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Implementation of the new ILAE classification of epilepsies into clinical practice — A cohort study

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ABSTRACT

Purpose: Appropriate management of patients with epilepsy requires precise classification of their disease. Implementation of the recent International League Against Epilepsy (ILAE) classification of seizures and epilepsies may affect data on the relative proportions of specific types of seizures or epilepsies and should be tested in everyday practice. The aim of the study was to determine the prevalence of specific epilepsy types, syndromes, and etiologies, as defined by the new ILAE classification, in a large cohort of adult patients with epilepsy.
Material and methods: The single-center cohort study involved consecutive adult patients with epilepsy seen at the university epilepsy clinic. Information about medical history, neurological examination, neuroimaging, electroencephalography (EEG), genetic tests, epilepsy treatment, and other investigations was collected from medical records and prospectively updated if necessary. Epilepsy types and etiology, as well as epileptic syndromes, were classified according to the new ILAE classifications.
Results: We studied 653 patients (mean age: 37.2 years, 59.9% were women). Epilepsy was classified as focal in 458 cases (70.2%), generalized in 155 subjects (23.7%), or as combined focal and generalized in 11 patients (1.7%). The epilepsy type was labeled as unknown in 29 (4.4%) patients. A definite cause of epilepsy was identified in 59.4% of the cases, with a structural etiology (n = 179, 27.4%) and genetic or presumed genetic etiology (n = 169, 25.9%) being the most common. In 167 (25.5%) patients, specific epilepsy syndromes, mostly genetic generalized epilepsy syndromes, were diagnosed.
Conclusion: The use of the recent ILAE classification of seizures and epilepsies in the cohort of patients with epilepsy seen in single epilepsy center enabled unequivocal characterization of epilepsy type in >95% of patients. A definite etiology of epilepsy could be established in about 60% of patients.

1. Introduction

Epilepsy, with the point prevalence of active disease 6.38 per 1000 persons, is one of the most common neurological disorders [1]. Epilepsy is not a single entity but the consequence of underlying neurological or systemic disorders with a multitude of different manifestations [2]. While the background for such a variety of seizure types is not fully understood, it is universally recognized that the management of epilepsy is critically dependent of both etiology and type of seizures/epilepsy experienced by individual patients. Thus, identifying the etiology of epilepsy and the precise classification of seizure/epilepsy type and epilepsy syndrome is an indispensable step in appropriate management and prognosis.

The International League Against Epilepsy (ILAE) has recently released the position paper on the new classification of epilepsies and their etiologies [3] as a reflection of the advances in our understanding of the pathophysiology of epilepsy. It was introduced, with the hope to enable the classification of the formerly unclassifiable seizure types, to provide more practical structure for the classification of epilepsies and, last but not the least, to improve communication and mutual understanding between physicians and patients [4]. The justification for the new classification, as well as the comprehensive discussions on its purpose, advantages, and limitations were published previously [5–9].

The new ILAE classifications of seizures [10] and epilepsies [3] are designed as a universal tool for all age groups, populations, and areas with the consideration taken to their inherent differences in sociodemographic characteristics and available resources. Geographic, socioeconomic, and cultural factors, e.g., ethnicity, prevalence of specific infectious diseases, or common consanguinity may influence the etiology of epilepsy, leading to potential differences in reported epidemiology of various types or causes of epilepsy. Also, the extent of the diagnostic work-up, often limited because of poor resources, might have impact on a rate of epilepsies

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classified as 'unknown'. In line with the views expressed by authors and commentators of the new ILAE classification [8,9], it seems reasonable to test applicability of that classification in different populations in order to evaluate its usefulness to the contemporary practice and to define possible difficulties with its implementation.

Only few papers incorporating the new ILAE classification of the epilepsies into clinical practice have been published so far and involved either children [11] or patients from rural regions of China [12].

The aim of the study was, therefore, to determine the prevalence of specific epilepsy types, syndromes, and etiologies, as defined by the new ILAE classification, in a large cohort of adult patients with epilepsy.

2. Material and methods

2.1. Patients

The single-center cohort study was performed among patients who visited the tertiary outpatient epilepsy clinic at the Department of Neurology within University Hospital in Krakow between January 1st, 2017 and October 31st, 2018.

Inclusion criteria consisted of the diagnosis of epilepsy made according to the ILAE practical clinical definition of epilepsy [13] and patient's age of at least 18 years during the initial visit in the study period. Brain magnetic resonance imaging (MRI) was required for inclusion; patients for whom only computed tomography (CT) was available were included only if they had a definite cause of epilepsy established previously (i.e., stroke or traumatic brain injury). Patients with incomplete medical history (i.e., institutionalized, adopted, or without hospital discharge reports) were excluded from the analysis. Overall, 67 out of 720 potentially eligible patients were excluded.

Protocol of the study followed the principles of Helsinki Declaration and received approval from the university bioethical committee.

2.2. Methods

Patients with epilepsy were identified from the electronic database of the university epilepsy outpatient clinic. During the first visit within study period, the following information were collected by means of structured questionnaire: age, sex, age at the diagnosis of epilepsy, seizure types, family history of epilepsy, electroencephalography (EEG), and neuroradiological findings. Patients were then asked to provide any additional data from their medical records (discharge summaries, results of genetic studies, etc.) that might be relevant for the appropriate classification. Each patient was seen at least three times before the study was completed; the time intervals between visits differed according to patient's current needs.

Routine interictal EEG was performed in each patient, followed by EEG after sleep deprivation and video-EEG, if routine EEG was normal. According to the inclusion criteria, each patient had MRI (in rare instances, CT) of the head performed. Most patients had their diagnostic work-up completed before the inclusion to the present study.

Epilepsies were classified according to the ILAE classification into four types: focal, generalized, combined (generalized & focal), and unknown [3]. Specific electroclinical syndromes were identified if possible, according to Berg et al. [14].The etiology of epilepsy was categorized as structural, genetic, infectious, metabolic, immune, or unknown [3]. The etiology or basic disorder underlying the epilepsy was identified by a systematic review of medical records, general physical and neurologic examination, EEG, laboratory tests, including genetic studies, and neuroimaging (1.5 T MRI). The instruction manual for the ILAE classification [15] was used to assure the same diagnostic approach for all patients involved.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [16].

Descriptive statistics included numbers and percentages, as well as means and ranges to characterize subgroups or specific variables. The 95% confidence intervals (CI) for proportions were also provided. Data were analyzed with Statistica v. 12.5 (StatSoft Inc., Tulsa, OK).

3. Results

3.1. Sample characteristics

A total of 653 patients with epilepsy were included in this study. All participants were Caucasians. The cohort comprised 391 (59.9%) women. Mean age at the moment of inclusion to the study was 37.2 years (range, 18–84), and mean age at onset of epilepsy was 19.5 years (range, 1–73).

3.2. Epilepsy type

Focal epilepsy was diagnosed in 458 (70.2%; 95% CI: 66.5–73.6%) patients whereas generalized epilepsy was found in 155 (23.7%; 95% CI: 20.5–27.2%) patients, including 151 with genetic generalized epilepsies and 4 with Unverricht–Lundborg disease. Combined focal and generalized epilepsy was diagnosed in 11 (1.7%; 95% CI: 0.8–3.0%) patients with Lennox–Gastaut syndrome. The epilepsy type could not be established (and labeled as 'unknown epilepsy') in 29 (4.4%; 95% CI: 3.0–6.3%) patients, mostly with generalized tonic–clonic seizures and normal MRI and EEG results.

3.3. Syndromic classification

A total of 151 (23.1%; 95% CI: 19.9–26.5%) patients had genetic generalized epilepsy with juvenile myoclonic epilepsy being the most common syndrome, followed by juvenile absence epilepsy. Lennox–Gastaut syndrome, progressive myoclonus epilepsy, and idiopathic photosensitive occipital lobe epilepsy were also recognized in our cohort (see Table 1 for details).

3.4. Etiology

Etiology of epilepsy in our patients is summarized in Table 2 and Fig. 1. The most prevalent etiologies were genetic/presumed genetic (169; 25.9%; 95% CI: 22.6–29.4%) and structural (179; 27.4%; 95% CI: 24.0–31.0%). Genetic generalized epilepsies were diagnosed in 151 patients. Rare inherited disorders underlying epilepsy were present in 18 patients, mostly with neurocutaneous syndromes. The most commonly diagnosed structural lesions underlying epilepsy were traumatic brain injury and brain tumors followed by malformations of cortical and brain development. Other common structural etiologies included stroke, cerebral vascular malformations, and perinatal insult. Postinfectious etiology of epilepsy was found in 38 (5.8%; 95% CI: 4.1–7.9%) patients with the history of encephalitis and/or meningitis. Only two patients had immune epilepsy related to anti-N-methyl-D-aspartate (NMDA) encephalitis. In 265 (40.6%; 95% CI: 36.8–44.5%) subjects, mostly with focal seizures, the cause of epilepsy remained unknown.

4. Discussion

Epilepsy is a complex disorder with multiple etiologies and different manifestations. Identification of the epilepsy type and etiology, as well as syndromic diagnosis, is crucial for appropriate management and prognosis. Recent advances in genetic, metabolic, and neuroimaging techniques have improved accuracy of the comprehensive diagnosis of epilepsy, and the newly developed ILAE classification system should potentially lead to more homogenous reporting of epidemiologic data along with the more precise characterization of studied cohorts of patients. Our study provides a practical feedback from the single-center cohort of patients with epilepsy in whom such a classification was applied.

To the best of our knowledge, this is the first Polish study implementing the recently published ILAE classification of the

Table 1
Epilepsy syndromes diagnosed in studied patients with epilepsy according to Berg et al. [14].

Epilepsy syndromes	167 (25.5%; 95% CI: 22.3–29.1%)
Genetic (idiopathic) generalized epilepsies	151 (90.4%; 95% CI: 84.9–94.4%)
Juvenile myoclonic epilepsy	75
Juvenile absence epilepsy	46
Epilepsy with generalized tonic–clonic seizures alone	23
Childhood absence epilepsy	5
Jeavons syndrome	2[a]
Lennox–Gastaut syndrome	11 (6.6%; 95% CI: 3.3–11.5%)
Progressive myoclonus epilepsy	4 (2.4%; 95% CI: 0.7–6.0%)
Idiopathic photosensitive occipital lobe epilepsy[a]	1 (0.6%; 95% CI: 0.02–3.3%)

Abbreviation: 95% CI — 95% confidence interval.
[a] Not listed by Berg et al. [14].

epilepsies, doing so in a large cohort of 653 adult patients with epilepsy. As expected, the majority of subjects (70.2%) had focal epilepsy [17,18]. The proportion of patients with genetic generalized epilepsies in our cohort (23.1%) was similar to previous estimations (15–20%) [19]. In a small proportion of patients (4.4%), we were not able to determine the epilepsy type. These patients had generalized tonic–clonic seizures, normal MRI, normal routine and sleep-deprived EEG, and no features in medical history that might enable the diagnosis of the specific epilepsy type. The subgroup of patients with combined epilepsy (both generalized and focal seizures) was very small (1.7%). These findings are in agreement with recently published population-based study from Norway [20]. The small proportion of patients with unknown epilepsy type suggests that the classification scheme will lead to unequivocal description of epilepsy in almost all patients and that the future studies focused on this group would require multicenter approach as the number of potential participants would be small.

Table 2
Etiology of epilepsy in a cohort of 653 patients according to the Position Paper of the ILAE Commission for Classification and Terminology (Scheffer et al. [3]).

Structural 179 (27.4%; 95% CI: 24.0–31.0%)
Stroke 25
Ischemic 12
Cerebral sinus thrombosis 4
Subarachnoid hemorrhage/aneurysm 9
Cerebral vascular malformations 20
Cavernous hemangioma 9
Arteriovenous malformation 11
Traumatic brain injury 37
Malformation of cortical or other brain development 29
Neurodegenerative disease 1
Perinatal insult 22
Brain neoplasm 35
DNET 9
Meningioma 9
Astrocytoma 4
Ganglioglioma 4
Hypothalamic hamartoma 1
Leukemia 1
Unknown 7
Others 10
Arachnoid cyst 7
Dermoid cyst 1
Neuroglial cyst 1
Hippocampal sclerosis 1
Genetic 169 (25.9%; 95% CI: 22.6–29.4%)
Genetic generalized epilepsies 151
Neurocutaneous syndromes 11
Tuberous sclerosis 6
Neurofibromatosis 3
Sturge–Weber disease 2
Unverricht–Lundborg disease 4
Coffin–Lowry syndrome 1
Gaucher disease 1
MELAS 1
Infectious 38 (5.8%; 95% CI: 4.1–7.9%)
Encephalitis/meningitis 38
Metabolic 0 (0%)
Immune 2 (0.3%; 95% CI: 0.04–1.1%)
Anti-NMDA-R encephalitis 2
Unknown 265 (40.6%; 95% CI: 36.8–44.5%)

Abbreviations: 95% CI — 95% confidence interval, DNET — dysembryoplastic neuroepithelial tumor, MELAS — mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes, NMDA-R: N-methyl-D-aspartate receptor.

In 167 patients (25.6%), specific electroclinical syndromes, mostly genetic generalized epilepsy syndromes, were diagnosed. We reckon that the specific syndromic diagnosis could be made in a higher proportion of patients with long-term video-EEG monitoring [21,22]. However, long-term video-EEG monitoring is not easily available in Poland, and the lack of resources is an obvious limiting step in the precise characterization of epilepsies in general.

The etiology of the epilepsy could be identified in nearly 60% of cases. This is in accordance with recent population-based studies from Scandinavia [19,22] and a cohort study from China [12]. The proportion of patients with genetic/presumed genetic (25.9%) and structural etiology (27.4%) was roughly similar to the findings of Sokka et al. [23], although their study population comprised children. Chinese authors, using the new ILAE classification of epilepsies [12], found structural etiology in 43% and genetic in 10%. This discrepancy can be partially explained by higher proportion (88%) of patients with focal epilepsy and methods of patient selection in that study. The cause of epilepsy was unknown in 40.5% of our patients, which is in line with the results of the population-based study from Rochester [24], although our study comprised adult patients only.

Epilepsy related to stroke or neurodegenerative diseases was diagnosed in a very small proportion of patients. This finding seems to be the result of the study design and the general organization of neurological care for patients suffering from cerebrovascular or neurodegenerative disorders. Such patients are often managed by other outpatient clinics dedicated to the etiology of their neurological problem or by geriatricians.

Malformations of cortical or other brain development were found only in 29 patients; it is worth noting that 13 of them were previously diagnosed with perinatal insult. We believe that many patients, especially with focal cortical dysplasia, may have been misdiagnosed. Hippocampal sclerosis, which is commonly seen in patients with temporal lobe epilepsy, was diagnosed in one patient only. Brain MRI of our patients came from different centers, not all of them were performed according to the specific epilepsy protocol and evaluated by qualified neuroradiologists. As a consequence, a number of subtle structural lesions may have gone unrecognized [25].

Only 18 (2.8%) of our patients suffered from definite genetic diseases. Genetic tests in 5 patients with suspected Unverricht–Lundborg disease, Dravet syndrome, and Glucose transporter type 1 (GLUT1) deficiency syndrome were underway at the time of the study. We believe that more patients from our cohort might have genetic conditions, but genetic tests are still expensive and not easily available.

All patients with genetically determined disorders were included in the 'genetic etiology' subgroup, although the cause of epilepsy could have been also classified as structural (tuberous sclerosis complex) or metabolic (Gaucher disease), which might evoke minor inconsistencies in future reports on etiology of epilepsy. We would like to highlight a small but important subgroup with immune etiology (due to autoimmune encephalitis). With the improvement of diagnostic methods, it may become more important.

Our study has several limitations. Firstly, the studied cohort involved adult patients followed up in the university epilepsy clinic and may be

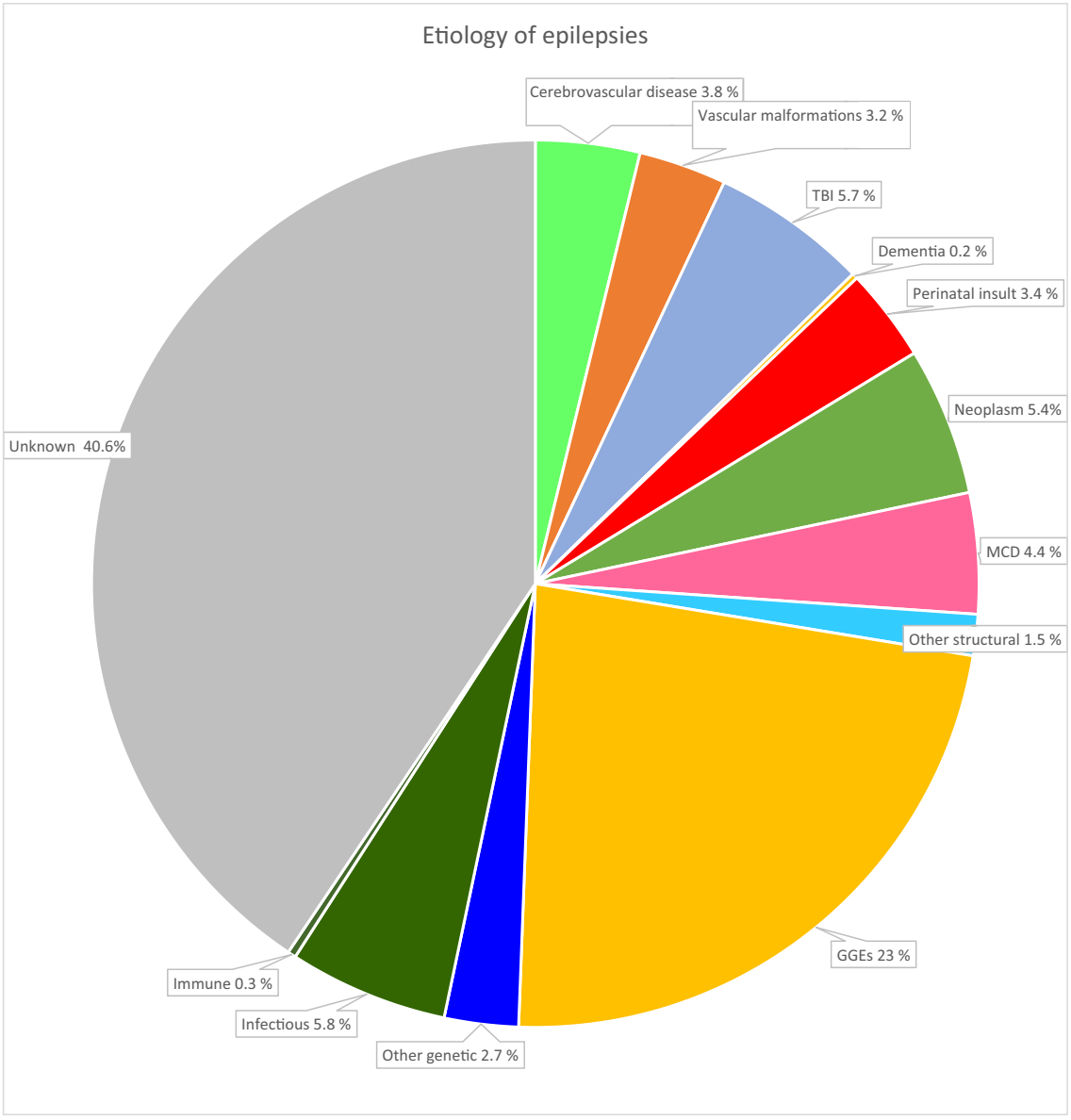

Fig. 1. Etiologies of epilepsy according to Scheffer et al. Abbreviations: TBI — traumatic brain injury, MCD — malformation of cortical development, GGEs — genetic generalized epilepsies.

not representative to general population. Our outpatient clinic serves to all patients regardless of the severity of epilepsy, but patients with some specific etiologies of epilepsy (cerebrovascular or neurodegenerative) are more likely to seek for help from the respective subspecialties. Consequently, the proportion of patients with undetermined etiology of their epilepsy might be relatively larger than expected. It is probably counterbalanced with the better-than-average access to more sophisticated diagnostic tools. Secondly, the study had retrospective design, and some information might be unavailable or less reliable. Lack of specific information (e.g., about perinatal insults, infections, or traumas in remote past) would obviously affect the ability to establish specific etiology of epilepsy.

5. Conclusion

The use of recent ILAE classification of seizures and epilepsies in the cohort of patients with epilepsy seen in single epilepsy center enabled unequivocal characterization of epilepsy type in >95% of patients. A definite etiology of epilepsy could be established in about 60% of patients. We found the recent ILAE classification of epilepsies easily applicable and useful in a routine clinical setting.

Declaration of interest

MB received honoraria for publications from Sanofi-Genzyme; honoraria for lectures, travel expenses, and conference fees from Sanofi, Adamed, Teva Pharmaceutical, Neuraxpharm, Glenmark, UCB Pharma.

AS received honoraria for lectures from Bayer, Boehringer Ingelheim, Novartis, Polpharma, Bristol-Myers Squibb, Novartis, Biogen, Teva Pharmaceutical, Medtronic; for the participation in advisory meetings from Bayer, Boehringer Ingelheim, Novartis.

RK reports no conflict of interest.

WT received honoraria for publications from Sanofi-Genzyme; honoraria for lectures, travel expenses, and conference fees from Shire and CSL Behring.

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