ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 04, pp. 45959-45962, April, 2021
https://doi.org/10.37118/ijdr.21560.04.2021

RESEARCH ARTICLE OPEN ACCESS

THE INFLUENCE OF ANATOMICAL VARIATIONS OF THE CEREBELLUM IN INDIVIDUALS WITH AUTISM SPECTRUM DISORDER

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ARTICLE INFO

Article History:
Received 09th January, 2021
Received in revised form
06th February, 2021
Accepted 15th March, 2021
Published online 13th April, 2021

Key Words:

Autism Spectrum Disorder, Cerebellum, Anatomical Pathological Condition, Neurological Disorder.

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ABSTRACT

Autism is characterized by the rupture in the fundamental processes of socialization, communication, and learning. The diagnosis of the disorder requires at least six behavioral criteria, such as the use of nonverbal forms of communication and social interaction, non-development of interpersonal relationships, lack of sharing experiences and communication, and lack of social or emotional reciprocity. as the cerebellum is primarily responsible for motor function, it also plays a role in multisensory integration, which in turn receives projections of all its modalities, such as self-movement that requires integration of vestibular, visual, proprioceptive, and somatosensory information. The objective of this work was to review the cerebellar anatomical changes in individuals diagnosed with ASD and discuss the complications of these alterations for the development and integration of body systems. This is an integrative review through a search strategy in the PubMed/MEDLINE, Scielo and Science Direct databases. The terms established to compart the search were "cerebellum", "autism, "anatomical alteration, "disturb" and "human". Some changes found in individuals with autism are hypoplasia in the vermis subregion, abnormal density of Purkinje cells, and abnormalities of their deep nuclei, including fastigeal, globous, and emboliform nuclei. Autism spectrum disorder is a syndrome from early changes. All characteristics of autism indicate that biological mechanisms are central in the etiology of the process.

Citation: ***Robson Arruda Souza, Anna Júllya Almeida da Silva Oliveira et al.*** "The influence of anatomical variations of the cerebellum in individuals with autism spectrum disorder*", International Journal of Development Research*, 11, (04), 45959-45962.

INTRODUCTION

Autism is the best known type of invasive developmental disorder that affects about 1 in 36 children (Sharma et al., 2018), denoting a diagnostic entity within a family of neurodevelopmental disorders, in which there is a rupture in the fundamental processes of socialization, communication and learning. Approximately 60 to 70% of individuals with autism function in the mental retardation range, reflecting a greater perception of the manifestations of the disorder with a high degree of functioning, which, in turn, seems to lead to a greater number of individuals being diagnosed with this condition. Sensory dysfunction is a central symptom of autism spectrum disorder (ASD), along with motor manifestations and other clinical signs (Klin, 2006).

The diagnosis of the disorder requires at least six behavioral criteria, such as the use of nonverbal forms of communication and social interaction, non-development of interpersonal relationships, absence of sharing of experiences and communication and lack of social or emotional reciprocity. In addition, stereotyped and restricted patterns of interest, inflexible adhering to specific non-functional routines or rituals, stereotyped and repetitive procedures and persistent concern with parts of objects are also characteristic of this disorder. There is a noticeable variation in the expression of symptoms in autism, therefore classifying the types of the disorder (Klin, 2006). Children with lower functioning are characteristically completely or largely mute and isolated from social interaction. At the next level, children can accept social interaction passively, but do not seek it, besides being able to observe some spontaneous language. Among those with

a higher degree of functioning and are slightly older, they may be interested in social interaction, but they cannot start or maintain it in a typical way (Bruchhage et al., 2018; Klin, 2006). In this context, the feeling of parents towards their child with disabilities becomes paramount for the adaptation and well-being of the family. A study reports that mothers feel hurt and suffering in relation to the difficult situation of their children with mental disorders, such feeling was also reported by parents, who took responsibility for their children's mental changes (Freedman & Foxe, 2018a; Silva & Dessen, 2001). In short, social pressures provoke unpleasant feelings, which leads parents to limit children's cultural activities, as well as contacts with friends, relatives, and neighbors. In addition, there are several factors that constitute an overload for these family members, such as the time invested in caring for them, also reducing their social and cultural contacts; financial resources, because they bear most of the care and finally, social and psychological limits, since society's attitudes towards people with mental disorders are not positive. (Freedman & Foxe, 2018a; Koziol et al., 2014; Silva &Dessen, 2001). Many areas of cognitive functioning are often preserved, and sometimes individuals with these conditions exhibit amazing and even prodigious abilities. Early onset, symptom profile and chronicity of these conditions imply that biological mechanisms are central to the etiology of the process. Advances in genetics, neurobiology and neuroimaging are jointly expanding our understanding of the nature of these conditions and the formation of the social brain in individuals with these characteristics (Klin, 2006).

As treatment measures for ASD, pharmacological and non-pharmacological measures are found. Pharmacological drugs include psychostimulant drugs, atypical antipsychotics, antidepressants, and alpha-2-adrenergic receptor agonists to relieve partial symptoms. Non-pharmacological interventions, in turn, aim to improve social and verbal communication through music therapy, cognitive behavioral therapy and social behavioral therapy. In addition, the use of vitamins, herbal medicines and supplements seem to have symptomatic improvement in the disorder, although studies are still needed to confirm its efficiency (Sharma et al., 2018; Wang et al., 2014). Even though the cerebellum is primarily responsible for motor function, it also plays a role in multisensory integration, which in turn receives projections of all its modalities, such as self-movement that requires integration of vestibular, visual, proprioceptive and somatosensory information. Therefore, cerebellar deficiency negatively affects responses to sensory stimuli, regardless of modality. Such cerebellar changes come from the vermis, hemispheres and purkinje cells (Cardon et al., 2017). Thus, the objective of this article was to review the anatomical cerebellar changes in individuals diagnosed with ASD and discuss the complications of these changes for the development and integration of body systems.

RESEARCH ELABORATIONS

This is a systematic review based on a previously established protocol. To conduct the review on the proposed theme, journals indexed in the MEDLINE electronic databases were searched, via PubMed, Scielo, LILACS and Science Direct. No restrictions in linguage and year of publication. The terms established to compose the search were determined by the MeSH / DeCS: "cerebellum", "autism," anatomical alteration, "disturb" and "human". The searches were crossed from the Boolean operators OR, AND andAND NOT were the same for all the bases searched. Studies developed with humans that quantified or qualified cerebellar changes in humans were included. As for the study design, cross-sectional studies, retrospective or prospective cohort, case-control, clinical trials, case reports, case series and systematic reviews were considered eligible. While the abstract of scientific events and study protocols were excluded. Exclusion criteria were studies that reported changes in other structures of the nervous system or changes in animal models. The review of the studies found with the aforementioned search strategy occurred with the conference on the computer screen of the titles and abstracts, carried out by four reviewers independently. The studies that met the proposed eligibility criteria or that raised questions were separated for reading and full analysis of the article. When there were disagreements in the selection process, consensus and opinion from a fifth evaluator was sought.

RESULTS OR FINDING

The execution of the search strategy indicated in this review resulted in a total of 13 articles included, whose main findings are discussed below. According to several studies, brain development during pregnancy can be disturbed by the alleles of risk for autism, with a 40% chance of acquiring ASD due to inherited genetic variation, thus most autistic children have neurotypic parents. The expression of genes related to the disorder was found during two different periods in human development, during the 10th to 24th gestational week and from the neonatal period at 6 years of age, being in this last period where the layer of granular cells of the cerebellum has strong expression (Wang et al., 2014). From the first two years of life, there are continuous changes in the volume of the cerebellum. In autistic children from 2 to 3 years of age, there may be vertebral hypoplasia, in addition to an increase in white matter in relation to the gray matter in the cerebellar hemispheres. In boys diagnosed with ASD aged 3 to 9 years, there is an increase in frontal volume, being associated with vermis. Some imaging studies have shown that in pediatric patients under 10 years of age a decrease in the transverse area in the posterior vermis, in lobes VI to VII (Wang et al., 2014; Wegiel et al., 2014)

Concomitantly, in adults diagnosed with autism since childhood, there is a hypoplasia in the vermis sub-region. At later ages, some of the abnormalities can be alleviated or returned. The inferior and deep olivary nucleus, considered the main structures of entry and exit of the cerebellum, in addition to Purkinje cells are related to sudden abnormalities of the cerebellum, differences that usually arise at the age of 4 years (Bruchhage et al., 2018; Cardon et al., 2017; Wang et al., 2014). The hypothesis that the abnormal density of Purkinje cells (PC), linked to the lowest total number of these cells in the cerebellum of autistic patients, may corroborate the clinical characteristics of the disorder phenotype. In addition, dysplastic changes in the lobe X together with the lowest number of PCs can contribute to changes in eye movement in autistic individuals (Fatemi et al., 2012; Muratori et al., 2001). In addition, some studies on the cerebellum have shown abnormalities of its deep nucleus, including fastigial, globular and emboliform nucleus. As well, in autistic patients over the age of 21 years it was seen that there is a significant drop in the number of pale neurons, while in children diagnosed with the disorder between the ages of 5 and 13 there is an exceptional increase in these same nuclear groups (Scott et al., 2009).

The cerebellum is composed of two hemispheres interconnected by a narrow unpaired portion, called vermis, which consists of a medial cortico-nuclear zone and is responsible for regulating posture and locomotion of the entire body (Coffman et al., 2011). There are studies that show that differences in the structure of the cerebellar vermis in patients with ASD may have developmental delays related also to the visual-sensory-motor in early childhood. These delays will culminate in the signs common to the disorder, such as difference in visual orientation, communication and social interaction (Freed man & Foxe, 2018b). The syndrome is divided into low functioning autism (LFA), high functioning autism (HFA) and Asperger's syndrome (AS). According to recent studies carried out through magnetic resonance imaging exams and post-mortem neuropathological studies, with patients from the three groups mentioned, we found in the AAF type (autism and IQ greater than 70- high functioning autism group) a hypoplasia of the vermis cerebellar. In patients with ABF and SA there was no result of significant hypoplasia (Allen et al., 2004; Sharma et al., 2018). This condition can cause behavioral deficits, visual deficits with altered saccadic amplitude and, therefore, sensorimotor difficulties (Freedman & Foxe, 2018b). Cerebellar vermis is also said to be involved in the social and affective processing of individuals and responsible for influencing shooting patterns in limbic structures, in addition to regulation and emotional processing. Therefore, changes in these structures are considered to

be associated with a deregulation of affect. The size of the vermis in individuals with ASD is also studied for this type of alteration, however in most studies there are no significant differences, although hypoplastic and hyperplastic worms have already been found in this context. Thus, it is only known that there is a heterogeneity of the vermis when there is this type of change (Laidi et al., 2017). Cerebellar vermis hypoplasia, mainly of VI and VII, was the first neuroanatomical alteration identified in patients diagnosed with ASD and since then many other studies have reported the same outcome. However, there are still studies that reach an equal volume result in the vermis of people affected and not affected by the disorder, stating that this is a very heterogeneous condition and that the level at which these patients find themselves will generate a different result (Becker &Stoodley, 2013; Cardon et al., 2017; Silva &Dessen, 2001). An alteration widely found in post-mortem analyzes of patients with ASD is the decrease in the size and number of Purkinje cells, especially in the neocerebellar, posterolateral and archicerebellar cortex, which may have a strong functional influence for these individuals (Donovan &Basson, 2017). It is still unclear which is the responsible cerebellar dysfunction that can give rise to the disorder, it was only elucidated that this region is very involved with cognition, language, visual, spatial, executive and working memory (Becker &Stoodley, 2013; Koziol et al., 2014). Basket cells (BC) and stellate cells (SE), which are cells that PCs rely on to survive, were evaluated in a study in which evidence of late loss of PC development was provided and no decrease in amount of CC and SE interneurons in the molecular layer of the cerebellum, suggesting that once Purkinje cells were generated, they migrated to their correct location and later died.

Thus, the moment when PCs are lost, seems to be prenatal (Fatemi et al., 2012). In the brain of autistic people with a decrease in the number of PCs, there is no neuronal loss in the synaptically related lower olive, where this relationship is established shortly before birth. Upon completion of the connection, any loss of PCs that occurs results in a mandatory retrograde cell loss of lower olivary neurons. In this lower olive, the neurons were found in a grouped form next to the entire periphery of nuclear convolutions, which is a pattern of pathology that can already be dated from an early prenatal period (Becker &Stoodley, 2013; Cardon et al., 2017; Fatemi et al., 2012). Multi-causal developmental disorder, autistic disorder is defined by the behavior that is associated with various neuropathologies. The most consistent reported is the reduction in Purkinje's cerebellar cells, the only outflow from the cerebellar cortex. As a direct or indirect consequence of the decrease in these cells, it is possible to find alterations in eye movements in ASD individuals, in addition to, in addition to other factors, an altered inhibition of the cerebellar nuclei is also possible, which directly affects the cerebellar-cortical production, consequently, leading to changes in motor behavior and cognition (Wegiel et al., 2014).

CONCLUSION

Autism spectrum disorder is a syndrome that comes from early and essential changes in the socialization process, causing a cascade of impacts on the development of social activity and adaptation, communication and imagination, among other impairments. Several regions of cognitive functioning are often preserved and, in some situations, individuals with these conditions reveal surprising and even prodigious skills. All characteristics of autism indicate that biological mechanisms are central to the etiology of the process. The evolution of genetics, neurobiology and neuroimaging are expanding our understanding of the nature of this pathology, the formation of the cerebellum and its relationship with the disorder. Associated with this new phase of prospective studies on autism is born a new perspective of social neuroscience on the pathogenesis and psychobiology of the factors that are emerging. Such effort may elucidate the mysteries of the etiology and pathogenesis of these conditions, in addition to the consequent transition from the focus of research to more effective treatments in addition to a probable prevention.

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