The diagnosis of epilepsies

ABSTRACT—Vague labels such as 'epilepsy', 'grand mal' or 'seizures' are detrimental to patient care, and should be universally abandoned in favour of the syndromic diagnosis of epilepsies.

The differentiation of 'fits' and 'faints and funny turns' is an issue familiar to all students of medicine. Having established the nature of the event as epileptic, the next step is to exclude an underlying progressive brain lesion. For patients without a structural epileptogenic abnormality, textbooks provide little guidance on diagnosis, prognosis or treatment; as a result, management is often empirical.

The inclusive term 'epilepsy', almost universally still used in social, psychological and medical studies, inadequately describes a highly heterogeneous population of patients with recurrent seizures. Such studies are often biased towards those more severely affected, and extrapolation to common, but more benign, epileptic syndromes can be highly misleading. The results are incorporated into textbook recommendations on drug treatment and management, which perpetuate inappropriate generalisations.

A diagnosis of 'epilepsy' unjustly carries a serious social stigma, with implications of loss of self-control, mental disease, physical handicaps and even demonic possession. Dictionary definitions are unhelpful, inadequate and inaccurate, often equating epilepsy with generalised tonic clonic seizures; it is a diagnostic label unsatisfactory to patient and physician alike. With progress in the field, patients will expect and demand more sophisticated and precise diagnosis. How can this be achieved?

The International League against Epilepsy (ILAE) has published a proposal for the classification of epilepsies and epileptic syndromes [1] based on observations made by astute clinicians. The identification of epileptic syndromes is an important medical advance which deserves widespread recognition. These syndromes are clusters of clinical and EEG features associated in a non-fortuitous manner which may represent distinct disease aetiologies. Yet syndromic diagnosis of epilepsies remains uncommon, even among neurologists who are familiar with the classification proposed by the ILAE [2,3]. Many such physicians are concerned about its complexity or doubt its relevance in current medical practice.

R A GRÜNEWALD, MA, DPhil, MRCP, *Clinical Lecturer in Neurology, University of Sheffield, Royal Hallamshire Hospital, Sheffield.*

C P PANAYIOTOPOULOS, MD, PhD, MRCP, *Department of Clinical Neurophysiology and Epilepsies, St Thomas' Hospital, London.*

In this article we advocate the proposed ILAE classification and address some of the questions that have been raised about its significance.

Seizure/symptom diagnosis

The principal, and often sole, clinical feature is the seizure itself, so traditional diagnosis and management of epilepsies have emphasised the importance of events occurring during the seizure. These may be classified as generalised (tonic, tonic-clonic, myoclonic, typical or atypical absences) or partial (simple or complex) [4]. Under such a diagnostic system, all clinically generalised tonic-clonic seizures (GTCS), whether the result of a static or progressive brain lesion, metabolic derangement, drug effect or inherited predisposition, are classified together; treatment is symptomatic and no aetiological or prognostic significance is conveyed. Avoidable morbidity results.

Syndromic diagnosis

Optimal diagnosis of epilepsies, as with any disease, should involve comparing detailed clinical features with the results of investigations (EEG and neuroimaging) to identify the underlying disease or syndrome.

The proposed International League against Epilepsy (ILAE) classification of epilepsies [1] is based on two major features:

- whether the predominant seizure type is localised (localisation-related syndromes) or generalised (generalised syndromes),
- whether the aetiology is idiopathic (with genetic predisposition), structural or cryptogenic (supposedly, but not demonstrably, structural).

These divisions shape the first two major groups of epileptic syndromes; a third group covers syndromes with seizures of uncertain type (often the case in nocturnal seizures), and a fourth encompasses seizures associated with a specific situation (fever, drugs, metabolic imbalance). The use of high-resolution magnetic resonance imaging has shown that many epilepsies previously categorised as cryptogenic can now be attributed to structural cortical lesions such as cortical dysgenesis and heterotopia.

Table 1 is a schematic presentation of epileptic syndromes in order of age at onset and severity of prognosis. Syndromes with similar seizure types, such as the myoclonic epilepsies of infancy, childhood and adolescence, may have markedly different prognoses.

Table 1. Principal age-related epileptic syndromes

Age	Good ← Prognosis → Bad
Days:	
1	
2	
3	Benign neonatal familial convulsions
4	Early myoclonic encephalopathy
5	Benign neonatal convulsions — Early infantile myoclonic encephalopathy with suppression burst
6	
Months:	
4	
5	
6	West syndrome
7	
8	Severe myoclonic epilepsy in infancy
Years:	
1	Benign myoclonic epilepsy in infancy
	Epilepsy with myoclonic-astatic seizures
2	Febrile convulsions
3	Lennox-Gastaut syndrome
4	Acquired epileptic aphasia (Landau-Kleffner syndrome)
5	Childhood epilepsy with occipital paroxysms
6	Childhood absence epilepsy — Chronic progressive epilepsia partialis continua of childhood
7	
8	Absences in juvenile myoclonic epilepsy
9	Benign childhood epilepsy with centro-temporal spikes
10	
11	Syndromes with seizures precipitated by specific modes of activation
12	
13	Juvenile myoclonic epilepsy (myoclonic and GTCS)

GTCS = generalised tonic-clonic seizures

Impact on management

Perhaps the best examples of the impact of syndromic diagnosis on patient management are provided by the common epileptic syndromes of benign childhood partial epilepsies (BCPEs) and juvenile myoclonic epilepsy (JME).

The BCPEs comprise about one-quarter of all epilepsies with onset between 2 and 13 years of age and have an excellent prognosis [5]. They are classified among the 'age and localisation-related idiopathic epilepsies':

- BCPEs occur only in children (age-related),
- the epileptic seizures and EEG abnormalities are focal (localisation-related),
- physical, mental and laboratory examinations other than EEG are normal (idiopathic).

The combination of a developmentally and neurologically normal child with infrequent seizures and an EEG with disproportionately severe focal epileptogenic activity is highly suggestive of BCPE. As 10–40% of children with BCPE may have only a single fit, the common practice of not requesting an EEG after a first seizure may underestimate its prevalence.

Unfortunately, current textbooks and even specialised journals pay scant attention to these syndromes, often considering childhood seizures under the heading 'epilepsy' without regard to aetiology and prognosis. BCPEs, like febrile convulsions

- are age-related,
- show genetic predisposition,
- may be manifested by only a single seizure,
- remit within a few years of onset,
- may or may not require a short course of anti-epileptic medication.

The risk of recurrent seizures in adult life (1–2%) is less than with febrile convulsions (4%) [5]. Recognition of the characteristic clinical and EEG features of BCPE invariably allows a benign prognosis to be given, with spontaneous resolution of the disorder by the middle teens. The prognostic implications are such that one of us (CPP) has suggested removing the label 'epilepsy' from these patients, as has already been done in the case of 'febrile convulsions' [5].

JME, an idiopathic epileptic syndrome with myoclonic jerks on awakening, GTCS and, more rarely, absences, has a prevalence of 8-10% amongst adult patients with seizures [6]. The management of JME differs in important respects from the standard medical practice for seizures [7]. Recommendations not to treat after the first GTCS are usually inappropriate as patients may have had minor events for years without appreciating their nature. JME is a lifelong disease with a high risk of major and minor seizures, particularly after sleep deprivation, fatigue, and alcohol indulgence. It is also inappropriate to withdraw medication after the patient has been free of seizures for 2–3 years, and to prescribe carbamazepine instead of sodium valproate, because relapses are all but inevitable [6,7].

Even those who are most sceptical about the clinical or practical significance of syndromic diagnosis of epilepsies must surely accept that BCPE, JME and symptomatic temporal lobe epilepsy have little in common other than an association with GTCS. There are distinct treatment strategies for each of them:

- BCPE may or may not require drug treatment for 1–2 years, mainly with carbamazepine;
- in JME, sodium valproate is the drug of choice and treatment is lifelong;
- symptomatic temporal lobe epilepsy may be resistant to carbamazepine, phenytoin and vigabatrin, and may require neurosurgery.

Some parts of the ILAE classification remain contentious, for example the inclusion of reading epilepsy (a mild form of reflex regional myoclonus) with benign idiopathic partial epilepsies. Some syndromes are ill- or broadly defined and require further clarification. There are patients whose clinical and EEG features do not appear to fit neatly into any recognised category or which appear to evolve from one syndrome to another. Some may represent new or 'overlap' syndromes, others may be unusual forms of known syndromes or cases where the clinical history is misleading. However, many syndromes are common, easily diagnosed and well-characterised. Syndromic diagnosis of epilepsies provides a firm foundation for short- and long-term therapeutic decisions, and enables their natural history, inheritance, treatment efficacy and prognosis to be studied scientifically. The benefits of syndromic diagnosis over seizure/symptom diagnosis or an inclusive diagnosis such as 'epilepsy' far outweigh any morbidity from miscategorisation that may arise in difficult cases.

Common misconceptions

'There is a continuum of clinical features in epilepsy'

Although most neurologists accept that there is a dichotomy between generalised and partial epilepsies, many are unwilling to accept the division of idiopathic generalised epilepsies (IGE) into syndromes. There is a widespread belief that IGEs represent a continuum of clinical features, with patients suffering typical absences, myoclonic jerks and GTCS in various combinations depending on age and individual susceptibility. Recent research makes this view untenable.

Some of these syndromes, like benign familial neonatal convulsions are age-related and age-limited whilst others, like JME, are lifelong. Their genetic differences have been documented [8–12]. Furthermore, analysis of clinical and video-EEG features in a group of young patients suffering from typical absences revealed the characteristic features of several syndromes [13,14]. Patients with the following syndromes could be clearly distinguished despite overlap of patient age:

- myoclonic absence epilepsy (rhythmic generalised myoclonic jerks during the absence) [15],
- childhood absence epilepsy (severe impairment of consciousness during the absence) [14],
- eyelid myoclonia with absences (brief eyelid myoclonus during the ictus with mild impairment of consciousness and photosensitivity) [16],
- JME (mild impairment of consciousness and characteristic EEG 'fragmentations') [13].

Even if these disorders are genetically similar, the differences in severity, long-term treatment strategies and prognosis make an accurate diagnosis mandatory. To take an analogy with muscular dystrophies, Duchenne and Becker muscular dystrophies are distinguished by neurologists, although the conditions are genetically linked and no curative treatment is at present available for either of them.

'Syndromic diagnosis makes no difference to management'

With the rapid advances in neuroimaging techniques and neurosurgical treatments there is now general agreement on the importance of a pathological diagnosis in patients with focal epilepsies. However, many neurologists believe syndromic classification to be an academic exercise of little benefit to the patient (a view that can be likened to the belief of Thomas Sydenham's 17th century contemporaries that there was no need to distinguish different causes of fever as all were treated by bleeding). This belief may have its origins in misinterpretation of the results of several published clinical trials of treatment of 'epilepsy' which failed to show any substantial differences in treatment outcome between patients with different types of seizures (mainly GTCS) treated with various anti-epileptic drugs [17–20]. These findings are in marked contrast to the results of other studies which show that some common epileptic syndromes respond better to certain drugs and are exacerbated by others [21–25]. For example, carbamazepine and vigabatrin, highly efficacious in partial epilepsies, are to be avoided in IGEs, particularly those with absences and myoclonic jerks, for which sodium valproate is the drug of choice, either alone or in combination with clonazepam, lamotrigine or ethosuximide [25].

A resolution of this apparent inconsistency can be found in the studies which have demonstrated that IGE is often misdiagnosed and that absences and myoclonic jerks are often undiagnosed or misinterpreted [2,3]. Unless a clinical trial is designed to detect a difference in the efficacy of a drug treatment between different epileptic syndromes, no conclusion can be drawn from it regarding the optimal medical therapy of different types of epilepsies.

Specific treatment regimens may be required even among different IGE syndromes. Although clonazepam is useful for myoclonic jerks, it should not be used alone in JME as it may not control the GTCS. It is the drug of choice in reading epilepsy. Eyelid myoclonia with absences is resistant to treatment and may need a combination of sodium valproate and ethosuximide. In childhood absence epilepsy, monotherapy with sodium valproate or ethosuximide is often sufficient, and withdrawal should be planned after 2–3 years absence-free.

Most such recommendations are based on clinical impression, and there is an urgent need for controlled trials to test syndrome-specificity of drugs and treatment regimens. This need has intensified as the result both of licensing 3–5 new drugs for 'epilepsy' in the last five years and of current trials of numerous others.

Advice on prognosis and inheritance is of critical importance in patient management, for example to permit appropriate career decisions and family planning. There is a vast difference between the 'epilepsy' of a child with benign partial seizures, childhood absence epilepsy or benign familial neonatal convulsions and the epilepsy of a child with Rasmussen's, Down's or Sturge-Weber syndrome. Prognosis is different even among similar conditions: unclassified childhood absences resolve in 70% of patients by the time they reach adulthood, but such a figure obscures marked differences between syndromes. Prognosis for spontaneous remission of absence syndromes can be predicted at diagnosis [14–16]:

- childhood absence epilepsy may be expected to remit,
- eyelid myoclonia with absences and JME is likely to persist into adulthood,
- myoclonic absence epilepsy may be associated with intellectual and neurological deficit.

'Syndromes are not diseases'

The possibility that identical syndromes may have different underlying aetiologies is a genuine concern. Undue reliance on any single feature to identify a syndrome will result in errors: for example, the EEG features of benign childhood epilepsy with occipital paroxysms, which is an idiopathic, age- and localisation-related syndrome, are occasionally found in normal children or patients with structural brain lesions [5]. Structural lesions may masquerade as IGE, and focal abnormalities on the EEG may be misleading. Even the combination of clinical, EEG and modern neuroimaging does not produce perfect diagnostic accuracy and, as in any field of medicine, some diagnoses may require revision with time.

A family history of seizures is common in many epileptic syndromes, raising the possibility that they are genetic diseases. Molecular genetic techniques have already identified genes on different chromosomes associated with a small number of such epileptic syndromes [8–12]. As a result of syndromic classification, Baltic and Mediterranean myoclonus have been linked to a marker on chromosome 21q [12], benign familial neonatal convulsions with markers on chromosome 20q [8] and 8 [9], and JME with a putative site on chromosome 6 [10] (although this has recently been questioned [11]). Further studies may be expected to elucidate inherited and acquired factors in the expression of other epilepsies, although there may be genetic heterogeneity even within well-characterised syndromes. This is a problem common to many fields of medicine; it should stimulate endeavour to improve diagnostic sophistication rather than serve as an excuse for diagnostic nihilism.

Diagnosis of the epilepsies

Syndromic diagnosis of epilepsies may be difficult, and a clear and detailed history is important. IGEs, which are genetically determined:

- represent one-third of all epilepsies,
- are not progressive,

- occur in normal subjects,
- are often relatively easy to control with the appropriate medication,
- do not require brain imaging.

Partial epilepsies with onset in adolescence or adulthood

- are often the result of structural brain lesions which require diagnostic imaging,
- are often resistant to anti-epileptic drug treatment,
- may require brain surgery.

A knowledge of the phenomenology of epileptic disorders is required to distinguish the characteristic ictal events and prevent misdiagnosis as partial seizures. The jerks of JME, for example, may be unilateral or reported as asymmetric, and as a result misconstrued as focal motor seizures [2]. Absences in adults are typically misdiagnosed as complex partial seizures [3]. The localised myoclonus of peri-oral myoclonia with absences [26] may be described as chewing movements by an eyewitness, suggesting a diagnosis of partial motor seizures or temporal lobe epilepsy to the unwary physician. Focal EEG abnormalities in IGE may be used as evidence to support an erroneous diagnosis of focal epilepsy [2,3].

Events surrounding a GTCS often provide more information than a detailed eyewitness account: for example, IGE is suggested by precipitation of seizures by sleep deprivation, flickering lights, alcohol or abrupt waking. Most patients with GTCS, whether idiopathic or symptomatic, also suffer minor seizure events. A patient presenting with a 'first seizure' may in fact have suffered myoclonic jerks, absences or complex partial seizures for many years, the significance of which may not have been appreciated [2,3,6,7]. Similarly, patients who are 'seizure-free' may continue to suffer subtle ictal events. These minor seizures often provide the clues to accurate syndromic diagnosis and are of therapeutic importance [7]. They may occur frequently, with adverse effects on employment, family life, driving and operating machinery. For patients with frequent or reproducible seizures, home video recording of seizures may reveal characteristic features essential for diagnosis, but video-EEG monitoring may also be required.

EEG investigation

EEG has an invaluable role in syndromic diagnosis, but must be tailored to individual requirements; for example, recording the EEG in circumstances reported by the patient to provoke the attack. Interpretation of the EEG recording can be performed only with full details of the patient's symptoms. Devoid of its clinical context, EEG becomes

> . . . one of the most abused investigations in clinical medicine . . . unquestionably responsible for great human suffering [27].

Non-specific—especially focal—EEG abnormalities may be a feature of IGE and partial epilepsies, and reports may be misleading if the EEG is interpreted without having adequate clinical details. A normal EEG from a patient with a history suggestive of IGE should initiate an EEG study following sleep-deprivation during which the patient is allowed to sleep with the aim of recording the characteristic abnormalities that occur when the patient wakes.

Conclusion

Although the common syndromes are easily diagnosed, many physicians who are familiar with a pragmatic approach to the management of epilepsy do not like having to use the more complex and evolving field of syndromic classification of epilepsies. They must now ask not only 'is this epilepsy or not?' but also 'what type of epilepsy is this?'. A unitary diagnosis of 'epilepsy' or the symptomatic diagnosis of 'seizures', 'grand mal' or 'petit mal' should be abandoned in favour of the syndromic diagnosis of epilepsies. As in all other fields of medicine, patients with epileptic seizures and their families are entitled to specific and precise diagnosis, prognosis and management.

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Address for correspondence: Dr R A Grünewald, Department of Clinical Neurology, University of Sheffield, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JP.