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(RESEARCH ARTICLE)

Findings in magnetic resonance spectroscopy in patients with Autism spectrum disorder

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Abstract

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition that has been the subject of extensive research, including studies using magnetic resonance imaging (MRI) to explore brain metabolites as potential biomarkers.

Methods: The objective of our study was to identify brain metabolites using magnetic resonance and proton spectroscopy that could serve as potential markers of ASD (Autism Spectrum Disorder).

Results: Magnetic resonance imaging did not reveal any brain morphological changes in ASD patients. However, the patients with ASD exhibited an elevated glutamate peak in 100% of cases.

Conclusions: Magnetic resonance imaging combined with cerebellar spectroscopy is an emerging tool for the diagnosis and management of autism. This approach shows promise in enhancing both the diagnosis and treatment of ASD.

Keywords: Magnetic resonance of the brain in ASD; Proton spectroscopy of the brain in ASD; Elevation of glutamate in the brain of ASD; Cerebellar spectroscopy of the brain in ASD

1. Introduction

The expression “autism” was used for the first time, to designate the loss of contact with reality, which caused a great difficulty or impossibility of communication [1].

Autism is not a single disease, but a complex developmental disorder, defined from a behavioral point of view, with multiple etiologies and varying degrees of severity [2]. The phenotypic presentation of autism can be influenced by associated factors that are not necessarily part of the main characteristics that define this disorder [3, 4, 5].

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Autism spectrum disorders (ASD) are neurological developmental disorders throughout life, which include different phenotypes, characterized by impaired social communication and stereotyped patterns of interests and activities. Due to a disorder in the central nervous system, it impairs development, occurring in any child, regardless of sex, race, or socioeconomic condition. Its current incidence is extremely high, occurring in one child out of seventy normal, beginning near the first year of life, being four to five times more frequent in males [6,7,8].

Locomotor activity is affected in these children and what should guarantee the integration of a child's behavior in the environment; therefore, playing a role in the child's communication. The three main components of locomotion include the production of basic locomotor rhythm, maintaining balance and adapting to the activity of moving towards goals [9]. Studies have shown significant deficits in the area of maintaining balance, which could interfere with locomotion and interfere in the field of communication [10, 11, 12].

Due to the presence of frequent comorbidities (epilepsy, mental retardation and psychiatric disorders), it is difficult to isolate the neuropathological substrate of autism, the underlying biological causes that have not yet been established. At this time, it can be assumed that genetic, immunological, and environmental factors are involved in its etiology [13].

Global and regional morphological changes in ASD have already been demonstrated by neuroimaging [14] and through pathological studies [15], have shown abnormal growth of the brain and head by the cephalic perimeter [16,17].

In addition, recent studies stress that the time elapsed from the beginning of brain development to the onset of symptoms is important since the product is autism. Suggesting that heterogeneity, both cell nucleus and comorbid characteristics, predict a heterogeneous pattern of neuropathology in autism. Phenotypes defined in larger samples of children and brain tissue will be necessary to characterize the neuroanatomy of autism. These contradictory data suggest that in the course of time, brain development and the onset of ASD, are the inducers of the type of disorder found in ASD patients [18].

In view of the early need for the treatment of ASD, there is an increasing momentum behind the identification of reliable biomarkers for the diagnosis of this disorder that would allow its diagnosis and treatment.

Magnetic resonance imaging today is emerging as the best way to study brain anatomy and metabolism, non-invasively and without exposing patients to life-threatening or brain biopsies that could lead to sequelae. It can be used for brain morphology evaluation and for functional and metabolic evaluation. Proton spectroscopy, which is a non-invasive neuroimaging technique that estimates measurements of specific chemical metabolites in vivo [19], emerged in this medium.

In proton magnetic resonance spectroscopy, signal strength is not only proportional to the metabolite concentration but is also affected by many variables, including relaxation rates of metabolites, pulse sequence parameters and coil sensitivity radio frequency. As a result of the difficulties inherent in obtaining absolute confidence concentrations, most in vivo magnetic resonance studies with spectroscopy report measures related to brain studies, assuming the calculated concentrations of creatinine as a constant and having its signal as a reference.

Direct measurement of brain metabolites is another potential strategy for identifying individuals with ASD. Brain metabolites are involved in processes of excitation and cell transmission and can provide the sites and indices of synaptic activity and plasticity in addition to supporting inferences about ongoing pathophysiology. Magnetic resonance imaging through spectroscopy allows non-invasive and simultaneous measurement of several neurometabolites and has been used in studies already published to study the pathophysiology of ASD. Commonly studied metabolites include n-acetylaspartate (NAA), a putative marker of neuronal integrity [20], creatine (Cr), involved in energy metabolism [21], choline (Cho), a component of cell membranes and linked to cell number [22], glutamine / glutamate (Glx), involved in excitatory neurotransmission [23] and myoinositol (Myo), which is believed to be a product of myelin breakdown and a possible glial cell marker [24].

The objective of our study was to examine imaging studies, using magnetic resonance imaging of the skull, by spectroscopy and diffusion, In search of common metabolites in patients with ASD.

2. Material and methods

Between March 2018 and November 2020, our Food Allergy and Autism Unit at Santa Casa da Misericórdia do Rio de Janeiro received 38 patients, 30 males and 8 females, diagnosed with Autism Spectrum Disorder (ASD).

The diagnosis of ASD was based on the CARS scale, with a score exceeding 30, along with two written diagnoses by two specialists in ASD, in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. All 38 patients were enrolled in the study and underwent a magnetic resonance examination of the skull to assess morphological brain changes and proton spectroscopy to evaluate brain metabolites. The studies were conducted using a GE 3T (GE Healthcare, Milwaukee, WI) full-body scanner with a high-resolution 8-channel skull coil (In vivo, Orlando, FL).

To perform the examination, the participant's head was positioned along the canthomeatal line and immobilized using a forehead brace. The spectra were obtained using the PRESS technique. Three-dimensional samples were placed in the left cerebellar hemisphere as well as in the frontal lobe. This acquisition allowed for the quantification of glutamate (Glu), N-acetyl-aspartate (NAA), creatine (Cr), phosphocreatine (PCr), glycerophosphocholine (GPC), phosphocholine (PCH), and myo-inositol (MI).

We gathered information through the review of medical records, classifying this study as a retrospective cross-sectional study.

3. Results

The magnetic resonance evaluation did not detect any brain morphological changes in any of the patients. Similarly, the diffusion magnetic resonance assessment revealed no signs of acute ischemia, neoplastic growth, or inflammatory brain lesions in any of the patients.

The spectroscopic evaluation indicated that all patients had elevated levels of glutamate and glutamine in the left cerebellar hemisphere (100%), while only one patient (2.6%) showed an increase in glutamate and glutamine in the frontal hemisphere

4. Discussion

Since 1943, when Dr. Kanner, a psychiatrist, studied 11 children with characteristics such as autism, he described that these children had good intellectual potential, echolalia, difficulties in spontaneous activity, and a loss of cognitive and emotional functions [25].

In light of the increasing prevalence of autism and its profound impact on both public health and the affected families, there is a pressing need for advancements in our comprehension, prevention, diagnosis, and treatment of this condition. These areas have emerged as critical global priorities [26] and hold significant importance within our own community [27]. Previously viewed primarily as a complex hub for motor coordination and execution, the cerebellum has now been recognized as playing a pivotal role in higher cognitive and emotional functions, even in the developing brain [28].

Recent theories regarding cerebellar function propose the concept that the cerebellum functions as a kind of modeling "machine" not only in motor activities but also in cognitive behaviors. Following this line of thinking, for example, for mastering motor function, when individuals are learning new movement patterns, the cerebellum processes information by comparing it to the various states of information processed in the prefrontal areas, facilitated by the basal ganglia, and even incorporates feedback from peripheral proprioception. These models of neuronal patterns enable the optimization of neuronal control in future processes. Drawing an analogy from this fundamental premise, it is suggested that the same principle holds true for non-motor functions, such as cognitive and emotional behaviors [29].

In recent years, a number of studies have indicated that the cerebellum plays a role in the pathophysiology of autism [30 - 34]. Notably, self-generated or maternal autoantibodies targeting neural cells, including cerebellar Purkinje cells, have been identified in the serum of children with Autism Spectrum Disorder (ASD) [35]. Furthermore, a recent study demonstrated that children with these autoantibodies exhibited a higher degree of aberrant behavior and cognitive functioning, along with lower adaptive function when compared to children without such autoantibodies [36].

The finding of cerebellar atrophy in a subset of celiac patients aligns with earlier autopsy reports that documented the selective loss of Purkinje cells in the cerebellar cortex of individuals with celiac disease and neurological disorders [37]. This discovery establishes a functional and clinical correlation, as patients often report experiencing balance disorders.

The precise mechanisms responsible for the loss of Purkinje cells in association with gluten sensitivity remain incompletely understood. However, the current theory suggests that this cellular damage is likely mediated by an

immune response, possibly involving transglutaminase autoantibodies [38]. Hence, it is reasonable to infer that the proliferation of glial cells and the reduction in neuron density play a significant role in the abnormal brain growth and the observed decrease in NAA levels in children with Autism Spectrum Disorder (ASD) [39].

The increased levels of prostaglandins could potentially be linked to the findings reported by Meltzer and Water [40] that immune dysregulation and inflammation serve as the primary etiological factors in autism. The notable rise in PGE2 levels in individuals with autism compared to age-matched control participants could be associated with glutamate toxicity [41]. Lozinsky's research demonstrated in 2010 that PGE2 has the capacity to disrupt intracellular calcium (Ca2+) homeostasis, influence glutamate release, and activate transcription factors [42]. Specifically, PGE2 leads to an increase in the release of intracellular Ca2+, with some extracellular calcium intake. This, in turn, may trigger the release of glutamate from astrocytes, resulting in abnormal neuron-astrocyte interactions. The elevated glutamate levels are associated with a decrease in GABA, likely due to reduced glutamic acid decarboxylase (GAD) expression in the cerebellar cortex, which is observed in the brains of individuals with autism. The high PGE2 levels reported in the current study could potentially be linked to the diminished GABA levels in autistic patients compared to control subjects [43]. However, it is essential to highlight that the direct measurement of glutamate (Glu) neurotransmission can be achieved using high-field resonance techniques, although this method measures both vesicular and metabolic glutamate [19]

Excessive glutamatergic activity has also been linked to neuronal degeneration, highlighting a significant correlation between glutamate (Glu) levels and N-acetylaspartate (NAA) in the caudate nucleus and cerebellum across all groups with Autism Spectrum Disorder (ASD). NAA, a prominent peak consistently observed in magnetic resonance spectroscopy, is primarily found in neurons and is recognized as an indicator of neuronal functional integrity and axonal mitochondrial metabolism [44]. Elevated NAA levels may be a result of increased axonal mitochondrial metabolism, aimed at sustaining axonal conduction [45]. It is not surprising that an increase in Glu, an excitatory neurotransmitter, would be associated with heightened local neuronal metabolism.

It is well-established that glutamate antagonists can induce both positive and negative psychotic symptoms, resembling those seen in schizophrenia, particularly the positive symptoms induced by dopamine agonists alone. This progression of deterioration has been suggested to be partially attributed to cortical neuronal toxicity, which is a consequence of increased glutamate exposure. This heightened glutamate exposure is believed to reflect a compensatory increase in cortical glutamatergic activity due to the hypofunction of the N-methyl-D-aspartate (NMDA) receptor [46]. Excessive glutamatergic activity is also associated with neuronal degeneration [47].

An appreciable increase in Glx in the left cerebellar hemisphere of patients with Attention Deficit Hyperactivity Disorder (ADHD) has previously been documented when compared to the corresponding region in control subjects. Differences in other metabolites measured in the left cerebellar hemisphere have also been noted, while no variations in the proportions of any metabolites were observed in the vermis and hemisphere. These findings are consistent with the results obtained in our study [48].

5. Conclusion

The discovery of elevated cerebellar glutamate in autistic patients through magnetic resonance imaging with cerebellar spectroscopy represents a novel tool in the management of autism. This tool can be valuable to all physicians, including those who are not specialists in autism, serving as a guide for the assessment and treatment of this challenging condition. It can be utilized for both diagnostic purposes and follow-up evaluations.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

All procedures for enrollment and conduction of this research project was reviewed and approved by the Institutional Review Board of the UNIGRANRIO University under number CAAE 66813917.0.0000.5283.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Authors' contributions

All authors contributed equally in preparing all parts of the work and approved the version submitted for revision

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