syndrome (Wu et al, 2017) (Kim et al, 2014)

2.3. Zebra fish-model for aggressiveness

The definition of aggressiveness in vertebrate behavior was carried out by Lorenz in 1974 following the observation of battles between two conspecific and among members belonging to different species. (Gregoris et al, 2015) he identified the increase in the state of aggressiveness experienced in the fight against an individual of another species. (Way et al, 2015)

2.3.1. Aggressiveness in persons with TSA

In the human species, this antagonistic behavior causes perishes: Energy (psychic and physical) and alternates interhuman relationships, some of which are destroyed. Thus, the effects can be seen on both sides of the conspecifics in difficulty. For TSA patients, a large proportion of them were aggressive: 56% are aggressive with their carers, and 32% with people in close circles. At the same time, 68% of people exposed to the study have a history of aggressive episodes and 49% of people in the community, regardless of their relationship. (Fitzpatrick et al, 2016) the factors triggering the condition are: Stereotypical behavior; cognitive deficiencies; social ones; impulsiveness and anxiety; (Zabergalov et al, 2019) stress and adopted (proactive or reactive) defense strategies. (Hubena et al, 2020) the stimuli of aggressiveness can be in two forms: Verbal and physical. (Fitzpatrick et al, 2016)

2.3.2. Aggressiveness in zebra fish

The state of aggressiveness felt is an important factor that underpins the process of adaptability such as: Hierarchy; dominance; competition for the source of food; reproduction. Fish fight for the territory according to the structure of the habitat, preferably the one with vegetation that makes visual space more difficult. (Spence et al, 2007) this status is a policy of social status assurance and functional adaptability. Aggressive behavior also allows the study of the brain area that stimulates psychological and physiological processes the front part; tonsil; hypocampus; thalamus; the amus; the amass nucleus of conspecify. (de Abreu et al, 2019) and self-control and control skills are mediated through neurotransmitters: Dopamine; serotonin; adrenaline and noradrenaline. (de Abreu et al, 2019) (Teles and Olivera, 2016) At the shoal level, adults observe when exposed to a mixed group of species, so aggressiveness increases and reproductive rate decreases.(Sykes et al, 2018)

2.3.2 Acquiring hierarchy, winning-losing ratio

The level of aggressiveness felt decreases even after the interplay of dominance. (Spence et al, 2018) the hierarchy is found in the zebra fish communities, adults with leading qualities being positioned at the center of the community. (Mesalkina et al, 2017) (Steward et al, 2014) conflict of hierarchy occurs in both sexes. (Spence et al, 2008) the dominating effect is maintained through the winning-loss report, and members pay attention to the participants in the battle and recognize the winner. (Mesalkina et al, 2017) the winning fish can explore the entire aquarium, illustrating a darker image than its subordinates.(Spcene et al, 2008) The females have a receptor which intensifies the reproduction process when the male has certain qualities. They aim to win a fight (Sykes et al, 2018); it is larger than the members of its group has a different phenotype (Spence et al, 2008) in particular the pigment. (Parichy et al, 2015) thus, it gains more space to explore and the dominant image increases the copy's

reproduction rate. It has been observed that individuals exhibiting extremist behavior: Not aggressive or too aggressive have very low rates of survival and multiplication processes. The process of determining the dominant-dominant ratio takes on average 5 days. (Spence et al, 2008)

2.3.2 Aggressive behavior. Time of the aggressive act

Episodes of aggressiveness include active chases; muscle and fin movements. (Steward et al, 2014) during the preparation of the fight, movement of the position of the fins is observed. The fins are raised: dorsal and anal with the combat position. Flanks are directed to your opponent. This position shall be adopted by both opponents. The trend for swimming in the circle is observed. (Way et al, 2018) the two swim toward each other, tightening the circle as they move forward in the battle. The mouth is always open. When close enough, attacks targeting extremities start: head and tail. It is attacked and the lateral area is accessible in the circle swim movement. Attacks are rapid, target the ventral and codal parts. They are followed by short and rapid withdrawals. The pierce can either move away from the aggressor or remain immobile, "frozen" with the fins still. The winner retains his posture and fight behavior, noting that the attacker does not become attacked (Figure 1). (Steward et al, 2014) (Teles and Olivera, 2016) (Hubena et al, 2020) (Way et al, 2018) The loss of fish is isolated, damaging the unit of the group and preferring the base or the top of the living medium. (Steward et al, 2014) this type of behavior is found throughout the animal world, the winner demonstrating skill in repeated battles. (Teles and Oliveira, 2016) (Olivera et al, 2011)

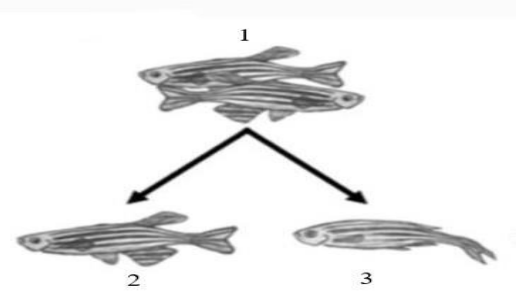

Figure 1: Aggressive interaction of zebra fish (1) with results: Winner (2) and loser (3) modified after Oliviera et al, 2011

2.3.3. Replicate aggressiveness – the mirror test

Aggressive behavior can be replicated by tests that include the presence of trigger stimuli such as: Mirror reflection; same species individuals; a video projection of a conspecific. (Way et al, 2015)

The behavior was observed in the mirror aggressiveness test. It`s dual role reflection: Person bias and social interaction with a conspecific or predator (social preference). This quantifies: Aggressiveness; sociability and daring of zebra fish

toward the predator. The levels of anxiety and stress felt are scored. The way the subject contacts the mirror increases the anxiety level when the mirror is inserted in the presence of fish. Friendly method that does not increase stress and anxiety when the mirror exists in the aquarium. They are studied: The time spent in the vicinity of the mirror and the area where it makes contact and distance between them. Also, the time before contact is made is relevant for this behavioral test. The action of the subject being watched is marked by the front mirror approaches; how and how long contact with the mirror takes place. The numeric frequency shows the level of aggressiveness that was induced to the subject. (Pharm et al, 2012) The reaction to the very type of behavior is followed: Attack or retreat from reflection. These actions are relevant for quantifying the social behavior of the subject in relation to a member of the community: sudden approach, bite, impact. When the reflection is removed, the fish tends to look back and swim faster or slower depending on its perception. The layout of the mirror stimulates the aggressive behavior of the fish zebra (Pharm et, 2012)

2.3.4. Other methods of quantifying aggressive behavior

In the same way, real and virtual stimuli amplify or blur the state. To the detriment of the nature of the stimuli, the behavior and compulsive attitude are preserved in the cases listed. When using two flat mirrors, frequent attacks and bites are observed on reflections. (Way et al, 2015) the tilted mirror position inwards caused a medium attack on the reflection with little bites. This test is beneficial to reduce the state of aggressiveness experienced when exposed to certain chemical compounds. (Way et al, 2015) (Zabergalov et al, 2019)

High frequencies of attacks and bites are maintained during the interaction with group members. Virtual stimuli: Virtual projections (of another fish or predator from the habitat in the aquarium or on a near-aquarium screen) or manufactured models (robot model) have a low frequency in the development of aggressive behavior, with bites and attacks being very low. (Way et al, 2015) (Geng and Peterson, 2019)

Other forms of aggressiveness measurement are the social test measuring of the diadic interaction (the second Member of the group may be the reflex peropia or an observer) within a certain time interval; the stimuli studied are the same as in the tests described above. (Zabergalov et al, 2019) (Geng and Peterson, 2019)

2.4 Substances which induce aggressive behavior

In zebra fish, the level of aggressiveness induced by the manner: neurogenomic; neuropsychiatric; psychiatric, toxicological; pharmacological and behavioral have been studied. (Gregoris and colab, 2015) different chemical compounds have been administered to the zebra fish, such as: methyl mercury chloride; (Zhang and colab, 2020) (Strungaru and colab, 2018) ethanol; (Michelotti and colab, 2018) ethanol and taurine mixture; (Fontana and colab, 2018) alcohol; (Fernandeset al, 2015) antibiotics; (Peterson and colab, 2021)

pesticides; (Zabegalov and colab, 2019) insecticides. (Hawkey and colab, 2020) Furthermore, aggressiveness effects were obtained by administration of hallucinogenic substances (Neelkantan and colab, 2013)

3.Model for the study of aggressiveness in autism induced by valproic acid:

3.1. Valproic acid

Valproic acid (2-propylpentanoic acid) is a fatty acid, teratogen synthesized from valeric acid extracted from the valerian plant (*Valeriana officinalis*). It has both benefits and negative reactions to living organisms. In the first category, the use of this antileptic drug for treatment of convulsions; migraines; bipolarity, epilepsy and a stabilizer of poor emotional States is subscribed. The central nervous system can be observed at the level of glutamate metabolism; the decrease in the activity of GABA receptors and the increase in activity of exciter neurotransmitters. (Deckmann et al, 2018) (Roullet et al, 2013)

3.2. Valproic acid-teratogen

In the second category, it shall be a teratogenic agent which induces phenotypic and developmental defects in the embryonal or fetal stage. (Rajesh et al, 2020) Deficiencies are also noted at cognitive level. Speech functions; attention and social interest are low as a result of exposure to the teratogenic agent. (Roullet et al, 2013) Administration of valproic acid during this pregnancy period is most frequently associated with the development of symptoms within the autism spectrum.(Roullet et al, 2013) Among studies on the influence of valproic acid and spectrum disorders, 8,9% showed the association of the compound with Autism and Asperjer's syndrome. (Roullet et al, 2013)

The first case to describe the misuse of the teratogen was in 1980. The prescribed dose is between 200-3.600 mg/day of high risk for fetal impairment. (Roullet et al, 2013) (Tartaglione et al, 2019) its administration in the first quarter of pregnancy produces malformations, including those associated with the pathology studied. (Rajesh et al, 2020) Valproic acid is one of the few environmental factors acting in the human genome. (Ranger et al, 2015) in vivo, valproic acid affects in two ways: The occurrence of anomalies and the impairment of cognitive functions with effects on behavior. (Lee et al, 2020) during this period the “Fetal valproate syndrome” is developed. (Nicolini and Fahnestock, 2017) (Christianson et al, 2008) some of the examples of congenital changes that result from administration in the first quarter of pregnancy are: Neural tube defects; trigonocephalic; small mouth sizes (very thin and long upper lip), (Rajesh et al, 2020) Food deficiencies; lung; skeletal and muscle system. (Roulet et al, 2013)

Valproic acid affects developing organs: Brain; heart; kidney, both in laboratory animals and in humans. It also slows down regeneration processes. (Lee et al, 2020) acid causes changes in the glial cells by increasing the number

and the acetyling process of cortex and hypocampus astrocytes. (Deckmann et al, 2018)

3.3. Mechanism of action for the valproic acid

Animal models for neurodevelopment and behavior are used to determine more accurately the causes. (Roulet et al, 3013) The mode of action of valproic acid administered during the in vivo period on the organism has been described in the rodent model. Teratogen modes of action aim at epigenetic Regulation at HDAC (deacetylase histone) (Ranger et al, 2015); inhibition of GSK3B (glycopene synthase kinase 3 beta) action; of the neurological cell growth and growth process (Nicolini and Fahnestock, 2017); GABA transmission inhibitor (Gamma-aminobutyric acid).

From an epigenetic perspective, the process of „reshaping the chromatin" by valproic acid is inhibited. (Nicolini and Fahnestock, 2018) Deoxyribonucleic acid (DNA) that is long and compressed inside the nucleus goes through the compression process, resulting in the formation of histons. Subsequently, nucleosomies, functional and structural core DNA unit will be formed. Deoxyribonucleic acid (DNA) that is long and compressed inside the nucleus goes through the compression process, resulting in the formation of histons. Subsequently, nucleosomies, functional and structural core DNA unit will be formed. The compression process can be influenced by various factors acting at the histone level and affecting the methylation; phosphorylating and acetyllation processes. This process is completed by two classes of Hats and HDAC enzymes. HATs (acetyltransferase histone) attaches acetyl groups to the rest of the lyine of the histone to activate it. HDAC (deacetylase histone) which removes acetyl groups from the histone level for better DNA adhesion to the protein. HDAC contains four enzyme classes: HDAC I-IV, valproic acid not affinity for a given class. This interferes with the removal of the acetyl group, resulting in hyperacetylation and disruption of processes. At the same time, it acts on several genes simultaneously. On the enzyme HDAC I valproic acid acts on the gene activation process, producing teratogenic effects associated with typical TSA behavior. The region of the brain in which it operates also varies; the age; the cell types at which the action takes place. (Ranger and colab, 2015) By inhibiting GSK3B (glycopene synthase kinase 3 beta) the entire axon remodeling and development mechanism is negatively influenced. Effects observed in the neuroneal network. Neurotic cells are equally affected in development and multiplication processes. Both the level of GABA acid and the activity of the GABA-ergic receptors show disturbances in the transmission and maturity processes of the neuroneal network. (Nicolini and Fahnestock, 2017) inhibition of GABA-ergic transmission this causes neuropathy accumulation. This makes it toxic, inhibiting cell growth. (Main and Kulesza, 2017)

In animal models, in 2005 Schneider and Przewlocki described the prenatal exposure effects of valproic acid administered to the rat females on the 12th day of the gestation period. (Nicolini and Fahnestock, 2017) Their puppies present the symptom of the autism spectrum: Very low social interactions; stereotypical behavior and locomotor difficulties; behavior with a Comulsive tence, high level of aggressiveness. Joint actions of the rodents developed from the desire to explore the new territory; playing with conspecifics and issuing sounds are actions that are poorly developed to no longer exist in the animal model. (Schneider and colab, 2006) (Nicolini and Fahnestock, 2017) (Norton et al,2020) The pattern of prenatal exposure of embryos (Zimmermann et al, 2015) (Chen et al, 2018) and larvae (Robea et al, 2021) (Deckmann et al, 2018) (Mesalkina et al, 2017) to the action of valproic acid has started both anatomical; morphological and functional changes of the vertebrate organism. It causes behavioral disorders; anxiety; anatomical changes observed both at the larval and embryonal stage. (Deckmann et al, 2018) (Mesalkina et al, 2017) (Zimmermann et al, 2015) (Lee et al, 2020) in larvae acts of aggressiveness (hit, bite), keeping distance from the fish group, preference for the lightened aquarium area (Deckmann et al, 2018) (Mesalkina et al, 2017) The stereotypical behavior in zebra fish was reported by mouth movements, preference for retrogins in one corner of the aquarium and the formation of the number eight during swimming. (Mesalkina et al, 2017) the administration of valproic acid influences social preferences. The social interaction that characterizes it as a forgiving effect on the vertebrate model. (Liu et al, 2016) There have been observed lottious difficulties at the exploration stage of the new territory, spontaneous movements, sudden responses to the touch action and hyperactivity during the night at both stages. The larvae jerked both their head and tail. At the level of the dynamometer, the aquatic model shall keep a considerable distance from its conspecs. (Chen et al, 2018) Anxiety conditions are observed during the time spent at the bottom or top of the aquarium. In the presence of another fish, the subject was recorded with parameters of anxiety such as high speed; a eventative attitude and spending time at the extremities of the test space.(Zimmermann et al, 2015)

3.4.Genetically modified valproic acid

At the genetic level, TSA has molecular malformations such as proteins; receptors; molecules that give adhesion to genetic information processing processes; (Lee et al, 2018) reduced number of neurones; decrease in Locomotor performance. (Rea et al, 2020). In terms of mutations at chromosomal level, the approximately equal number of chromosomes is an advantage. Thus, the man has 23 pairs of chromosomes; the rotors have: Mice 20 pairs, rats 21 pairs of chromosomes and the zebra fish 25 pairs of chromosomes and over 26.000 similar proteins. (Kalueff et al, 2014)

About 800-858 genes have been identified and referenced to the described pathology. (Genovese et al, 2020)

Of these, 12 genes were identified in mammals and the two types of vertebrates: Rats and zebra fish that lost their basic functions, their new activity being linked to the symptom of the disease. These are: ARID1B, CHD8, FMR1, MECP2 and PTEN (available for research) and the other 7: CNTNAP2, DYRK1A, GRIN2B, NRXN1, SCN2A, SHANK3 and SYNGAP1 are not available.The aquatic model has dublated genes from the human counterpart with a factor of risk to the development of pathology. (Sakai et al, 2018) (Retailer et al, 2019)

At the same time, these genes were categorized according to the degree of affectivity in 3 groups: 1. High degree; 2. High degree and 3. Very high degree. The genes that work in the foreground on neuroneal connections are: ARID1B; FMR1; PTEN; SHANK3 and SYNGAP1 at the dendrite level and the axon level, the action of the genes is found: PTEN and CNTNAP2. Rail training being hampered by the deficient action mechanisms of the genes: FMR1, MECP2, CNTNAP2, NRXN1, SCN2A and SHANK3. (REA et al, 2020) (Pensado-López et al, 2020) (Verghesa et al, 2017) (Kozol et al, 2016) (Meshalkina et al, 2018)

In order to describe a genetic molecular basis that departs the causes of autiste pathology, several genetic models have been described which are or are not associated with the 12 genes with direct implications. Genes such as adsl, mdbs, tsclb and shank3 studied on the Danio rerio model are directly influenced by valproic acid (Rea et al, 2020) the adsl, ief41 md5; rxn; tsc1 and shank3 genes are most affected by the teratogenic factor. This affects neurodevelopmental processes and neurological migration in the embryonic stage. From a behavioral point of view, the Locomotor activity was low in relation to neurotypical values, including travel speed.(Lee et al, 2018) the shank3 gene (over zebra) is associated with symptoms such as smaller or larger head sizes, along with genes: KCTD13; AUTS2. (Steward et al, 2014) the counterpart gene for AUTS2 in zebra fish, auts2 produces death of neuroneal populations and intellectual difficulties. (Sakai et al, 2018)

Conclusion

In **conclusion**, ASD is one of the most complex neurodevelopment pathologies whose origin is given by the multifactorial aspect of the environment. The influence of the vast symptom on neurodevelopment processes which in turn affect the development, behavior and integration of the collective ib leads to a complicated path of decipher its mechanisms. Agression seems also to be an important component of its pathophysiological context.

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