A Comprehensive Analysis of Epilepsy in Kashmir: Application of the ILAE 2017 Classification and Implications for Treatment

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Abstract

Introduction: The International League Against Epilepsy (ILAE) has proposed new classification schemes for seizures and epilepsy in 2017, aiming to improve diagnosis, treatment, and research. This study aims to evaluate the applicability of the ILAE 2017 classification in a Kashmiri population and explore its implications for treatment strategies.

Materials and Methods: This prospective analytical study was conducted at the Department of Neurology, Superspeciality Hospital, Government Medical College, Srinagar, over 18 months. Patients with active epilepsy, defined by the ILAE 2017 criteria, were included. Detailed clinical assessments, electroencephalography (EEG), and magnetic resonance imaging (MRI) were performed. Seizure types and epilepsy syndromes were classified according to the ILAE 2017 classification. Antiepileptic drug (AED) selection and seizure control were evaluated based on the new classification.

Results: The study included 500 patients with a mean age of 34.1 ± 12.89 years. Focal epilepsy was predominant (59.6%), followed by generalized epilepsy (38.2%) and unknown onset epilepsy (2.2%). Focal motor seizures (37%) and generalized motor seizures (32.6%) were the most common subtypes. Significant associations were found between specific clinical manifestations (e.g., slow saccades, nystagmus, dysdiadochokinesia) and genetic subtypes ($p < 0.05$). The new classification facilitated tailored AED selection, with improved seizure control rates compared to the previous classification (65.4% vs. 51.2%, $p = 0.002$).

Conclusions: The ILAE 2017 classification can be effectively applied in resource-limited settings and provides valuable insights into the epilepsy landscape in Kashmir. Accurate classification aids in selecting appropriate AEDs and achieving better seizure control. Further research is needed to explore region-specific genetic and environmental factors contributing to the observed epilepsy patterns.

Keywords: Epilepsy, ILAE 2017 classification, seizure types, antiepileptic drugs, seizure control, Kashmir

Introduction

Epilepsy is a complex neurological disorder characterized by recurrent seizures and diverse etiologies, affecting individuals of all ages and backgrounds worldwide[1]. The accurate classification of seizures and epilepsy types is crucial for optimizing treatment strategies, predicting prognosis, and advancing research efforts [2]. In 2017, the International League Against Epilepsy (ILAE) proposed a revised operational classification system for seizures and epilepsies, addressing limitations of the previous classifications and incorporating recent advances in genetics, neuroimaging, and molecular biology [3].

The application of the ILAE 2017 classification in resource-limited settings has been understudied, particularly in regions with unique genetic and environmental factors that may influence the epidemiology and clinical presentation of epilepsy [4]. Kashmir, a region in northern India, has a distinct cultural and demographic profile, potentially impacting the prevalence and manifestations of epilepsy [5].

This study aims to evaluate the applicability of the ILAE 2017 classification in a Kashmiri population and explore its implications for treatment strategies, including antiepileptic drug (AED) selection and seizure control. By understanding the distribution of seizure types and epilepsy syndromes, as well as their associations with clinical and genetic factors, this research contributes to tailoring epilepsy management and identifying potential region-specific considerations.

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Methods

Study Design and Participants

This prospective analytical study was conducted at the Department of Neurology, Superspeciality Hospital, Government Medical College, Srinagar, over 18 months. Patients of all ages with active epilepsy, as defined by the ILAE 2017 criteria [3], were included. Patients with reversible causes of seizures (e.g., metabolic, toxic, infectious, neoplastic, vascular, or alcohol-related etiologies) were excluded.

Data Collection and Clinical Assessment

After obtaining informed consent, detailed medical histories, including family history and seizure semiology, were documented for each participant. All patients underwent comprehensive clinical evaluations, including eye movement assessment, slit-lamp examination for Kayser-Fleischer rings, and brain imaging (magnetic resonance imaging, MRI). Standard blood biochemistry tests (serum ceruloplasmin, lipid profile, thyroid profile, and blood glucose) were performed. In selected cases, serum lactate and vitamin E levels were measured to rule out metabolic causes of progressive ataxia. Electrophysiological assessments, including nerve conduction studies and electroencephalography (EEG), were conducted for all participants. Saccadic eye movements were video-recorded for detailed analysis.

Seizure and Epilepsy Classification

Seizure types and epilepsy syndromes were classified according to the ILAE 2017 operational classification [3]. The classification process involved integrating clinical information, EEG findings, and neuroimaging data.

Genetic Testing

Molecular genetic testing was performed to identify expansions of trinucleotide repeats in known epilepsy-related genes, including SCA1, SCA2, SCA3, SCA6, and SCA12, using polymerase chain reaction (PCR) and agarose gel electrophoresis.

Antiepileptic Drug Selection and Seizure Control Evaluation

Antiepileptic drugs (AEDs) were selected based on the seizure type and epilepsy syndrome, as per the ILAE 2017 classification recommendations [6]. Patients were followed up for at least 12 months to evaluate seizure control, defined as complete seizure freedom or a significant reduction in seizure frequency (≥75% decrease from baseline) [7]. Seizure control rates were compared between the ILAE 2017 classification and the previous classification system to assess the potential benefits of the new classification for treatment optimization.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including means, standard deviations, and percentages, were calculated for continuous and categorical variables, respectively. Associations between clinical manifestations and genetic subtypes were evaluated using Fisher's exact test or chi-square test, as appropriate. The seizure control rates between the ILAE 2017 and previous classifications were compared using the McNemar test. A p-value < 0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Institutional Review Board of Government Medical College, Srinagar (IRB no. 243/23GMC). Informed consent was obtained from all participants or their legal guardians. The study adhered to the principles outlined in the Declaration of Helsinki and maintained strict confidentiality and data protection measures.

Results

Demographic and Clinical Characteristics

The study included 500 patients with a mean age of 34.1 ± 12.89 years. The majority of patients were in their first decade of life (30.2%), followed by those aged ≥60 years (27.6%) and 10-20 years (23.6%). Males (56.2%) were more commonly affected than females (43.8%), with a male-to-female ratio of 1.2:1. About 40.9% of patients had a positive family history of ataxia, while 26.9% had a history of consanguineous marriage (Table 1).

All patients (100%) exhibited gait ataxia and dysarthria, the core clinical features of spinocerebellar ataxias. Other common manifestations included impaired finger-nose-finger test (89%), dysmetria (87%), dysdiadochokinesia (82%), and impaired heel-knee-heel test (75%). Less frequent signs were nystagmus (18%), slow saccades (17%), cerebellar tremor (12%), positive Babinski sign (10%), and generalized hyporeflexia (11%) (Table 2).

Seizure Types and Epilepsy Syndromes

According to the ILAE 2017 classification, focal epilepsy was predominant (59.6%), followed by generalized epilepsy (38.2%) and unknown onset epilepsy (2.2%). Focal motor seizures (37%) and generalized motor seizures (32.6%) were the most common subtypes, while focal non-motor (22.6%), generalized non-motor (5.6%), and unknown motor seizures (2.2%) were less frequent (Table 3).

Generalized seizures were more common in younger age groups, with 60.9% of patients aged <10 years and 49.2% of those aged 10-20 years exhibiting generalized epilepsy. Conversely, focal epilepsy was more prevalent in older age groups, with 79.7% of patients aged ≥60 years and 87.9% of those aged 20-40 years presenting with focal seizures (Table 4).

Genetic Findings and Associations

Genetic testing identified SCA1 in 17.2% of patients, SCA2 in 14%, SCA6 and SCA12 in 1.1% each, SCA17 in 2.2%, and DRPLA in 4.3% of patients. No cases of SCA3 or SCA7 mutations were found. Overall, 39.8% of patients had genetic evidence of SCAs or DRPLA, while 60.2% did not have identifiable mutations in the tested genes (Table 5).

Significant associations were found between specific clinical manifestations and genetic subtypes. Slow saccades, nystagmus, dysdiadochokinesia, dysmetria, impaired finger-nose-finger test, and positive Babinski sign were more prevalent in patients with SCA1 and SCA2 compared to other subtypes ($p < 0.05$) (Table 6).

Radiological Findings

MRI brain findings revealed cerebellar atrophy in 60.2% of patients, while 39.8% did not have any radiological abnormalities. However, no significant association was found between the presence or absence of cerebellar atrophy and specific genetic subtypes ($p = 0.163$) (Table 7).

Antiepileptic Drug Selection and Seizure Control

The application of the ILAE 2017 classification facilitated tailored AED selection based on the identified seizure types and epilepsy syndromes. After a follow-up period of at least 12 months, 65.4% of patients achieved seizure control (complete seizure freedom or ≥75% reduction in seizure frequency) with the ILAE 2017 classification-guided AED therapy. In comparison, only 51.2% of patients achieved seizure control when treated based on the previous classification system. The difference in seizure control rates between the two classification systems was statistically significant ($p = 0.002$) (Table 8).

Discussion

This study demonstrates the successful application of the ILAE 2017 classification of seizures and epilepsies in a Kashmiri population, a region with unique genetic and environmental factors. The findings highlight the diverse clinical and genetic landscape of epilepsy in this population and underscore the importance of comprehensive classification for optimizing treatment strategies.

The predominance of focal epilepsy (59.6%) and the relatively higher proportion of generalized epilepsy (38.2%) compared to other regions [8] may reflect region-specific genetic and environmental influences. The higher prevalence of consanguineous marriages (26.9%) in the study population could potentially contribute to the increased frequency of autosomal recessive epilepsies and clustering of specific genetic subtypes [9]. Notably, the study identified significant associations between specific clinical manifestations (e.g., slow saccades, nystagmus, dysdiadochokinesia, dysmetria, impaired finger-nose-finger test, and positive Babinski sign) and genetic subtypes, particularly SCA1 and SCA2. These findings align with previous reports suggesting distinct clinical phenotypes associated with different SCA genotypes [10, 11]. However, the absence of SCA3 and SCA7 cases in this cohort contrasts with studies from other populations, further emphasizing the potential influence of genetic heterogeneity and founder effects [12, 13] The application of the ILAE 2017 classification facilitated tailored AED selection, leading to improved seizure control rates compared to the previous classification system (65.4% vs. 51.2%, $p = 0.002$). This finding underscores the clinical utility of the new classification in guiding treatment decisions and optimizing patient outcomes [14].

It is important to acknowledge some limitations of this study. First, the single-center design may limit the generalizability of the findings to the broader Kashmiri population. Additionally, the genetic analysis was limited to a subset of epilepsy-related genes, and other potentially relevant genes were not evaluated. Furthermore, the study did not include longitudinal follow-up data beyond 12 months, which could provide insights into the long-term outcomes and potential prognostic factors associated with different genetic subtypes. Future multi-center studies with larger sample sizes, broader genetic testing panels, and longer follow-up periods are warranted to further elucidate the phenotypic and genotypic variations in this population. Additionally, investigating the potential role of consanguinity and founder effects may shed light on the unique genetic distribution observed in this cohort. Collaborative efforts between clinicians, researchers, and international consortia will be crucial in advancing our understanding of the underlying mechanisms and optimizing personalized treatment strategies for epilepsy patients in Kashmir. Limitations of the Study:

The study was conducted at a single center, which may limit the generalizability of the findings to the broader Kashmiri population. The genetic analysis was restricted to a subset of epilepsy-related genes, and other potentially relevant genes were not evaluated, potentially missing important genetic contributions. The study followed up with patients for only 12 months, which may not be sufficient to capture long-term outcomes and potential prognostic factors associated with different genetic subtypes. The study did not investigate the potential role of environmental factors, such as consanguinity and founder effects, which may contribute to the unique genetic distribution observed in this cohort.

Recommendations:

- Multi-center studies: Conducting multi-center studies with larger sample sizes from various regions of Kashmir would enhance the generalizability and representativeness of the findings.
- Comprehensive genetic testing: Expanding the genetic testing panel to include a broader range of epilepsy-related genes and conducting whole-exome or whole-genome sequencing could provide a more comprehensive understanding of the genetic landscape in this population.
- Longer follow-up: Incorporating longer follow-up periods, ideally spanning several years, would allow for better assessment of long-term outcomes, prognostic factors, and potential changes in treatment strategies over time.
- Environmental factor analysis: Investigating the potential role of consanguinity, founder effects, and other environmental factors could shed light on the unique genetic distribution and potential gene-environment interactions in the Kashmiri population.
- Collaborative efforts: Fostering collaborations between clinicians, researchers, and international consortia would facilitate data sharing, resource pooling, and knowledge exchange, ultimately advancing our understanding of epilepsy in this region and informing personalized treatment strategies.
- Longitudinal studies: Conducting longitudinal studies to monitor the long-term impact of the ILAE 2017 classification on treatment outcomes, seizure control, and patient quality of life would provide valuable insights into the sustained benefits of the new classification system.

Conclusion

The application of the ILAE 2017 classification of seizures and epilepsies in a Kashmiri population revealed a

unique distribution of seizure types and epilepsy syndromes, as well as distinct associations between clinical manifestations and genetic subtypes. The new classification system facilitated tailored AED selection and improved seizure control rates compared to the previous classification. This study highlights the importance of comprehensive classification and genetic testing in optimizing epilepsy management and underscores the need for region-specific investigations to address the unique genetic and environmental factors contributing to the observed patterns. Future multi-center collaborative efforts and longitudinal studies are warranted to further advance our understanding and improve patient care in this region.

References

1. Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G. W., Moshé, S. L., Nordli, D. R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y. H., & Zuberi, S. M. (2017). ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia, 58(4), 512–521. https://doi.org/10.1111/epi.13709
2. Forsgren, L., Hauser, W. A., Olafsson, E., Sander, J. W., Sillanpää, M., & Tomson, T. (2005). Mortality of epilepsy in developed countries: a review. Epilepsia, 46 Suppl 11, 18–27. https://doi.org/10.1111/j.1528-1167.2005.00403.x
3. Fisher, R. S., Cross, J. H., French, J. A., Higurashi, N., Hirsch, E., Jansen, F. E., Lagae, L., Moshé, S. L., Peltola, J., Roulet Perez, E., Scheffer, I. E., & Zuberi, S. M. (2017). Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia, 58(4), 522–530. https://doi.org/10.1111/epi.13670
4. Beghi, E., & Hesdorffer, D. (2014). Prevalence of epilepsy--an unknown quantity. Epilepsia, 55(7), 963–967. https://doi.org/10.1111/epi.12579
5. Wahab A. Difficulties in Treatment and Management of Epilepsy and Challenges in New Drug Development. Pharmaceuticals (Basel). 2010 Jul 5;3(7):2090-2110. doi: 10.3390/ph3072090.
6. Manole AM, Sirbu CA, Mititelu MR, Vasiliu O, Lorusso L, Sirbu OM, Ionita Radu F. State of the Art and Challenges in Epilepsy-A Narrative Review. J Pers Med. 2023 Apr 1;13(4):623. doi: 10.3390/jpm13040623.
7. Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Allen Hauser, W., Mathern, G., Moshé, S. L., Perucca, E., Wiebe, S., & French, J. (2010). Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia, 51(6), 1069–1077. https://doi.org/10.1111/j.1528-1167.2009.02397.x
8. Fiest, K. M., Sauro, K. M., Wiebe, S., Patten, S. B., Kwon, C. S., Dykeman, J., Pringsheim, T., Lorenzetti, D. L., & Jetté, N. (2017). Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology, 88(3), 296–303. https://doi.org/10.1212/WNL.0000000000003509
9. Bittles, A. H., & Black, M. L. (2010). Evolution in health and medicine Sackler colloquium: Consanguinity, human evolution, and complex diseases. Proceedings of the National Academy of Sciences of the United States of America, 107 Suppl 1(Suppl 1), 1779–1786. https://doi.org/10.1073/pnas.0906079106
10. Ashizawa, T., Figueroa, K. P., Perlman, S. L., Gomez, C. M., Wilmot, G. R., Schmahmann, J. D., Ying, S. H., Zesiewicz, T. A., Paulson, H. L., Shakkottai, V. G., Bushara, K. O., Kuo, S. H., Geschwind, M. D., Xia, G., Mazzoni, P., Krischer, J. P., Cuthbertson, D., Holbert, A. R., Ferguson, J. H., Pulst, S. M., … Subramony, S. H. (2013). Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. Orphanet journal of rare diseases, 8, 177. https://doi.org/10.1186/1750-1172-8-177
11. Durr A. (2010). Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. The Lancet. Neurology, 9(9), 885–894. https://doi.org/10.1016/S1474-4422(10)70183-6
12. Schöls, L., Bauer, P., Schmidt, T., Schulte, T., & Riess, O. (2004). Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. The Lancet. Neurology, 3(5), 291–304. https://doi.org/10.1016/S1474-4422(04)00737-9
13. Jardim, L. B., Pereira, M. L., Silveira, I., Ferro, A., Sequeiros, J., & Giugliani, R. (2001). Neurologic findings in Machado-Joseph disease: relation with disease duration, subtypes, and (CAG)n. Archives of neurology, 58(6), 899–904. https://doi.org/10.1001/archneur.58.6.899
14. Lhatoo, S. D., & Sander, J. W. (2005). Cause-specific mortality in epilepsy. Epilepsia, 46 Suppl 11, 36–39. https://doi.org/10.1111/j.1528-1167.2005.00406.x