Yozawitz Elissa (Orcid ID: 0000-0001-8230-8364)
Moshé Solomon L. (Orcid ID: 0000-0001-9427-9476)
Nunes Magda Lahorgue (Orcid ID: 0000-0002-3402-6810)
Pressler Ronit (Orcid ID: 0000-0002-2905-6839)

ILAE REPORT

Application of the ILAE Neonatal Seizure Framework to an international panel of medical personnel

Elissa G Yozawitz, MD[1], Maria R Cilio MD, PhD[2], Eli M Mizrahi MD[3], Jee-Young Moon Ph.D.[4], Solomon L Moshé MD [5], Magda L Nunes Md, PhD[6], Perrine Plouin MD[7], Sampsa Vanhatalo MD, PhD[8], Sameer Zuberi MB ChB, MD, FRCP, FRCPCH[9], Ronit M Pressler MD, PhD[10]

[1]Isabelle Rapin Division of Child Neurology of the Saul R Korey Department of Neurology and Department of Pediatrics, Albert Einstein College of Medicine and Montefiore Medical Center Bronx New York, USA
[2]Department of Pediatrics, Saint-Luc University Hospital, Catholic University of Louvain, Brussels, Belgium
[3]Departments of Neurology and Pediatrics, Baylor College of Medicine, Houston, Texas, USA
[4]Department of Epidemiology and Population Health, Albert Einstein College of Medicine and Montefiore Medical Center Bronx New York, USA
[5]Isabelle Rapin Division of Child Neurology of the Saul R Korey Department of Neurology, Department of Pediatrics, and Dominick P. Purpura Department of Neuroscience Albert Einstein College of Medicine and Montefiore Medical Center Bronx New York, USA
[6]Pontifical Catholic University of Rio Grande do Sul School of Medicine and Brain Institute (BraIns) Porto Alegre RS Brazil, USA
[7]Clinical Neurophysiology Unit in Saint Vincent de Paul and in Necker Hospital Paris France
[8]BABA Center, Departments of Clinical Neurophysiology and Physiology, Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
[9]Fraser of Allander Neurosciences Unit Royal Hospital for Children Glasgow Glasgow, UK
[10]Clinical Neuroscience, UCL- GOS Institute of Child Health and Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Correspondence:
Elissa Yozawitz
Isabelle Rapin Division of Child Neurology of the Saul R Korey Department of Neurology and Department of Pediatrics,
Albert Einstein College of Medicine and Montefiore Medical Center,
Bronx New York, USA
<eyozawit@montefiore.org>

Running title: Applying the ILAE Neonatal Seizure Framework

Received June 3rd, 2022; Accepted September 13th, 2022

This work is original and has not been presented at a meeting or in another publication.

ABSTRACT

Objective: The International League Against Epilepsy (ILAE) Neonatal Seizure Framework was tested by medical personnel. ***Methods:*** Attendees at the 2016 ILAE European Congress on Epileptology in Prague, the International Video-EEG Course in Pediatric Epilepsies in Madrid 2017, and a local meeting in Utrecht, The Netherlands, were introduced to the proposed ILAE neonatal classification system with teaching videos covering the seven types of clinical seizures in the proposed neonatal classification system. Five test digital video recordings of EEG-confirmed motor neonatal seizures were then shown and classified by the rater based on their knowledge of the proposed ILAE Neonatal Seizure Framework. A multirater Kappa statistic was used to assess agreement between observers and the true diagnosis. ***Results:*** The responses of 194 raters were obtained. There was no single predominant classification system that was currently used by the raters. Using the ILAE framework, 78-93% of raters correctly identified the clinical seizure type for each neonate; the overall inter-rater agreement (Kappa statistic) was 0.67. The clonic motor seizure type was most frequently identified (93% of the time; Kappa = 0.870). EEG technicians correctly identified all presented motor seizure types more frequently than any other group (accuracy = 0.9). ***Significance:*** The ILAE Neonatal Seizure Framework was judged by most raters to be better than other systems for the classification of clinical seizures. Among all seizure types presented, clonic seizures appeared to be the easiest to accurately identify. Average accuracy across the five seizure types was 84.5%. These data suggest that the ILAE neonatal seizure classification may be used by all healthcare professionals to accurately identify the predominant clinical seizure type.

Key words: neonatal seizure, classification, semiology

Seizures are a common neurologic emergency in the neonatal period. Most neonatal seizures are acute symptomatic seizures with acute and often treatable etiologies. Seizures can present with different clinical characteristics and at specific times depending on the underlying cause [1], with the vast majority occurring during the first week of life [2]. The seizure semiology in neonates tends to be less obvious clinically and may not easily fit into previously known classification systems for seizures and epilepsies developed for older children and adults. The International League Against Epilepsy (ILAE) neonatal classification provides a common language amongst medical personnel and may have clinical implications to help determine etiology (*e.g.*, clonic: stroke, sequential: genetic) [3, 4]. The previous classification systems include those by Mizrahi, Volpe, and the ILAE [5-10].

The use of EEG or amplitude-integrated electroencephalography (aEEG) is crucial to determine if the clinically observed movement of a neonate is a seizure. This is because neonates presenting with seizures are often critically ill and their clinical manifestations may be overlooked or subclinical and thus would be missed without an EEG. Additionally, important components of seizure semiology in older children and adults (*i.e.*, awareness, language, and sensory function) cannot be assessed in neonates. Lastly, because seizures in the neonatal period have been shown to have only focal onset, it is not necessary to separate them into focal and generalized categories. Therefore, in recognition of these differences, neonatal seizures did not easily fit into previously available classifications.

The ILAE Task Force on Neonatal Seizures was established in 2014 to create the Neonatal Seizure Framework [11] that can be integrated into the 2017 ILAE classification of the epilepsies [10]. The Neonatal Seizure Framework uses the same categories and terminology of recently published ILAE seizure classification [8, 10], but is: (1) adapted for neonates, and (2) developed to emphasize the role of EEG or aEEG in diagnosis [11].

Methods

The goal of this study was to determine the ease of use and assess agreement between the raters of individualized seizure types. This was a survey conducted based on the 2016 ILAE European Congress on Epileptology in Prague, Czech Republic, the International Video-EEG Course in Pediatric Epilepsies, Madrid, Spain, 2017, and a meeting in Utrecht, Netherlands.

The participants of the meetings voluntarily tested the proposed framework. The participants were introduced to the proposed neonatal classification system with a "teaching video", illustrating the different seizure types. Participants were informed that the purpose of the study was to determine the prominent motor semiology of the seizures presented to them based on what they learned in the "teaching video". They then were asked to apply the proposed framework to classify the seizure types for events presented on a subsequent test "clinical video". The five videos were selected by two of the authors (EY and RP) and approved by all other authors. The five seizure types selected were clonic, epileptic spasm, myoclonic, tonic, and sequential. All five were EEG-confirmed motor seizures and considered by all co-authors to be classic representations of that seizure type. Each seizure was thought to have an obvious clinical semiology with the baby clearly seen on the video. Raters were additionally asked to professionally identify themselves, state the classification system they currently use, and if the proposed diagnostic framework and seizure classification was an improvement over what they currently use. The choices for currently used classification systems included: the Volpe classification [7], the Mizrahi classification [6], the Fisher 2017 ILAE classification [9, 10], "none", and "do not know".

Participants were then introduced to the proposed ILAE neonatal classification system and were asked to classify the test clinical seizures as either clonic, tonic, myoclonic, automatisms, epileptic spasms, autonomic, or sequential [10, 11]. The latter was used when there were several seizure manifestations occurring in sequence (not necessarily simultaneously) in a given seizure. This typically occurred in longer seizures where a sequence of clinical features was seen, often with changing lateralization and no predominant seizure type. Each rater was asked to identify the predominant clinical feature of each of the five electroclinical seizures shown in the video samples. Raters additionally were requested to provide information about their preferred system for classifying seizures and to answer questions regarding the proposed system. This information and the individual ratings using the proposed framework were compiled and analyzed.

Statistical analysis

Data analysis included the percentages of the raters by profession, currently used classification system, correct responses for each clinical video, judgment on proposed framework vs. the current system, and all correct responses to five videos by profession. A multi-rater agreement was measured using Fleiss' exact Kappa statistic [12] to assess the agreement on categorical responses to the five clinical videos among multiple (n=194) raters beyond chance agreement. The Kappa statistic assesses the agreement among raters after chance agreement is excluded. Kappa values range between -1 and 1, indicating the magnitude of agreement to be <0 as poor, 0.00-0.2 as slight, 0.21-0.4 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1 as almost perfect agreement [13]. In addition, the category-specific Kappa statistic was calculated. The interobserver agreement was calculated, and the proportion of each type of seizure that was correctly diagnosed among raters was calculated. In addition, Kappa statistics for each category of seizure among 194 raters were also computed.

Results

The 194 raters included adult/child neurologists (*n*=44/62), clinical neurophysiologists (*n*=25), pediatricians/neonatologists (*n*=23), EEG technicians (*n*=9), nurses (*n*=16), and students (*n*=15) (*table 1*). Before learning the proposed system, raters stated that they did not consistently use one of the classification system choices to describe seizures in the neonate (*figure 1*). There was no predominant classification system that was currently used by the raters: Fisher ILAE Classification (34%) [10], Mizrahi Classification (8%) [6], Volpe Classification (15%) [7], "none" (20%), and "do not know" (22%).

Using the proposed framework, the overall accuracy of correct classification was 84.5% with 78-93% accuracy for each clinical seizure type (clonic, spasm, myoclonic, tonic, and sequential) (*figure 2*). The interobserver reliability of agreement (Kappa) from 187 raters for five videos was 0.676, demonstrating substantial agreement. The clonic type was most frequently correctly identified (93% of the time) with a Kappa value of 0.870. Although the remaining seizure types were less recognized, there was still more than 78% correct identifications. Focal tonic, myoclonic, and sequential seizures were correctly identified by >80% of the raters. For clonic seizures, the Kappa was 0.870. Epileptic spasm (0.683), myoclonic (0.673), and tonic (0.614) also yielded substantial rater agreement. Additionally, a Kappa value of 0.590 for sequential seizures indicated moderate rater agreement.

There were differences in accuracy and agreement according to profession (*table 1, 2*). EEG technicians correctly identified all the five seizure types presented 95.6% of the time, which was the highest of any group. Their rater reliability also was greater than any group (Kappa =0.9) (*table 1, 2*). However, there was also proficiency in detecting epileptic spasms and myoclonic and sequential seizures with 100% accuracy and high rater agreement in some rater groups (*e.g.*, EEG technicians) (*table 1, 2*). A majority (74% of the raters) judged the proposed framework to be better than the current system they used (*table 3*).

Discussion

The ILAE neonatal classification [11] uses terminology consistent with the 2017 ILAE Classification of Seizures and the Epilepsies [10] while taking into account the specificities of seizures occurring in the neonatal period based on their electroclinical phenotype. The classification is intended to be applied to all seizures in the neonate to give clinicians and researchers a common language to describe seizures. Although neonates can present with a variety of clinical manifestations, most of their seizures occur with one predominant feature that can be recognized by the observer.

This study demonstrates that the new classification can be reliably used by all categories of medical professionals to determine the predominant clinical seizure type. Although the new classification includes both electroclinical and electrographic only seizures, this study focused on electroclinical seizures. Clonic seizures yielded the highest agreement amongst all rater groups. Myoclonic seizures, epileptic spasms, and tonic seizures also garnered substantial rater agreement. Sequential seizures revealed somewhat less rater agreement, but moderate nevertheless. Malone, *et al.* [14] reported a similar correct identification rate of 66% (*n*=90/137) for clonic seizures. Additionally, Mizrahi and Kellaway [6] found that the most reliable and distinctive clinical signs were observed in clonic seizures followed by focal tonic seizures.

The proposed seizure classification framework was created in order to improve the management and treatment of neonatal seizures in all healthcare settings. To accomplish this goal, the framework was specifically designed to uncover the pathophysiological origin / etiology of neonatal seizures with emphasis on the role of EEG in determining diagnosis. It has been suggested that certain clinical seizure types may be associated with specific etiologies [3, 11]. By including the EEG in the framework process, clinical events without an EEG correlate may be excluded as non-epileptic in origin. Heretofore, without EEG, observations of abnormal movements in sick babies may have resulted in over-diagnosing seizures and over-prescribing antiseizure medications. Conversely, subclinical seizures in critically ill babies may have been undetected and untreated.

Capturing a seizure on continuous EEG monitoring is the gold standard for diagnosis [15]. In contrast, aEEG is less accurate because it employs fewer electrodes over a smaller area of the head. The latter may be used as an initial or complementary tool since it is easily applied, more widely available, and easily interpreted at bedside. However, aEEG is not recommended if continuous EEG is available [15, 16].

Neurophysiological monitoring, important in the initial assessment, is not available worldwide. However, the proposed framework can still be usefully applied in centers with limited resources (*i.e.*, without EEG) to identify seizure types. Pellegrin *et al.* [17] described case definitions of seizures that may be applied, based on "Levels of Diagnostic Certainty," when EEG is not available. They proposed that: (1) a clinical event with EEG correlation provides Level 1 diagnostic certainty as a "definite seizure" [17]; and (2) focal clonic or focal tonic seizures, directly witnessed or reviewed on video by experienced medical personal, can be considered "probable seizures" even in the absence of EEG confirmation (Level 2).

In agreement with other studies, our findings lead us to conclude that: (1) focal clonic seizures may be more easily clinically identified than other seizure types [14], and (2) focal tonic seizures can often be correctly identified as seizures. These may therefore be considered as "probable seizures". Other seizure types, including myoclonic jerks, epileptic spasms, automatisms, autonomic changes, and behavioral arrest, are more difficult to characterize and may be missed without a bedside EEG. They are conceptualized as "possible seizures".

The proposed classification framework was judged to be better than the current system by 74% of raters. When raters were asked to use the framework to classify the predominant seizure semiology, most were able to correctly identify the seizure type. Depending on the seizure type, 78-93% of raters were able to employ it, to correctly and reliably identify the main seizure type.

A methodological limitation of this study is that raters were not randomly selected. The participation in the survey was based on self-selection from having attended the specific conferences, and was then voluntary, also creating a bias. The raters were not asked to identify their country of origin or their years of experience. The study also comprised a relatively small sample size with 194 raters. This small number reduces the power of the study and can increase the margin of error. Lastly, the videos were preselected for visual clarity rather than randomly selected. This may be a potential limitation for the generalizability of these findings, since the seizures were selected as "classic" examples of each type. There is therefore a need for further large-scale clinical studies using real-life scenarios for better validation of the utility and applicability of the new framework across the various geographic settings.

Conclusion

This study provides evidence that the new ILAE neonatal classification can be used by multiple healthcare professionals to accurately identify predominant clinical seizure types using classic examples of five motor seizure types. Correct determination of clinical seizure types can aid in appropriate and rapid treatment of seizures. The proposed classification yielded substantial agreement across 187 raters based on five videos (*i.e.*, Kappa = 0.676), demonstrating its utility as a promising tool to improve treatment for neonatal seizures. Correctly identifying seizure semiology can aid clinical management. Further research is needed to determine whether certain seizure semiologies are specific to certain etiologies.

Key points:

- The ILAE Neonatal Seizure Framework is a new classification system to classify neonatal seizures based on predominant clinical features.
- Clonic seizures appear to be the easiest motor seizure to accurately identify.
- Even without EEG confirmation, certain clinical motor seizures can be probable seizures, while other clinical seizure types can be "possible" seizures.

Acknowledgments
The Task Force on Neonatal Seizures: Maria R Cilio MD, PhD, Eli M Mizrahi MD, Solomon L Moshé MD, Magda L Nunes MD, PhD, Perrine Plouin MD, Ronit M Pressler MD, PhD, Sampsa Vanhatalo MD, PhD, Elissa G Yozawitz MD, Sameer Zuberi MB, ChB, MD, FRCP, FRCPCH. Linda S. de Vries MD organized the meeting in Utrecht, The Netherlands.

Disclosures
The authors are members of the Task Force on Neonatal Seizures and were involved in the creation of the new ILAE neonatal seizure classification used in this paper.

References

1. Walsh BH, Low E, Bogue CO, Murray DM, Boylan GB. Early continuous video electroencephalography in neonatal stroke. *Dev Med Child Neurol* 2011; 53(1): 89-92.

2. Winkler L TAMC. Intracranial hemorrhage resulting in apneic seizures in a full-term infant: A case report and review of literature. *West Virginia Medical Journal OA* 2017: 3112.

3. Nunes ML, Yozawitz EG, Zuberi S, Mizrahi EM, Cilio MR, Moshe SL, *et al.* Neonatal seizures: Is there a relationship between ictal electroclinical features and etiology? A critical appraisal based on a systematic literature review. *Epilepsia Open* 2019; 4(1): 10-29.

4. Pressler RM, Cilio M, Mizrahi E, Moshé S, Nunes M, Plouin P, *et al.* The ILAE Classification of Seizures & the Epilepsies: Modification for Seizures in the Neonate. Proposal from the ILAE Task Force on Neonatal Seizures 2018. Available at: https://www.ilae.org/files/dmfile/NeonatalSeizureClassification-ProofForWeb.pdf

5. Volpe JJ. Neonatal seizures. *Clin Perinatol* 1977; 4(1): 43-63.

6. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology* 1987; 37(12): 1837-44.

7. Volpe JJ. Neonatal seizures: current concepts and revised classification. *Pediatrics* 1989; 84(3): 422-8.

8. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, *et al.* Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* 2017; 58(4): 531-42.

9. 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(4): 512-21.

10. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, *et al.* Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; 58(4): 522-30.

11. Pressler RM, Cilio MR, Mizrahi EM, Moshe SL, Nunes ML, Plouin P, *et al*. The ILAE classification of seizures and the epilepsies: Modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. *Epilepsia* 2021; 62(3): 615-28.

12. AJ C. Integration and generalization of kappas for multiple raters. Psychological Bulletin 1980; 88(2): 322-8.

13. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33(1): 159-74.

14. Malone A, Ryan CA, Fitzgerald A, Burgoyne L, Connolly S, Boylan GB. Interobserver agreement in neonatal seizure identification. *Epilepsia* 2009; 50(9): 2097-101.

15. Shellhaas RA. Continuous long-term electroencephalography: the gold standard for neonatal seizure diagnosis. *Semin Fetal Neonatal Med* 2015; 20(3): 149-53.

16. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. *Pediatrics* 2007; 120(4): 770-7.

17. Pellegrin S, Munoz FM, Padula M, Heath PT, Meller L, Top K, *et al.* Neonatal seizures: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2019; 37(52): 7596-609.

Legends

Figure 1. Classification system used to describe neonatal seizures.

Figure 2. Results of testing the neonatal classification system.

TEST YOURSELF

1. Which of the following motor seizures can be considered a "probable" seizure without EEG confirmation?
A. Clonic
B. Myoclonic jerks
C. Epileptic spasms

2. Which of the following seizure types is most likely to be recognized at the bedside?
A. Myoclonic
B. Automatism
C. Epileptic spasm
D. Clonic

3. The new ILAE neonatal classification system is of benefit because it:
A. creates a common language to describe seizures
B. does not include non-epileptic movements
C. may provide clinical implications that aid in determining etiology
D. All of the above

Table 1. Accuracy of the proposed framework: rater responses to each of the clinical seizures.

%	**Clonic**	**Spasm**	**Myoclonic**	**Tonic**	**Sequential**	**Average accuracy**
Adult neurologist (*n*=44)	86.4	75.0	79.5	81.8	81.8	80.9
Child neurologist (*n*=62)	95.2	79.0	77.4	80.6	85.5	83.5
Clinical neurophysiologist (adult/child) (*n*=25)	100.0	72.0	96.0	88.0	80.0	87.2
Neonatologist / pediatrician (*n*=23)	100.0	87.0	86.4	87.0	91.3	90.3
EEG technician/physiologist (*n*=9)	100.0	100.0	100.0	77.8	100.0	95.6
Nurse / other health professional (*n*=16)	93.8	81.3	87.5	81.3	93.8	87.5

Table 2. Kappa statistics by profession.

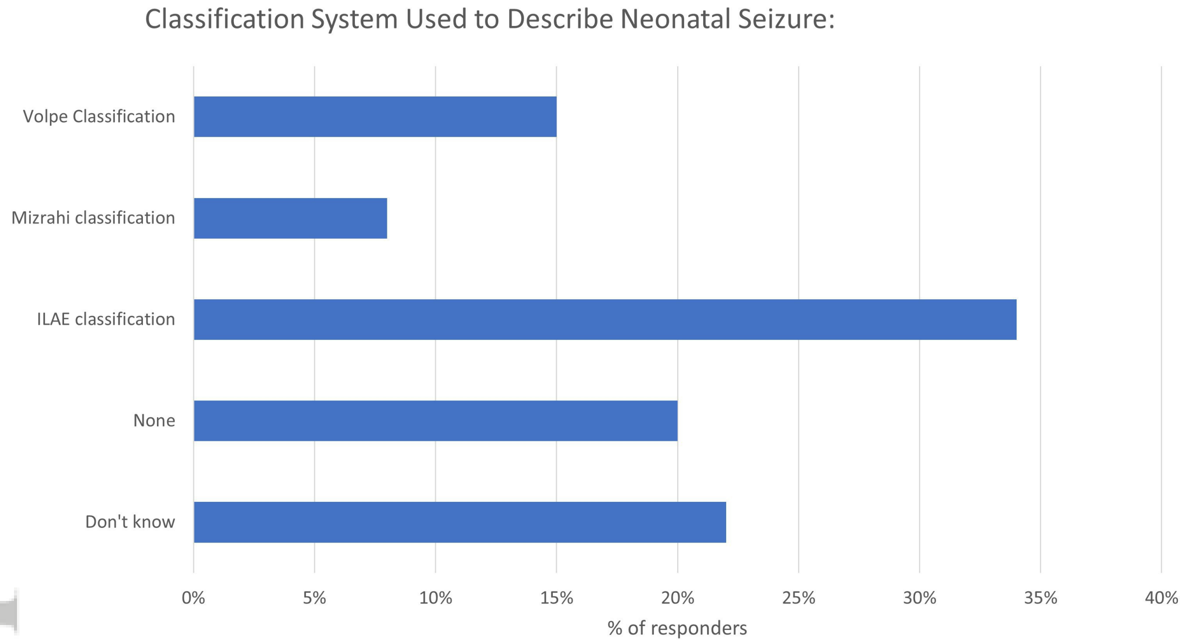
Profession		**Kappa**
Adult neurologist	Overall	0.58
	Clonic	0.73
	Myoclonic	0.52
	Sequential	0.50
	Spasm	0.60
	Tonic	0.59
Child neurologist	Overall	0.66
	Clonic	0.90
	Myoclonic	0.65
	Sequential	0.51
	Spasm	0.73
	Tonic	0.59
Clinical neurophysiologist (adult/child)	Overall	0.72
	Clonic	1.00

	Myoclonic	0.82
	Sequential	0.55
	Spasm	0.61
	Tonic	0.62
EEG technician	Overall	0.90
	Clonic	1.00
	Myoclonic	1.00
	Sequential	0.87
	Spasm	0.87
	Tonic	0.70
Neonatologist / pediatrician	Overall	0.79
	Clonic	1.00
	Myoclonic	0.77
	Sequential	0.74
	Spasm	0.77
	Tonic	0.66
Nurse / other health professional	Overall	0.74
	Clonic	0.83
	Myoclonic	0.68
	Sequential	0.83
	Spasm	0.75
	Tonic	0.68
Student	Overall	0.56
	Clonic	0.71
	Myoclonic	0.65
	Sequential	0.71
	Spasm	0.45
	Tonic	0.54

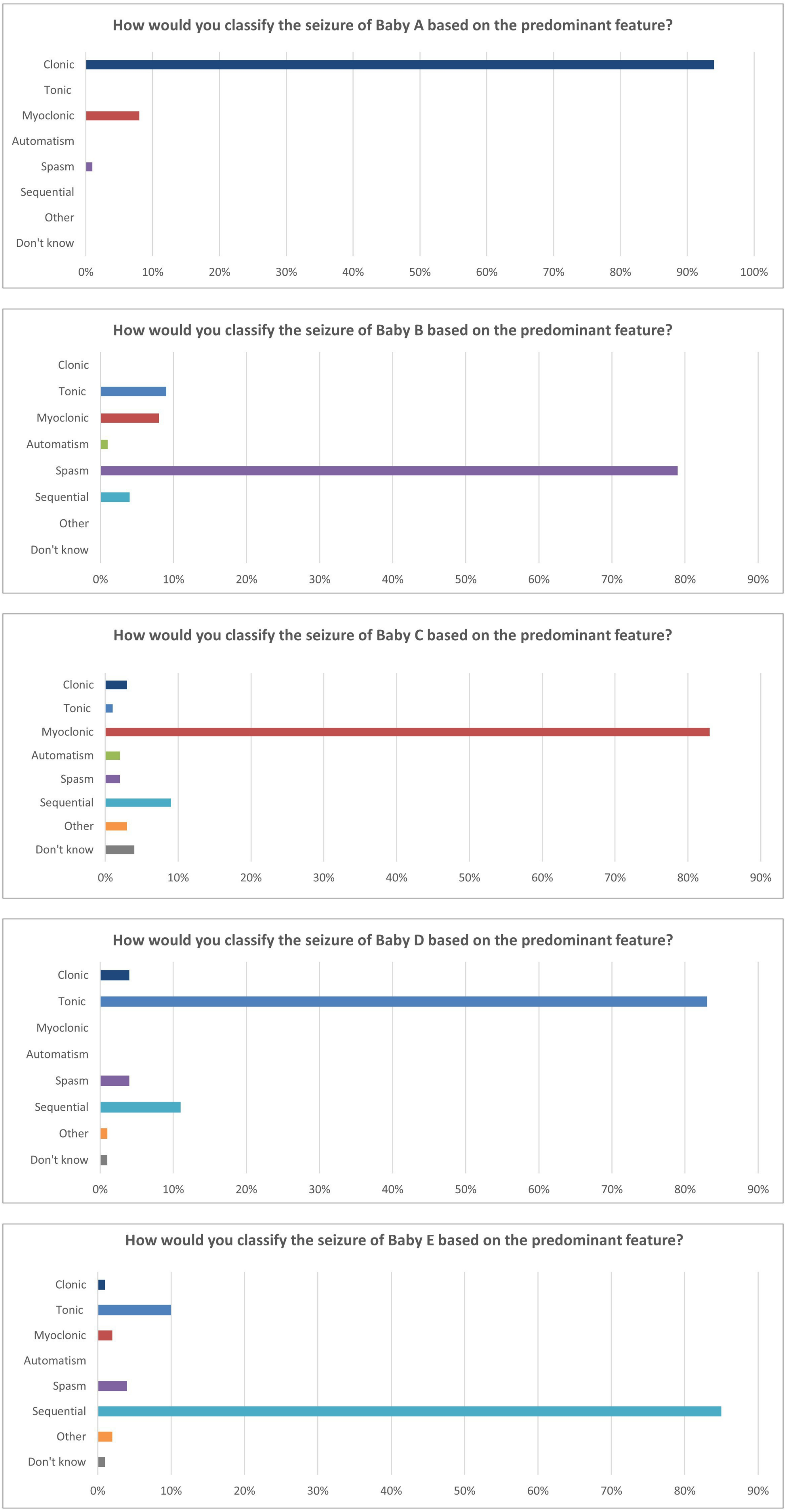
Table 3. Previous system and preference of the new system.

		Preference			
		Yes	**Maybe**	**No**	**Do not know**
Previous system	ILAE classification	49 (75.4%)	13 (20%)	1 (1.5%)	2 (3.1%)
	Mizrahi classification	16 (94.1%)	1 (5.9%)	0 (0%)	0 (0%)
	Volpe classification	22 (75.9%)	3 (10.3%)	1 (3.4%)	3 (10.3%)
	None	29 (72.5%)	4 (10%)	1 (2.5%)	6 (15%)
	Do not know / descriptive	26 (61.9%)	9 (21.4%)	0 (0%)	7 (16.7%)

There was no significant association between previous system and preference of new system based on the Chi-square test (p=0.198), which was also the case after excluding raters with no previous system ("none" or "do not know") and simplifying preference answers into ("yes" vs "maybe" vs "no"+"do not know", "yes" vs "maybe"+"no"+"do not know", "yes" + "maybe" vs "no" + "do not know").



ED-2022-06-0147.R2 (Figure 1).jpg



ED-2022-06-0147.R2 (Figure 2).jpg