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NEUROIMAGING ASPECTS IN AICARDI-GOUTIÈRES SYNDROME: AN INTEGRATIVE REVIEW

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Abstract: Objective: To investigate and synthesize neuroimaging findings in Aicardi Syndrome, with the aim of providing a comprehensive understanding of the brain structural features observed in this condition. 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: "Aicardi Syndrome", "Neuroimaging", "Neurology" and "Rare diseases". Combined with the Boolean operators OR / AND. Results: The selected studies highlight significant brain changes in Aicardi-Goutières Syndrome (GAS), such as agenesis of the corpus callosum, nodular heterotopies, polymicrogyria and intracranial cysts. Prenatal characteristics were identified, such as cortical malformations and optic nerve coloboma, differentiating GAS from other conditions. Another showed seizures, severe intellectual disability and frequent visual problems. It also revealed early epileptic seizures and basal ganglia dysmorphisms. Furthermore, he highlighted new discoveries such as frontal polymicrogyria and enlargement of the thalamus, suggesting the diagnosis of GAS through the combination of these radiological characteristics. Conclusion: Neuroimaging is essential in the management of Aicardi-Goutières Syndrome (GAS), allowing diagnosis and monitoring through the identification of specific brain characteristics, such as calcifications, atrophy and white matter abnormalities. Furthermore, it helps to understand the mechanisms of the disease, reflecting inflammatory and neurodegenerative processes. Despite the challenges, new techniques promise advances in the understanding of GAS, offering opportunities for research and more effective therapies, highlighting the importance of neuroimaging to improve patients' care and quality of life.

Keywords: Aicardi Syndrome, Neuroimaging, Neurology and Rare diseases.

INTRODUCTION

Aicardi-Goutières syndrome (GAS) is a rare, genetically heterogeneous encephalopathy, often caused by autosomal recessive transmission (DELL'ISOLA et al., 2023). It was first described in 1965 by French neurologist Dr. Jean Aicardi. He identified and characterized this rare syndrome by observing a group of patients who presented with a specific triad of symptoms: agenesis of the corpus callosum, infantile spasms (a specific type of seizure), and chorioretinal anomalies. This unique combination of clinical manifestations allowed Aicardi to identify the syndrome as a distinct entity. Since then, Aicardi Syndrome has been widely recognized as a condition that mainly affects girls, with few cases reported in boys, often associated with genetic mosaicism or chromosomal abnormalities (LIMNAIOS et al., 1979).

The prevalence of Aicardi syndrome varies globally, with estimated transfer rates of 1 per 105,000 births in the United States, 1 per 93,000 in the Netherlands, 0.63 per 100,000 women in Norway, and a worldwide prevalence of several thousand cases. A study in Sweden found 18 cases of Aicardi syndrome in girls born between 1975 and 2002, with a prevalence rate ranging from 2 to 15 per 100,000 girls. A syndrome predominantly affects females, with males typically not surviving to term due to their X-linked dominant inheritance pattern. When it affects males, they typically do not survive to term due to the X-linked dominant inheritance pattern of the syndrome. In these cases, the patient may present a 47XXY karyotype

(chromosomal anomaly also associated with Klinefelter syndrome) or continue with 46 chromosomes, which generally results in lethality. More than 4,000 cases of SA are known worldwide. The average survival age, even in the most affected individuals, is 16 years, whereas in the past it was only 6 years. The probability of an individual surviving to 27 years of age is 0.62%, with 49 years being the longest reported life span of an individual with a mild form of the syndrome (DE OLIVEIRA MENEZES et al., 2018)

The GAS is marked by the presence of total or partial corpus, agenesis of the corpus callosum (CC), chorioretinal lacunae, and infantile spasms. Over time, imaging exams better demonstrated the neuroradiological phenotype of the syndrome, which manifests with the concomitant presence of multiple surgical malformations, such as nodular heterotopies polymicrogyria and intracranial cysts. Clinical manifestations vary according to the severity and extent of the malformations, and may appear late. The clinical presentation may include seizures, delayed neuropsychomotor development, motor deficits and sensory changes (LIEB JM et. al., 2018).

Neuroimaging plays a crucial role in the diagnosis of Aicardi Syndrome, providing valuable information about the structural characteristics of the brain and identifying typical anomalies of the disease. Techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) are essential for visualizing brain structures and detecting specific abnormalities indicative of the syndrome. MRI allows detailed visualization of brain structures, including the affected skull, which can be identified using MRI. CT can also reveal other brain abnormalities associated with the syndrome, such as poncephalic cysts and changes in the branchial substance. In addition to structural imaging techniques, optical examinations are important for the diagnosis of Aicardi Syndrome, as ocular anomalies, such as chorioretinal gaps, are clinically distinct characteristics of the disease (VENKATESAN et al., 2022).

Investigate and synthesize neuroimaging findings in Aicardi Syndrome, with the aim of providing a comprehensive understanding of the brain structural features observed in this condition.

METHOD

This is an integrative review of the literature that addresses aspects of neuroimaging in Aicardi syndrome.

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 created: What are the main neuroimaging changes in Aicardi Syndrome? 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	Aicardi syndrome
I	Neuroimaging
Co	Neurological aspects

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 "Aicardi Syndrome", "Neuroimaging", "Neurology" and

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"Rare Diseases", 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 6 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. Between brain anomalies and Aicardi Syndrome, studies report the presence of dysgenesis of the corpus callosum, anterior polymicrogyria, periventricular heterotopies with a predilection for the body of the lateral ventricle and cerebral asymmetry in all patients. In relation to new characteristics, dysmorphisms of the basal ganglia were presented.

In the studies, magnetic resonance imaging (MRI) and computed tomography (CT) of the brain were used, without contrast. The most used neuroimaging equipment was MRI, with sagittal images in T1 and axial images in T1 and T2, considered an imaging test to observe brain changes with greater precision.

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

Registration after removing duplicates and reading titles and abstracts (n=21 publications)

Full articles assessed for eligibility (n=14 publications)

Included studies (n=4)

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

Source: Elaborated by the author

DISCUSSION

In the results of the selected studies, the significant alteration of the brain in aicardi-goutières syndrome is clearly evident. Research shows that in all cases of GAS there is agenesis of the corpus callosum, nodular heterotopies, polymicrogyria and intracranial cysts.

The E1 study used intrauterine magnetic resonance imaging (iuMRI) to investigate the prenatal features of Aicardi syndrome (AIC) in 10 confirmed cases and compare them with 12 similar cases (SAG). All fetuses with SAG presented diffuse cortical malformations, nodular heterotopies, posterior fundus abnormalities and optic nerve coloboma, differing significantly from SAG in terms of ventriculomegaly, cerebral asymmetry, intracranial cysts and cerebellar malformations. Statistical analysis identified predictive variables such as cortical malformations, coloboma and female sex, concluding that iuMRI is a valuable tool for the prenatal diagnosis of GAS, allowing the detection of specific characteristics of the syndrome and differentiating it from similar fetal conditions.

Aicardi-Goutières Syndrome, marked by a unique set of characteristics, manifests itself in individuals with seizures, intellectual disability and brain malformations, according to study E2. In the case of seizures, present in more than 95% of cases, they generally begin with infantile spasms in the first months of life, evolving into other types over time. In intellectual disability, ranging from severe to profound, it is a universal aspect of the syndrome. Brain malformations, including agenesis of the corpus callosum, heterotopies, and cysts, are present in 100% of patients. Regarding visual problems, they are also common: chorioretinal gaps, present in all cases, can affect vision, especially if they involve the macula, and can be bilateral or unilateral. Optic nerve abnormalities such as

IDENTIFICATION	ARTICLE	AUTHOR	PLACE OF STUDY, YEAR	GOAL
E1	Aicardi Syndrome: Key Fetal MRI Features and Prenatal Differential Diagnosis	Silvia Masnada, Doneda Chiara‡, Izzo Giana‡, Formica Manuela, Scarabello Marco, Accogli Andrea, Accorsi Patrizia, Bahi-Buisson Nadia, Capra Valeria, Cavallin Mara, Dalla Bernardina Bernardo, Darra Francesca, De Giorgis Valentina, Fazzi Elisa, Fontanillas R. L. Miguel, Fusco Carlo, Giordano Lucio, Orcesi Simona, Pinelli Lorenzo, Rebessi Erika, Romeo Antonino, Severino Mariasavina, Spagnoli Carlotta, Veggiotti Pierangelo, Pichiecchio Anna, Righini Andrea, Parazzini Cecilia	"Vittore Buzzi" Children's Hospital, 2020	To investigate prenatal findings in Aicardi syndrome (AGS) by intrauterine magnetic resonance imaging (iuMRI) suggesting possible diagnostic criteria and differential diagnosis.
E2	Aicardi Syndrome	V Reid Sutton, Ignatia B Van den Veyver Margaret P Adam, Jerry Feldman, Ghayda M Mirzaa, Roberta A Pagon, Stephanie E Wallace, Lora JH Bean, Karen W Gripp, Anne Amemiya, editors	Universidade de Washington, Seattle, 2020	Identify the clinical, genetic and neuroimaging characteristics of Aicardi-Goutières Syndrome
E3	Basal Ganglia Dysmorphism in Patients with Aicardi Syndrome	Pierangelo Veggiotti	Centros da Itália, França, Suíça, Dinamarca e Alemanha; 2021	To detect associations between neuroradiological and EEG assessments and long-term clinical outcome, in order to detect possible prognostic factors, we performed a detailed clinical and neuroimaging characterization of 67 cases of Aicardi syndrome (GAS), collected through a multicenter collaboration.
E4	Neuroimaging Aspects of Aicardi Syndrome	Bobbi Hopkins, V. Reid Sutton, Richard Alan Lewis, Ignatia Van den Veyver and Gary Clark	Departamento de Pediatria, Baylor College of Medicine, Houston, TX EUA	Provide a detailed study of the prevalence of previously identified developmental brain abnormalities and identify new manifestations.

Table 1: Synthesis of information extracted from selected articles

IDENTIFICATION	PREVALENCE IN THE SAMPLE
E1	In all cases of SAG, iuMRI was able to detect CC agenesis-dysgenesis and developmental anomalies. Postnatal MRI revealed some additional findings, mainly including other cystic lesions and in two cases small coloboma. A statistically significant difference between SAG and SAG mimic was found in relation to sex, nodular heterotopies, posterior fossa abnormalities, coloboma, and cortical rotation abnormalities. The most predictive variables in the logistic regression model were cortical rotation abnormalities, coloboma and sex.
E2	The prevalence of features in people with Aicardi syndrome is significant. More than 95% of these people experience seizures, with infantile spasms being common in the first months of life, followed by other types of seizures over time. All those affected have some degree of intellectual disability or developmental delay, ranging from severe to profound. Furthermore, 100% of people with Aicardi syndrome have brain malformations, such as agenesis of the corpus callosum, heterotopies, and cysts. Chorioretinal lacunae, present in all cases, can affect vision, especially if they involve the macula, and can be bilateral or unilateral. Optic nerve abnormalities, such as colobomas and hypoplasia, are observed in more than 90% of cases, contributing to possible vision problems.

E3	Patients had early-onset epilepsy that progressed to drug-resistant seizures. GAS has a variable clinical course, leading to permanent disability in most cases; however, some cases showed residual motor skills. Chorioretinal lacunae were present in 86.56% of our patients. Statistical analysis revealed correlations between MRI, EEG at baseline, and clinical outcome. On brain imaging, 100% of patients had corpus callosum malformations, 98% had cortical dysplasia and nodular heterotopies, and 96.36% had intracranial cysts (with similar rates of 2b and 2d). In addition to demonstrating that posterior fossa abnormalities (found in 63.63% of cases) must also be considered a common feature in GAS, our study highlighted the presence (in 76.36%) of basal ganglia dysmorphisms (never previously reported).
E4	All patients presented polymicrogyria, predominantly frontal and perisylvian, and frequently associated with subopercular hypoperculation. Periventricular nodular heterotopies, present in all patients, were more frequent than previously reported; 10 had single intracranial cysts and 11 had multiple. Posterior fundus abnormalities were also more frequent than previously described. Cerebellar abnormalities were noted in 95% of studies in which they could be assessed. As an unprecedented finding, we noticed enlargement of the thalamus in 10 patients. As cases of mildly affected girls with variable callosal dysgenesis have now been reported, the combination of frontal-dominant and perisylvian polymicrogyria, periventricular nodular heterotopies, intracranial cysts, and posterior fundal abnormalities, including enlargement of the thalamus, must suggest consideration of the diagnosis of Aicardi syndrome. We further propose that improved characterization of the neurological phenotype will benefit the selection of candidate genes for mutation analysis.

Table 2: Synthesis of information extracted from selected articles

Source: Author

coloboma and hypoplasia, seen in more than 90% of cases, also contribute to possible vision problems.

The in-depth E3 study reveals that GAS begins early with refractory epileptic seizures, but has a variable clinical course. Key radiological features include corpus callosum malformations, cortical dysplasia, nodular heterotopies, intracranial cysts, and posterior fossa abnormalities. An unprecedented finding is the presence of basal ganglia dysmorphisms, which may be related to the neurological deficits observed. Statistical analysis demonstrates correlations between radiological characteristics and patients' clinical outcome. This study contributes to a better understanding of AIC, reinforcing the importance of comprehensive clinical and radiological evaluation for the accurate diagnosis and adequate management of the disease. The discovery of basal ganglia dysmorphisms opens new perspectives for research and therapies, and the heterogeneity of GAS highlights the need for an individualized assessment of each patient.

According to article E4, seizures, present in more than 95% of cases, generally begin with infantile spasms in the first months of life, evolving into other types over time. Intellectual disability, ranging from severe to profound, is a universal aspect of the syndrome. Brain malformations, including agenesis of the corpus callosum, heterotopies and cysts, are present in 100% of patients. However, there were new discoveries such as polymicrogyria in which all patients presented polymicrogyria, predominantly frontal and perisylvian, and often associated with subopercular hypoperculation. Nodular heterotopies: periventricular nodular heterotopies, present in all patients, were more frequent than previously reported. Intracranial cysts, ten patients had single intracranial cysts and eleven had multiple. Posterior fundus abnormalities were more frequent than those previously described. The enlargement of the thalamus as an unprecedented finding, enlargement of the thalamus was noted in 10 patients. The combination of frontal-dominant and perisylvian polymicrogyria, periventricular nodular heterotopies, intracranial cysts, and posterior fundal abnormalities, including enlargement of the thalamus, must suggest consideration of the diagnosis of Aicardi syndrome.

FINAL CONSIDERATIONS

Neuroimaging plays an indispensable role in the management of Aicardi-Goutières Syndrome (GAS), a rare genetic disease characterized by neuroinflammation and severe neurological dysfunction. Brain magnetic resonance imaging (MRI), as the main diagnostic tool, allows the identification of intracranial calcifications, cerebral atrophy, leukoencephalopathy and white matter anomalies, helping to differentiate GAS from other neurological diseases. In addition to the initial diagnosis, neuroimaging techniques are essential for monitoring disease progression, providing information on the effectiveness of therapeutic interventions and the natural course of GAS. Neuroimaging studies have been crucial for understanding the underlying pathophysiological mechanisms, reflecting inflammatory and neurodegenerative processes and opening possibilities for new research into biomarkers and therapeutic targets. Despite advances, challenges such as the variability of clinical presentations and the need for sedation in young children persist, making early and frequent diagnosis difficult. The development of new imaging techniques, such as fMRI and MRS, promises to improve understanding of GAS, revealing new aspects of the disease not visible with conventional methods. In short, neuroimaging not only enriches the understanding of GAS, but is also crucial for providing more accurate and effective care, improving patients' quality of life.

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