

Etiological Analysis and Classification of 108 Patients with Infantile Epileptic Spasms Syndrome Based on the 2017 International League Against Epilepsy Classification

Nilüfer ELDES HACIFAZLIOĞLU¹, Emek UYUR², Derya GÜDER³, Kutlay GÜR⁴, Olcay ÜNVER⁵, Yüksel YILMAZ⁵

¹Department of Pediatric Neurology, University of Health Sciences, Zeynep Kamil Maternity and Children Hospital, Istanbul, Türkiye

²Department of Pediatric Neurology, Zeynep Kamil Maternity and Children Hospital, Istanbul, Türkiye

³Department of Pediatric Neurology, Mardin Training and Research Hospital, Mardin, Türkiye

⁴Iskenderun State Hospital, Iskenderun, Türkiye

⁵Retired Faculty Member, Department of Pediatric Neurology, Marmara University, Istanbul, Türkiye

ABSTRACT

Introduction: Infantile Epileptic Spasms Syndrome (IESS) is an age-related developmental and epileptic encephalopathy that may be resistant to treatment and can negatively affect neurodevelopment. The classification of the etiology of IESS is important for its treatment, considering prognosis, and for future studies. The present study aimed to investigate the difficulties in etiologic classification of IESS based on the International League Against Epilepsy (ILAE, 2017).

Material and Methods: The data of patients diagnosed with IESS between 2014 and 2023 were reviewed retrospectively. The diagnosis of IESS was made by the presence of epileptic spasm and/or hypsarrhythmia on electroencephalography (EEG). Etiological classification was made based on the 2017 (ILAE) etiologic classification and the difficulties encountered were examined.

Results: In this study, 108 patients, 63 (%58) girls and (%42)45 boys, with a mean age of 22±13 (3-72) months, were included. The etiology remained unclear in 30 patients (27.7%) and was detected in 78 patients (72.2%). The underlying causes of patients were genetic 16

(14.8%), structural 57 (61.5%), inherited metabolic diseases 4 (3.7%), and infectious 1 (0.9%). Congenital metabolic diseases were included in the metabolic diseases group. Since different etiologies could cause IESS, either alone or in combination, difficulties were encountered especially in grouping the patients with a genetic origin of the disease, resulting in structural anomalies and inherited metabolic diseases.

Conclusion: The basic difficulty encountered during the ILAE classification of this large group of patients was to classify the genetic causes that result in structural anomalies and congenital metabolic diseases. Previous experience, along with the findings of the present study, suggest that ILAE 2017 etiologic classification may be revised, genetic reasons resulting in structural and/or metabolic abnormalities should be classified under the name of genetic origin and that genetic titles should be divided into subgroups such as genetic metabolic, genetic structural, and other genetic categories.

Keywords: Epilepsy, Infantile, Spasm

Cite this article as: Eldes Hacifazlıoğlu N, Uyur E, Güder D, Gür K, Ünver O, Yılmaz Y. Etiological Analysis and Classification of 108 Patients with Infantile Epileptic Spasms Syndrome Based on the 2017 International League Against Epilepsy Classification. Arch Neuropsychiatry 2026;63:163–168. doi: 10.29399/npa.28983

INTRODUCTION

Infantile Epileptic Spasms Syndrome (IESS) is an age-related developmental and epileptic encephalopathy characterized by epileptic spasms that are associated with developmental arrest or regression (1). Infantile spasm and West Syndrome (WS) was first described in 1841 by Dr. William West as a triad of infantile spasms, hypsarrhythmia on electroencephalography (EEG), resulting in developmental arrest or regression (1,2,3,4,5,6,7). Since then, several studies on the terminology of epileptic spasms (infantile spasms vs. clinical spasms), exploration of various clinical and electroencephalographic (EEG) features, investigation of its etiopathogenesis, and exploration of effective treatment options and related outcomes, have been reported.

Highlights

- Different etiologies, alone or in combination, can cause IESS.
- Patients were classified according to the ILAE 2017 etiologic classification.
- Difficulties were encountered when etiologically classifying patients.
- Genetic causes can be divided into subgroups.

Correspondence Address: Nilüfer Eldes Hacifazlıoğlu, University of Health Sciences, Department of Pediatric Neurology, Zeynep Kamil Maternity and Children Hospital, Istanbul, Türkiye •

E-mail: niluferhacifazlioglu@gmail.com

Received: 13.11.2024, **Accepted:** 08.01.2025, **Available Online Date:** 16.02.2026

©Copyright 2025 by Turkish Association of Neuropsychiatry - Available online at www.noropskiyatriarsivi.com

The revised International League Against Epilepsy (ILAE) classification and terminology of seizures and epilepsies, which was published in 2010, categorizes West Syndrome as an electro-clinical syndrome, with onset in infancy, while the epileptic spasms are identified as a specific type of seizure (8). In 2022, ILAE proposed replacing the term WS with IESS (2,1). This term IESS includes individuals presenting with epileptic spasms who do not fulfil the criteria for West Syndrome. This modification of the term underscores the significance of early diagnosis (even prior to the onset of hypsarrhythmia) and treatment, as a shorter lag time to treatment might be associated with a better outcome (1,6,9).

Numerous studies reported over the past years have established that structural, genetic, infectious, and metabolic causes may result in IESS (1,3,4,6,7,9). However, despite the availability of advanced diagnostic tools, the etiology of IESS in a significant number of patients remains unclear. In this context, elucidating the underlying etiology of brain dysfunction resulting from IESS might allow the concerned clinician to begin specific treatment modalities immediately, such as for tuberous sclerosis and inherited metabolic disorders. The ILAE 2017 classification of epilepsies involved a novel approach to classify epilepsies based on, in addition to the clinical findings, etiological features (structural, genetic, metabolic, infectious, immune, unknown) (10).

The present study, therefore, attempted to categorize the etiologies of patients diagnosed with IESS according to the new 2017 ILAE classification and then investigate the difficulties encountered in the etiological classification of IESS.

METHODS

Patients

Demographic and clinical findings, medical history, laboratory examination results, findings of EEG and Cranial Magnetic Resonance Imaging (MRI), and the data from the clinical follow-up of 108 children diagnosed with IESS in the Zeynep Kamil Maternity and Children Hospital between 2014 and 2023 were documented. The diagnosis of IESS was established based on the following criteria: the presence of epileptic spasms (observed in home videos or mobile phone recordings) and/or hypsarrhythmia on EEG, along with developmental arrest or regression.

Baseline clinical and laboratory data

Medical history and neurological findings were carefully analyzed to determine the underlying etiology. The following data were documented retrospectively: age, gender, age at the onset of spasms, age at the diagnosis of IESS, mode of delivery, weight at birth, early childhood life-threatening events, parental consanguinity, developmental assessment, physical abnormalities, EEG findings, cranial MRI findings, and treatments. All patients underwent metabolic tests [arterial blood gas analysis, determination of the serum levels of Biotinidase enzyme, ammonia, lactate, pyruvate, Acylcarnitine profile, total and free carnitine, serum and cerebrospinal fluid (CSF) analyses for lactate and glucose, amino acids, and urine organic acids].

Genetic examinations such as chromosome analysis (n=30), array comparative genomic hybridization (aCGH) (n=15), epilepsy gene panel (n=10), and whole exome sequencing (WES) (n=10) were performed for patients for whom the diagnosis could not be established based on the findings of the other tests and clinical data.

EEG examinations were performed using the 18-channel digital Nihon Kohden and the International 10-20 system of electrode placement, including a full wake and sleep cycle for all patients at the time of diagnosis and then at a time point within four weeks after the diagnosis. Clinical and laboratory findings of the patients were shown in Table 1.

Etiological classification

The etiological causes of IESS were categorized as genetic, structural, metabolic, infectious, immune, and unknown based on the ILAE 2017 classification (17). A structural etiology refers to abnormalities visible in structural neuroimaging. Certain structural etiologies could be acquired, such as perinatal complications, stroke, trauma, and infection, while others, such as malformations of cortical development, could be genetic. A genetic etiology refers to the scenario when IESS is associated directly with a known or presumed genetic mutation, while the association of IESS with metabolic disorders is classified as a metabolic etiology. Infectious etiology refers to the IESS that results directly from prenatal or perinatal infections (10). The structural etiology is further divided into the subcategories of perinatal complications and congenital brain malformation. The difficulties encountered during the etiological classification in the present study were then detailed in the discussion section.

Table 1. Study population

Male/Female		1.4/1	
Age at onset of epileptic spasms (mean±SD) months		6.68±3.68 (3-12)	
Consanguineous marriage (n/%)		26 (24.1%)	
Abnormal neurological examination (n/%)	Microcephaly	37 (34.2%)	
	Neurocutaneous signs	5 (4.6%)	
	Dysmorphism	12 (11.1%)	
	Cerebral palsy	70 (64.8%)	
Lag of time for treatment (mean±SD) months		2.75±4.67 (0-9)	
Hypsarrhythmia on interictal EEG (n/%)		106 (98.1%)	
Cranial MRI, n (%)	Normal	37 (34.3%)	
	Abnormal	Congenital Structural Lesion	22 (20.3%)
		Genetic metabolic disease	4 (3.7%)
		Perinatal Complications	45 (41.7%)

MRI: Magnetic Resonance Imaging. SD: Standard Deviation

Treatment modalities

The first choice of treatment was VGB for patients with Tuberous Sclerosis (TS) and vitamin B6 (100 mg per day) for the remaining patients. The ACTH treatment (intramuscular administration of synthetic ACTH at a dosage of 0.025 mg/kg twice weekly, for 4 weeks, and then once a week for the next 4 weeks, followed by the administration of the last 4 doses every other two weeks) was begun for patients who did not respond to the vitamin B6 treatment by the 3rd day. Treatment modalities involving other antiseizure drugs (sodium valproate, topiramate, clobazam, levetiracetam, and rufinamide) were attempted for patients who did not respond to the above treatment protocol.

Follow-up records

EEG monitoring was performed four weeks after initiating the treatment and then every six months for patients who remained free from seizures as well as for those who experienced a relapse or progression to other seizure types. Patients were accordingly categorized into the following three groups: those in which the epileptic spasms disappeared and/or hypsarrhythmia improved in the EEG, those who presented a relapse of the epileptic spasms and/or any seizure type and/or hypsarrhythmia in the EEG, and those with continued epileptic spasms and/or hypsarrhythmia in the EEG.

The study adhered to the principles of the Declaration of Helsinki and was approved by the Ministry of Health of Turkey and the ethics committee of Zeynep Kamil Maternity and Children Hospital, Istanbul, Turkey (approval date: 24.11.2021; approval number: 178).

RESULTS

Table 1 presents the demographic information and clinical findings of the patients. The mean age of the patients was 6.68 ± 3.68 (3–12) months

at the onset of the epileptic spasms. Twenty-six patients (24.1%) were born in consanguineous marriages. The duration between the onset of the epileptic spasms and the diagnosis was 2.75 ± 4.67 (0–9) months. Prior to the onset of spasms, other types of seizures were present in 29 patients (27.1%) and neurologic examination results were abnormal in 83 patients (76.9%) [microcephaly 37 (34.2%), neurocutaneous signs 5 (4.6%), dysmorphism 12 (11.1%), and cerebral palsy 70 (64.8%)].

Hypsarrhythmia was detected in the EEG examination of 106 patients (98.1%). Hypsarrhythmia developed during the EEG examinations of two patients undergoing ACTH treatment, who initially presented with epileptic spasms and normal EEGs.

Cranial MRI examinations were normal in 37 patients (34.3%) and abnormal in 71 patients (65.7%). Cranial MRI abnormalities were as follows: congenital structural abnormalities in 22 patients (20.3%), genetic metabolic disease in 4 patients (3.7%), and findings related to perinatal complications in 45 patients (41.7%).

Etiological Analysis

The underlying cause was detected in 78 patients (72.2%), among which 16 patients (14.8%) had genetic causes, 57 patients (61.5%) had structural causes, 4 patients (3.7%) had metabolic causes, and 1 patient (0.9%) had infectious cause underlying the IESS. The etiology could not be elucidated in 30 patients (27.7%), and these patients were categorized as having an unknown etiology. The information regarding patients with an underlying etiology based on the ILAE 2017 classification is provided in Table 2.

Treatment Response

Epileptic spasms disappeared after the first-line treatment was administered, which included the treatment of 3 patients (2.7%) with the

Table 2. Etiologies of the patients with underlying causes based on ILAE 2017 classification of the epilepsies.

Unknown etiology, n(%)		30 (27.7%)	
Clarified etiology, n(%)		78 (72.3)	
Genetic, n (%) 16 (14.8 %)	Down Syndrome	8 (7.4%)	
	Tuberous Sclerosis	3 (2.8%)	
	EMC gen 1	2 (1.9%)	
	Jansen de Vries Syndrome	1 (0.9%)	
	ARX gene	1 (0.9%)	
	GABGR2 gene	1 (0.9%)	
Structural, n(%) 57 (61.5 %)	Acquired 45(41.6%)	Hypoxic ischemic encephalopathy	23 (21.3%)
		Premature birth and related complications*	19 (17.6%)
		Neonatal hypoglycemia	3 (2.8 %)
	Congenital brain malformation 13 (12.0%)	Corpus callosum agenesis	3 (2.8 %)
		Focal cortical dysplasia	2 (1.8%)
		Lissencephaly	2 (1.8%)
		Encephalocele	1 (0.9%)
		Dandy Walker malformation	1 (0.9%)
		Hemangiopericytoma	1 (0.9%)
		Pontocerebellar hypoplasia	1 (0.9%)
		Subcortical band heterotrophy	1 (0.9%)
		Hydrocephalus	1 (0.9%)
		Metabolic, n(%) 4 (3.7 %)	Propionic Acidemia
Non-ketotic hyperglycinemia	2 (1.9%)		
Adenylosuccinate lyase deficiency	1 (0.9%)		
Infectious, n(%) 1 (0.9 %)	Neonatal meningitis	1 (0.9%)	

*Hidrocefali, Periventriküler lökomalazi, İntrakranial kanama

*Hydrocephaly, Periventricular Leucomalacia, Intracranial bleeding

GABGR2: GABA receptor $\gamma 2$ subunit gene, EMC1: Endoplasmic reticulum membrane protein complex subunit 1 gene, ARX: Aristaless-related homeobox gene.

diagnosis of TSC treated with Vigabatrin (VGB), 3 patients (2.7%) with a high dose of pyridoxine, and 40 patients (40.7%) with ACTH. The relapse of epileptic spasms or other types of seizures and/or hypsarrhythmia appeared on the EEG for 25 patients (23.1%), including 2 patients with VGB and 23 patients with ACTH, after the first-line treatment. Complete spasm cessation occurred in 21 patients (46.4%).

Clinical spasms disappearance and normal EEG after the first line treatment were recorded for 8 patients (7.4%) with unknown etiology and 8 patients (7.4%) with an underlying etiology. The relapse of clinical spasms or other types of seizures and/or hypsarrhythmia appeared on the EEG 4 weeks after administering the first line treatment in 6 patients (5.5%) with unknown etiology and 20 patients (18.5%) with an underlying etiology. In 64 patients (59.2%), clinical spasms persisted even after the first-line treatment, and all of these patients had an underlying pathology.

DISCUSSION

Epileptic syndromes are characterized by a range of clinical and EEG features that are frequently associated with age-dependent presentations supported by specific etiological findings, such as structural, genetic, metabolic, and immune-related findings (1,10). The ILAE Epileptic Task Force on Nosology and Definitions proposed the classification of epileptic syndromes with onset up to 2 years of age into separate groups of self-limited syndromes and developmental and epileptic encephalopathies (DEE) (1). IESS is a severe, early-onset DEE characterized by neurodevelopmental comorbidity resulting from both the primary cause and the impact of uncontrolled seizures (1). IESS is the most commonly observed epileptic encephalopathy among infants during the first two years of life. The incidence of IESS is 2–3/10,000, with an overall prevalence of 1 in 10,000 children aged 10 years (3,7,11,12).

The cases of IESS include infants who do not fulfill all the criteria of West Syndrome (epileptic spasms, hypsarrhythmia, and developmental regression) (1). Epileptic spasms are sudden tonic contractions appearing between the ages of 4 and 9 months in infants and lasting a few seconds, often accompanied by episodes of crying or screaming (12). The presence of epileptic spasms is necessary and important to exclude the presence of other benign infantile movements such as Moro-reflex, benign sleep myoclonus, etc. (1,11).

The precise pathophysiology of IESS and the mechanism through which the various etiologies lead to the same occurrence of epileptic spasms and hypsarrhythmia remain unknown to date. Damages to the developing brain, immune mechanisms, and the release of stress-activated mediators, such as stress/corticotropin-releasing hormone (CRH), in the limbic and brain stem regions are indicated to induce pro-convulsant stress mechanisms in IESS (12,13,14). In particular, the cases that respond to ACTH support the possibility of the mechanism underlying IESS being related to the release of CRH (3,6,12,15–18).

The ictal recording of an epileptic spasm has a low amplitude and rapid activity, often accompanied by a short electro-decrement prior to the generalized, high-amplitude, sharp or slow wave. Interictally, hypsarrhythmia manifests with chaotic, high-amplitude, excessively slow, and multifocal epileptiform discharges (6,7). Early in the course and also in certain patients, interictal EEG may be normal (1,6,10,19,20–21). In addition, different patterns such as “modified” or atypical hypsarrhythmia, such as semi-periodic burst-suppression, focal discharges, and asymmetric features might be observed (7). ILAE recommends that a diagnosis of IESS must be established if an experienced clinician observes epileptic spasms in cases where EEG examination cannot be performed due to various reasons, to facilitate the early initiation of treatment (1). Moreover, the EEG might be compatible with hypsarrhythmia or be normal (1,6,10,19–

21). In the present study, the interictal EEGs of two patients were normal, and hypsarrhythmia was developed during the treatment period. Clinicians should, therefore, not delay beginning therapy for children with epileptic spasms who do not exhibit hypsarrhythmia in the EEG examination.

Etiological classification of IESS is important because of the potential therapeutic consequences, as well as to facilitate genetic counseling, predict prognosis, and conduct future studies (7,10). Previously, IESS was etiologically classified into symptomatic (patients with an underlying cause), cryptogenic (manifesting with neurological symptoms or developmental delay although not detectable using the available methods), and idiopathic (3,4,9). In 2010, ILAE expanded this classification to include structural, genetic, metabolic, and unknown cause categories (8). The United Kingdom Infantile Spasms Study (UKISS) recommended the etiological classification based on the 10th edition of the International Classification of Diseases (ICD-10), which is a pediatric classification into the categories of proven etiology, identified etiology, and not fully investigated etiology (22). In 2015, Wirrell et al. proposed a further classification that included structural-congenital (brain malformation without a documented genetic etiology), structural-acquired (structural changes in the brain due to HIE, PVL, or tumor), genetic-structural (genetic factors leading to structural abnormalities in the brain, such as tuberous sclerosis), genetic, metabolic, immune, infectious, and unknown categories (7). Finally, in 2017, ILAE classified epilepsies based on their etiology, into structural, metabolic, genetic, infectious, immune, and unknown categories (10). In 2021, the South Asian West Syndrome Research Group (SAWSRG) proposed the subgroup of incompletely investigated etiology due to resource limitations in developing nations in the classification of IESS (23).

Various etiologies could exert influence as a single causal event or in complex associations. For instance, structural abnormalities may be genetic in origin, acquired, or resulting from intrauterine infections (10). TSC, for example, is a genetic disorder resulting in structural abnormalities appearing on cranial MRI due to abnormalities in proliferation (6). The TSC1 and TSC2 genes produce hamartin and tuberin proteins, respectively, which regulate cell division and growth in the brain. Mutations in these genes may, therefore, lead to structural lesions such as tubers and hamartomas (24,25). ILAE proposed that both structural and genetic etiological terms could be used for TSC in 2022 (10). However, TSC is a genetic disorder, and structural lesions are a result of genetic mutations. Using two different etiological terms for single genetic disorder may lead to conceptual ambiguity. On the other hand, classifying the same disease into two different groups could cause difficulties in future studies and meta-analyses. Therefore, the authors of the present study proposes that genetic etiologies may be categorized into two subgroups: resulting in structural lesions and not resulting in structural lesions. Lissencephaly is a structural abnormality of the brain, which could arise due to various causes, including viral infections such as infection with cytomegalovirus (CMV), insufficient blood flow to the developing brain, or genetic conditions (LIS1, Miller-Dieker Syndrome, RELN, NDE1, KATNB1, TUBA1A, CDKL5, DCX, and ARX) (12,18,26). If the cases with lissencephaly are classified to have a structural etiology, it could result in underestimating the underlying genetic causes and infectious causes such as CMV.

Similar challenges in the etiological classification based on the ILAE 2017 criteria are encountered in Inherited Metabolic Disorders (IMD). Biotinidase deficiency is a genetic disorder developing due to mutations in the Biotinidase (BTD) gene. Biotinidase deficiency may lead to seizures due to the disrupted functioning of biotin-dependent carboxylases, causing the accumulation of potentially toxic substances in the brain (27). Therefore, whether Biotinidase deficiency should be classified as

a genetic etiology, metabolic etiology, or both, according to the latest classification criteria, has to be explored.

The proportion of patients with established etiology was 58%–85% according to the reports published in different decades (4,7,10,22). The reasons for this wide range of proportion in the etiological classification of IESS are the differences in the data used in these studies, methodological differences, and lack of adequate investigations. For example, in 1981, Yamatogi et al. reported cerebral palsy as the underlying pathology of West Syndrome (28). Ohtahara also reported cerebral palsy as the underlying pathology of WS in 1984 (29).

In the future, the use of advanced genetic technologies, such as array CGH, epilepsy gene panels, WES, WGS, and Single Nucleotide Polymorphism (SNP), would enable obtaining further information regarding the genetic causes of metabolic diseases, brain structural abnormalities, and autoimmune mechanisms that occur in childhood epilepsy, and consequently, the proportion of genetically defined etiologies is expected to increase. Advances in the field of genetics and the increasing importance of genetic causes in the etiology of epilepsy necessitate better and functional classifications. The studies being conducted currently also hold responsibility toward future scientific studies in the name of continuity in science and the use of common nomenclature. Accordingly, patients with a genetic pathology resulting in structural and/or metabolic abnormalities should be classified under the category of genetic etiology only. Therefore, the genetic etiology group may be divided into subgroups based on whether or not it results in structural abnormalities or metabolic abnormalities.

The risk of infantile spasms is elevated in families with individuals affected by other forms of epilepsy, which suggests a genetic predisposition for IESS. In the Epilepsy Phenome/Genome Project (EPGP), genetic etiology was identified in up to 5.8–41% of the cases, Copy Number Variants (CNV) were present in over 10% of the cases, and Variants of Uncertain Significance (VUS) were detected in 14.8% of the patients with epileptic spasms (7,11). Pathogenic mutations were identified in nearly 10–23.5% of patients without known etiology, and delayed patients have a higher yield (7,11). Genetic etiologies of IESS are chromosomal abnormalities, including Down Syndrome, 1p36 deletion, copy number variants, and specific genes such as TSC1, TSC2, CDKL5, ARX, STXBP1, and several others (3,6,7, 11,12). In the present study, genetic etiology was identified in 8 patients (7.4%), and half of these patients had Down syndrome. “National Infantile Spasms Consortium” in North America identified the underlying etiology in 64.4% of the patients, with structural-acquired subgroup accounting for 22.4%, genetic etiology accounting for 14.4%, genetic-structural subgroup accounting for 10%, structural-congenital subgroup accounting for 10.8%, inherited metabolic diseases subgroup accounting for 4.8%, and infectious causes accounting for 2% of the cases (7). Consanguineous marriage, which is common in a few nations, may also be a risk factor for genetic and inherited metabolic diseases. In the present study, 26 patients (24%) were born in a consanguineous marriage. Therefore, it is important to understand the genetic causes of IESS and other childhood epilepsies in nations where consanguineous marriage is common.

Inherited metabolic diseases (IMDs) such as phenylketonuria, nonketotic hyperglycinemia, and organic acidemias, among others (3.1%–22%) are important causes of IESS (3,7,22,27). A variation in the frequency of metabolic diseases could arise due to frequent consanguineous marriages in the population, ethnic origins, different diagnostic methods used, and national screening programs. Early diagnosis of certain metabolic etiologies could, therefore, allow for the early initiation of appropriate treatments for IESS, particularly in certain cases such as Biotinidase deficiency, phenylketonuria, and pyridoxine dependency (27). Such cases

emphasize the importance of genetic or metabolic screening of newborns when they are suspected to have metabolic diseases. In cases of unknown etiology, a trial of pyridoxine should be considered for pyridoxine dependency (6). Four patients (3.7%) in the present study were diagnosed with inherited metabolic disease, and 3 patients remained seizure-free after the pyridoxine treatment.

As with all research, the present study also had certain limitations, such as the retrospective nature of the study and that genetic and autoimmune tests could not be performed for all patients.

In conclusion, it is proposed that the ILAE 2017-based classification of epilepsy is difficult to implement for certain patients with IESS. While a perfect etiological classification might not be possible for all patients with IESS in the near future, it is essential to provide the best possible classification by using all relevant data available at present. It is recommended that the genetic etiology group of patients be divided into subgroups of genetic origin resulting in structural abnormalities and genetic origin resulting in metabolic abnormalities. It is particularly important for studies in which treatment results are monitored, and considering that the current studies would serve as the foundation for future scientific research, the nomenclature used for the evaluation of current data should be useful in the long term.

Ethics Committee Approval: The study adhered to the principles of the Declaration of Helsinki and was approved by the Ministry of Health of Turkey and the ethics committee of Zeynep Kamil Maternity and Children Hospital, Istanbul, Turkey (approval date: 24.11.2021; approval number: 178).

Informed Consent: Patient consent has been obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- NEH, YY, EU, OÜ; Design- SNEH, EU, DG; Supervision- NEH, EU; Materials- NEH, DG, KG; Data Collection and/or Processing- NEH, DG, KG; Analysis and/or Interpretation- NEH, EU, DG, KG, OÜ, YY; Literature Search- NEH, EU, DG; Writing- NEH, EU, DG, OÜ, KG, YY; Critical Reviews- NEH, OÜ, YY, EU.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: No financial support was received.

REFERENCES

- Zuberi SM, Wirrell E, Yozowitz E, Wilmshurst JM, Specchio N, Riney K, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: position statement by the ILAE task force on nosology and definitions. *Epilepsia*. 2022;63:1349-1397. [Crossref]
- TE Cone Jr. On a peculiar form of infantile convulsions (hypsarrhythmia) as described in his own infant son by Dr. W.J. West in 1841 *Pediatrics*. 1970;46:603. [Crossref]
- Pavone P, Striano P, Falsaperla R, Pavone L, Ruggieri M. Infantile spasms syndrome. IESS and related phenotypes: what we know in 2013. *Brain Dev*. 2014;36:739-751. [Crossref]
- Kaushik JS, Patra B, Sharma S, Yadav D, Aneja S. Clinical spectrum and treatment outcome of West Syndrome in children from Northern India. *Seizure*. 2013;22:617-621. [Crossref]
- Mytinger JR, Vidaurre J, Moore-Clingenpeel M, Stanek JR, Albert DVF. A reliable interictal EEG grading scale for children with infantile spasms- The 2021 BASED score. *Epilepsy Research*, 2021;173:106631 [Crossref]
- Baba S, Okanishi T, Homma Y, Yoshida T, Goto T, Fukasawa T, et al. Efficacy of long-term adrenocorticotropic hormone therapy for West syndrome: A retrospective multicenter case series. *Epilepsia Open*. 2021; 6: 402-412. [Crossref]
- Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG. Pediatric Epilepsy Research Consortium. How should children with West Syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. *Epilepsia*. 2015;56:617-625. [Crossref]
- Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology,

- 2005-2009. *Epilepsia*. 2010;51:676-685. [\[Crossref\]](#)
9. Gowda VK, Mohanty SB, Sugumar K, Srinivasan VM. Etiological Evaluation of Infantile Epileptic Spasms Syndrome (West Syndrome) Based on the New 2017 International League Against Epilepsy Seizure Classification from Southern India. *J Pediatr Neurosci* 2023. in press. [\[Crossref\]](#)
 10. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58:512-521. [\[Crossref\]](#)
 11. Nelson GR. Management of infantile spasms. *Transl Pediatr* 2015;4:260-270. [\[Crossref\]](#)
 12. Pavone P, Polizzi A, Marino SD, Corsello G, Falsaperla R, Marino S, et al. West syndrome: a comprehensive review. *Neurol Sci*. 2020;41:3547-3562. [\[Crossref\]](#)
 13. Brunson KL, Khan N, Eghbal-Ahmadi M, Baram TZ. Corticotropin (ACTH) acts directly on amygdala neurons to down-regulate corticotropin-releasing hormone gene expression. *Ann Neurol*. 2001;49:304-312. [\[Crossref\]](#)
 14. Baram TZ. Models for infantile spasms: an arduous journey to the Holy Grail. *Ann Neurol*. 2007;61:89-91. [\[Crossref\]](#)
 15. Velisek L, Jehle K, Asche S, Veliskova J. Model of infantile spasms induced by N-methyl-D-aspartic acid in prenatally impaired brain. *Ann Neurol*. 2007;61:109-119. [\[Crossref\]](#)
 16. Lee CL, Frost JD Jr, Swann JW, Hrachovy RA. A new animal model of infantile spasms with unprovoked persistent seizures. *Epilepsia*. 2008;49:298-307. [\[Crossref\]](#)
 17. Granata T, Cross H, Theodore W, Avanzini G. Immune-mediated epilepsies. *Epilepsia*. 2011;52:5-11. [\[Crossref\]](#)
 18. Peng J, Wang Y, He F, Chen C, Wu LW, Yang LF, et al. Novel West syndrome candidate genes in a Chinese cohort. *CNS Neurosci Ther*. 2018;24:1196-1206. [\[Crossref\]](#)
 19. Mytinger JR. Definitions and Diagnostic Criteria for Infantile Spasms and IESS Historical Perspectives and Practical Considerations. *Semin Pediatr Neurol*. 2021;38:100893. [\[Crossref\]](#)
 20. Kalra V, Gulati S, Pandey RM, Menon S. West syndrome and other infantile epileptic encephalopathies-Indian hospital experience. *Brain Dev*. 2002;24:130-139. [\[Crossref\]](#)
 21. Rahman M, Fatema K. Clinical Features and Treatment Outcome of West Syndrome Patients treated in a Tertiary Care Hospital: Bangladesh Perspective. *EAR*. 2018; 6:2638-2652.
 22. Osborne JP, Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes and their classification. *Epilepsia*. 2010;51:2168-2174. [\[Crossref\]](#)
 23. Wanigasinghe J, Sahu JK, Madaan P, Fatema K, Linn K, Chand P, et al. Classifying etiology of infantile spasms syndrome in resource-limited settings: A study from the South Asian region. *Epilepsia Open*. 2021; 6: 736-747. [\[Crossref\]](#)
 24. Gruber V, Scholl T, Samueli S, Gröppel G, Mühlebner A, Hainfellner JA, et al. Pathophysiology of neurodevelopmental mTOR pathway-associated epileptic conditions: Current status of biomedical research. *Clin Neuropathol*. 2019;38:210-224. [\[Crossref\]](#)
 25. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost MD, Kuperman R, et al. Long-term use of everolimus in patients with tuberous sclerosis complex: final results from the EXIST-1 study. *PLoS One*. 2016;28;11:e0158476. doi: 10.1371/journal.pone.0158476. [\[Crossref\]](#)
 26. Pesch MH, Saunders NA, Abdelnabi S. Cytomegalovirus Infection in Pregnancy: Prevention, Presentation, Management and Neonatal Outcomes. *J Midwifery Womens Health* 2021;66:397-402. [\[Crossref\]](#)
 27. Salar S, Moshe SL, Galanopoulou AS. Metabolic etiologies in West syndrome. *Epilepsia Open*. 2018;3:134-166. [\[Crossref\]](#)
 28. Yamatogi Y, Ohtahara S. Age-dependent epileptic encephalopathy: a longitudinal study. *Folia Psychiatr Neurol Jpn*. 1981;35:321-332. [\[Crossref\]](#)
 29. S Ohtahara. Seizure disorders in infancy and childhood. *Brain Dev* 1984;6:509-519. [\[Crossref\]](#)