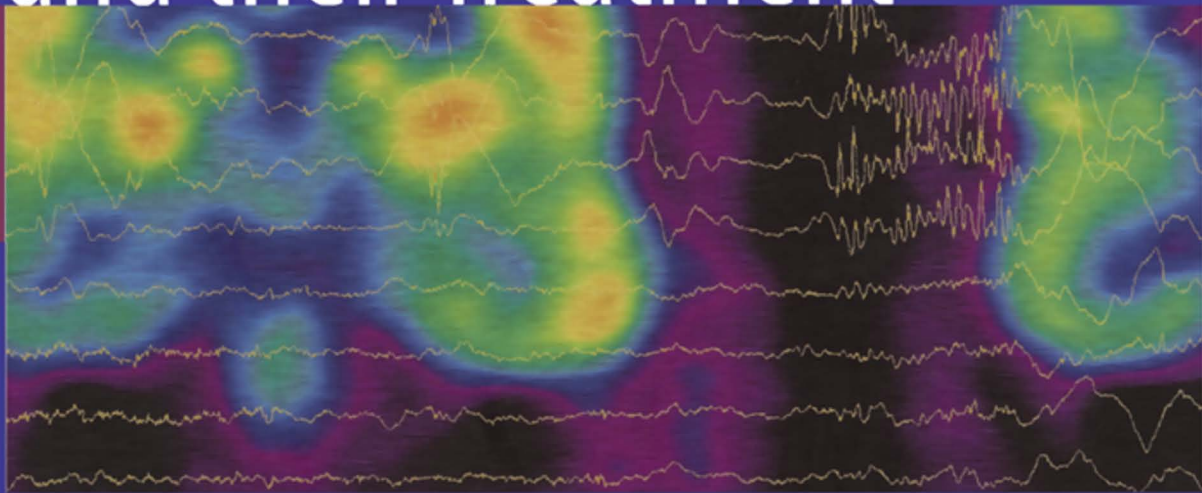


CP Panayiotopoulos

A Clinical Guide to

Epileptic Syndromes and their Treatment



Second Edition

Based on the ILAE classifications
and practice parameter guidelines

 Springer

CP Panayiotopoulos

A Clinical Guide to

Epileptic Syndromes and their Treatment

Revised Second Edition

Based on the ILAE classifications
and practice parameter guidelines

 Springer

British Library Cataloguing in Publication Data:

A catalogue record for this book is available from the British Library

ISBN: 978-1-84996-160-8

Apart from any fair dealing for the purposes of research or private study, or criticism or review, as permitted under the Copyright, Designs and Patents Act 1988, this publication may only be reproduced, stored or transmitted, in any form or by any means, with the prior permission in writing of the publishers, or in the case of reprographic reproduction in accordance with the terms of licenses issued by the Copyright Licensing Agency. Enquiries concerning reproduction outside those terms should be sent to the publishers.

Springer Science+Business Media
springeronline.com

© Springer Healthcare Ltd 2010

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant laws and regulations and therefore free for general use.

Product liability: The publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check its accuracy by consulting other pharmaceutical literature.

To my wife Thalia
because
she is a beautiful woman
my muse
the flower, the smile and the angel in my life



acknowledgements

I am grateful to the following eminent experts who have frequently provided me with valuable advice over the last 10 years during the preparation of my books on epilepsies:

Adachi, N.	Livingston, J.H.
Akanuma, N.	Martinovic, Z.
Benbadis, S.	Mole, S.
Berg, A.	Morrow, J.I.
Berkovic, S.F.	Moshe, S.L.
Blumenfeld, H.	Nordli, D.R., Jr.
Boyd, S.G.	Oguni, H.
Caraballo, R.H.	Ohtahara, S.
Covanis, A.	Patsalos, P.
Crawford, P.	Plouin, P.
Eeg-Olofsson, O.	Sander, J.W.A.S.
Dravet, C.	Scott, R.C.
Duncan, J.S.	Shorvon, S.D.
Engel, J., Jr.	Sisodiya, S.M.
Fejerman, N.	Stephenson, J.B.P.
Ferrie, C.D.	Thomas, P.
Galanopoulou, A.S.	Tomson, T.
Genton, P.	Vajda, F.J.E.
Grünewald, R.A.	Vigevano, F.
Hirsch, E.	Walker, M.C.
Jallon, P.	Watanabe, K.
Kanazawa, O.	Whitehouse, W.
Kasteleijn-Nolst Trenite, D.G.A.	Wilkins, A.
Koutroumanidis, M.	Yoshinaga, H.
Kuzniecky, R.	Zifkin, B.G.
Kwan, P.	Zuberi, S.M.

The continuing assistance of S. Sanders and S. Rowlinson, both expert EEG technologists, is, as always, greatly appreciated.

I would also like to thank Ian Stoneham, Publisher, and his team, particularly Hannah Cole and Nadine Lemmens, Editors, and Keith Baker, Designer; their professionalism, dedication and enthusiasm have made this a better book and enabled me to continue updating it to just a few weeks before publication in December 2009. They have been a pleasure for an author to work with.



Preface	xiii
Abbreviations.....	xiv
1 General aspects of epilepsies	1
What is epilepsy? Definitions	2
Comment on the new ILAE definition	2
Other formal definitions of epilepsy	2
Making the correct diagnosis in epilepsies.....	3
Medical history	3
Laboratory diagnostic procedures.....	4
Differential diagnosis	5
Epilepsy or epilepsies.....	10
The ILAE classification of epileptic seizures and epileptic syndromes.....	11
On classifications: concepts,clarifications and difficulties in reaching a consensus in the classification of epileptic seizures and syndromes	13
Author's clarifications on the ILAE terminology and classifications	15
Epidemiology of epilepsies	16
Incidence and prevalence of epilepsies	16
Mortality and epilepsies.....	17
References.....	18
2 Epileptic seizures and their classification	21
The definition of epileptic seizures	21
Other useful or ILAE seizure-related terminology.....	24
Classification of epileptic seizures	24
Epileptic seizures in accordance with the 1981 ILEA classification	24
Seizure classification in the new ILAE Task Force reports	28
Debate on the distinction between generalised and focal seizures	31
Generalised epileptic seizures	32
Generalised tonic–clonic seizures.....	32
Generalised tonic seizures	43
Generalised clonic seizures.....	44
Epileptic spasms.....	45
Myoclonus	46
Atonic seizures	50
Typical absence seizures.....	51
Atypical absence seizures.....	55

Focal epileptic seizures.....	57
ILAE terminology and classification of focal seizures	57
Reflex epileptic seizures	61
References.....	61
3 Status epilepticus.....	65
Definition and classification.....	65
Generalised tonic–clonic status epilepticus.....	67
Physiological stages of GTC-SE.....	68
Epidemiology of GTC-SE.....	70
Aetiology	70
Differential diagnosis	71
Prognosis	71
Generalised tonic status epilepticus.....	71
Generalised myoclonic status epilepticus	71
Idiopathic myoclonic SE.....	72
Symptomatic/cryptogenic myoclonic SE.....	72
Absence status epilepticus.....	72
Typical absence (idiopathic absence) SE.....	73
Atypical absence SE.....	76
Obtundation SE.....	76
Situation-related and <i>de novo</i> absence SE	77
Focal status epilepticus.....	77
Epilepsia partialis continua.....	77
Supplementary motor area SE.....	77
Aura continua	78
Dyscognitive focal (psychomotor, complex partial) SE.....	78
Hippocampal SE.....	79
Focal SE of frontal lobe origin	81
Focal SE of occipital lobe origin	81
Focal SE of parietal lobe origin.....	81
Autonomic SE.....	81
Opercular SE	82
Management of status epilepticus.....	82
Management of GTC-SE and other convulsive SE.....	82
Absence SE.....	86
Focal simple and complex SE.....	86
Antiepileptic drugs in the treatment of status epilepticus	87
References.....	92
4 Imitators of epileptic seizures	97
Main types of epileptic seizures and their imitators	98
Generalised tonic–clonic seizures.....	98
Epileptic myoclonic jerks.....	100

Absence seizures	100
Tonic seizures	101
Epileptic spasms.....	101
Epileptic drop attacks	101
Focal epileptic seizures	101
Syncopal attacks imitating epileptic seizures	102
Neurally mediated syncope.....	102
Cardiogenic syncopes	105
Syncopal attacks provoking epileptic seizures.....	106
Epileptic seizures imitating syncope	106
Psychogenic NEPEs imitating epileptic seizures	106
Convulsive psychogenic status epilepticus.....	107
Suffocation in Munchausen syndrome by proxy	108
Panic attacks.....	108
Hyperventilation syndrome.....	108
Management of PNEPEs	109
Non-epileptic paroxysmal movement disorders imitating epileptic seizures	109
Tics, compulsions, stereotypies and mannerisms	110
Tremor	110
Non-epileptic movement disorders in neonates and infants imitating seizures	110
Other non-epileptic paroxysmal movement disorders.....	114
Non-epileptic severe amnesic and confusional attacks imitating epileptic seizures.....	115
Transient global amnesia.....	116
Psychogenic (dissociative) fugues	116
Prolonged confusional states	116
Non-epileptic staring spells, childhood preoccupation and daydreaming.....	117
NEPEs occurring during sleep and sleep disorders.....	117
Sleep-related non-epileptic movement disorders	118
Sleep-related non-epileptic behavioural and other disorders	120
Narcolepsy	121
Sleep apnoea	123
Sleep disorders in the elderly	123
Subjective non-epileptic paroxysmal symptoms imitating simple focal seizures.....	123
Visual, auditory, somatosensory, olfactory, gustatory and autonomic paroxysmal symptoms imitating simple focal seizures	123
Cyclic vomiting, paroxysmal vertigo or motion sickness	124
Migraine, migralepsy, basilar migraine with EEG occipital paroxysms and diagnostic errors	125
Visual aura of migraine.....	126
Visual seizures	129
Cerebrovascular NEPEs imitating epileptic seizures	130
References.....	130

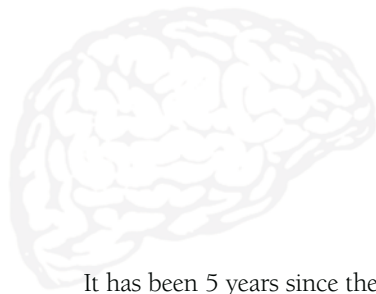
5	Epileptic syndromes and their classification	135
	ILAE definitions of epilepsies and epileptic syndromes and clarifications of terminology	135
	Epileptic syndrome	136
	Epilepsy disease	136
	Idiopathic epilepsy syndrome	136
	Symptomatic epilepsy syndrome	137
	Cryptogenic or probably symptomatic epilepsy syndrome	137
	Benign epilepsy syndrome	138
	Genetic epilepsy	139
	The ILAE 1989 classification of epileptic syndromes	139
	Localisation-related (focal) epilepsies and syndromes	140
	Generalised epilepsies and syndromes	141
	Epilepsies and syndromes undetermined as to whether they are focal or generalised	141
	Special syndromes	143
	Syndromic classification of the new diagnostic ILAE scheme	143
	References	146
6	EEG and brain imaging	147
	EEG in the diagnosis and management of epilepsies	147
	The value of routine inter-ictal or ictal EEGs in epilepsies	147
	Sources of error in EEGs	150
	Physiological activators of EEG abnormalities	152
	Video-EEG recording should be made routine clinical practice	155
	The role of EEG technologists	155
	The significance of the EEG after the first afebrile seizure	155
	Value of EEG in stopping AED treatment	155
	Improving the EEG contribution to the diagnosis of epilepsies	156
	Illustrative cases of good EEG practice	157
	Brain imaging in the diagnosis and management of epilepsies	159
	Recommendations for neuroimaging of patients with epilepsy	164
	Functional neuroimaging in clinical practice	164
	Magnetoencephalography	168
	References	170
7	Principles of therapy in the epilepsies	173
	AED prophylactic treatment	173
	Clarifications on terminology of AED treatment	176
	Choosing the best AED option	177
	Newest generation AEDs licensed in the treatment of focal epilepsies: lacosamide and eslicarbazepine	184
	Newly diagnosed epilepsy	185
	Monotherapy	186
	Rational polytherapy	187

Total AED withdrawal	188
Generic versus brand or generic to generic AED prescribing	189
Evidence for AED treatment recommendations in clinical practice	190
Therapeutic drug monitoring	193
Considerations of adverse antiepileptic drug reactions in the treatment of epilepsies	197
Principles of management in women with epilepsies	204
Oral hormonal contraception and AEDs	204
Pregnancy	205
Teratogenicity	205
Breastfeeding and AEDs	214
Principles of AED therapy in women of childbearing age in clinical practice	215
Principles of management in the elderly with epileptic seizures	219
Difficulties in diagnosing epileptic seizures in the elderly	219
Frequency of seizures and their severity in the elderly	220
EEG and other investigative procedures in the elderly	220
Physiological and other changes in the elderly that may affect AEDs	221
Principles of AED treatment in the elderly	221
Surgery for epilepsies	223
Criteria for surgical referral	223
Strategy of a surgical work-up	224
Types of surgical procedures	224
Vagus nerve stimulation	226
Ketogenic diet	228
Corticosteroids in the treatment of childhood epilepsies	229
References	229
8 Neonatal epileptic seizures and neonatal epileptic syndromes	237
Neonatal epileptic seizures	237
Neonatal epileptic syndromes	247
Benign familial neonatal seizures	248
Benign neonatal seizures (non-familial)	250
Early myoclonic encephalopathy	252
Ohtahara syndrome	254
References	257
9 Idiopathic epileptic seizures and syndromes in infancy	259
Febrile seizures	259
Epilepsy with febrile seizures plus	265
Benign infantile seizures	267
Myoclonic epilepsy in infancy	269
References	271

10	Epileptic encephalopathies in infancy and early childhood.....	275
	West syndrome	276
	Dravet syndrome.....	283
	Lennox–Gastaut syndrome.....	287
	Landau–Kleffner syndrome.....	303
	Epileptic encephalopathy with continuous spike-and-wave during sleep	309
	Myoclonic encephalopathy in non-progressive disorders	313
	Atypical benign partial epilepsy of childhood.....	315
	Hypothalamic epilepsy	317
	References.....	321
11	Severe neocortical epileptic syndromes in infancy and childhood.....	327
	Kozhevnikov–Rasmussen syndrome	327
	Migrating focal seizures of infancy	332
	Hemiconvulsion–hemiplegia epilepsy.....	333
	References.....	335
12	Benign childhood focal seizures and related epileptic syndromes.....	339
	Benign childhood epilepsy with centrotemporal spikes.....	340
	Panayiotopoulos syndrome	347
	Idiopathic childhood occipital epilepsy of Gastaut.....	357
	Other phenotypes of BCSSS.....	363
	Benign childhood seizures with affective symptoms.....	363
	Benign childhood epilepsy with parietal spikes and frequent ESEs.....	364
	Benign childhood focal seizures associated with frontal or midline spikes	364
	Benign infantile focal epilepsy with midline spikes and waves during sleep.....	364
	Benign childhood seizure susceptibility syndrome: a unified concept.....	365
	Febrile seizures and BCSSS	366
	Benign (isolated) focal seizures of adolescence	367
	Management of benign childhood focal seizures	368
	References.....	371
13	Idiopathic generalised epilepsies	377
	Syndromes of IGE recognised by the ILAE	378
	Epilepsy with myoclonic–astatic seizures.....	378
	Childhood absence epilepsy.....	383
	Epilepsy with myoclonic absences	388
	Juvenile absence epilepsy	391
	Juvenile myoclonic epilepsy.....	394
	Epilepsy with GTCSs only.....	401

	Other probable syndromes of IGE to consider	404
	IGE with absences of early childhood	404
	Perioral myoclonia with absences.....	405
	IGE with phantom absences.....	407
	Autosomal dominant cortical tremor, myoclonus and epilepsy	410
	AED treatment of IGEs	411
	References.....	416
14	Familial (autosomal dominant) focal epilepsies	423
	Autosomal dominant nocturnal frontal lobe epilepsy	426
	Familial (autosomal dominant) temporal lobe epilepsy.....	428
	Familial mesial temporal lobe epilepsy	428
	Familial lateral temporal lobe epilepsy.....	430
	Familial focal epilepsy with variable foci	431
	Other possible familial (autosomal dominant) focal epilepsies not yet recognised	432
	Autosomal dominant rolandic epilepsy and speech dyspraxia	432
	Focal epilepsy with pericentral spikes	432
	References.....	433
15	Symptomatic and cryptogenic (probably symptomatic) focal epilepsies	435
	Temporal lobe epilepsies	436
	Mesial TLE with hippocampal sclerosis.....	445
	MTLE defined by specific aetiologies other than hippocampal sclerosis.....	454
	Lateral temporal lobe epilepsy	454
	Frontal lobe epilepsies	456
	Epilepsia partialis continua of Kozhevnikov	462
	Parietal lobe epilepsies	468
	Occipital lobe epilepsies.....	473
	AED therapy of focal epilepsies	482
	References.....	489
16	Reflex seizures and related epileptic syndromes	497
	Visually induced seizures and epilepsies	500
	Photosensitivity, epileptic seizures and epileptic syndromes.....	500
	Idiopathic photosensitive occipital lobe epilepsy	509
	Jeavons syndrome	513
	Pattern-sensitive epilepsy.....	517
	Fixation-off sensitivity.....	520
	Complex reflex epilepsies	522
	Seizures induced by thinking and praxis	522
	Primary (idiopathic) reading epilepsy	522
	Startle seizures.....	524

Hot water epilepsy	526
References.....	528
17 Diseases frequently associated with epileptic seizures	533
Progressive myoclonic epilepsies	535
Unverricht disease.....	536
Lafora disease.....	540
Neuronal ceroid lipofuscinoses	542
Sialidoses (type I and II).....	547
Myoclonic epilepsy associated with ragged-red fibres	549
Dentatorubral-pallidoluysian atrophy.....	551
Angelman syndrome	552
Management of myoclonus	555
References.....	559
18 Pharmacopoeia.....	565
Acetazolamide	566
Benzodiazepines.....	567
Carbamazepine.....	568
Clobazam	571
Clonazepam.....	573
Eslicarbazepine acetate.....	574
Ethosuximide	576
Felbamate	577
Gabapentin	579
Lacosamide	581
Lamotrigine	582
Levetiracetam	587
Oxycarbazepine	590
Phenobarbital.....	593
Phenytoin.....	594
Pregabalin	596
Rufinamide.....	597
Stiripentol.....	599
Sulthiame.....	600
Tiagabine	601
Topiramate	602
Valproate.....	605
Vigabatrin.....	609
Zonisamide	611
References.....	613
Index.....	621



preface to the second edition

It has been 5 years since the first edition of this book was published. I have been encouraged to write a new edition by the success of the first, which sold over 10,000 copies and received excellent reviews. Even more rewarding than this has been the feedback from physicians who have been using the book in the environment for which it was written: the clinic. It is gratifying that patients and their families have also found it useful and recommend it in dedicated websites as a reliable source of information. A particularly reassuring aspect is that proposals made in the previous edition have been adopted by the ILAE Task Force in their latest report, published in 2006.

This second edition has been systematically updated to include the most recent advances in clinical epileptology. It has been written with the same principles and aims in mind as its predecessor and remains a relatively concise book, the main purpose of which is to promote proper diagnosis and appropriate management of epileptic seizures and syndromes. It is evidenced-based, achieved by integrating years of clinical experience with the best available external evidence from clinical research.

The opening chapters concentrate on the definitions and general aspects of epilepsies, describe epileptic seizures and status epilepticus, detail the imitators of epileptic seizures, provide advice on the optimal use of EEG and brain imaging in the diagnosis of epilepsies and offer insights into the principles of management. The subsequent chapters are devoted to the epileptic syndromes, which are organised according to age at onset and their main category in the ILAE classification. The presentation of each syndrome follows a common format: classification, demographic data, clinical manifestations, aetiology, diagnostic procedures, differential diagnosis, prognosis and management.

Following the advice and recommendations of reviewers and colleagues, I have included new chapters dedicated to the non-epileptic paroxysmal

disorders that imitate epileptic seizures and the diseases frequently associated with epileptic seizures, in particular progressive myoclonic epilepsies. Some clinically useful sections from my previous, more specialist-orientated book, *'The Epilepsies: Seizures, Syndromes and Management'*, have also been added and properly modified to suit the intended audience.

With regards to classification, particular emphasis has been given to the new ILAE report and I have provided further evidence-based proposals for consideration. The refreshing impact of Peter Wolf, President of the ILAE, Anne Berg, Chair of the ILAE Classification Committee, Phil Schwartzkroin and Simon Shorvon, Editors-in-Chief of *Epilepsia* is felt and appreciated.

The most difficult parts to prepare were the sections on anti-epileptic drugs. My recommendations are evidence-based, drawing on laborious and in-depth assessment of clinical trials, meta-analyses, formal guidelines and the best clinical evidence from eminent practising physicians. This approach has been verified because much of the advice offered in the previous edition has since been confirmed in subsequent controlled trials and in clinical practice. I am confident that my updated recommendations in this book will prove just as reliable and useful.

Realistically, I have to accept that there may be some unintentional errors and I regret any such instances. I would welcome these being brought to my attention along with any comments and suggestions for the improvement of future editions or reprints.

Finally, new practices are emerging that allow for the proper diagnosis and treatment of patients with epileptic seizures. As in all other areas of medicine, diagnostic precision is a prerequisite for meaningful management in the epilepsies, and I wish that this text will help advance and disseminate this knowledge.

C P Panayiotopoulos MD PhD FRCP

London, 28th June 2007

preface to the revised second edition



It is rewarding that the second edition of *A Clinical Guide to Epileptic Syndromes and their Treatment* published in 2007 appears to be fulfilling its purpose as a concise book promoting the accurate diagnosis and appropriate management of epilepsies. Like its predecessor, it has received excellent reviews and has been widely used and cited by readers, including seasoned and novice physicians, and other healthcare professionals, as well as patients and their families.

With the first print run now sold out, I felt that the time was ripe to revise rather than to reprint the second edition. This is mandated by the need to update with information on emerging therapies, important recent publications and new guidelines and ILAE proposals.

This book is mainly based on the ILAE classifications and practice parameter guidelines. A new ILAE report on classification and terminology that is currently under consultation is an important document for consideration and reflection as it contains the thoughts of the leading authorities in the epilepsies. Regarding practice parameters, the American Academy of Neurology and the American Epilepsy Society have published a three part evidence-based review focusing on pregnancy in women with epilepsy. These new proposals and guidelines are discussed extensively in this revision.

The sections concerning therapy have been expanded to include newly licensed AEDs, new indications for previously approved drugs and

adverse reactions that have emerged since the first publication. Again, the recommendations made aim to be of practical use and to follow as truly as possible the principles of evidence-based medicine. New sections have been added on the principles of pharmacological management in women and the elderly, and on psychological, behavioural and cardiac adverse effects of AEDs. The recent ILAE position paper on therapeutic drug monitoring is also extensively covered.

This revision has also been updated to include significant advances, reports, reviews and debates; new citations up to a few weeks before publication have been added.

The goal of this book, as with all previous editions, is to encourage the accurate syndromic diagnosis of the epilepsies. To some extent this has now been achieved, as all current formal recommendations and guidelines make clear that a syndromic diagnosis is a prerequisite for appropriate management and good clinical practice. However, there are still uncertainties over the precise features and boundaries for each epileptic syndrome and a lack of terminological precision, which this revised edition addresses. Overall, this book remains a guide for practising physicians on how best to diagnose the epileptic syndromes and achieve optimal management.

C P Panayiotopoulos MD PhD FRCP

London, 2nd December 2009



abbreviations

AAN-AES	American Academy of Neurology– American Epilepsy Society	EFS+	epilepsy with febrile seizures plus
ACTH	adrenocorticotrophic hormone	EGTCSA	epilepsy with GTCS on awakening
ADCME	autosomal dominant cortical tremor, myoclonus and epilepsy	EM-AS	epilepsy with myoclonic–astatic seizure
ADNFLE	autosomal dominant nocturnal frontal lobe epilepsy	eMC	electronic Medicines Compendium
ADR	adverse drug reaction	EMEA	European Medicines Agency
AED	anti-epileptic drug	EMG	electromyography
AHS	anticonvulsant hypersensitivity syndrome	EPC	epilepsia partialis continua
APEC	atypical benign partial epilepsy of childhood	ERG	electroretinogram
BCECTS	benign childhood epilepsy with centrotemporal spike	ESES	extreme somatosensory evoked spike
BCSSS	benign childhood seizure susceptibility syndrome	EURAP	European and International Registry of Antiepileptic Drugs in Pregnancy
BOLD	blood oxygen level dependent	EUROCAT	European Surveillance of Congenital Anomalies
CAE	childhood absence epilepsy	FDA	US Food & Drug Administration
cAMP	cyclic adenosine monophosphate	FDG	[¹⁸ F]fluorodeoxyglucose
CI	confidence interval	FLAIR	fluid-attenuated inversion recovery
CNS	central nervous system	FLTLE	familial lateral temporal lobe epilepsy
CONSERT	Consolidated Standards for Reporting of Trials	fMRI	functional magnetic resonance imaging
CRMP	collapsin response mediator protein	FMTLE	familial mesial temporal lobe epilepsy
CSE	convulsive status epilepticus	FMZ	[¹¹ C]flumazenil
CSF	cerebrospinal fluid	FOS	fixation-off sensitivity
CSTB	cystatin B	FS+	febrile seizures plus
CSWS	continuous spike-and-wave during sleep	GABA	Gamma-aminobutyric acid
CT	computed tomography	GABA-T	GABA-transaminase
CTS	centrotemporal spike	GEFS+	generalised epilepsy with febrile seizures plus
CVS	cyclic vomiting syndrome	GEPR	genetically epilepsy-prone rat
CYP	cytochrome P450	GnRH	gonadotrophin-releasing hormone
DMS	<i>Diagnostic and Statistical Manual of Mental Disorders</i>	GPSWD	generalised polyspike–wave discharge
DRPLA	dentatorubral-pallidoluysian atrophy	GSWD	generalised spike–wave discharges
EBM	evidence-based medicine	GTCS	generalised tonic–clonic seizure
ECG	electrocardiogram	GTC-SE	generalised tonic–clonic status epilepticus
EEG	electroencephalogram	HLA	human leukocyte antigen
		HR	hazard ratio
		IBE	International Bureau of Epilepsy
		ICOE-G	idiopathic childhood occipital epilepsy of Gastaut
		IGE	idiopathic generalised epilepsy

IL	interleukin	PET	positron emission tomography
ILAE	International League Against Epilepsy	PGTCS	primarily generalised tonic–clonic seizure
IM	intramuscular	PI	package insert
IPOE	idiopathic photosensitive occipital lobe epilepsy	PIL	patient information leaflet
IPS	intermittent photic stimulation	PLED	pseudoperiodic lateralised epileptiform discharge
IQ	intelligence quotient	PMA	perioral myoclonia with absences
IV	intravenous	PME	progressive myoclonic epilepsy
JAE	juvenile absence epilepsy	PNEPE	psychogenic non-epileptic paroxysmal event
JME	juvenile myoclonic epilepsy	PPR	photoparoxysmal response
LGI	leucine-rich, glioma-inactivated	PPT	palmitoyl-protein thioesterase
LKS	Landau–Kleffner syndrome	PS	Panayiotopoulos syndrome
LTLE	lateral temporal lobe epilepsy MAE epilepsy with myoclonic absences	RBD	REM sleep behaviour disorder
MCM	major congenital malformation	RCT	randomised controlled trial
MDVU	Movement Disorders Virtual University	REM	rapid eye movement
MEG	magnetoencephalography	SE	status epilepticus
MEI	myoclonic epilepsy in infancy	SGTCS	secondarily generalised tonic–clonic seizure
MELAS	mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes	SMA	supplementary motor area
MERRF	myoclonus epilepsy with ragged-red fibers	SmPC	Summary of Product Characteristics
MRI	magnetic resonance imaging	SMR	standardised mortality ratio
MRS	magnetic resonance spectroscopy	SPECT	single photon emission computed tomography
MSA	multiple source analysis	SSEP	somatosensory evoked potential
MSI	magnetic source imaging	SUDEP	sudden unexpected death in epilepsy
MSLT	multiple sleep latency test	SV2A	synaptic vesicle protein 2A
mtDNA	mitochondrial DNA	SWI	spike–wave index
MTLE	mesial temporal lobe epilepsy	TAS	typical absence seizures
MTLE-HS	mesial temporal lobe epilepsy with hippocampal sclerosis	TDM	therapeutic drug monitoring
nAChR	neuronal nicotinic acetylcholine receptor	TLE	temporal lobe epilepsy
NCL	neuronal ceroid lipofuscinosis	TPP	tripeptidyl-peptidase
NEPE	non-epileptic paroxysmal event	UGT	uridine diphosphate glucuronosyltransferase
NMDA	N-methyl D-aspartate	VDU	visual display unit
NREM	non-rapid eye movement	VEP	visual evoked potential
OPS	occipital seizures precipitated by photic stimuli	VER	visual evoked response
PAS	periodic acid–Schiff	VGSC	voltage gated sodium channel
PCR	polymerase chain reaction	VNS	vagus nerve stimulation
PEHO	progressive encephalopathy with edema, hypsarrhythmia and optic atrophy	WEMOVE	Worldwide Education and Awareness for Movement Disorders
		WHO	World Health Organisation



General aspects of epilepsies

Epileptic seizures and epileptic syndromes have high prevalence and incidence rates affecting all ages and all races of both sexes. They constitute an important part of the everyday clinical practice of general and specialist health care professionals.

Patients with epileptic seizures and their families are entitled to diagnosis, prognosis and management that are specific and precise.

Medical diagnosis is the identification of a disease by investigation of its symptoms and history, which provides a solid basis for the treatment and prognosis of the individual patient.

Accurate diagnosis is the golden rule in medicine and epilepsies should not be an exception to this. Current practice that limits the diagnosis to 'epilepsy' or 'seizures' is unsatisfactory to the patient and physician alike, and may result in avoidable morbidity and mortality. Such a non-specific diagnostic label fails to provide guidance on important items such as severity of disease, prognosis, short- and long-term therapeutic decisions, and genetics (research and counselling), which are all factors that crucially affect personal, family and social life, education and career choices of patients.

'Epilepsy' is not a single disease entity. Epilepsies are many syndromes and diseases that have a multitude of different manifestations and causes. Epileptic syndromes and diseases are now largely well defined and easy to diagnose. Defining the type of epilepsy should be considered mandatory because it offers the best guide to both management and prognosis. The short- and long-term management of epilepsies is

syndrome related and differs markedly between the various syndromes, thereby emphasising the need for accurate diagnosis. 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.

Unspecified diagnosis in epilepsies commonly results in avoidable morbidity and sometimes mortality.

Important reminder

Traditional medical teaching and attitudes to the diagnosis and management of epilepsies often differ from those applied in other medical conditions. This should be corrected.

Physicians who rightly seek bedside confirmation of muscle fatigability in a patient with a clear-cut history of myasthenia gravis, should also request to view the seizures, which if frequent can be easily captured even by mobile phones.

Physicians who rightly emphasise the differential diagnosis between spinal muscular atrophies and limb girdle muscular dystrophy should give the same emphasis to the differentiation between absence seizures of idiopathic generalised epilepsies and complex focal seizures.

Major paediatric journals that often emphasise a rare disease should at least give the same space to highlighting the fact that childhood autonomous status epilepticus is a common and costly cause of misdiagnosis and mismanagement, adversely affecting thousands of children around the world (see page 81).

What is epilepsy? Definitions

The definition of epilepsies should be simple, brief, precise and unambiguous. However, this is not the case and there is no consensus.

The newly proposed ILAE definition is:

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition.¹

This definition of epilepsy ‘requires the occurrence of at least one epileptic seizure’ with the precondition that this is ‘in association with an enduring disturbance of the brain capable of giving rise to other seizures’.¹ It would not require ‘at least two seizures’ or that the seizure be ‘unprovoked’, which were prerequisites of previous definitions of epilepsy.

The central concept in [this] definition is an enduring alteration in the brain that increases the likelihood of future seizures... A single epileptic seizure due to an enduring epileptogenic abnormality that increases the likelihood of future seizures would indicate epilepsy, and a single epileptic seizure in a normal brain would not.¹

This definition also proposes that part of the epileptic condition can involve behavioural disturbances, psychological consequences for the patient and for the family, and social stigma, exclusion, restrictions, overprotection and isolation.

Comment on the new ILAE definition

This proposal has been rightly criticised by eminent epileptologists² with whom I share the following concerns.

First: What is ‘enduring’ and how long does this last? This word ‘enduring’ has created the same questions and problems when used in the definition of status epilepticus. Enduring (adj.) = lasting, continuing, durable, unceasing, abiding, imperishable; perma-

nent, continuing or enduring without marked change in status or condition or place.

Second: Most patients do not have at least one of the preconditions ‘cognitive, psychological and social consequences’ attached to epilepsy.

Third: Why is the singular ‘epilepsy’ preferred to the plural ‘epilepsies’? This contradicts the facts and I quote from the same report ‘Epilepsy is not one condition, but is a diverse family of disorders, having in common an abnormally increased predisposition to seizures... Some writers prefer the plural term, “the epilepsies,” but we will use the singular phrase while recognizing this diversity’.¹

Certainly, there must be a better definition of what epilepsies are. The following would be my proposal:

Epilepsies are disorders of the brain with a clinically manifested liability to epileptic seizures.

Other formal definitions of epilepsy

Epileptic disorder: A chronic neurological condition characterised by recurrent epileptic seizures.³

Epilepsies: Those conditions involving chronic recurrent epileptic seizures that can be considered to be epileptic disorders.³

Epilepsy: A condition characterised by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause (operational definition for epidemiological purposes).^{4,5} Multiple seizures occurring in a 24-h period are considered as a single event. An episode of status epilepticus is considered to be a single event. People who have had only febrile seizures or only neonatal seizures, as herein defined, are excluded from this category.^{4,5} *Author’s note:* in this definition the type of ‘epileptic seizures’ is not defined, but this probably refers to generalised tonic–clonic seizures (GTCs).

‘Active’ epilepsy: A prevalent case of active epilepsy is defined as a person with epilepsy who has had at

least one epileptic seizure in the previous 5 years, regardless of anti-epileptic drug (AED) treatment. A case under treatment is someone with the correct diagnosis of epilepsy receiving (or having received) AEDs on prevalence day.^{4,5}

Epilepsy in remission with treatment: A prevalent case of epilepsy with no seizures for ≥ 5 years and

receiving AED treatment at the time of ascertainment.^{4,5}

Epilepsy in remission without treatment: A prevalent case of epilepsy with no seizures for ≥ 5 years and not receiving AED treatment at the time of ascertainment.^{4,5}

Making the correct diagnosis in epilepsies

The assessment of a patient referred for epileptic seizures should follow the same approach as any other disorder:

- medical history
- physical examination (and developmental assessment in children)
- presumptive diagnosis
- differential diagnosis
- comprehensive investigative procedures
- final diagnosis (which could be definite, probable, possible or undiagnosed)
- management (including that of the family).

Medical history

The diagnosis of epileptic or non-epileptic seizures is almost always based solely on the clinical history, which should be obtained in an expert way, often requiring lengthy interrogation(s) of the patient and witnesses. Children also (if verbal) have a surprising insight into their illnesses. In certain cultures children are often left outside the consultation process by overprotective parents, and this should be approached with sensitivity.

Inadequate history is the most common reason for misdiagnosis.

In taking the medical history, every piece of information should be patiently gathered in order to synthesise the whole pattern of these transient events from the time that they started to their end,

and up to normality. The medical history should include:

- details of the paroxysmal events (not only the most dramatic ones) as they have been experienced by the patient and witnesses
- the circumstances under which the paroxysmal events occurred
- timing and circadian distribution
- position (standing, sitting or lying)
- leisure or occupation (at rest or during exercise)
- possible triggering, precipitating or facilitating factors
- personal and family medical history.

Circadian distribution (on awakening, nocturnal and diurnal) and precipitating factors (flickering lights, sleep deprivation, alcohol indulgence, stress and reading) often provide invaluable clues for the correct diagnosis and may also prompt the appropriate EEG procedure.

Useful clinical note

The presence or absence of a single symptom is not sufficiently diagnostic of a particular disease and may be misleading.

The clinical diagnosis is often easy and secured only if individual elements of clinical events are meaningfully synthesised with regard to quantity, quality, location, onset, chronological sequence, development, speed of progress and duration.

Lengthy medical interviews may seem to be ‘luxury’ medicine, but this is by far outweighed by the benefits to patients, their families and their physicians. Constraints on the physicians’ time should not be an excuse for allowing misdiagnosis and mismanagement to occur. With experience the time taken for an appropriate medical history is significantly shortened. Personally, I devote more time to eliciting the events preceding a GTCS than detailing what happened during the convulsive phase (if I am satisfied that this was a genuine GTCS), and directing the witnesses to portray what they saw rather than allocating time to endless descriptions of how they felt and what they did (although I fully respect this).

A second interview frequently provides more observations and recollections after learning what is desired during the initial consultation.

Useful recommended practice

Asking the patient/guardian to complete a purposely designed questionnaire, which should be made available prior to consultation, has many advantages:

- it provides the patient/guardian with an understanding of the type of information needed and allows them time to collect such information
- written information is often more reliable than verbal communication during a time-limited and often emotionally loaded interview
- it provides the physician with a good insight of the case prior to the consultation.

‘That’s it!’ phenomenon⁶

It is often necessary for the physician to imitate and demonstrate physically or, when in doubt, show video-taped examples of different epileptic or non-epileptic seizures to patients and witnesses. ‘That’s it’ is their common reaction for the presentation that closely resembles the events under investigation.

Home-made video recordings

Sometimes the diagnosis is easy, based on clinical history alone. Home-made video recording should be routinely requested if diagnosis is uncertain.

Videotaping the clinical events is the only practical means of demonstrating and objectively documenting the symptoms of paroxysmal disorders. Genuine epileptic seizures or non-epileptic paroxysmal events (NEPEs) are often frequent and sometimes predictable. They can be recorded by relatives or friends and sometimes by the patients themselves. Today this is easier with the availability of digital recording and mobile phones.

Laboratory diagnostic procedures

Laboratory procedures (blood and urine tests, ECG, EEG, brain imaging and others such as metabolic or toxicology screening, CSF analysis, molecular genetic testing) should be appropriately prioritised and tailored to the particular clinical problem and individual patient. The aim is to obtain supplementary evidence of the clinical suspicion, which may provide definite diagnosis of a specific disorder. Investigative procedures are more demanding in children than in adults, or in those in whom seizures are the presenting symptom of a disease than in those where the underlying disease has already been established.

The EEG, the most significant investigative procedure in the diagnosis of epilepsies, is often misunderstood, undermined and misused. Brain imaging, another top diagnostic procedure, provides *in vivo* visualisation of structural causes of epilepsy such as hippocampal sclerosis, malformations of brain development and tumours, as well as other brain diseases.

Blood, urine and sometimes CSF studies have an important role in the evaluation of the child with epilepsy.⁷

Genetic testing has become available for a growing number of hereditary disorders associated with epileptic seizures (see Chapters 14 and 17).

The significance and the role of the EEG and brain imaging in the diagnosis and management of epilepsies is outlined in Chapter 6. Other laboratory procedures are discussed when appropriate in the relevant chapters.

Differential diagnosis

Misdiagnosis in epilepsies, when considering their dimensions and consequences, is a colossal and costly medical problem. Common disorders and even normal phenomena may imitate epileptic seizures and, conversely, certain types of epileptic seizures may imitate symptoms of other diseases. Misdiagnosis has serious repercussions. Patients with non-epileptic disorders incorrectly diagnosed as having epileptic seizures are likely to be mistreated with AEDs and also denied specific and possibly life-saving treatment (Figure 1.1). Similarly, patients with epileptic seizures erroneously diagnosed as migraine, encephalitis or other NEPEs are likely to be mismanaged with inappropriate treatments and also deprived of specific therapies (Figure 1.2).

It should also be emphasised that serious and adverse consequences to patient management often arise from misdiagnosing one type of epileptic seizure for another, or one type of epileptic syndrome for another.

There are three important steps to take in order to make a correct specific diagnosis, which will determine prognosis and management:

1. *First step:* are the paroxysmal events epileptic seizures?
2. *Second step:* what type of epileptic seizures?
3. *Third step:* what is their cause and what is the epileptic syndrome or disease?

First step: Are the paroxysmal events epileptic seizures?

The first step towards the correct diagnosis of epilepsies is to establish whether a paroxysmal clinical event was actually an epileptic seizure or a non-epileptic paroxysmal event (NEPE). The differential diagnosis includes all causes of episodic impairment of awareness, aberrations of mental function, falls, sensory/motor phenomena and generalised convulsive movements, which are common presenting symptoms of epileptic seizures. This is often easy for physicians adequately trained in the recognition of the various forms of epileptic seizures, who are able to obtain a clear history of the events from the patient and witnesses. However, even the most experienced

epileptologists repeatedly have great difficulties in reaching an unequivocal diagnosis for reasons such as atypical seizure presentations, inadequate historical data or overlapping symptom manifestations.

The differentiation between seizures and other causes of transient neurological disturbance and collapse is epitomised by the familiar theme ‘fits, faints and funny turns’.^{6,8} Distinguishing epileptic (*fits*) from paroxysmal symptoms of non-epileptic disorders, particularly syncopal (*faints*) or psychogenic attacks (*funny turns*), should be a core skill of all trained physicians as detailed in any medical textbook. However, this is often simplistic and frequently perpetuates certain myths such as that urinary incontinence or postsyncopal confusion are rare in syncopes (Figure 1.1) or tongue biting and injuries are exceptional features in psychogenic non-epileptic seizures, as further detailed in Chapter 4.

NEPEs that have been misdiagnosed as epileptic seizures affect as many as 20–30% of patients diagnosed with epilepsy; these patients have often received treatment for epilepsy for many years or have been admitted to tertiary care epilepsy units.^{9–11} The problem is complicated by the fact that approximately 30% of patients with genuine epileptic seizures also suffer from non-epileptic, mainly psychogenic seizures. In one study, the mean time lapse between the first attack and the correct diagnosis of non-epileptic seizures was over 9 years.¹² In financial terms the annual cost of such a misdiagnosis was estimated at US\$4 billion.¹³

NEPEs^{14–16} are common and are numerous episodic clinical manifestations of diverse aetiologies that mimic or look like, but are not, epileptic seizures. These imitators of epileptic seizures are detailed in Chapter 4.

Epileptic seizures imitating non-epileptic attacks

Epileptic seizures may imitate syncope, psychogenic attacks, migraine, sleep disorders or sinister acute brain insults. Their diagnosis is also demanding, as documented by the fact that, until recently:

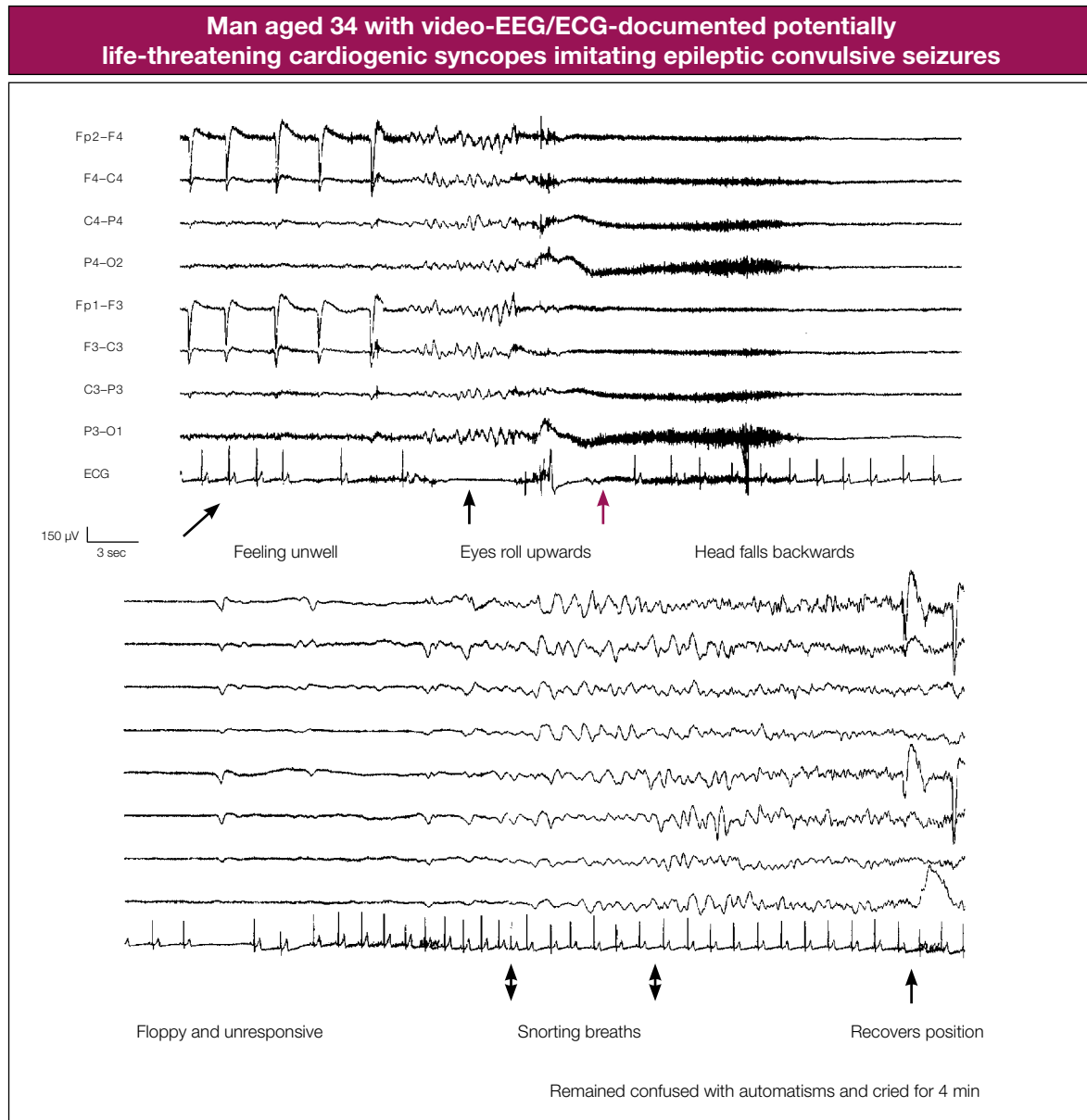


Figure 1.1 A 34-year-old man was referred for routine EEG because of 'two episodes of GTCSs in the last 2 months. The first occurred on his way home after work. He does not recall events until waking in the ambulance with the paramedics telling him that he had a seizure. He had no memory of the preceding 20 minutes. He did bite his tongue but there was no incontinence... This is likely to be generalised epilepsy... Treatment with valproate was initiated'. In accordance with our policy this was a video-EEG (page 155). A few minutes after the start of the recording he developed sinus bradycardia and then ventricular standstill for 9 s with one escape ectopic beat as documented with ECG (bottom trace). Clinically, at the oblique arrow the technician asked him if he felt okay and he said no. At the first vertical black arrow his eyes rolled slowly upwards to the extreme. At the red arrow, his head dropped backwards and he became flaccid and unresponsive. Some recovery started at the double-headed arrows when he took two snorting breaths. At the second black arrow, he resumed his position as before the syncope. Afterwards he was confused, he could not answer questions and, when asked again what happened to him, he was distressed and cried. He did not come back to normal until after more than 4 min from the start of the syncope. A cardiac pacemaker has been implanted and the patient remained well in the next 6 months of follow-up.

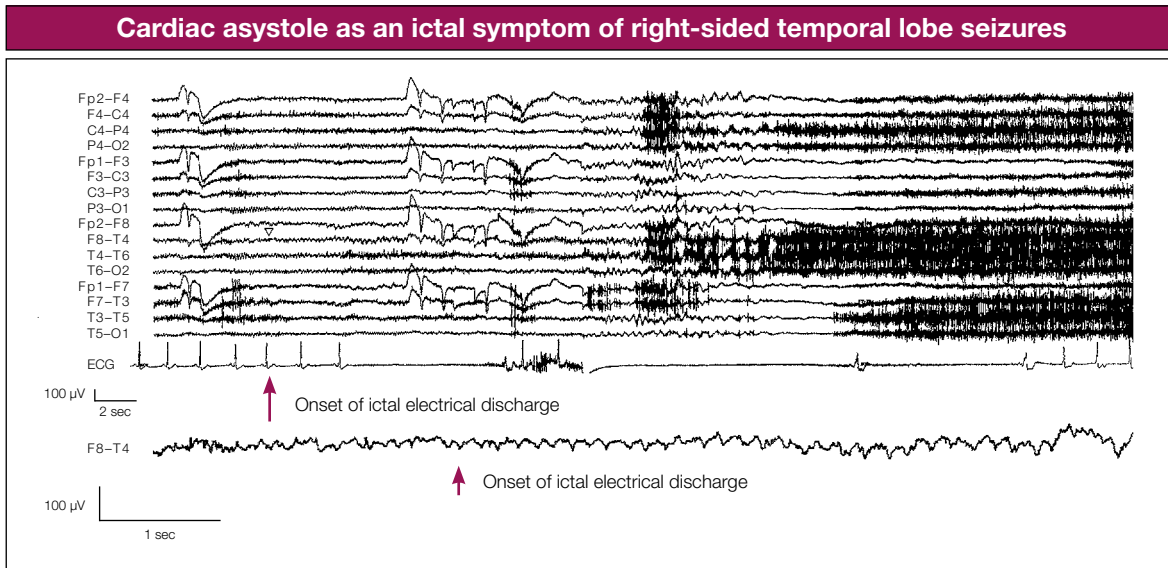


Figure 1.2 One day prior to this video-EEG a 60-year-old man said he felt unwell, went for a walk, but half an hour later became confused with repetitive questioning about his orientation and when the next meeting was to take place. On examination he was globally amnesic with a period of retrograde amnesia for about 1 month, which gradually shortened as he recovered after about 2 to 3 hours. His past medical history at that stage was thought to be unremarkable. He was known to have high cholesterol. There was a strong family history of early ischaemic heart disease. Physical and thorough neurological and cardiological examinations were normal. All relevant blood tests, ECG and brain MRI were normal. It was the video-EEG that established the diagnosis. He had three focal epileptic seizures with onset from the right temporal areas. The most severe one started with a rising epigastric sensation, which he retrospectively recalled as the same feeling that he had experienced the previous day. This led to almost immediate complete cardiac asystole for 26 s. During this seizure he became pale, lost consciousness and had a number of myoclonic jerks. He recovered without immediate need for cardiac resuscitation. The patient was treated with an appropriate AED and permanent cardiac pacemaker. He is well at follow up 6 months later. *Figure courtesy of Dr Michael Koutroumanidis, Department of Clinical Neurophysiology and Epilepsies, St. Thomas' Hospital, UK. Patient history courtesy of Dr Paul Holmes, Department of Neurology, St. Thomas' Hospital, London, UK.*

- frontal seizures from the supplementary sensorimotor area were considered to be sleep disorders (see page 459)
- ictus emeticus and autonomic status epilepticus, common in children, were dismissed as non-epileptic events or misdiagnosed as migraine or encephalitis (see page 355)
- visual seizures were confused with basilar migraine or migraine with visual aura (see page 125).

Simple focal seizures of epigastric aura and 'panic attacks' are unlikely to raise suspicion of epilepsy either by the patient or by the general physician (see Figures 1.2 and page 15.4). These patients are often investigated for gastroenterological and psychological

disorders or hypoglycaemia, until more salient seizure features appear with the development of complex focal seizures and secondarily GTCSs (see page 451).

Second step: What type of epileptic seizures?

Having established that a paroxysmal event is genuinely epileptic, the next, but not the final, step is to define the type of seizure(s).

There are numerous types of epileptic seizures, as detailed in Chapter 2. Their features may be minor or dramatic, brief or long, frequent or sparse, or singular. Clinical manifestations of seizures range from the dramatic events of a GTCS to the mild myoclonic flickering of the eyelids or a focal numb-

sample content of A Clinical Guide to Epileptic Syndromes and their Treatment (New Ilae Diagnostic Scheme)

- [**download online Sherlock Holmes: The Man Who Never Lived and Will Never Die**](#)
- [download online The City As a Tangled Bank](#)
- [*click Three to See the King*](#)
- [download online Designing with Glass: Great Glass Buildings](#)
- [**download Lost Dorsai \(Childe Cycle, Book 6\) book**](#)

- <http://flog.co.id/library/Sherlock-Holmes--The-Man-Who-Never-Lived-and-Will-Never-Die.pdf>
- <http://korplast.gr/lib/The-City-As-a-Tangled-Bank.pdf>
- <http://weddingcellist.com/lib/Branches--Nature-s-Patterns--A-Tapestry-in-Three-Parts.pdf>
- <http://weddingcellist.com/lib/Difficult-Mothers--Understanding-and-Overcoming-Their-Power.pdf>
- <http://conexdx.com/library/Lost-Dorsai--Childe-Cycle--Book-6-.pdf>