Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 04/02/2024
Approved on: 05/16/2024

ORIGINAL ARTICLE

Application and Evaluation of a Clinical Protocol for Epilepsies Without Etiological Diagnosis: Case Series

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Keywords:
Epilepsy,
Seizures,
Clinical protocols,
Pediatrics.

Abstract

Objective: To establish the genetic etiology as the cause of epilepsy that is refractory to treatment and associated with delayed neuropsychomotor development. **Methods:** Retrospective case series study, with data collection through review of medical records, including children aged 0 to 10 years who were hospitalized in pediatric units or followed on an outpatient basis and who, obligatorily, underwent genetic evaluation due to seizures. **Results:** Nine patients in whom the protocol was applied were selected, one pathogenic and two probable pathogenic genetic variants were found. **Conclusion:** It was possible to further investigate cases of epilepsy without a defined etiology and establish appropriate treatment and genetic counseling.

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Resid Pediatr. 2025;15(2).
DOI: 10.25060/residpediatr-2025.v15n2-1270

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INTRODUCTION

Epilepsy is a complex brain disorder characterized by neurons that exhibit repeated abnormal, excessive, and synchronous electrical discharges in the brain[1]. Episodes can last from seconds to minutes, affecting either a specific part of the brain and remaining restricted to that region, or spreading to other areas of the brain[2]. The diagnostic framework developed by the International League Against Epilepsy (ILAE) categorizes the disorder into three levels, considering investigative findings related to patient-specific pathophysiology, and concludes with exploring possible etiologies while considering comorbidities.

Each level necessitates additional layers of diagnostic information and resources. Diagnosis should be established whenever feasible based on findings from all three levels. The first level involves confirming whether seizures are epileptic and ruling out non-epileptic paroxysmal events.

The type of epilepsy (generalized, focal, generalized and focal, or unknown) is defined at the second level. Seizures originating from a region encompassing a network and extending bilaterally are described as generalized. Seizures that affect one cerebral hemisphere, as observed in an electroencephalogram (EEG) or based on symptoms and generally confined to a subcortical network, are referred to as focal. Seizures can also be generalized and focal, as long as they present with both forms described above. Characterization occurs through clinical investigation, alongside electroencephalogram findings. At the third level, the diagnosis of an epileptic syndrome relies on clinical, EEG, and imaging findings. Some seizures manifest at a specific age, have a well-defined etiology, and consequently, a predictable prognosis. Additionally, many epileptic syndromes are distinct enough to be identified through multilevel investigation, such as West and Dravet syndromes and childhood absence epilepsy[3].

When investigating the etiology of epilepsy, one encounters structural, genetic, infectious, metabolic, immunological, or unknown causes. Infectious etiology is the most common worldwide. Structural origins are demonstrated in imaging tests and may be secondary to infection, trauma, stroke, hypoxic-ischemic encephalopathy, or genetic causes due to malformations or alterations in genes. When the etiology is genetic, proof is provided by a genetic variant. It is important to remember that despite a genetic origin, the presence of epileptic triggering factors such as sleep deprivation, stress, and others should not be overlooked. For metabolic etiology, epilepsy is secondary to a known or presumed disorder with systemic clinical manifestations. Examples of conditions include porphyria, uremia, aminoacidopathies, or pyridoxine-dependent seizures[1-3].

Worldwide, the prevalence of epilepsy varies from 10 to 15 per 1000 people[3]. In Brazil, it is estimated that there are 340,000 new cases of epilepsy each year, with 1.8 million patients experiencing active epilepsy[1]. In the pediatric and adolescent age group, the incidence of seizures in children under one year of age is noteworthy, estimated at 5 per 1,000 live births[1].

Table 1. Types of epileptic syndromes by age group.

Age group	Epileptic syndromes
Neonatal	Benign neonatal seizures Benign familial neonatal epilepsy Early myoclonic encephalopathy Ohtahara syndrome
Infants	Febrile seizures and febrile seizures plus Benign infantile epilepsy Benign familial infantile epilepsy West syndrome Dravet syndrome Myoclonic epilepsy of infancy Myoclonic encephalopathy in non-progressive disorders Epilepsy of infancy with migrating focal seizures
Childhood	Febrile seizures and febrile seizures plus Early-onset benign childhood occipital seizures (Panayiotopoulos syndrome) Epilepsy with myoclonic-atonic seizures Childhood absence epilepsy Benign epilepsy with centrotemporal spikes Autosomal dominant nocturnal frontal lobe epilepsy Late-onset childhood occipital epilepsy (Gastaut type) Epilepsy with myoclonic absences Lennox-Gastaut syndrome Epileptic encephalopathy with continuous spike-wave during sleep Landau-Kleffner syndrome
Adolescence	Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with generalized tonic-clonic seizures alone Progressive myoclonic epilepsy Autosomal dominant epilepsy with auditory features Other familial temporal lobe epilepsies with variable age of onset Familial focal epilepsy

Adapted from Costa LLO, et al, 2020

Given the broad spectrum of epilepsies and their varied etiologies, along with the high prevalence in both the general and pediatric populations, it is clear that using clinical tools to guide investigations and facilitate diagnoses is necessary. Therefore, this study reviewed cases of epilepsy where a protocol developed by the authors was applied, considering the following criteria: seizures that are not fully controlled, seizures with undefined etiology, and seizures requiring genetic testing.

METHODS

This retrospective case series study included children admitted to the pediatric units of the University Hospital or followed at the Outpatient Clinic of the Neonatal Intensive Care Unit who underwent genetic evaluation for seizures of unknown etiology. A clinical protocol was developed to reassess children who had seizures poorly responsive or unresponsive to anticonvulsants and were experiencing global developmental delay (Appendix 1). The protocol was imple-

mented in 2019 and included variables such as prenatal and perinatal data, family history, type and progression of seizures, developmental milestones, medications prescribed, and tests performed. A pediatrics resident collected the data by reviewing medical records and genetic consultations from 2019 to 2022 and selected cases where the protocol was applied. All patients aged 0 to 10 years were included, while those who did not undergo genetic evaluation were excluded. Each patient underwent pediatric, neurological, and genetic assessments. In addition to the clinical genetic evaluation, diagnostic genetic panels provided free of charge by the Mendelics and Fleury Laboratories were utilized in the protocol. The interpretation of the genetic panel reports followed the American College of Medical Genetics (ACMG) variant classification. Once the panel results were available, a local geneticist performed Genetic Counseling (GC) as recommended. Reclassification might be required depending on the variant found, making ongoing genetic monitoring essential. Patient data were anonymized, and tables were analyzed using Microsoft Excel 2016 MSO version 16. 0. The study design was approved by the Research Ethics Committee of the Federal University of Rio Grande (CEP-FURG) and granted certificate 64099922.2.0000.5324. Patient guardians signed an informed consent form before genetic tests were performed; all were provided genetic counseling at the local outpatient clinic when they received the test results. Test reports were handed to them and were not made available to third parties.

RESULTS

The most prevalent comorbid condition in the gestational history of the selected patients was pregnancy-induced hypertension (PIH). There was one case of third-degree parental consanguinity. None had 1- or 5-minute APGAR scores lower than seven. Three were preterm infants, all of whom developed epileptic seizures before the age of two. Other characteristics are shown in Table 2. Two patients had syndromes with anatomical malformations: one had a patent ductus arteriosus, a patent foramen ovale, and pulmonary stenosis, while the other had micrognathia.

On neurological examination, seven patients exhibited hypotonia, clonus, hyperreflexia or hyporeflexia, muscle weakness, and gait disturbances. Global developmental delay, whether isolated to speech or affecting all domains, was observed in all patients. Imaging studies, particularly tomography and/or MRI of the CNS, showed abnormalities in four children, although one lacked such data. The findings from magnetic resonance imaging included myelin rarefaction or hypomyelination, foci of gliosis, and signal changes in the cortical diffusion sequence involving the left cerebral hemisphere, predominantly in the parietal, temporal, and occipital regions, with affected areas noted in the corpus callosum and midbrain. The EEG results were abnormal in six participants, with no data available for one patient (Table 3).

Table 2. Patient characteristics.

Characteristics	N	%
Sex		
Male	3	33.3
Female	6	66.7
Gestational age		
>37 weeks	6	33.3
<37 weeks	3	66.7
Ahe of onset of seizures		
<1 month	3	33.3
1 to 6 months	4	44.4
6 months to 1 year	1	11.1
1 to 2 years	1	11.1
Syndrome		
Yes	2	22.2
No	7	77.8
>2 antiepileptic drugs		
Yes	8	88.9
No	1	11.1

The genetic panels for movement and neurodevelopmental disorders provided by Mendelics were performed on eight patients, of whom one had a genetic alteration, one had an inborn error of metabolism (succinic semialdehyde dehydrogenase deficiency), one had a probable gene alteration, two had a variant of uncertain significance, and two did not present any alterations. Genetic panels were not performed for one patient as his epileptic seizures were related to an underlying condition, Cornelia de Lange syndrome. Only three patients were tested with the genetic panel for epilepsies and ataxias, as the first had not shown alterations, and the condition was severe and persistent. One child presented a probable pathogenic variant in SCN2 with signs and symptoms supporting the diagnosis (Table 4).

DISCUSSION

Succinic semialdehyde dehydrogenase (SSADH) deficiency, the inborn error of metabolism identified in one of the genetic panels, is extremely rare, with an estimated prevalence of 1:460,000 cases in developed countries[4]. Approximately 450 cases of SSADH deficiency have been identified globally. Clinical manifestations include nonspecific symptoms, and the natural history of the disease varies with age, although global neurodevelopmental delay, hypotonia, epilepsy, and ataxia are frequently observed during childhood[5]. On average, symptom onset occurs at 11 months of age[6], as seen in the patient in our study. In terms of pathophysiology, the condition causes the accumulation of gamma-hydroxybutyric acid, a neurotoxic metabolite, due to the non-degradation of the inhibitory neurotransmitter GABA by the enzyme succinic semialdehyde

Table 3. Diagnostic tests.

Diagnostic tests	N	%
Altered neurological tests		
Yest	7	77.8
No	2	22.2
Global developmental delay		
Yes	9	100
No	0	
Alterations in head computed tomography scans		
Yes	4	44.4
No	4	44.4
Not performed/found	1	11.1
Alterations in electroencephalogram		
Yes	7	77.8
No	1	11.1
Not performed/found	1	11.1

Table 4. Genetic panel results.

Genetic panels	N	%
Movement and neurodevelopmental disorders		
Pathogenic variant	1	11.1
Variant of uncertain significance	2	22.2
Probable pathogenic variant	1	11.1
No variants	3	33.3
Not performed	1	11.1
Epilepsies and ataxias		
Pathogenic variant	1	11.1
Variant of uncertain significance	1	11.1
Benign variant	1	11.1
Not performed	6	66.7

dehydrogenase. Diagnosis is exclusion-based and relies on analyzing body fluids such as urine and cerebrospinal fluid, which show an increase in gamma-hydroxybutyric acid in individuals with the condition[7]. Diagnosis can also be confirmed through next-generation sequencing genetic tests, either with a panel or by exome sequencing, in which a mutation in the ALDH5A1 gene is present in affected persons. However, due to its non-specific clinical presentation that overlaps with several neurological disorders, SSADH deficiency is likely underdiagnosed. Consequently, a high level of clinical suspicion is necessary to initiate diagnostic investigations[6]. Patients with the condition require genetic counseling since the inheritance pattern for SSADH deficiency is autosomal recessive[8]. Only supportive care is available for individuals with SSADH deficiency, although targeted gene therapies are under development[4].

The variants described in the results of genetic panels are considered pathogenic when they prevent the production of a normal protein, leading to alterations in essential biological functions. Probable pathogenic variants are more frequently found in individuals with a disease; however, they have not yet been classified as pathogenic, despite this probability being 90%. Additionally, there are variants of uncertain significance (VUS), whose effects remain unknown. When the test results indicate a VUS, no action is necessary. Nonetheless, it is recommended that the variant be reassessed if, after an extended period, the condition continues without a defined etiology. A probable benign variant is not associated with any disease in 90% of cases, and a benign variant is not linked to any clinical condition[9]. Thus, patients diagnosed with a probable pathogenic variant are likely to have a genetic condition, which is diagnosed based on correlations with clinical manifestations or the reclassification of the variant.

Epilepsy remains a disease characterized by inequality. Underdiagnosis and lack of access to treatment are significant issues in developing countries. However, even in developed nations, there is still considerable inequality in access to accurate diagnosis and specific treatment for this disease, which has high morbidity and mortality rates, especially in more complex patients[10]. Further investigation into difficult-to-control epilepsy associated with global developmental delay is necessary. The protocol analyzed in this article facilitated further examination of inconclusive cases of epilepsy, impacting diagnosis and etiology definition. This was exemplified by the patient with a rare inborn error of metabolism and the case with a probable pathogenic variant in the SCN2 gene that resulted in clinical manifestations consistent with the disease. Additional investigations led to the identification of a genetic alteration as the cause of the disease and the initiation of genetic counseling for the patient's families, one due to an autosomal recessive inheritance pattern and the other due to a de novo variant, respectively. Treatment and therapies were directed according to the diagnosis. These results suggest that systematic data organization and comparison can enhance and expedite adequate investigation and improve outcomes.

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APPENDIX 1. CLINICAL PROTOCOL DEVELOPED FOR THE REASSESSMENT OF CHILDREN WITH CONVULSIVE CRISES THAT ARE NOT RESPONSIVE TO ANTICONVULSANTS AND DELAYED DEVELOPMENT.

Name: Date of consultation:

Date of birth: Sex: M ( ) F ( ) Medical chart:

Name of the mother:

Perinatal data: BW: Length: HC: 1- and 5-minute Apgar scores: GA:

Referral from: ( ) Medical Genetics Lab ( ) NICU Outpatient Clinic

Age of onset of seizures: months years

Has the patient taken any of these medications?

( ) Phenobarbital	( ) Taking	( ) Not taking anymore
( ) Phenytoin	( ) Taking	( ) Not taking anymore
( ) Carbamazepine	( ) Taking	( ) Not taking anymore
( ) Oxcarbazepine	( ) Taking	( ) Not taking anymore
( ) Lamotrigine	( ) Taking	( ) Not taking anymore
( ) L-dopa	( ) Taking	( ) Not taking anymore
( ) Valproic acid	( ) Taking	( ) Not taking anymore
( ) Levetiracetam	( ) Taking	( ) Not taking anymore
( ) Nitrazepam	( ) Taking	( ) Not taking anymore
( ) Clonazepam	( ) Taking	( ) Not taking anymore
( ) Lorazepam	( ) Taking	( ) Not taking anymore
( ) Ethosuximide	( ) Taking	( ) Not taking anymore
( ) Vigabatrin	( ) Taking	( ) Not taking anymore

How old was the patient when he/she was started on medication? Months Years

Was there a complete response to the prescribed drugs? ( ) Yes ( ) No

Was there a partial response to the prescribed drugs? ( ) Yes ( ) No

What type of seizures did the patient experience? (Tick one or more)

( ) Generalized tonic-clonic seizures ( ) Focal ( ) Partial

Has the patient ever been diagnosed with hypoglycemia? ( ) Yes ( ) No

Has anyone else in the patient's family suffered from seizures?

( ) Father ( ) Mother ( ) Sibling ( ) Half-sibling

( ) Other family members:

Are the patient's parents consanguineous relatives? ( ) Yes ( ) No

Neonatal screening tests ( ) Normal ( ) Altered

Development (describe landmarks seen in current consultation):

Physical examination (tick positive findings and describe ordered tests):

( ) Dysmorphias (describe)

( ) Myopathic face ( ) Nystagmus ( ) Blinking

( ) Eyelid ptosis ( ) Unilateral ( ) Bilateral

( ) Tongue protrusion ( ) Ocular eversion

( ) Athetoid movements/extrapyramidal symptoms

( ) Hypotonia ( ) Hypotrophy ( ) Dystonia

( ) Occasional diarrhea ( ) Marfanoid habitus

( ) Hepatomegaly ( ) Psychomotor agitation

( ) Café-au-lait spots ( ) Hemangiomas

Diagnostic tests (test, date, conclusion)

EEG

Transfontanellar ultrasound

Head CT

Brain MRI

ENMG

Prolactin

STORCH

CSF

IEM

Organic acid chromatography

HPLC

Acylcarnitine profile

Other IEM

Karyotype

Array CGH

Conclusion: In addition to seizures, the patient presents the following:

( ) Static developmental delay

( ) Progressive developmental delay

( ) Intellectual disability

NOTES:

PEDIGREE: