Epidemiologycal Study of Childhood Epilepsy Using the Newly Classification Proposed

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Abstract: *Objectives*: The aim of this study is to determine the distribution of electroclinical syndromes and other epilepsies in a population-based group of children, using the newly classification proposed by the ILAE. *Material & Methods*: The study is based on data obtained from the review of the 454 medical records of patients with active epilepsy who were checked in correspondent follow up consultation from January until December 2009. The newly proposed Report of the ILAE Commission on Classification and terminology 2005—2009 has been applied for diagnosis and classification. *Results*: Most of the clinical entities were electroclinical syndromes (54.8%). In infants, West syndrome and Dravet syndrome were the most prevalent syndromes. In childhood, the main syndromes were benign epilepsy with centrotemporal spikes and childhood absence epilepsy. In adolescents, juvenile absence epilepsy. Epilepsies attributed to and organized by structural-metabolic causes were seen in 20.8% of the patients, with perinatal insults and cerebral malformations as the most prevalent causes. Epilepsies of unknown cause were seen in 24.1% of patients. *Conclusions*: Using the most recent ILAE classification of epileptic seizures and the epilepsies we were able to identify most cases. The 2005-2009 ILAE classification may serve as the basis for organizing knowledge about recognized forms of epilepsy and facilitate identification of new forms.

Keywords: Child Neurology, Epilepsy, Pediatric Neurology.

INTRODUCTION

Epileptic seizures and epileptic syndromes are frequently diagnosed during childhood, with an incidence rate ranging from 41 to 67 per 100 000 cases [1-8]. The syndromic classification has demonstrated to be useful for therapeutic approaches and to define prognosis [9]. The currently valid 1989 ILAE syndromic classification of epilepsies is based on topographic and etiologic criteria [10]. In fact, it separates epilepsies with generalized seizures (generalized epilepsies) from epilepsies with partial seizures (localization-related epilepsies). Moreover, these classification epilepsies are also separated in those with a known etiology (symptomatic) and those without an unknown etiology (idiopathic and cryptogenic). In this way, there are four major classes of syndromes: localization-related epilepsies and syndromes, generalized epilepsies and syndromes, epilepsies and syndromes that are undetermined as to whether they are focal or generalised, and special syndromes [11-18].

However, this classification does not include new concepts of modern neuroimaging, genomic technologies and molecular biology that are arising in epilepsy research [19,20]. The ILAE Task Force on Classification and Terminology has been evaluating this 1989 classification to incorporate these significant advances reached in the last decade. The modifications and new recommendations were published in 2001 [21]; they were updated and revised in 2006 [22] and, ultimately, in 2010 as *Revised terminology and concepts for organization of seizures and epilepsies, 2005-2009* [23]. New conceptions of genetic, structural-metabolic, and unknown have replaced idiopathic, symptomatic, and cryptogenic old concepts; and thus epilepsies are renowned as electroclinical syndromes, nonsyndromic epilepsies with structural-metabolic causes and epilepsies of unknown etiology.

The aim of this study was to determine the distribution of electroclinical syndromes and other epilepsies in a population-based group of children, using the newly proposed Report of the ILAE Commission on Classification and Terminology 2005—2009 [23].

METHODS

The community of Navarre has a population of 605.876 inhabitants (2008 census, National Institute of Statistics), 88.055 of whom are children (<15 years of age; 45.105 boys [51.2%] and 42.950 girls [48.5%]). The Navarre Hospital Complex of Pamplona is the neuropediatric reference centre in Navarre and is the place where the neuropediatric and neurophysiology and magnetic resonance imaging units are located. The functional and structural organization of the health service in Navarre provides referral of all patients with suspected seizures or epilepsy from the health care centres or secondary hospitals (located in Tudela and

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E-ISSN: 2309-6179/14

Estella) to the reference hospital. A neuropediatric evaluation and follow-up are performed, and, finally, a syndromic diagnosis is established in most patients of our community.

The study is based on data obtained from the review of the medical records of all patients with active epilepsy who were checked in correspondent follow up consultation from January until December 2009 in the Paediatric Neurology Unit of the Navarre Hospital Complex. The resulting study sample was 454 patients.

Information recorded from every patient includes epidemiologic data (sex, age at onset, and personal and familial history of epilepsy and febrile seizures), clinical data (seizure types, neurological findings, and associated pathologic conditions), as well as the results of complementary studies (electroencephalogram and neuroimaging) and genetic, metabolic, and neurophysiologic studies (when required) in order to classify electroclinical syndromes and other epilepsies. Magnetic resonance imaging was performed in all patients at the onset of diagnosis according to a standardized pediatric seizure protocol.

The newly proposed Report of the ILAE Commission on Classification and terminology 2005—2009 has been applied for diagnosis and classification [23]. Thus, epilepsy was diagnosed at the time of a second unprovoked seizure, and multiple seizures in a 24-h period were considered a single episode. Patients with neonatal seizures only, febrile seizures, and other acute symptomatic seizures were excluded.

The computer program SPSS 20.0 for Windows (Chicago, Illinois, USA) was used to perform the statistical analysis (descriptive study).

RESULTS

The whole group was 454 patients (232 males and 222 females). Age distribution was 78 infants (from one to 12 months of age), 288 childhood (from one to 10 years), and 88 adolescents (from 10 to 15 years).

Table **1** shows the distribution of the electroclinical syndromes and other epilepsies in infants (37 males and 41 females). Most of the clinical entities were electroclinical syndromes (56.4%), whereas others were epilepsies attributed to and organized by structural-metabolic causes (34.6%) or epilepsies of known cause (8.9%). West syndrome and Dravet syndrome were the most prevalent electroclinical syndromes, and epilepsies secondary to perinatal insults were the most prevalent structural/metabolic epilepsies.

Table **2** shows the distribution of the electroclinical syndromes and other epilepsies in childhood (156 males and 132 females). In this group of patients, the clinical entities were electroclinical syndromes in 50%, epilepsies of unknown causes in 29.5% and epilepsies attributed to and organized by structural-metabolic causes in 20.5% of them. Benign epilepsy with centrotemporal spikes and childhood absence epilepsy were the most prevalent electroclinical syndromes, and epilepsies secondary to perinatal insults and cerebral malformations were the most prevalent structural/ metabolic epilepsies.

Among patients diagnosed with West syndrome, etiology was attributed to and organized by structural-metabolic causes in 69.2% of the cases (n=18); this means, related to subcortical band heterotopia (1 case), semilobar holoprosencephaly (1 case), Down syndrome (3 cases), tuberous sclerosis (2 cases), prematurity with periventricular leucomalacia (1 case), neonatal meningoencephalitis with multiple cyst encephalopathy (1 case), perinatal asphyxia with periventricular leucomalacia (3 case) or multiple cyst encephalopathy (1 case), perinatal grade IV intracranial hemorrhage plus hydrocephalus (1 case) or cortico-subcortical atrophy (1 case) and periventricular leucomalacia (3 cases).

Table **3** shows the distribution of the electroclinical syndromes and other epilepsies in adolescents (39 males and 49 females). Most of the clinical entities were electroclinical syndromes (69.3%), whereas others were epilepsies of known cause (19.3%) or epilepsies attributed to and organized by structural-metabolic causes (10.2%). Juvenil absence epilepsy was the most prevalent electroclinical syndromes.

Table **4** shows the distribution of the electroclinical syndromes and other epilepsies syndromes in the overall sample (232 males and 222 females). Most of the clinical entities were electroclinical syndromes (54.8%), whereas others were epilepsies of known cause (24%) or epilepsies attributed to and organized by structural-metabolic causes (20.9%). Benign epilepsy with centrotemporal spikes and childhood absence epilepsy were the most prevalent electroclinical syndromes, and epilepsies secondary to perinatal insults and cerebral malformations were the most prevalent epilepsies attributed to and organized by structural-metabolic causes.

Table 1: Distribution of Electroclinical Syndromes and Other Epilepsies in Infants (n=78)

Electroclinical syndromes	44 (56.4%)
West syndrome	24
Myoclonic epilepsy in infancy	5
Benign infantile epilepsy	1
Benign familial infantile epilepsy	3
Dravet syndrome	10
Reflex epilepsy (tactile evoked myoclonic seizures)	1
Epilepsies attributed to and organized by structural-metabolic causes	27 (34.6%)
Perinatal insults	10
Cerebral infections	
Bacterial meningitis *(Str. Pneumoniae)*	1
Malformations of cortical development	
Schizencephalies	2
Focal cortical dysplasia	1
Polymicrogyria	1
Other cerebral malformations	
Aicardi syndrome	1
Holoprosencephaly	2
Inherited metabolic disorders	
Non-ketotic hyperglycinemia	1
Tay-Sachs disease	1
Alpers disease	1
Mucopolysaccharidosis (Hunter syndrome)	1
Neurocutaneous disorders	
Tuberous sclerosis complex	4
Vascular lesion	
Sagittal sinus thrombosis	1
Epilepsies of unknown cause	7 (8.9%)

Table 2: Distribution of the Different Epilepsies and Epileptic Syndromes in Childhood (n=288)

Electroclinical syndromes	144 (50.0%)
West syndrome	2
Myoclonic epilepsy	4
Febrile seizures plus	1
Panayiotopoulos syndrome	14
Epilepsy with myoclonic atonic seizures	10
Benign epilepsy with centrotemporal spikes	52
Autosomal-dominant nocturnal frontal lobe epilepsy	1
Late onset childhood occipital epilepsy (Gastaut type)	5
Epilepsy with myoclonic absences	1
Lennox-Gastaut syndrome	2
Epilepsy with continuous spike-and-wave during sleep	11
Landau-Kleffner syndrome	2
Childhood absence epilepsy	38
Reflex epilepsy (photosensitive epilepsies)	1
Epilepsies attributed to and organized by structural-metabolic causes	59 (20.5%)
Perinatal insults	14
Cerebral infections	
Subdural empyema	1
Herpes simplex encephalitis	2
EBV encephalitis	1
Cysticercosis	1
Malaria	1

Table 2 Continue …..

Malformations of cortical development	
Focal cortical dysplasia	3
Band heterotopia (double cortex)	2
Subependymal heterotopia	2
Polymicrogyria	3
Schizencephalies	2
Other cerebral malformations	
Dandy-Walker malformations	1
Chiari I malformations	1
Inherited metabolic disorders	
Alpers disease	1
Others	2
Neurocutaneous disorders	
Tuberous sclerosis complex	3
Chromosomal abnormalities	
Down syndrome (trysomy 21)	1
Angelman syndrome	3
Deletion 8p23	1
Deletion 5q syndrome	1
Duplication 15q syndrome	1
Stroke	
Middle cerebral artery infarction	5
Vascular malformations	
Arteriovenous malformation	1
Cavernous malformations	1
Tumors	
Supratentorial ependymoma	1
Desmoplastic neuroepithelial tumors	1
Prominence of extra-axial fluid space	
Suprasellar arachnoid cyst	1
Drug toxicity	
Leukoencephalopathy due to vinca alkaloids	1
Epilepsies of unknown cause	85 (29.5%)

Table 3: Distribution of Electroclinical Syndromes and Other Epilepsies in Adolescents (n=88)

Electroclinical syndromes	61 (69.3%)
Panayiotopoulos syndrome	3
Benign epilepsy with centrotemporal spikes	13
Late onset childhood occipital epilepsy (Gastaut type)	1
Juvenile absence epilepsy	20
Juvenile mioclonic epilepsy	13
Epilepsy with generalized tonic-clonic seizures alone	8
Progressive mioclonus epilepsy (Lafora disease)	1
Reflex epilepsies (photosensitive epilepsies)	2
Distinctive constellations	
Mesial temporal lobe epilepsy with hippocampal sclerosis	1 (1.1%)
Epilepsies attributed to and organized by structural-metabolic causes	9 (10.2%)
Perinatal insults	1
Malformations of cortical development	
Focal cortical dysplasia	1
Stroke	
Vascular malformations	1
Vasculopathies (neurofibromatosis)	1

Table 3 Continue…

Vascular malformations	
Venous malformations	1
Chromosomal abnormalities	
Mycrodeletion 17p13.3	1
Prominence of extra-axial fluid space	
Arachnoid cyst	1
Ependimal cyst	1
Parenchymal cyst	1
Epilepsies of unknown cause	17 (19.3%)

Table 4: Distribution of Electroclinical Syndromes and Other Epilepsies in the Overall Sample (n=454)

Electroclinical syndromes	249 (54.8%)
West syndrome	26
Myoclonic epilepsy in infancy	9
Benign infantile epilepsy	1
Benign familial infantile epilepsy	3
Dravet syndrome	10
Febrile seizures plus	1
Panayiotopoulos syndrome	17
Epilepsy with myoclonic atonic seizures	10
Benign epilepsy with centrotemporal spikes	65
Autosomal-dominant nocturnal frontal lobe epilepsy	1
Late onset childhood occipital epilepsy (Gastaut type)	6
Epilepsy with myoclonic absences	1
Lennox-Gastaut syndrome	2
Epilepsy with continuous spike-and-wave during sleep	11
Landau-Kleffner syndrome	2
Childhood absence epilepsy	38
Juvenile absence epilepsy	20
Juvenile mioclonic epilepsy	13
Epilepsy with generalized tonic-clonic seizures alone	8
Progressive mioclonus epilepsy (Lafora disease)	1
Reflex epilepsies	4
Distinctive constellations	
Mesial temporal lobe epilepsy with hippocampal sclerosis	1 (0.2%)
Epilepsies attributed to and organized by structural-metabolic causes	95 (20.9%)
Perinatal insults	25
Cerebral infections	7
Cerebral malformations	22
Inherited metabolic disorders	7
Neurocutaneous disorders	7
Tumors	2
Stroke	7
Vascular malformations	4
Vascular lesions	1
Chromosomal abnormalities	8
Prominence of extra-axial fluid space	4
Drug toxicity	1
Epilepsies of unknown cause	109 (24.0%)

Age at onset was significantly correlated with some categories of recognized epilepsies. For example, structural-metabolic epilepsies were significantly more likely in infants (34.6%) than in childhood (20.5%) or

adolescents (10.2%). Conversely, epilepsies of unknown cause were significantly more likely in childhood (29.5%) or adolescents (19.3%) than in infants (8.9%). The electroclinical syndromes were significantly more likely in adolescents (69.3%) than in infants (56.4%) or childhood (50%).

DISCUSSION

The currently accepted ILAE classification systems preclude new advances in neuroimaging, genetic and molecular diagnostic techniques. The modern technology is currently applied in clinical practice and clearly calls for a renewed approach to classification of epileptic seizures and the epilepsies. The 1989 International Classification of the Epilepsies categorizes all the epilepsies according to localization and aetiology, although these apparently separated concepts did not represent a clear dichotomy. The notions of partial and generalized epileptogenicity generated the false impression that epileptic seizures were due to either localized disturbances in one hemisphere or disturbances involving the entire brain; nevertheless, all seizures begin somewhere, and very few, if any, involve the whole brain. Moreover, the terms idiopathic, symptomatic, and cryptogenic supports multiple concepts into a single word, and this had caused considerable confusion. Consequently, the topographic and etiologic criteria on which 1989 classification is based have been revised by the report of the ILAE Commission on Classification and Terminology in order to incorporate the continuous advances in epilepsy research [24].

For pragmatic reasons, the ILAE has decided to retain the terms focal and generalized as they apply to epileptic seizures, but providing network definitions that state that seizures are not purely focal or purely generalized. The ILAE has remarked the concept of ‘‘electroclinical syndrome’’ and defined it as a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder, which are almost all pediatric age-related genetic epilepsies. Moreover, there are a number of entities that are not truly electroclinical syndromes but represent clinically distinctive groups on the basis of specific lesions or other causes. These are significant diagnostic forms of epilepsy and may have implications for clinical treatment, especially surgery (mesial temporal lobe epilepsy with hippocampal sclerosis, hypothalamic hamartoma with gelastic seizures, epilepsy with hemiconvulsion and hemiplegia, and Rasmussen syndrome). A different group (structural/metabolic epilepsies) includes epilepsies secondary to specific structural or metabolic lesions or conditions (perinatal insults, infections, cerebral malformations, inherited metabolic disorders, tumours, stroke, etc.) but do not present a particular electroclinical pattern. And, finally, those epilepsies, which were termed cryptogenic, are now of unknown cause [23].

The advances in different areas of research (electrophysiology, neuroimaging, genomic technologies, molecular biology, and neurochemistry) have allowed us to recognize new clinical entities identified by a cluster of electroclinical characteristics (electroclinical syndromes). Using the most recent ILAE classification, we were able to identify an electroclinical syndrome in 55% of the patients. In addition, some epileptic syndromes were predominant in some age groups, such as West syndrome and Dravet syndrome in infants, benign epilepsy with centrotemporal spikes and childhood absence epilepsy in childhood, or juvenile absence epilepsy in adolescents. However, we found that distinctive constellations were rare in our population-based pediatric cohort, with only one child (0.2%) meeting the definition for a specific constellation. Epilepsies attributed to and organized by structural-metabolic causes were seen in 20.8% of the patients, with perinatal insults (ischemic or anoxic lesions) and cerebral malformations (malformations of cortical development) as the most prevalent causes. Epilepsies of unknown cause were seen in 24.1% of patients. The prognosis for such patients is unclear and more work would be necessary to define more specific etiologies for this group. However, a major problem of 2005-2009 ILA revised classification is that the same child could be in two different groups; for example, the most of cases with West syndrome are related to structural or metabolic lesions or conditions (perinatal insults, chromosomal abnormalities, neurocutaneous disorders, cerebral malformations, etc.).

Our data cannot be compared with those in other studies because this study is the second to classify a population-based cohort of children using the most recently proposed classification system. Nevertheless, the first study reported a higher proportion of epilepsies of unknown cause (almost half of patients) probably because magnetic resonance imaging was not routinely used [8]. However, in our Paediatric Neurology Unit, structural neuroimaging (magnetic resonance imaging) has been requested in all patients with epilepsy at onset. The MRI is considered the current anatomic "gold standard". The principal role of

MRI is in the definition of the structural abnormalities that underlie seizure disorders (malformations of cortical development, hippocampal sclerosis, neurocutaneous diseases, vascular malformations, traumatic lesions, strokes, residual lesions, etc.) and to contribute to the etiological diagnosis and classification of the different epilepsies and epileptic syndromes, and thereby provide an accurate prognosis for patients [19,26,27].

In our experience the newly proposed ILAE classification is a modern approach to classification of epileptic seizures and the epilepsies. Despite various limitations [28-30] we were able to classify most cases. In conclusion, the 2005-2009 ILAE classification may serve as the basis for organizing knowledge about recognized forms of epilepsy and facilitate identification of new forms.

DISCLOSURE

The authors state that there are no conflicts of interest.

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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Received on 25-03-2014 Accepted on 31-03-2014 Published on 29-05-2014

DOI: http://dx.doi.org/10.12974/2309-6179.2014.01.01.7