v. 4, n. 63, 2024

International Journal of Health Science

THE ROLE OF MUTANT GFAP PROTEINS IN THE PATHOGENESIS OF ALEXANDER'S DISEASE: AN INTEGRATIVE REVIEW

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Abstract: Objective: To analyze and synthesize the available scientific evidence on the role of the mutant protein GFAP (glial fibrillary acidic protein) in the pathophysiology of Alexander disease. Method: This is an integrative review of the literature, research was carried out using databases available in the Virtual Health Library (VHL), Medical Literature Analysis and Retrieval System Online (MEDLINE), National Library of Medicine/PubMed, SciELO. The descriptors used were: The descriptors used were: "Alexander's Disease", "Mutant Protein", "Pathogenesis", "Rare Diseases" and "Glial Fibrillar Acid Protein". Combined with the Boolean operators OR and AND. Results: Studies on Alexander disease emphasize the effects of mutations in the GFAP gene, which cause abnormalities in GFAP intermediate filaments, resulting in excessive aggregation in the astroglial cell. This is associated with mitochondrial dysfunctions, oxidative stress and changes in organelle distribution, contributing to the pathophysiology of the disease, including clinical manifestations such as partial epilepsy continua. Cellular and animal models reveal that such mutations compromise the proper formation of GFAP filaments, leading to the formation of Rosenthal fibers and worsening neurodegeneration. Specific studies such as the R239C mutation indicate that these changes not only impair the structure of the filaments, but also negatively affect the solubility of GFAP, impacting astrocytic function and the integrity of the blood-brain barrier in Alexander disease. Conclusion: The investigation of mutated GFAP proteins in Alexander disease represents a significant advance in clinical neuroscience, highlighting complex molecular pathways involved in pathogenesis. Detailed analysis of the structural and functional changes of these proteins offers crucial insights to overcome diagnostic and therapeutic challenges,

essential for improving patients' quality of life and driving the development of new treatments.

Keywords: Alexander Disease", "Mutant Protein", "Pathogenesis", "Rare Diseases" and "Glial Fibrillar Acid Protein".

INTRODUCTION

Mutations in the glial fibrillary acidic protein (GFAP) gene are associated with Alexander disease (AxD), a neurodegenerative disease characterized by astrocytic dysfunction, GFAP aggregation, and Rosenthal fiber accumulation (LIN et al., 2021). GFAP is a crucial intermediate filament in astrocytes, responsible for cytoarchitecture, mechanical resistance and support of neuronal functions (MCKEON; BENARROCH, 2018). Studies have shown that mutations in the GFAP gene lead to altered splicing, resulting in increased expression of GFAP isoforms such as GFAP-δ and GFAP-κ, which are prone to aggregation and compromise the function of astrocytes, eventually contributing to neurodegeneration through of impaired glutamate transport (NWOSU et al., 2022). Furthermore, GFAP mutations have been associated with adult-onset Alexander disease (AOAD), presenting with symptoms such as pyramidal and bulbar signs, abnormal behavior, memory disorders, and abnormalities in the medulla oblongata and cervical spinal cord on MRI (GANNE et al., 2022).

Alexander disease is a rare autosomal dominant disease. This presents with a wide range of clinical manifestations in different age groups, including infantile, juvenile and adult onset, with symptoms such as macrocephaly, developmental delay, muscle weakness, spasticity and seizures such as atonic seizures (YOSHIDA, 2020). Alexander disease subtypes include type I, type II, and type III with distinct clinical features and radiological findings such as tadpole-like brainstem atrophy and ventricular garlands. Diagnosis is usually based on specific MRI findings, helping to confirm the disease through analysis of the GFAP mutation (VAIA; MURA; TONDUTI, 2023).

The AxD presents with three distinct clinical subtypes based on age of onset: infantile (0-2 years), juvenile (2-13 years) and adult (>13 years) (CIAMMOLA et al., 2019). The infantile form typically involves rapid neurological decline, psychomotor retardation, seizures, and macrocephaly, while the juvenile subtype is characterized by spastic paresis, brainstem symptoms, and milestone regression (ULLAH et al., 2022). In contrast, the adult form of AxD tends to have milder symptoms and a longer survival period, often manifesting as spastic gait, cerebellar ataxia, and spinal cord atrophy (ANIS et al., 2023). Clinical presentation and prognosis vary significantly between these subtypes, with age at onset playing a crucial role in determining disease severity and progression.

The pathophysiology is intrinsically linked to mutations in the GFAP (glial fibrillary acidic protein) gene, located on chromosome 17q21.31, which encodes the glial fibrillary acidic protein. This protein is a main component of the cytoskeleton of glial cells, particularly astrocytes, playing a crucial role in maintaining the homeostatic environment of the central nervous system and in the formation and maintenance of myelin, which coats and protects neuron axons (PAJARES et al., 2023). However, mutations in the GFAP gene result in the production of anomalous proteins, which accumulate within astrocytes in the form of inclusions known as "Rosenthal fibers". These fibers are eosinophilic bodies, containing misfolded proteins and other cellular components, and are considered a hallmark of Alexander disease (HAGEMANN, 2022).

The accumulation of Rosenthal fibers leads to dysfunction of astrocytes, compromising their ability to support neurons and maintain the integrity of the blood-brain barrier. This astrocytic dysfunction results in a series of pathological events, including inflammation, oxidative stress, and degeneration of the brain's white matter. Continuous cellular stress in astrocytes causes the activation of inflammatory responses that exacerbate the destruction of myelin, the protective layer that surrounds neuronal axons (HAGEMANN, 2022).

Radiologically, the disease presents characteristics such as frontalization, lateral ventricle contrast enhancement, atrophy and dilation of the ventricles, abnormalities in the corpus callosum and changes in brain chemistry detected by magnetic resonance spectroscopy (MRS) (MESSING, 2018).

Analyze and synthesize the available scientific evidence on the role of mutant GFAP (glial fibrillary acidic protein) proteins in the pathogenesis of Alexander disease.

METHOD

This is an integrative review of the literature that addresses the role of mutant GAFAP proteins in the pathogenesis of Alexander disease.

To prepare the study, the sequence of steps proposed by Mendes, Silveira and Galvão was followed: formulation of the theme, establishment of criteria for inclusion and exclusion of studies, definition of information to be extracted from selected studies, evaluation of studies, interpretation of results and synthesis of knowledge.

During the formulation of the study, the following guiding question was developed: What are the functions of mutant GFAP proteins in the pathogenesis of Alexander disease? To prepare this question, the PICo strategy was used, which consists of the following steps: P - Problem or target population; I - Intervention or phenomenon of interest; Co - Context.

ACRONYM	DESCRIPTORS
P	Mutant GFAP proteins
I	Pathogenesis
Co	Alexander disease

Searches were carried out in virtual databases, including the Virtual Health Library (VHL), Medical Literature Analysis and Retrieval System Online (MEDLINE), National Library of Medicine/PubMed and SciELO. The descriptors used were "Alexander's Disease", "Mutant Protein", "Pathogenesis", "Rare Diseases" and "Glial Fibrillar Acid Protein", combined with the Boolean operators OR / AND. To establish inclusion and exclusion criteria, articles that were not related to the topic discussed were discarded, as well as course completion works, theses and dissertations. The selection of articles was carried out by reading the articles in the databases and selecting 10 articles for analysis. Therefore, a synthesis of knowledge was carried out, analyzing the main results of the analysis of the articles included in the study.

RESULTS

Of the selected articles, the majority were cross-sectional. Articles with research on populations in America, Europe and Asia.

The articles reviewed discuss the effects of mutations in the GFAP gene, which result in changes in the structure and organization of GFAP intermediate filaments. The findings suggest that GFAP toxicity is a multifaceted process, influenced by several factors, including the type of mutation in the GFAP gene, the cellular environment, and interactions with other proteins.

Articles on Alexander disease have adopted a variety of methods to investigate the effects of mutations in the GFAP gene and their cellular and clinical implications. These approaches have included genetic analysis through sequencing of the GFAP gene to identify specific mutations linked to the disease. In vitro studies were conducted using cell lines transfected with constructs containing mutations in GFAP, allowing the assessment of impacts on the structure, organization and function of intermediate filaments. Microscopy, such as electron and fluorescence, was employed to visualize the morphology and distribution of GFAP intermediate filaments in affected cells. Detailed biochemical assays, including solubility, oxidation, and protein-protein interaction analyses, were performed to investigate the properties and behavior of the mutant GFAP proteins.

Furthermore, neuropathological studies have been conducted using brain tissue samples obtained by biopsy or autopsy, allowing detailed evaluation of histopathological findings, such as the presence of Rosenthal bodies. Advanced imaging techniques, such as magnetic resonance imaging, have been employed to characterize the radiological patterns associated with Alexander disease.

Records identified in Databases/ Libraries/ Search Engines (n=100 publications)

Registration after removing duplicates and reading titles and abstracts (n=47 publications)

Full articles assessed for eligibility (n=21 publications)

Studies Included (n=8)

Figure 1: Process of identification, selection, eligibility and inclusion of articles

Source: Written by the author

DISCUSSION

The reviewed articles present converging results on the effects of mutations in the GFAP gene, responsible for Alexander disease. In general, studies demonstrate that mutations in GFAP cause changes in the structure and organization of GFAP intermediate filaments, leading to an abnormal accumulation and aggregation of this protein in astroglial cells. These pathological modifications of GFAP are associated with mitochondrial dysfunction, oxidative stress, and altered distribution of organelles in cells, contributing to the pathophysiology of Alexander disease. Furthermore, some articles report new clinical phenotypes, such as partial epilepsy continua, associated with specific mutations in GFAP.

The article, titled "Effects of Alexander disease–associated mutations on the assembly and dynamics of GFAP," indicates that mutations in GFAP compromise the ability of this protein to organize properly into intermediate filaments, essential for maintaining cellular structure and functionality. astrocytes. Specifically, the mutations cause difficulties in the correct assembly of these filaments, leading to the formation of toxic aggregates known as Rosenthal fibers, a distinctive feature of Alexander disease. The researchers used mouse models and cells derived from patients with Alexander disease to demonstrate that the mutations lead to an abnormal accumulation of GFAP, resulting in cellular toxicity and astrocyte dysfunction, exacerbating neurodegeneration. Thus, the article emphasizes that mutations profoundly alter GFAP dynamics, initiating a cycle of stress and cellular damage that culminates in significant neurodegeneration.

E2's article elucidated that the mutant GFAP conglomerate leads to the genesis of Rosenthal fibers, thus disrupting the cytoskeleton of astrocytes. This results in reduced cell proliferation, increasing cell

IDENTIFICATION	ARTICLE	AUTHOR	LOCATION OF STUDY, YEAR	OBJECTIVE
E1	Effects of Alexander disease–associated mutations on the assembly and organization of GFAP intermediate filaments	Ai-Wen Yang, Ni-Hsuan Lin, Ting-Hung Yeh, Natasha Snider, e Ming-Der Perng.	Taiwan, 2022	To investigate how mutations located in the GFAP rod domain affect in vitro filament assembly
E2	Mutations in GFAP Disrupt the Distribution and Function of Organelles in Human Astrocytes	Jeffrey R. Jones, Linghai Kong, Michael G. Hanna, IV, Brianna Hoffman, Robert Krencik, Robert Bradley, Tracy Hagemann, Jeea Choi, Matthew Doers, Marina Dubovis, Mohammad Amin Sherafat, Anita Bhattacharyya, Christina Kendziorski, Anjon Audhya, Albee Messing, and Su-Chun_Zhang	University of Wisconsin-Madison, Madison, WI 53706, USA, 2018	To study the structure function relationship of GFAP on astrocytes using Alexander disease patient-derived induced pluripotent stem cells.
E3	Alexander-disease mutation of GFAP causes filament disorganization and decreased solubility of GFAP	Victoria C Hsiao, Rujin Tian, Heather Long, Ming Der Perng, Michael Brenner, Roy A Quinlan, James E Goldman	Department of Pathology and the Center for Neurobiology and Behavior, Columbia University, New York, NY 10032, USA. 2005	To understand of the effects of these mutations on GFAP polymerization and organization
E4	Glial fibrillary acidic protein is pathologically modified in Alexander disease	Ni-Hsuan Lin, Wan-Syuan Jian, Natasha Snider, Ming-Der Perng	National Tsing Hua University, Hsinchu, Taiwan. 2024	To describe pathological events potentially involved in the disease pathogenesis of Alexander disease (AxD).
E5	Refining the concept of GFAP toxicity in Alexander disease	Albee Messing	Department of Pathology and the Center for Neurobiology and Behavior, Columbia University, New York, NY 10032, USA. 2019	To stress the broader concept that the initiating event in disease pathogenesis must be mutant GFAP, and that this occurs prior to any change in levels. Any subsequent rise in total GFAP would then act to exacerbate the disease process.
E6	Alexander disease GFAP R239C mutant shows increased susceptibility to lipoxidation and elicits mitochondrial dysfunction and oxidative stress.	Álvaro Viedma-Poyatos, Patricia González-Jiménez, María A Pajares, Dolores Pérez-Sala	Department of Structural and Chemical Biology, Centro de Investigaciones Biológicas Margarita Salas, C.S.I.C., 28040, Madrid, Spain. 2022	To investigate whether an increased susceptibility of GFAP AxC mutants to oxidative and/or lipoxidative modifications could contribute to the pathogenesis of AxD.
E7	NG2 and GFAP co-expression after differentiation in cells transfected with mutant GFAP and in undifferentiated glioma cells.	U Gómez-Pinedo, S Sirerol-Piquer, M Durán-Moreno, J A Matias-Guiu, J A Barcia, J M García-Verdugo, J Matias-Guiu	Neurobiology Laboratory, Neuroscience Institute, IdISSC, San Carlos Clinical Hospital, Complutense University of Madrid, Madrid, Spain. 2017	To determine the effect of molecular marker mutations in comparison to undifferentiated glioma cells simultaneously expressing GFAP and NG2.
E8	Alexander Disease: A novel mutation in GFAP leading to epilepsia partialis continua	Daniel J. Bonthius, and Bahri Karacay.	Division of Child Neurology, Department of Pediatrics, University of Iowa, Iowa City, IA 52242, USA.2015	To describe a novel GFAP mutation associated with a previously undescribed clinical problem – epilepsia partialis continua.

Table 1: Synthesis of information extracted from selected articles

IDENTIFICATION	PREVALENCE IN THE SAMPLE
E1	Whereas the internal rod mutants assembled into filaments that were shorter than those of wild type, the rod end mutants formed structures with one or more of several atypical characteristics, including short filament length, irregular width, roughness of filament surface, and filament aggregation. When transduced into primary astrocytes, GFAP mutants with in vitro assembly defects usually formed cytoplasmic aggregates, which were more resistant to biochemical extraction. The resistance of GFAP to solubilization was also observed in brain tissues of patients with Alexander disease, in which a significant proportion of insoluble GFAP were accumulated in Rosenthal fiber fractions. These findings provide clinically relevant evidence that link GFAP assembly defects to disease pathology at the tissue level and suggest that altered filament assembly and properties as a result of GFAP mutation are critical initiating factors for the pathogenesis of Alexander disease.
E2	AxD astrocytes displayed GFAP aggregates, recapitulating the pathological hallmark of AxD. RNA sequencing implicated the endoplasmic reticulum, vesicle regulation, and cellular metabolism. Corroborating this analysis, we observed enlarged and heterogeneous morphology coupled with perinuclear localization of endoplasmic reticulum and lysosomes in AxD astrocytes. Functionally, AxD astrocytes showed impaired extracellular ATP release, which is responsible for attenuated calcium wave propagation. These results reveal that AxD-causing mutations in GFAP disrupt intracellular vesicle regulation and impair astrocyte secretion, resulting in astrocyte dysfunction and AxD pathogenesis.
E3	In SW13Vim$^-$ cells, which have no endogenous cytoplasmic intermediate filaments, wild-type human GFAP frequently formed filamentous bundles, whereas the R239C GFAP formed `diffuse' and irregular patterns. Filamentous bundles of R239C GFAP were sometimes formed in SW13Vim$^-$ cells when wild-type GFAP was co-transfected. Although the presence of a suitable coassembly partner (vimentin or GFAP) reduced the potential negative effects of the R239C mutation on GFAP network formation, the mutation affected the stability of GFAP in cells in a dominant fashion. Extraction of transfected SW13Vim$^-$ cells with Triton-X-100-containing buffers showed that the mutant GFAP was more resistant to solubilization at elevated KCl concentrations. Both wild-type and R239C GFAP assembled into 10 nm filaments with similar morphology in vitro. Thus, although the R239C mutation does not appear to affect filament formation per se, the mutation alters the normal solubility and organization of GFAP networks.
E4	To found high molecular weight GFAP species in the RFs of AxD brains, indicating abnormal GFAP crosslinking as a prominent pathological feature of this disease. In vitro and cell-based studies demonstrate that cystine-generating mutations promote GFAP crosslinking by cysteine-dependent oxidation, resulting in defective GFAP assembly and decreased filament solubility. Moreover, we found GFAP was ubiquitinated in Rosenthal fibers of AxD patients and rodent models, supporting this modification as a critical factor linked to GFAP aggregation. Finally, we found that arginine could increase the solubility of aggregation-prone mutant GFAP by decreasing its ubiquitination and aggregation. Our study suggests a series of pathogenic events leading to AxD, involving interplay between GFAP aggregation and abnormal modifications by GFAP ubiquitination and oxidation
E5	In addition to the sequence variants that represent the origin of disease, GFAP accumulation also takes place, together leading to a gain-of-function that has sometimes been referred to as "GFAP toxicity." Whether the nature of GFAP toxicity in patients, who have mixtures of both mutant and normal protein, is the same as that produced by simple GFAP excess, is not yet clear.
E6	To show that GFAP R239C expression induces a more oxidized cellular status, with decreased free thiol content and increased mitochondrial superoxide generation. In addition, mitochondria show decreased mass, increased colocalization with GFAP and altered morphology. Notably, a GFP-GFAP R239H mutant recapitulates R239C-elicited alterations whereas an R239G mutant induces a milder phenotype. Together, our results outline a deleterious cycle involving altered GFAP R239C organization, mitochondrial dysfunction, oxidative stress, and further GFAP R239C protein damage and network disruption, which could contribute to astrocyte derangement in Alexander disease.
E7	Both the cells transfected with GFAP mutations and GBM cells showed increased NG2 and GFAP expression. However, expression of caspase-3-positive cells was found to be considerably higher in transfected cells than in GBM cells.
E8	Genetic analysis revealed a heterozygous point mutation in exon 6 of the GFAP gene. The guanine-to-adenine change causes substitution of the normal glutamic acid codon (GAG) with a mutant lysine codon (AAG) at position 312 (E312K mutation). At the age of four years, the child developed epilepsia partialis continua, consisting of unabating motor seizures involving the unilateral perioral muscles. Epilepsia partialis continua has not previously been reported in association with Alexander disease. Whether and how the E312K mutation produces pathologic changes and clinical signs that are unique from other Alexander disease-inducing mutations in GFAP remain to be determined.

Table 2: Synthesis of information extracted from selected articles

Source: Author

mortality and impacting proteasomal activity. These genetic changes culminate in the accumulation of GFAP and trigger autophagy through the p38/MAPK and mTOR pathways to eliminate aggregated proteins. Astrocytes harboring GFAP mutations exhibit irregularities in the endoplasmic reticulum and lysosomal structure, as well as influencing mitochondrial transfer and CD38 expression, essential for mitochondrial operation and metabolic energy. Mutant GFAP also hinders crucial astrocytic functions, such as ATP secretion and the ability to regulate glutamate, compromising intercellular communication and exerting detrimental effects on neurons. Furthermore, these mutations prevent the propagation and myelination of oligodendrocyte precursor cells, contributing to the leukodystrophy characteristic of Alexander disease, as well as compromising the integrity of the white matter and blood-brain barrier, resulting in demyelination and barrier malfunction.

The article "Alexander-disease mutation of GFAP causes filament disorganization and decreased solubility of GFAP" describes analysis of the most common Alexander disease mutation, R239C, in cultured cells. Expression of mutant GFAP in primary astrocyte cells and Cos-7 cells showed that the mutant was incorporated into filament networks together with endogenous GFAP and vimentin. However, in SW13Vim(-) cells lacking intermediate filaments, the mutant GFAP formed irregular, diffuse patterns rather than filamentous bundles. Although the presence of a suitable coassembly partner (vimentin or GFAP) reduced the negative effects of the mutation, the stability of GFAP was dominantly affected. Extraction of cells transfected with Triton-X-100 showed that mutant GFAP was more insoluble than wild-type GFAP. These results suggest that the R239C mutation does not affect filament formation per se, but alters the organization and normal solubility of GFAP.

The article "Glial fibrillary acidic protein is pathologically modified in Alexander disease" describes pathological events involved in the pathogenesis of Alexander disease. The disease is characterized by the abundance of protein aggregates in astrocytes, which leads to the progressive destruction of the white matter of the brain and the formation of Rosenthal fibers. These aggregates are composed of glial proteins, including glial fibrillary acidic protein (GFAP), which is predominantly expressed in astrocytes. Genetic analysis revealed that mutations in the GFAP gene are responsible for the disease, with 42 coding changes associated with Alexander disease, involving 31 different sites on the protein. Furthermore, expression of the mutant protein in cultured astrocytes demonstrated that it compromises the glutamate transporter, contributing to neuronal and oligodendroitic degeneration.

Article E5 argues that GFAP toxicity may not be a simple process, but rather a multifaceted phenomenon with different underlying mechanisms. Through analyzes of cellular and animal models, the study demonstrates that GFAP toxicity can be influenced by several factors, including the type of mutation in the GFAP gene, the cellular environment and the interaction with other proteins. The results suggest that the mutant form of GFAP may have deleterious effects on cells, leading to neuronal dysfunction and cell death. In the discussion, the authors propose a more refined model of GFAP toxicity in Alexander Disease. This model considers the complex interaction between the mutant protein, the cellular environment and other pathogenic factors.

According to article E6, the Alexander disease GFAP R239C mutant presents greater susceptibility to lipoxidation and induces

mitochondrial dysfunction and oxidative stress in a cellular model of the disease. Specifically, the GFAP R239C mutant appears more oxidized than the wild type under normal conditions, with less accessibility of cysteine residues and a greater presence of oligomers linked by disulfide bonds. Furthermore, GFAP R239C undergoes lipoxidation to a greater extent than wild-type GFAP upon treatment with the electrophilic mediator 15-deoxy-Δ12,14-prostaglandin J2. This greater susceptibility to oxidation and lipoxidation of the GFAP R239C mutant leads to changes in the organization of GFAP filaments, which are exacerbated in the presence of oxidants and electrophilic compounds. Furthermore, the expression of GFAP R239C induces a more oxidized cellular state, with a decrease in the content of free thiols and an increase in the generation of mitochondrial superoxide, in addition to changes in mitochondrial morphology and function. These results suggest that oxidative damage caused by this GFAP mutant may contribute to the changes in astrocytes characteristic of Alexander disease.

The article "NG2 and GFAP co-expression after differentiation in cells transfected with mutant GFAP and in undifferentiated glioma cells" presents results demonstrating the co-expression of NG2 and GFAP proteins in cells transfected with mutations in the GFAP gene and in glioblastoma multiforme cells (GBM) undifferentiated. During differentiation, GFAP expression increases significantly in all cells, including those transfected with the mutant gene and GBM cells.

Furthermore, NG2 expression also increases during differentiation, although it is more intense in cells transfected with the mutant gene than in GBM cells. These findings suggest that co-expression of NG2 and GFAP is a common pattern in glial cells, regardless of the presence of mutations in the GFAP gene. This is important for understanding the pathogenesis of Alexander disease, a rare disease caused by mutations in the GFAP gene encoding glial fibrillary acidic protein (GFAP).

The article "Alexander Disease: A novel mutation in GFAP leading to epilepsia partialis continua" describes a case of Alexander disease, a rare and progressive genetic disease that affects the central nervous system. The disease is caused by mutations in the glial fibrillary acidic protein (GFAP) gene, which codes for glial fibrillary acidic protein (GFAP). The case presented is a boy with developmental delay and hypertonia who developed partial epilepsy continua, a type of epilepsy characterized by involuntary motor seizures. Genetic analysis revealed a heterozygous mutation in exon 6 of the GFAP gene, which causes a glutamic to lysine substitution at amino acid 312. This mutation was associated with Alexander disease with a new phenotype, characterized by epilepsy partialis continua. The diagnosis was confirmed by radiological and neuropathological findings, including the presence of Rosenthal bodies in astroglial cells.

In summary, the articles reviewed present the effects of mutations in the GFAP gene. These mutations cause changes in the structure and organization of GFAP intermediate filaments, leading to an abnormal accumulation and aggregation of this protein in astroglial cells. Furthermore, mutations compromise the ability of astrocytes to remain healthy and functional, contributing to the pathophysiology of the disease. The findings suggest that GFAP toxicity is a multifaceted process, influenced by several factors, including the type of mutation in the GFAP gene, the cellular environment and the interaction with other proteins.

FINAL CONSIDERATIONS

Understanding the function of mutated GFAP proteins in Alexander disease signifies a remarkable progression in the field of clinical neuroscience. This research has drawn attention to the intricate molecular pathways that underlie the development of the disease. Meticulous analysis of structural and functional changes in mutated GFAP proteins provides valuable insights into diagnostic and therapeutic hurdles related to Alexander disease. Therefore, further scientific exploration targeting these proteins is critical to improving the well-being of affected individuals and instilling optimism for the advancement of effective treatments in the coming days.

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