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Pasquale Striano *Editor*

Epilepsy Towards the Next Decade

New Trends and Hopes in Epileptology

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Preface

Epilepsy is a common chronic neurological disorder affecting approximately 0.5–1% of the population worldwide (~50,000,000 people) and the main goal of the treatment is to eliminate seizures without producing significant side effects. The drug therapy of epilepsy has evolved tremendously in the last twenty years and several antiepileptic drugs have been approved and marketed, offering a good number of options for treatment a large variety of seizure types and epilepsy syndromes. Nevertheless, despite optimal medical treatment, up to 30% of patients continue to experience recurrent seizures, which may lead to a severe medically, physically, and socially disabling condition. The intent of *Epilepsy Towards the Next Decade: New Trends and Hopes in Epileptology* is to provide a comprehensive overview of recent advances in the field of epileptology as well as of the recent advances and current knowledge regarding epilepsy research from leading experts in the field. This book aims to provide a handy and updated reference for most recent knowledge regarding the biological basis and the modern clinical approach to epilepsy, bridging the gap between fundamental aspects and clinical implications.

Epilepsy accounts for a variety of neurological disorders characterized by recurrent seizures. More than half of all epilepsies have some genetic basis and single gene defects in ion channels or neurotransmitter receptors are associated with inherited forms of epilepsy. In the last ten years, advances in the genetic techniques including oligonucleotide array and the following large scale studies have yielded to the identification of recurrent copy number variants associated with epilepsy. The book starts by reviewing the increasingly reported copy number variants in association with distinct epileptic phenotypes (Chap. 1), delineating emerging epileptic syndromes. Once that the features and prognosis of these conditions have been completely delineated a proposal for inclusion within the International Classification of the Epileptic Syndromes should be considered. Moreover, in the last few years, genetic research in the field of epilepsy disorders is increasing in term of testing platform for the investigation of sequence and structural variation. In particular, epileptogenic mutations have been identified in several ion channel genes, leading to the concept that several epilepsies can be considered channelopathies. Functional studies have in some cases provided significant advances in the understanding of the molecular and cellular dysfunctions caused by mutations. However, the

relationships between molecular deficits and clinical phenotypes are still unclear. Moreover, mutant channels that cause a distinct epilepsy syndrome show functional heterogeneity, which is in part produced by the different experimental conditions used in the studies: cell background, cDNA from other species or isoforms, and splicing variants. This aspects are fully reviewed in Chap. 2.

Although ion channels play an important role in genetic epilepsies, we should not overlook the fact that other pathways can lead to neuronal hyperexcitability. Mutations in the Leucine rich glioma inactivated 1 (LGI-1 or epitempin), a nonion channel gene that is implicated in autosomal dominant lateral temporal lobe epilepsy, a rare syndrome whose symptoms usually begin in adolescence. The molecular mechanisms for LGI1-mediated epilepsy are very complex and largely unknown. However, it seems that the defects in this gene can arrest the developmental maturation of excitatory circuits results in heightened seizure susceptibility. These data could also have clinical implications as pathways linked to LGI1 might become targets for epilepsy therapy (Chap. 3).

The aetiology of epilepsy is extremely complex and heterogeneous and both genetic and acquired factors can be responsible of this condition. Symptomatic epilepsies have mainly acquired causes, including malformations of cortical development, tumours, and metabolic diseases. The cellular mechanisms underlying the epileptogenicity of glioneuronal tumors depend on tumor histology, integrity of the blood-brain barrier, characteristics of the peritumoral environment, circuit abnormalities, or cellular and molecular defects. An evolving understanding of the mechanisms of tumor-related epileptogenicity may lead to improve surgical treatment and to identify more effective therapeutic strategies (Chap. 4). The main inborn errors of metabolism associated with epilepsy are reviewed in the Chap. 5. The diagnosis of a genetic defect or an inborn error of metabolism often results in requests for a vast array of biochemical and molecular tests leading to an expensive workup. However, a specific diagnosis of metabolic disorders in epileptic patients may provide the possibility of specific treatments that can improve seizures.

Although the diagnosis of epilepsy remains mainly clinical, Magnetic Resonance Imaging plays a crucial role in the detection of lesions that can cause epilepsy, with high impact on the diagnostic work-up as well as on therapeutic planning (reviewed in Chap. 6). Morphologic MR imaging is still the main technique for identifying lesions responsible for the epilepsy, providing images with high spatial resolution, excellent soft-tissue contrast, and multiplanar view. Functional MR imaging is used for lateralizing language functions, and also for surgical planning predicting functional deficits following epilepsy surgery. Functional imaging and other methods have contributed to understanding how these seizures arise, as observed in patients with reflex seizures, which are provoked by specific external stimuli and that are important clues for investigating complex mechanisms of epileptogenesis (Chap. 7). Future technical progress will hopefully offer the opportunity for further investigating cortical areas and brain networks involved in cerebral functions and in epileptic discharges, thus contributing to the comprehension of mechanisms of epileptogenesis.

A large section of the book is then dedicated to pathophysiological aspects of epilepsy and related conditions as well as the implications for the quest of new therapies. Insights into commonalities in the pathophysiology of epilepsy and other paroxysmal disorders may suggest new treatment approaches. Of special interest is the association between epilepsy and migraine (Chap. 8). The link between these conditions has been matter of debate for over many decades. However, new data have been now emerging in favour of a non-random relationship between these two entities and it has been also suggested that a headache may be sometimes the isolated ictal manifestation of an epileptic seizure, namely, "ictal epileptic headache", a new entity that has recently been quoted in the last International classification of headache disorders (ICHD-III). Another intriguing link is that between epilepsy and immune system. It is widely acknowledged that immune system influences several aspects of the central nervous system. Indeed, very recent evidences of specific antibodies found in epileptic encephalitis, the good response to immune therapy in refractory epileptic syndromes and the strong relationship between systemic autoimmune disease and epilepsy suggest a plausible role for the immune system also in paroxysmal neurological disorders (Chap. 9). This 'autoimmune hypothesis' represents a new potential approach to target antiepileptic therapy and deserves special attention the next years. In fact, still nowadays up to 30% of patients continue to present recurrent seizures and the challenge for new more efficacious and better tolerated drugs is continuing. Advances in understanding of pathophysiology of epilepsy and in the physiology of ion channels and other molecular targets provide opportunities to create new and improved therapies. Potentially interesting molecular targets include KCNQ-type K+ channels, SV2A synaptic vesicle protein, ionotropic and metabotropic glutamate receptors. The pipeline for the development of new AEDs with novel mechanisms of action is narrowing with only a few interesting compounds on the immediate horizon. Chapter 10 reviews the available information on various classes of molecules that are in the pipeline for the treatment of epilepsy. There is also increasing interested about the use of possible alternative treatments. Reproductive hormones have for years suggested for this purpose (Chap. 11). Progesterone has been reported as effective, but only in studies coming from a single research group. More recently, synthetic neurosteroids have been proposed as a possible treatment devoid of unwanted side effects associated with natural steroids. In spite of the long standing interest in this therapeutic approach, clinical experience from controlled studies is at the present time still very limited.

The final section of the book (Chaps. 12 and 13) discusses the role of surgical neuromodulation for epilepsy treatment, i.e., procedures involving the electrical stimulation of cortical, diencephalic, cerebellar and peripheral targets, e.g., vagus nerve. Stereotactic radiosurgery also provides a neuromodulatory approach, affecting the discharging behavior of epileptic neurons in absence of evident target necrosis. Electrical stimulation and stereotactic radiosurgery are emerging procedures for the treatment of medically refractory epilepsy in patients not amenable to resective surgery due to inability to map the focus, presence of multiple epileptogenic foci and/or involvement of eloquent cortex.

I warmly thank all the authors and friends for their timely and insightful contributions, the series editor Dr. Mario Manto for suggesting this book, Ms. Simina Calin and Jacob Rosati at Springer for keeping things moving along. I also thank my coworkers Maria Stella Vari, Giovanna Giudizioso, and Francesca Pinto for their input into the chapters and my beloved family for being so patient with me.

I hope this book will serve as a helpful guide for adult and pediatric neurologists, including those beginning their careers and hone their skills, as well as for medical students and residents, and sophisticated patients and other lay persons who want to learn more about the pathophysiology, epidemiology and burden, comorbidities, treatment, research, and recourses for the management of persons with epilepsy.

Pasquale Striano MD, PhD

Contents

Copy Number Variants and Epilepsy: New Emerging Syndromes

Antonietta Coppola and Maurizio Elia

Abstract In the last 10 years, advances in the genetic techniques including oligonucleotide array and the following large scale studies have yielded to the identification of recurrent copy number variants (CNVs) associated with epilepsy. Among these a small number has been increasingly reported in association with a distinct epileptic phenotype, delineating emerging epileptic syndromes. To date, none of these CNVs underlying a specific epileptic condition has been included in the ILAE Classification of the Epileptic Syndromes as a distinct form. However once the features and prognosis of these conditions have been completely delineated a proposal for new epileptic syndromes should be considered.

Introduction

The classification of epilepsies of the International League against epilepsy includes the categories of genetic, structural-metabolic and unknown causes (Berg et al. 2010). Many studies have proven that genetic plays a major role in epilepsy, mainly by identifying the involvement of ion channels subunits and neurotransmitters mutations. More recently, thanks to the whole genome higher definition technique, some CNVs have been increasingly reported in association with a peculiar epilepsy phenotype or syndrome. Again genes codifying for ion channels subunits or neurotransmitter protein are often the candidate genes within these segments (Mulley and Mefford 2011; Poduri and Lowenstein 2011). Even if rare, the clinical features and prognosis of these conditions are now better known defining new emerging syndromes. Here we describe an overview of the most reported CNVs associated syndromes presenting with a distinctive epilepsy phenotype.

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Genetic Method for Detecting Copy Number Variation

Routine cytogenetic analysis, namely G-banding karyotype and fluorescence in situ hybridization, have been implemented by "molecular karyotype" techniques. These refer to the evaluation of chromosome content using DNA hybridization, such as array-comparative genomic hybridization (CGH), multiplex ligation-dependent probe amplification (MLPA), single nucleotide polymorphisms (SNP) array, rather than direct observation of chromosome under the microscope, allowing clinicians and researchers to investigate the entire genome for CNVs in one experiment. The defects are then referred as genomic coordinates from the human DNA reference sequence. These have allowed the identification of micro-rearrangements including apparent "balanced" reciprocal translocation as diagnosed by light microscopy. However classical cytogenetic analysis cannot be completely replaced by "molecular karyotype", because the latter cannot detect truly balanced translocations or inversion.

Emerging Epilepsy Syndrome Associated to CNVs

Among the genome, some regions are more prone to micro-rearrangements because of the presence of breakpoint (BP) hotspots (blocks of segmental duplications that flank the deleted or duplicated sequence). Micro-rearrangements usually recur within these regions through a mechanism called nonallelic homologous recombination (NAHR). These CNVs have thus the same size and are known as "recurrent". In the last ten years many recurrent micro-rearrangements have been reported in association with epileptic phenotype (Striano et al. 2011a; Scheffer and Berkovic 2010; Heinzen et al. 2010; Dibbens et al. 2009). Among these, some present with distinct epileptic features or a specific epilepsy syndrome as the hallmark of the clinical condition. We will discuss here the emerging phenotype of epileptic conditions underlined by a micro-rearrangement including 2q24.4 deletion, 5q14.3 deletion, 6q terminal deletion, 14q12 deletion and duplication, 15q13.3 deletion and Xp11.2 duplication. Table 1 summarizes the clinical features of these emerging phenotypes. Other CNVs associated with epilepsy of minor interest are also reported (2q23.1 deletion and 7q11.23 deletion) (Mizugishi et al. 1998; Marshall et al. 2008; van Bon et al. 2010).

2q24.4 Deletion

Patients with a clinical and EEG picture of Dravet syndrome (DS) who result negative for SCN1A mutations may present SCN1A exonic or larger deletions involving SCN1A and contiguous genes (Madia et al. 2006; Mulley et al. 2006;

Table 1 Summary of the clinical features of the emerging CNVs syndromes associated to epilepsy

CNV (candidate gene)	Epileptic phenotype/ syndrome	Seizure's onset/type	EEG features	Dysmorphisms	Other neurological abnormalities	Brain abnormalities	Other associated condition	Ref
2q23.1 del (EPC2 and MBD5)	Rett-like	0–10 yo/ absences	Not reported	Broad forehead, microcephaly, brachycephaly, synophrys, arched eyebrows, long palpebral fissures, full everted lower lip, broad chin, downturned corners of the mouth, teeth anomalies	Severe MR, absent speech, ataxia, disturbed sleep, behavioral problems	Slight atrophy or normal	Hirsutism, hyperphagia	(van Bon et al 2010)
2q24.4 del (SCN1A and contiguous genes)	Dravet-like	2–10 mo/ absences, GTCS, myoclonic, febrile seizures, febrile SE, CPS	Those typically reported in DS	Microcephaly, bitemporal narrowing or frontal bossing, down-slanting or short palpebral fissures, bulbous nose or broad nasal bridge, low-implanted ears, thick helix, bow-shaped mouth, anterior open bite, single palmar creases bilaterally, and partial syndactyly of 2nd–3rd toes	Mild to severe MR, ataxia, muscle hypotonia, autistic behavior	One patient with diffuse lesions in the periventricular white matter and basal ganglia (postmortem abnormalities as seen in Leigh syndrome: spongiosis and increased gliosis of the internal and external pallidum, and less pronounced lesions in the brainstem	Not reported	(Madia et al. 2006; Suls et al. 2006; Davidsson et al. 2008; Marini et al. 2009)
5q14.3 (MEF2C)	Rett-like	1–10 mo/ febrile, CPS, spasms, myoclonic	Not reported	Broad, high forehead, relatively large, backward rotated ear lobes, mildly upward-slanting palpebral fissures and cupid bowed or tented upper lip	Severe MR, hypotonia, strabism	Periventricular heterotopia, mild undermyelinisation	Not reported	(Le Meur et al. 2010; Engels et al. 2009; Zweier et al. 2010)

Table 1 (continued)

CNV (candidate gene)	Epileptic phenotype/ syndrome	Seizure's onset/type	EEG features	Dysmorphisms	Other neurological abnormalities	Brain abnormalities	Other associated condition	Ref
6qter del	Occipital epilepsy	4 mo–4 yo/CPS	Posterior SW complexes, more pronounced during sleep	Low frontal hairline, abnormal hair pattern, asymmetric face, bilateral epicanthus, horizontal or upslanting or short palpebral fissures, broad nasal bridge, micrognathia, high palate, a large gap between upper central incisors, posteriorly rotated or low-set ears, short neck, camptodactyly, phimosis, hypospadia, flat feet with valgus position of the calcaneus	Mild-moderate MR, hypotonia, diffuse joint laxity, strabism	Colpocephaly, dysgenesis of the corpus callosum and brainstem, hypertrophic massa intermedia	Not reported	(Elia et al. 2006; Striano et al. 2006; Bertini et al. 2006; Lee et al. 2011)
7q11.23-q21.11 del (MAGI2)	IS	Infancy/ spasms focal seizures	Hypsarrhytmia	Same as in Williams-Beuren syndrome; microcephaly	Hypotonia, severe MR	Not reported		(Mizugishi et al. 1998; Marshall et al. 2008)
14q12 del (FOXg1)	Rett-like	Infancy/ mainly generalized	Multifocal pattern with spikes and sharp waves	Microcephaly, downslanting palpebral fissures, bilateral epicanthic folds, depressed nasal bridge, bulbous nasal tip, tented upper lip, everted lower lip and large ears	Stereotypies; severe MR	Thin CC	Feeding problems	(Mencarelli et al. 2009)
14q12 dup (FOXg1)	IS	3–8 m/IS	Hypsarrhytmia, modified hypsarrhytmia	Frontal hairline, deep set eyes, hypotelorism	Delay/absent speech, MR	Thin CC	Non reported	(Brunetti-Pierri et al. 2011; Striano et al. 2011b)

Table 1 (continued)

CNV (candidate gene)	Epileptic phenotype/ syndrome	Seizure's onset/type	EEG features	Dysmorphisms	Other neurological abnormalities	Brain abnormalities	Other associated condition	Ref
15q13.3 (CHRNA7)	"Idiopathic generalized epilepsy"	Infancy/ absences, myoclonic absences, GTCS	Generalized S, PS, SW	Hypertelorism, upslanting palpebral fissures, prominent philtrum with full everted lips, clinodactyly	Mild MR, psychiatric problems	Absent	Not reported	(Dibbens et al. 2009; Sharp et al. 2008; Masurel-Paulet et al. 2010; Helbig et al. 2009; Muhle et al. 2011)
Xp11.22-11.23 dup	ESES	6 mo–12 yo/ absences, myoclonic, GTCS	Focal SW, generalized SW, PSW	Non specific facial dysmorphic features, lower-extremity anomalies, (flat or arched feet, fifth-toe hypoplasia, and syndactyly)	Borderline functioning to severe MR, speech delay, poor speech articulation, hoarse and/or nasal voice	Lateral ventricles and subarachnoid spaces dilation, slight peritrigonal hyperintensity	early puberty, overweight	(Giorda et al. 2009; Broli et al. 2011)

CC corpus callosum, *CPS* complex partial seizures, *DS* Dravet syndrome, *ESES* electrical status epilepticus during slow sleeps, *GTCS* generalized tonic clonic seizures, *IS* infantile spasms, *MR* mental retardation, *PS* polispike, *S* spikes, *PSW* polyspike-and-wave, *SE* status epilepticus, *SW* spike-and-wave, *yo* years old

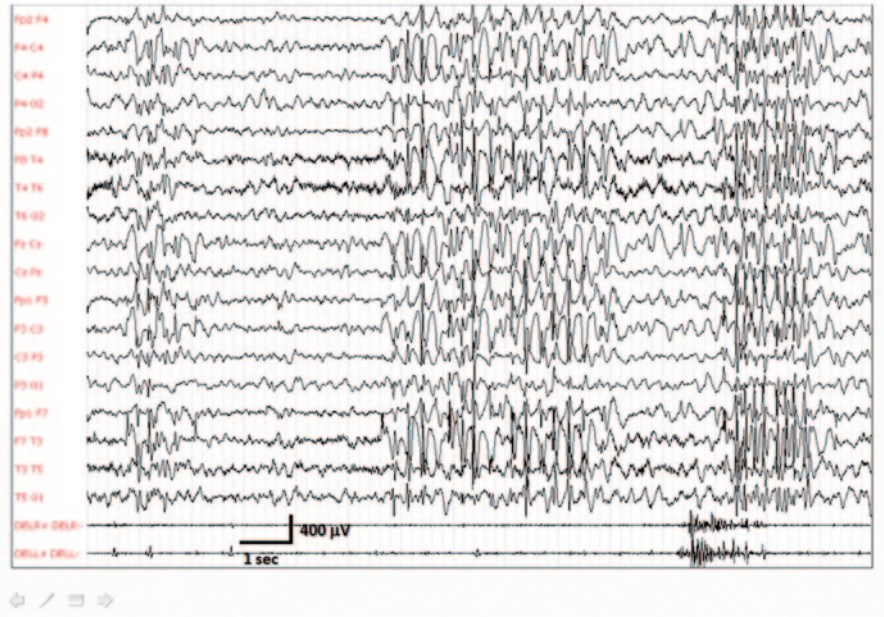

Fig. 1 Wakefulness EEG of a 4-year-old male with 2q24.4 deletion showing some generalized spike-and wave discharges

Suls et al. 2006; Davidsson et al. 2008) . These deletions account for 2–3 % of all DS cases and for about 12.5 % of patients with DS who are negative for mutations on sequencing (Marini et al. 2009).

Deletions extending beyond SCN1A and including variable numbers of contiguous genes can be associated with additional dysmorphic features, depending on the genes involved (Madia et al. 2006), or with a more severe epilepsy phenotype when other voltage-gated sodium channels (VGSC) α subunit genes clustered on chromosome 2q such as SCN2A, SCN3A, SCN7A, and SCN9A are involved (Davidsson et al. 2008; Pereira et al. 2004).

In particular, facial features were reported, such as microcephaly, bitemporal narrowing or frontal bossing, down-slanting or short palpebral fissures, bulbous nose or broad nasal bridge, low-implanted ears, thick helix, bow-shaped mouth, anterior open bite, single palmar creases bilaterally, and partial syndactyly between the second and third toes (Madia et al. 2006; Pereira et al. 2004). Davidsson et al. 2008 reviewed 43 previously published cases with a del(2)(q24.3q31.1). For the 22 seizure-positive cases, 2q24.3 region constituted the smallest commonly deleted region among the majority of the cases, where 2q22.1 and 2q33.3 regions represented the most proximal and distal breakpoint, respectively. The most common dysmorphic features were ear abnormalities, microcephaly, micrognatia and brachysyndactyly.

Seizures start always in the first year of life. The clinical and EEG picture (Fig. 1) is that typical of the classical DS with severe drug resistance, mild to severe mental retardation (MR), autistic behavior, ataxia, muscle hypotonia.

However, other studies did not find significant clinical differences between DS patients with deletions involving only SCN1A and those with deletions of contiguous genes (Mulley et al. 2006; Suls et al. 2006; Marini et al. 2009). It has been suggested that the usually severe DS phenotype might mask subtle clinical differences which may be determined by contiguous genes (Marini et al. 2009).

MRI is usually normal, although Suls et al. (2006) reported one patient who at 14 months of age showed diffuse lesions in the periventricular white matter and basal ganglia. Postmortem brain examination showed abnormalities as seen in Leigh syndrome, with spongiosis and increased gliosis of the internal and external pallidum, and less pronounced lesions in the pons and mesencephalon (central tegmental tract).

Such deletions can be easily identified by means of multiplex ligation-dependent probe amplification (MPLA) and array-comparative genomic hybridization (CGH) is able to determine the size of the abnormality and the additional genes involved. Haplotype analysis with microsatellite markers and single nucleotide polymorphisms (SNPs) can also be used to identify small chromosomal abnormalities affecting SCN1A (Madia et al. 2006; Suls et al. 2006; Marini et al. 2009).

5q14.3 Deletion

Microdeletions within chromosomal bands 5q14.3q15 were recently identified as a current cause of a Rett-like phenotype. Most of these patients do not show classical Rett syndrome with acquired microcephaly and developmental regression after an initial normal interval, but show primary hypotonia, severe mental and motor retardation, early onset seizures, and occasionally autistic behavior, stereotypic hand movements and episodic hyperventilation (Le Meur et al. 2010; Cardoso et al. 2009; Engels et al. 2009). Seizures onset between 1 and 10 months of age, usually with infantile spasms. Febrile seizures, myoclonic and complex partial seizures may also occur. These patients can also present with distinctive dysmorphic features including broad, high forehead, relatively large, backward rotated ear lobes, mildly upward-slanting palpebral fissures and cupid bowed or tented upper lip (Zweier et al. 2010) . The finding of periventricular heterotopia on a brain MRI scan is also possible (Cardoso 2009). MEF2C is the candidate gene for this phenotype. It encodes for a transcriptor factor and its activity relies on the recruitment of, and cooperation with, many other transcription factors, as well as on translational and posttranscriptional modifications (Potthoff and Olson 2007). Its deleterious activity resulting in a Rett-like phenotype may be explained by a common pathway among MEF2C, MECP2 and CDKL5 which are the main mutations responsible for classical Rett syndrome and atypical Rett syndrome respectively. Indeed patients with MEF2C defects showed diminished MECP2 and CDKL5 expression, and MEF2C mutations in vitro resulted in diminished transactivation of both the MECP2 and CDKL5 promoters (Zweier et al. 2010). A mutational screening for MEF2C microdeletion can be considered in patients with early onset Rett-like phenotype and negative for MECP2, CDKL5 and FOXG1 deletion.

6q Terminal Deletion

In 2006 a peculiar clinical, EEG, and neuroradiologic pattern was reported in five unrelated patients with a 6q terminal deletion ranging between 9 and 16 Mb (Elia et al. 2006).

The phenotype was characterized by low frontal hairline, abnormal hair pattern, asymmetric face, bilateral epicanthus, horizontal or upslanting or short palpebral fissures, broad nasal bridge, micrognathia, high palate, a large gap between upper central incisors, posteriorly rotated or low-set ears, short neck, camptodactyly, phimosis, hypospadia, flat feet with valgus position of the calcaneus.

Neurological picture was characterized by mild-moderate mental retardation, hypotonia, diffuse joint laxity, strabismus.

Interestingly, epilepsy was a feature of 6q terminal deletions in all patients. In particular, they shared a distinct clinical and EEG pattern not previously reported in this condition. Epilepsy started in the first or second decade of life. In all cases, seizures had a focal onset, characterized by the ictal signs of vomiting, cyanosis, and head and eye version with or without loss of consciousness. No status epilepticus or prolonged seizures occurred. Prognosis of epilepsy was generally good in our patients, in terms of both seizure control and evolution. In all subjects but one, interictal EEG was characterized by posterior spike-and-wave complexes which became more pronounced during sleep. The ictal signs and the EEG patterns in our patients suggested that the seizures originated in the occipital lobes. Given the early onset of seizures (between ages 4 months and 4 years), it was conceivable that an age-related low threshold of emetic centers caused the ictal vomiting, as occurs in Panayiotopoulos-type occipital epilepsy.

However, the occipital epilepsy in these patients should be considered symptomatic because of the mild/moderate mental retardation and brain anomalies.

In four of five cases, MRI revealed colpocephaly and dysgenesis of the corpus callosum and of the brainstem; three patients also had a hypertrophic massa intermedia (or interthalamic adhesion).

Subsequently, other seven patients with 6q subtelomere deletions and a similar clinical and EEG pattern were ascertained with a size of the deletion ranging from 3 to 13 Mb (Striano et al. 2006; Bertini et al. 2006).

In a recent review, 28 cases with pure 6q terminal deletion were counted (Lee et al. 2011). The most common breakpoint found in 14 cases was in the 8.0–9.0 Mb interval from the 6q terminus. There are approximately 34 known genes and six OMIM morbid genes in this ~9.0 Mb region.

A comparison of the case with the smallest deletion (~ 0.4 Mb; 3 known genes) reported to date and the case that has the largest deletion (<11 Mb;>34 known genes) showed no specific phenotype differences, with respect to developmental delay, intellectual disability, dysmorphic features, hypotonia, microcephaly, seizure and brain anomalies. The region of greatest interest resulted the smallest overlapped portion of the most distal part of chromosome 6q. The genes located in the region within 0.4 Mb of the 6q terminus were PSMB1, TBP and PDCD2. The TBP gene

has been implicated as a candidate gene for phenotypes in patients with 6q terminal deletion; mutations of TBP gene are associated with spinocerebellar ataxia 17. However, the possibility of other genes playing a role in the phenotypes resulting from this deleted region cannot be ruled out.

The mechanism of chromosome 6q terminal deletion, in some cases, may be related to the fragile site, FRA6E.

It has been estimated that 6q terminal deletion is present in ~0.05% of patients with intellectual disability and/or development delay (Lee et al. 2011). 6q terminal deletion should be suspected in children with occipital epilepsy, MR, colpocephaly and malformative features, and in these cases multiprobe FISH, MLPA or array-CGH should be included in the diagnostic work-up.

14q12 Deletion and Duplication

14q12 microdeletion has been claimed as responsible for the congenital variant of Rett syndrome (Ariani et al. 2008). This CNV encompasses FOXG1 gene, a brain specific forkhead-box transcriptional repressor which is now considered the third gene responsible for Rett syndrome (Mencarelli et al. 2009) . The phenotype is characterized by early deterioration, postnatal microcephaly, hypotonia, seizures, stereotypies (Ariani et al. 2008; Mencarelli et al. 2009). Patients with 14q12 deletion differ from MECP2 mutated patients because they tend to exhibit abnormal development in early infancy, while also lacking the characteristic autonomic disturbances of Rett syndrome (Brunetti-Pierri et al. 2011). Seizures onset is in infancy with mainly generalized tonic-clonic convulsions. EEG can show multifocal pattern with spikes and sharp waves (Ariani et al. 2008). The clinical picture also includes mild dysmorphic features such as downslanting palpebral fissures, bilateral epicanthic folds, depressed nasal bridge, bulbous nasal tip, tented upper lip, everted lower lip and large ears (Mencarelli et al. 2009). Corpus callosum thinning can be reported (Mencarelli et al. 2009). FOXG1 deletion should be considered in children with atypical presentation of Rett syndrome including early onset infantile spasms, severe developmental delay, postnatal microcephaly, stereotypies and absence of autonomic features.

14q12 duplications have been reported in patients with various degree of developmental delay, delayed/absent speech and epilepsy, especially infantile spasms (Brunetti-Pierri et al. 2011; Striano et al. 2011b). The phenotype is different from that showed by patients with 14q12 deletions and inactivating mutations of FOXG1. Patient with duplication show a major involvement of speech and an early onset (3–8 months) developmental epilepsy mainly characterized by infantile spasms (Brunetti-Pierri et al. 2011; Striano et al. 2011b). This can be accompanied or not by hypsarrhytmic pattern at the EEG (Brunetti-Pierri et al. 2011). Dysmorphic features, when present, are mild and include high frontal hairline, deep set eyes, hypotelorism (Brunetti-Pierri et al. 2011).

15q13.3 Deletion

Among the CNV associated epileptic phenotype the 15q13.2-13.3 microdeletion has raised the highest interest in the field. It has been first described by Sharp as a recurrent CNV associated with mental retardation and epilepsy (Sharp et al. 2008) . Soon after many reports described this abnormality together with a broad variety of phenotype including schizophrenia, severe neurodevelopmental disorders, autism and epilepsy (Dibbens et al. 2009; Ben-Shachar et al. 2009; Masurel-Paulet et al. 2010; van Bon et al. 2009; Shinawi et al. 2009). The different clinical manifestations have been correlated to the different breakpoints where the interruption occurs, and the breakpoints 4 and 5 (BP4 and BP5) have been associated to the epilepsy phenotype (Sharp et al. 2008). Furthermore a major severe phenotype has been mainly reported in the homozygous loss situation (Lepichon et al. 2010; Endris et al. 2010).

In the last few years the 15q13.3 CNV has been widely reported as a common risk factor for epilepsy, being detected in about 1% of patients with idiopathic generalized epilepsy with or without other neurological manifestations (Dibbens et al. 2009; Helbig et al. 2009). Interestingly, the 15q13.3 deletion resulted to be negative in a wide group of 3000 patients with partial epilepsies, suggesting that the deletion may confer a specific risk for generalized epilepsy (Heinzen et al. 2010; Kasperaviciute et al. 2010). Dibbens et al indicated a complex inheritance and incomplete penetrance for the IGE component of the phenotype in multiplex families (Dibbens et al. 2009). Among the idiopathic generalized epileptic syndromes, absences have been recently described in three out of 570 children with epilepsy and a various degree of intellectual disability (Muhle et al. 2011).

No brain abnormalities have been reported in association to this CNV. Dysmorphisms are not always present and the most common are hypertelorism, upslanting palpebral fissures, prominent philtrum with full everted lips, clinodactyly (Sharp et al. 2008).

Haploinsufficiency of CHRNA7, which encodes for the α7 subunit of the acetylcholine receptor is postulated as the most likely responsible factor for this phenotype (Dibbens et al. 2009; Mulley and Dibbens 2009). We recently observed two families with multiple affected individuals presenting with absences or myoclonic absences associated to mild intellectual disability, confirming the data reported by Muhle et al (Coppola et al. 2013). The ictal EEG showed generalized polispike and wave or spike and waves discharges (Fig. 2). Apparently these patients presented with a common idiopathic generalized epilepsy; however their seizures tended to persist in the elderly and were difficult to control requiring an association of at least two AEDs (Coppola et al. 2013). These features together with the occurrence of intellectual disability make the diagnosis of idiopathic generalized epilepsy unlikely. Thus in the presence of apparently generalized idiopathic epilepsy with absences and mild intellectual disability clinicians should consider a genetic test for 15q13.3 deletion.

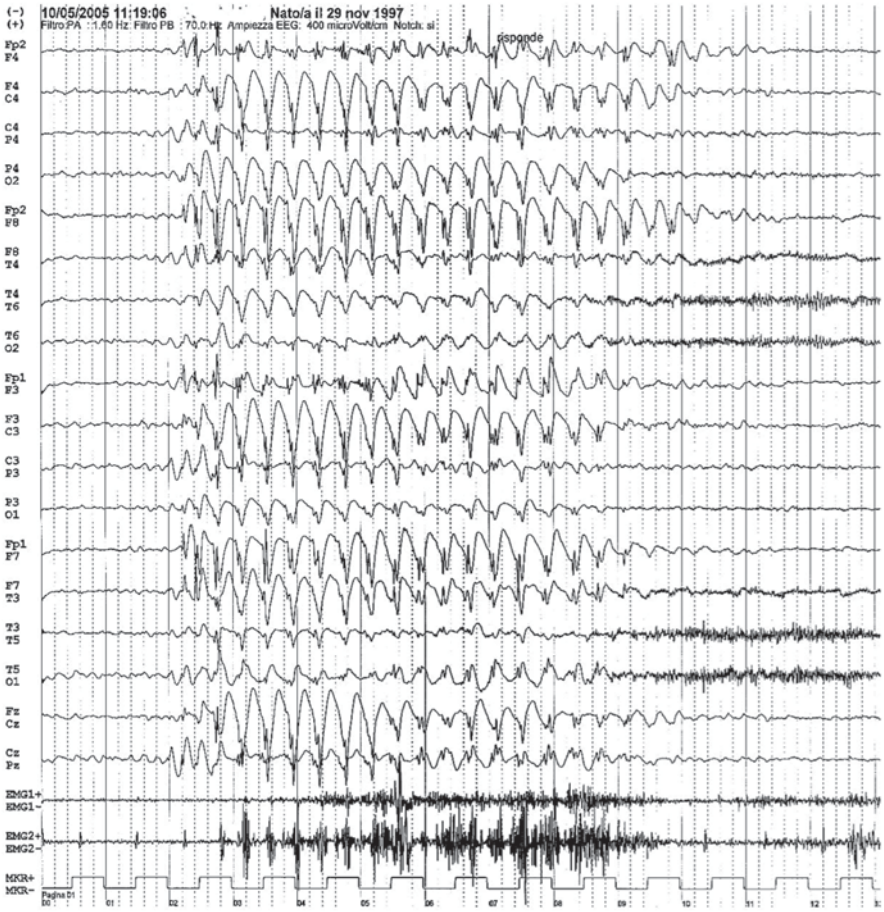

Fig. 2 Critical EEG of a 15q13.3 deletion patient showing generalized spike and wave activity

Xp11.22–11.23 Duplication

Recently a group of 9 subjects (2 males and 7 females) with a microduplication at Xp11.22-11.23 were identified at a diagnostic genome array screening of 2400 subjects with MR, either isolated or associated with a more complex phenotype. The duplication was either familial or sporadic (Giorda et al. 2009).

The clinical phenotype is characterized by a cognitive disturbance (from borderline functioning to severe MR), speech delay, poor speech articulation, hoarse and/or nasal voice, early puberty, overweight, non specific facial dysmorphic features, lower-extremity anomalies, including flat or arched feet, fifth-toe hypoplasia, and syndactyly.

A subsequent study was aimed to better define the neurological phenotype of this new syndrome (Broli et al. 2011). Electrical status epilepticus during sleep (ESES)

was observed in five of nine patients, particularly in younger ones (from 5 to 13 years), and was associated with speech delay in all cases. ESES was controlled by antiepileptic drugs in three out of five patients; the other two patients remained untreated. Neuroimaging did not disclose specific abnormalities. Therefore, the speech delay may be correlated to the ESES, able to cause local EEG slow-wave activity damage, impairing the plastic changes associated with language development.

Epilepsy was also reported in three of nine patients, with different types of seizures starting in infancy or in childhood, such as clonic jerks of the limbs and stare, generalized tonic-clonic seizures during sleep, absences. Outcome was benign.

Xp11.2 is a gene-rich, rearrangement-prone region within the critical linkage interval for several neurogenetic disorders harboring X-linked mental retardation (MRX) genes which could be responsible for the syndrome phenotype (Giorda et al 2009).

In the presence of MR, speech delay and ESES, array-CGH array should be performed in order to disclose Xp11.22-11.23 duplication.

Conclusions

The availability of whole genome high resolution techniques has shed light on new emerging syndromes underlined by chromosomal micro-rearrangements. Epileptic seizures are often a symptom of these complex conditions and sometimes epilepsy is the distinctive feature of the clinical phenotype. In few such cases the natural history, drug responsiveness and prognosis can resemble well known syndromes. However the association with other neurological symptoms and/or somatic defects and/or dysmorphic features render these conditions unique arising the question whether they can be considered new distinctive syndromes. At least for the conditions here reported it appears that a sufficient knowledge has been reached to consider them unique entities.

A genotype-phenotype correlation of further population studies can help delineating new epileptic phenotypes that recur in such genetic conditions. To this purpose it can be also helpful to report sporadic but well characterized cases. This should allow the clinicians to address the genetic test only in candidate patients avoiding expensive and time consuming analysis where not necessary.

Lastly, the study of the genes involved in these CNVs can be also crucial to better understand the physiopathology underlying some epileptic syndromes (i.e. ESES) or simply epileptic seizures.

In the future, the up coming newer techniques, namely high resolution customized array-CGH and next generation sequencing, will hopefully allow the identification of a greater number of CNV-related syndromes and the role of the clinicians will be in parallel important to validate the genetic data.

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Mutations of Ion Channels in Genetic Epilepsies

Massimo Mantegazza, Raffaella Rusconi and Sandrine Cestèle

Abstract Epileptogenic mutations have been identified in several ion channel genes, leading to the concept that several epilepsies can be considered channelopathies. However, increasing number of genes involved in a diversity of functional and developmental processes are being recognized through whole exome or genome sequencing, confirming that there is remarkable complexity underlying epileptogenesis. Additionally, recent studies of large cohorts of patients suggest that many patient-specific mutations in several genes are important for generating a particular phenotype, rather than mutations in a few genes common to most of the patients.

We will review the epilepsy syndromes linked to ion channel gene mutations and the main results of genetic and functional studies, highlighting that also other genes can be important but stressing the central role of ion channels in the pathophysiology of genetic epilepsies. Although the picture is becoming more complex than previously thought, the identification of epileptogenic mutations in patients before epilepsy onset and the possibility to develop therapeutic strategies tested in experimental models may facilitate experimental approaches that prevent epilepsy or decrease its severity.

Because neuronal excitability depends on the activity of voltage-dependent or receptor-activated membrane ion channels, their dysfunctions have been hypothesized to have a central role in epilepsy. In fact, early observations have shown that epileptiform neuronal activity can be induced by spontaneous or experimental modifications of the properties of ion channels leading to alterations of neuronal excitability or synaptic transmission (McCormick and Contreras 2001; Avanzini and Franceschetti 2003).

However, the first demonstration that a human disorder of excitability is caused by a genetic mutation of an ion channel came from the identification of a $Na_V1.4$ Na^+ channel α subunit mutant (gene *SCN4A*), causing a skeletal muscle disease: hyperkalemic periodic paralysis (Ptacek et al. 1991). Since then, mutations of ion

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channels have been identified in several diseases whose pathological mechanism involves defects of cellular excitability, the "channelopathies" (Ptacek 1997), including hemiplegic migraine, episodic ataxias, myotonias, hyperekplexia and cardiac syndromes (Kass 2005; Ashcroft 2006; Kullmann 2010). These diseases, similarly to idiopathic epilepsies, show acute and transient presentation of symptoms in individuals that otherwise appear normal. Indeed, few years after the discovery of hyperkalemic periodic paralysis mutations, the first epileptogenic mutation of an ion channel was identified in the α4 subunit of the neuronal acetylcholine receptor of patients affected by autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (Steinlein et al. 1995). Since then numerous other mutations and genetic variants of ion channel genes have been identified in different forms of epilepsy (Fig. 1; Avanzini et al. 2007; Helbig et al. 2008; Reid et al. 2009; Kullmann 2010; Mantegazza et al. 2010b; Guerrini et al. 2014), but the picture is becoming less clear than it was foreseen.

Several genes that do not codify for ion channels and sometimes have still unidentified functions have been implicated in genetic epilepsy. Moreover, phenotypic variability is often large, making more difficult the correlation between mutations in specific genes and specific epileptic syndromes, and complicating early diagnosis and genetic counseling. Phenotypic variability has been ascribed to genetic modifiers: polymorphisms or other genetic variants that can modulate the effect of the mutation. Notably, mutations are defined as modifications in the sequence of a gene that are clearly identified as the cause of the disease, thus the term should be used for mendelian monogenic disorders. Genetic variants are instead modifications that contribute to disease susceptibility, and their implication in disease is often inferred from the fact that the variants are mainly found in patients and that they induce functional effects. In polygenic epilepsies, a specific epilepsy phenotype can be generated by the combination of less penetrant alleles with large effect and of polygenic alleles with small effect. Novel technologies have allowed the sequencing of whole genomes (whole genome sequencing, WGS) or of their coding part (whole exome sequencing, WES), identifying an increasing number of genetic variants. However, the identification of their importance for determining a specific phenotype is not straightforward. Moreover, in many cases both genetic and acquired factors can contribute to the determinism of epilepsy, and environmental factors can have an important role in determining phenotypes also in forms with Mendelian pattern of inheritance (Berkovic et al. 2006).

However, despite these complications, several studies have indisputably linked ion channels to specific epileptic syndromes and pathogenic mechanisms.

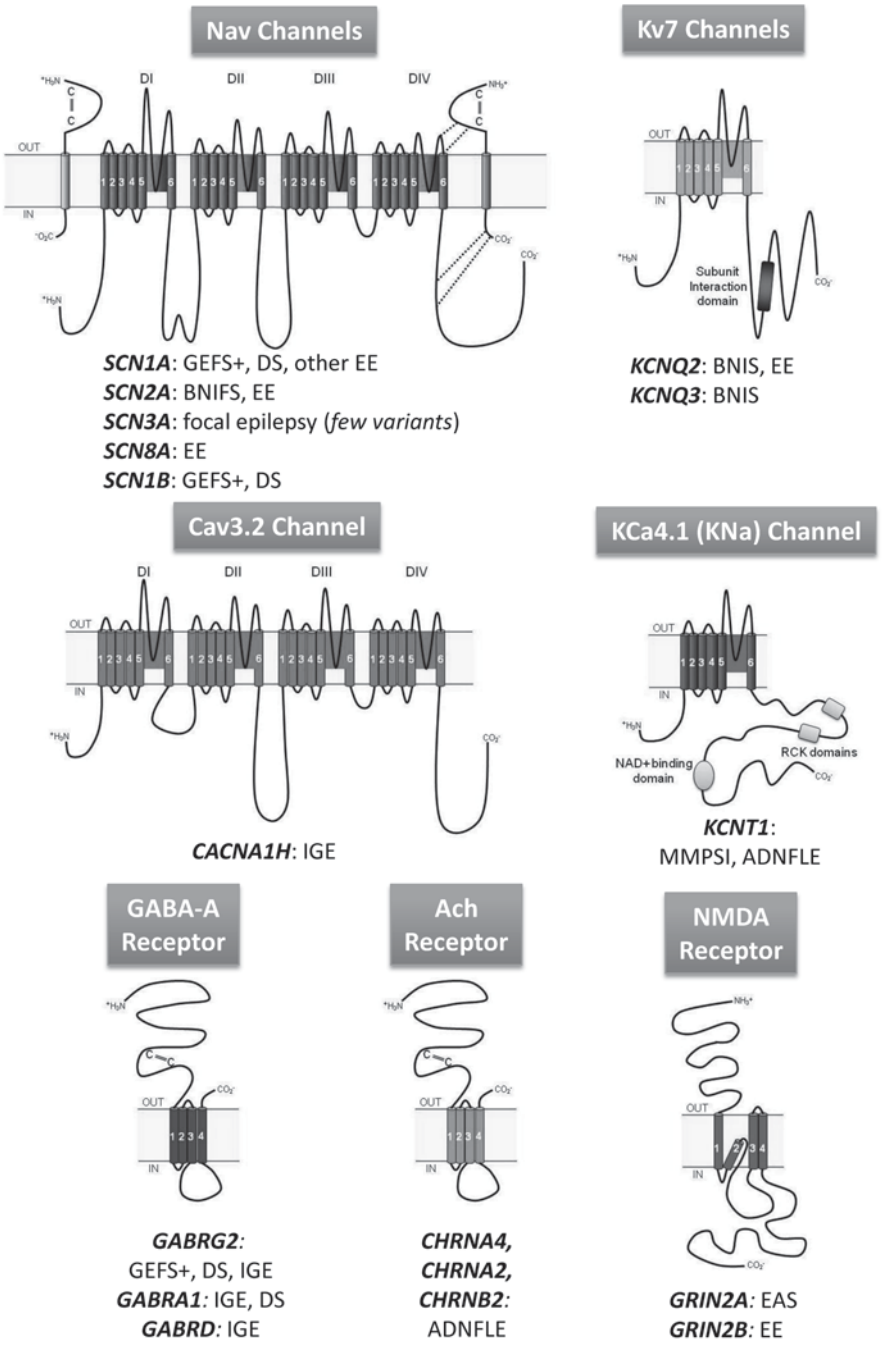

Fig. 1 Basic structure of main voltage- and ligand-gated ion channel proteins involved in genetic epilepsy. The structure of the subunits targeted by mutations/variants identified in genetic forms of epilepsy are shown. The names of the genes and the forms of epilepsy in which they are involved

Voltage-gated Na^+ Channel SCN1A Gene-related Epilepsies and Epileptic Encephalopathies: A Prototypical Spectrum of Severity

Voltage gated Na^+ channels (Na_V) are essential for the generation of cellular excitability, target of antiepileptic drugs and their mutations are important causes of genetic epilepsy (Mantegazza et al. 2010a; Marini and Mantegazza 2010; Catterall 2012). Na_V are composed by a principal pore-forming α subunit (nine isoforms: $Na_V1.1$-$Na_V1.9$ for the proteins, SCN1A-SCN11A for the genes), and by auxiliary β subunits (four isoforms: β1-β4 for the proteins, SCN1B-SCN4B for the genes) (Mantegazza and Catterall 2012). The primary sequence of α subunits contains four homologous domains (DI-DIV), each comprising six predicted transmembrane segments (S1-S6) that form voltage-sensing modules (S1-S4; S4 is the voltage sensor) and pore modules (S5-S6) in each domain. The β subunits contain a single transmembrane segment.

SCN1A/$Na_V1.1$ is one of the most clinically relevant epilepsy genes (Marini and Mantegazza 2010; Guerrini et al. 2014), with hundreds of mutations reported thus far in different epilepsy syndromes characterized by variable phenotypes, and is also the target of some familial hemiplegic migraine (FHM-type III) mutations; see www.molgen.ua.ac.be/SCN1AMutations and http://www.scn1a.info/ for *SCN1A* variant databases. The most severe epileptic phenotype associated with $Na_V1.1$ mutations is Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy of Infancy (SMEI), an extremely severe epileptic encephalopathy (i.e. a disorder in which it is hypothesized that epileptic seizures and epileptiform activity impair brain function, although this causal link has not been clearly demonstrated yet). DS is characterized by onset in the first year of life as prolonged seizures triggered by fever and later appearance of severe afebrile seizures of various type, drug resistance, ataxia, delayed psychomotor development, cognitive impairment and behavioral dysfunctions (Dravet et al. 2005). In general, it is caused by de novo deletions or missense mutations of $Na_V1.1$ (Claes et al. 2001; Depienne et al. 2009), which are found in > 80 % of patients.

Genetic (Generalized) Epilepsy with Febrile Seizures Plus (GEFS+) patients shows large phenotypic heterogeneity in families, including febrile seizures (FS) and febrile seizures plus (FS+: FS after 6 years of age). The course and response

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are indicated below the diagram of the protein. Nav voltage-gated Na+ channels, Cav3.2 voltage-gated Ca2+ channels, T-type-1H, Kv7 voltage-gated K+ channels, M-type, KCa4.1 Na+-activated K+ (KNa) channel, SLACK-SLO2.2 type; GABA-A gamma-aminobutyric acid receptor, type A, Ach nicotinic acetylcholine receptor, NMDA glutamate receptor, N-methyl-D-aspartate (NMDA) type, DS Dravet syndrome, GEFS+ generalized (genetic) epilepsy with febrile seizures plus, EE epileptic encephalopathies, BFNIS benign familial neonatal-infantile seizures, BNIS benign neonatal familial seizures, IGE idiopathic generalized epilepsies, MMPSI malignant migrating partial seizures of infancy, ADNFLE autosomal dominant nocturnal frontal lobe epilepsy, EAS epilepsy-aphasia syndromes

to antiepileptic drugs may be considerably variable within the same family: some patients experience rare febrile or non-febrile seizures that remit after a few years, while others, even within the same family, have drug resistant epilepsy, with Dravet syndrome as the extreme of the spectrum (Scheffer and Berkovic 1997). GEFS+ was originally recognized thanks to large autosomal dominant pedigrees with 60–70% penetrance, but it is likely that most cases occur in small families or are sporadic. It is caused in general by missense $Na_V1.1$ mutations, which are found in about 10% of families (Marini and Mantegazza 2010).

$Na_V1.1$ mutations have also been identified in some patients presenting with different epileptic encephalopathies, ranging from Lennox-Gastaut syndrome to epilepsy aphasia syndrome (Depienne et al. 2009; Marini and Mantegazza 2010; Carvill et al. 2013b; Guerrini et al. 2014). One of the mildest epileptic phenotypes associated with missense $Na_V1.1$ mutations is benign simple febrile seizures (sFS) (Mantegazza et al. 2005), although some patients of this family developed also mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE&HS). Interestingly, genome-wide association studies have linked *SCN1A* single nucleotide polymorphisms (rs7587026 and rs11692675) to development of MTLE&HS upon a history of febrile seizures (Kasperaviciute et al. 2013), and a further *SCN1A* polymorphism has been identified as risk factor for idiopathic/genetic generalized epilepsies (rs11890028) (Steffens et al. 2012). Familial hemiplegic migraine (FHM) is a rare severe autosomal dominant inherited subtype of migraine with aura characterized by hemiparesis during the attacks (Vecchia and Pietrobon 2012). Some FHM families carry missense $Na_V1.1$ mutations, in some cases without any signs of epileptic phenotypes (Cestele et al. 2013a).

In vitro functional studies of missense epileptogenic $Na_V1.1$ mutations in heterologous systems have initially shown controversial results (Mantegazza et al. 2010b; Mantegazza 2011), revealing both gain- and loss-of-function effects, but loss-of function seems to be the predominant mechanism of action of both truncations and missense mutations. In fact, consistently with the phenotype of DS patients, mouse models of $Na_V1.1$ truncating DS mutations exhibit spontaneous seizures, cognitive impairment and reduction of Na^+ current selectively in GABAergic inhibitory interneurons, causing reduction of their excitability and of GABAergic inhibition, leading to network hyperexcitability (Yu et al. 2006; Ogiwara et al. 2007; Han et al. 2012; Ito et al. 2012; Liautard et al. 2013). $Na_V1.1$ truncations lead to haploinsufficiency without negative dominance (Bechi et al. 2012). Studies of animal models have confirmed that also GEFS+ mutations cause loss of function of $Na_V1.1$ and induce reduced excitability of GABAergic neurons (Tang et al. 2009; Martin et al. 2010).

Although some light has been shed on the pathomechanism of $Na_V1.1$ mutations, the causes of the striking phenotypic variability observed in some patients are still not clear. For instance, some $Na_V1.1$ mutations can cause phenotypes extending from different types of epilepsy to familial hemiplegic migraine (Cestele et al. 2013b). Some of the phenotypic variability can be linked to the combined action of mutations/variants in different genes. It has been shown that a $Na_V1.1$ missense mutant, identified in families with extreme phenotypes comprising Dravet syndrome,

causes loss of function because of folding defects that can be rescued by molecular interactions with associated proteins or pharmacological chaperones (Cestele et al. 2008). These results have been confirmed and extended to typical GEFS+ families and Dravet syndrome patients with de novo mutations (Rusconi et al. 2009; Sugiura et al. 2012; Thompson et al. 2012). This mechanism may generate phenotypic variability because of genetic background-dependent variability in rescue, and also be possibly used in the development of therapeutic approaches. As recently shown for a missense *SCN1A* mutant identified in a family with pure FHM (Cestele et al. 2013a), rescue of folding defects may also transform non-functional loss of function mutants (effect that is consistent with severe epilepsy) into gain of function ones, effect that is consistent with familial hemiplegic migraine (Cestele et al. 2008). Genetic background can modulate also the effect of $Na_V1.1$ truncating mutations, because there are reports of mild phenotypes or no phenotype in some individuals carrying these mutations (Orrico et al. 2009; Klassen et al. 2011).

Rare mutations in the *SCN1B* gene, coding for the Na^+ channel β1 subunit have been identified in both GEFS+ (Wallace et al. 1998; Meadows et al. 2002) and DS (Patino et al. 2009).

Similarly, few mutations of the *GABRG2* gene (coding the γ2 subunit of the gamma-aminobutyric acid receptor type A, GABA-A, ionotropic heteropentameric receptor of the main inhibitory neutrotransmitter of the brain) can cause GEFS+, sometimes with DS phenotypes (Baulac et al. 2001). Functional expression of some *GABRG2* mutations, identified in patients with GEFS+, revealed a pronounced loss-of-function by altered gating or defective trafficking and reduced surface expression as a common pathogenic mechanism (Macdonald et al. 2010). Knock-in mouse models of the R43Q *GABRG2* mutation shows generalized seizures and reduced GABAergic inhibition (Chiu et al. 2008). Recently, also mutations of the GABRA1 gene (coding for the α1 subunit of the GABA-A receptor) have been identified in few Dravet syndrome patients (Carvill et al. 2014). Hence, these mutations could reduce GABAergic neurotransmission, the main mechanism for neuronal inhibition in the brain, similarly to *SCN1A* mutations, which may explain the occurrence of seizures.

Mutations of the SCN2A Voltage Gated Na^+ Channel and of KCNQ2-KCNQ3 K^+ Channels: An Unexpected Spectrum of Severity

SCN2A/$Na_V1.2$, KCNQ2 and KCNQ3 have been initially involved in mild benign epilepsies of newborns and infants, but more recently their mutations have also been linked to severe epileptic encephalopathies, showing a spectrum of severity that is similar to that observed for $Na_V1.1$ mutations.

K^+ channels are composed by four subunits forming the ion-conducting pore and generate repolarizing currents that oppose depolarizing currents generated by, e.g. Na^+ channels. KCNQ channels, which consist of homomeric or heteromeric

tetramers, are responsible for the so called M-current (muscarinic receptor regulated), which is a non-inactivating K^+ current that activates at subthreshold membrane potentials counteracting membrane depolarizations that would lead to action potential generation. Thus, it plays an important role in influencing neuronal firing activity, limiting spiking frequency and reducing the responsiveness to synaptic inputs. *KCNQ2* and *KCNQ3* form a heteromeric K^+ channel (Fig. 1), which is particularly important in the axon initial segment and nodes of Ranvier of glutamatergic neurons (Delmas and Brown 2005).

Mutations or deletions/duplications involving one or more exons of *KCNQ2* and, in a smaller number of patients, mutations of KCNQ3 have been identified in benign familial neonatal seizures (BFNS) (Biervert et al. 1998; Singh et al. 1998; Singh et al. 2003). BFNS is characterized by clusters of seizures that appear from the first days of life up to the third month to spontaneously disappear after weeks to months. Seizures have focal onset, often with hemi-tonic or hemiclonic symptoms or apneic spells, or can clinically appear as generalized. Interictal EEG is usually normal. The risk of seizures recurring later in life is about 15 % (44). Functional studies in in-vitro systems performed co-expressing heteromeric wild-type and mutant KCNQ2/3 channels revealed a reduction of about 20–30 % in the resulting K^+ current, which is apparently sufficient to cause BFNS (Maljevic et al. 2008). Although the reduction of the K^+ current can cause epileptic seizures by subthreshold membrane depolarization, which increases neuronal firing, it is not fully understood why seizures preferentially occur in neonates (Weber and Lerche 2008). It is possible that the neonatal brain is more vulnerable to changes, even small, of neuronal excitability. Alternatively, *KCNQ2* and *KCNQ3* channels, when mutated, might be replaced by other K^+ channels that become functional after the first months of life. Transgenic and knock-in BFNS mice have been generated. Transgenic mice expressing a dominant negative *KCNQ2* mutant (Peters et al. 2005) show spontaneous partial and generalized tonic-clonic seizures, but also pronounced hyperactivity and cell loss in the hippocampus, with impaired hippocampus-related memory, which are not consistent with the typical BNFS human phenotype. Knock-in mice of *KCNQ2* A306T or G311V mutations (Singh et al. 2008) show spontaneous tonic-clonic seizures and, consistently with BNFS, no hippocampal neurodegeneration; however, only homozygous mice manifest epilepsy and they also tend to have seizures in adulthood.

Mutations in *SCN2A*/$Na_V1.2$ have been identified in benign familial neonatal-infantile seizures (BFNIS) (Berkovic et al. 2004). BFNIS are characterized by seizures similar to those observed in children with BFNS, but age at seizure onset ranges from the neonatal period to infancy in different family members, with a mean onset age of 3 months. In general, remission occurs by 12 months with a very low risk of later seizures. $Na_V1.2$ (Fig. 1) is particularly important for the excitability of the axon initial segment and nodes of Ranvier in glutamatergic neurons early in development. Mutations causing BFNIS have been studied in both transfected neocortical neurons and cell lines identifying gain of function effects (Scalmani et al. 2006; Liao et al. 2010) consistent with hyperexcitability of excitatory neurons. The remission may depend on a developmental switch between $Na_V1.2$ and $Na_V1.6$

in myelinated axons that occur at early developmental stages (Scalmani et al. 2006; Liao et al. 2010). No animal models reproducing a BFNIS mutation have been developed yet.

Similarly to $Na_V1.1$ mutations, *KCNQ2* and $Na_V1.2$ mutations can cause a wide phenotypic spectrum that includes severe epileptic encephalopathies. In particular, *KCNQ2* mutations have been identified in severe neonatal epileptic encephalopathies associated with intellectual disability and motor impairment, with a burst-suppression EEG pattern or multifocal epileptiform activity, but also in milder forms (Weckhuysen et al. 2012; Weckhuysen et al. 2013). Functional studies of these mutations have been recently performed in Xenopus Oocytes, showing that they can have more severe loss of function than those causing BFNS (Miceli et al. 2013) or, in some cases, they can cause negative dominance inhibiting function of wild type *KCNQ2* (Orhan et al. 2014). A transgenic mouse model expressing a *KCNQ2* dominant negative mutant may model these forms (Peters et al. 2005).

Similarly, de novo $Na_V1.2$ truncating and missense mutations have been identified in early onset intractable childhood epilepsies, with features ranging from Ohtahara syndrome to Dravet syndrome (Lossin et al. 2012; Nakamura et al. 2013; Touma et al. 2013). Contrary to BFNIS mutants, functional analysis of some of these mutants using in-vitro expression systems has shown loss of function (Lossin et al. 2012), although it is not yet clear how loss-of-function in a Na^+ channel predominantly expressed in excitatory neurons would lead to network hyperexcitability. Notably, a loss of function *Scn2a* knockout mouse does not show an overt epileptic phenotype, although this has not been studied in detail (Planells-Cases et al. 2002).

Neuronal Nicotinic Acetylcholine Receptors and KCNT1 K^+ Channel Mutations in Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Neuronal nicotinic acetylcholine receptors (nAchR) have important neuromodulatory functions (including modulation of GABA and glutamate release, the main inhibitory and excitatory neurotransmitters of the brain, respectively) and consist of homo- or heteromeric pentamers of various combinations of at least 17 subunits: α1—10, β1—4, δ, ε and γ. The α4-β2 combination is the most common in the thalamus and cerebral cortex. A mutation in the gene *CHRNA4*, encoding the α4-subunit of a neuronal nicotinic acetylcholine receptor (nAchR), was the first ion channel mutation found in an inherited form of epilepsy (Steinlein et al. 1995): autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). About 15 mutations in *CHRNA4*, five in *CHRNB2*, which encodes the β2-subunit of nAchR, and one in *CHRNA2*, encoding the neuronal nAchR α2-subunit, have been reported so far and account for < 10 % of the tested ADNFLE families (Ferini-Strambi et al. 2012). All the identified mutations are located in the pore-forming M2 transmembrane segments.

ADNFLE includes frequent, usually brief, seizures with onset on average at around 10 years of age, with hyperkinetic or tonic manifestations, typically in clusters at night during slow-wave sleep. Paroxysmal arousals, dystonia-like attacks and epileptic nocturnal wanderings are also part of the phenotype. Functional studies of nAchR have produced controversial results, which make the underlying pathogenic mechanisms still unclear. Expression of α4 mutants in heterologous systems resulted in various effects consistent with either gain or loss of function: increased sensitivity to acetylcholine (gain of function); decreased Ca^{2+} potentiation or accelerated desensitization (loss of function) (Bertrand et al. 2002). Mutations of β2 showed gain of function by increased sensitivity to acetylcholine or slower desensitization (De Fusco et al. 2000) and the α2 mutation showed gain of function by increased sensitivity to acetylcholine (Aridon et al. 2006). The α4 mutations S252F and +L264 engineered in knock-in mice (Klaassen et al. 2006) induced spontaneous seizures of various types, in some cases similar to those of the human phenotype, but no paroxysmal arousal and dystonia-like manifestations; whereas the α4 subunit S248F knock-in mice show no spontaneous seizures but nicotine-induced dystonic attacks (Teper et al. 2007). α4-subunit S284L transgenic rats (Zhu et al. 2008) show a more complete ADNFLE phenotype, with spontaneous attacks during slow-wave sleep, comprising of paroxysmal arousals (frightened behavior), dystonic activity and epileptic wandering. Notably, the pathogenic mechanisms are also different in these models: upon application of nicotine, GABAergic inhibition is increased in frontal cortex of S252F and +L264 knock-in mice (Klaassen et al. 2006), whereas it is reduced in somatosensory cortex of S284L transgenic rats (Zhu et al. 2008).

Missense mutations in the Na^+-activated K^+ channel gene *KCNT1* (KCa4.1-SLACK-SLO2.2 type; Fig. 1) have been recently reported in 4 unrelated families with a severe form of ADNFLE (Heron et al. 2012). *KCNT1* is activated by the inward flux of Na^+ ions during neuronal firing and its activity contributes to the slow hyperpolarization that follows repetitive firing. Thus, its action negatively modulates high frequency firing. There is no information about the effect of its ADNFLE mutations because functional analysis was not performed. Patients had an earlier mean age of onset (6 years) compared to other ADNFLE forms and frequently exhibited psychiatric features and intellectual disability. Thus, the phenotype has some features that are typical of epileptic encephalopathies and, interestingly, mutations of KCNT1 have also been identified in the epileptic encephalopathy malignant migrating partial seizures in infancy (see below).

Therefore, genetic variability is evident in this clinically relatively homogenous epileptic form.

Ion Channel Mutations Recently Identified with Whole Exome Sequencing Studies

Current efforts of whole exome sequencing (WES) are generating a great amount of information that is improving our understanding of the pathophysiology of genetic epilepsies, in particular for rare epileptic encephalopathies. Most of the mutations

that have been thus far interpreted as causative arise as de novo mutations or are inherited in an autosomal recessive fashion, often as compound heterozygous mutations. Notably, mutations in these new epilepsy genes associated with epileptic encephalopathies with variable phenotypes, occasionally resembling known syndromes including Dravet syndrome, are found in a small number of patients (Allen et al. 2013; Carvill et al. 2013b; Suls et al. 2013). Although mutations in non-ion channel genes have been identified, genes coding for ion channels are still common ones. For instance, mutations of the *HCN1* gene (coding for the type 1 subunit of the hyperpolarization-activated, cyclic nucleotide-gated channel that contributes to the cationic Ih current in neurons and can regulate the excitability of neuronal networks) have been identified in patients with Dravet syndrome-like phenotypes (Nava et al. 2014). Mutations of *SCN8A*/$Na_V1.6$ are associated with other types of early onset epileptic encephalopathies (109, 112); this is the fifth Na^+-channel gene to be mutated in epilepsy when variants of *SCN3A*/$Na_V1.3$ are included (Vanoye et al. 2014; Fig. 1).

Mutations in the GRIN2B gene (encoding the NR2B subunit of the heterotetrameric N-methyl-D-aspartate, NMDA, receptor, a ionotropic receptor of the main excitatory neurotransmitter of the brain: glutamate) have also been recently identified in 3 patients with phenotypes that include West syndrome and focal epilepsy with intellectual disability (Lemke et al. 2014).

Mutations in the *GRIN2A* gene encoding the NR2A subunit of the NMDA glutamate receptor have been identified in epilepsy-aphasia syndromes (EAS), which are a group of severe epileptic encephalopathies with a characteristic EEG pattern and developmental regression particularly affecting language that include Landau-Kleffner Syndrome (LKS) and continuous spike-waves in slow sleep (CSWS); functional analysis of these mutations using in-vitro systems has shown gain of function (Carvill et al. 2013a; Lemke et al. 2013; Lesca et al. 2013). Phenotypes of GRIN2A patients appear to be very different from those of GRIN2B mutations.

WES and targeted sequencing studies have also showed that ion channel genes previously associated with milder phenotypes can also cause epileptic encephalopathies in some patients (Carvill et al. 2013b), including *GABRA1* (coding for the α1 subunit of the GABA-A receptor), which has been previously involved in mild idiopathic generalized epilepsy (see below) and, as highlighted above, *SCN2A* Na^+ channel and *KCNQ2* K^+ channel genes. Similarly, de-novo gain of function mutations in the *KCNT1* gene have been identified in patients with malignant migrating partial seizures of infancy (MMPSI), a rare syndrome with infantile onset intractable and migrating focal seizures with severe impairment of psychomotor development (Barcia et al. 2012), but KCNT1 mutations have also been associated to other and very different epilepsy phenotypes, including autosomal dominant nocturnal frontal lobe epilepsy (Heron et al. 2012) (see above).

Idiopathic Generalized Epilepsies with Complex Inheritance

The idiopathic generalized epilepsies (IGE) represent 20–30 % of all epilepsies and are formed by a group of syndromes including childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic-clonic seizures alone. Among epilepsies with complex inheritance, IGEs have long been considered to be particularly suitable for genetic studies because they are common, have a relatively well-defined phenotype and often occur in familial clusters. It has been initially suggested that they might result from the interaction of two or few genes (Berkovic and Scheffer 2001), but a high degree of genetic complexity appears from large scale exome sequencing of ion channels, which showed that rare missense variations in known Mendelian disease genes are equally prevalent in healthy individuals and in those with idiopathic generalized epilepsy, revealing that even probably deleterious ion channel mutations confer an uncertain risk to an individual, depending on the other variants with which they are combined (Klassen et al. 2011). Linkage studies on a large number of families with IGE have suggested several susceptibility loci (Sander et al. 2000; Durner et al. 2001) and some variants have been identified. In rare families pathogenic mutations in single ion channel genes have been reported. Mutations in the *GABRG2* gene (coding the γ2 subunit of the GABA-A receptor, which is mutated also in GEFS+, see above) were identified in families with febrile seizures and childhood absence epilepsy and cause loss of function by reduced membrane targeting (trafficking defects) or by accelerated desensitization and reduced sensitivity to benzodiazezine, consistently with reduced GABAergic inhibition (Wallace et al. 2001; Kang et al. 2006). Mutations in the *GABRA1* gene (coding the α1 subunit of the GABA-A receptor) were identified in families with juvenile myoclonic epilepsy or childhood absence epilepsy, and cause loss of function by protein truncation or folding/trafficking defects (Cossette et al. 2002; Gallagher et al. 2007). Mutations of the *GABRB3* gene, coding for the GABA-A receptor β3 subunit have been identified in small families showing childhood absence epilepsy, and cause loss of function but with an unclear mechanism (Tanaka et al. 2008). Mutations in *CLCN2* (coding the ClC2 Cl^- channel) were identified in families with heterogeneous IGE phenotypes, including childhood absences epilepsy (D'Agostino et al. 2004). Variants in *CACNA1H*, coding for the Cav3.2 T-type voltage-gated Ca^{2+} channel (Fig. 1) that is mainly targeted to neuronal cell bodies and dendrites (highly expressed in thalamic neurons), have been identified in childhood absence epilepsy and other generalized epilepsy phenotypes; they cause various modifications in gating properties often consistent with gain of function, but differences in functional effects have been observed between rat and human clones, and between splicing variants (Chen et al. 2003; Khosravani et al. 2004). Consistently with the human findings, it has been shown that the *Cacna1h* variant R1584P is a susceptibility factor in a spontaneous rat model of absences (GAERS) (Powell et al. 2009).

Other Ion Channels Involved in Genetic Epilepsy

Other mutations or variants of other ion channels have been identified in few families or sporadic patients. Some of them show mendelian inheritance with high penetrance, but many are probably limited to few families.

For instance, a gain of function mutation of the *KCNMA1* gene coding the KCa1.1 large conductance Ca^{2+} activated K^+ channel (BK), which is activated by depolarizations and intracellular Ca^{2+} and is implicated in action potential repolarization and after-hyperpolarizations, has been identified in a family with generalized epilepsy and paroxysmal dyskinesia. Gain of function may increase excitability by inducing more rapid repolarization and increasing firing frequency (Du et al. 2005).

A loss of function mutations of the *KCNA1* gene, coding for the Kv1.1 subunit of delayed rectifier voltage gated K^+ channels that forms homo- or hetero-tetramers with other Kv1 subunits, have been identified in a family with partial epilepsy associated with myokymia (Eunson et al. 2000).

Loss of function mutations of the *KCNJ10* gene, coding for the Kir4.1 glial ATP-dependent inwardly rectifier K^+ channel implicated in K^+ buffering in the brain have been identified in complex phenotypes comprising generalized epilepsy, ataxia, sensori-neural deafness, tubulopathy and mental retardation; they probably impair K^+ buffering (Bockenhauer et al. 2009; Scholl et al. 2009).

Mutations of the *CACNA1A* gene, coding for the $Ca_v2.1$ P/Q high voltage activated (HVA) Ca^{2+} channel that is mainly targeted to presynaptic terminals, have been found in few families showing childhood absence epilepsia and ataxia, and cause loss of function consistent with decreased neurotransmission (Imbrici et al. 2004). Interestingly, mutations of $Ca_v2.1$ have been also involved in familial hemiplegic migraine, and data from animal models show that they induce gain of function selectively in glutamatergic neurons (Vecchia and Pietrobon 2012). Mutations of *CACNB4* coding for the β4 auxiliary subunit of HVA Ca^{2+} channels (Cav1.x, Cav2.x) have been identified in few families showing IGE and episodic ataxia, but their functional effect was consistent with gain of function, differently than for epileptogenic $Ca_v2.1$ mutations (Escayg et al. 2000).

A recessive loss-of-function missense mutation in the HCN2 gene (coding for the type2 subunit of the hyperpolarization-activated, cyclic nucleotide-gated channel) has been found in a patient with sporadic idiopathic generalized epilepsy; the proband was the only affected member of the family and homozygous for the mutation (DiFrancesco et al. 2011). Functional analysis revealed that the homomeric mutants, but not heteromeric wild-type/mutant channels, show loss of function and induce hyperexcitability in transfected cultured neurons.

Among intracellular channels, mutations of the ATP synthase proton channel (respiratory chain complex V) have been definitively identified as the cause of NARP, in which seizures are part of a complex phenotype comprising neuropathy, ataxia and retinitis pigmentosa (DiMauro and Schon 2008).

Beyond Channelopathies

Although mutations of ion channels are a main pathomechanism of genetic epilepsies, as outlined above, several genes that do not encode for ion channels have been implicated as well. For instance, mutations of protocadherin delta-2 subclass of the cadherin super family (PCDH19), Aristaless-related homeobox (ARX), cyclin-dependent, kinase-like 5 (CDKL5) and syntaxin binding protein 1 (STXBP1) genes have been identified in monogenic epilepsies without brain malformations that often manifest as severe forms, with features of epileptic encephalopathy, often having early seizure onset and developmental delay, even if with diverse and distinctive phenotypes, sometimes resembling Dravet syndrome (Guerrini et al. 2014).

Other examples are mutations of the *LGI1* gene (leucine-rich, glioma-inactivated 1) that have been associated to autosomal dominant temporal lobe epilepsy (ADTLE), a form of autosomal dominant partial epilepsy associated to auditory symptoms and audiogenic seizures (Kalachikov et al. 2002; Morante-Redolat et al. 2002). The pathogenetic mechanism related to *LGI1* mutations remains to be clarified. Results obtained from animal models are more consistent with a direct presynaptic mechanism of hyperexcitability involving modulation of K^+ channels, whereas postsynaptic effects may be more involved in glutamatergic synapse maturation and dendritic pruning (Schulte et al. 2006; Zhou et al. 2009).

Recent studies have identified in some families presenting with familial focal epilepsy with variable foci mutations in Dishevelled, Egl-10 and Pleckstrin domain-containing (DEPDC5) protein, whose function is still unclear but might be involved in membrane trafficking, G protein signaling and/or modulation of the mTOR complex 1 (Dibbens et al. 2013; Picard et al. 2014). Most mutations resulted in a truncated protein and are consistent with loss of function.

De-novo mutations of CHD2 (encoding chromodomain helicase DNA binding protein 2) have been recently identified in three patients with a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome (Suls et al. 2013).

Conclusions

Numerous epileptogenic mutations have been identified in plasma-membrane ion channel genes in part also because of the bias induced by the prior knowledge of their importance for neuronal excitability. Recent unbiased research efforts have identified epileptogenic mutations also in genes that do not code for ion channels and in the future the list of these genes will probably be expanded, also expanding the type and number of epileptogenic mechanisms. However, it is feasible that for several of them a role in ion channel regulation, targeting or expression will be discovered.

The hypothesis that mutations in a ‘few and common genes’ might cause phenotypes with overlapping clinical features needs to be revised, because genetic findings emerging from WES studies of large cohorts of patients, realized by consortia of

laboratories, rather suggest several patient-specific mutations in several genes to be at play (Allen et al. 2013). The proteins codified by the genes whose mutations/variants contribute to a specific phenotype might be localized within a so-called "functional network system".

Thus, phenotypic and genetic heterogeneity are common in genetic epilepsies and may be explained by pleiotropic expression of a single-gene mutation, modifying genes, or by several genes producing a similar phenotype, at times because they affect the same developmental or functional pathway. Thus, it will be essential to compare clinical and experimental studies in order to better disclose pathogenic mechanisms that lead to a particular form of epilepsy.

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LGI1 Dysfunction in Inherited and Acquired Epileptic Disorders

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Abstract LGI1 is a multifunctional brain protein whose dysfunction is related to several neurologic disorders as diverse as autosomal dominant lateral temporal epilepsy (ADLTE), autoimmune limbic encephalitis (LE), and glioma tumor progression. ADLTE is a genetic focal epilepsy characterized by auditory or aphasic aura and onset in infancy/adolescence, whereas autoimmune LE occurs in adult life and is characterized by amnesia, confusion, and seizures. The complex molecular mechanisms underlying these epileptic conditions are largely unknown. In this chapter, I outline the clinical features, the genetic or autoimmune causes, and a molecular mechanism possibly underlying both ADLTE and autoimmune LE.

Introduction

The leucine-rich, glioma inactivated 1 (LGI1) gene has been associated with clinical phenotypes as different as malignant glioma, autosomal dominant lateral temporal epilepsy (ADLTE), a rare genetic focal epilepsy syndrome, and autoimmune limbic encephalitis (LE), an acquired immunological disorder of the brain. Although very different in nature, these brain disorders result from a reduction of the physiological level of the Lgi1 protein.

In 1998, LGI1 was cloned due to its rearrangements in the T98G glioblastoma multiforme (GBM) cell line and was found to be downregulated in many malignant gliomas, suggesting a possible tumor suppressor function (Chernova et al. 1998). Subsequent studies failed to reveal point mutations in the LGI1 coding sequence and differential methylation of its core promoter region in GBM tumors, arguing against a role of LGI1 as a tumor suppressor gene (Somerville et al. 2000; Piepoli et al. 2006). However, LGI1 has been shown to control proliferation and invasiveness of glioma cell lines by regulating expression of the matrix

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metalloproteinases MMP1 and MMP3, suggesting that LGI1 may serve as a tumor metastasis suppressor gene (Kunapuli et al. 2003; 2004). In 2002, LGI1 heterozygous mutations were shown to cause ADLTE in several American and European families (Kalachikov et al. 2002; Morante-Redolat et al. 2002). Subsequent studies showed that LGI1 mutations account for about 50% of ADLTE families (Michelucci et al 2003; Ottman et al. 2004). ADLTE is clinically characterized by auras with auditory features and is also named autosomal dominant partial epilepsy with auditory features (ADPEAF). Finally, in 2010, LGI1 was implicated in acquired autoimmune limbic encephalitis, a neurological disorder of adulthood (Irani et al. 2010; Lai et al. 2010). Patients with autoantibodies directed against the Lgi1 protein suffer from psychiatric symptoms, including memory loss and confusion, as well as epilepsy.

The LGI1 gene consists of eight exons with a coding region of 1671 bp. It is expressed mainly in neurons, particularly in the neocortex and limbic regions (Kalachikov et al. 2002; Senechal et al. 2005) and encodes a protein of 557 amino acids with no similarities to ion channels. The Lgi1 protein is secreted (Senechal et al. 2005), and its structure consists of an N-terminal signal peptide and two distinct structural domains: the N-terminal region contains four leucine-rich repeats (LRR) flanked by conserved cysteine clusters (Kobe and Kajava 2001), whereas the C-terminal region consists of seven copies of a repeat named EPTP (Staub et al. 2002), which form a beta-propeller structural domain (Paoli 2001). Both LRR and beta-propeller motifs mediate protein-protein interactions (Kobe and Kajava 2001; Paoli 2001).

In this chapter I describe the clinical features of ADLTE and LE, the role of LGI1 as a cause of these syndromes, and outline the current views about the possible functions of LGI1.

ADLTE

Clinical Features

ADLTE is a rare familial condition characterized by focal seizures with prominent ictal auditory symptoms, negative MRI findings, and relatively benign evolution (Ottman et al. 1995; Michelucci et al. 2009). Its prevalence is unknown but it may account for about 19% of genetic focal epilepsies (Ottman et al. 2004). Since the first description of the syndrome (Ottman et al. 1995), 39 families, most of which with unique LGI1 mutations have been reported. The syndrome segregates with an autosomal dominant inheritance pattern with reduced penetrance. Familial diagnosis is based on the existence of at least two cases with unprovoked focal or secondarily generalized seizures whose symptoms suggest a lateral temporal lobe onset.

The age of onset ranges between 1 and 60 years with a mean of 18 years. The ictal semiology includes focal seizures and secondarily generalized tonic-clonic sei-

zures. Focal seizures are characterized by auditory auras in about 2/3 of the cases. In most cases, auditory symptoms are described as simple sounds (such as humming, buzzing, ringing); complex hallucinations (i.e. music, voices) are less frequent, and, sometimes, the aura is characterized by a distortion of sounds (becoming louder and louder or suddenly low). Aphasic seizures associated with auditory phenomena are reported, but may also be the only clinical symptom in some pedigrees (see Michelucci et al. 2003). Other less frequent auras include complex visual, psychic, autonomic, vertiginous, and other sensory symptoms, usually accompanying auditory phenomena.

Secondary tonic-clonic seizures are common, occurring in 90% of cases, both during wakefulness and sleep, and may unmask an otherwise undiagnosed history of elementary focal seizures with auditory symptoms. Interictal EEGs show temporal abnormalities (described as mild slow/sharp waves) in about half of the patients, with a clear left predominance of the abnormalities in some families (Brodtkorb et al. 2005; Pisano et al. 2005). Standard MRI shows no abnormalities, but a study of 8 ADLTE patients with LGI1 mutations performed by voxel-based MRI and diffusion tensor imaging demonstrated a cluster of fractional anisotropy in the left lateral temporal cortex, suggesting a malformative origin of the abnormality (Tessa et al. 2007).

Genetic studies have revealed mutations of LGI1 in about 30–50% of the families, providing evidence for genetic heterogeneity (Michelucci et al. 2003; 2013). Detailed analysis of families with and without LGI1 mutations showed no phenotypic differences between the pedigrees.

Sporadic, non-familial cases with auditory seizures have been reported (Bisulli et al. 2004a). Despite their negative family history, they had a clinical picture indistinguishable from that of ADLTE patients, characterized by focal seizures with auditory auras, a mean age of onset of 19 years, a high rate of secondary generalized tonic-clonic seizures, low seizure frequency, good response to antiepileptic treatment, unrevealing EEGs and normal MRIs. *De novo* LGI1 mutations have been found in two sporadic LTE cases (see below).

LGI1 Pathogenic Mutations

To date, a total of 37 LGI1 mutations have been described, either segregating in ADLTE families or occurring *de novo* in sporadic LTE patients (Fig. 1 and Table 1; nucleotide numbering uses the A of the ATG translation initiation start site as nucleotide +1). Thirty-six mutations segregate in 39 affected families, whereas two, c.406C>T and c.1420C>T, are *de novo* mutations identified in non-familial cases, the latter occurring in both a family and a sporadic case (Morante-Redolat et al. 2002; Bisulli et al. 2004b). Of these mutations, 23 allow single amino acid substitutions, 13 result in protein truncation due to frameshift deletions or insertion, and to non-sense or splice site mutations, whereas one in frame deletion mutation (c.377–379delACA) results in the deletion of an asparagine in the encoded protein. In addition, an internal deletion of exons 3–4, resulting from altered splicing

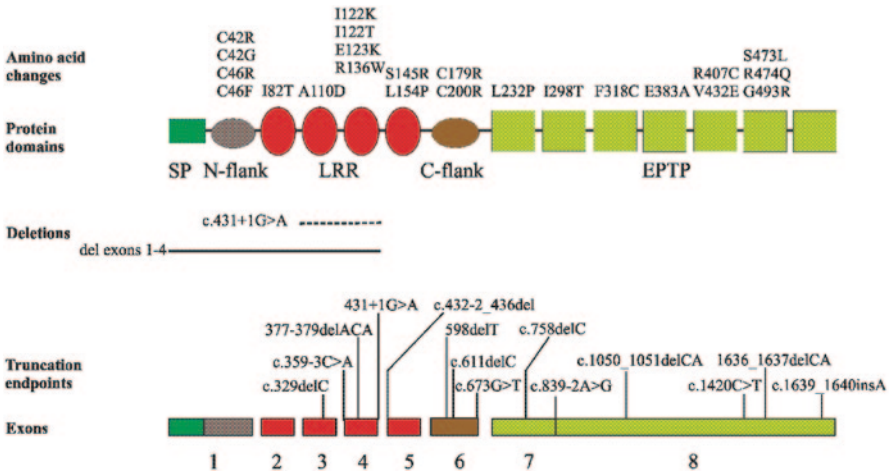

Fig. 1 Distribution of the pathogenic LGI1 mutations described so far. Most of them are single amino acid substitutions. Mutations are uniformely distrubuted along the gene, though a higher density of mutations appears to occur in exons 3–5 , which correspond to the N-terminal LRR repeat 2–4

(c.431 + 1G > A), and a genomic microdeletion spanning the first 4 LGI1 exons have been identified (Table 1). Thus, the majority of the mutations as yet identified are missense nucleotide changes. The mutation distribution along the gene is somewhat uniform, though a higher density of mutations appears to occur in exons 3–5, which correspond to the N-terminal LRR repeat 2–4 (Ho et al. 2012; see Fig. 1). The overall penetrance estimate of LGI1 mutations was 66 % (Rosanoff and Ottman 2008) and the proportion of families with penetrance > = 75 % was similar among those with missense vs truncation mutations (Ho et al. 2012).

The Lgi1 protein is expressed mainly in neurons and is secreted into the extracellular compartment (Senechal et al. 2005; Fukata et al. 2010). All but one LGI1 mutations reported so far inhibit protein secretion (Nobile et al. 2009), suggesting a loss-of-function effect of mutations. Only one missense mutation (R407C) has been shown to allow protein secretion (Striano et al. 2011), and its effect in the extracellular comparment of the brain is unclear. A three-dimensional protein model predicts that this mutation may perturb extracellular interactions of Lgi1 with other proteins, and that this effect may not be limited to this mutation (Leonardi et al. 2011).

Lgi1 Protein Function

The function of LGI1 and the mechanisms of LGI1-related epilepsy remain unclear. Three main functions have been proposed for LGI1 in the CNS: (1) inhibition of inactivation of the presynaptic voltage-gated potassium channel Kv1.1

Table 1 LGI1 mutations reported in literature

Nucleotide change	Gene region	Predicted effect	Reference
c.124T>C	Exon 1	p.C42R	Ottman et al. (2004)
c.124T>G	Exon 1	p.C42G	Berkovic et al. (2004)
c.136T>C	Exon 1	p.C46R	Gu et al. (2002); Pizzuti et al. (2005)
c.137G>T	Exon 1	p.C46F	Lee et al. (2014)
c.245T>C	Exon 2	p.I82T	Sadleir et al. (2013)
c.329C>A	Exon 3	p.A110D	Ottman et al. (2004)
c.329delC	Exon 3	Truncation	Hedera et al. (2004)
c.359-3C>A	Intron 3	Truncation	Kalachikov et al. (2002)
c.365T>A	Exon 4	p.I122K	Striano et al. (2008)
c.365T>C	Exon 4	p.I122T	Di Bonaventura et al. (2011)
c.367G>A	Exon 4	p.E123K	Di Bonaventura et al. (2009)
c.377-379delACA	Exon 4	p.Asn126del	de Bellescize et al. (2009)
c.406C>T	Exon 4	p.R136W	Di Bonaventura et al. (2011); Michelucci et al. (2007)
Genomic deletion	Exon 1–4	Deletion	Fanciulli et al. (2012)
c.431+1G>A	Intron 4	Deletion	Chabrol et al. (2007); Berghuis et al. (2013)
c.432-2_436del	Exon 5	Truncation	Sadleir et al. (2013)
c.435C>G	Exon 5	p.S145R	Hedera et al. (2004)
c.461T>C	Exon 5	p.L154P	Pisano et al. (2005)
c.535T>C	Exon 6	p.C179R	Di Bonaventura et al. (2011)
c.598T>C	Exon 6	p.C200R	Michelucci et al. (2003)
c.598delT	Exon 6	Truncation	Heiman et al. (2010)
c.611delC	Exon 6	Truncation	Kalachikov et al. (2002)
c.673G>T	Exon 6	Truncation	Sadleir et al. (2013)
c.695T>C	Exon 7	p.L232P	Chabrol et al. (2007)
c.758delC	Exon 7	Truncation	Morante-Redolat et al. (2002)
c.839-2A>G	Intron 7	Truncation	Kobayashi et al. (2003)
c.893T>C	Exon 8	p.I298T	Ottman et al. (2004)
c.953T>G	Exon 8	p.F318C	Fertig et al. (2003)
c.1050_1051delCA	Exon 8	Truncation	Kalachikov et al. (2002)
c.1148A>C	Exon 8	p.E383A	Kalachikov et al. (2002)
c.1219C>T	Exon 8	p.R407C	Striano et al. (2011)
c.1295T>A	Exon 8	p.V432E	Michelucci et al. (2003)
c.1418C>T	Exon 8	p.S473L	Berkovic et al. (2004); Kawamata et al. (2010)

Table 1 (continued)

Nucleotide change	Gene region	Predicted effect	Reference
c.1420C>T	Exon 8	Truncation	Morante-Redolat et al. (2002); Bisulli et al. (2004)
c.1421G>A	Exon 8	p.R474Q	Kawamata et al. (2010)
c.1477G>A	Exon 8	p.G493R	Heiman et al. (2010)
c.1636_1637delCA	Exon 8	Truncation	Heiman et al. (2010)
c.1639_1640insA	Exon 8	Truncation	Kalachikov et al. (2002)

LGI1 GenBank reference sequence: NM_005097.2. Nucleotide numbering uses the A of the ATG translation initiation start site as nucleotide +1

(Schulte et al. 2006); (2) potentiation ofAMPA receptor-mediated synaptic transmission in the hippocampus through interaction with the transmembrane receptors ADAM22 and ADAM23 (Fukata et al. 2006; 2010; Ohkawa et al. 2013); (3) postnatal maturation of glutamatergic synapses, regulation of spine density, and dendritic pruning (Zhou et al. 2009). Remarkably, Lgi1- knockout mice (Fukata et al. 2010; Chabrol et al. 2010; Yu et al. 2010) display spontaneous seizures. Homozygous Lgi1 knockout (KO) mice have spontaneous seizures with onset at postnatal day 10 and all pups die before the end of the third postnatal week, while heterozygous Lgi1+/− mice exhibit increased susceptibility to sound-induced or pentylenetetrazole-induced seizures (Chabrol et al. 2010; Fukata et al. 2010). The "intermediate" phenotype of heterozygous +/− mice supports the loss-of-function model, whereas the phenotypic features of mice overexpressing a truncated protein in the presence of normal endogenous Lgi1 suggest that some mutations may have a dominant negative effect (Zhou et al. 2009).

Acquired Immune-Mediated Disorders

LE

The pivotal role of LGI1 in epileptic disorders has been expanded with the recent finding of autoantibodies against Lgi1 in patients with autoimmune LE, a neurological disorder of adulthood characterized by amnesia, confusion, seizures, which mostly involve the temporal lobes, and personality change or psychosis (Irani et al. 2010; Lai et al. 2010). Autoimmune LE belongs to the group of autoimmune synaptic encephalopathies, in which patients develop antibodies against synaptic proteins, including the excitatory N-Methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and voltage-gated potassium channel (VGKC)-complexes (Kv1). Because of the crucial role of these

receptors in synaptic transmission and plasticity, the autoimmunity usually causes seizures and neuropsychiatric symptoms, ranging from alterations in memory, behaviour, and cognition, to psychosis. The resulting disorders are severe but treatable, and some of them can be individually classified on the basis of a particular immune response (for example, anti-NMDA receptor encephalitis (Dalmau et al. 2008; Gable et al. 2009); or anti-VGKC LE (Vincent et al. 2004; Tan et al. 2008). The VGKC complex antibodies have traditionally been measured by immunoprecipitation of VGKC Kv1 subunits solubilized in detergent from rabbit brain tissue and radioactively labeled by 125I-dendrotoxin, a snake toxin that binds very strongly to Kv1. Recently, a series of experiments has shown that the antibodies do not bind directly to Kv1 subunits but rather to other molecules that are complexed with the Kv1 in brain extracts. The most frequently associated molecules identified so far are Lgi1 and Contactin-associated protein 2 (CASPR2), with the great majority of the LE patients having antibodies to Lgi1 (Lai et al 2010). Commonly, these antibodies are detected using an immunofluorescence cell-based method which detects the binding of patients' sera to the surface of cells transfected with cDNA encoding the protein.

LE patients with autoantibodies directed against Lgi1 protein suffer from psychiatric symptoms and epilepsy. Clinical seizures, generalized or involving the temporal lobes, occur in about 80% of LE patients, whereas 40% have myoclonus; 60% of patients have hyponatraemia On MRI, increased T2 signal involving one or both medial temporal lobes are frequently observed (Lai et al. 2010). Lgi1-positive LE usually is not associated with tumors. Immunotherapy, consisting of intravenous immunoglobulin, glucocorticoids, plasma exchange, or a combination thereof, results in full recovery or mild residual memory impairment in most cases. Relapses only occur in a minority of cases.

In a proportion of patients, autoimmune LE is associated with faciobrachial dystonic seizures (FBDS), which is characterized by typical episodes of facial grimacing and ipsilateral arm dystonia (Irani et al. 2008; 2013). Seizures occur at high frequency (up to 360 episodes per day). The onset is variable (22–83 years) and is sometimes triggered by auditory stimuli or high emotion. EEG abnormalities, i.e. rhythmic frontotemporal spikes, are detectable in about one-fourth of FBDS cases. This syndrome has been found consistently associated with antibodies against Lgi1 (Irani et al. 2008; 2011; Vincent et al. 2011). Response to anti-epileptic drugs is poor whereas immunotherapy yields excellent results. Most FBDS patients subsequently develop the full LE phenotype, whereas in a minority of cases FBDS occur in isolation or follows LE. Early immunotherapy for faciobrachial dystonic seizures may postpone or even prevent progression to the cognitive impairment that characterizes LE (Irani et al. 2011).

Neuromyotonia and Morvan Syndrome

Lgi1 autoantibodies are also found in acquired immune-mediated peripheral nerve disorders neuromyotonia and Morvan syndrome, though often associated with other antibodies. Acquired neuromyotonia is characterized by the presence of spontaneous activity including positive sharp-waves and fibrillation potentials, fasciculations, myokymia, multiple discharges, muscle cramps and repetitive after-discharges in response to a voluntary contraction (Warmolts and Mendell 1980; Hart et al. 1997). Acquired neuromyotonia may be clinically misdiagnosed as amyotrophic lateral sclerosis (ALS), particularly in the early stages of ALS where widespread fasciculations may be evident in the absence of other clinical features of ALS.

Morvan's syndrome has been recognized as a rare constellation of peripheral nerve neuromyotonia combined with sensory abnormalities and central nervous system (CNS) features, such as dysautonomia and encephalopathy with marked insomnia (Hart et al. 2002). Some of the patients had a thymoma, but many do not have a tumor. In patients with neuromyotonia or Morvan syndrome CASPR2 antibodies are mainly detected, whereas Lgi1 antibodies are much less frequent and, when occur, are frequently associated with CASPR2 antibodies (Irani et al. 2012).

Whether Lgi1 autoantibodies are pathogenic or represent an epiphenomenon is still uncertain. However, immunotherapies can lead to a marked improvement of these syndromes paralleling with antibody titer decrease, suggesting a possible direct role of antibodies on neuronal function.

LGI1 Functional Models

Despite definitive genetic evidence, the pathophysiological function of LGI1 in the brain remains controversial. Several studies have shown that the secreted Lgi1 protein binds to ADAM22 and ADAM23 receptors on the surface of neuronal cells and that these protein complexes exert various functions during neuronal maturation and synaptic transmission (Fukata et al. 2006; 2010; Owuor et al. 2009). The involvement of both ADAM22 and ADAM23 in epilepsy is suggested by studies of knock-out mice, showing that lack of expression of either of these genes results in spontaneous seizures (Owuor et al. 2009; Sagane et al. 2005). It has been shown that the ligand-receptor complexes between Lgi1 and ADAM22/ADAM23 regulates AMPA receptor-mediated synaptic transmission in the hippocampus, suggesting a possible molecular mechanism underlying ADLTE (Fukata 2006; 2010). This mechanism is further supported by recent findings showing that Lgi1 antibodies associated with LE neutralize the specific protein-protein interaction between LGI1 and ADAM22/ADAM23, and that disruption of this complex is sufficient to reduce AMPA receptors in rat hippocampal neurons (Ohkawa 2013). Thus, a unifying view is emerging, suggesting that reduced binding of Lgi1 to ADAM22/23 may be a pathogenic mechanism for both genetically inherited ADLTE and acquired LE, providing further support to the central role of LGI1 in mechanisms for regulating brain function and excitability.

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Glioneuronal Tumors and Epilepsy: Clinico-Diagnostic Features and Surgical Strategies

Alessandro Consales, Paolo Nozza, Maria Luisa Zoli, Giovanni Morana and Armando Cama

Abstract Glioneuronal tumors (GNTs) are a set of tumors of the Central Nervous System (CNS) composed entirely or partially of cells with neuronal differentiation. The description applies to several tumors referred to in the Classification of the World Health Organization (WHO) as neuronal and mixed neuronal-glial tumors. Some of them arise tipically in the cerebral cortex and represent a common cause of drug-resistant focal epilepsies in children and young adults. Three groups of tumors are of considerable relevance: ganglion cell tumors (GCTs), ganglioglioma (GG) being the typical example, dysembryoplastic neuroepithelial tumors (DNTs) and neurocytic tumors, namely extraventricular neurocytoma. GNTs commonly arise from a cortex housing developmental malformations, that are able to provoke seizures, such as focal cortical dysplasia (FCD) and, less frequently, hyppocampal sclerosis (HS). Management of patients with GNTs includes dealing with both tumor and epilepsy. From the neuro-oncological point of view, consistently with the long clinical history, these tumors are generally considered as low-grade gliomas (LGGs). They correspond to grades I or II of the WHO classification and their therapy relies mainly on surgery. However, tumor progression or transformation into higher grade tumors may occur.

From the neurological point of view, it is noteworthy that seizures are likely to respond very well to surgical treatment. Despite the favorable seizure outcome, the best surgical strategy has not been fully established yet. Indeed, while some authors regard tumor resection (the so-called lesionectomy) alone as sufficient for complete

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seizure control, other investigators also recommend the additional resection of peritumoral epileptogenic zones to maximize the seizure outcome.

Anyway, surgical treatment should be planned on the basis of anatomo-electroclinical correlation defining the epileptogenic zone to be resected.

To conclude, in patients with GNTs-related epilepsies, surgery should be proposed in order to obtain complete seizure control with freedom from antiepileptic drugs (AEDs), and to prevent tumor growth and risk of malignant transformation.

List of abbreviations

ADC	Apparent Diffusion Coefficient
AED(s)	Antiepileptic Drug(s)
BBB	Blood Brain Barrier
CNS	Central Nervous System
Cho	Choline
CT	Computed Tomography
DWI	Diffusion Weighted Imaging
DNT(s)	Dysembryoplastic Neuroepithelial Tumor
ECoG	Electrocorticography
EEG	Electroencephalography
FCD	Focal Cortical Dysplasia
GCT(s)	Ganglion Cell Tumor(s)
GG(s)	Gangliоglioma(s)
GNT(s)	Glioneuronal Tumor(s)
H&E	Hematoxylin & Eosin
HS	Hyppocampal sclerosis
LGG(s)	Low-grade glioma(s)
mI	myo-inositol
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-acetyl aspartate
PWI	Perfusion Weighted Imaging
rCBV	relative Cerebral Blood Volume
VFD(s)	Visual Field Defect(s)
WHO	World Health Organization

Glioneuronal tumors (GNTs) are a set of tumors of the Central Nervous System (CNS) composed entirely or partially of cells with neuronal differentiation, diagnosed mainly by means of histochemical and immunohistochemical stainings and, more rarely, by electron microscopy. The description applies to several tumors referred to in the Classification of the World Health Organization (WHO) as neuronal and mixed neuronal-glial tumors (Daumas-Duport et al. 1988; Louis et al. 2007a; Allende and Prayson 2009). Some of them arise tipically in the cerebral cortex and represent a common cause of drug-resistant focal epilepsies in children and young adults (Aronica et al. 2001; Benifla et al. 2006; Cataltepe et al. 2005; Consales

et al. 2013; Clusmann et al. 2004; Daumas-Duport et al. 1988; Giulioni et al. 2005; Morris et al. 1998; Nolan et al. 2004). Three groups of tumors are of considerable relevance: ganglion cell tumors (GCTs), gangliоglioma (GG) being the typical example, dysembryoplastic neuroepithelial tumors (DNTs) and neurocytic tumors, namely extraventricular neurocytoma. However, this classification scheme is rather arbitrary and provisional. Tumors with composite features, such as GG and DNT may occur and new entities will probably be described. On the other hand, it could sometimes be difficult to distinguish a tumor from a malformation of cortical development (Prayson and Napekoski 2012). From a more general point of view, it should be kept in mind that also tumors not included in the chapter of neuronal and neuronal glial tumors, should be included in the more general classification of 'long-term epilepsy-associated tumors'. Some of them, such as the pleomorphic xanthoastrocytoma, may show neuronal differentiation, while some others, such as the pilocytic astrocytoma or 'isomorphic astrocytoma', are astrocytic tumors. All of them make clear however that, to induce long-term epilepsy, a tumor need not be composed of neuronal cells (Blümcke et al. 2004).

Furthermore, GNTs commonly arise from a cortex housing developmental malformations, that are able to provoke seizures, such as focal cortical dysplasia (FCD) (40–80% of cases) and, less frequently (up to 25% of cases), hyppocampal sclerosis (HS) (Aronica et al. 2001; Bilginer et al. 2009; Blümcke and Wiestler 2002; Cataltepe et al. 2005; Chang et al. 2010; Minkin et al. 2008; Nolan et al. 2004; Prayson et al. 2010; Sharma et al. 2009).

Therefore, management of these cases includes dealing with both tumor and epilepsy.

From the neuro-oncological point of view, consistently with the long clinical history, these tumors are generally considered as low-grade gliomas (LGGs). They correspond to grades I or II of the WHO classification and their therapy relies mainly on surgery (Becker et al. 2007; Daumas-Duport et al. 2007). However, tumor progression or transformation into higher grade tumors may occur (Aronica et al. 2001; Nolan et al. 2004; Hall et al. 1986; Hammond et al. 2000; Kim et al. 2003; Luyken et al. 2004).

From the neurological point of view, it is noteworthy that seizures are likely to respond very well to surgical treatment (Aronica et al. 2001; Cataltepe et al. 2005; Luyken et al. 2003; Clusmann et al. 2002; Clusmann et al. 2004).

Despite the favorable seizure outcome, the best surgical strategy has not been fully established yet. Indeed, while some authors regard tumor resection (the so-called *lesionectomy*) alone as sufficient for complete seizure control (Giulioni et al. 2005; Bourgeois et al. 2006; Iannelli et al. 2000; Montes et al. 1995), others recommend the resection of peritumoral epileptogenic zones (Aronica et al. 2001; Clusmann et al. 2004; Morris et al. 1998; Cossu et al. 2008; Kim et al. 2008; Luyken et al. 2003).

The aim of this chapter is to elaborate on the current concepts concerning the diagnosis and surgical management of patients with medically intractable focal epilepsy related to GNTs.

Epidemiology and Type of Tumors

GNTs account for 0.4–1.3 % of all brain tumors (Becker et al. 2007; Daumas-Duport et al. 2007) and are an increasingly recognized cause of epilepsy in children and young adults (Aronica et al. 2001; Benifla et al. 2006; Cataltepe et al. 2005; Consales et al. 2013; Clusmann et al. 2004; Daumas-Duport et al. 1988; Giulioni et al. 2005; Morris et al. 1998; Nolan et al. 2004).

Their incidence in the pediatric population is about 8 %, accounting for up to 30 % of long-standing medically intractable epilepsies (Aronica et al. 2001; Daumas-Duport et al. 1988; Johnson et al. 1997; Obeid et al. 2009; Zaghloul and Schramm 2011). Among telencephalic GNTs (box 1), seizures are reported in up to 100 % of DNTs and in 80–90 % of GGs (Chang et al. 2008; Englot et al. 2011; van Breemen et al. 2007; Zaghloul and Schramm 2011).

Box 1

Neuronal and mixed neuronal-glial tumors (WHO Classification) (Louis et al. 2007b)

(in bold are tumors relevant for epilepsy surgeons)

Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	WHO Grade I
Desmoplastic infantile astrocytoma/ganglioglioma	WHO Grade I
Dysembryoplastic neuroepithelial tumor	**WHO Grade I**
Gangliocytoma	**WHO Grade I**
Ganglioglioma	**WHO Grade I**
Anaplastic ganglioglioma	WHO Grade III
Central neurocytoma	WHO Grade II
Extraventricular neurocytoma	**WHO Grade II**
Cerebellar liponeurocytoma	WHO Grade I
Papillary glioneuronal tumor	WHO Grade I
Rosette-forming glioneuronal tumor of the fourth ventricle	WHO Grade I
Paraganglioma	WHO Grade I

Mechanisms of Epileptogenesis Associated with GNTs

The pathophysiological mechanisms of epileptogenesis associated with brain tumors are not well understood. Several pathogenetic factors have been advocated to explain the tumor-related epileptogenesis.

Schematically, three types of mechanisms have been hypothesized, namely: (a) intrinsic to the lesion itself, including the expression of various ion channels and the relative proportion of different cell types within the tumor (Aronica et al. 2001;

Ventureyra et al. 1986; Rossi et al. 1999); (b) intrinsic to the tumor location, including peritumoral amino acid disturbances, local metabolic imbalance, cerebral edema, pH abnormalities, neuropil changes, neuronal/glial enzyme changes, altered protein expression and immunological activity (Beaumont and Whittle 2000); (c) unique to the patient harboring the disease (Gaggero et al. 2009; Wetjen et al. 2004).

There is significant evidence in the literature supporting the view that GNTs have intrinsic epileptogenic activities due to their neuronal and glial components (Aronica et al. 2001; Blümcke and Wiestler 2002; Daumas-Duport et al. 1988; Prayson et al. 1995; Prayson et al. 1996; Prayson 1999; Zentner et al. 1994). The neurochemical profile of GNTs shows some similarities in expression of various enzymes and receptors to that of neocortical neurons (Aronica et al. 2001; Aronica et al. 2007; de Groot et al. 2010; Lee et al. 2006). Moreover, the relatively low incidence of HS associated with temporal GNTs suggests that these tumors may be the primary source of epilepsy (Beaumont and Whittle 2000; Blümcke and Wiestler 2002).

The association between GNTs and other epileptogenic lesions (as FCD) has been frequently reported, however the specific role of each of them in determining epilepsy is not well understood (Beaumont and Whittle 2000; Louis et al. 2007b; Prayson et al. 2010). This implicates that simple tumor resection in patients affected also by FCD may determine unsatisfactory seizure outcome.

Finally, it is important to consider that the epileptogenic focus is not located within the tumor in about 30–40 % of patients. The presence of a secondary epileptogenic focus must be postulated, particularly in patients affected by temporal tumors (van Breemen et al. 2007).

Electroclinical Features

Focal epilepsy represents the most common clinical feature. Seizures are often the only symptom. Neurological deficits are quite rare, probably because of the slow growth of GNTs. Epilepsy can present at any age, even if most cases are diagnosed during the adolescence. Seizure type depends on tumor location. Status epilepticus is rare. There does not seem to be differences ascribable to tumor type (DNT, GG, or rarer tumors). The response of GNTs-related epilepsy to antiepileptic drugs (AEDs) is often discouraging, with frequent development of drug-resistance. Short duration of epilepsy, partial seizures and lack of secondary generalization are the most important clinical prognostic factors for a successful seizure outcome. There are two differences between children and young adults concerning the characteristics of GNTs-related epilepsy: a) aura is diagnosed more frequently in young adults; b) mean age at seizure onset is lower in children. This can be explained, respectively, by the limited capability of children to describe their symptoms and their lower seizure threshold (Ozlen et al. 2010).

In the non-invasive diagnostic work-up of patients, long-term neurophysiological monitoring, such as Video-EEG, is very useful in recording seizures and identifying the epileptogenic zone.

Concerning EEG features, interictal data usually consist of spikes and/or sharp waves, sometimes intermixed with slow activities. There is also the possibility of

a normal EEG. The abnormal features are usually lateralized to the tumor side. This does not guarantee good seizure outcome after tumor resection. In addition, it should be stressed that satisfactory seizure outcome can be achieved after tumor surgery even in patients whose EEG epileptiform activities are not localized to the tumor site (Morris et al. 1998).

When it is not possible to determine the lateralization of seizure focus by means on non-invasive diagnostic investigations, intracranial EEG (Stereo-EEG, depth electrodes, ECoG) may provide useful information. However, intracranial recordings are mainly aimed at mapping eloquent cortex when tumor resection in critical areas is planned. Thus, little is presently known, for example, about ECoG spike discharge patterns in patients with GNTs (Ferrier et al. 2006).

On the other hand, it is commonly acknowledged that patients with GNTs and FCDs may have similar invasive EEG patterns (Chassoux et al. 2000; Chassoux and Daumas-Duport 2013).

Ganglion Cell Tumors (GCTs)

GG and gangliocytoma are neuroepithelial tumors composed of ganglion cells (gangliocytoma) or both ganglion and glial cells (GG). The distinction seems slightly artificial and seldom acquires a deep, practical significance. Thus, these tumors can be lumped together under the designation 'GCTs'.

They are the most common tumors determining drug-resistant epilepsy and account for over 40% of all epileptogenic tumors in most surgical series (Lawson and Duchowny 2004).

GCTs of the cerebral cortex mainly occur in the temporal lobe and, secondarily, in the frontal lobe (Casazza et al. 1989; Otsubo et al. 1990–1991). They can occur throughout the neuraxis (Becker et al. 2007).

Neuroimaging characteristics are variable (Fig. 1a, b, c, d and Fig. 2a, b) as these tumors may present as a mixed lesion (solid and cystic), as a purely solid mass or, less commonly, as a cyst (Zentner et al. 1994; Castillo et al. 1990; Raybaud et al. 2006). Classically, GG has been described as a cystic mass with a mural nodule in approximately 40% of cases. On non contrast CT, most GGs are hypodense to gray matter, but some can have mixed or high density. Calcifications are relatively common and are reported in about 35–50% of cases (Castillo 1998). Scalloping of the calvarium may be seen. Sometimes this neoplasm may be undetectable on CT. On MRI, the signal behavior is variable as well, with a spectrum of signal intensity depending on the neuropathological features of the different components. Solid portions are iso- to hypointense on T1-weighted images, with a variable degree of hyperintensity on T2-weighted images.

Cystic components, hypointense on T1- and hyperintense on T2-weighted images, may or may not show wall enhancement following gadolinium injection (Zhang et al. 2008). Enhancement of the solid portion is highly variable, ranging from no enhancement to intense homogeneity; grossly half of tumors display at least some degree of enhancement. There is usually little associated mass effect or surrounding

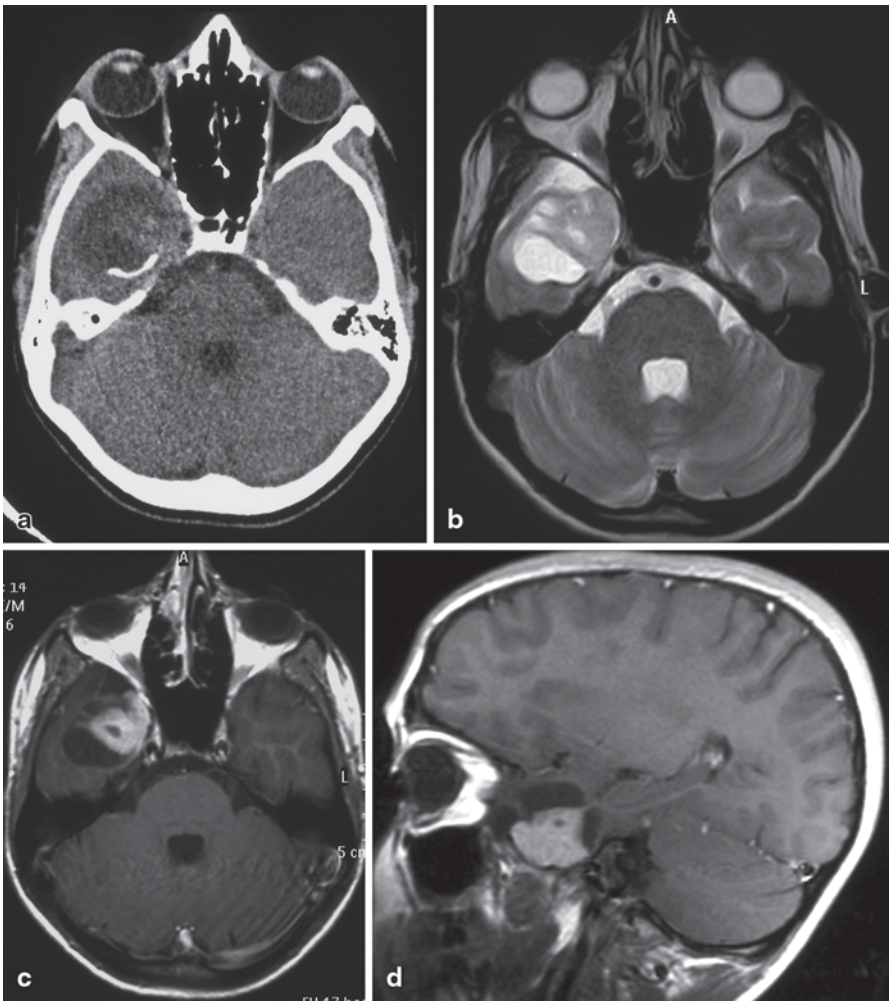

Fig. 1 GG in a 10-year-old girl.**a** Axial CT scan. **b** Axial T2-weighted image. **c** Axial Gd-enhanced T1-weighted image. **d** Sagittal Gd-enhanced T1-weighted image. CT shows an heterogeneous, prevailingly hypodense, mass lesion in the right temporal pole with gross, shell-like calcifications (**a**). The tumor has a cortical location and cystic and solid appearance (**b**). The solid component is mildly hyperintense on T2-weighted image (**b**) with marked enhancement following gadolinium injection (**c**, **d**)

vasogenic edema. Intratumoral hemorrhage is uncommon. Leptomeningeal or ependymal seeding may rarely occur (Adachi and Yagishita 2008).

Diffusion weighted imaging (DWI) shows increased diffusivity (high signal on ADC maps), whereas perfusion weighted imaging (PWI) demonstrates lower rCBV values compared to normal parenchyma. On magnetic resonance spectroscopy (MRS), most GGs display the features of a LGG, with decreased N-acetyl aspartate (NAA) and mildly elevated Choline (Cho).

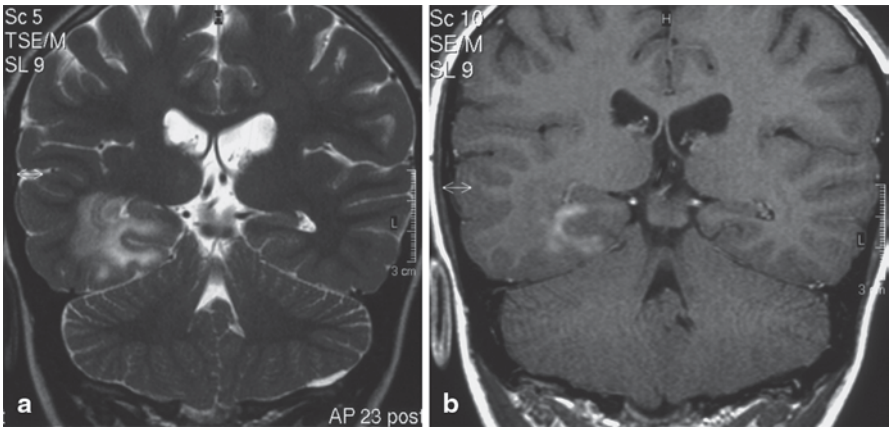

Fig. 2 GG in a 10-year-old boy.**a** Coronal T2-weighted image. **b** Coronal Gd-enhanced T1-weighted image. Lesion involving the right mesial temporal structures, with mild swelling of the parahippocampal region, hyperintense on T2-weighted image (**a**). Following gadolinium injection the lesion enhances. No cystic components are present

From the neuropathological point of view, the key feature is the presence of neoplastic ganglion cells. They differ from normal ganglion cells—large cells with vesicular nuclei, central and prominent nucleoli, and abundant cytoplasm—because of abnormalities of size, shape, cell processes, irregular accumulation of Nissl substance and cytoplasmic vacuolization. Cellular gigantism and bi- or multinucleation are a common finding (Fig. 3a). These cells do not achieve any degree of architectural uniformity.

Neurofibrillary tangles, granulo-vacuolar degeneration and basic cellular neuronal lesions typical of neurodegenerative diseases may be observed.

Neoplastic glial cells, whose presence is a requisite for the diagnosis of GG, have a variable morphology, which can make the tumor resemble a pilocytic astrocytoma,

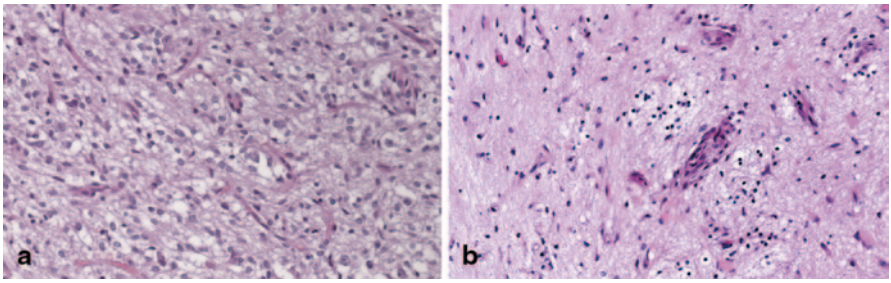

Fig. 3 GG**a** H&E, 200x. Gangliogliomas are typically non-infiltrating tumors; several multinucleated cells, which immunohistochemistry can prove to be neurons, are seen. **b** H&E. Lymphocytes are common

a diffusely infiltrating astrocytoma or even an oligodendroglial tumor. Melanotic cells may be found (Soffer et al. 1992).

The stroma is rich in reticular fibers, which encircle not only vessels, as in normal brain, but also neoplastic cells.

Vascular proliferation may be seen. The presence of hemosiderin deposits is an evidence of prior hemorrhage and, like contrast enhancement, is related to an impairment of the blood brain barrier (BBB). Intratumoral BBB dysfunction in concert with subsequent accumulation of albumin by neoplastic glial cells may represent an epileptogenic mechanism underlying tumor-associated long-term epilepsy (Schmitz et al. 2013).

Rosenthal fibers, basic astrocytic lesions, typical of fibrillary gliosis, and eosinophilic granular bodies are often observed. Lymphocytic infiltration is typical (Fig. 3b)

Necrosis is rare except in anaplastic cases.

It is interesting to note that temporal lobe GGs express CD34 glycoprotein, which apparently is not expressed in the frontal or parietal lobe tumors and it could be a marker of epileptogenic dysplasia (Kerkhof and Vecht 2013; Blümcke and Wiestler 2002).

GGs Grading

The third edition of the WHO Classification of CNS Tumors (Kleihues and Cavenee 2000) admitted the existence of atypical GGs, corresponding to grade II. Atypical tumors should have been distinguished from typical ones on the basis of cellularity, nuclear pleomorphism, microvascular proliferation, and proliferation index (>5%). Furthermore, necrosis and a proliferation index (>10%) should have been the hallmarks of anaplastic tumors. Unluckily, these criteria are unable to reliably predict the clinical behavior (Wolf et al. 1994; Luyken et al. 2004; Selvanathan et al. 2011). The fourth edition of the Classification includes no longer grade II (Louis et al. 2007b).

Although microscopic signs of atypia or anaplasia mostly occur in the glial component, they may occur in neuronal cells, too (Jay et al. 1994). Although anaplastic tumors typically appear *de novo*, one tenth of them is the result of the transformation of a GG. Anaplastic transformation is more common in pediatric cases and is associated with previous subtotal tumor resection and radiotherapy (Im et al. 2002).

Dysembryoplastic Neuroepithelial Tumor (DNT)

Although they may occur throughout the CNS, DNTs are cortical-based tumors, that typically affect children and young adults with long-standing pharmacoresistant epilepsy (Daumas-Duport et al. 1988, 2007).

DNTs of the cerebral cortex typically appear in the *isocortex* or in the *allocortex* of the temporal lobe; these tumors can arise in the frontal lobe and, sporadically, in the parietal and occipital lobes (Daumas-Duport et al. 1988; Thom et al. 2011).

Although there seems to be a relationship between DNTs and the development of the cerebral cortex, and cortical malformations may coexist alongside, from the neuro-oncologic point of view DNTs are considered as LGGs corresponding to grade I of the WHO Classification (Thom et al. 2011; Louis et al. 2007b).

Initially, the cells of the subpial granular layer were considered the source of this tumor(Daumas-Duport et al. 1988).

DNT coexistence with FCD (Daumas-Duport et al. 2007), neuronal heterotopia (Honavar et al. 1999), microdysgenesis (Rojiani et al. 1996) and neurofibromatosis type 1 (Lellouch-Tubiana et al. 1995) supports the hypothesis of a developmental origin.

DNTs show minimal or no mass effect and absence of peritumoral edema. On CT scan, they appear as a hypoattenuating lesion that may occasionally present areas of calcification and remodeling of the adjacent inner table of the skull. On MRI, the typical appearance consists of a well demarcated pseudocystic lesion, strongly hyperintense on T2- and hypointense on T1-weighted images, with variable FLAIR signal (hypo-isointense or hyperintense). DNTs may have a gyriform or a triangular-shaped pattern with the base pointing to the cortical surface. Hyperintense stripes on FLAIR images are visible both along the surface (bright rim) and on thin septa, resulting in a multicystic, bubbly appearance. Additional small cysts are often located in the vicinity, separated from the main mass.

Some lesions may show a more heterogeneous signal consistent with solid, cystic or semiliquid structures. Solid tissue is usually interspersed between the pseudocysts and it is often found in the adjacent subcortical white matter. Contrast enhancement is rare, variable, and often ring-like (Fig. 4a, b, c, d and Fig. 5a, b, c). Hemorrhage is also uncommon (Daumas-Duport et al. 1988; Daumas-Duport 1993; Ostertun et al. 1996; Campos et al. 2009). Diffusion and perfusion weighted images show respectively increased diffusivity and low rCBV values. The MRS pattern is nonspecific with increase in myo-inositol (mI) and slight reduction of NAA. Lactate and lipids are usually absent (Bulakbasi et al. 2007).

The neuropathological key feature is a microscopic structure, the *specific glioneuronal element*, which assumes the leading role in the *simple* forms, sharing the stage with the *glial nodules* in the *complex* forms. A highly controversial set of neuroepithelial tumors lacking the specific glioneuronal element has been classified as nonspecific or diffuse forms (Thom et al. 2011; Honavar et al. 1999; Bodi et al. 2012).

Simple and complex DNTs are generally circumscribed cystic lesions corresponding to type 1 of some neuroimaging classifications. The diffuse forms of the *neocortex* are quite nodular and sometimes calcific (type 2), the diffuse forms of the *allocortex* (mesial temporal lobe) tend to have dim outlines (type 3) (Chassoux and Daumas-Duport 2013; Chassoux et al. 2012).

The glioneuronal element is characterized by a mucoid matrix in which cells resembling oligodendrocytes align in a columnar fashion along bundles of axons and capillaries arrayed perpendicular to the pial surface. Mature neurons seem to float among the columns (Fig. 6a, b, c). Binucleate cells can be present; perineuronal satellitosis is not generally seen.

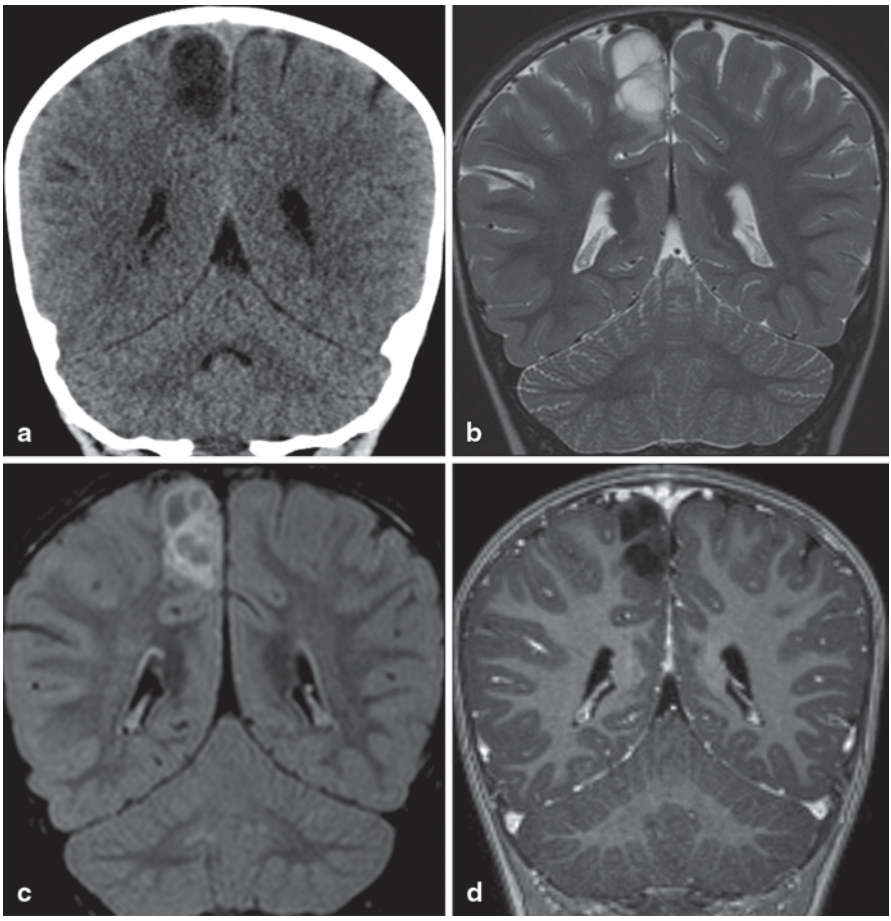

Fig. 4 DNT in a 6-year-old boy.**a** Coronal CT scan. **b** Coronal T2-weighted image. **c** Coronal FLAIR image. **d** Coronal Gd-enhanced T1-weighted image. Right paracentral lobule, cortical-subcortical, lesion whose density (**a**) and signal intensity on T2 (**b**) is cystlike. Corresponding FLAIR image (**c**) shows bright internal septa and lesion periphery producing a multicystic "bubbly" appearance. Following gadolinium administration enhancement is absent (**d**)

The glial nodules, which may contain neurons, are made up of astrocytes and oligodendrocytes, showing a variable degree of differentiation or pleomorphism. The nodules may resemble pilocytic astrocytoma or 'diffuse gliomas' (Fig. 6d).

Calcifications may be observed (Daumas-Duport et al. 1988; Thom et al. 2011); ossification is an exceptional finding (Thom et al. 2011).

These tumors have the capability both to cross the cortical sulci and to extend into the white matter and the leptomeninges (Thom et al. 2011; Zhang et al. 2013). White matter may show loss of myelin, gliosis and mycrocysts (Thom et al. 2011). HS, more commonly atypical (end-folium sclerosis) than classic, is common (Thom et al. 2011). Neurofibrillary tangles may be observed. The presence of intracellular pigments, such as iron or melanin, is quite common (Thom et al. 2011).

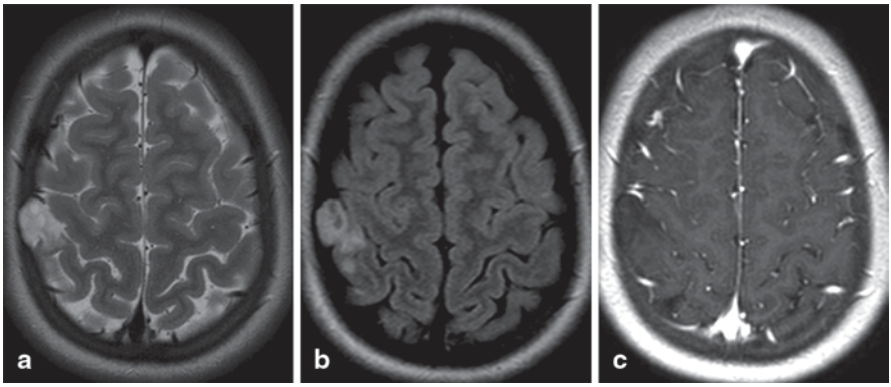

Fig. 5 DNT in a 9-year-old girl.**a** Axial T2-weighted image. **b** Axial FLAIR image. **c** Axial Gd-enhanced T1-weighted image.Superficially located tumor involving the right postcentral gyrus with remodeling of the adjacent calvarium (**a**). Two small internal pseudocysts are visibile on FLAIR image (**b**). There is no enhancement on post contrast T1-weighted image (**c**)

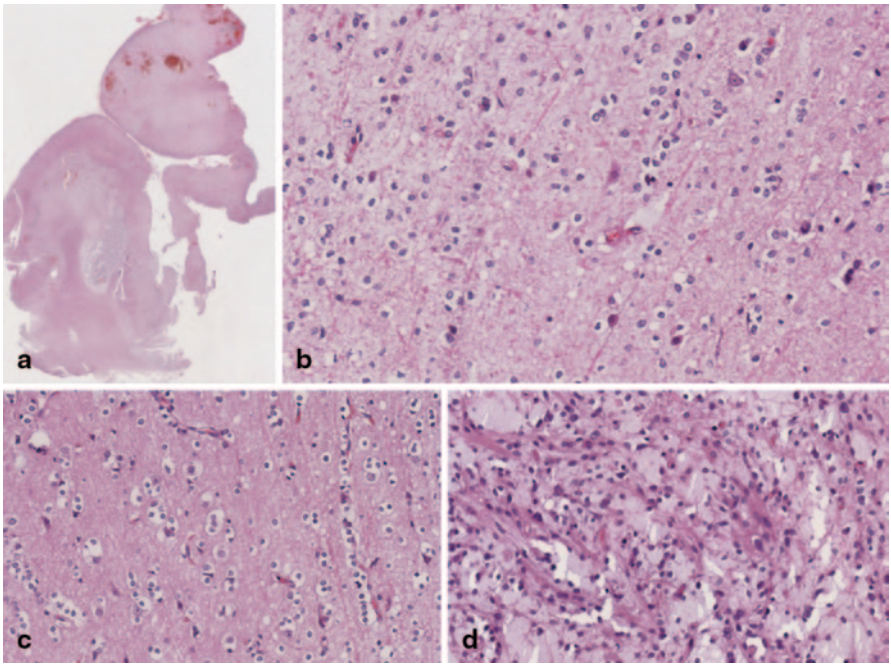

Fig. 6 DNT**a** Low-power of a DNT. **b** H&E, 200x. Bundles of axons and capillaries cross a mucoid matrix, in which some pyramidal neurons float. **c** H&E, 200x. Columns of cells resembling oligodendrocytes line up around axons. **d** H&E, 200x. Some areas may resemble to an pilocytic astrocytoma or ganglioglioma

Mitotic figures are very rare in the typical cases and the proliferative index is low. Although prominent vessels can be seen, endothelial proliferation is generally absent.

Necrosis is unexpected.

These tumors are able to regrow even after apparently complete resections showing a typical or atypical morphology (Daghistani et al. 2013; Schittenhelm et al. 2007). In some cases tumors seem to turn into something similar to anaplastic astrocytomas (Ray et al. 2009), glioblastoma (Duggal et al. 2008; Chuang et al. 2013) or oligoastrocytoma (Gonzales et al. 2007).

Neurocytic Tumors (Extraventricular Neurocytoma)

Neurocytic tumors of the cerebral cortex may cause focal drug-resistant epilepsy (Giulioni et al. 2011). These rare tumors, corresponding to grade II of the WHO Classification, typically appear in the *frontal lobe*, although they can arise in the parietal lobe and, sporadically, in the temporal and occipital lobes (Brat et al. 2001).

Temporal lobe tumors may coexist with FCD (Giulioni et al. 2011).

Neurocytic tumors are well demarcated lesions with variable and nonspecific appearance on neuroimaging studies depending on cellularity and anatomic location. On plain CT scan, they can appear as hypodense or isodense to gray matter; areas of patchy calcifications are common. On MRI, they have been described as hypointense or isointense on T1- and iso- to hyperintense on T2-weighted images with heterogeneous enhancement following the administration of a contrast agent. They commonly display cystic areas and mild to moderate peritumoral edema; intratumoral hemorrhage can occur. DWI studies showed nonspecific features with variable degree of diffusivity. On MRS, strongly decreased or no NAA peak and prominent Cho peak have been reported (Liu et al. 2013; Tortori-Donati et al. 1999; Han et al. 2013; Patil et al. 2014).

The key neuropathological feature is the presence of neurocytes, which are small round cells with modest quantity of cytoplasm, which can look clear, and nuclei with finely granular chromatin and one or more small nucleoli (Fig. 7a, b). Larger ganglioid cells or even larger ganglion cells may be found (Giangaspero et al.

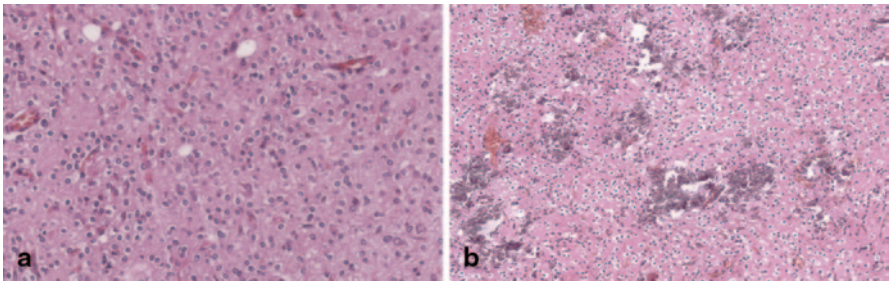

Fig. 7 Neurocytoma. **a** H&E, 200x. Neurocytomas are typically composed of uniform cells, whose clear halo may be prominent. **b** H&E, 100x. Calcifications are common

1997; Tortori-Donati et al. 1999). Tumor cells arrange in sheets, clusters, ribbons, or rosettes, with fine neuropil separating cell aggregates (Scheithauer et al. 2001). Immunohistochemical stainings consistently demonstrate synaptophysin, a major synaptic vesicle protein, in the neurocytes.

Some tumors (gangliogliomas) harbor an astrocytic component.

The mitotic index is generally inconspicuous. Atypical features (high mitotic index, vascular proliferation, necrosis) and high cell proliferation may herald an aggressive clinical behavior.

Multinodular and Vacuolating Neuronal Tumor (MVNT)

This new entity is a purely neuronal tumor of the cerebral hemispheres, which seems to arise mainly from the temporal lobe, displaying a benign clinical behavior. This tumor has been associated with intractable epilepsy (Bodi et al. 2014; Huse et al. 2013).

Surgical Strategies and Complications

Surgery can be considered the treatment of choice for GNTs-related epilepsy. Focal epilepsies caused by GNTs are scarcely responsive to antiepileptic drugs and the surgical treatment of these epileptogenic tumors can offer seizure-freedom in up to 90% of cases (Daumas-Duport et al. 1988; Giulioni et al. 2005; Kirkpatrick et al. 1993).

Furthermore, surgical resection prevents tumor growth and the risk of anaplastic transformation. Last, the surgical approach leads to neuropathological diagnosis.

Although surgery in patients with GNTs-related epilepsy yields a good seizure outcome, the optimal surgical strategy for these tumors has not been fully established. In fact, some authors consider that tumor resection alone (the so-called "lesionectomy") is sufficient to achieve complete seizure control (Bourgeois et al. 2006; Giulioni et al. 2005; Iannelli et al. 2000; Montes et al. 1995). On the other hand, other investigators also recommend the additional resection of peritumoral epileptogenic zones to maximize the seizure outcome (Aronica et al. 2001; Clusmann et al. 2004; Cossu et al. 2008; Morris et al. 1998; Kim et al. 2008; Luyken et al. 2003).

In the surgical management of GNTs, it is of paramount importance to consider some differences between these tumors and other groups of low-grade intra-axial neoplasms. First of all, GNTs are benign tumors in which epilepsy is generally the only clinical feature. Conversely, other types of LGG may present many other clinical findings (intracranial hypertension, focal neurological deficits, etc.). Second, unlike other LGG, GNTs are often located on temporal or temporo-mesial regions. Third, the pathophysiological mechanism of epilepsy in GNTs differs

greatly compared to other LGG. GNTs have a so-called intrinsic epileptogenicity due to their neuronal and glial components. In addition, other epileptogenic diseases (above all, FCD) may be associated with GNTs, may contribute to determine the epileptogenic zone in some patients and are not always well distinguishable from the tumoral tissue on MRI. Finally, in temporal GNTs, the hippocampus may contribute to the epileptogenesis of these lesions even without apparent involvement at MRI or pathological examination (Chang et al. 2008; Englot et al. 2011; Smits and Duffau 2011; van Breemen et al. 2007; Blümcke et al. 2011; Tassi et al. 2002; Giulioni et al. 2009; Schramm and Aliashkevich 2008; Morioka et al. 2007).

Considering these features, the target of surgery for GNTs to obtain the best seizure outcome is not only the anatomical (tumoral) lesion, but the entire epileptogenic zone, which sometimes is larger than the simple structural lesion. Thus, the surgical strategy must be based on the anatomo-electro-clinical correlations that are necessary to identify the epileptogenic zone (Lüders et al. 2006). This principle is particularly important especially for lesions located in the temporal lobe, where the epileptogenic network is usually much more complex and extended than the tumoral area.

Thus, from the surgical point of view, distinctive "philosophies" of treatment may be adopted, usually depending on the location of the tumors.

For lesions located in extratemporal regions the target of surgical resection is the tumoral lesion only. In other words, only a so-called "lesionectomy" is performed (Bourgeois et al. 2006; Montes et al. 1995).

For lesions located in the temporal lobe (the most frequent site of GNTs), several approaches have been described, including lesionectomy, extended lesionectomy, tailored resection and anterior temporal lobectomy (Casazza et al. 1997; Clusmann et al. 2004; Cossu et al. 2008; Jooma et al. 1995; Quarato et al. 2005).

To our knowledge, presently few studies correlate the best surgical strategy to obtain the best seizure outcome to tumor location (Cataltepe et al. 2005; Giulioni et al. 2009; Luyken et al. 2003). There is some consensus that the best seizure outcome for epileptogenic GNTs located in extratemporal and temporo-lateral regions is provided by simple lesionectomy. For temporo-mesial GNTs, the results of a simple lesionectomy are not particularly encouraging, while more extended surgeries (tailored resection) offer better seizure outcomes (Giulioni et al. 2009).

Finally, another important issue concerning the surgical strategy for GNTs is the additional resection of the hippocampal-parahippocampal complex when it is not invaded by GNTs and does not show other signal abnormalities on MR imaging. In fact, if a more extended surgery than simple lesionectomy for temporo-mesial GNTs is a generally accepted concept (Schramm 2008), the correct balance between the extent of resection necessary to provide the best seizure outcome and the avoidance of neuropsychological deficits is still an open problem deserving further studies (Helmstaedter et al. 2011).

Neurosurgery has become safer in the last decades, thanks to the improvement of diagnostic and operative techniques and anaesthesiological procedures.

However, craniotomy and brain surgery imply the risk of complications, whose rate is quite low; mortality is between 0.5 and 1 % (Pilcher and Rusyniak 1993).

The neurosurgical complications of GNTs surgery can be subdivided into craniotomy-related complications (general neurosurgical complications) and complications more specifically related to resective brain surgery.

The first group is represented by hematomas (extradural, subdural, and intracerebral), infections, cerebrospinal fluid leak and, rarely, air embolism and pulmonary embolism. These complications are responsive to appropriate treatment and do not usually influence surgical outcome.

Concerning the second group of complications, we can distinguish between major complications (when severe neurological deficit or daily activity impairment occur) and minor complications (disappearing within 3 months).

Neurological complications depend on the site of resection. Considering that lesionectomy and tailored resection are the surgical strategies commonly adopted in the management of GNTs and these neoplasms are preferentially located in the temporal lobe, typical major neurological complications of temporal lobe surgery (TLS) include contralateral hemiparesis or hemiplegia, homolateral third nerve palsy or paresis, contralateral visual field defects (VFDs) and speech disturbance (Pilcher and Rusyniak 1993; Polkey 2004).

The hemiplegia or hemiparesis can be related mainly to vascular causes (manipulation of middle cerebral artery branches and/or other arteries) (Polkey 2004).

VFD consists classically in superior quadrantanopia contralateral to the resection (Egan et al. 2000). This finding is caused by injury of Meyer's loop (the most anterior part of the optic radiation). Other VFDs in temporal lobe surgery can also occur because of injuries of the optic tract or lateral geniculate body. However VFDs should be considered as an expected event in TLS. Today recent advances in neuroimaging techniques as diffusion tensor imaging (DTI) allowing a better anatomic definition of the optic radiation could contribute to reduce post-resection VFDs.

Other rare complications of TLS include hemorrhage distant from the site of surgery (Toczek et al. 1996; Giulioni et al. 2006; Yacubian et al. 1999), probably due to transmural venous pressure variations (Giulioni and Martinoni 2011) and middle fossa cyst causing raised pressure (Weaver et al. 1996). The global incidence of major neurological complications of TLS is 0.37–4% (Pilcher and Rusyniak 1993; Polkey 2004).

Surgery-related complications in frontal lobe GNTs include hemiparesis if the resection encroaches upon the gyrus anterior to the precentral gyrus. Broca's area must be preserved in the dominant hemisphere. Some authors recommended such resections should be performed under local anaesthesia (Polkey 2004) and/or using a certain number of localizing techniques such as functional MRI and transcranial magnetic stimulation for motor cortex localization (Macdonell et al. 1999).

In spite of these precautions, any resection centered on the central area (primary motor and sensory area) carries the risk of loss of its function.

Resections for lesions located in parietal and posterior temporal regions of dominant hemisphere can determine receptive aphasia, dyslexia, disgraphia and dyscalculia.

Finally, for occipital resections, some degree of VFD(s) can be expected, even if some authors noted that the patients adapted to their VFD within 1 year after surgery (Williamson et al. 1992).

Seizure Outcome

The post-operative seizure outcome is currently assessed according to Engel's Classification (Engel 1996).

The rate of seizure-free outcomes (Engel Class I) in GNTs –related focal epilepsies is about 90%.

Several factors have been correlated with seizure outcome: extension of surgical resection, histotype, duration of epilepsy, age at surgery, association of the tumor with perilesional cortical dysplasia (Aronica et al. 2001; Daumas-Duport et al. 1988; Im et al. 2002; Morris et al. 1998; Nolan et al. 2004).

The main predictor of excellent seizure outcome is the complete removal of the tumor (Morris et al. 1998; Nolan et al. 2004; Khajavi et al. 1995; Kim et al. 2001).

Concerning the completeness of resection, it must be emphasized that only few studies attempted to establish a correlation between tumor site (i.e., temporo-mesial versus temporo-lateral and extra-temporal) and surgical strategy (lesionectomy versus resection of the epileptogenic focus, including the tumor).

Giulioni et al. (2005, 2006) observed that patients affected by extra-temporal and temporo-lateral GNTs had better seizure outcome than those with temporo-mesial GNTs after lesionectomy alone. In addition, in a study comparing retrospectively seizure outcome between two homogeneous series of temporo-mesial epileptogenic GNTs treated respectively by lesionectomy alone and tailored surgery, the same authors reported a much better seizure outcome (93% vs 42.8%) in patients who underwent tailored resection (Giulioni et al. 2009).

These observations and other evidences concerning the role of the temporo-polar cortex in temporal lobe seizures (Chabardès et al. 2005) and the frequent association of GNTs with other epileptogenic abnormalities (Daumas-Duport et al. 2007) suggest that tailored resection for temporo-mesial GNTs is to be preferred to obtain a better seizure outcome.

Future Trends

In the future, optimal therapeutic management of GNTs will need a better understanding of the epileptogenic mechanisms related to these neoplasms.

In addition, further studies are required to elucidate GNTs preference for the temporal lobe.

Neuronal precursors in the subgranular zone of the dentate gyrus and the occurrence of postnatal life neurogenesis have been recently described (González-Martínez et al. 2007; Paradisi et al. 2010; Siebzehnrubl and Blümcke 2008). These data could contribute to explain more complex epileptogenic mechanisms and/or the occurrence of GNTs.

Moreover, the well known association between GNTs and FCD needs further investigations. If common precursor cells for these two diseases can be hypothesized,

either at an embryological stage or during postnatal life, it still remains to be clarified whether FCD coexists with GNTs or has some potential to change into neoplastic cells (Daumas-Duport et al. 2007).

Conclusions

GNTs are one of the most common causes of drug-resistant epilepsy in children and young adults. GNTs-related epilepsies usually respond very well to surgical treatment with an extremely favorable seizure outcome and important effects on cognitive development and patients' quality of life.

Surgical treatment should be planned on the basis of anatomo-electro-clinical correlation defining the epileptogenic zone (which may involve a larger area than the tumor) to be resected.

Tumor location is another important factor (temporo-mesial, temporo-lateral, extratemporal site) to be considered in planning surgical resection.

Finally, even in the event of sporadic seizures and/or seizures responsive to AEDs, surgery should be proposed in order to obtain complete seizure control with freedom from AEDs, and to prevent tumor growth and risk of malignant transformation.

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Metabolic Causes of Epilepsy

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Abstract Inborn errors of metabolism comprise a large class of genetic diseases involving disorders of metabolism. Presentation is usually in the neonatal period or infancy but can occur at any time, even in adulthood. Seizures are frequent symptom in inborn errors of metabolism, with no specific seizure types or EEG signatures. The diagnosis of a genetic defect or an inborn error of metabolism often results in requests for a vast array of biochemical and molecular tests leading to an expensive workup. However a specific diagnosis of metabolic disorders in epileptic patients may provide the possibility of specific treatments that can improve seizures. In a few metabolic diseases, epilepsy responds to specific treatments based on diet or supplementation of cofactors (vitamin-responsive epilepsies), but for most of them specific treatment is unfortunately not available, and conventional antiepileptic drugs must be used, often with no satisfactory success. In this review we present an overview of metabolic epilepsies based on various criteria such as treatability, age of onset, seizure type, and pathogenetic background.

Introduction

A very large number of inherited errors of metabolism (IEM) may occur with neurologic symptoms such as seizures, developmental delay, mental deterioration, cranial nerve deficits and movement disorders (Wolf et al. 2005). Epilepsy may dominate the clinical picture, especially in newborns and infants, or may be part of a larger clinical spectrum with other extraneurologic findings (osseous, cutaneous, visceral, endocrine, sensorial, and metabolic). Indeed, the presence of extraneurologic signs raises a strong probability of finding systemic metabolic disturbances (Wolf et al. 2009a, b). Epilepsy associated with IEM has usually the features of a "catastrophic encephalopathy" because seizures begin usually at early age, they are often refractory to conventional antiepileptic drugs (AEDs) and epileptic activity is associated

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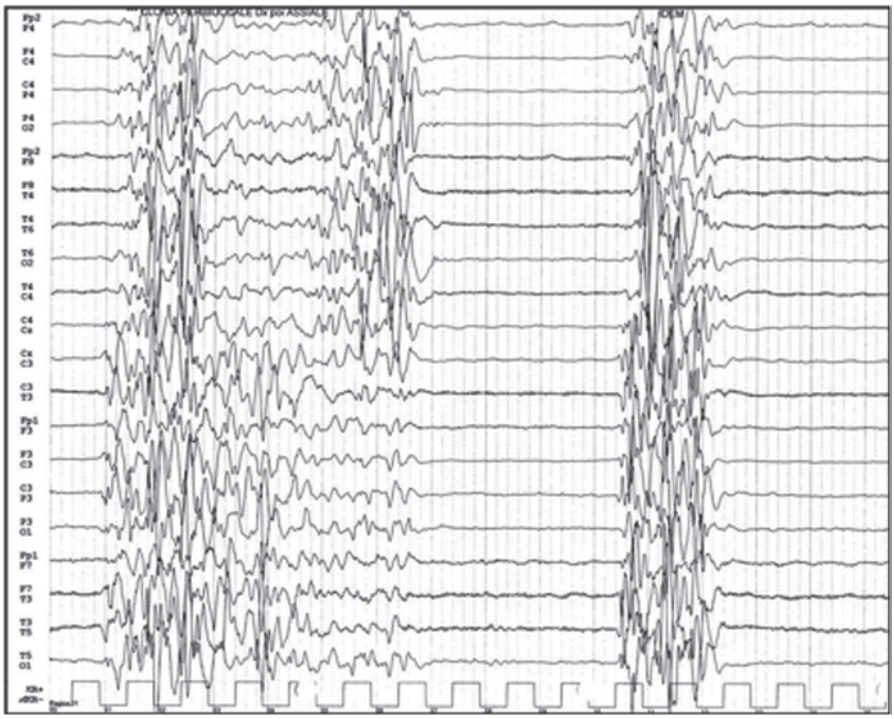

Fig. 1 EEG pattern of burst suppression

with severe cognitive, sensorial, and/or motor functions deterioration (Wolf et al. 2005, 2009a, b). Metabolic epileptic encephalopathies display an age dependent susceptibility and expression in the clinical phenotype. The seizure phenotype thus can be seen to evolve over time to fit descriptions of different epilepsy syndromes (Wolf et al. 2005). The EEG findings can be strikingly abnormal but they lack specificity and overlapping findings are frequent in different IEMs. EEG changes range from disorganized and slow background rhythms, focal and multifocal epileptiform patterns, generalized abnormalities as well as suppression-burst patterns (Wolf et al. 2005; Papetti et al. 2013; Fig. 1). The MRI findings may be normal or reveal associated structural abnormalities. MR spectroscopy is able to none invasively identify several metabolites peaks related to metabolic encephalopathies (Wolf et al. 2005). The diagnosis of metabolic disorders in epileptic patients may provide the possibility of specific treatments that can improve seizures. In a few metabolic diseases, epilepsy responds to specific treatments based on diet or supplementation of cofactors (vitamin responsive epilepsies), but for most of them specific treatment is unfortunately not available, and conventional antiepileptic drugs must be used, often with no satisfactory success (Wolf et al. 2009a, b). Neurometabolic epilepsies can be classified according to different criteria, i.e., type of biochemical defects and clinical presentation. More recently the age of onset of metabolic epilepsy has been considered for classification (Table 1; Papetti et al. 2013).

Table 1 Metabolic epilepsies according to age at onset

Neonatal onset	Infantile onset	Childhood onset
Pyridoxine dependent seizures; PNPO deficiency; Folinic acid response; Non-ketotic hyperglycinaemia; Organic acidemias; Urea cycle defects; Holocarboxylase synthase deficiency; GABA transaminase deficiency	GLUT1 deficiency; Non-ketotic hyperglycinaemia; Organic aciduria; Creatine deficiency; Biotinidase deficiency; Aminoacid disorders; Infantile neuronal lipofuscinosis; Late pyridoxine dependency; Ethylmalonic encephalopathy; Congenital disorders of glycosylation; Purine metabolism defects	Late infantile neuronal lipofuscinoses; Mitochondrial disorders; Storage disorders; Purine metabolism defects; Lafora disease; GLUT1 deficiency; Creatine transporter deficiency

In this chapter we will focus on diseases and conditions where epilepsy is the predominant clinical manifestation and especially where the disease course can be positively influenced by specific metabolic therapies (Table 2; Papetti et al. 2013; Pascual et al. 2008).

Neonatal Onset Seizures

Vitamin B Response Epileptic Seizures

Pyridoxal phosphate (PSP), the active form of vitamin B6, is the cofactor for over 100 enzyme-catalyzed reactions in the body, including many involved in the synthesis or catabolism of neurotransmitters (e.g., dopamine, serotonin, and inhibitory transmitter c-aminobutyric acid) (Gospe 2010). Inadequate levels of pyridoxal phosphate in the brain cause neurological dysfunction, particularly epilepsy (Plecko and Stöckler 2009). Three genetic epilepsies are recognized to be cause PSP deficiency: Pyridoxine-dependent seizures, Pyridoxal phosphate (PLP) dependent epilepsy and hypophosphatasia. They do so by different mechanisms: the first by inactivation, the second by blocking conversion of other forms of vitamin B6 to PLP, and the third by reducing transport into the brain and into cells (Baxter 2003).

Pyridoxine-dependent seizures (PDS) are due to an autosomal recessive inborn error of metabolism and they are characterized by neonatal seizures that are not controlled with anticonvulsants but that respond both clinically and electrographically to large daily supplements of pyridoxine (vitamin B6). The disorder may present within few hours of birth as an epileptic encephalopathy; sometimes intrauterine fetal seizures occur. Other cases may present with seizures at a later time during the first several weeks of life. In rare instances, children with this condition do not have seizures until before 2 years of age, and these are considered to be late-onset cases

Table 2 Diagnosis and treatment of metabolic epilepsies. a-AASA, a-amino adipic semialdehyde; iv, intravenous; PNPO, Pyridox(am)ine 5¢-phosphate oxidase; PLP pyridoxal 5¢-phosphate; HCS, holocarboxylase synthetase; EMA, ethylmalonic acid

Disease	Diagnosis	Specific therapy
Pyridoxine dependent seizures	α-AASA in urine and/or plasma and CSF	Single 100 mg dose of iv pyridoxine followed by oral maintenance dose of 5–15 mg/kg/day in two divided doses
PNPO deficiency	Reduced CSF PLP and monoamine metabolites; mutation analysis of the PNPO gene	Oral PLP 10 and 30 mg/kg/day
Folinic acid response seizures	CSF high-performance liquid chromatography	Folinic acid 3–5 mg/kg/day
HCS deficiency	Plasma ammonia; plasma and CSF lactate; plasma, urine and CSF organic acid; lymphocyte or fibroblast carboxylase activity; molecular analysis	Oral biotin 5–10 mg/day
Biotinidase deficiency	Biotin in plasma and urine; serum biotinidase enzyme activity; molecular analysis	Oral biotin 5–10 mg/day
Non-ketotic hyperglycinaemia	Plasma and CSF amino acids	Sodium benzoate and dextromethorphan
Serine biosynthesis defects	Plasma and CSF amino acids	Oral L-serine 200–600 mg/kg/dye
Organic acidemias	Urine organic acids, blood spot acylcamitine profile, and plasma and urine amino acids; enzymatic activity in fibroblasts; molecular analysis	Dietary restrictions; adjunctive compounds to (a) dispose of toxic metabolites or (b) increase activity of deficient enzymes
Urea cycle defects	Ammonemia, aminoacids, urinary orotic acid	Dietary restrictions; adjunctive compounds
Menkes disease	Serum copper and caeruloplasmin; ratio of urinary dopamine to noradrenaline; analysis of *ATP7A* gene	Subcutaneous injections of copper histidine
Peroxisomal disorders	Plasma VLCFA; biochemical studies in cultured fibroblasts; molecular analyses	Dietary restrictions; adjunctive compounds
GABA transaminase deficiency	Levels of GABA in the CSF or on brain MR spectroscopy; enzyme assay in cultured lymphocytes; analysis of *AB AT* gene	No specific therapy
GLUT1 deficiency	CSF glucose (CSF to plasma glucose ratio); analysis of *SLC2A1* gene	Ketogenic diet
Creatine deficiency	Guanidinoacetate, creatine, nd creatinine levels in plasma and urine; creatine levels on brain MR spectroscopy; analysis of *GAMT, GATM,* and *SLC6A8* genes	Oral creatine monohydrate 350–500 mg/kg/dye, dietary arginine restriction, ornithine supplementation

Table 2 (continued)

Disease	Diagnosis	Specific therapy
Neuronal ceroid lipofuscinosis	Enzyme activity in dried blood spots; molecular analysis of CLN genes	No specific therapy
Ethylmalonic encephalopathy	Plasma acylcamitines; plasma and urine EMA; urine organic acids; skeletal muscle biopsy; analysis of *ETHE1* gene	Carnitine and riboflavin
Congenital disorders of glycosylation	Isoelectric focusing of serum transferrin.	No specific therapy
Mitochondrial disorders	Plasma and CSF lactate, brain MR spectroscopy; skeletal muscle biopsy; molecular analysis	Adjunctive compounds
Purine metabolism defects	Urinary purine profile; molecular analysis	No specific therapy
Lysosomal storage disorders	Abnormal storage cells (lymphocytes, fibroblasts): molecular analysis (*CLN3*, *NPC1* and *NPC 2* genes)	Glycosphingolipid synthesis inhibitor in Niemann-Kck type C
Lafora disease	*EPM1* gene	No specific therapy

(Gospe 2010). Affected newborn typically experience prolonged seizures which either recur serially or evolve into status epilepticus. Seizures generally include partial seizures, generalized tonic clonic seizures (GTCS), spasms and myoclonus. Additional features of pyridoxinedependent epilepsy include hypothermia, poor muscle tone, and neurodevelopment disabilities (Plecko and Stöckler 2009). These patients are not pyridoxine-deficient, but they are metabolically dependent on the vitamin, so that the institution of either parenteral or oral pyridoxine rapidly results in seizure control and improvement in the encephalopathy (Gospe 2010). The EEG is usually severely abnormal and the possible patterns include burst suppression, hypsarrhytmia and multiple spike-wave discharges (Fig. 2, Nabbout and Dulac 2008; Papetti et al. 2013). Imaging may be normal or may demonstrate cerebellar dysplasia, hemispheric hypoplasia or atrophy, neuronal dysplasia, periventricular hyperintensity or intracerebral hemorrhage (Baxter 2003).

PDS is caused by mutations in the *ALDH7A1 gene* that encodes the protein antiquitin (a-aminoadipic semialdehyde dehydrogenase), that functions within the cerebral lysine catabolism pathway (Scharer et al. 2010). The deficient activity of antiquitin results in the accumulation of a-aminoadipic semialdehyde (AASA) and piperideine-6-carboxylic acid (P6C). The P6C was shown to inactivate pyridoxalphosphate (PLP), the active vitamer of pyridoxine, by a Knoevenagel condensation reaction, leading to severe secondary PLP deficiency. The PLP is a cofactor of various enzymes in the central nervous system, so that seizures in PDS are due to a decrease in GABA levels in the brain with an imbalance between the excitatory and inhibitory neurotransmitters (Mill et al. 2010; Scharer et al. 2010).

Diagnosis may be made by concurrently administering pyridoxine (100 mg) intravenously while monitoring the EEG, oxygen saturation, and vital signs. In individuals with PDS, clinical seizures generally cease over several minutes. If a

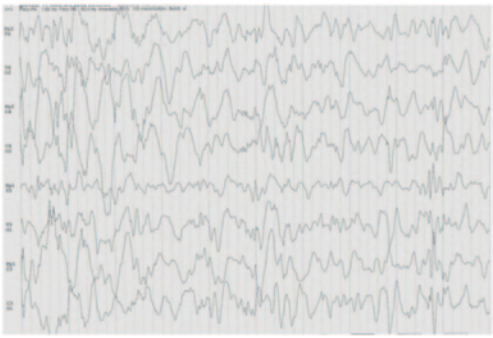

Fig. 2 EEG pattern of hypsarythmia

clinical response is not demonstrated, the dose should be repeated up to a maximum of 500 mg. An alternate diagnostic approach is suggested for patients who are experiencing frequent short anticonvulsant-resistant seizures. In those cases, oral pyridoxine (up to 30 mg/kg/day) should be prescribed, and patients with PDS should have a resolution of clinical seizures within 3–7 days. Biochemical tests include measurement of the specific biomarker a-AASA and pipecolid acid (PA) in the urine, plasma and CSF. Molecular genetic testing of *ALDH7A1* is also recommended as confirmatory testing (Gospe 2010). When the diagnosis of PDS is established, the lifelong therapy with pyridoxine should be instituted. The daily administration of 50–200 mg (given once daily or in two divided doses) is generally effective in preventing seizures in most patients (Gospe 2010).

Pyridoxal phosphate (PLP) dependent epilepsy is characterized by neonatal seizures refractory both to conventional AEDs and pyridoxine administration (Kuo and Wang 2002). Instead, individuals with this type of epilepsy are responsive to large daily doses of pyridoxal 5′-phosphate (30 mg/kg/day in three or four divided doses enterally) (Hoffmann et al. 2007). PLP dependent epilepsy is inherited with an autosomal recessive pattern. The gene involved is the PNPO gene that encodes an enzyme called pyridoxine 50-phosphate oxidase involved in the conversion of vitamin B6 derived from food (in the form of pyridoxine and pyridoxamine) to the active form of vitamin B6 that is PLP (Mills et al. 2005).

Affected babies are usually born prematurely and may have immediate signs of encephalopathy, lactic acidosis and hypoglycemia. Clinical seizures may consist of myoclonus, clonic movements and ocular, facial and other automatisms (Baxter 2010). Untreated, the disorder results either in death or in profound neurodevelopment impairment. In treated patients, particularly those in whom the disorder was recognized early, near normal development may be possible (Bagci et al. 2008).

CSF and urine analyses in affected children show evidence of secondary deficiencies of several PLP dependent enzymes including aromatic L-amino acid decarboxylase (decreased CSF concentrations of homovanillic acid and 5-hydroxyindoleacetic acid and increased L-DOPA and 3-methoxytyrosine as well as increased urinary concentrations of vanillactic acid) (Plecko and Stöckler 2009).

Chronic therapy for confirmed PLP dependent epilepsy consists of administration of PLP 30–50 mg/kg/day divided in four to six doses (Plecko 2005).

Hypophosphatasia is an inherited disorder that affects the development of bones and teeth. However it can also led to PDS in neonates as pyridoxal phosphate is not dephoshorilated and therefore cannot cross membranes (Plecko 2005). Biochemically, this disorder consists of deficient activity of the tissue non-specific isoenzyme of alkaline phosphatase. The enzymatic deficiency results from mutations in the liver/bone/kidney alkaline phosphatase gene *ALPL*. Laboratory diagnosis is confirmed by reduced levels of serum alkaline phosphatase, and raised levels of urinary phosphoethanolamine (PEA) (Balasubramaniam et al. 2010).

Folinic acid-responsive seizures are characterized by cessation of seizures after administration of folinic acid (3–5 mg/kg/day enterally, for 3 to 5 days) (Plecko 2005). Only a few affected infants were published. Patients present with seizures, either myoclonic or clonic, apnea and irritability within 5 days after birth (Gallagher et al. 2009). A characteristic pattern of peaks, reflecting two unidentified compounds, was recognized in the cerebrospinal fluid (CSF) when analyzed by high-performance liquid chromatography (HPCC) with electrochemical detection to quantify monoamine metabolites. Recently, it has been demonstrated that folinic acid responsive seizures are also caused by mutations in *ALDH7A1* and therefore should be treated with adequate doses of pyridoxine. Whether additional treatment of these children with folinic acid is of added benefit, remains to be shown (Gallagher et al. 2009).

Disorders of Amino Acid Metabolism

Some disorders of amino acid metabolism such as nonketotic (NKH), methylene tetrahydrofolate reductase (MTHFR) deficiency, GABA transaminase deficiency, serine deficiency, and congenital glutamine deficiency, can also give rise to this epileptic syndrome, each with its specific biochemical traits (Wolf et al. 2009a, b).

Nonketotic hyperglycinemia (NKH) is a metabolic disorder with autosomal recessive inheritance, causing severe, frequently lethal, neurological symptoms in the neonatal period. NKH derives from a defect of a larger enzyme complex, known as glycine cleavage enzyme (GCS) that is responsible for the glycine degradation. When glycine cleavage enzyme is defective, excess glycine can build up to toxic levels in the body's organs and tissues (Applegarth and Toone 2004). The three genes known to be associated with glycine encephalopathy are: *GLDC* (encoding the P-protein component of the GCS complex and accounting for 70–75 % of disease), *AMT* (encoding the T-protein component of the GCS complex and accounting for ~20 % of disease), and *GCSH* (encoding the H-protein component of the GCS complex and accounting for < 1 % of disease) (Hamosh et al. 2009).

The majority of glycine encephalopathy presents in the neonatal period (85 % as the neonatal severe form and 15 % as the neonatal mild form). Of those presenting in infancy, 50 % have the infantile mild form and 50 % have the infantile severe form (Rossi et al. 2009). Patients with classical neonatal NKH present in the first days of life with seizures or with encephalopathy, abnormal jerking movements, lethargy and severe hypotonia. Affected newborns will have repeated episodes of severe and

prolonged apnea that require ventilatory support. Hiccuping is frequent and brain ultrasound scans may show defects of the corpus callosum (Hamosh et al. 2009). Epilepsy associated with NKH may reflects the early myoclonic encephalopathy (EME) with erratic or fragmentary myoclonus, simple focal seizures, focal tonic seizures, and tonic spasms, generally after 1 month of age and with an EEG patter of burst-suppression (SB) and progression towards hypsarrhytmia (Rossi et al. 2009). Untreated, the neonatal form of non-ketotic hyperglycinaemia is associated with death in the first months of life. Therapy with sodium benzoate and dextromethorphan may be helpful in some milder forms of the disease, alongside AEDs and general supportive care. The epilepsy remains drug resistant, infantile spasms may emerge, and the EEG evolves to hypsarrhythmia or multifocal discharges on a back- ground without normal activity. Atypical neonatal form of NKH can be similar to classical NKH, with hypotonia and apnea episodes that may require assisted ventilation, though seizures are less severe. Subsequently psychomotor development is significantly better than in the majority of patients with the classical NKH (Dinopoulos et al. 2005).

Atypical variants of NKH include also the infantile and late onset forms. Children with this condition develop normally until they are about 6 months old, when they experience delayed development and may begin having seizures. As they get older, many develop intellectual disability, abnormal movements, and behavioral problems. The late onset form is less common and more heterogeneous. The clinical presentation is after the second birthday and even during adulthood, mainly with mild cognitive decline and behavioral problems (Hamosh et al. 2009).

Transient neonatal hyperglycinemia (TNH) is characterized by elevated plasma and CSF glycine levels at births that are normalized within 2–8 weeks. TNH is clinically and biochemically indistinguishable from typical nonketotic hyperglycinemia at onset (Dinopoulos et al. 2005). The biochemical hallmark of NKH is increased glycine concentration in the plasma and, to an even greater extent, in the cerebrospinal fluid (CSF), with an abnormally high ratio between CSF and plasma levels. Confirmatory tests include enzymatic analysis in liver tissue and/or mutation analysis (Pascual 2003). Some babies have structural brain abnormalities evident on MRI, apparently as a result of the toxic effect of glycine on the developing brain. Treatment consists of reducing the intake of glycine and serine as well as improving its elimination by administering benzoate and by exchange transfusion (Pascual 2003).

Defects in the synthesis of *L-serine* lead to a syndrome of congenital microcephaly, neurodevelopmental disability, and epilepsy which may have neonatal onset (Pearl 2009). Two serine-deficiency syndromes have been described, namely 3-phosphoglycerate dehydrogenase (3-PGDH) deficiency and 3-phosphoserine phosphatase (3-PSP) deficiency (de Koning and Klomp 2004). The 3-PGDH deficiency is an autosomal recessive disorder characterized by neurological symptoms which dominate the clinical phenotype (i.e., microcephaly, seizures, and neurodevelopmental delay). Seizures either started as generalized tonic clonic seizures or as flexor spasms with West syndrome. In older patients, diagnosed at ages 5–9, tonic, atonic and myoclonic seizures as well as absences were described (Tabatabaie et al. 2010). The EEG of patients with 3-PGDH showed hypsarrhytmia or severe multifocal epileptic abnormalities with poor background activity (de Koning

and Klomp 2004). The 3-PGDH gene is located on chromosome 1q12. Two different homozygous missense mutations were described. Both mutations lead to a significant reduction of enzyme activity after expression of the mutant enzymes in vitro (de Koning and Klomp 2004). Low concentrations of serine and, to a variable degree, of glycine in plasma and CSF, are the biochemical hallmark of the disease. Oral supplementation of l-serine is proved to be very effective in the treatment of seizures (Tabatabaie et al. 2010).

Phenylketonuria (PKU) is a disorder of phenylalanine metabolism that frequently results in epilepsy if a dietary restriction was not implemented at birth (Blau et al. 2010). Classical PKU is an autosomal recessive disorder, caused by mutations in both alleles of the gene for phenylalanine hydroxylase (PAH), found on chromosome 12. In the body, phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine. As consequence of mutations in both copies of the gene for PAH, the enzyme is inactive or is less efficient, and the concentration of phenylalanine in the body can build up to toxic levels. In some cases, mutations in PAH will result in a phenotypically mild form of PKU called hyperphenylalanemia. Both diseases are the result of a variety of mutations in the PAH locus; in those cases where a patient is heterozygous for two mutations of PAH (i.e., each copy of the gene has a different mutation), the milder mutation will predominate (Blau et al. 2010). A small minority of PKU cases results from defects in the metabolism of tetrahydrobiopterin, the obligate cofactor of PAH. The symptoms of untreated PKU, which manifest primarily in the brain, are diverse, and can range from mild cognitive impairment to severe mental retardation, with motor impairment and pyramidal signs (Martynyuk et al. 2007). Refractory epilepsy is common, with infantile spasms or GTCs; PKU has been also reported in patients with West syndrome. At present, for almost all patients with phenylketonuria, diagnosis and the start of treatment result from neonatal screening rather than clinical symptoms. Treatment consists of dietary restriction and L-dopa, 5-hydroxytryptophan and folinic acid supplements (Martynyuk et al. 2007).

Urea Cycle Disorders

Urea cycle disorders (UCD) represent a group of inborn errors of metabolism result from single gene defects involved in the detoxification pathway of ammonia to urea (Zhongshu et al. 2001). The components of the pathway are: carbamyl phosphate synthase I (CPSI); ornithine transcarbamylase (OTC); argininosuccinic acid synthetase (ASS); argininosuccinic acid lyase (ASL); arginase (ARG) and the cofactor, N-acetyl glutamate synthetase (NAGS). Deficiencies of CPSI, ASS, ASL, NAGS, and ARG are inherited in an autosomal recessive manner. OTC deficiency is inherited in an X-linked manner (Braissant 2010; Summar 2005). Infants with a UCD often appear normal initially but rapidly develop cerebral edema and the related signs of lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, seizures, neurologic posturing, and coma. In milder (or partial) UCD, ammonia accumulation may be triggered by illness or stress at almost any time of life, resulting in multiple

mild elevations of plasma ammonia concentration; the hyperammonemia is less severe and the symptoms more subtle. In individuals with partial enzyme deficiencies, the first recognized clinical episode might be delayed for months or years (Braissant 2010). Seizures are frequent during the early stages of hyperammonaemia, especially in newborns. The EEG may show variable pattern of epileptic discharge, i.e., multifocal independent spike- and sharp-wave discharges, repetitive paroxysmal activity, unusually low-voltage fast activity, and findings consistent with complex partial seizures (Summar 2005). In late-onset UCD cases, EEG may show continuous semirhythmic activity with sharp components, leading to diagnosis of complex partial status epilepticus (Gropman et al. 2007).

The therapy of UCD include dialysis to reduce plasma ammonia concentration, intravenous administration of arginine chloride and nitrogen scavenger drugs to allow alternative pathway excretion of excess nitrogen, restriction of protein for 24–48 h to reduce the amount of nitrogen in the diet, providing calories as carbohydrates and fat reduce catabolism, and physiologic stabilization with intravenous fluids and cardiac pressors to reduce the risk of neurologic damage (Clague 2002).

Organic Acidemias

Organic acidemias (OA) consist of a group of disorders characterized by the excretion of non-amino organic acids in urine. Most organic acidemias result from dysfunction of a specific step in amino acid catabolism, usually the result of deficient enzyme activity. The majority of the classic organic acid disorders are caused by abnormal amino acid catabolism of branched-chain amino acids or lysine. The main types of OA include maple syrup urine disease (MSUD), propionic acidemia, methylmalonic acidemia, isovaleric acidemia and glutaric acidemia type I (GA-1) (Clague and Thomas 2002).

A neonate affected with an OA is usually well at birth and for the first few days of life. The usual clinical presentation is that of toxic encephalopathy and includes vomiting, poor feeding, neurologic symptoms such as seizures and abnormal tone, and lethargy progressing to coma. Outcome is enhanced by diagnosis and treatment in the first 10 days of life. In the older child or adolescent, variant forms of the OAs can present as loss of intellectual function, ataxia or other focal neurologic signs, Reye syndrome, recurrent ketoacidosis, or psychiatric symptoms (Van Gosen 2008; Seashore 2009).

MSUD (OMIM 248600) is caused by a deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC). The mammalian BCKD complex consists of three catalytic components: E1, E2, and E3, and two regulatory enzymes. Mutations in these regions lead to the accumulation of three branched-chain amino acids (BCAA) (leucine, isoleucine, and valine) and their toxic by-products in the blood and urine. The major clinical features of maple syrup urine disease are mental and physical retardation, feeding problems, and a maple syrup odor to the urine (Rahman et al. 2013)

There are presently five known clinical phenotypes for MSUD: classic, intermediate, intermittent, thiamin responsive, and dihydrolipoamide dehydrogenase (E3)-deficient, based on severity of the disease, response to thiamin therapy, and the gene locus affected (Wang et al. 2003).

Classic MSUD is the most frequent form and the affected newborns appear normal at birth, with symptoms developing between 4 and 7 days of age. The infants show lethargy, weight loss, metabolic derangement, and progressive neurologic signs of altering hypotonia and hypertonia, reflecting a severe encephalopathy. Seizures and coma usually occur, followed by death if untreated (Seashore 2009). The seizures can be of different types, with occasionally presenting with status epilepticus and early treatment may improve the prognosis (Wang et al. 2003). The EEG pattern is variable and it includes spikes, polyspikes, spike-wave complexes, triphasic waves, severe slowing and bursts of periodic suppression ad are not related to blood BCAA levels (Korein et al. 1994).

Propionic acidemia (PA) (OMIM 606054) is characterized by the accumulation of propionic acid due to a deficiency in Propionyl CoA Carboxylase, a biotin dependent enzyme involved in amino acid catabolism. Patients may present with vomiting, dehydration, lethargy, and encephalopathy. Among the neurological complication often observed, developmental delay, seizures, cerebral atrophy and EEG abnormalities have been the most prominent. Seizures generally have onset in the neonatal period and they may include focal seizures, spasms, and generalized tonic and myoclonic seizures (Haberlandt et al. 2009). In 40 % of affected children, generalized convulsions and myoclonic seizures develop in later infancy, and older children may have atypical absence seizures (Aicardi 2007). Photosensitivity and fever induced seizures have also been described at the beginning in patients with PA. Intractable seizures may develop. The EEG pattern is variable and it may show hypsarrhythmia, burst suppression and diffuses delta wave activity with generalized or focal temporal spikes during the encephalopatic phase. MRI usually reveals alterated signal in the caudate, putamen, and globus pallidus. MRS shows decreased NNA and myo-inositol and increased glutamate/glutamine in the basal ganglia (Chemelli et al. 2000).

Glutaric aciduria type 1 (GA-1, OMIM 608801) is an autosomal recessive disease due to an inborn error of the metabolism of the amino acids lysine, hydroxylysine, and tryptophan due to mutations in the glutarylcoenzyme. A dehydrogenase gene (GCDH), on chromosome 19p13.2 (McClelland et al. 2009). Clinical expression usually involves an acute encephalopathic episode in infancy, followed by the development of severe dystonia-dyskinesia. Seizures may occur at presentation in the context of acute encephalopathy, but ongoing seizures are not common in GA-1 unless accompanied by severe brain damage (McClelland et al. 2009). Many children may have sudden dystonic spasms that could be mistaken for seizures. Although chronic epilepsy is rare, glutaric aciduria type I patients may present with epileptic seizures that are difficult to control with first- or second-line anticonvulsants as the sole clinical feature (Cerisola et al. 2009). This disorder can be identified by increased glutaryl (C5DC) carnitine on newborn screening. Urine organic acid analysis indicates the presence of excess 3-OH-glutaric acid, and urine acylcarnitine profile shows glutaryl carnitine as the major peak (McClelland et al. 2009).

The brain MRI is helpful for the diagnosis. Atrophy or hypoplasia of the frontotemporal regions of the cerebral hemispheres, enlarged pretemporal middle cranial fossa subarachnoid spaces, and cyst-like dilatation of the Sylvian fissures are often early findings in glutaric acidemia type I with "batwing" or "box-like" fissures (Neumaier-Probst et al. 2004).

The aim of therapy in OA is to restore biochemical and physiologic homeostasis. Neonates require emergency diagnosis and treatment depending on the specific biochemical lesion, the position of the metabolic block, and the effects of the toxic compounds. Treatment strategies include: (1) dietary restriction of the precursor amino acids and (2) use of adjunctive compounds to (a) dispose of toxic metabolites or (b) increase activity of deficient enzymes. Decompensation caused by catabolic stress (e.g., from vomiting, diarrhea, febrile illness, and decreased oral intake) requires prompt and aggressive intervention (Seashore 2009).

Peroxisomal Disorders

Zellweger syndrome (ZS, OMIM 214100) may be responsible for epilepsy in the neonatal period. Individuals with ZS develop signs and symptoms of the condition during the newborn period. These infants experience hypotonia, feeding problems, hearing loss, vision loss, and seizures. Children with ZS also develop life-threatening problems in other organs and tissues, such as the liver, heart, and kidneys. They may have skeletal abnormalities, including a large space between the bones of the skull (fontanels) and characteristic bone spots known as chondrodysplasia punctata that can be seen with an X-ray (Rahman et al. 2013). Affected individuals have distinctive facial features, including a flattened face, broad nasal bridge, and high forehead. Children with ZS typically do not survive beyond the first year of life (Steinberg et al. 2003). Areas of polymicrogyria are often frontal or opercular, resulting in a focal EEG and seizure semiology, and there are often focal motor seizures (Takahashi et al. 1997). Mutations in the *PEX1* gene are the most common cause of the Zellweger spectrum and are found in nearly 70% of affected individuals. The other genes associated with the Zellweger spectrum each account for a smaller percentage of cases of this condition (Steinberg et al. 2003).

Infantile Onset Seizures

Biotin Response Epileptic Seizures

Characteristic organic aciduria, cutaneous and neurologic symptoms with frequent seizures are present in holocarboxylase synthetase (HCS) and biotinidase deficiencies (BTD). Both disorders in biotin metabolism lead to multiple carboxylase deficiency and respond dramatically to biotin therapy (Joshi et al. 2010).

Biotinidase deficiency (BTD) (OMIM 253260) is an autosomal recessively inherited disorder in which the vitamin, biotin, cannot be appropriately recycled (Wolf 2011a, b). BTD is the only gene known to be associated with biotinidase deficiency. The BTD gene provides instructions for making an enzyme called biotinidase that removes biotin that is bound to proteins in food, leaving the vitamin in its free state. Mutations in the BTD gene reduce or eliminate the activity of biotinidase. Deficiency of BTD leads to decrease biotin available resulting in reduced conversion of apocarboxylases to holocarboxylases or multiple carboxylase deficiency (Wolf 2011a, b). This subsequently causes the accumulation of abnormally high concentrations of toxic metabolites (Pindolia et al. 2010). Profound biotinidase deficiency results when the activity of biotinidase is reduced to less than 10% of normal. Partial biotinidase deficiency occurs when biotinidase activity is reduced to between 10 and 30% of normal (Thoene and Wolf 1983). If untreated, young children with profound BTD deficiency usually exhibit neurologic abnormalities including seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, and cutaneous abnormalities (Bhardwaj et al. 2010). Seizures are the presenting symptom in 38% of patients with biotinidase deficiency and are found in up to 55% of patients at some time before treatment. Seizures often start after the first 3 or 4 months of life, and often as infantile spasms or GCTS (tonic-clonic, clonic and myoclonic). The refractory seizures respond promptly to small doses of biotin (5–20 mg/day) (Zempleni et al. 2008).

Holocarboxylase synthetase (HCS) deficiency is an inherited disorder in which the body is unable to use the vitamin biotin effectively. Mutations in the HLCS gene cause holocarboxylase synthetase (Suzuki et al. 2005). The signs and symptoms of holocarboxylase synthetase deficiency typically appear within the first few months of life, but the age of onset varies. Symptoms are very similar to biotinidase deficiency and treatment (large doses of biotin) is also the same. Seizures are less frequent, occurring in 25–50% of all children (Pascual et al. 2008).

Disorders of Creatine Metabolism

Creatine deficiency syndromes represent a group of inborn errors of creatine metabolism that is responsible for mental retardation, language delay and early-onset epilepsy (Nasrallah et al. 2010). Three inherited defects in the biosynthesis and transport of creatine have been described. The biosynthetic defects include deficiencies of the enzymes L-arginine–glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT) (Nasrallah et al. 2010). The third is the deficiency of the creatine transporter 1 (CT1). Epilepsy is one of the main symptoms in two of these conditions, GAMT and CT1 deficiency, whereas the occurrence of febrile convulsions in infancy is a relatively common presenting symptom in all (Leuzzi 2002).

Clinical presentation of GAMT deficiency is usually characterized by normal developmental milestones in the first months of life, which can be abruptly discontinued by arrest/regression of psychomotor development with or without seizures.

arrest/regression of psychomotor development with or without seizures. Epilepsy is the second most frequent symptom in GAMT deficiency after intellectual disability. Febrile seizures have often been reported in the early phase of the disease occurring during the first 24 months of life (mainly 3–6 months). The pattern of seizures is not consistent, and more than one type of seizures can occur in the same patient at different ages. Life-threatening tonic seizures with apnea or myoclonic seizures can be observed in the first months of life, whereas myoclonic astatic seizures, generalized tonic–clonic seizures, partial seizures with secondary generalization, drop attacks, absences, and staring episodes appear in early infancy or in adolescence. Febrile seizures, generalized tonic–clonic seizures, and myoclonic astatic seizures are the most commonly reported seizure types. No typical electroencephalography (EEG) pattern can be defined in GAMT deficiency. An early derangement of background organization and interictal multifocal spikes and slow wave discharges are frequently recorded. Focal EEG abnormalities, with a prominent involvement of frontal regions, have also been reported. Severe epilepsy has been reported in almost all cases. Movement disorders, such as athetosis, chorea, choreoathetosis, ballismus, and dystonia may be present (Leuzzi 2002).

The most typical neuroimaging alteration in GAMT deficiency is represented by bilateral pallidal lesions (hypointensity in T1-weighted and hyperintensity in T2-MRI images). In a few cases the lesion extended in the brainstem and selectively involved the white matter of the floor of fourth ventricle or the posterior pontine region (Leuzzi et al. 2013).

Biochemical findings associated with GAMT deficiency include the following: (1) reduced concentration of creatine in plasma, urine, cerebrospinal fluid (CSF), muscle, and brain; and (2) marked increase of guanidinoacetic acid (GAA) in all the biologic fluids, mainly in the CSF. High values of GAA can be detected also in dry blood spot since the first days of life. A mild increase of GAA over the normal range has been detected in blood and/or urine of some carriers of GAMT gene mutations. GAMT enzyme activity may be tested in liver tissue, skin fibroblasts, and lymphoblasts. The aim of treatment is to correct both the depletion of creatine/creatine-phosphate pools and the accumulation of GAA. In GAMT deficiency, a lifelong oral supplementation with high doses of creatine monohydrate (350 mg/kg/day–2 g/kg/day) has been shown, by plasma creatine assessment (muscle creatine pool) and brain H-MRS (brain creatine pool), to replenish body creatine pools. A further abating effect on AGAT activity can be obtained through a dietary restriction of arginine (15 mg/kg/day) coupled with ornithine supplementation (ornithine aspartate 350–800 mg/kg/day). Medicaments such as sodium benzoate and phenylbutyrate, which remove arginine and glycine, respectively, have also been proposed according to a similar substrate inhibition approach. Among the different clinical manifestations of GAMT deficiency, epilepsy is by far the most responsive to treatment (Nasrallah et al. 2010; Verhoeven et al. 2005).

CT1 deficiency is one of the main causes of X-linked mental retardation in males, and it is caused by *SLC6A8* gene mutations. Mental retardation and specific language derangement (oral-verbal dyspraxia of speech) are, in fact, the core symptoms of the disease. CT1 deficiency. It is rarely severe and it is usually re-

sponsive to conventional antiepileptic drugs. Its onset ranges between 16 months and 12 years. Febrile convulsions represent the first seizure-type in a number of subjects, and in a single case they led to subcontinuous generalized tonic–clonic seizures. Seizure pattern and EEG alterations can be extremely variable. Seizure-types include myoclonic seizures, generalized tonic–clonic seizures, convulsive status epilepticus, and partial seizures with secondary generalization. EEG recordings include normal tracing, diffuse slowing, aspecific sharp abnormalities, and focal/generalized paroxysmal or slow abnormalities, with or without sleep activation (Leuzzi et al. 2013). However, paroxysmal abnormalities are generally less severe as the child grows older. *SLC6A8* genotype is not associated with epilepsy, as exemplified by personal observations and cases from the literature. Neuroimaging and clinical features suggest in some patients a possible perinatal ischemic insult. This aspect may be confounding from the diagnostic point of view because clinical history rarely justifies this suspect. However, these lesions are congruent with the concept of creatine as a protective factor against potentially ischemic damage. Their possible role in the determinism of epilepsy needs to be elucidated. There are a few clinical reports on females carrying *SLC8A6* gene mutations. When symptomatic, they express a milder phenotype, including mild intellectual disability, behavioral disorders, problems of language development, learning difficulties, impairment of visual-constructional and fine motor skills, mild cerebellar symptoms, and constipation. Late occasional epileptic seizures have been described but not systematically studied (Leuzzi 2002).

The main biochemical alteration of patients with CT1 defect is the lack of brain creatine on H-MRS. Creatine is one of the major peaks in proton MR spectroscopy and is almost absent in all disorders of creatine synthesis and transport (Leuzzi 2002).

The urinary ratio creatine/creatinine (Cr/Crn) was proposed and confirmed as diagnostic marker of the disease. Diagnostic urinary Cr/Crn ratio ranged from 1.4 to 5.5 (reference values 0.006–1.2 in children under 4 years, 0.017–0.72 in patients between 4 and 12 years, 0.011–0.24 after 12 years of age). However, urinary Cr/Crn may be influenced by various nutritional and individual factors (Verhoeven et al. 2005).

Fibroblast and lymphoblast express SLC6A8 gene, and creatine uptake can be tested in these cells in patient with suspect CT1 defect. In contrast, muscle creatine is normal on both biochemical and H-MRS examination. No key clinical and/or neuropsychological cues have been identified to suggest the diagnosis of CT1 deficiency in girls with epilepsy and intellectual disability or learning difficulties. For these reasons gene sequencing seems to be the best diagnostic tool for females with a clinical suspect of CT1 (Verhoeven et al. 2005).

No effective treatment is available for males with CT1 defect. The supplementation of creatine, also at high dosages, does not improve H-MRS detectable brain creatine pool and/or clinical status. In contrast, creatine, as well as creatine precursor, supplementation is potentially effective in symptomatic females where the defect of CT1 is partial (Leuzzi et al. 2013).

Diagnosis is based on concentration of creatine and its precursors, measurement of enzyme activity for AGAT and GAMT, creatine uptake test for the diagnosis of CT1 defect, and mutation analysis.

The AGAT and GAMT deficiencies are inherited as an autosomal recessive trait; the *SLC6A8* deficiency is X-linked inherited. In humans, the AGAT protein is encoded by the gene *GATM* (15q21.1). The human *GAMT* gene is located on chromosome 19p13.3, while the gene CT1 (alias CRTR, SLC6A8) has been mapped to chromosome band Xq28 (Nasrallah et al. 2010).

Disorders of GABA Metabolism

Amino butyric acid (GABA) metabolism is associated with several disorders, including GABA-transaminase deficiency, and succinic semialdehyde dehydrogenase deficiency (SSADH) (Wolf et al. 2005).

GABA-transaminase deficiency is a rare disease with only few reported cases and it is characterized by abnormal development, seizures, and high levels of GABA in serum and cerebrospinal fluid (Jaeken 2002).

SSADH deficiency is an uncommon autosomal recessively inherited neurotransmitter disease involving GABA degradation. *ALDH5A1* is the only gene currently known to be associated with SSADH deficiency. SSADH is an enzyme that catalyzes the oxidation of succinate semialdehyde to succinate, the second and final step of the degradation of the inhibitory neurotransmitter GABA. Clinical manifestations in patients with SSADH deficiency are varied, and may range from mild mental retardation, speech delay, or behavioral problems, to severe psychomotor retardation with intractable seizures (Pearl and Gibson 2004).

Approximately half of patients with SSADH deficiency have epilepsy, usually with GTCS and also atypical absence and myoclonic seizures. The EEG may reveal background slowing and disorganization as well as diffused and multifocal epileptiform abnormalities. MRI shows increased T2-weighted signal involving the globus pallidi bilaterally and symmetrically, in addition to the cerebellar dentate nuclei and subthalamic nuclei (Pearl et al. 2007).

Vigabatrin, an irreversible inhibitor of GABAtransaminase, inhibits the formation of succinic semialdehyde and thus is one of the most widely prescribed AEDs in this disorder (Matern et al. 1996). However, vigabatrin has shown inconsistent results and MRI signal changes have been observed in patients treated with high doses (Pearl et al. 2009).

Glucose Transporter Deficiency

Glucose Transporter 1 (GLUT1) is a membrane transporter that facilitates glucose transport across the blood–brain barrier. GLUT1 deficiency syndrome (OMIM #606777) is disorder that primarily affects the brain. Glucose transporter-1 (GLUT1)

is encoded by *SLC2A1* gene and usually mutations occur de novo, although the disease can also be inherited as autosomal dominant trait (Brockmann 2009). GLUT1 is highly expressed in the endothelial cells of erythrocytes and the blood–brain barrier and is exclusively responsible for glucose transport into the brain (Vannucci et al. 1997). Its deficiency leads to low glucose concentration in the cerebrospinal fluid (hypoglycorrhachia) (not associated with hypoglycaemia), in combination with a low to normal lactate in the cerebrospinal fluid. The classic patient with GLUT1 deficiency syndrome generally has drug resistant seizures beginning in the first year of life (Seidner et al. 1998).

Babies with GLUT1 deficiency syndrome have a normal head size at birth, but growth of the brain and skull is often slow, in severe cases resulting in microcephaly (Rotstein et al. 2010). Patients present with early-onset epilepsy, developmental delay, and a complex movement disorder as hypotonia, spasticity, ataxia and dystonia (Klepper and Leiendecker 2007; Schneider et al. 2009). The phenotype is highly variable and several atypical variants have been described (Klepper 2008). Seizures begin between age 1 and 4 months in 90 % of cases. Apneic episodes and abnormal episodic eye movements simulating opsoclonus may precede the onset of seizures by several months. Five seizure types occur: generalized tonic or clonic, myoclonic, atypical absence, atonic, and unclassified (Wang et al. 2009). The interictal EEG may be normal. The ictal EEG may show focal slowing or discharges, including 2.5–4 Hz spike and wave. A striking difference between pre- and postprandial EEG may be seen, with a decrease in epileptic discharges following carbohydrate intake. GLUT1 deficiency is now known to be a cause of drug-resistant childhood absence epilepsy and of adult-onset absence epilepsy with a normal CSF glucose. Patients with a non-classical phenotype have been described, characterized by developmental delay and movement disorders without epilepsy or familial and sporadic paroxysmal exercise induced dyskinesia with or without epilepsy (Overweg-Plandsoen et al. 2003; Friedman et al. 2006; Klepper and Leiendecker 2007; Suls et al. 2008).

When GLUT1 deficiency syndrome is suspected, a lumbar puncture in the fasting state should be performed. Diagnosis is made by documenting CSF glucose levels below 40 mg/dl (2.5 mmol/l) and low CSF/blood glucose ratio (< 0.50). CSF lactate is normal or low. The degree of hypoglycorrhacia and absolute 'cut-off' for a diagnosis of GLUT1 deficiency remain a source of debate, and mild clinical phenotypes have been reported with normoglycorrhacia and a normal CSF to blood glucose ratio; thus molecular genetic analysis of the SLC2A1 gene is considered the standard criterion for diagnosis. Approximately 80 % of patients harbour pathogenic mutations (Wang et al. 2009).

Epilepsy in GLUT1 deficiency is drug resistant and may be aggravated by fasting and by AEDs that inhibit GLUT1 (phenobarbitone, valproate, diazepam). The ketogenic diet is highly effective in controlling the seizures and is generally well tolerated. However, neurobehavioral and motor deficits persist in most cases. This high-fat, low-carbohydrate diet provides an alternative source of energy for the brain as ketone bodies, which are produced in the liver and which can easily penetrate the blood–brain barrier (Klepper 2008; Rahman et al. 2013).

Defects of Purine and Pyrimidine Metabolism

Adenylosuccinate lyase (ADSL) deficiency is an autosomal recessive defect of purine metabolism causing serious neurological and physiological symptoms. ASL catalyzes two distinct reactions in the synthesis of purine nucleotides, both of which involve the b-elimination of fumarate. The deficiency of ADSL results in the accumulation of succinylpurines in CFS, plasma and urine (Spiegel et al. 2006).

The human *ADSL* gene has been mapped to chromosome 22q13.1–13.2. Most ADSL deficiency patients are compound heterozygotes and in cases in which the parents have been genotyped, each parent carries one mutant and one normal allele and is asymptomatic. No individuals with ADSL deficiency are completely lacking in enzyme activity; complete lack of ADSL activity in humans is probably incompatible with life (Spiegel et al. 2006). The potential mechanisms whereby ADSL may provoke neurological manifestations include deficiency of purine nucleotides, impairment of energy metabolism, and toxic effects by accumulated intermediates (Ciardo et al. 2001).

The clinical presentation is characterized by severe neurologic involvement including seizures, developmental delay, hypotonia, and autistic features. Neonatal seizures and a severe infantile epileptic encephalopathy are often the first manifestations of this disorder. The epileptic phenotype consists of myoclonias, partial epilepsy, GTCS, spasms and status epilepticus (Ciardo et al. 2001).

Epilepsy in ADSL deficiency is usually associated with psychomotor delay, autism and signs of cerebellar and pyramidal dysfunction (Wolf et al. 2005).

Mitochondrial Diseases

Mitochondrial diseases (MCDs) are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. They can be caused by mutations of nuclear or mitochondrial DNA (mtDNA) (Cree et al. 2009). Nuclear gene defects may be inherited in an autosomal recessive or autosomal dominant manner. Mitochondrial DNA defects are transmitted by maternal inheritance. Epilepsy is also a frequent CNS manifestation of MCDs. Seizure may start at infancy as infantile spasms, West syndrome, myoclonic jerks, astatic seizures, or juvenile myoclonic epilepsy. Epilepsy is particularly prevalent in patients with MELAS, MERRF, LS, or NARP (Finsterer 2006).

Several mitochondrial diseases have been linked to ineffective mtDNA replication by mitochondrial DNA polymerase gamma (POLG). Mutations in POLG, are associated with Alpers syndrome (and Alpers-like encephalopathy), childhood Myocerebrohepatopathy spectrum disorders, ataxia-neuropathy syndromes, myoclonus epilepsy myopathy sensory ataxia, and dominant and recessive forms of progressive external ophthalmalplegia (PEO) (Milone and Massie 2010).

Mitochondrial DNA depletion syndrome, also known as *Alpers syndrome* (OMIM #203700), is an autosomal recessive disorder characterized by a clinical triad of psychomotor retardation, intractable epilepsy, and liver failure. Seizures

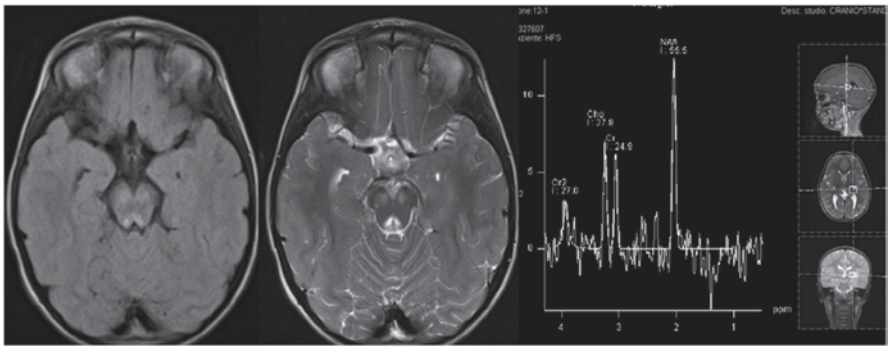

Fig. 3 MRI of a boy with Leigh phenotype with complex I deficiency. Axial T2-weighted images show focal bilateral lesions in the brainstem. The MR-spectroscopy show a lactate peak in deep gray matter

may initially be focal and subsequently generalize. Epilepsia partialis continua and convulsive status epilepticus are common. The disorder, diagnosed in infants and young children, is progressive and often leads to death from hepatic failure or status epilepticus before age 3 years. MtDNA in muscle and liver samples of Alpers syndrome patients is depleted (Milone and Massie 2010). The EEG features of posterior rhythmic high amplitude delta with superimposed polyspikes (RHADS) are very helpful although not mandatory in all cases. The course is usually rapidly progressive; most affected infants die before the age of 3 years (Wolf et al. 2009a, b).

Magnetic resonance imaging changes may be nonspecific, such as atrophy (both general and involving specific structures, such as cerebellum), more suggestive of particular disorders such as focal and often bilateral lesions confined to deep brain nuclei, or clearly characteristic of a given disorder such as stroke-like lesions that do not respect vascular boundaries in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episode (MELAS). White matter hyperintensities with or without associated gray matter involvement may also be observed (Fig. 3; Friedman et al. 2010; Papetti et al. 2013).

Secondary mitochondrial dysfunction is also seen in a number of different genetic disorders, including *ethylmalonic aciduria* (EE, OMIM # 602473) (Tiranti et al. 2009). EE is an autosomal recessive metabolic disorder of infancy affecting the brain, the gastrointestinal tract and peripheral vessels. It is caused by a defect in the ETHE1 gene product, which a mitochondrial dioxygenase involved in hydrogen sulfide (H (2) S) detoxification. Patients present in infancy with psychomotor retardation, chronic diarrhea, orthostatic acrocyanosis and relapsing petechiae. High levels of lactic acid, ethylmalonic acid (EMA) and methylsuccinic acid (MSA) are detected in body fluids. The signs and symptoms of EE are apparent at birth or begin in the first few months of life. Seizures start early as tonic seizure, spasms and West syndrome (Fig. 2; Papetti et al. 2013). MRI generally shows symmetrical increased signals on T2-weighted images in the basal ganglia which correspond to symmetrical necrotic lesions (Fig. 4). They occasionally have signal anomalies in subcortical areas, white matter, and brainstem (Pigeon et al. 2009).

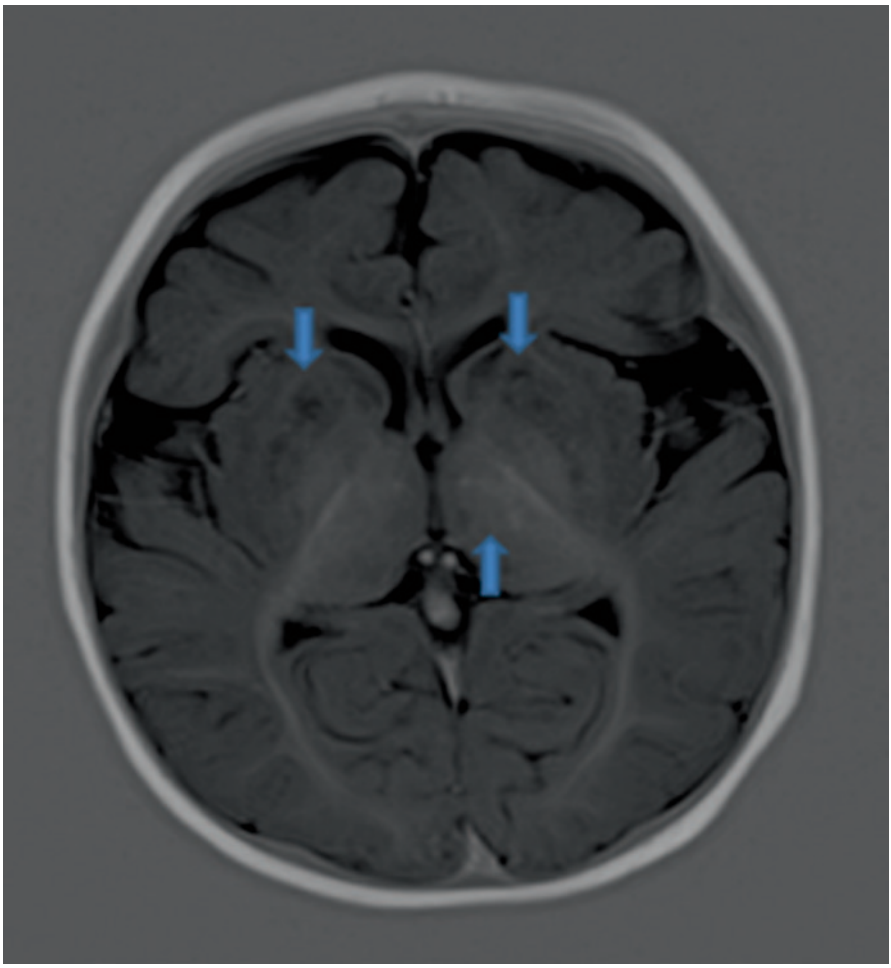

Fig. 4 MRI of 4 months-girl with Ethylmalonic aciduria. Axial flair- sequence image shows bilateral hypointense lesions of basal nuclei (n. caudati; n. lentiformi)

Diagnostic approach in MCDs should include patient and family history, laboratory examination, and neurological workup as initial workups, then specific biochemical studies, muscle biopsy, and molecular genetic studies as the further workups. The most useful basic test is to check serum lactate level (Kang et al. 2013). In patients with mitochondrial encephalopathy, when pyruvate oxidation in mitochondria is disturbed due to abnormalities in pyruvate dehydrogenase complex, Krebs cycle, or electron transport chain, excessive pyruvate can be either transformed into alanine or reduced to lactate, increasing blood lactate level. The ratio of lactate to pyruvate depends on the degree of oxidation–reduction in tissue. Since the increase in serum lactate level can be equivocal in patients with mitochondrial encephalopathy, it is

sometimes helpful to evaluate lactate level of cerebrospinal fluid. More specifically, a particularly significant increase in the ratio of lactate to pyruvate and 3-hydroxybutyrate to acetoacetate may suggest respiratory chain defect. The further diagnostic approaches to mitochondrial diseases include morphological observation using microscopic tools, biochemical assays that measure enzyme activities of respiratory chain reaction in skeletal muscles (most commonly complex I defect), and molecular genetic studies to examine mtDNA or nuclear DNA mutation (Kang et al. 2013).

To treat epilepsy with mitochondrial diseases, general supportive care is first provided to treat multiorgan involvement. Then, the children are given antioxidants and respiratory chain cofactors, along with recommendation for diet change to the ketogenic diet or caloric restriction. Finally, antiepileptic drugs (AEDs) are used to control seizure (Kang et al. 2013).

Coenzyme Q10 has been reported to have two functions, as an electron carrier in the mitochondrial respiratory chain reaction and as a scavenger molecule. It is important to identify and treat disorders of CoQ10 biosynthesis, since these remain the only readily treatable forms of mitochondrial epilepsy (Steele et al. 2004; Rahman et al. 2010, 2013). Many present in infancy with a multisystem syndrome including epilepsy, frequently associated with sensorineural hearing loss and a prominent steroid- resistant nephropathy. Other neurological features in these patients include nystagmus, ataxia, spasticity, and dystonia. Mutations in five genes (COQ2, PDSS1, PDSS2, COQ9, and COQ6) have so far been reported to cause infantile onset of CoQ10 deficiency. Treatment is with oral CoQ10 supple mentation; 10–30 mg/kg/day in three divided doses is usually sufficient. The best outcome in this disorder was reported in a female who was diagnosed early because of an affected older sibling, and in whom treatment was initiated at the first manifestation of disease (Montini et al. 2008; Rahman et al. 2010). Riboflavin, tocopherol (vitamin E), succinate, ascorbate (vitamin C), menadione, and nicotinamide have also been used to treat mitochondrial diseases with deficiency in specific enzymes (Kang et al. 2013).

Males with the X-linked form of *pyruvate dehydrogenase complex (PDHc) deficiency* usually present with Leigh syndrome (OMIM 308930), but females who are heterozygous for a severe mutation in the PDHA1 gene can present in the first 6 months of life with infantile spasms, an EEG showing hypsarrhythmia, and developmental regression (West syndrome), or just with severe myoclonic seizures (OMIM 312170). MRI may show periventricular multicystic leukoencephalopathy and agenesis of the corpus callosum. CSF lactate is often elevated, usually with an elevation of blood lactate, and fibroblast studies show reduced pyruvate dehydrogenase complex activity. Some cases of pyruvate dehydrogenase complex deficiency respond well to treatment with thiamine and/or a ketogenic diet, and this reduction in seizure severity (Barnerias et al. 2010).

Childhood Onset Seizures

Storage Disorders

The neuronal ceroid-lipofuscinoses (NCLs) are a group of inherited, neurodegenerative, lysosomalstorage disorders characterized by progressive intellectual and motor deterioration, seizures, and early death. Visual loss is a feature of most forms. NCLs variants are classified by age of onset and order of appearance of the clinical features: infantile neuronal ceroid-lipofuscinosis (INCL), late-infantile (LINCL), juvenile (JNCL), adult (ANCL), and Northern epilepsy (NE, progressive epilepsy with intellectual disability) (Mole and Williams 2010). In INCL seizures start at the end of the first year of life, with myoclonus, atonic and GTCS followed by dementia and movement disorders. The EEG shows a depression of background activity (Pascual et al. 2008). Symptoms of LINCL generally appear after the second year of life. The seizures are GTCS, tonic clonic, atonic, myoclonic and myoclonic-astatic. The EEG can show epileptic discharges during intermittent photostimulation at 1 Hz (Wolf et al. 2009a, b). The JNCL form is characterized by seizures that typically appear between ages 5 and 18 years. Northern epilepsy is characterized by tonic-clonic or complexpartial seizures, intellectual disability, and motor dysfunction. Onset occurs between ages 2 and 10 years (Mole and Williams 2010).

The genes *PPT1 (CNL1), TPP1 (CNL2), CLN3, CLN5, CLN6, MFSD8 (CLN7), CLN8,* and *CTSD (CNL10)* are known to be associated with NCLs. In INCL, a lysosomal enzyme, palmitoyl protein thioesterase 1 (PPT1) is deficient. Patients with LINCL are deficient in a pepstatin-insensitive lysosomal peptidasetripeptidyl peptidase 1 (TTP1). JNCL is due to mutation of CLN3 gene that encodes a protein that is thought to be a part of the lysosomal membrane. The ANCL is associated with mutations of the CLN4 gene (not mapped yet). Mutations in another gene, CLN5 is associated with Finnish variant LINCL that occurs predominantly in the Finnish population (Mole and Williams 2010).

Myoclonic epilepsy of Lafora (EPM2, OMIM #254780) is a severe autosomal recessive disorder characterized by fragmentary, symmetric, or generalized myoclonus and/or GTCS, occipital seizures, and progressive neurologic degeneration including cognitive and/or behavioral deterioration, dysarthria, and ataxia beginning in previously healthy adolescents between ages 12 and 17 years. The frequency and intractability of seizures increase over time. Survival is short, less than 10 years after onset. The disease is characterized by intracellular polyglucosan inclusions (Lafora bodies) in the brain, liver, skin and muscles (Monaghan and Delanty 2010). Two genetic forms are known, one of which (EPM2A) is caused by mutations in the *laforin* gene and another (NHLRC1)–by mutations in the *malin* gene. The *EMP2A* encodes a protein phosphatase and *NHLRC1* encodes an ubiquitin ligase. These two proteins interact with each other and, as a complex, are thought to regulate critical neuronal functions (Singh and Ganesh 2009).

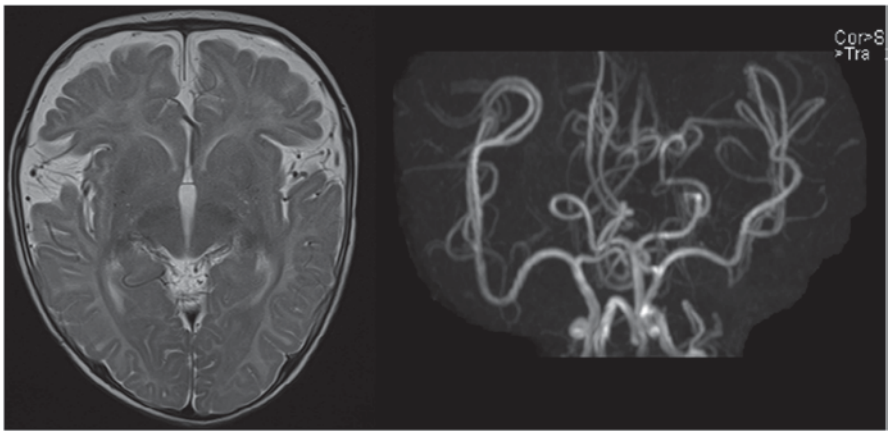

Fig. 5 MRI of 6 months-boy with Menkes disease. Axial T2-weighted image show dilatation of fronto-insular subarachnoid spaces and enlargement of anterior interhemispheric fissure. Axial MR angiography shows tortuous intracranial vessels

Copper Metabolism Errors

Menkes disease (MD) is a multisystemic disorder of copper metabolism. Progressive neurodegeneration and connective tissue disturbances, together with the peculiar 'kinky' hair are the main manifestations. MD is inherited as an X-linked recessive trait, and is due to mutations in the *ATP7A* gene. The vast majority of *ATP7A* mutations are intragenic mutations or partial gene deletions. ATP7A is an energy dependent transmembrane protein, which is involved in the delivery of copper to the secreted copper enzymes and in the export of surplus copper from cells (Tümer and Møller 2010). Seizures may occur during the first few months of life, although there are mild forms of the defect with later onset and include myoclonus, spasms and multifocal seizures. Three successive periods in the course of epilepsy have been observed: early focal status, then infantile spasms, and then myoclonic and multifocal epilepsy after age 2 years (Bahi-Buisson et al. 2006).

Radiological findings are various and combine cortical and cerebellar atrophy, delayed myelinisation, tortuosity and dilatation of the intra- and extracranial vessels, and subdural fluid collections (Fig. 5) (Bahi-Buisson et al. 2006; Papetti et al. 2013).

Congenital Disorders of Glycosylation (Cdg)

Congenital disorders of glycosylation (CDG) are a group of disorders of abnormal glycosylation of Nlinked oligosaccharides caused by deficiency in 21 different enzymes in the N-linked oligosaccharide synthetic pathway. Most commonly,

the disorders begin in infancy; manifestations range from severe developmental delay and hypotonia with multiple organ system involvement to hypoglycemia and protein-losing enteropathy with normal development (Sparks and Krasnewich 2011). Mutations identified in the 15 genes (*PMM2, MPI, DPAGT1, ALG1, ALG2, ALG3, ALG9, ALG12, ALG6, ALG8, DOLK, DPM1, DPM3, MPDU1,* and *RFT1*) yield a deficiency of dolichol-linked oligosaccharide biosynthesis resulting in CDG (Haeuptle and Hennet 2009). Epilepsy associated with developmental delay, dysmorphisms and hypotonia has been described more frequently in CDG-1d. Seizures generally start in the infancy and the EEG revealed generalized epileptic changes, while brain MRI shows evidence of leukodystrophy (Grünewald et al. 2000).

Lysosomal Storage Disorder

Gaucher disease (GD) is a lipid storage disease characterized by the recessively inherited deficiency of lysosomal glucocerebrosidase, encoded by GBA (OMIM# 606463). GD manifests with diverse symptoms, and is commonly divided into three types, based on the absence (type 1) and rate of progression of neurological manifestations (types 2 and 3) (Mignot et al. 2006). GD3 comprises a heterogeneous group of patients suffering either mild or severe systemic disease combined with variable neurological involvement. Two further subtypes of GD3 patients have been reported differentiating those with mild systemic involvement associated with progressive myoclonic epilepsy (PME), called GD3a, from those with severe systemic involvement associated with oculomotor apraxia (OMA), called GD3b (Kraoua et al. 2011). In a recent perspective study conducted by the International Collaborative Gaucher Group, seizures were reported in 19 out of 122 patients (16%). Some patients had experienced more than one type of seizure. The types reported were tonic–clonic seizures (7 out of 122, 6%), clonic seizures (5 out of 122, 4%), tonic seizures (3 out of 120, 3%), myoclonic seizures (3 out of 121, 2%), typical absence seizures (2 out of 119, 2%), and atypical absence seizures (1 out of 119, 1%) (Tylki-Szymańska et al. 2010).

Niemann–Pick type C (NPC; OMIM 257220) is a progressive neurodegenerative disorder characterized by accumulation of free cholesterol, sphingomyelin, glycosphingolipids (GSLs) and sphingosine in lysosomes, mainly due to a mutation in the NPC1 gene. The clinical spectrum of the disease ranges from a neonatal rapidly fatal disorder to an adult-onset chronic neurodegenerative disease. Epilepsy is generally a late onset manifestation with partial, generalized tonic–clonic and atonic seizures (Sévin et al. 2007).

Peroxisomal Disorders

X-linked adrenoleukodystrophy (X-ALD, OMIM 300100) is an inherited, recessive, neurodegenerative disease affecting brain white matter, adrenal cortex and testis.

The disorder is caused by mutations in the *ABCD1* gene, which impair peroxisomal b-oxidation, resulting in the accumulation of very long-chain fatty acids (VLCFa) in plasma. There are several distinct clinical phenotypes ranging from cerebral forms, adrenomyeloneuropathy (AMN) to asymptomatic persons or isolated adrenal insufficiency without CNS involvement (Addison's disease only). Cerebral X-ALD is further divided into childhood (CCALD), adolescent (AdolCALD) and adult form (ADCALD). Affected boys with CCALD present before the age of 10 years a rapidly progressive disorder with ataxia, spasticity, deafness, visual deficits, personality changes and seizures. The less common adolescent form after the age of 10 years demonstrates similar course. Cerebral X-ALD is frequently associated with Addison's disease, but the primary adrenal insufficiency may precede, coexist or develop after neurological disturbances. In one large series, 20 out of 485 individuals presented with seizures: focal seizures in six males and generalized in the remainder, with four having status epilepticus (Stephensons et al. 2000). Typical MR findings in the brain of X-ALD patients have been well documented recently and consist of bilateral white matter abnormalities. Typically they occur initially in the posterior cerebral regions and progress to parietal, temporal and frontal lobes sequentially. Such a pattern is found in approximately 80 % of cases; therefore MR strongly suggests the diagnosis of X-ALD (Poll-The 2012).

Conclusions

Inborn errors of metabolism are a rare cause of epilepsy in pediatric age. The suspicious of metabolic epilepsy should rise if seizures are refractory to standard antiepileptic drugs, and if additional symptoms are present such as mental retardation, dysmorphism, movement disorders, and visceral abnormalities. The recognition of metabolic causes of epilepsy requires a multidisciplinary approach and several investigations such as EEG, evoked potentials, neuroimaging (MRI-spectroscopy, SPECT), blood exams, urinary exams and CSF analysis. The diagnosis of metabolic disorders in epileptic patients may provide the possibility of specific treatments that can improve seizures.

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New Insights into Mechanisms Underlying Generalized Reflex Seizures

Edoardo Ferlazzo, Domenico Italiano, Sara Gasparini, Giovanbattista Gaspare Tripodi, Tiziana D'Agostino and Umberto Aguglia

Abstract "Apparently generalized" reflex seizures usually occur in the setting of idiopathic generalized epilepsies. Several animal, neurophysiological and neuroimaging evidences strongly suggest that such reflex seizures should be considered as focal with quick secondary generalization through cortico-reticular or cortico-cortical pathways. The aim of this article is to highlight mechanisms underlying "apparently generalized" reflex seizures provoked by intermittent light stimulations, reading, thinking and praxis.

Introduction

Reflex seizures are epileptic events triggered by specific motor, sensory or cognitive stimulations.

Currently, reflex epilepsies are defined as specific syndromes "in which all epileptic seizures are precipitated by sensory stimuli" (Engel 2001), excluding therefore reflex seizures occurring in the setting of focal and generalized conditions that are also associated with spontaneous seizures. Simple reflex seizures are evoked by simple, unstructured sensory stimuli. Complex reflex seizures are triggered by relatively elaborate stimuli, often with an emotional component, involving integration of higher cortical function. Latency from stimulus onset to the clinical seizure or evoked epileptic EEG activity is typically longer (minutes) in complex than simple reflex seizures (seconds) and, therefore, diagnosis can be challenging in the former. Eating, music, proprioceptive or somatosensory stimuli and hot water usually provoke focal seizures and will not be discussed in this review.

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The aim of this article is to highlight mechanisms underlying "apparently generalized" reflex seizures provoked by intermittent light stimulations, reading, thinking and praxis.

Seizures Induced by Visual Stimuli

Reflex seizures provoked by visual stimulation, especially flashing lights, are the commonest and well known. Photosensitive patients present seizures when exposed to environmental flicker (such as sun shining through trees and discotheque lights), or with more complex stimuli such as television and videogames. Seizures are commonly characterized by subtle eyelid myoclonus with or without impairment of consciousness, symmetric or asymmetric jerks of the arms or absence seizures. If exposure to stimulus persists, generalized tonic–clonic seizures (GTCS) may occur (Kasteleijn-Nolst Trenité 1989, 2012). The EEG usually shows a photoparoxysmal response (PPR) with intermittent photic stimulation (IPS); usually between 10 and 30 flashes per sec. Photosensitivity is more frequent in women and has an important genetic component with likely autosomal dominant inheritance with reduced penetrance. No major gene has been identified (Waltz and Stephani 2000; Stephani et al. 2004). Several loci probably underlie the trait, possibly with subtle differences in phenotypic expression. An interaction of several susceptibility genes and environmental factors cannot be ruled out (de Kovel CG et al. 2010).

Photosensitivity can occur in different epilepsy syndromes, the most frequent association being with idiopathic generalized epilepsies (IGE), especially with juvenile myoclonic epilepsy (JME) in which it is reported in 40–90 % of patients (Appleton et al. 2000). A continuum phenotypic spectrum, ranging from the generalized epilepsies to the idiopathic photosensitive occipital epilepsy has been postulated by Taylor et al. (2013). Shared genetic determinants between these two entities are likely to contribute to the complex inheritance pattern of photosensitivity. Visual stimuli can also induce focal seizures (Guerrini et al. 1994, 1995). Some subjects have idiopathic focal photosensitive occipital seizures (Guerrini et al. 1995).

Pattern sensitivity is characterized by seizures provoked by viewing environmental patterns such as escalator steps, striped wallpaper or clothing. Almost all these patients show a PPR to IPS.

Eye-closure sensitivity is a specific type of visual sensitive epilepsy in which brief, mainly generalized epileptiform changes appear in EEG within 2–4 s after closing the eyes. It is more common in females and may overlap with photosensitivity, even if eye-closure sensitivity is independent phenomenon. It may be seen in different epilepsy syndromes including Childhood Absence Epilepsy, Juvenile Absence Epilepsy (JAE), JME, Jeavons Syndrome (for review see Striano et al. 2009; Italiano et al. 2014). The paroxysmal activity underlying this phenomenon is unknown but it could be related to a mechanism of alpha rhythm augmentation (Sevgi et al. 2007).

Patients with all types of visually-induced seizures may self-induce attacks by compulsively repeated eye rolling and eyelid flicker movement, gazing at the sun ("sunflower epilepsy") or a bright light and moving one hand in front of the eyes (Tassinari et al. 1998). These patients may be either intellectually disabled or healthy photosensitive individuals. Other psychiatric conditions as obsessive-compulsive disorder may be present. Absences and myoclonic jerks are the most common seizure types in self-induction (Belcastro and Striano 2014).

After the 1997 Pokemon incident (Ishida et al. 1998), it was found that rapid changes of blue and red color frames elicit PPR more frequently than monochromatic ones, and that sensitivity to specific sequences of colors at certain frequencies may also play an important role in the generation of seizures (Tobimatsu et al. 1999). Animal and human data suggest that photosensitive patients have a predisposition to develop PPR due to hyperexcitability of the visual cortex (Ferlazzo et al. 2005). When appropriate stimuli reach the striate and parastriate areas activating a sufficient and critical amount of cortical tissue and inducing synchronization of neuronal activity, a local epileptic discharge is produced; the latter would rapidly involve the cortico-reticular or cortico-cortical pathways with propagation from the parieto-occipital areas and a generalized epileptic discharge (Ferlazzo et al. 2005).

Treatment involves a combination of preventive and pharmacological measures (Covanis et al. 2004). Avoidance of the stimulus (for example by looking away or covering one eye), watching television from a distance of at least 2 m and using a remote control to change channels are often effective precautions. Wearing a particular type of blue lens, named Z1, was found to be highly effective in controlling PPR in most of photosensitive patients (Capovilla et al. 2006). Viewing LCD/plasma screen is strongly suggested since they use a transistor for each pixel allowing the pixel to keep its state and they do not manifest flickering.

The most useful drugs are represented by valproate (VPA) (85 % of patients becoming seizure-free); benzodiazepines (clobazam or clonazepam) and ethosuximide can be given as second choice. Newer antiepileptic drugs such as lamotrigine (LTG) and levetiracetam may also be used (Italiano et al. 2014)

Seizures Induced by Non-Verbal Cognitive Stimuli

Seizures induced by thinking have been reported in response to mental activity such as calculation, or playing chess or similar games (Goossens et al. 1990). Seizures usually start during adolescence and consist of generalized tonic–clonic seizures, myoclonic jerks with or without absences and absences. Rare spontaneous seizures may occur in 76 % of patients. The EEG shows generalized epileptic discharges in 68 % of patients. Photosensitivity may occur. Activation by mathematics or spatial tasks is found in 72 %. Although there seems to be no mendelian inheritance, the family history is similar to that of patients with IGE (Goossens et al. 1990). The clinical pattern is also suggestive of IGE, especially JME or JAE. Unlike photosensitive patients, avoiding the triggering stimuli in this condition is not possible,

and the majority of these patients have seizures usually controlled by VPA or CNZ (Goossens et al. 1990).

Wilkins et al. (1982) stressed the importance of the spatial components of the task in inducing epileptiform abnormalities: complex multiplication and division with remainder were epileptogenic, while addition, subtraction and simple multiplication and division, thought to involve fewer spatial components, were not.

Inoue et al. (1994) reviewed 79 patients with seizures provoked by higher brain functions and emphasized the role of a motor component in seizure activation. They introduced the term 'praxis-induced epilepsy' for patients whose seizures are provoked by 'contemplating complicated spatial task in a sequential fashion, making a decision and practically responding by using part of the body'. This was also stressed by Matsuoka et al. (2000) who studied the effects of higher mental activity on the EEG of 480 patients with epilepsy, monitored during cognitive tasks. Thirty-eight patients (36 having IGE) had triggered generalized or bilateral epileptic discharges often associated with bilateral myoclonic jerks or absences. Cognitive tasks requiring the use of the hands, such as writing, were found to be more epileptogenic than higher mental activities not requiring hand movement, such as mental calculation (Matsuoka et al. 2000). Thus, thinking in a non-verbal way seems to be the essential triggering element in this form of reflex seizures.

Reading Epilepsy

Reading epilepsy (RE) is a rare syndrome characterized by involuntary jaw jerks that occur only while reading, and that may progress to a generalized tonic–clonic seizure (Ramani 1998). Seizures characterized by alexia, associated with focal EEG abnormalities, have been reported (Koutroumanidis et al. 1998). Family history of seizures occur in about 41 % of subjects. Age of onset is usually in adolescence and young adulthood with a slight preponderance in men. Interictal EEG is normal in 80 % of patients, spontaneous spike and wave discharges are present in 11 % and temporal paroxysmal discharges in 5 %. Reading provokes epileptiform discharges in 77 % of patients. Those abnormalities may be bilateral and symmetrical (32 %), bilateral but asymmetrical (38 %) or focal (30 %). Lateralization is more frequent to the language-dominant hemisphere preferentially over the temporo-parietal region.

Autosomal inheritance with incomplete penetrance overlapping with a genetic background for IGE was proposed for some families (Daly and Forster 1975). A recent combined EEG/fMRI study showed that precipitation of reading-induced seizures involves the activation of dominant motor and premotor areas, striatum and mesiotemporal/limbic areas (Salek-Haddadi et al. 2009).

The mechanism by which reading precipitates seizures is still obscure. The most relevant factor seems to be the transformation of the linguistic material from graphemes into language (Wolf et al. 1992). In many patients, reading aloud was more activating than silent reading. Some authors stressed the importance of emo-

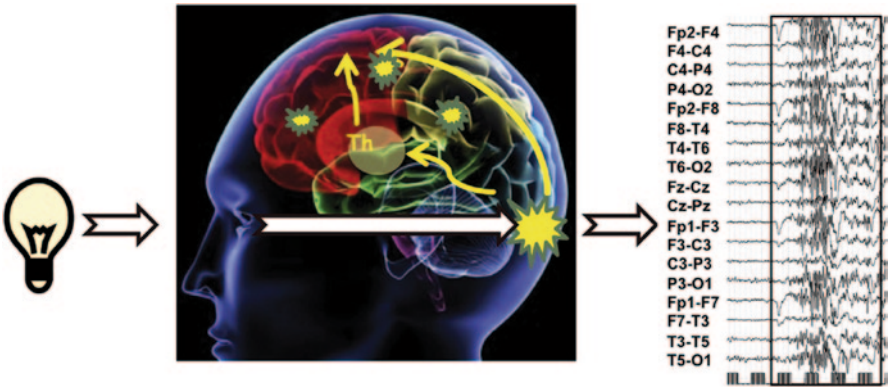

Fig. 1 *Example of "generalized" reflex seizures***.** Photic stimulation induces an initial occipital lobe epileptic discharge in a patient with JME. Diffuse or multifocal hyperexcitable areas accounts for quick secondary generalization through cortico-thalamic or cortico-cortical pathways, with the final appearance of a generalized epileptic discharge. *Th* = thalami. (Reprinted from Italiano et al. 2014, with permission from Elsevier)

tional involvement with the text (Critchley et al. 1959/1960) or its comprehension (Kartsounis 1988). However nonsense text or foreign languages may also be effective (Wolf 1992).

Most patients have seizures well controlled by VPA or CNZ, and only a few decide to prevent convulsive seizures by stopping reading as soon as seizures begin (Wolf et al. 1994).

Conclusions

"Generalized" reflex seizures usually occur in the setting of IGEs. Several animal, neurophysiological and neuroimaging evidences strongly suggest that "generalized" reflex seizures should be considered as focal with quick secondary generalization through cortico-reticular or cortico-cortical pathways. IGE-patients with "generalized" reflex seizures may have focal (i.e. occipital lobe in photosensitivity) or multifocal (i.e. dominant fronto-temporal lobes on reading epilepsy) areas of hyperexcitability that, when appropriately stimulated, give rise to an epileptic activity that quickly generalizes (Fig. 1; Italiano et al. 2014).

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Current Status and Future Prospective of Neuroimaging for Epilepsy

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Abstract Although the diagnosis of epilepsy remains mainly clinical, Magnetic Resonance Imaging (MRI) plays a crucial role in the detection of lesions that can cause epilepsy, with high impact on the diagnostic work-up as well as on therapeutic planning. Morphologic MR imaging is still the main technique for identifying lesions responsible for the epilepsy, providing images with high spatial resolution, excellent soft-tissue contrast, and multiplanar view. Quantitative MR image analysis (segmentation, voxel-based morhometry), based on 3D T1-weighted images, offers an objective means of analyzing MR images thereby improving the capability of detecting subtle lesions, often interpreted as negative by qualitative assessment of the morphologic MR imaging. Diffusion tensor imaging allows the quantification of water molecules diffusion and characterizes the degree and direction of anisotropy. Areas of abnormal diffusion, responsible for epilepsy, may be related to occult dysgenesis, or to acquired damage, resulting in neuronal loss, gliosis, and extracellular space expansion; these changes often result in reduced anisotropy and in an increase in mean diffusivity. Magnetic resonance spectroscopy provides information about the biochemical environment of the brain, thereby helping in lateralizing the epilepsy focus. Functional MR imaging is used for lateralizing language functions, and also for surgical planning predicting functional deficits following epilepsy surgery. The interpretation of MR data should always be done by a neuroradiologist expert in the field of epilepsy imaging, trying to correlate the images with clinical and electrophysiological data.

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Introduction

Modern neuroimaging techniques have had a major impact on our understanding of epilepsy. They provide high degree anatomical resolution and functional/metabolic information about the epileptic lesion, contributing to the proper classification of several epileptic disorders.

Magnetic Resonance Imaging (MRI) is a powerful tool in identifying epileptogenic tumors (gangliogliomas, DNETs, hypothalamic hamartoma, pleomorphic xanthoastrocytoma, etc.), vascular malformation (cavernous hemangiomas), severe developmental causes of intractable epilepsy (hemimegalencephaly, schizencephaly) and other syndromes that can lead to intractable seizures (neurocutaneous syndromes, such as Sturge-Weber syndrome and tuberous sclerosis). By using modern MR systems, that provide high image resolution and multiparametric reconstructions, it is often possible to recognize also small anatomical substrates responsible for epilepsy such as focal cortical malformations (focal cortical dysplasia, heterotopia, polymicrogyria) and hippocampal sclerosis. These are the most common causes of epilepsy, but they can be depicted only with a dedicated MR protocol; the sensitivity of MR imaging for such small structural abnormalities also depends on the experience of the interpreting physician (Widjaja and Raybaud 2008).

However, MRI is not always able to detect structural abnormalities in patients with seizures. Considering large case series of patients with intractable epilepsy, MRI showed a sensitivity from 82 to 86 % in identifying the epileptogenic substrate (Scott et al. 1999, Berg et al. 2000), while in children with a new diagnosis of epilepsy MRI detected epileptogenic substrates in only 13 % of cases (Bronen et al. 1996).

In recent years, new advanced MR imaging such as diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), quantitative MR imaging, functional MR imaging (fMRI), together with nuclear medicine procedures (positron emission tomography—PET and single-photon emission computed tomography-SPECT) have increased the sensitivity in the diagnosis of epileptic anatomical substrates and the knowledge of the mechanisms of seizures; moreover, in pre-surgical evaluation of epilepsy, the combined use of multiple imaging modalities for precise localization of the epileptogenic focus provides a better planning and ensures better surgical outcome.

The aim of this chapter is to provide an overview of structural and advanced imaging of epilepsy focusing on the best protocol tailored to the clinical diagnosis; in the second part, the MR appearance of the most important causes of epilepsy will be schematically described.

Imaging Modalities

Computed Tomography

Computed tomography (CT) uses ionizing radiation and can generate excellent hard tissue imaging contrast with moderately good soft tissue resolution. The advantages

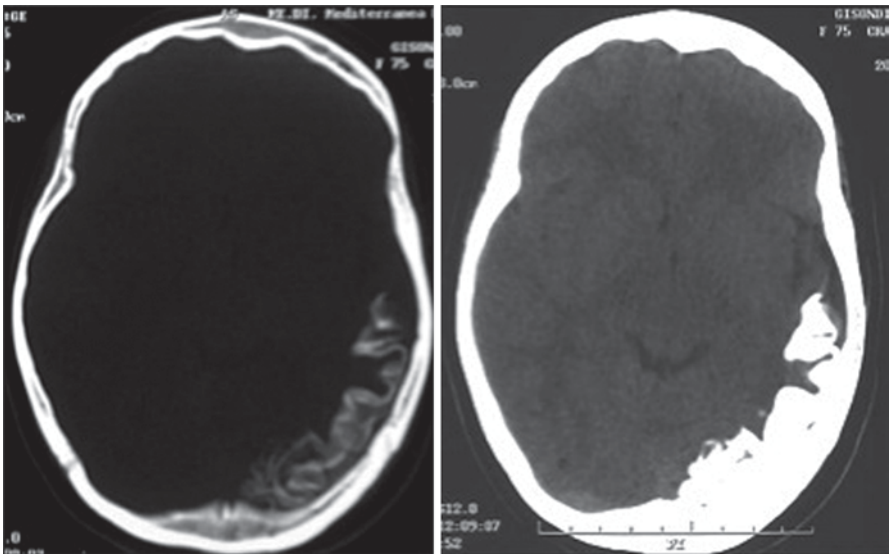

Fig. 1 CT scan of a patient with Sturge-Weber syndrome. Cortical and subcortical "*tram-track*" calcifications in the *left* posterior hemisphere are evident

of CT are wide accessibility, low cost, high speed (last CT generation can obtain a complete brain scan in few seconds) and thus it is considered a reliable brain imaging modality for most patients especially in emergency. CT can easily identify hemorrhage, infarctions, gross malformations, ventricular system pathologies, and lesions with underlying calcification (Trishit Roy and Alak 2011).

The sensitivity of CT in patients with epilepsy has not been found to be higher than 30 % in unselected patient populations (Hankey et al. 1989; Wyllie et al. 1989; Gastaut and Gastaut 1979). This is due to the low resolution of CT for detecting mesial temporal lobe sclerosis (the most common epileptogenic substrates in adults) and temporal epileptogenic tumors (such as gangliogliomas or DNETs).

The use of CT for patients with epilepsy has been greatly diminished by the availability of MRI. Even if sometimes CT scan is used in neonates and infants following a pathological ultrasound (Hankey et al. 1989; Wyllie et al. 1989), it is always better to use, if available, MRI (under sedation) to better characterize the brain abnormalities.

Moreover, the role of CT in the diagnosis of tuberous sclerosis, Sturge-Weber syndrome (Fig. 1), and other pathologies with intracranial calcifications remains complementary, because MRI provides more information (noncalcified tubers).

CT can be still considered the technique of choice in the postoperative evaluation of patients undergoing surgery for uncontrolled seizures, because it can rapidly detect early complications of surgery such as hemorrhage, hydrocephalus, and major structural changes (Trishit Roy and Alak 2011).

Table 1 Epilepsy MRI protocol.

GE 3D T1	Isotropic voxel < 1 mm
Axial FLAIR & T2	2–4 mm slice thickness
Coronal FLAIR/HR T2	In temporal lobe epilepsy: coronal sections perpendicular to the long axis of hippocampus, axial sections parallel to the long axis of hippocampus
3D FLAIR	Suspect of cortical dysplasia
Axial or coronal GE T2*/axial SWI	Suspect of cavernous hemangioma, occult calcified lesions
DWI/ADC	Water restriction: cytotoxic edema
Contrast-enhanced T1	Brain tumors, Sturge-Weber syndrome

Structural Magnetic Resonance Imaging

MRI is the imaging procedure of choice in the investigation of patients with epilepsy. The advantages of MRI include the use of nonionizing radiation, high sensitivity and higher specificity than CT, multiplanar imaging capability, improved contrast of soft tissue, and high anatomical resolution. The sensitivity of MRI in detecting abnormalities in patients with epilepsy is strictly dependent on the type of pathologic substrate of the epilepsy, on the MRI protocol used, and on the experience of the interpreting physician (Widjaja and Raybaud 2008). Clinical data and electroencephalographic (EEG) findings should always guide the interpretation of MR images.

An optimal MRI protocol in an epileptic patient should use sequences with the minimum slice thickness, covering the whole brain and providing a high contrast resolution (that is the ability to distinguish between differences in intensity in an image) (Opplet 2006).

The use of 3 Tesla MR scanners, providing a better image resolution, improves the evaluation of patients with focal epilepsy when compared to 1.5 Tesla scanners (Mueller et al. 2011), with an important impact in the correct presurgical identification of the epilectic focus and thus in the treatment.

A dedicated MRI protocol should include (De Cocker et al. 2012, Table 1):

1. **3D T1 images with ≤1.5 mm slice thickness,** useful in assessing cortical thickness and gray/white matter interface (Fig. 2) and reformattable in any orthogonal or nonorthogonal planes (Widjaja and Raybaud 2008). In order to better evaluate the cortical thickening in case of focal cortical dysplasia (FCD), some authors suggest to add curvilinear reformatting using 3D data (Widjaja and Raybaud 2008; Montenegro et al. 2002). The complexity of the brain gyration is not perfectly studied using the orthogonal planes only, since the plan of analysis can be oblique to some gyri, thereby leading to apparent cortical thickening and thus to a false-positive diagnosis of FCD. In these cases, a curvilinear reconstruction can be useful to clarify the nature of a suspect area of cortical malformation detected on orthogonal planes.

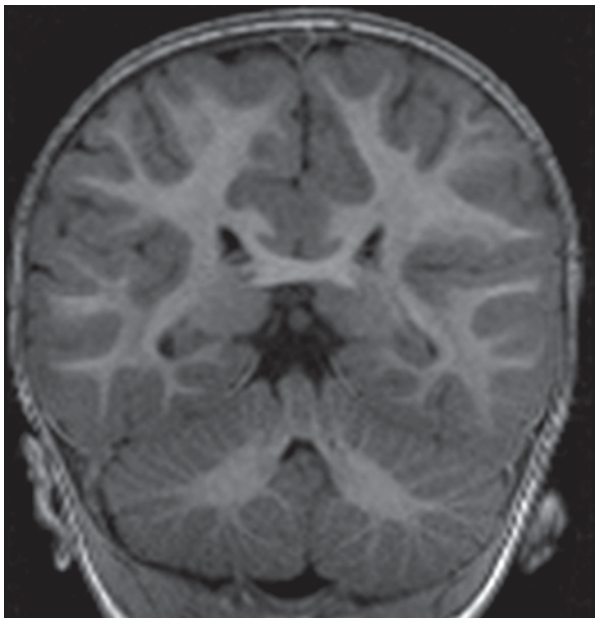

Fig. 2 3D T1 weighted image reformatted on coronal plane, with excellent *gray/white* matter contrast

In <2 year-old children, 3D T2 w images are preferred to better evaluate the white matter because of the still incomplete myelination;

2. **T2 and FLAIR images** in axial and coronal planes, necessary to detect subtle cortical and subcotical hyperintensities (focal cortical dysplasia, small tumors, gliosis, hippocampal sclerosis); it is important to note that the best way to detect the presence of hippocampal sclerosis is to orientate the axial T2 and FLAIR sections parallel to the hippocampal axis, and the coronal slices perpendicular to it;
3. **T2* gradient echo or susceptibility weighted images (SWI) images,** helpful for identifying hemoglobin breakdown products as in post-traumatic changes and cavernomas, or when searching calcifications in tuberous sclerosis, Sturge-Weber syndrome and gangliogliomas;
4. C**ontrast-enhanced T1 w images** (at least in two orthogonal planes) in case of brain tumors or Sturge-Weber syndrome;
5. **Diffusion weighted imaging** for the detection of foci of diffusion restriction consistent with cytotoxic ede ma or increased cellularity.

Some authors have proposed the use of **Double Inversion Recovery pulse sequence (DIR)** in case of suspected hippocampal sclerosis (Li et al. 2011). This sequence provides two different inversion pulses, which attenuates the cerebrospinal fluid (CSF) as well as the whole white matter, thus achieving a superior delineation between gray and white matter (Wattjes et al. 2007); it is considered superior to conventional MR sequences in the evaluation of subtle intensity changes in hippocampal sclerosis (Li et al. 2011).

Fetal MRI is a relatively new technique that provides increased diagnostic accuracy in the evaluation of fetal brain. This technique allows to detect small brain malformations very early during pregnancy, even not detectable by ultrasonography (US): a case of abnormal cortex and heterotopic gray matter has been described in a 24 weeks old fetus (Iaccarino et al. 2009).

Quantitative MR Imaging

Pathological examination of surgical specimens obtained in patients with intractable focal epilepsy and in whom the qualitative assessment of structural MR images was unconclusive, has shown the presence of subtle lesions such as loss of neurons, gliosis and microdysgenesis (cortical dyslamination and cytoarchitectural abnormalities) (Widjaja and Raybaud 2008; Al Sufiani and Ang 2012).

Quantitative volumetric analysis of MR images, usually performed by 3D T1-weighted images, can increase the sensitivity of MR in detecting epileptogenic foci especially in case of mesial temporal lobe epilepsy (TLE).

Volume reduction in hippocampus and in extrahippocampal regions has been demonstrated in mesial TLE (Guimaraes et al. 2007): a recent meta-analysis of voxel-based morphometry (VBM) studies on unilateral refractory temporal lobe epilepsy (Widjaja et al. 2012) showed significant reductions in ipsilateral mesiotemporal structures and in bilateral thalamus in both refractory left TLE and refractory right TLE. Bilateral abnormalities of frontal lobe and right cingulate gyrus were also found in the refractory left TLE patients, whereas right insular atrophy was found in the refractory right TLE group. Thus, quantitative MR imaging can depict the presence and laterality of hippocampal atrophy in TLE with accuracy rates, that may exceed those achieved with visual inspection of clinical MR imaging studies. Quantitative MR imaging can therefore enhance standard visual analysis, providing a useful and viable means for translating volumetric analysis into clinical practice (Farid et al. 2012)**.**

Volumetric abnormalities affecting the thalamus and the frontal lobe were also found in generalized epilepsy (Widjaja et al. 2012). Moreover, in children with new-onset seizures a significant reduction in cortical thickness has been reported (Widjaja et al. 2012), while no significant differences in hippocampal and thalamic volumes were observed, suggesting that structural changes in cortical gray matter may predispose the patients to seizures while other changes can be due to the cumulative effects of recurrent seizures.

Diffusion Tensor Imaging (DTI)

Diffusion MRI is a MR modality that allows the mapping of the diffusion process of molecules of water in human tissues.

In the brain, water diffusion is restricted by myelin, membranes and macromolecules; in the white matter, the diffusion is mainly parallel to the white matter tracts

and minimally perpendicular to them. This can explain the concept of **anisotropy** that expresses the asymmetric diffusion of water molecules in three dimensions.

Diffusion Tensor Imaging (DTI) allows the calculation of the degree and of the direction of anisotropy (Widjaja and Raybaud 2008).

From a mathematical point of view, DTI is a model of an ellipsoid that has a principal long axis and two more small axes. These three axes are perpendicular to each other and cross at the center point of the ellipsoid: the axes in this setting are called **eigenvectors** and the measures of their lengths **eigenvalues**; eigenvectors are the directions of the diffusion while each eigenvalue represents the magnitude of diffusion along each axis.

From a practical point of view, some diffusion parameters can be calculated in order to obtain information about the microstructural features of brain tissue: (1) the mean diffusivity (MD), that provides an evaluation of the magnitude of the diffusion motion in a voxel region and is measured in square millimeters per seconds; (2) the fractional anysotropy (FA), that is a scalar value between 0 and 1 that describes the values of the anisotropy. A FA value of 0 represents absence of anisotropy (the diffusion is isotropic) as in a perfect sphere, while a values of 1 represents maximal anisotropic diffusion.

Most acquired lesions and malformations of cortical development cause microstructural changes in the brain (reduction in cell denisity, impairment of normal myelin architecture, expansion of extracellular space), leading to reduced FA and increased MD (Widjaja and Raybaud 2008).

Several studies based on DTI in epileptic patients showed abnormal FA and MD.

Reduced FA was found in the white matter both ipsilateral and contralateral to the seizure focus (Widjaja et al. 2014); reduced FA and increased MD was found adjacent to cortical malformations visible on MR (Eriksson et al. 2001) and also beyond the margins of malformations detectable on MR imaging (Widjaja and Raybaud 2008) 'consistent with the EEG changes extending beyond the boundaries of focal cortical dysplasia visible on imaging, allowing a better surgical outcome' or distant from visible malformation of cortical development (Dumas de la Roque et al. 2005). Finally, significantly decreased FA values were observed in the cerebellum of patients with generalized tonic-clonic seizures (Li et al. 2010). The areas of abnormal diffusion detected using DTI in epileptic patients are thought to be caused by damage of the brain microstructure (neuronal loss, extracellular space expansion and gliosis) related to dysgenesis, acquired injuries or secondary to repeated seizures. For these reasons, DTI is considered a powerful tool in studying the anatomical substrates of epilepsy as well as the microstructural changes related to seizures. However the complexity of the analysis of the DTI data and the time-consuming post-processing limit the use of DTI parameters in routinary MR studies.

Finally, it is possible to obtain virtual 3D maps of eloquent white matter tracts (such as cortico-spinal tracts, optic radiations and arcuate fasciculus) by using DTI raw data (diffusion tensor tractography, Fig. 3); this technique is very useful in preoperative evaluation of epileptogenic lesions since it allows to localize white matter tracts and to assess their spatial relationship to the lesions (Lee et al. 2013).

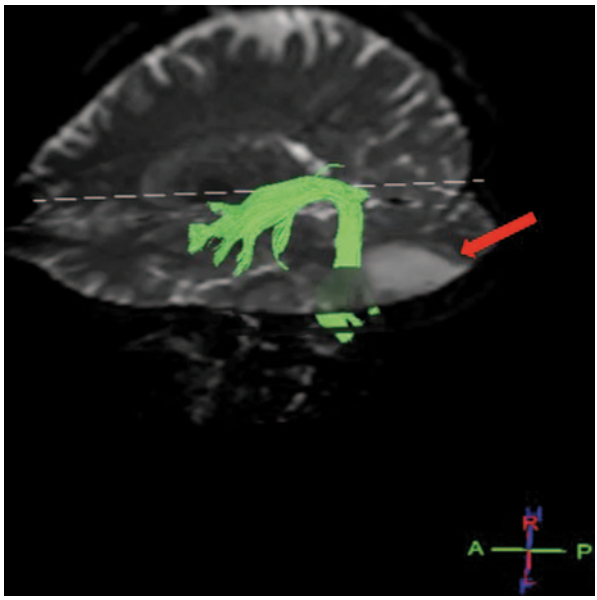

Fig. 3 Diffusion tensor tractography. 3D reconstruction of the left arcuate fasciculus (*green*) and its relationship with an epileptogenic tumor of the posterior temporal lobe (*red arrow*)

Magnetic Resonance Spectroscopy (MRS)

Magnetic resonance spectroscopy (MRS) is an analytical technique capable of evaluating the biochemical environment of the brain, and used to complement structural MRI in the characterization of tissues.

In clinical practice MRI uses signals from hydrogen protons (H^1) to determine the relative concentrations of target brain metabolites (Fig. 4). The most important brain metabolites assessed by MRS are: N-acetylaspartate (NAA), choline (Cho), creatine (Crea), lipids (Lip), lactate (Lac), glutamate-glutamine (Glx), Alanine (Ala) and myoinositol (Myo).

NAA is normally present in neurons and in axons and thus reflects the number of functioning neurons. Decrease in NAA levels indicates neuronal tissue loss or damage and axonal integrity loss.

Cho is a major component of cell membranes and the concentration of this metabolite provides information about cell density, membrane turnover and degree of myelination. An increase in Cho concentration indicates increase in cell production and/or membrane breakdown (brain tumors, demyelination).

Crea is a marker of cellular metabolism; it can be reduced in some pathological conditions such as lack of blood supply, but it can also be increased in response to cranio-cerebral trauma. However, because the concentration of Crea is relatively constant and is considered the most stable cerebral metabolite, it can be used as internal reference for calculating metabolite ratios.

Lac is not normally visible in MRS; when present, it indicates anaerobic metabolism (ischemia, hypoxia, necrotic brain tumors).

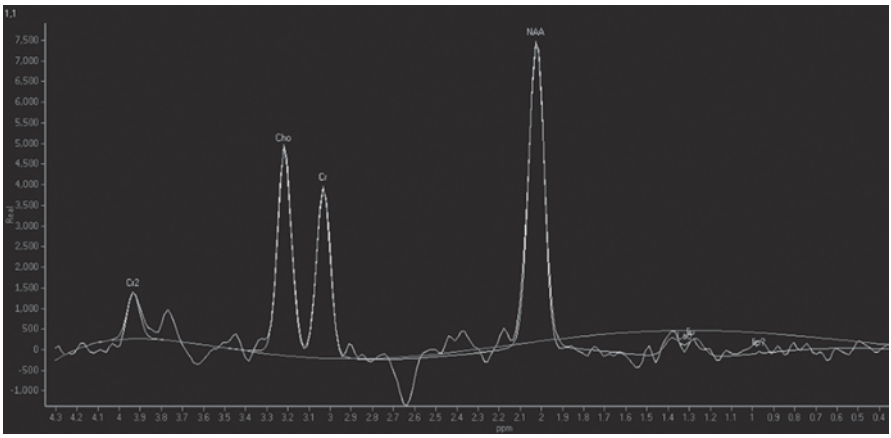

Fig. 4 Normal MRS of the brain (*single voxel, long TE*), placed in the white matter of the parietal lobe in a normal subject. Note the normal peak of NAA, higher than the Cho peak, and the absence of the pathological peaks of Lac and Lip

Lip are components of cell membranes normally not visualized on MRS. Lip peaks can be seen when there is cellular membrane breakdown or necrosis such as in metastases or primary malignant tumors.

Glx concentration reflects the glutamate concentration in glutamatergic neurons.

Ala is thought to play a role in citric acid cycle; increase of Ala concentration occurs in oxidative metabolism defects and in meningiomas.

Myo is a glial marker because is present almost exclusively in astrocytes. Myo may represent a marker of myelin degradation: elevated Myo is found in inflammation, gliosis, astrocytosis and in Alzheimer's disease.

Abnormalities on MR spectroscopy, such as reduced NAA and increased Cho levels, ipsilateral to EEG focus in patients with normal MRI findings (Widjaja and Raybaud 2008), have been used for lateralizing TLE: these results are consistent with loss of neurons, increased glial cells and neuronal dysfunction that are the pathological substrates of epilepsy. Another finding in TLE is high level of Glx, ipsilateral to the seizure onset, also in patient with "normal" MR (Savic et al. 2000).

For these reasons, MRS can play an adjunctive role in the presurgical evaluation of medically refractory TLE: by using reduced NAA/Cr ratios as a marker of neuronal loss, MRS agreed with the lateralization determined by EEG better than MR imaging volumetry alone (Caruso et al. 2013).

On the other hand, in extratemporal lobe epilepsy MRS was less specific in lateralizing the epilepsy focus (Widjaja and Raybaud 2008; Striano et al. 2008).

Abnormal metabolite concentrations have been found in patients with focal cortical dysplasia (FCD), correlating with the frequency of seizures, while normal NAA ratios have been found in patients with polymicrogyria and gray matter heterotopia (Widjaja and Raybaud 2008).

It is important to highlight that in case of FCD an abnormal spectrum is expected, because this is a malformation secondary to abnormal neuronal proliferation and differentiation.

Conversely, in case of polymicrogyria the neurons are more mature compared to FCD because this is a malformation related to abnormal cortical organization, while in gray matter heterotopias, a malformation due to abnormal migration, there is an increased number of neurons in an abnormal location. These features can explain the normal MRS findings in case of polymicrogyria and heterotopia.

Functional MR Imaging (fMRI)

Functional MRI (fMRI) is based on the quantification of the increased blood flow in areas of increased neuronal activity: this leads to a decreased oxyhemoglobin/deoxyhemoglobin ratio that is detectable using fMRI sequences (so called "BOLD" effect).

This imaging technique can be used for mapping neuronal activity during visual, language and sensorimotor activities in presurgical planning for epileptogenic lesions.

The understanding of the relationship between the areas of major neuronal activity and the epileptogenic lesion is useful to predict the post-surgical outcome and it is used for this purpose together with the location of main white matter tracts obtained using tractography.

In particular, a major role of fMRI is in lateralizing language functions in case of lesions that are close to language areas of the brain and in showing sensorimotor areas in case of lesions close to perirolandic cortex as this can predict possible language or sensorimotor deficits after surgery (Fig. 5).

In order to elicitate the BOLD effect numerous motor, sensory, verbal fluency and language comprehension tasks have been proposed and are widely used in clinical practice.

fMRI has also been used to probe the integrity of the functional connections among different brain regions, which can be detected when a subject is not performing an explicit task (resting-state fMRI, RS-fMRI) (Biswal 2012). Resting-state networks (RSNs) are the brain regions that exhibit spontaneous low-frequency synchronous fluctuations and represent brain functional connectivity. In particular, region-wise functional connectivity among the frontal, parietal, and temporal lobe, is normally present across the so-called Default-Mode Network (DMN, Fig. 6).

On the basis of PET, SPECT and EEG studies, epilepsy has been postulated to be a disorder of neuronal networks (Widjaja et al. 2013). Several studies have evaluated RSNs in patients with TLE epilepsy, generalized seizures, absence epilepsy and frontal lobe epilepsy revealing abnormal connectivity in different RSNs and negative correlation with epilepsy duration (Widjaja et al. 2013; Luo et al. 2011).

Therefore resting-state fMRI seems to be a promising technique to understand the pathological changes in neuronal connectivity in patients with different forms of epilepsy.

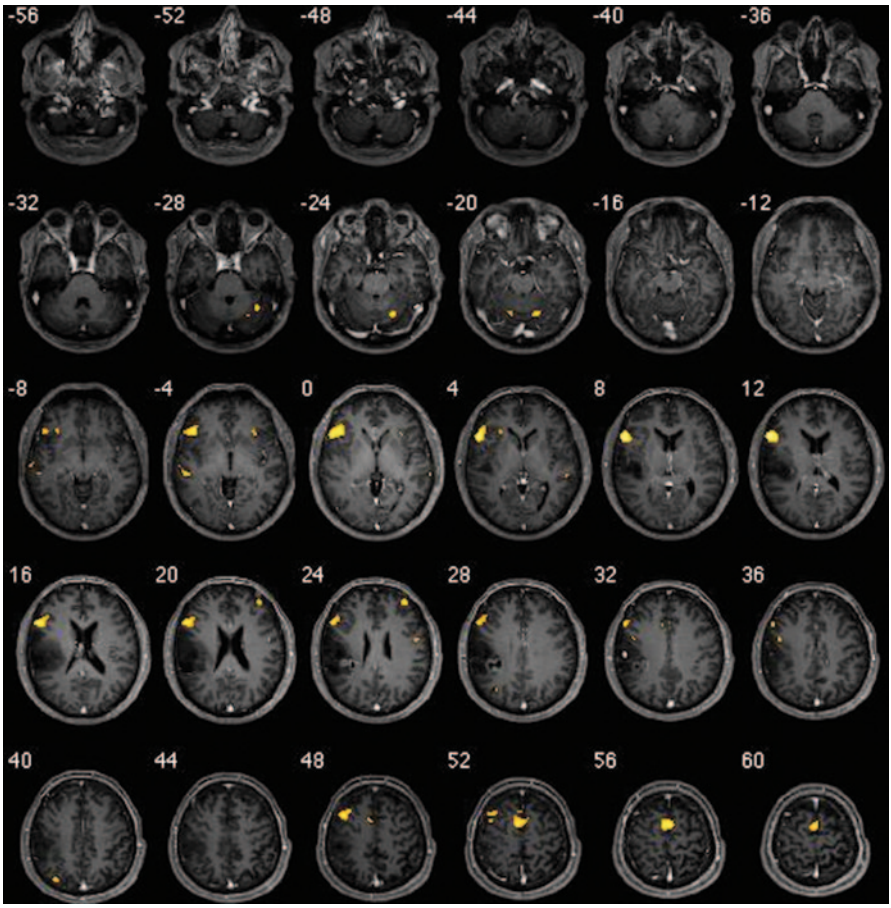

Fig. 5 fMRI (language task) after surgical excision of an epileptogenic tumor. Close relationship between the post-surgical cavity and the activation of the Broca's area, in the *left* inferior frontal gyrus

Positron Emission Tomography (PET)

The role of interictal PET with fluorodeoxyglucose (FDG-PET) is to determine the lateralization of the epileptic focus in the presurgical assessment of intractable epilepsy (Widjaja and Raybaud 2008). The spatial resolution of this technique is around 4 mm, therefore the images should be viewed side-by-side with MRI, or, even better, co-registered with MRI (Chugani et al. 1990).

The area of most severe glucose hypometabolism is tipically located in the site of ictal onset; however, the volume of hypometabolism is often widespread. This is the reason why FDG-PET hypometabolism can be used to lateralize the side of seizure onset and to determine the prognosis for complete seizure control only when it correlates with EEG recordings, MRI and/or clinical data (Widjaja and Raybaud 2008).

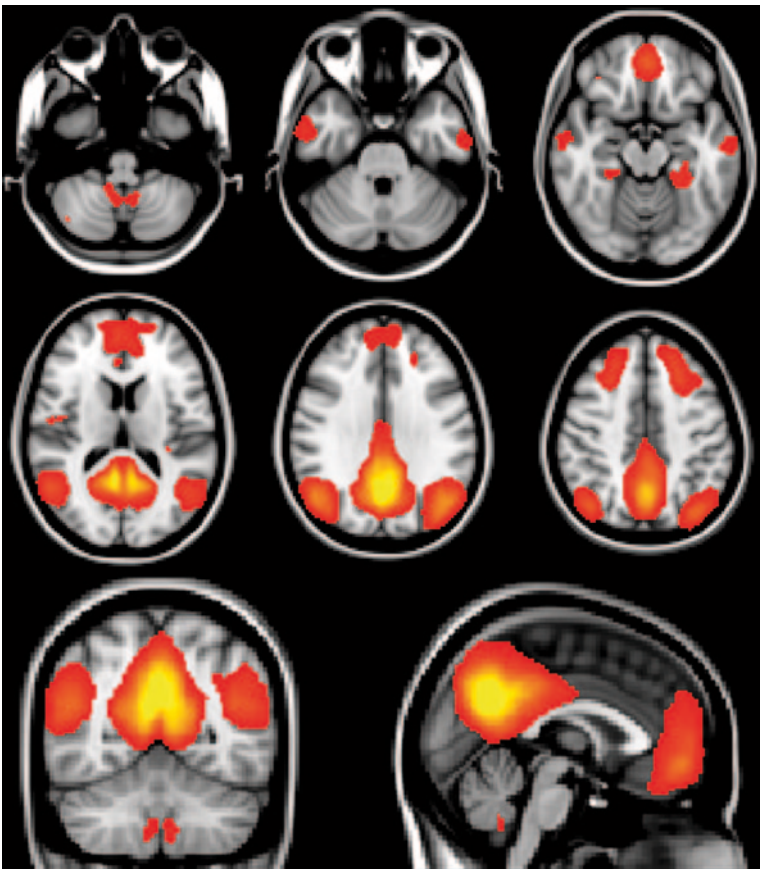

Fig. 6 Color map of the DMN as detected by Independent Component Analysis of the Resting-State fMRI data acquired at 3T in a group of 20 healthy subjects. The main components of the DMN in the inferior parietal regions, posterior cingulate and adjacent precuneus, as well as medial temporal and prefrontal cortices can be appreciated as *yellow-red* areas

In mesial TLE, interictal studies show hypometabolic areas in the epileptogenic regions in approximately 80% of patients; the changes, however, are more extensive than the structural and EEG abnormalities and may involve the lateral temporal lobe, ipsilateral frontal lobe, ipsilateral parietal lobe and basal ganglia (epileptic network) (Widjaja and Raybaud 2008; Pittau et al. 2014).

In extratemporal lobe epilepsy, interictal PET-FDG studies are less useful, especially if the MRI is normal and the scalp EEG is nonfocal. However, PET has been reported to be more sensitive in neonates and infants with focal seizures because of a possible developmental malformation. This is particularly the case in patients with infantile spasms and focal features on EEG. PET has also improved the understanding of the pathophysiology of infantile spasms by demonstrating activation of cortical regions, brainstem, and lenticular nuclei (Chugani et al. 1990).

The mechanisms underlying this hypometabolism in the epileptogenic cortex are still unresolved: it is thought that FDG-PET distribution reflects mainly synaptic activity, rather than cellular loss (Pittau et al. 2014).

In conclusion, the high sensitivity of MRI in detecting the anatomical substrates of epilepsy has diminished the role of FDG-PET in the presurgical investigation of such patients. Nevertheless, when MRI is normal, PET can be indicated to aid in localization or can be used as a guide for reviewing MRI in search for subtle overlooked cortical dysplasia or other epileptic substrates.

Single Photon Emission Computed Tomography (SPECT)

SPECT has been utilized in patients with epilepsy in the past decades, mainly using diffusible tracers for assessing brain perfusion (such as hexamethylpropylene amine oxime or ethyl cysteinate dimer). The main role of SPECT is to localize the epileptogenic zone when imaging and other non-invasive exams are unable to identify the site of seizure onset (Widjaja and Raybaud 2008).

Numerous studies using dynamic and static SPECT techniques in the ictal and interictal state have been published.

The ictal SPECT examination can identify focal hyperperfusion, while the interictal examination demonstrates hypoperfusion in the corresponding epileptogenic region. However, the diagnostic value of the interictal SPECT alone is poor, and a combined ictal/interictal SPECT study should be performed, possibly with subtraction of interictal images from the ictal ones and then coregistration with MR images, in order to achieve a better anatomical definition of the site of the seizure (Widjaja and Raybaud 2008).

Imaging of Epileptogenic Diseases

Mesial Temporal Sclerosis

The most useful MR sequences for detecting mesial temporal sclerosis (MST) are **coronal IR and/or 3D T1 weighted images,** that show a shrunken hippocampus associated with a widening of adjacent temporal horn and choroid fissure, and **coronal FLAIR (or T2)** that shows an increased hyperintensity and loss of the internal architecture of the involved hippocampus (Fig. 7a). Using 3D T1 weighted images it is also possible to detect the atrophy of the fornix and of the mamillary body ipsilateral to the affected hippocampus (Osborn 2013; Caranci et al. 2007; Iaccarino et al. 2009).

MRS typically shows a reduction of NAA (Fig. 7b) related to the neuronal loss both in hippocampal and extrahippocampal regions, while Cho and Cr are unchanged (Mueller et al. 2011).

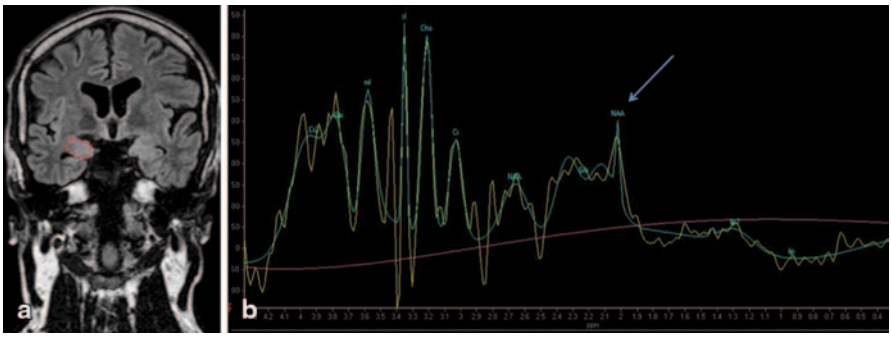

Fig. 7 Mesial temporal sclerosis. Coronal FLAIR image **a** shows mild atrophy and hyperintensity of the right hippocampus (*red box*); MRS **b** demonstrates a reduction of the NAA peak (*blue arrow*)

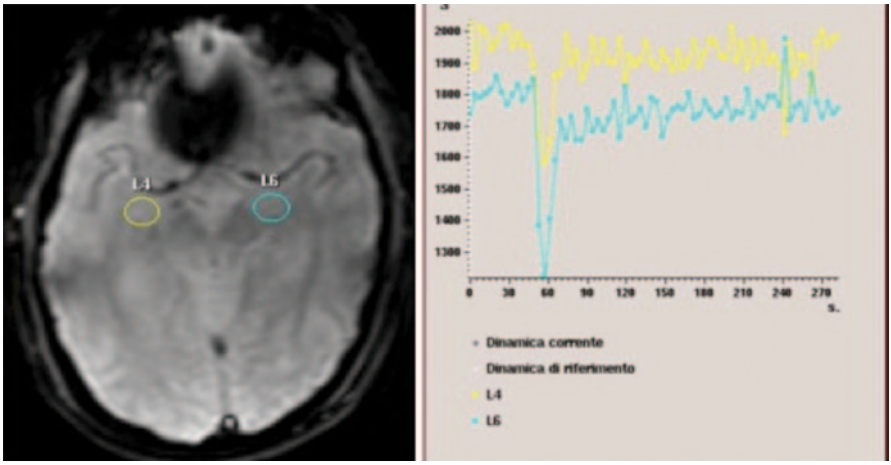

Fig. 8 Mesial temporal sclerosis. Quantitative PWI analysis in the same patient of Fig. 7 shows reduced perfusion in the right hippocampus (*yellow*) compared with the controlateral side (*blue*)

DWI shows increased diffusivity (high ADC values), while perfusion-weighted images show an interictal hypoperfusion of the affected side compared with the contralateral (Wolf et al. 2001; Fig. 8).

Volumetric analysis of hippocampi, parahippocampal giri and entorhinal cortex is used to quantify temporal lobe abnormalities in comparison with healthy controls; this is very useful in case of bilateral MST (Keller and Roberts 2007).

Finally, fMRI can be used in pre-operative planning to assess the language lateralizaton and the risk of memory disorders.

FDG-PET tipically shows hypometabolism in the affected temporal lobe in the interictal phase and is a very sensitive imaging modality for diagnosis of MTS (Osborn 2013).

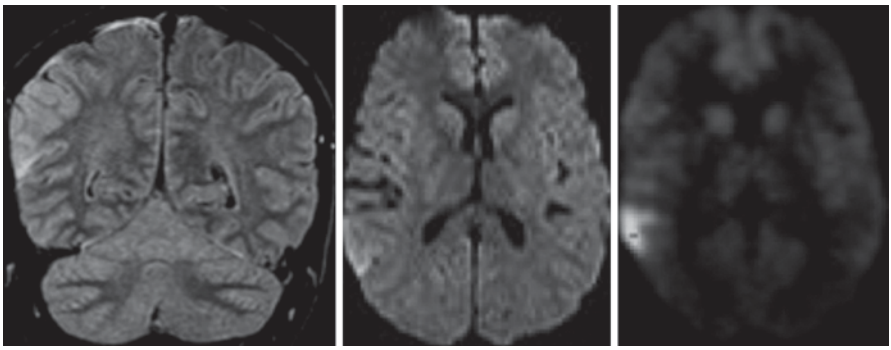

Fig. 9 Status Epilepticus. Coronal FLAIR image (**a**) showing hyperintensity and swelling of the temporo-occipital cortex; axial DWI (**b**) and FDG-PET (**c**) showing regional diffusion restriction and hypermetabolism, respectively

The differential diagnosis is with diseases that can cause seizures and FLAIR/T2 hyperintensity in the temporal lobe, including status epilepticus, characterized by gyral swelling instead of shrinking, and DWI/ADC restriction, and temporal lobe low grade glioma, that also causes mass effect instead of volume loss.

Status Epilepticus

MR findings of status epilepticus (SE) include T2/FLAIR hyperintensity and gyral swelling involving the gray matter (cortex, thalami, hippocampi) in a non-vascular distribution with sparing of both subcortical and deep white matter (Fig. 9).

Contrast enhanced T1 weighted images usually do not show any enhancement, only sometimes a variable enhancement of the gray matter; the acute phase is typically also characterized by restricted diffusion on DWI (low ADC values), hyperperfusion on PWI and hypermetabolism on FDG-PET.

Most of the MR findings in SE normalize in few days, however some patients can have permanent damage such as cortical laminar necrosis and brain atrophy (Osborn 2013; Milligan et al. 2009).

The major differential diagnosis is with cerebral ischemia, that typically shows a vascular distribution and involves both gray and white matter.

Focal Cortical Dysplasia

MR features of focal cortical dysplasia (FCD) depend on its type. The most common is FCD type II b, located most often at the bottom of a sulcus and histopathologically characterized by altered cortical layering, dysmorphic neurons and balloon cells. MRI of FCD II b shows: (1) focal cortical thickening (Fig. 10); (2) blurred interface between gray and white matter; (3) subcortical T2/FLAIR hyperintensity;

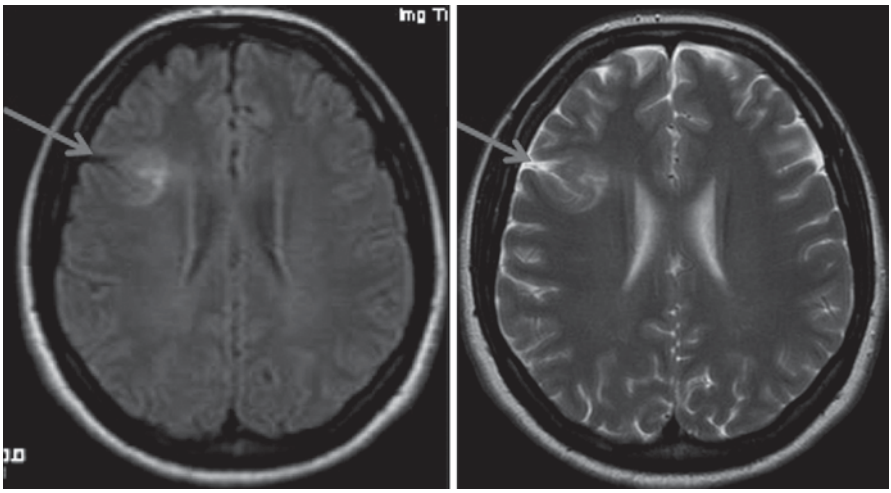

Fig. 10 Focal Cortical Dysplasia. Axial FLAIR **a** and T2 **b** images show thickening of the cortex at the bottom of a frontal sulcus with subcortical white matter hyperintensity (*arrows*)

(4) "transmantle sign" (not always present), i.e. a stripe of T2/FLAIR hyperintensity extending from the subcortical area to the margin of the ventricle due to a defect of neuronal migration (Fig. 11; Colombo et al. 2009).

CT scan is only able to detect the presence of calcifications associated with FDC (possible but rare).

The differential diagnosis of FCD includes cortically-based tumors associated with seizures such as dysembryoplastic neuroepithelial tumors (DNET), gangliogliomas and oligodendrogliomas.

MRS has been proposed as a reliable tool for differentiating FCD from a neoplasm, showing a reduced NAA/Cr ratio and no elevation in Cho/NAA (Widjaja and Raybaud 2008; Caruso et al. 2013) in the former.

Other advanced techniques can be used in the assessment of FDC: PWI shows increased perfusion in the area of FCD (Wintermark et al. 2013), while DTI can demonstrate microstructural abnormalities of the white matter extending beyond the main lesion seen on MRI (Widjaja and Raybaud 2008; Fonseca Vda et al. 2012).

Polymicrogyria and schizencephaly

Polymicrogyria (PMG) is a malformation due to abnormal late neuronal migration and cortical organization. PMG can be unilateral o bilateral and is located more often around the sylvian fissure (particularly in its posterior part), although it has been reported in any part of the cerebral cortex (Barkovich 2010).

MR findings of PMG include at least three possible aspects of the cortex (Barkovich 2010):

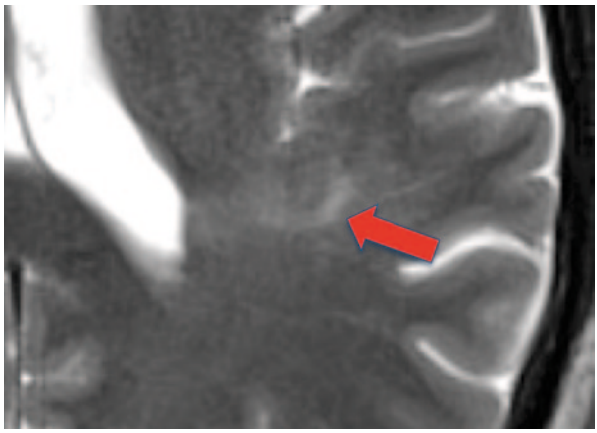

Fig. 11 "Transmantle" sign. T2w image shows a hyperintense stripe extending from the subcortical area to the margin of the ventricle due to a defect of neuronal migration (*red arrow*)

1. cortical surface with multiple small, delicate gyri;
2. thick and bumpy cortex;
3. "paradoxically" smooth cortex.

Moreover, an irregular gray/white matter interface is always present (Fig. 12a).

Sulci at the level of PMG are shallow or flat, and T2w and post-contrast T1w images can show enlarged pial veins overlying PMG (Barkovich 2007).

MRS shows relatively normal NAA ratios (Widjaja and Raybaud 2008). Using DTI it is possible to demonstrate abnormalities in the white matter underlying the polymicrogyric areas (Fig. 12b; Bonilha et al. 2007).

CT can show periventricular calcifications in case of PMG associated with congenital cytomegalovirus infection.

FDG-PET in the interictal phase can show hypometabolism in the PMG and surrounding areas (Fig. 12c; Barkovich 2007).

Schizencephaly is a disorder of neuronal migration and cortical organization, consisting in an abnormal hemispheric cleft that connects the ventricle with the subarachnoid space. Typical feature of schizencephaly is dysplastic gray matter lining its lips (PMG, pachigyria or normal-sized gyri).

Heterotopic Gray Matter

Heterotopic foci of gray matter are collections of nerve cells in abnormal locations secondary to the arrest of normal migration of neurons along the radial path between the ventricular walls (ependyma) and the subcortical regions (Bentivoglio et al. 2003).

Heterotopic gray matter may have different morphologies, but the most common are (Guerrini et al. 2006):

1. subependymal (periventricular nodular heterotopia, PVNH);
2. focal subcortical (FSH).

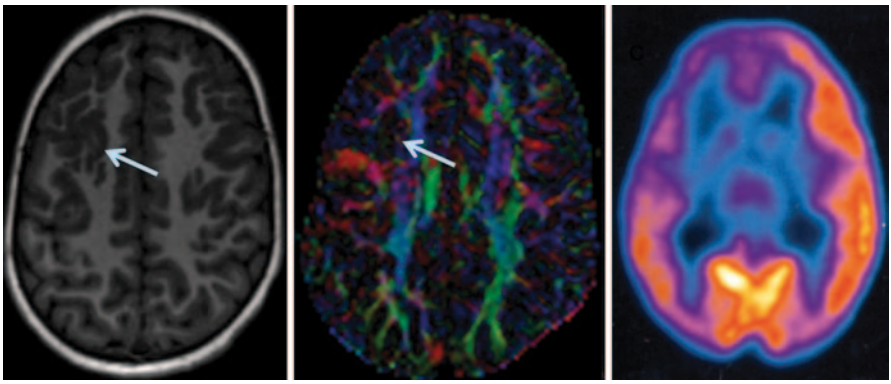

Fig. 12 Polymicrogyria. Axial 3D T1w (**a**) and DTI color map (**b**) show PMG in the left frontal lobe with associated abnormalities in the underlying white matter (*arrows*). FDG-PET (**c**) shows area of hypometabolism in the left frontal lobe

In both types, CT may rarely show dysplastic calcifications.

On MRI sequences heterotopic gray matter foci are always isointense to gray matter with distinct or blurred margins. They do not enhance after administration of contrast agents (Barkovich and Raybaud 2012).

PVNH are usually smooth, round or ovoid masses sometimes exophytic, protruding into the adjacent lateral ventricle (Wieck et al. 2005; Fig. 13).

Focal subcortical heterotopia are usually large and heterogeneous masses, which may appear as multinodular or composed of swirling, curvilinear bands of gray matter, extending from the cortex to the ventricles, and often containing blood vessels and CSF (Lim et al. 2005).

MRS may show elevated creatine and choline with normal NAA (Marsh et al. 1996), but the NAA/Cr ratio may be variable, ranging from normal to low (Li et al. 1998).

PWI, in some cases, can identify areas of hyperperfusion, and fMRI usually shows activated areas responding to stimuli just like the normal cortex (Lange et al. 2004), suggesting the participation of heterotopic cortex to integrated functional networks (Guerrini et al. 2004).

FDG-PET may show hypermetabolism or glucose uptake similar to the normal cortex (Barkovich 2007).

PVNH can be differentiated from subependymal hamartomas occurring in tuberous sclerosis, which are irregular in shape with the long axis perpendicular to the ventricular walls, are iso-hypointense on MRI sequences to white matter and enhance after intravenous infusion of contrast agents.

FSH must be differentiated from tumors, which enlarge the affected hemisphere, and are associated with normal overlying cortex and surrounding edema (Barkovich and Raybaud 2012).

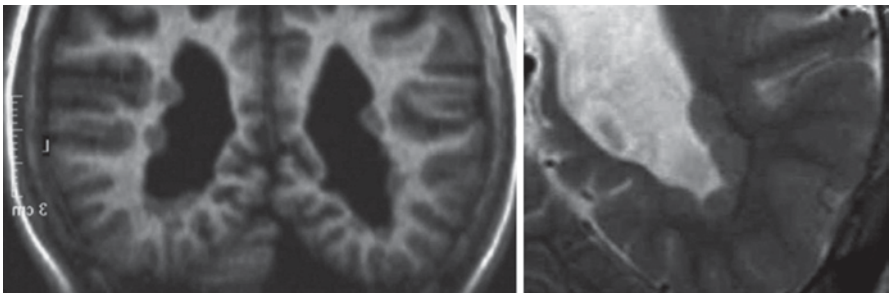

Fig. 13 T1 3D and enlarged T2 images show heterotopic gray matter nodules of subependymal heterotopia (PVNH)

Lissencephalies

The term lissencephaly means "smooth brain" and refers to the paucity of gyral and sulcal development on the surface of the brain. In lissencephaly, the cerebral cortex is abnormally thick, usually measuring 10–15 mm (Francis et al. 2006).

Lissencephalies include:

1. classical lissencephaly (type I lissencephaly);
2. subcortical band heterotopia (SBH).

They are part of a malformative complex, the agyria-pachygyria-band spectrum.

Classic lissencephaly may be complete or incomplete with absent (agyria) or decreased (pachygyria) surface convolutions, respectively (Sicca et al. 2003).

CT scan rarely shows small midline septal calcifications (Barkovich 2007).

MRI findings include (Sicca et al. 2003; Barkovich 2007):

1. smooth brain surface;
2. diminished white matter;
3. shallow and vertically oriented Sylvian fissure, configuring a figure-of-eight appearance of the cerebrum on axial images;
4. the cell-sparse zone, which is a zone of white matter separating a thin outer cortical layer from a thick deeper cortical layer.

Additional abnormalities include: hypoplasia of the corticospinal tracts, heterotopia of the inferior olives, and mild dysplasia of the cerebellar cortex.

On T1w and T2w sequences it is possible to distinguish gray and white matter layers and to identify the cell-sparse zone as areas appearing hypointense in T1w hyperintense in T2w (Barkovich 2007).

SBH is the mildest form of classic lissencephaly. In SBH, the cerebral convolutions appear either normal or mildly broad, but just beneath the cortical ribbon a thin band of white matter separates the cortex from the bands of gray matter (Fig. 14). Band heterotopia may be complete or partial. In T2w sequences, it is sometimes possible to identify foci of hyperintensity in white matter, associated with a poor motor outcome (Gleeson et al. 2000; Mai et al. 2003).

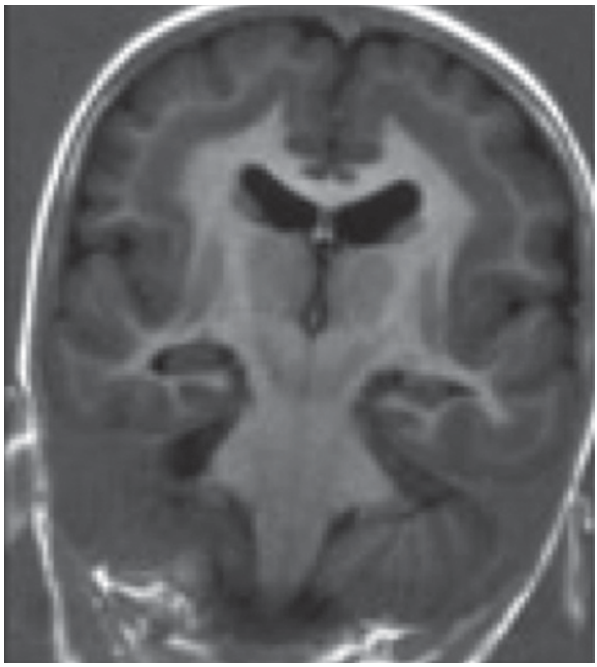

Fig. 14 Coronal T1 weigthed shows subcortical band heterotopia.

MRS may identify decreased levels of NAA in the affected cortex (Barkovich 2007). FDG-PET may show glucose uptake similar to or greater than normal cortex (De Volder et al. 1994).

Differential diagnosis include lissencephaly variants (without cell-sparse zone) and bilateral and diffuse subependymal heterotopia.

Tuberous Sclerosis

Tuberous sclerosis, or tuberous sclerosis complex (TSC), belongs to the group of the phakomatoses and involves primarily the central nervous system, the skin and the kidney (Luat et al. 2007).

The characteristic brain lesions are (Jahodova et al. 2014):

1. cortical tubers;
2. subependymal nodules (SEN);
3. subependymal giant cell astrocytomas (SEGAs);
4. white matter abnormalities.

Cortical tubers are the most characteristic lesions of tuberous sclerosis and they are most commonly supratentorial, appearing as pyramidal-shaped gyral expansions.

On CT scans, cortical tubers in neonates and infants appear hyperdense, while in children and adults they may be difficult to identify if they are not calcified (Kalantari and Salamon 2008).

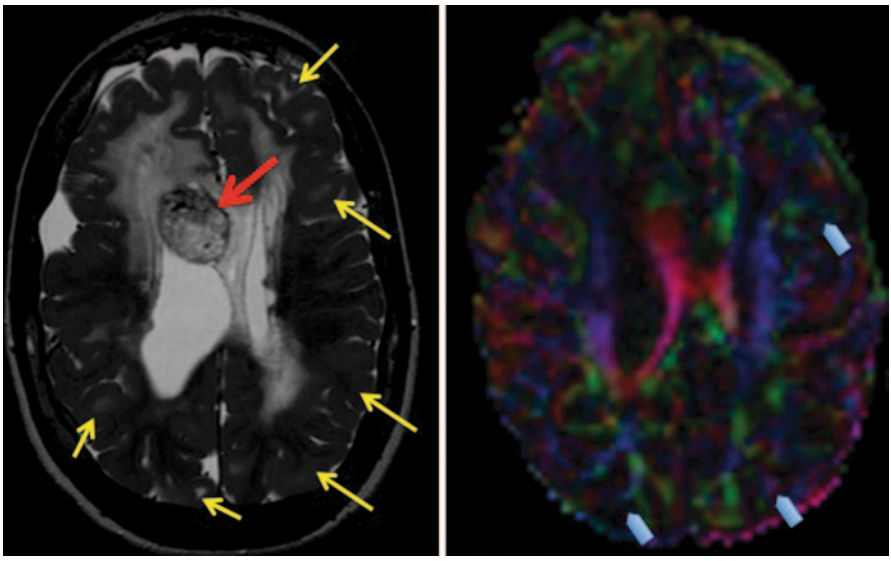

Fig. 15 Axial T2 weigthed and DTI FA color map show subependymal giant cell astrocytoma (SEGA) in the right foramen of Monro (*red arrow*) surrounded by oedema, and multiple cortical tubers (*yellow arrows*). In the DTI FA color map, decreased anisotropy of the tubers (*arrowheads*), compared with normal white matter, can be appreciated

The MRI appearance also changes with ages, as white matter myelinates, and cortical tubers may have different imaging patterns called "gyral core" and "sulcal island". In neonates they are hyperintense in T1w and hypointense in T2w sequences compared to unmyelinated white matter. In older infants and children, they become hypointense in T1w and hyperintense in T2w and FLAIR sequences, the latter being the most sensitive sequence for the detection of tubers in children and in adults (Kalantari and Salamon 2008).

When cortical tubers calcify, they may appear hyperintense on T1w images. Generally, they do not enhance after administration of contrast medium (Jahodova et al. 2014; Kalantari and Salamon 2008).

On DWI and DTI, they have increased diffusivity and decreased anisotropy compared to normal white matter (Peters et al. 2013 Fig. 15).

MRS has been proposed as a reliable tool for the differential diagnosis of cortical tubers versus neoplasms, especially when cortical tubers are solitary. In cortical tubers, MRS shows normal to slightly elevated levels of choline and slightly diminished levels of NAA, while neoplasms have marked elevation of choline and marked diminution of NAA, with an increased peak of myo-inositol (Kalantari and Salamon 2008; Jahodova et al. 2014). However, low-grade tumors may have MRS findings similar to tubers. In these cases, PWI may be helpful: most cortical tubers are generally hypoperfused compared to gray matter (Jahodova et al. 2014).

SEN are the most common brain hamartomas in tuberous sclerosis. They are more frequently located along the ventricular surface of the caudate nucleus.

On CT scans they may be difficult to identify in infants, but become more easily and progressively detected as they calcify (Barkovich 2007).

On MRI, their appearance changes as the surrounding white matter myelinates. In neonates they are hyperintense on T1w and hypointense on T2w sequences, while they become more isointense to gray matter with age and are better identified on T1w images. If they calcify, they may appear hypointense on T2*w GE or susceptibility-weighted images. After intravenous administration of contrast material, SEN show variable enhancement; they also have increased diffusivity and reduced fractional anisotropy compared to surrounding white matter (Luat et al. 2007).

SEGA is an enlarged subependymal nodule, usually located near the foramen of Monro. Their incidence in TSC is 5–10 % and they may result in a clinical presentation of hydrocephalus, as they tend to enlarge (Barkovich 2007).

On imaging studies, SEGAs are identified by the demonstration of tumor growth on serial studies or by the development of hydrocephalus associated with tumor near the foramen of Monro. They tend to grow into the ventricle and rarely infiltrate the adjacent nervous tissue: in this case, they frequently have degenerated into high-grade neoplasms (Barkovich 2007).

The major differential diagnosis of TSC include subependymal heterotopia, TORCH and Taylor type cortical dysplasia.

Sturge-Weber Syndrome

Sturge-Weber Syndrome (SWS) is a sporadic phakomatosis characterized by angiomatosis involving the face (port-wine stain), the choroid of the eye and the leptomeninges. Venous occlusion and ischemia lead to angiomatosis with cortical calcium deposition and atrophy (Barkovich 2007).

CT findings include gyral and subcortical calcifications, occurring exclusively in brain areas near the angioma (Barkovich 2007).

MRI in patients with Sturge-Weber can show (Juhász et al. 2007b):

1. atrophy;
2. high signal on T2WI due to gliosis;
3. low signal in areas with calcifications;
4. leptomeningeal enhancement (Fig. 16).

On MRI, in neonatal cases, the white matter appears hypointense on T2w images in the affected hemisphere because of “accelerated” myelin maturation. The affected hemisphere becomes progressively atrophic with hyperpneumatization of the paranasal sinuses, thick diploe, and enlarged ipsilateral choroid plexus (Juhász et al. 2007b).

Calcifications may be identified on SWI or T2*w GE images as a thin ribbon of low signal intensity adjacent to the cerebral cortex in the affected areas. SWI sequences appears superior also in assessing the enlarged transmedullary veins, the pathological periventricular veins and the cortical gyriform abnormalities (Wu et al. 2011).

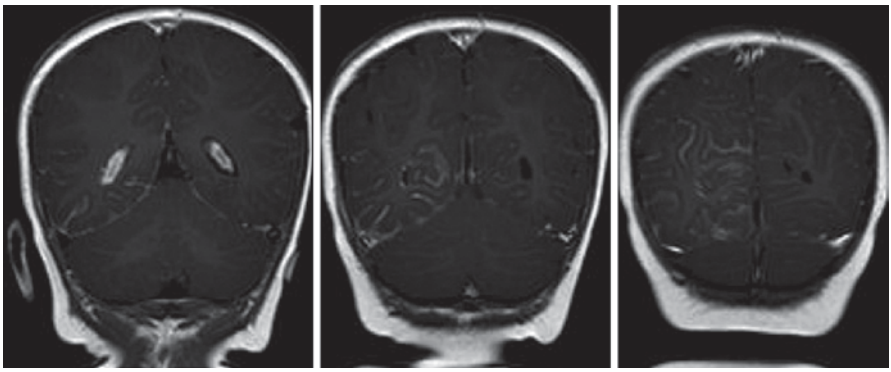

Fig. 16 Coronal contrast-enhanced T1of leptomeningeal angiomatosis involving the right occipital lobe, a feature consistent with Sturge-Weber Syndrome

After gadolinium administration, subcortical, leptomeningeal, and choroidal serpentine T1 hyperintensity is the rule, due to the enhancement of the pial angiomatous malformation mainly localized in the occipital lobes (Barkovich 2007; Juhász et al. 2007a).

PWI may be useful in detecting cerebral hypoperfusion of the brain underlying the enhancing pial angioma, due to impaired venous drainage (Miao et al. 2011).

MRS of the affected brain regions reveals reduced NAA, elevated choline and lactate (Batista et al. 2008).

FDG-PET shows hypermetabolism in the affected area in the early stages with subsequent hypometabolism, and it may be useful in surgical planning of cortical resection for intractable seizures (Juhász et al. 2007a).

For the differential diagnosis, it is important to consider leptomeningeal enhancement and other neurocutaneous syndromes.

Hemimegalencephaly

Hemimegalencephaly is a rare disease characterized by hamartomatous growth of one cerebral hemisphere or part of it.

Associated findings include macrocephaly and somatic hemihypertrophy of the body.

On CT and MRI, part or all of a hemisphere may be affected (Flores-Sarnat 2002).

The most typical findings are (Kamiya et al. 2013):

1. enlarged hemisphere with ipsilateral ventriculomegaly (Fig. 17);
2. abnormal gyral pattern with broad gyri, shallow sulci, blurring of the cortical-white matter junction and cortical thickening;
3. thickened cortex with a wide spectrum of abnormalities, such as lissencephaly, pachygyria or polymicrogyria;

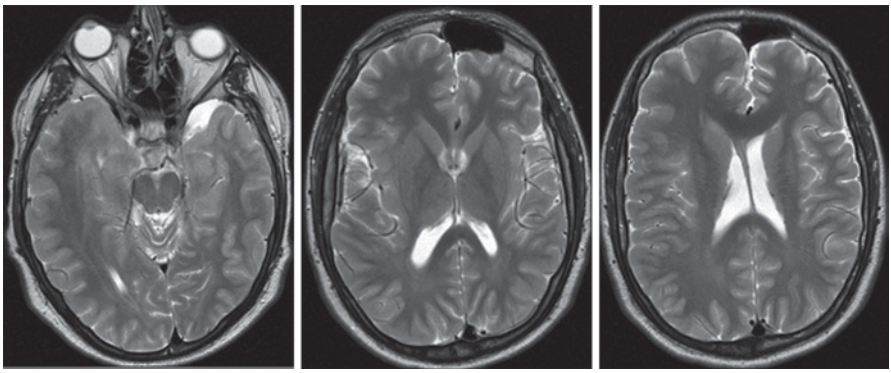

Fig. 17 Axial T2 weighted images showing right hemimegalencephaly

4. abnormal white matter, frequently hypodense on CT scans and heterogeneous on T2w MRI images, due to heterotopia and dysplastic neurons;
5. resultant midline shift.

In the late stage, the involved hemisphere may be atrophic due to constant seizure activity.

MRS shows reduction of NAA and glutamate peaks in the affected white matter, correlated to a diminished metabolic activity on FDG-PET (Flores-Sarnat 2002).

Ganglioglioma

Gangliogliomas are rare tumors, accounting for 3 % of all pediatric brain neoplasms, and 6–7 % of supratentorial tumors in children. Affected patients usually present in their second decade of life (Barkovich and Raybaud 2012).

Ganglioglioma typically involves the cortex of the cerebral lobes, especially the temporal lobe (85 % of cases), and is the most common tumor associated with temporal lobe epilepsy (Barkovich and Raybaud 2012).

The most typical imaging findings are (Barkovich and Raybaud 2012):

1. presentation as a cyst with enhancing mural nodule (although it may be entirely solid);
2. calcifications in up to 50 %.

On CT scan, gangliogliomas appear as hypodense, well circumscribed lesions with calcifications and little edema, tipically located within the cerebral cortex. Solid portions of the tumor may appear isodense, hypodense or mixed, with variable contrast enhancement. Erosion of the adjacent inner table of the calvarium may occur when the ganglioglioma is located peripherally (Gelabert-González et al. 2011).

On MRI, the ganglioglioma may have sharply or poorly defined margins. It may be solid, cystic, cystic with mural nodule or multi-cystic. It is usually hyperintense on T2w sequences and heterogeneous on T1w. The solid portion of the lesion may enhance (Barkovich 2012).

Differentiation from DNET and pleomorphic xanthoastrocytoma is difficult and calcifications are important distinguishing factors (Raz et al. 2012).

Dysembryoplastic Neuroepithelial Tumor (DNETs)

DNET are benign lesions of the cerebral cortex and are the cause of 20 % of the cases of medically refractory epilepsy in children and young adults (Ozlen et al. 2010).

The key findings on imaging are (Barkovich and Raybaud 2012):

1. swollen gyrus;
2. bubbly cystic appearance;
3. wedge-shaped and pointing toward the ventricle;
4. usually no or only little enhancement;
5. association with focal cortical dysplasia.

On CT studies, DNETs are quite well-demarcated, lobulated cortical lesions hypodense to white matter. Calcifications are present in one third of the cases and erosion of the inner table of the calvarium may be observed (Ozlen et al. 2010).

On MRI, DNET in typical cases present as a bubbly mass which expands the affected gyri. The bubbly cystic appearance is seen as small cyst-like intratumoral structures that are very hyperintense on T2w sequences and hypointense on T1w sequences, with a variable signal on FLAIR images (from hypointense to hyperintense). Diffusivity is elevated compared to the normal gray and white matter. Contrast enhancement is seen in 20–40 % of the cases and is usually patchy (Barkovich and Raybaud 2012).

MRS shows no significant difference of the metabolite ratios from normal cortex, while PWI reveals lower CBV than normal cortex (Ozlen et al. 2010; Barkovich and Raybaud 2012).

Furthermore, DNETs are metabolically inactive tumors with no significant glucose uptake on FDG-PET (Barkovich and Raybaud 2012).

Hypothalamic Hamartoma (HH)

Hypothalamic hamartoma is also known as diencephalic or tuber cinereum hamartoma.

It represents nonneoplastic congenital grey matter heterotopia in the region of tuber cinereum of the hypothalamus. It is seen in infants presenting with epilepsy (gelastic type) and precocious puberty (Mittal et al. 2013; Chung et al. 2012).

A clinical-topographical classification by Valdueza et al. (Valdueza et al. 1994) distinguished 4 types of HH:

1. Ia hamartomas, small lesions with a peduncolated attachment to the tuber cinereum, generally asymptomatic;
2. Ib hamartomas, small peduncolated masses attached to a mammillary body, usually associated to precocious puberty;

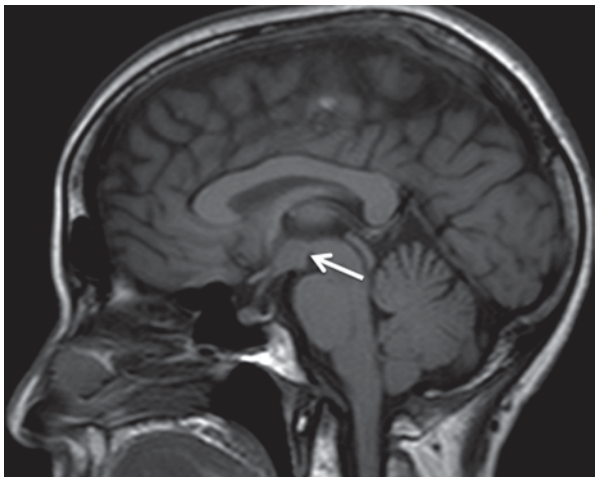

Fig. 18 Sagittal T1 weighted image shows a II A hypothalamic hamartoma (*arrow*)

3. IIa hamartomas, sessile masses (larger than 1.5 cm in diameter) attached to the floor of the third ventricle and mammillary bodies, typically presenting with gelastic seizures;
4. IIb hamartomas, large sessile masses (larger than 1.5 cm in diameter) distorting the walls and the floor of the third ventricle, associated with mental and behavioral disorders in addition to gelastic and mixed epilepsy.

CT studies are sensitive only in detecting large hamartomas, which appear as homogeneous, hypodense rounded masses, without contrast enhancement (Chung et al. 2012).

MRI represents the gold standard imaging modality. The MRI appearance is that of a well defined, round or ovoid mass lying within the hypothalamus (Fig. 18). HH are isointense on T1w sequences compared to gray matter and isointense to slightly hyperintense on T2w images. No enhancement is seen after contrast administration (Amstutz et al. 2006).

Reports in the literature suggest that on MRS the myo-inositol is higher and NAA lower than in the adjacent thalamus, probably due to astrogliosis (Martina et al. 2003).

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The Complex Relationship Between Epilepsy and Headache and the Concept of Ictal Epileptic Headache

Pasquale Parisi

Key Points

- Headache/migraine is often associated with epilepsy in children, as a pre-ictal, ictal, post-ictal or inter-ictal phenomenon.
-Epidemiological aspects of the co-morbidity between epilepsy and headache are clearly different in children and adults.
- Headache as a symptom, with migraine characteristics and/or tension-type headache characteristics, may be the only clinical ictal manifestation of an epileptic seizure: this condition is now classified as "ictal epileptic headache".
- In particular, according to published criteria, the term "ictal epileptic headache" must be used in cases of a headache/migraine attack as the sole clinical ictal symptom of epileptic origin, confirmed by ictal-EEG recording and clinical-EEG responsiveness to intravenous antiepileptic drugs.
- EEG is not recommended as a routine examination for children diagnosed with headache, but is mandatory and must be carried out promptly in cases of prolonged migraine/headache that does not respond to antimigraine drugs and in which epilepsy is suspected.
- This is not a marginal question, because these possible, isolated, non-motor, ictal manifestations (i.e. ictal epileptic headache) should be taken into account before declaring an epileptic patient as "seizure free" so as to be able to suspend anticonvulsant therapy safely.

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Summary

The possible link/comorbidity (causal or not causal) between epilepsy and headaches has been a topic of debate for over a hundred years, ever Since William Richard Gowers's time. In recent decades, new data have emerged in favor of a non-random relationship between these two entities. They are both characterized by transient attacks of altered brain function with a clinical, pathophysiological, genetic and therapeutic overlap, and may thus mimic each other. Indeed, the clinical distinction between headache and epilepsy may make the differential diagnosis a highly challenging task. Both are common and often co-morbid, with headache attacks in epilepsy being temporally related to the occurrence of epileptic seizures as a pre-ictal, ictal, post-ictal or inter-ictal event. Yet, they are both paroxysmal and chronic neurological disorders that share many clinical and epidemiological aspects, and they may both present with visual, cognitive, sensitive-sensorial and motor signs/symptoms; these neurophysiologicl phenomena arise from the cerebral cortex and are modulated by sub-cortical connections. Even from an epidemiological point of view, data in the literature regarding the co-morbidity between headache and epilepsy appear to be quite distinct in children. What makes this scenario even more variegated and complex are new data suggesting that a headache may, in some cases, even be the only ictal manifestation of an epileptic seizure. The latter condition, the so-called "ictal epileptic headache", is a new entity that has recently been cited in the new classification of headache disorders (ICHD-III), whose diagnostic criteria have very recently been defined and published. The data that have led, over the last decade, to the proposed "diagnostic criteria" for "ictal epileptic headache" are reported below. In this regard, it is crucial to stress that the authors who proposed the diagnostic criteria for ictal epileptic headache, have deliberately and consciously chosen "criteria" that underestimate the phenomenon so as to avoid spreading panic among both patients and physicians, who tend to be reluctant to accept this concept because of the stigma attached to the diagnosis of epilepsy. In the future, once this concept (i.e. "headache" as the sole ictal epileptic manifestation) has been more widely accepted, it will hopefully be possible to propose "different and less restrictive" criteria than those recently published.

Abstract Since William Richard Gowers' time, for over a hundred years, it has been discussing the possible link/comorbidity (causal or not causal) between epilepsy and headaches. During the latest decades, new data have emerged in favor of a non-random relationship between these two entities. They are both characterized by transient attacks of altered brain function with a clinical, pathophysiological, common genetic factors and therapeutic overlap, thus, they may also mimic each other. In fact, the clinical distinction between headache and epilepsy can be so difficult to make the differential diagnosis sometimes highly problematic. Both are common, often co-morbid and, in this latter case, headache attacks can be temporally related with the occurrence of epileptic seizures as pre-ictal, ictal, post-ictal

or inter-ictal phenomenon. Yet, they are both paroxysmal and chronic neurological disorders that share many clinical and epidemiological aspects, and they may, both, present with visual, cognitive, sensitive-sensorial and motor signs/symptoms; these neurophysiologic phenomenon arise from the cerebral cortex and are modulated by sub-cortical connections.

Even from an epidemiological point of view data from the Literature about the co-morbidity between headache and epilepsy seem to be clearly different in children.

In addition, to make this scene even more variegated and complex, new data, supporting the possibility that a headache may even be, in some cases, "*the only ictal manifestation of an epileptic seizure*", became available. This latter condition, the so-called "Ictal Epileptic Headache", is a new entity that has recently been quoted in the new classification of headache disorders (ICHD-III, third edition, published in July 2013 in Cephalalgia), whose diagnostic criteria have also been suggested and published very recently.

Here it have been reported, in their essential aspects, the available data that during the latest decade have led to propose "diagnostic criteria" for "Ictal Epileptic Headache". In this regards, in particular, it is crucial to stress that the Authors who proposed the diagnostic criteria for the "Ictal Epileptic Headache", have "deliberately" and "consciously" chose to formulate "criteria" that underestimate the phenomenon rather than to spread the "panic" among patients and physicians who are reluctant to accept this concept because the stigma attached to the diagnosis of epilepsy. In the future, when this concept (an "headache" as sole ictal epileptic manifestation) will be "metabolized", we will be able to propose "different and less restrictive" criteria than those recently published.

Keywords Ictal epileptic headache (IEH) · Epilepsy · Migraine headache · Autonomic seizures · Autonomic status epilepticus · Criteria for IEH diagnosis

Epilepsy and Headache: Diagnostic Challenges and Their Reasons

Clinical Issues

Both occipital seizures and migraine/headache may be characterized by the presence of a transitory visual disturbance that follows headache and other autonomic symptoms. A mis-diagnosis of visual seizures as migraine with visual aura is frequent and costly. The main factor that contributes to such an error is that the description of a visual hallucination is often limited to terms such as scintillations, fortification spectrum, teichopsia, phosphenes, and variations of these signs (Panayiotopoulos 1987, 1999a, b, c). Elementary visual hallucinations of occipital seizures are usually different from the visual aura of migraine. "Ictal" elementary

visual hallucinations are defined according to color, shape, size, location, movement, speed of appearance, duration, frequency and associated symptoms of progression. Elementary visual hallucinations are mainly colored and circular, develop within seconds, and are brief in duration (2–3 min); they often appear on the periphery of a temporal visual hemi-field, becoming larger and multiplying in the course of the seizure, frequently moving horizontally toward the other side (Panayiotopoulos 1987, 1999a, b, c). Significantly, post-ictal headache, which is often indistinguishable from migraine, occurs in more than half of patients, even after brief visual seizures. Post-ictal headache frequently occurs 3–15 min after the seizure ends, in a situation known in migraine as the "asymptomatic interval". Thus, occipital seizures often generate migraine-like attacks, i.e. an "epilepsy-migraine sequence" (Panayiotopoulos 1987, 1999a, b, c). In migraine, visual aura usually starts as a flickering, uncolored, zigzag line in the center of the visual field and affects the central vision. It gradually spreads over 4 min toward the periphery of one hemi-field, and usually lasts < 30 min, often leaving a scotoma. The total duration of visual auras is less than 60 min. Furthermore, migraine visual aura rarely occurs daily, and is not associated with non-visual ictal occipital symptoms, such as eye and head deviation and repetitive eyelid closures. Less typical features of migraine visual aura, such as spots, circles and beads, with or without colors, maybe experienced during migraine visual aura, though they are rarely dominant. Clustering of other symptoms, such as those described above, betray their migraine nature (Panayiotopoulos 1987, 1999a, b, c).

Electroencephalographic Issues

Children with a definitive diagnosis of epilepsy may not have epileptic EEG abnormalities recordable from the scalp (for example, as may occur in some cases of "nocturnal frontal lobe epilepsy", Nobili 2007), whereas EEG abnormalities that resemble paroxysmal abnormalities (usually present during an epileptic seizure) may be recorded during a migraine attack.

In general, EEG is of less diagnostic importance in the study of patients suffering from migraine. However, the temporal and spatial pattern of EEG anomalies in headache is usually extremely different from that observed during a real epileptic seizure (Andermann 1987; Andermann and Zifkin 1998). In the few cases of ictal epileptic headaches reported in the literature, the patients had headache/migraine as the only manifestation of a non-convulsive epileptic seizure, diagnosed on the basis of an EEG recording alone (Parisi et al. 2007, 2012a, b, 2013a, b; Parisi 2009a, b, 2011; Parisi and Kasteleijn-Nolst Trenité 2010). Intravenous administration of AEDs in these patients was able to control the seizure, as demonstrated by means of a scalp EEG as well as resolution of the headache symptoms (Parisi et al. 2012a, b). However, some isolated cases of "ictal epileptic headache" reported in the literature were incidentally detected when the critical focus was being recorded by means of deep electrodes (Laplante et al. 1983; Fusco et al. 2011). Therefore, although the EEG recording may not prove very useful as a screening instrument for migraine,

it does play a fundamental role in pediatric patients who have headache/migraine symptoms that do not respond to commonly-used anti-migraine drugs (Parisi et al. 2012a, b).

Furthermore, the ictal EEG abnormalities recorded in IEH patients display aspecific features; indeed, various ictal EEG patterns have been recorded during migraine-like complaints in both symptomatic and idiopathic cases (Belcastro et al. 2011a, b; Parisi et al. 2012a, b).

Epidemiological Issues: Beyond the Controversial Evidence

An "editorial" dedicated exclusively to these epidemiological aspects, to their possible biases and to the underestimation potentially related particularly to pediatric age has recently been published (Belcastro et al. 2012).

The prevalence and incidence of co-morbid epilepsy and headache in the general population, including all stages of life, vary (Olafsson et al. 2005). Indeed, headache predominates in males before puberty, whereas it is more common in females afterwards. By contrast, epilepsy predominates in males at all ages (Olafsson et al. 2005). The age at the peak incidence of these two conditions also differs. The peak age for migraine occurs during the working years (Lyngberg et al. 2005), whereas for epilepsy it is under the age of one year and over the age of 60 years (Hauser et al. 1993). The fact that data in the literature on this topic are somewhat conflicting (Lipton et al. 1994a, b; Andermann 1987; Tonini et al. 2012) may be attributed to the co-occurrence (synergistic and/or divergent) of confounding variables adopted in the different sampling methods and study designs. These conflicting results may partly be explained by differences in the target populations, study design, age range, methods, by inclusion criteria that are limited to referral patients with epilepsy or tertiary headache centers, by the lack of appropriate control groups, and/or by different or ill-defined diagnostic criteria (Tonini et al. 2012). Thus, these studies cannot easily be compared with one another.

Although there is not yet any conclusive evidence of a real causal relationship between the two disorders, we must bear in mind that the comorbidity of headache and epilepsy is, beyond any doubt, different in children and in adults. Children are more likely to have an autonomic symptomatology in both epilepsy and headache attacks (Fogarasi et al. 2006; Kasteleijn-Nolst Trenité and Parisi 2012). Moreover, they may have isolated, long-lasting ictal autonomic manifestations, while ictal autonomic manifestations (in both epilepsy and headache) in adults are usually associated, whether simultaneously or sequentially, with other motor or sensory ictal signs and symptoms (Fogarasi et al. 2006; Kasteleijn-Nolst Trenité and Parisi 2012). Furthermore, it should be borne in mind, despite the limited number of studies in the literature (Yamamane et al. 2004; Piccinelli et al. 2006; Toldo et al. 2010), that the framework assumes markedly different shapes in the pediatric population.

Among 50 children with epilepsy, Yamamane et al. (2004) found that 46 % had headache, and that 10 (43.5 %) out of the 23 headache sufferers had migraine. Most

patients with headache were older than 10 years (54.5%) and had idiopathic epilepsy (65.2%). In some specific childhood epilepsy syndromes, migraine/headaches appear to be more prevalent (Kinast et al. 1982; Bladin 1987; Andermann and Zifkin 1998; Panayiotopoulos 1999b; Yankovsky et al. 2005; Wirrell and Hamiwka 2006; Clarke et al. 2009). The best known of these syndromes are benign occipital epilepsy of childhood with occipital paroxysms and benign rolandic epilepsy; remarkably, in the majority of the cases reported (95%), the headache started in the same year as, or after, the diagnosis of epilepsy (Andermann and Zifkin 1998; Panayiotopoulos 1999b; (Ito et al. 1996, 2003, 2004; Leniger et al. 2001; Toldo et al. 2010; Verrotti et al. 2011a).

Piccinelli et al. (2006) found EEG interictal abnormalities in 16 (12.8%) out of 137 children and adolescents with headache, particularly in those with migraine with aura. Another intriguing issue is the comorbidity of headache in patients with idiopathic epilepsy of infancy. Indeed, it is widely known that patients with epilepsy with rolandic or occipital paroxysms, or even those without seizures, have concomitant migraine in up to 60% of cases (Panayiotopoulos 1999a, b, c; Tonini et al. 2012). When they investigated a large, consecutive, pediatric population of 1795 patients with headache under 18 years of age diagnosed at a headache center, Toldo et al. (2010) found a strong association between migraine and epilepsy. In that study, migraineurs displayed a risk for epilepsy that was 3.2 times higher than that for tension-type headache, with no significant difference between migraine with and without aura. Migraineurs affected by focal epilepsies had a risk for cryptogenic epilepsy that was three times higher than that for idiopathic epilepsy. Recently, adolescents with any headache type were reported (Lateef et al. 2012) to have significantly higher rates of epilepsy, as previously confirmed by Baca et al. (2011), who found the comorbidity of migraine and epilepsy in 15% of the children they studied. Interestingly, Colombo et al. (2011), whose data confirmed previous findings (Sasmaz et al. 2004) showing that almost 36% of parents of children with headache are unaware of the headache, stressed that pediatric headache is still under-diagnosed and is not adequately considered as a health problem either by the medical community or in social settings: on the one hand, this indicates the extent to which headache is underestimated, on the other, it confirms that the clinical picture in co-morbid cases is dominated by the diagnosis of epilepsy.

In recent years, following several reported cases of headache as the sole manifestation of an epileptic seizure (Parisi et al. 2007, 2008a, b, 2012a, b; Parisi 2009a, b; Parisi and Kasteleijn-Nolst Trenité 2010; Belcastro et al. 2011a, b; Verrotti et al. 2011b), the term ictal epileptic headache has been proposed to identify these events (Parisi 2011, 2012a, b). In particular, ictal epileptic headache is recognized as a headache ("as the sole ictal manifestation" and without presenting a "specific" clinical picture of migraine, migraine with aura or tension-type headache), lasting from seconds to days, with evidence of ictal epileptiform EEG discharges, which immediately resolve upon administration of intravenous antiepileptic medications (Parisi et al. 2012a).

In conclusion, although controversial epidemiological data in adults are often used as evidence that no association exists between these two conditions,

some studies, particularly those conducted in pediatric populations, point to the comorbidity of headache and epilepsy. Thus, further studies on larger pediatric populations are warranted to definitively confirm this comorbidity (Belcastro et al. 2012).

Shared Pathophysiology, Classification and Genetic Aspects

Common Pathways, Substrates and Genetics

Many studies support the hypothesis of excessive neocortical cellular excitability as the main pathological mechanism underlying the onset of attacks in both diseases (Somjen 2001; Berger et al. 2008). Indeed, since hypo- and hyper-excitation in migraine occur sequentially as rebound phenomena (during a spreading depression), the term "dys-excitability" may better describe migraine pathophysiology than hyper-excitability (Somjen 2001; Berger et al. 2008; Tottene et al. 2009, 2011; Fabricius et al. 2008; Parisi et al. 2012a, b). Cortical Spreading Depression (CSD), which may be considered the link between headache and epilepsy (Moskowitz et al. 1993; Bolay et al. 2002; Ayata et al. 2006; Ayata 2010; Parisi et al. 2008a, b; Parisi 2009a, b; Eikermann-Haerter & Ayata 2010; Belcastro et al. 2011a, b; Zhang et al. 2011; Parisi et al. 2012a; Ghadiri et al. 2012), is characterized by a slowly propagating wave of sustained strong neuronal depolarization that generates transient intense spike activity, followed by neural suppression, which may last for minutes. The depolarization phase is associated with an increase in regional cerebral blood flow, whereas the phase of reduced neural activity is associated with a reduction in blood flow. On the other hand, CSD activates the trigeminovascular system, inducing the cascade release of numerous inflammatory molecules and neurotransmitters, which results in pain during the migraine attack (Zhang et al. 2011, Parisi et al. 2012a, b).

There is emerging evidence from both basic and clinical neurosciences that cortical spreading depression and an epileptic focus may facilitate each other, though to different extents (Parisi et al. 2008; Parisi 2009a, b; Belcastro et al. 2011a, b, c; Parisi et al. 2012a). When a certain threshold is reached, the onset and propagation of neuronal depolarisation are triggered in both CSD and a seizure. The required threshold is presumed to be lower for CSD than for a seizure, which would explain why it is far more likely to observe an epileptic patient who presents a peri-ictal headache than a migraine patient who presents an epileptic seizure (Verrotti et al. 2011b, c; Parisi et al. 2012a, b).

Once the cortical event has started, spreading subsequently depends on the size of the onset zone, velocity, semiology and type of propagation (Parisi et al. 2008; Parisi 2009b). Moreover, the onset of both CSD and that of the epileptic seizure may facilitate each other (Berger et al. 2008; Fabricius et al. 2008; Zhang et al. 2011; Parisi et al. 2012b), with these two phenomena possibly being triggered by

more than one pathway converging upon the same destination: depolarization and hyper-synchronization (Parisi et al. 2008, 2012a; Parisi 2009a,b; Belcastro et al. 2011a, b; Ghadiri et al. 2012). The triggering causes, which may be environmental or individual (whether genetically determined or not), result in a flow of ions that mediate CSD through neuronal and glial cytoplasmic bridges rather than through interstitial spaces, as instead usually occurs in the spreading of epileptic seizures (Gigout et al. 2006; Parisi et al. 2008; Parisi 2009b; Tamura et al. 2011; Tottene et al. 2009, 2011). As mentioned above, the threshold required for the onset of CSD is likely to be lower than that required for the epileptic seizure. In this regard, a "migraleptic" event would be unlikely to occur (Belcastro et al. 2011a; Verrotti et al. 2011b; Parisi et al. 2012b).

As regards the role of "photosensitivity" in this topic, it should be stressed that flashes, phosphenes and other positive or negative visual manifestations are often part of the clinical picture in both headache and occipital epilepsy (Wendorff et al. 2005; Kasteleijn-Nolst Trenité and Parisi 2012). Moreover, intermittent photic stimulation (IPS) induces "flashes and phosphenes" as well as migraine/headache and seizures. Moreover, IPS may induce photoparoxysmal EEG responses (PPR), migraine and epileptic seizures (Kasteleijn-Nolst Trenité and Parisi 2012). Although occipital lobe epilepsy already has much in common with migraine (visual aura, positive and negative ictal signs, and autonomic disturbances such as pallor and vomiting), the photosensitive variant of occipital epilepsy, and photosensitive epilepsy in general, share even more similarities, such as a higher prevalence in women (female/male ratio 3:2) and a sensitivity to flickering light stimuli and striped patterns that induce attacks (Kasteleijn-Nolst Trenitè et al. 2010a, b).

Both migraine and epilepsy have an important genetic component, with strong evidence pointing to a shared genetic basis between headache and epilepsy emerging from clinical/EEG and genetic studies on Familial Hemiplegic Migraine (FHM) (Haglund and Schwartzkroin 1990; De Fusco et al. 2003; Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009, 2011; Gambardella and Marini 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010; Uchitel et al. 2012). Errors in the same gene may be associated with migraine in some cases and with epilepsy in others. Recent data suggest shared genetic substrates and phenotypic–genotypic correlations with mutations in some ion transporter genes, including CACNA1A, ATP1A2 and SCN1A (Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009; Gambardella and Marini 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010). Other genetic findings pointing to a link between migraine and epilepsy have been published. They include mutations on SLC1A3, a member of the solute carrier family that encodes excitatory amino acid transporter 1, and 57 POLG58, C10 and F259, which encode mitochondrial DNA polymerase and helicase twinkle (Tzoulis et al. 2006; Lonnqvist et al. 2009).

In addition, glutamate metabolism (Jen et al. 2005), serotonin metabolism (Johnson and Griffiths 2005), dopamine metabolism (Chen 2006) and ion channel (sodium, potassium and chloride) function might be impaired in both epilepsy and migraine (Steinlein 2004; Pietrobon 2010). In particular, it is likely that voltage-

gated ion channels play a critical role in the pathways associated with migraine and epilepsy (Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009; Gambardella and Marini 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010).

Temporal Relationship and Classification Issues

Seizures and epilepsy syndromes are classified according to guidelines of the ILAE (Panayiotopoulos 2012), and headaches according to the International Classification of Headache Disorders (ICHD). The current version, the ICHD-III, was published in Cephalalgia in July 2013 (Headache Classification Committee of the International Headache Society 2013).

Seizure-related headaches may be peri-ictal (40–75 %) or inter-ictal headaches (25–60 %) (Verrotti et al. 2011a; Cai et al 2008; Ito et al 1996, 2003, 2004). Peri-ictal headache can be divided into pre-ictal, ictal and post-ictal headache; among the peri-ictal forms, the "post-ictal" is, without doubt, the most frequently reported (15–50 %), probably because both children and adults tend to remember the events more easily once the seizure has resolved (post-ictal). (Verrotti et al. 2011a; Cai et al. 2008; Ito et al. 1996, 2003, 2004). "Ictal Headache" (i.e. a "headache" with either migraine or tension-type characteristics associated with other sensory–motor–autonomic–psychiatric ictal epileptic manifestations) occurs in as few as 3–5 % of cases (Forderreuter et al. 2002).

The latest edition of the International Headache Classification (ICHD-III) (Headache Classification Committee of the International Headache Society 2013) makes a distinction between three entities (Table 1): (1) epilepsy induced by migraine with aura or "migraine-triggered seizure" (previously referred to as migralepsy) (code 1.4.4); (2) epileptic migraine (code 7.6.1); (3) post-convulsive headache (code 7.6.2). Diagnostic criteria for the new entity ictal epileptic headache (IEH) (Table 1) have recently been proposed (Parisi et al. 2012a) and more recently cited in the Appendix of the new ICHD-3 edition (Headache Classification Committee of the International Headache Society 2013).

Hemicrania Epileptica or "Epileptic Migraine" (code ICHD-3 7.6.1)

This condition, despite being very rare, has been included in the ICHD Classification and confirmed in the new ICHD-III classification. The diagnostic criteria are: (a) headache lasting seconds-to-minutes, with migraine features that satisfy criteria C and D; (b) patient presenting a partial seizure; (c) the headache develops together with the seizure and is homo-lateral to the ictal event; (d) headache resolves immediately after the convulsion.

Table 1 Current ICHD-3 classification of headache-related seizures and proposed criteria for ictal epileptic headache (IEH)

Current ICHD-3 classification of headache-related seizures
Migraine-triggered seizure (Migralepsy) (1.4.4)
Diagnostic Criteria:
A. Migraine fulfilling criteria for 1.2 ("*Migraine with aura*")
B. A seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 h of a migraine aura
Hemicrania Epileptica or "Epileptic Migraine" (7.6.1)
Diagnostic Criteria:
A. Headache lasting seconds to minutes, with features of migraine fulfilling criteria C and D
B. The patient is having a partial epileptic seizure
C. Headache develops synchronously with the seizure and is ipsilateral to the ictal discharge
D. Headache resolves immediately after the seizure
Post-ictal Headache (7.6.2)
Diagnostic Criteria:
A. Headache with features of "*tension-type headache*" or, in a patient with migraine of "*migraine headache*" and fulfilling criteria C and D
B. The patient has had a partial or generalized epileptic seizure
C. Headache develops within three hours of the seizure
D. Headache resolves within 72 h of the seizure
Proposed criteria for ictal epileptic headache (IEH)
Diagnostic criteria A-D must all be fulfilled to make a diagnosis of "IEH"
A. Headache[a] lasting minutes, hours or days;
B. Headache that is ipsilateral or contralateral to lateralised ictal epileptiform EEG discharges (if EEG discharges are lateralised);
C. Evidence of epileptiform (localised[b], lateralised or generalised) discharges on scalp EEG concomitantly with headache; different types of EEG anomalies may be observed (generalized spike-and-wave or polyspike-and-wave, focal or generalised rhythmic activity or focal sub-continuous spikes or theta activity that may be intermingled with sharp waves) with or without photoparoxysmal response (PPRs)
D. Headache resolves immediately (within minutes) of i.v. antiepileptic drug administration

[a] A specific headache pattern is not required (Migraine with or without aura, or tension-type headache are all admitted)

[b] Any localisation (frontal, temporal, parietal, occipital) is admitted

Post-ictal Headache (code ICHD-3 7.6.2)

Headache with migraine characteristics that manifests itself in about 50% of patients after a convulsive epileptic seizure. The criteria of ictal headache in the ICHD classification are: (1) tension headache, or migraine that satisfies criteria C and D; (2) the patient presents a partial or general epileptic seizure; (3) headache develops

within 3 h of seizure onset; (4) headache resolves within 72 h of the convulsion. Post-ictal headache, though often associated with symptomatic epilepsy, is a frequent event in idiopathic occipital epilepsy in children.

Epilepsy Induced by Migraine with Aura ("migralepsy") (code ICHD-3 1.4.4)

According to the ICHD-III, migralepsy is a recognized complication of migraine (Table 1).

It does not exist in the international classifications of epilepsy (ILAE).

The term migralepsy, which was first used in 1960 (Lennox and Lennox 1960) to define a condition of "opthalmic migraine with associated nausea and vomiting followed by symptoms characteristic of epilepsy", was reintroduced in 1993 by Marks and Ehrenberg (1993). However, the term migralepsy used to refer to a temporal sequence of a migraine with aura attack that evolves into tonic-clonic seizures was widely criticized by many authors, and patients classified as having migralepsy were subsequently defined as having epileptic seizures of the occipital lobe. Unfortunately, there is no clear EEG documentation of cases of migralepsy showing a critical surge of the scalp EEG in patients in whom migraine with aura is followed by a tonic-clonic seizure. Despite the skepticism expressed by various authors regarding the concept of "migralepsy", this clinical condition was inserted in the ICHD-2 classification (Headache Classification Committee of the International Headache Society 2004) as a complication of migraine (code 1.5.5), whereas in the latest revision of the ICHD-3 classification (Headache Classification Committee of the International Headache Society 2013), this condition is codified as epilepsy induced by migraine with aura (code 1.4.4), the term migralepsy being omitted. According to the ICHD-III criteria (Headache Classification Committee of the International Headache Society 2013), epilepsy induced by migraine with aura is defined as an epileptic fit that manifests itself within an hour of a migraine with aura attack in the absence of other causes. Although epilepsy and migraine are among the most common neurological illnesses, this event is very rare in children. Indeed, Sances et al. (2009) recently demonstrated that of the 50 cases of migralepsy mentioned in the literature, only two patients satisfied the migralepsy criteria according to ICHD 2 (Headache Classification Committee of the International Headache Society 2004)

Sunset of the "Migralepsy" Concept

Most reported cases of "migralepsy" do not allow a meaningful and unequivocal migraine-epilepsy sequence to be detected (Sances et al. 2009; Verrotti et al. 2011b, c). There are approximately 50 cases of potential migralepsy reported in the literature (Sances et al. 2009). The majority of these cases have been the subject of criticism by various authors because the diagnosis in the majority of the patients is uncertain for the following reasons: the information available is not clear (38%),

the cases do not fulfil the current ICHD-III criteria (30 %), the diagnosis is questionable (28 %). Indeed, most previous reports of "migralepsy" may have been occipital seizures imitating migraine with aura (Verrotti et al. 2011a, b, c; Barrè et al. 2008).

It has recently even been suggested (Belcastro et al. 2011a; Parisi et al. 2012b) that many of the "published" migralepsy cases may be an "ictal epileptic headache" followed by other sensori-motor or autonomic ictal signs/symptoms. Indeed, although unequivocal epileptiform abnormalities in patients with paroxysmal sensations or behavioural changes usually point to a diagnosis of epilepsy, the lack of clear ictal epileptic spike-wave activity is frequent in autonomic epilepsies, such as Panayiotopoulos syndrome (Koutroumanidis 2007), or even in frontal lobe epilepsy (Nobili 2007). In such cases, ictal epileptic EEG activity might be recorded as unspecific slow wave abnormalities without any spike activity (Belcastro et al. 2011a; Parisi et al. 2012b). Interestingly, there may, on rare occasions, be an isolated epileptic headache that has no associated ictal epileptic manifestations or scalp EEG abnormalities but whose ictal epileptic origin can be demonstrated by depth electrode studies, even purely by chance (Laplante et al. 1983; Fusco et al. 2011).

This misunderstanding has perpetuated the concept of "migralepsy" since the 1960s (Lennox and Lennox 1960) to the detriment of the entity we now define as ictal epileptic headache. We believe that this has led to ictal epileptic headache being severely underestimated, on the one hand, and to migralepsy being clearly overestimated, on the other (Parisi et al. 2012b, 2013a, b).

The Rise of the "Ictal Epileptic Headache" Concept: "A Long and Winding Road…."

Sir Gowers's famous book, published in 1907 (Gowers 1907), first stated that "migraine is in the borderland of epilepsy", and in an epoch before electroencephalography (EEG), Gowers stated: "…the most frequent relation of migraine to epilepsy is as source of error;….in extremely rare instances one affection may develop while the other goes on".

More than 100 years later, we can firmly state that on occasion "migraine itself may be epilepsy" (Parisi et al. 2007, 2008a, b, 2012a, b, 2013a, b). The overlap between these two conditions is partial or complete, not always synchronous (i.e. mainly a peri-ictal phenomenon), but in some cases (whose number is probably largely underestimated) "the headache represents the only ictal phenomenon": we recently named this condition "ictal epileptic headache" (Parisi et al. 2012a). Since 1971, fewer than 20 IEH cases diagnosed according to proposed criteria (Table 1, Parisi et al. 2012b) have been reported (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013). Verrotti et al. recently published 16 other potential ictal epileptic headache cases from a large multicentre

neuropediatric sample (Verrotti et al. 2011b), stressing the concept of "probable underestimate phenomenon" (Parisi et al. 2012a; Parisi et al. 2013a, b).

Nonetheless, this belief goes back a long way. Indeed, it is ever since the 1950s that cases have been reported in German (Heyck and Hess 1955), English (Nymgard 1956) and Italian (Lugaresi 1955; Morocutti and Vizioli 1957) literature in which it has been suggested that "headache" may actually be "an epileptic headache" and "… may even be the only clinical manifestation of idiopathic epilepsy" (Morocutti and Vizioli 1957). Thus, the concept of "ictal headache" dates from a long time ago (Lugaresi 1955; Heyck and Hess 1955; Nymgard 1956; Morocutti and Vizioli 1957). However, the term migralepsy was subsequently coined in the 1960s (Lennox and Lennox 1960) and has permeated the epilepsy and headache culture ever since.

With regard to migralepsy cases reported in the literature, recent articles (Sances et al. 2009; Verrotti et al. 2011a, b, c) have provided a clear demonstration of the inadequacy of both the ICHD-2 and ICHD-3 definitions of this condition. Following the introduction of the migralepsy concept by Lennox and Lennox (1960), an increasing number of ictal epileptic headaches have been reported since the 1970s (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013). It has also been suggested (Parisi and Kasteleijn-Nolst Trenité 2010; Belcastro et al. 2011a; Verrotti et al. 2011a, b; Striano et al. 2011, 2012; Parisi et al. 2012a, 2013a, b) that the migralepsy sequence may not exist at all and that the initial part of the "migralepsy sequence" may merely be an "ictal epileptic headache" (Parisi et al. 2012a) followed by other ictal autonomic, sensory, motor or psychic features.

It should be borne in mind that cortical and subcortical areas appear to be hierarchically divided according to how likely they are to develop CSD, with the occipital lobe appearing to be the most likely area (Verrotti et al. 2011a, b; Parisi et al. 2012b).

How can CSD and epileptic discharges facilitate each other, though to a varying extent? In other words, why may the onset of an epileptic seizure facilitate the onset of CSD to a greater extent that CSD facilitates the onset of an epileptic seizure (Belcastro et al. 2011a; Parisi et al. 2012b)? Some experimental and clinical data in the literature discuss this topic. The most interesting data on genetic defects leading to both epilepsy and migraine are related to FHM, as stated above (Haglund and Schwartzkroin 1990; De Fusco et al. 2003; Vanmolkot et al. 2003; Kors et al. 2004; Dichgans et al. 2005; De Vries et al. 2009; Tottene et al. 2009; Gambardella and Marini, 2009; Van Den Maagdenberg et al. 2010; Riant et al. 2010; Pietrobon 2010; Escayg and Goldin2010; Uchitel et al. 2012).

With regard to the concept of "cortex dys-excitability" in migraine subjects, new advances now support this point of view (Berger et al. 2008; Fabricius et al. 2008; Tottene et al. 2009, 2011; Faragauna et al. 2010; De Souza et al. 2011). Indeed, if we consider the specific polysynaptic inhibitory sub-circuit involving fast-spiking (FS) inter-neurons and pyramidal cells (PC) that have been investigated in FHM1

mice (Berger et al. 2008; Fabricius et al. 2008; Tottene et al. 2009, 2011; Faragauna et al. 2010; De Souza et al. 2011), the gain in function following glutamate release at the recurrent synapses between pyramidal cells would certainly increase network excitation; by contrast, the gain in function following glutamate release at the PC-FS synapses would lead to enhanced recruitment of inter-neurons and enhanced inhibition. Although this analysis is restricted to a specific sub-circuit, it does raise the important point that the differential effect of FHM1 mutations on excitatory and inhibitory neurotransmission may produce over-excitation in certain brain conditions, while leaving the excitation-inhibition balance within physiological limits in others. This would explain the episodic nature of the disease with alternate hyper-excitation and hypo-excitation in the same subject at different times (thus supporting the dis-excitability concept in migraine subjects) (Pinto et al. 2005; Berger et al. 2008; Fabricius et al. 2008; Tottene et al. 2009, 2011; Faragauna et al. 2010; De Souza et al 2011; Tamura et al. 2011; Escayg and Goldin 2010; Uchitel et al. 2012).

A possible explanation for the clearly different extent to which CSD and epileptic seizures facilitate each other is that although these two conditions are triggered by similar mechanisms, their evolution is different depending on whether the neuronal hyperactivity and consequent increase in (K+) exceed a critical level that causes self-regeneration of the depolarization; according to this hypothesis, CSD may be defined as "a poorly-controlled seizure" in which (K+) regulation is completely disrupted. Indeed, local neuronal hyperactivity that progressively recruits a synchronous discharge via recurrent excitatory collaterals and (K+) accumulation has been hypothesized to initiate epileptic discharge in slice models (Pinto et al. 2005). CSD, experimentally induced in rats, increases cortico-cortical evoked responses and strongly induces "brain-derived neurotrophic factor" with synaptic potentiation in vivo (Faraguna et al. 2010), while the induction of a "long-term potentiation-like" (LTP-like) phenomenon by CSD receives support from experimental evidence. In vivo data that lend support to the idea of a CSD-induced LTP-like phenomenon also exist (De Souza et al. 2011). Another recent and intriguing finding regarding CSD propagation is the model according to which interstitial (K) diffusion initiates the positive feedback cycle that ignites CSD in adjacent dendrites, and which is in contrast to the hypothesis that CSD spreads through gap junctions. In particular, according to this hypothesis, the opening of the gap junctions would not be required for CSD propagation, but is instead required for extracellular homeostasis following CSD (Tamura et al. 2011). A causative link between enhanced glutamate release and CSD facilitation has been demonstrated by means of an in vitro model of CSD (Tottene et al. 2009). The synapse-specific effect of FHM1 mutations points to the disruption of the excitation-inhibition balance and neuronal hyperactivity as the bases for episodic vulnerability to CSD ignition in migraine. This finding provides direct evidence that the gain in function following glutamate release at synapses onto pyramidal cells is likely to facilitate experimental CSD in FHM1 mutant mice, and thus provides novel insights into the controversial mechanisms of CSD initiation and propagation.

These data are consistent with and support a model of CSD initiation, in which activation of pre-synaptic voltage-gated Ca channels, and the consequent release of

glutamate from recurrent cortical pyramidal cell synapses and activation of NMDA receptors, are key components of the positive feedback cycle that ignites CSD. In this regard, the role of different voltage-gated Ca2+ channels in CSD has recently been investigated (Tottene et al. 2011). After blockade of either the P-/Q-type Ca2+ channels or the NMDA receptors, CSD cannot be induced in wild-type mouse cortical slices. By contrast, the blockade of N- or R-type Ca2 channels only has a slight inhibitory effect on the CSD threshold and velocity of propagation. These findings support a model according to which the initiation and propagation of the CSD involved in migraine require the influx of Ca2+ through pre-synaptic P-/Q-type Ca2+ channels, which in turn releases glutamate from the recurrent cortical pyramidal cell synapses and activates NMDA receptors (Tottene et al. 2009, 2011).

The temporal and spatial associations between CSD and seizures have been studied by means of electro-corticographic (ECoG) recordings in patients with acutely injured cerebral cortex (Fabricius et al. 2008). The authors reported clinically overt seizures in only one patient, while each of the patients with both CSD and seizures displayed one of the following four different patterns of interaction between CSD and seizures: (a) in four patients, CSD was immediately preceded by prolonged seizure activity; (b) in three patients, the two phenomena were separated in time, with multiple CSDs being replaced by ictal activity; (c) in one patient, seizures appeared to trigger repeated CSDs at the adjacent electrode; (d) in two patients, ongoing repeated seizures were interrupted whenever CSD occurred. These four patterns were consistent within recordings from the same patient, but were different in each of the patients.

Patients 3 and 4 described by Fabricius et al. (2008) are particularly interesting as seizure activity in these two subjects spread from electrode to electrode at the same slow speed as CSD, but preceded it by several minutes. This is noteworthy because seizure activity under other conditions spreads much faster than CSD. To better understand the relevance of this finding, it should be borne in mind that a Ferrari can be driven at the top speed of a Fiat 500, though not vice versa. This example may help to understand why the onset of an epileptic seizure facilitates the onset of CSD to a greater degree than CSD facilitates the onset of an epileptic seizure. Indeed, a Ferrari is usually driven on fast roads, such as highways (myelinic), whereas a Fiat 500 tends to be driven on minor roads (amyelinic), though it must be stressed that a Ferrari can easily be driven on roads (amyelinic) usually taken by a Fiat 500, while the reverse is not true. According to these reflections, it is noteworthy that the patterns recorded by Fabricius et al. (2008) were consistent within the same patient, but differed between patients: highways (myelinic) and minor roads (amyelinic) within the same patient do not usually vary to any great extent, at least not over a relatively short period of time.

Yet another important finding reported by Fabricius et al. (2008), which confirmed our hypothesis (Parisi et al. 2008, 2012a, b, 2013a, b; Belcastro et al. 2011a, 2013; Kasteleijn-Nolst Trenité et al. 2010), is that CSD in their sample was encountered more often than seizures, as demonstrated by the fact that there were twice as many patients with CSD/peri-infarct depolarization alone than with CSD/peri-infarct depolarization plus seizures. Moreoever, 10 of the 11 patients with sei-

zure activity also had CSD, while clinical overt seizures were only observed in 1 of the 11 patients, and seizures were not suspected on clinical grounds in any of the remaining 10 patients.

Interestingly, in the so-called IEH case reports (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013), patients were both idiopathic (whether photosensitive or not) and symptomatic; moreover, they also often presented a clinical history (personal and/or familial) of epilepsy and migraine. Intermittent photic stimulation evokes headache in patients with a positive photo-paroxysmal response, who may also have visually induced seizures (Table 1) (Parisi et al. 2012b). With regard to the EEG abnormalities recorded in "ictal epileptic headache" cases (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013), the same wide spectrum of different EEG patterns (spike-wave activity, "theta" or even "delta" shape, without any spike activity) associated with both CSD and/or seizures were also confirmed "in vivo" by electrocorticography (Fabricius et al. 2008).

Drawbacks: The Current "Ictal Epileptic Headache" Definition Will Inevitably Underestimate the Phenomenon

The proposed IEH criteria are reported in Table 1. Nonetheless, we wish to stress that the IEH criteria inevitably underestimate the number of cases with "ictal epileptic headache" events. Besides highlighting the strengths of "our published criteria" (Parisi et al. 2012a), we would also like to point out "their inevitable drawbacks".

Headache and epilepsy classifications have so far ignored each other. In the ILAE classification, headache is considered exclusively as a possible semiological ictal phenomenon that is included among the "non-motor" features. In particular, headache is described as a "cephalic" sensation, but is not considered as the sole ictal expression of an epileptic seizure. Moreover, headache is not classified as a "pain" (among the "somatosensory" features) or "autonomic" sensation, whereas signs of involvement of the autonomic nervous system, including cardiovascular, gastrointestinal, vasomotor and thermoregulatory functions, are classified as autonomic features. Despite still being considered a controversial issue, we must consider that headache pain may actually originate in the terminal nervous fibers ("vasomotor") in cerebral blood vessels; consequently, headache should be classified as an "autonomic" sensation in the ILAE Glossary and Terminology (Berg et al. 2010). It may thus be possible to interpret headache as the sole expression of an epileptic seizure and classify it as an autonomic seizure.

To explain why headache may be the sole ictal epileptic symptom, Parisi et al. (2012a, b, 2013a, b) previously suggested that an autonomic seizure (i.e. in IEH) remains purely autonomic if ictal neuronal activation of non-autonomic cortical areas fails to reach the symptomatogenic threshold, as previously described for other ictal autonomic manifestations in Panayiotopoulos syndrome (Koutromanidis 2007). In this regard, Parisi et al. have suggested that ictal epileptic headache may be considered an autonomic form of epilepsy, like Panayiotopoulos syndrome, and cases with long-lasting ictal epileptic headache episodes may accordingly even fulfil the criteria that allow them to be considered as "autonomic status epilepticus" (Ferrie et al. 2007).

In addition, it has been suggested (see all Papers by Parisi et al. from 2008 to 2013) that the social stigma attached to epilepsy may explain a general reluctance (Parisi 2009a) (not only in the general public, but even among physicians) to recognize the growing number of documented cases of IEH. Another noteworthy point is that while unequivocal epileptiform abnormalities usually point to a diagnosis of epilepsy, the lack of clear epileptic spike-and-wave activity is frequent in other ictal autonomic manifestations, as well as in patients with a deep epileptic focus arising, for example, from the orbitomesial frontal zone (Nobili 2007). In such cases, ictal epileptic EEG activity may be recorded from the scalp or exclusively by means of deep stereo-EEG recording, sometimes purely by chance (Laplante et al. 1983; Fusco et al. 2011).

Yet another point that deserves attention is the lack of a clear, repetitive EEG headache-associated pattern owing to the fact that ictal EEG recording in such patients does not yield a specific EEG picture. Indeed, different EEG patterns have been recorded during migraine-like complaints in both symptomatic and idiopathic cases (Grossman et al. 1971; Walser and Isler 1982; Laplante et al. 1983; Isler et al. 1987; Niedermeyer 1993; Marks and Ehrenberg 1993; Walker et al. 1995; Ghofrani et al. 2006; Parisi et al. 2007; Piccioli et al. 2009; Perucca et al. 2010; Belcastro et al. 2011c; Fusco et al. 2011; Italiano et al. 2011; Fanella et al. 2012; Cianchetti et al. 2013). Moreover, when EEG anomalies are recorded, no specific cortical correlations emerge (e.g. focal frontal, parietal, temporal, occipital and primary or secondary generalized), as has also been reported (thus confirming our hypothesis) for autonomic manifestations in children affected by Panayiotopoulos syndrome. Lastly, the criteria we propose do not offer the possibility of confirming all suspected cases of ictal epileptic headache by means of intravenous anticonvulsant administration, just as it is not always possible for other types of epileptic seizures; indeed, although there appears to be a clinical response in the vast majority of published cases affected by autonomic seizures as well as in ictal epileptic headache, we cannot be sure whether intravenous anticonvulsant drug administration has the ability to stop a seizure.

For all the afore-mentioned reasons, we firmly believe that the diagnosis of IEH (even according to our proposed new criteria) will remain an underestimated phenomenon owing, in particular, to:

a. the psychosocial stigma attached to this disease;
b. the fact that IEH cannot always be detected from the scalp by means of EEG recording;
c. IEH is rarely refractory to i.v. antiepileptic drug administration, as can instead occur in other type of seizures.

Conclusions

A clear clinical picture of IEH appears to be difficult to obtain. Since its epileptic nature can only be documented by means of ictal EEG recording and simultaneous intravenous antiepileptic drug administration, it is difficult to obtain firm conclusions regarding the frequency of IEH in epidemiological studies. Headache/migraine of epileptic origin must always be suspected in pediatric patients who do not respond to treatment with anti-migraine drugs in order to promptly perform an EEG and thus make a correct diagnosis.

Moreover, ictal epileptic headache may not have the characteristics of migraine with or without aura, or those of a tension headache; indeed, any "type" of headache may be defined as an ictal epileptic headache in the presence of symptoms associated with ictal EEG anomalies (whether focal or generalized) that resolve immediately after i.v. administration of an anticonvulsant drug.

On the basis of current knowledge and clinical experiences, "migralepsy" or a migraine-triggered seizure is highly unlikely to exist. We thus believe that these terms should be removed from the Appendix of International Headache Disorders Classifications until clear evidence is provided of the existence of such conditions.

Ictal Epileptic Headache criteria (Table 1) should be used to classify the rare events in which headache may represent the sole ictal epileptic manifestation. "These findings further highlight the important role of EEG recording in patients with headache, which has traditionally been opposed by fierce ancestral adversity (Parisi 2009a) against the possible link between headache and epilepsy".

We as a group thus suggest that the term ictal epileptic headache be maintained for cases in which headache is "the sole ictal manifestation", and that the term "ictal headache" be maintained for cases in which the headache, whether brief or long-lasting, is merely part of a more complex seizure including ictal manifestations that are either sequential or overlapping (sensory–motor, psychiatric or other non-autonomic manifestations). In our opinion, this distinction is crucial, as has been explained in detail in this chapter, owing to the markedly different prognosis it entails. In fact, this is not a marginal question, because these possible, isolated, non-motor, ictal manifestations (i.e. ictal epileptic headache) should be taken into account before declaring an epileptic patient as "seizure free" so as to be able to suspend anticonvulsant therapy safely.

In conclusion, by applying the ictal epileptic headache criteria proposed here (Table 1) to a large pediatric population in the future, we should be able to understand whether ictal epileptic headache is a marginal phenomenon or is, instead, an underestimated event that deserves greater attention.

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Epilepsy and Immune System: A Tour Around the Current Literature

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Abstract It is widely acknowledged that immune system influences several aspects of the central nervous system. Literature data have shown that immune system and autoimmune response play an important role in the pathogenesis of several neurodegenerative/neurological diseases (i.e Parkinson's and Alzheimer's Diseases, Multiple Sclerosis). However, very recent evidences of specific antibodies found in epileptic encephalitis, the good response to immune therapy in refractory epileptic syndromes and the strong relationship between systemic autoimmune disease and epilepsy suggest a plausible role for the immune system also in paroxysmal neurological disorders. In fact, an immune hypothesis represents a new way to approach epilepsy and could contribute to clarify several unanswered questions in the next future. In this review, we analysed these points mimicking a tour around current evidences from experimental animal models to clinical suggestions.

First Stop: Background

Although it is widely accepted that epilepsy can be defined as the persistent spontaneous tendency to generate seizure that underlies a persistent brain hyperexcitability, the exact physiopathology of epileptogenesis still remains unclear (Goldberg and Coulter 2013).

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Throughout the last few decades different hypotheses spanning from genetics to environmental or infective factors have been proposed to explain this latter phenomenon but unfortunately each attempt failed to give a unique and satisfactory explanation; even though the general knowledge has been widely improved (Goldberg and Coulter 2013).

Since 1977, several reports documented the efficacy of immunomodulating therapy (e.g. corticosteroids, immunoglobulin) in refractory epilepsy and based on this clinical observation a plausible immune origin has been postulated (Peachardre et al. 1977).

Currently, the recent findings of experimental studies have shown that the brain innate immunological cells such as microglia and astrocytes are able to produce cytokines and other mediators of inflammation contributing to seizure activity (Friedman and Dingledine 2011; Granata et al. 2011). These latest discoveries together with the detection of specific autoantibodies against channels or neuronal surface proteins in epileptic syndromes (Vincent et al. 2011b; Zuliani et al. 2012) and the intriguing findings that some mutated genes (LG1, KCNQ2-KCNQ3) are the cause of some types of epileptic syndromes have contributed to the immune theory as a plausible trigger or contributor of epilepsy.

In this article, we reviewed evidences for the immune system involvement in epilepsy, mostly focusing our attention on epilepsy syndromes strongly or suggestively linked to the immune system. We first describe what is our current knowledge obtained from experimental models, secondly from clinical studies showing a close relationship between the immune system and epilepsy.

Second Stop: Immunity Involvement in Experimental Models of Epilepsy

The role of immune activation in the generation of acute seizures and epilepsy has been investigated in animal models. While the role of inflammation during or after seizures in several models has been more systematically studied (Vezzani et al. 2011b, 2012), in comparison, only few studies have been pointed to the study of the immune system response and seizures following infections or the injection of LPS (Harvey and Boksa 2012). Some interesting results have been obtained studying seizures' generation in models of bacterial meningitis involving injection of group B streptococcus in infant rats (Kim et al. 1995; Kolarova et al. 2003) and models of viral CNS infection involving administration of Theiler's murine encephalomyelitis virus in young mice (Libbey and Fujinami 2011; Libbey et al. 2011). On the other hand, an enhancement in seizure susceptibility to convulsant drugs (e.g. lithium-pilocarpine, kainic acid) or an increase in seizure number and severity following LPS has also been characterized (Arican et al. 2006; Dmowska et al. 2010; Lee et al. 2000; Mirrione et al. 2010; Russo et al. 2013, 2014). Furthermore, several research groups provided evidence that, early in postnatal life, infection/immune activation can lead to long-lasting increased seizure susceptibility in adulthood.

Stewart et al. (Stewart et al. 2010) showed that young mice (P28–35) developed spontaneous epileptic seizures 2–7 months following injection of Theiler's murine encephalomyelitis virus. Similarly, Galic et al. (2009) have shown that intracerebroventricular injection of poly (I:C) in P14 rat pups increases seizure's susceptibility at adulthood; these data supports the concept that early exposure to either bacterial or viral immunogens can contribute or can be the cause of seizures and epilepsy also in adulthood.

Inflammation consists of the production of a cascade of inflammatory mediators, as well as anti-inflammatory molecules and other molecules induced to resolve inflammation, as a response to noxious stimuli (such as infection or injury), or immune stimulation, and is designed to defend the host against pathogenic threats (Vezzani et al. 2011b). The innate/adaptive immunity have been implicated in epilepsy; microglia, astrocytes and neurons are believed to contribute to the innate immunity-type processes causing brain's inflammation (Vezzani et al. 2011b). The activation of innate immunity and the transition to adaptive immunity are mediated by a large variety of inflammatory mediators, including cytokines-polypeptides, which play a pivotal role (Nguyen et al. 2002; Vezzani et al. 2011a, c). Cytokines are released by immunocompetent and endothelial cells, as well as by glia and neurons in the CNS, thereby enabling communication between effector and target cells during an immune challenge or tissue injury (Vezzani et al. 2011b). The most extensively studied are represented by IL-1beta, TNF-alpha and IL-6 (Friedman and Dingledine 2011). The major results in the field both support the concept that inflammation causes seizures or seizures cause neuroinflammation. Regarding the latter, several evidences have been reported regarding neuroinflammation-induction in the brain following single or prolonged seizures in various models in areas directly involved in seizure activity (Devinsky et al. 2013; Dhote et al. 2007; Foresti et al. 2011; Librizzi et al. 2012; Maroso et al. 2011; Ravizza et al. 2008; Reid et al. 2013). On the other hand, several studies support the role of inflammation in seizure generation (Auvin et al. 2007, 2009, 2010a, b, 2012; Galic et al. 2012; Marchi et al. 2012; Vezzani et al. 2008), even if it has recently been reported that LPS intrahippocampal infusion inhibits the development of kindling in rats (Ahmadi et al. 2013).

Neuronal hyperexcitability may be affected by cytokines in different ways (Silveira et al. 2012). IL-1beta contribute to excitotoxicity increasing calcium influx into neurons by N-methyl-D-aspartate (NMDA) receptors activation (Viviani et al. 2003), inhibiting glutamate reuptake by astrocytes (Hu et al. 2000). In addition, application of IL-1beta to hippocampal neurons results in the block of gamma-aminobutyric acid type A (GABAA) receptor function (Wang et al. 2000). Similarly, TNF-alpha has also been implicated in GABAA transmission decrease by endocytosis of its receptors in hippocampal pyramidal cells (Stellwagen et al. 2005). Neuroanatomic, imaging, neurochemical, and mechanistic approaches in vivo have been employed, and effector molecules of the cytokine have been described (Balosso et al. 2008; Friedman and Dingledine 2011; Maroso et al. 2010; Viviani et al. 2003). The involvement of TNF-alpha in programming neuronal excitability acutely and long term has also been examined (Riazi et al. 2010). Involvement of glutamate receptors in these TNF-alpha–mediated effects is suggested by the evidenced changes in

glutamate receptor subunit expression after LPS administration (Harre et al. 2008) as well as in TNF-alpha receptor subtypes knockout mice (Balosso et al. 2009), and by the ability of TNF-alpha to induce rapid changes in AMPA receptor subunit expression and function (Stellwagen et al. 2005). Finally, the recent involvement of mTOR pathway during epileptogenesis might also be considered as suggestive of an involvement of immune system (Russo et al. 2014). The role of the mTOR signaling pathway on the innate immune system and neuroinflammatory processes in the diseased brain has now begun to receive considerable attention (Maiese et al. 2013; Russo et al. 2013; Wang et al. 2013); this is despite the fact that the general immunomodulatory functions of mTOR have been widely studied, and rapamycin (RAP), a specific mTOR inhibitor, is a commonly used and successful immunosuppressant drug (Chi 2012). Recent findings support a specific interplay between neuroinflammation and mTOR pathway indicating the latter as a suitable target for the treatment of epilepsy and epileptogenesis (Curatolo and Moavero 2013; Liu et al. 2014; Russo et al. 2014).

Third Stop: Clinical Evidence of the Relationship Between Immune System and Epilepsy

Types of Epilepsy Strongly Linked with an Immune–Involvement

Rasmussen Encephalitis

The first evidence of fascinating relationship between seizures and immune-system dates back to 1958 when Theodore Rasmussen described a case of encephalitis later called Rasmussen encephalitis (RE). RE is a dramatic rare acquired disease with unfavourable prognosis that is characterized by progressive focal cortical unilateral hemispheric atrophy. Epilepsy is one of main feature of RE, especially unilateral untreatable motor partial seizure is the first sign of RE and remains for all the course of disease. It's possible to identify three clinical phases in RE: initially a prodromal stage (mean duration 7.1 months) characterized by low seizure frequency and mild hemiparesis (this phase could be absent in several cases); secondly an acute stage (RE could present directly in this stage) (mean duration 8 months) identified by high rate of simple partial untreatable motor seizure called "epilepsia partialis continua" (Bien et al. 2005; Granata et al. 2003b) reported it in 56–92 % of subjects) plus the appearance of neurological signs as progressive cognitive deterioration, hemiparesis, hemiatrophia and aphasia (if the dominant hemisphere is involved); finally, a residual stage characterized by stable neurological deficits and seizures with a lower frequency compared to acute phase. The duration of each stage is correlated with the severity of destructive processes even if there is a high rate of variability for each case.

Recently, new scientific discoveries have been achieved leading to an expansion of RE's syndrome spectrum, modifying and completing previous concepts. In fact, despite RE was considered a childhood's disease, it is currently accepted that it could occur at all ages especially in adolescent and even in adult subjects (Gambardella et al. 2008). An adulthood onset of RE is usually less severe, tends not only to progress more slowly but also more likely to respond to immunologic treatment (Hart et al. 1997; Leach et al. 1999; McLachlan et al. 1993). Furthermore, the clinical manifestations of RE related to "epilepsia partialis continua" and movement disorders as hemidystonia and hemiathetosis are emerging as adjunctive signs of RE and it seems to correlate with atrophy of the head of caudate nucleus (Gambardella et al. 2008). This latter radiological finding in addition to a progressive mono-hemispheric focal cortical atrophy and grey/white matter T2/FLAIR hyperintensities are considered one of the diagnostic neuroimaging criteria to diagnose RE (Bien et al. 2005). There are also very few reports of bilateral RE usually showing the presence of an underlying dual pathology (for example RE plus low grade tumour, cortical dysplasia, tuberosis sclerosis) (Chinchilla et al. 1994; Firlik et al. 1999; McLachlan et al. 1993; Palmer et al. 1999; Tobias et al. 2003).

It is very well-known that an early surgical exclusion of the affected hemisphere played a major role in seizure treatment (Wennberg et al. 1997) however, clinical experiences suggested that a combinations of corticosteroids, apheresis and high-dose IV immunoglobulin immunomodulatory treatment could be considered in some selective cases (Granata et al. 2003a).

The only unsolved concern regards the possible immune genesis of RE. Neuropathological studies of RE showing the presence of inflammatory infiltrates of T cells plus astrogliosis, suggest an involvement of adaptive part of immune system in RE disease (Bauer et al. 2007). In fact, histopathological-immunohistochemical studies on RE brain have shown that T lymphocytes not only are the main pathologic features of disease but are involved in neuronal death and damage through an apoptosis phase due to the release of granzyme B (Bien et al. 2002). The reasons for this attack against neurons and microglia activated by T lymphocytes is still unknown and needs to be clarified even if a viral hypothesis could be suggested but never definitely demonstrate.

Additionally, in 1990s the evidence in RE patients' serum of antibodies against glutamate receptor 3 (GluR3) has been pointed out as the possible cause for neuronal death through a damage mediated by antibodies or complement (Saiz et al. 2008).

Conversely, other studies have demonstrated that GluR3 antibodies are not present in all RE patients and are not specific of RE being observed in other epileptic syndromes, too (Mantegazza et al. 2002; Watson et al. 2004; Wiendl et al. 2001)

Limbic Encephalitis "neuronal surface antibodies syndrome"

Since upon the first description of Corsellis and colleagues (1968) limbic encephalitis (LE) was considered a rare paraneoplastic disorder with poor prognosis. The

underlying immune-mediated pathogenesis was identified in a cytotoxic response of T cell induced by onco-neuronal antibodies against intracellular antigens (Tuzun and Dalmau 2007). The disorder is characterized by a subacute onset of episodic memory loss, disorientation and behavioural changes associated with seizures, hallucinations, sleep disturbance. Neuroimaging usually shows signal changes in T2-weighted images, FLAIR sequences or diffusion in medial temporal lobe (Asztely and Kumlien 2012). It is becoming frequent the evidence that LE is not a classical onco-neuronal disorder but is associated with antibodies binding cell surface called "neuronal surface antibodies" (NSAbs) (Zuliani et al. 2012). This new entity is clinically similar to paraneoplastic LE with an important exception, namely the prognosis is favourable. In fact, these types of LE respond so well to immunotherapy to determine a substantial complete recovery (Vincent et al. 2011a). Although the incidence of this disorder is not well-established, current data seems to suggest that is more frequent than all encephalitis associated with paraneoplastic antibodies (Lancaster et al. 2011).

VGKC Complex Encephalitis

This represents a new fascinating chapter where the representative form is the LE associated to antibodies against voltage gated potassium channel complex (VGKC-Ab). Vincent et al. described a series of cases as a potentially reversible form of limbic encephalitis responsive to immunotherapy. Clinical and neuropsychological features of patients with VGKC-Ab are characterized by a subacute amnesia (1–52 week), global impairment of memory with sparing general intellect, confusion, sleep disturbance, hypothermia and seizure that occur mainly in adulthood males. Typically, MRI studies revealed either unilateral or bilateral change of signal in medial temporal lobes, especially on T2 or FLAIR weighted sequences, moreover this feature could be absent in 45 % of patients at onset (Irani et al. 2008).

In almost 80 % of cases, paraneoplastic screening (including paraneoplastic antibodies) is always negative and serum VGKC-Ab ranges from 450 to 5128 pM. These values decrease (from 2 to 88 % in comparison to basal level) after treatment with steroids, plasma exchange and intravenous immunoglobulin. The decrement of VGKC-Ab is correlated with improvement of neuropsychological performances and all symptoms are broadly revertible after immunotherapy (Vincent et al., 2004). This last point represents the substantial difference between VGCK syndrome and other untreatable rapidly progressive dementia conditions such as Creutzfeld-Jakob disease (Geschwind et al. 2008).

Previous reports postulated that VGKC complex belongs to two proteins: the leucine rich glioma inactivated 1 protein (LGI1) and contactin associated protein 2 (CASPR2), but nowadays the results of several investigators indicate that these are two diverse entities from VGKC (Irani et al. 2010; Lai et al. 2010).

LGI1 is a secreted neuronal protein highly expressed in hippocampus and neocortex that interacts with a presynaptic protein called ADAM23 and postsynaptic ADAM 22, modulating presynaptic Kv1 potassium channels (Lancaster et al. 2011).

Previously, genetic studies have demonstrated that LGI1 plays an important role in epilepsy field in fact mutations of LGI1 are responsible of some autosomal dominant partial epilepsy with auditory seizures indeed the studies performed on models of transgenic mouse have shown that LGI1 mutations increase the excitatory synaptic transmission modifying dendritic morphology (Nobile et al. 2009; Zhou et al. 2009).

Despite a common substrate, the clinical spectrum correlated to LGI1 mutation is different by LE with LGI1-Ab. In fact LE with LGI1Ab is characterized by an encephalitis rapidly progressive, with two peculiar findings: hyponatraemia and antiepileptic drug refractory facio-brachial dystonic seizures, in almost all cases without surface EEG ictal pattern but always reversible after immunotherapy (Irani et al. 2008).

NMDAR-Ab Encephalitis

A distinctive entity among LE field is the encephalitis N-methyl-D-aspartate-antibody related (NMDAR-Ab). The target of this syndrome is represented by NMDA receptors (NMDARs) which are ligand-gated cation channels involved in neuronal plasticity and synaptic transmission, widely expressed in the amygdala, thalamus, hippocampus and prefrontal cortex. It is known that the pathogenic mechanism of anti NMDAR antibodies is based by a selective and reversible reduction of density of NMDAR surface protein with a subsequent decrease of synaptic NMDAR-mediated current. It has been suggested that a reduction of NMDAR activity might promote epileptogenesis through an increase in glutamatergic activity (Dalmau et al. 2011).

The spectrum of LE NMDAR-Ab differs by other LE for demographic, clinical and instrumental findings. In fact, people affected by LE NMDAR-Ab is peculiar since it is mainly represented by children and young woman. The symptomatology profile is characterized by a prodromal phase presenting as viral illness followed by psychiatric disorders (including anxiety, behavioural changes and psychosis) thereafter followed by the occurrence of seizures, alteration of consciousness and dysautonomia. Sometimes autonomic disturbance may require admission to intensive care unit for central hypoventilation and a temporary pacemaker for cardiac rhythmic alterations (Sansing et al. 2007). Although the first descriptions of LE NMDAR-Ab was related to a ovaric teratoma, recent data showed that less than 5% of cases are related to tumours. This LE has a good response to immune-treatment including plasma exchange, steroids, intravenous immunoglobulin or combination. Some uncontrolled studies have suggested a second-line treatment with immunotherapy, ciclophosphamide, rituximab or both (Titulaer et al. 2013)

Forth Stop: Practical Evidence of Autoimmune Disease and Epilepsy

It is very well known how the incidence of seizures is very high in course of systemic autoimmune diseases (Vincent and Crino 2011).

Based on this, several authors have postulated that immune system might be involved in the pathogenesis of some forms of epilepsy and hyperexcitabilty. The forth stop of our tour will focus on autoimmune diseases that are strongly linked to seizures trying to give a key for understanding this close relationship.

Systemic Lupus Erythematous

Seizures occur in almost 10–20% of patients affected by systemic lupus erythematous (SLE) and the prevalence of epilepsy in these patients is eight times higher than general population. Furthermore, in a significant quote of patients (5–10%) seizures can precede the clinical onset of SLE of several years (Aarli 2000).

These seizures are mainly generalized while seizures occurring during SLE are either focal or generalized-tonic (Mackworth-Young and Hughes 1985).

An important prognostic factor in patients with a single epileptic seizure is the presence of antiphospholipid antibodies since they are correlated with a greater risk of developing new seizures (Peltola et al. 2000).

Several theories speculate that an immune-mediated damage of antinuclear antibodies that cross-react with neuronal antigens or an immune complex-mediated vasculitis could underlie epileptogenic mechanism in patients with SLE. On the other hand, there still is an important unanswered question: what is the meaning of increased level of antinuclear antibodies in patients with idiopathic epilepsy? Some authors reported that the use of antiepileptic drugs might responsible for the increment of antinuclear and antiphospholipid antibodies (Billiau et al. 2005). Although the real cause is almost unknown, epilepsy plays an important role in SLE representing one of the diagnostic criteria for its diagnosis.

Coeliac Disease

Coeliac disease (CD) is a chronic immune T cell-mediated disease against gluten and related proteins that occurs in individuals with a genetic predisposition. In the last years, an increasing number of reports have shown that CD is not only confined to gastrointestinal system, in fact other systems such as nervous system are involved in this disease. The association between CD and epilepsy is controversial and it ranges from 0.5 to 7.2% (Ruggieri et al. 2008; Zelnik et al. 2004), but a recent meta-analysis showed that paediatric population with CD has a 2.1 fold increased risk of developing epilepsy (Lionetti et al. 2010). On the other hand, some authors

reported in epileptic population a greater prevalence of CD (about 2–3 %) (Cronin et al. 1998; Emami et al. 2008; Labate et al. 2001). Recently, a population-based cohort analysis confirmed a moderate risk of epilepsy in individuals with CD reinforcing the potential role of immunologic pathogenesis in the development of epilepsy (Ludvigsson et al. 2012).

This role is also supported by the exposure to gliadin determining an immune response through the activation of T cell against transglutaminase (especially form 6 that is expressed mainly on cerebral cortex, amygdala, hippocampus, cerebellum) and the production of aggressive pro-inflammatory cytokines. Although temporal lobe epilepsy represents the most common type of epilepsy associated with CD, especially in patients with hippocampal sclerosis (Peltola et al. 2009), Labate et al. among other has reported a high rate of silent CD in partial epilepsy with occipital paroxysms, with and without cerebral calcifications and proposing a routine sierological screening of CD antibodies in this population. In fact, it is already accepted as indicator of silent or latent CD the positivity to antibodies to gliadin or transglutaminase in patients without signs of gastrointestinal involvement (Vincent and Crino 2011).

This condition is extremely common in adulthood, when CD is often asymptomatic and neurological illness, including epilepsy, is reported as the first sign preceding the diagnosis of CD (Maki and Collin 1997).

The correlation between seizure and gluten is demonstrated by the successful control of refractory seizures in patients with CD after a treatment with gluten-free diet (Harper et al. 2007; Mavroudi et al. 2005).

A recent study of Ranua et al. (Ranua et al. 2005)reported that the presence of CD antibodies did not differ between patients with epilepsy compared to control group, but the prevalence of antigliadin antibodies is higher in patients with primary generalized epilepsy, suggesting a genetic predisposition. However, several aspects remain obscure and further studies are needed to better clarify the link between immune system and epilepsy in CD patients.

Multiple Sclerosis

Multiple Sclerosis (MS) is an immune-mediated disease of the central nervous system of unknown origin (Vincent and Crino 2011).

Seizures are considered part of MS spectrum and can occur in every phase of the disease either before or after the onset of MS but mainly during relapses. In the majority of cases, seizures appear after several years of MS onset and occasionally can be the unique presenting manifestation of MS (Gambardella et al. 2003; Trouillas and Courjon 1972).

Although the prevalence of epilepsy in MS is more common than in the general population (mean value is assessed about 2.3 %) the rate is extremely heterogeneous ranging from 0.5 to 10.8 % (Drake and Macrae 1961; Ghezzi et al. 1990; Kinnunen and Wikstrom 1986; Matthews 1962).

Each type of seizure have been reported in association with MS, however, secondary generalized tonic-clonic are the most frequent types of seizures (Sander et al. 1990; Striano et al. 2003).

Moreover, several studies reported the occurrence of uncommon forms of epilepsy associated to MS as sensory partial seizures, musicogenic epilepsy and aphasic status epilepticus in particular aphasia is been noted as a predominant symptom of seizure in MS.

Although seizures might occur at any time during the course and in every form of MS (primary or secondary progressive as well as relapsing-remitting), most typically, seizures appearing during relapses are self-limiting and do not generally require antiepileptic treatment.

Several hypotheses have been proposed regarding the pathogenic mechanism underlying epilepsy in MS. Some suggested that epileptogenesis is either sustained by oedema originated by active demyelinating lesions by pro-inflammatory cytokines such as tumour necrosis factor-α, specific interleukins that are produced by activation of microglia in MS lesions.

Hashimoto Encephalopathy

Since 1966, Hashimoto encephalopathy (HE) is considered a rare steroid-responsive treatable encephalopathy associated with autoimmune thyroiditis (Hashimoto thyroiditis)(Chong et al. 2003). HE has only a gender predilection (as other autoimmune diseases, it affects 4–5 times more females than males) but it is not age dependent. There are two clinical HE-correlated subtypes: a vasculitic-like pattern (acute or subacute multiple stroke-like episodes associated with focal neurological deficit and variable degrees of cognitive and consciousness dysfunction) and a diffuse gradual cognitive impairment with dementia, neuropsychiatric symptoms and impairment of consciousness (Afshari et al. 2012).

Seizures affect 66% of HE patients, especially in childhood when HE might be very insidious and it might be suspected when new onset unexplained deterioration is associated with refractory epilepsy (Berger et al. 2010; Vasconcellos et al. 1999).

Type of seizures reported in HE subject are focal or secondary generalized convulsions, whereas very rarely status epilepticus or absence status have been described (Ferlazzo et al. 2006; Vasconcellos et al. 1999). EEG findings are not specific and show a diffuse background slowing as reported in other encephalopathy (Chong et al. 2003; Kothbauer-Margreiter et al. 1996), a resolution of EEG pattern is correlated with clinical improvement (Henchey et al. 1995).

Brain imaging is not useful, in fact, half cases show normal MRI while the others show non specific alterations (Chong et al. 2003; Kothbauer-Margreiter et al. 1996).

Conversely, in 60–85% of subject with HE, elevated protein concentration and less commonly lymphocytic pleocytosis is present at CSF analysis. However, two are the hallmark features of HE: firstly the detection in serum of antithyroid antibodies (but is not specific in fact are positive in 10% of general population) independently of thyroid hormonal profile and the gravity of disease; secondly the rapid

and dramatic response to high–dose to steroid-treatment with a complete recovery within 2 months. The combination of these characteristics is distinctive and exclusive of HE and allows an easy differential diagnosis by other autoimmune forms of encephalitis. Disease relapse is possible after steroids' tapering, and in some cases, a combined immunomodulatory treatment with rituximab, cyclophosphamide, immunoglobulins and plasma exchange is necessary (Vincent and Crino 2011).

How antithyroid antibodies can trigger seizures and neurological manifestations still remains unclear. Post–mortem studies showed a lymphocyte infiltration around small vessels in brain parenchyma of HE patients, thus suggesting a microvascular inflammation damage for an immune complex deposition mediated by antithyroid antibodies (Duffey et al. 2003; Nolte et al. 2000).

Nevertheless, it is unknown the mechanism by which anti-thyroids antibodies can reverse neuronal and thyroid tissue damage, actually, it is not possible to exclude other antibodies or/and other mechanism underlying HE.

Fifth Stop: Practical Evidence of Probable Dysimmune Epilepsy

In these last years, there is a growing interest about catastrophic childhood epileptic encephalophaties, to prevent neurological complications and negative cognitive influences. To achieve these purposes, it is necessary to know the real underlying causes to establish a correct early clinical and therapeutic approach to obtain better outcomes. Based on the effectiveness of immunomodulatory treatments in these epilepsies (Eriksson et al. 2001; Lousa et al. 2000; Wiendl et al. 2001) a potential role of immunity in their pathogenesis is reasonable. In this stop we focus the attention on these severe epileptic syndromes.

West Syndrome

West syndrome (WS) is an infancy epileptic syndrome with onset in the first years of life characterized by brief tonic spasms, arrest or regression of psychomotor development and a chaotic pattern on electroencephalogram called as " hypsarrhythmia". Essentially, it is possible to distinguish two subgroups in WS: symptomatic (underlying a brain damage such as neonatal asphyxia, meningoencephalitis, cerebral dysgenesis, and congenital metabolic disorders) or cryptogenic, if occurred in previously healthy children *(International League Against Epilepsy Task Force, 1989)*.

Independently by subgroups of origin, the hallmark of WS is the responsiveness to immune suppressants therapy as adrenocorticotropic hormone (ACTH) or glucocorticoids, which is responsible of cessation of spasms in more than 90 % of patients (Kondo et al. 2005; Tsuji et al. 2007; Yamamoto et al. 2007).

Hence, an immune mechanism in the pathophysiology of WS is highly supported. Therefore, in order to clarify the immune pathophysiology of WS, several studies have faced the question, however, the profile of cytokine patterns produced by lymphocytes and other pro and anti-inflammatory molecules in plasma e CSF fluid of patients with WS were inconclusive (Haginoya et al. 2009; Liu et al. 2001).

Takashi Shiiharaa et al. (2010) studying peripheral blood lymphocyte subset and serum cytokine profiles have suggested that, in WS, T-cell and B-cell activation played a role and ACTH therapy may associate with T-cell inactivation, unfortunately these data were not confirmed by other reports. The efficacy of ACTH and the superiority to corticosteroids can be explained through a suppression of endogenous convulsant hormone CRH (highly expressed in WS brain) through a direct activation melanocortin receptor and a block of transcription of nuclear factor-kB (this factor is involved in inflammation and epileptogenesis)(Baram et al. 1992; Baram and Schultz 1991).

To date, even if conceivable, an immune mechanism in the pathophysiology of WS has been suggested, however, the exact mechanisms remain unknown and yet might be seriously investigated.

Landau-Kleffner Syndrome

Landau-Kleffner syndrome (LKS) is another rare developmental syndrome, characterized by acquired aphasia during early childhood epileptic seizures, behavioral problems, abnormal epileptic activity on EEG during sleep. Since the first description by Landau and Kleffner in 1957, several hypotheses were investigated to discover the pathogenesis, but of all only an immune pathologic cause seems to be more reliable. This theory was suggested by Mikati et al. and Lagae et al., following the observation of a significant improvement of language function and EEG abnormalities after treatment with corticosteroids and/or repeated IVIG infusions (Lagae et al. 1998; Mikati and Saab 2000)

Moreover Fayad et al. (1997) and then other investigators (Mikati and Saab 2000) have strengthened an immune origin through the evidence of intrathecal IgG index in liquor in patients affected by LKS observing that the rate of IgG was normalized after immunoglobulin treatment. Another evidence of immunological mechanism for epilepsy in LKS was documented by Connolly et al. (Connolly et al. 1999, 2006) through the demonstration of the presence of serum autoantibodies anti-brain endothelial cells and cell nuclei IgG in 45 % of patients affected by LKS in comparison to control. All these observations support the hypothesis that an autoimmune mechanism could be the cause of this epileptic syndrome.

Febrile Infection-Related Epilepsy Syndrome (FIRES)

An expanding interest has been focused on a new important subtype of childhood syndromes called febrile infection related epilepsy syndrome (FIRES).

Just the name of syndrome includes and defines the clinical spectrum of FIRES that is represented by a febrile infection followed, after weeks, by acute onset of an extraordinary high seizure activity most difficult to treat. As first described by van Baalen et al (2010) and Kramer et al. (2011) the population involved in this syndrome is younger than 15 and a slight male predominance. All patients had suffered an infection, mainly respiratory in the weeks prior the onset of symptoms. This syndrome has a poor prognosis and it is burdened by a mortality rate of about 9 % and many patients have cognitive sequelae.

The preceding infection and the lacking evidence of infectious encephalitis support an immune-mediated patho-mechanism for FIRES. Apart from antibody-related encephalitis, alternative hypotheses grant a special role to the innate immune system even to a genetic predisposition in FIRES pathogenesis (Howell et al. 2012; Nabbout et al. 2011)

To date the failure of antibody-detection against the known neuronal antigens as well as the ineffectiveness of immunotherapy questions a role for autoantibodies in the epileptogenesis of classical FIRES (van Baalen et al. 2012).

Despite these limits, the literature data on this syndrome is growing up and an immune involvement is not possible to be excluded. In fact, (Specchio et al. 2010), the presence of severe epileptic syndrome in previously normal children preceded by fever is a highly suggesting element of an immune-mediated or inflammatory processes and it deserves further consideration.

Last Stop: Future Directions

The hypothesis that immune system might have a crucial role in epilepsy was first postulated 20 years ago. Since then, the discoveries in biochemical mediators in epilepsy models plus the possibility to identify an association with specific autoantibodies in several epileptic syndromes are strengthening the relationship between epilepsy and immunity. On the other hand, very interesting is the proven efficacy of immunotherapies such as adrenocorticotropic hormone (ACTH), corticosteroids (dexamethasone, hydrocortisone, prednisone/prednisolone, and methylprednisolone), cyclophosphamide, methotrexate, and rituximab in several forms of refractory epilepsies supporting this link.

Overall, in preclinical settings, the link between inflammation, immune system and epilepsy has to be considered determined, however, more research is warranted in order to better define possible targets for pharmacological interventions and the role played by the various mediators, which is still debated with controversial results being published.

Furthermore some antiepileptic drugs (AEDs) such as valproate, carbamazepine, phenytoin, vigabatrin, levetiracetam, and diazepam have been found to modulate the immune system activity by affecting humoral and cellular immunity (Beghi and Shorvon 2011). Based on these considerations immunity might be considered a promising and enchanting challenge to understand the epilepsy.

Ethical Publication We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Novel Molecular Targets for Drug-Treatment of Epilepsy

Vincenzo Belcastro and Alberto Verrotti

Abstract Nowadays several antiepileptic drugs (AEDs) are available for the treatment of patients with epilepsy. Nevertheless, up to 30% of patients continue to present recurrent seizures. So, the challenge for new more efficacious and better tolerated drugs is continuing. Advances in understanding of pathophysiology of epilepsy and in the physiology of ion channels and other molecular targets provide opportunities to create new and improved AEDs. Potentially interesting molecular targets include KCNQ-type K+ channels, SV2A synaptic vesicle protein, ionotropic and metabotropic glutamate receptors. The pipeline for the development of new AEDs with novel mechanisms of action is narrowing with only a few interesting compounds on the immediate horizon. In fact, only perampanel (modulates AMPA mediated neurotransmission) and brivaracetam (binds to SV2A protein and sodium channel) are likely to reach the market-place in the next 3 years. Eslicarbazepine has approved in the last year as add-on treatment for partial onset seizures.

This chapter reviews the available information on various classes of molecules that are in the pipeline for the treatment of epilepsy.

Introduction

The armamentarium to treat epilepsy includes today more than 20 drugs. These are classically distinguished as standard, traditional or first generation antiepileptic drugs (AEDs), which include phenobarbital, phenytoin, carbamazepine, valproic acid, ethosuximide and benzodiazepines, and new or second generation AEDs, which are vigabatrin, lamotrigine, felbamate, gabapentin, oxcarbazepine, tiagabine, topiramate, stiripentol, pregabalin, levetiracetam, rufinamide, zonisamide. More recently, other three compounds have been introduced, i.e. lacosamide, retigabine and eslicarbazepine acetate, also defined as third generation AEDs. However, despite

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the therapeutic arsenal of old and new AEDs, approximately 30% of patients with epilepsy still suffer from seizures (Brodie 2010). Noteworthy, none of the AEDs that have been introduced since 1990, including those that act on newly identified targets, can be considered a 'magic bullet' that reliably cures a patient's seizures. Nevertheless, when compared with the old AEDs (developed before 1990), the new AEDs that have since been developed have provided considerable improvements in terms of safety, tolerability and pharmacokinetics (Brodie 2010). Of equal importance, the existence of more than 20 AEDs offers a broad range of therapeutic options, which may lead to better personalized medicine (Sander 2004; Perucca and Tomson 2011).

The ways for developing new AEDs and innovative therapeutic strategies are multiple and different. One possibility is the evolution of pre-existing drugs with the objective of enhancing their efficacy or eliminating troublesome side effects. The alternative strategy is the research of new compounds identified through the study of mechanisms of drug-resistance and of additional molecular targets or, of course, through the characterization of the biological activity of molecules identified through sheer serendipity (Meldrum and Rogawski 2007). Currently marketed AEDs predominantly target voltage-gated channels (e.g., alpha-subunits of voltage-gated Na+ channels, T-type voltage-gated Ca2+ channels) or influence GABA-mediated inhibition (Rogawski and Loscher 2004). Recently identified new and potentially interesting molecular targets include KCNQ-type K+ channels, SV2A synaptic vesicle protein, ionotropic and metabotropic glutamate receptors (Löscher et al. 2013).

In this chapter we review the available information on new classes of molecules that are in the pipeline for the treatment of epilepsy in the next future.

Novel Structural Analogues of Pre-existing AEDs

Many of the traditional AEDs are highly efficacious but their tolerance and safety profile can be disappointing. Therefore, the attempt to enhance the efficacy of pre-existing drugs by manipulation of their structure is a logical approach to obtain drugs with greater efficacy or better tolerability.

UCB Pharma is currently developing two levetiracetam (LEV) analogues: brivaracetam and seletracetam (ucb 44212). Compared with LEV, both compounds have higher affinity for the SV2A-binding site, which mediates the antiepileptic activity of LEV, and show much greater potency in animal models of seizures and epilepsy.

Eslicarbazepine acetate (ESL), a prodrug of eslicarbazepine (S-licarbazepine), shares with carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitute but is structurally different at the 10,11-position. This structural variation is expected to result in different metabolism (with once daily dosing) and improved tolerability (Verrotti et al. 2014).

Carisbamate, a compound endowed with broad-spectrum anticonvulsant activity in animal models, is a monocarbamate with some structural relation to the dicarbamate felbamate.

Brivaracetam: Mechanism of Action, Pharmacokinetic Profile, Efficacy and Safety

Brivaracetam (BRV) is a highly selective and reversible SV2A ligand with a 15- to 30-fold higher affinity than LEV in rat and human brain. At therapeutically relevant doses, BRV occupies 80–90 % of SV2A within 5–15 min, representing maximal protection against seizures in animal models (Matagne et al. 2008; Gillard et al. 2011). The high anticonvulsant activity of BRV compared with LEV, observed in several animal models of epilepsy, seems not simply explained by the high affinity to SV2A but probably resides in the way BRV modulates SV2A function. In this regard, it is important to point that the exact role of SV2A in synaptic transmission is not completely clear (Matagne et al. 2008; Gillard et al. 2011). However, a strong functional correlation has been established between SV2A binding and the anticonvulsant potency for both focal and generalized seizures (Kaminski et al. 2008). In addition, BRV displays inhibitory activity at neuronal voltage-dependent sodium channels (Zona et al. 2010). How much such effect contributes to the anticonvulsant potency of BRV is not fully elucidated yet. At any rate, the sodium channel modulation represents a distinct activity of BRV compared with LEV (Margineanu et al. 2009) and might explain why BRV, and not LEV, is also active on the maximal electroshock-induced model (Matagne et al. 2008). It appears evident that further studies are needed to fully understand the neurobiology of BRV.

BRV has nearly complete bioavailability after oral administration. Single-dose studies under fasting conditions show a t_{max} of about 1 h and a dose proportional C_{max} for a dose range between 10 and 1400 mg. However, area under the curve (AUC) deviates from dose linearity above 600 mg, and high fat meals seem to slightly delay t_{max} to 3 h and to slightly decrease C_{max} of about 28 % (Sargentini-Maier et al. 2007; Von Rosenstiel 2007). BRV is less than 20 % protein bound with a volume of distribution of 0.6 l/kg (Rolan et al. 2008). BRV has a half-life of about 8 h and is primarily metabolized via hydrolysis of the acetamide group and CYP2C19-mediated hydroxylation, but all metabolites are not pharmacologically active (Von Rosenstiel 2007). CYP2C19 mutations affect slightly the BRV metabolism with a 30 % decreased clearance which does not seem to be clinically relevant. Patients with severe renal impairment without dialysis require no major adjustments in dosage. However, subjects with severe hepatic failure present a 50–60 % increase in plasma concentrations compared with healthy controls (Sargentini-Maier et al. 2012; Stockis et al. 2013). Data from add-on trials show no significant effect of BRV on plasma concentrations of concomitant AEDs such as lamotrigine, phenobarbital, phenytoin, topiramate, valproic acid or zonisamide. Preliminary data suggest no significant interactions with oral contraceptives (Bialer et al. 2013).

The efficacy of BRV as an adjunctive therapy for patients with focal epilepsy has been evaluated in three phase III studies. Two of which use a fixed-dose design and include patients with focal epilepsy only (Biton et al. 2014; Ryvlin et al. 2014), while the third study adopts a flexible dose design and also enrols patients with generalized seizures (Kwan et al. 2014). In study NO1252, the efficacy of BRV (20 mg, 50 mg and 100 mg/day) was investigated against placebo in patients aged 16–70 years with uncontrolled partial-onset seizures (POS) with/without secondary generalization, despite treatment with one to two concomitant AEDs at a stable and optimal dosage. The primary efficacy endpoint (percentage reduction over placebo in baseline-adjusted focal seizure frequency per week over the 12-week treatment period) was statistically significant only for BRV 100 mg/day (Ryvlin et al. 2014). In study NO1253, patients aged 16–70 years were randomized (1:1:1:1) to placebo or BRV 5 mg, 20 mg or 50 mg/day without up titration. The primary efficacy endpoint (percentage reduction over placebo in baseline adjusted POS frequency per week during the 12-week treatment period) was statistically significant only for BRV 50 mg (Biton et al. 2014). Finally, study NO1254 adopted a flexible dose design in adults (16–70 years) with uncontrolled epilepsy; however, up to 20% were patients with generalized epilepsies. After a prospective 4-week baseline, patients were randomized to BRV or placebo, initiated at 20 mg/day and increased, as needed, to 150 mg/day during an 8-week dose-finding period followed by another 8-week stable dose maintenance period. During the 16-week treatment period, median percentage reduction from baseline in POS frequency per week was not statistically significant, while 50% responder rate is 30.3% for BRV and 16.7% for placebo ($p = 0.006$) (Kwan et al. 2014).

In general terms, all studies report no difference in the treatment-emergent adverse events (TEAEs) for patients treated with BRV compared with placebo. The most commonly reported TEAEs leading to discontinuation were psychiatric adverse events represented mainly by aggression, anxiety, irritability, depression and insomnia.

Seletracetam: Profile of a New Pyrrolidone Derivative in Animal Models of Epilepsy

Seletracetam (SEL) is a pyrrolidone derivative with a one-log-unit higher affinity for the synaptic vesicle protein 2A (SV2A) than LEV (Bennett et al. 2007). SEL shows a potent anti-seizure activity in animal models mimicking partial-onset (kindled animals) and generalized epilepsy (audiogenic seizure susceptible mice and genetic absence epilepsy rats from Strasbourg (GAERS)). In amygdala-kindled rats, SEL increased the generalized seizure threshold current and decreased the duration of the after-discharge and the seizure severity observed at the after-discharge threshold current, and generally had a much more potent effect than previously observed for LEV (Bennett et al. 2007). SEL showed no psychomimetic effects and a very high central nervous system (CNS) tolerability in both kindled

and GAERS rats, markedly superior to that of LEV and other AEDs (Matagne et al. 2009). A number of in vitro studies have been conducted with whole-cell patch clamp techniques to ascertain if SEL modulates voltage- and/or ligand-operated ion channels. SEL, in contrast to another new pyrrolidone derivative, BRV, did not modify tetrodotoxin-sensitive fast Na+ currents in rat cortical neurons and did not alter persistent Na+ currents, like phenytoin, in neurons from the CAI region of rat hippocampal slices (Zona et al. 2005). Likewise, another study on rat hippocampal neurons reported that SEL is devoid of any significant effect on GABA-, glycine-, N-methyl-D-aspartate (NMDA)-, kainic acid- and AMPA-gated currents, with the exception of a minor inhibition of the plateau phase of the NMDA current (Bennett et al. 2007). Therefore, SEL does not appear to directly modulate Na+ channels as well as other key ligand-gated ion channels involved in inhibitory and excitatory neurotransmission. In a preliminary study in patients with photosensitive epilepsy, SEL was effective in suppressing light-induced electroencephalographic discharges (Perucca et al. 2007).

Eslicarbazepine Acetate: Mechanism of Action, Pharmacokinetic Profile, Efficacy and Safety

Eslicarbazepine acetate (ESL) is a new active compound that uses as the mechanism of action of blocking the voltage-gated sodium channel (VGSC) to obtain anticonvulsant activity on the CNS (Benes et al. 1999). ESL has a huge blocking power of VGSC like many AEDs that interact with ion channels and neurotransmitter receptors to block VGSC reducing excitability of the membrane. Several examples can be found such as carbamazepine, lamotrigine, oxcarbazepine and phenytoin (Rogawski 2002).

ESL has no interaction with receptors of benzodiazepines, GABA and glutamate (Ambrosio et al 2000; Ambrosio et al. 2001; Parada and Soares da Silva 2002; Cunha et al. 2002) and, like carbamazepine, it works on the inactive state of the channel but it has three times less efficacy on the stand-by state, this characteristic makes ESL something more selective on neurons that tend to be rapidly firing with respect to normal ones, this means that the probability of adverse neurological consequences is lower (Brown and El-Mallakh 2010).

ESL administration is oral, its absorption by the intestine is high. An extensive and rapid biotransformation takes place and the drug is metabolized into eslicarbazepine which delivers the pharmacological effect (Almeida et al. 2009). The process is immediate and as a consequence the plasma concentration stays low and under the quantification limit.

The bio transformation is carried out by hepatic first-pass metabolism and the metabolites in the circulation are eliminated via renal excretion (Almeida et al. 2009). One oral dose of ESL can be found more than 90% in urine as metabolites, of the remaining part 92% is eslicarbazepine that is excreted in urine too, by on third as glucuronide conjugate and two thirds as unconjugated form.

Regarding the interaction between this drug and other AEDs several studies are available in vitro and in vivo (Almeida and Soares da Silva 2007; Almeida et al. 2009; Vaz-da-Silva et al. 2009; Rocha et al. 2009). Treatment in concomitance with carbamazepine shows a significant increase of clearance of ESL and no change in exposure to carbamazepine, this indicates that ESL dose may need to be increased. Treatment of patients in concomitance with phenytoin and phenobarbital did show increased clearance of eslicarbazepine too but with a significant increase of phenytoin exposure, this may suggest to increase ESL dose and decrease phenytoin dose (Almeida et al. 2009). The pharmacokinetic interaction between ESL and other AEDs is not relevant. There are other non AEDs medications that interact with ESL, the most notable of which are warfarin (Almeida and Soares da Silva 2007), simvastatin (Falcao et al. 2013a) and oral contraceptives (Falcao et al. 2013b).

The efficacy of ESL for the treatment of POS has been the object of a number of randomized clinical trials (Elger et al. 2007; Elger et al. 2009; Ben-Menachem et al. 2010). These studies addressed patients that had at least four POS monthly and that were refractory to treatment with 1–3 AEDs. Overall these studies showed that ESL single-daily doses of 800 and 1200 mg were effective and safe in patients who were refractory to treatment with one or two concomitant AEDs and displayed that the percentage of subjects who responded increased together with increase of ESL dose. A recent study on efficacy and safety of ESL analyzed the data of a population of 1049 patients enrolled in all of the three phase III studies to focus on a broader population and subpopulations (Gil-Nagel et al. 2013). The data showed that single-daily doses of 800 and 1200 mg work well as adjunctive therapy of POS, and are also well tolerated. The good outcome in efficacy and safety of these doses showed to be independent of population characteristics (gender, geographic area, epilepsy duration, age at diagnosis time, type of seizure) and the type and number of concomitant AEDs therapy. Noteworthy, the long term efficacy of single-daily doses of ESL was addressed in open label extension studies during a 1 year period. The drug was used as adjunctive treatment in adult subjects with POS in trials conducted in double-blind and placebo controlled. The dose for the trial was of 800 mg once-daily for 4 weeks, after that the dose could be changed raising or lowering it in the range 400 and 1200 mg without altering the doses of concomitant AEDs (Halasz et al. 2010; Hufnagel et al. 2013). In all these open label extension studies ESL, in single-daily doses, showed to be effective in reducing the frequency of seizures and well tolerated as an adjunctive long-term therapy in adults with refractory POS (Halasz et al. 2010; Hufnagel et al. 2013).

ESL is currently approved by EMEA in the European Union for adjunctive use in partial epilepsy in adults at the daily dosage of 400–1200 mg/day. ESL is not recommended below 18 years and only few data about efficacy and safety of this drug in pediatric patients are available. A low-dose tablet formulation (200 mg) and ad oral suspension formulation (50 mg/ml) were developed. Currently there is only one published trial which analyzed pharmacokinetics, efficacy and safety of this drug in pediatric population (Almeida et al. 2008). In each age group (2–6 years, 7–11 years and 12–17 years) three different dosages were studied. The study demonstrated a clear dose-related reduction in seizure frequency with good tolerability.

Regarding the safety, the analysis performed in the multicenter studies previously illustrated showed that the incidence of TEAEs increased with the increase in the dose of ESL, both for all TEAEs as well as for those considered at least possibly related to treatment (Elger et al. 2009; Gil-Nagel et al. 2009; Ben-Menachem et al. 2010; Halasz et al. 2010; Gil-Nagel et al. 2013). The incidence of TEAEs was more marked during the early treatment phase. In fact, from day 42 to the end of the studies there was only a little difference between ESL and placebo groups of each trial (Gil-Nagel et al. 2009; Ben-Menachem et al. 2010). TEAEs were usually mild to moderate in intensity, while the incidence of serious TEAEs was very low and similar in each of the ESL treatment groups (Elger et al. 2007; Elger et al. 2009; Gil-Nagel et al. 2009; Gil-Nagel et al. 2013; Ben-Menachem et al. 2010; Halasz et al. 2010). The most common adverse events with an incidence >2% were: dizziness, somnolence, nausea, diplopia, headache, vomiting, abnormal coordination, blurred vision, vertigo and fatigue. The incidence of rash, which is the most common idiosyncratic reaction with all AEDs (Zaccara et al. 2007), occurred in approximately 1% in all phase III studies (Elger et al. 2009; Gil-Nagel et al. 2009; Ben-Menachem et al. 2010), while this incidence has been reported to be up to 10% in subjects treated with oxcarbazepine (Shorvon 2000) and 11% in subjects treated with carbamazepine (Mattson et al. 1992). The incidence of behavior or psychiatric adverse events is low and there was no case of suicide or suicide attempt.

Carisbamate

Carisbamate (Ortho-McNeil Janssen, Titusville, NJ, USA), a compound endowed with broad-spectrum anticonvulsant activity in animal models, is a monocarbamate with some structural relation to the dicarbamate felbamate. The mechanism of action contributing to the broad-spectrum anticonvulsant activity has not been fully elucidated but it is of considerable interest that the drug displays antiepileptogenic and neuroprotective activity when administered repeatedly after lithium-pilocarpine status epilepticus in rats (Francois et al. 2005). After an initial study with positive results against POS at doses of more than 200 mg/day (Faught et al. 2008), three placebo-controlled adjunctive-therapy trials assessing doses of 200, 400, 800 and 1200 mg/day found inconsistent evidence of only modest efficacy (Sperling et al. 2010). As a result, carisbamate's development in epilepsy has been discontinued.

Novel Investigated AEDs: Focus on the Photosensitivity Epilepsy Model

The photosensitivity epilepsy model provides a means of assessing the effects of potential AEDs in patients in a controlled laboratory setting. Photosensitivity describes the ability to produce an epileptiform electroencephalography (EEG)

response evoked by intermittent photic stimulation (IPS). This EEG pattern is called a photoparoxysmal response (PPR). Administration of approved and experimental AEDs, as single or repeated doses, clearly diminishes or even abolishes the response to IPS (Binnie et al. 1986). A standardized method for eliciting PPR in response to IPS has been devised to quantify the effects of promising new therapies for epilepsy (Kasteleijn-Nolst Trenité et al. 2012).

This clinical photosensitivity epilepsy proof-of -concept model has been applied to determine and evaluate a potentially effective AED. In fact, this assay allows investigators to establish that the compound under study is penetrating to the CNS compartment and engaging the target channel or receptor under study by suppressing the epileptiform EEG discharges. Currently, these studies refer as phase II studies.

JNJ-26489112

JNJ-26489112 [(S)-N-(6-Chloro-2,3-dihydrobenzo(1,4)dioxin-2-yl)methyl)sulfamide] is a centrally active, broad spectrum investigational anticonvulsant having in vitro activity at multiple CNS targets including N-methyl-D-aspartate(NMDA), kainate, gamma-aminobutyric acid (GABA), TypeII Na, KCNQ and N-type calcium channels. In addition, JNJ-26489112 demonstrates modest activity at the 5-HT-2creceptor, dopamine transporter, and dopamine and serotonin uptake sites (Di Prospero et al. 2014). Although the precise mechanism of action of JNJ-26489112 is unknown, it has demonstrated significant anticonvulsant activity in a wide range of pre-clinical seizure models. In fact, JNJ-26489112 has anticonvulsant activity against audiogenic, electrically-and chemically induced seizures. By limiting seizure spread and elevating seizure threshold, JNJ-26489112 is more effective pre clinically than marketed anti-epileptic drugs in several severe seizure models including metrazol-induced seizures and hippocampal kindling. Based on its activity in these models, JNJ-26489112 may be useful in treating generalized tonic-clonic, complex partial and absence seizures; in addition, it might also be effective in pharmaco-resistant epilepsy (Di Prospero et al. 2014).

In a recent small study, JNJ-26489112 showed a positive response at all investigated doses with complete suppression of the IPS induced PPR (Di Prospero et al. 2014).

ICA-105665

ICA-105665, identified by Icagen, Inc. (Durham, NC, U.S.A.), is a novel small molecule that opens Kv7.2/7.3 and Kv7.3/7.5 potassium channels (Roeloffs et al. 2008), also known as KCNQ2/3 and KCNQ3/5 channels. The compound has demonstrated broad spectrum antiseizure activity in multiple animal models including maximal electroshock, 6 Hz seizures, pentylenetetrazole, and electrical kindling at

doses from <1–5 mg/kg (Roeloffs et al. 2008). ICA-105665 was well-tolerated in both a single ascending dose study in healthy volunteers at doses up to 400 mg and in healthy volunteers and patients with epilepsy when administered twice daily in a 7-day repeat dose study at total daily doses up to 600 mg (Kasteleijn-Nolst Trenité et al. 2013). Moreover, ICA-105665 reduced the PPR in patients with photosensitivity epilepsy at single doses of 100, 400, and 500 mg (Kasteleijn-Nolst Trenité et al. 2013). Interestingly ICA-105665 is the first activator of neuronal Kv7 potassium channels tested for activity in the photosensitive epilepsy model in humans. In fact, retigabine another activator of Kv7 potassium channels (Rogawski and Bazil 2008), is effective for the treatment of partial seizures in humans and has been approved for use in Europe and the United States, but it has never been assessed in patients with photosensitive epilepsy or in patients with IGE. The reduction of PPR in patients with photosensitivity epilepsy provides evidence of CNS penetration by ICA-105665, and preliminary evidence that engagement with neuronal Kv7 potassium channels has antiseizure effects.

The most common TEAEs following ICA-105665 administration included dizziness, somnolence, ataxia, and tremor. Both efficacy and emergence of dizziness appeared to correlate with increasing plasma concentrations of ICA-105665.

Pitolisant (BF2.649)

The potential benefit of pitolisant (BF2.649), a histamine 3 receptor (H3R) antagonist, has been evaluated in different seizure models in rats and mice, predictive for generalized and partial types of seizures. The occurrence and duration of EEG discharges and seizures were determined in: (i) the genetic absence epilepsy rats from Strasbourg (GAERS), where BF2.649 (20 mg/kg, i.p.) significantly decreased both the number and cumulated durations of spike-and-wave discharges; (ii) the maximal electroshock test, where a complete suppression of EEG epileptiform activity and seizures was observed in mice treated with BF2.649; (iii) the kainate-induced hippocampal seizures in mice, where pitolisant is extremely effective to reduce the cumulated duration of hippocampal discharges.

Recently, the pharmacodynamic effect of pitolisant was tested in patients with epilepsy using the photosensitivity proof of concept model. A total of 14 adult patients were studied for 3 days to evaluate the effect of a single oral dose of pitolisant on EEG photosensitivity ranges (Kasteleijn-Nolst Trenité et al. 2013). In this study, a statistically significant suppressive effect (standardized photosensitive response [SPR] reduction) for 20-, 40-, or 60-mg doses of pitolisant was seen in 9/14 (64 %) patients of whom 6/14 (43 %) showed abolition of the response to IPS. Patients on the highest dosage (60 mg) showed the strongest effect with an effect lasting up to 28 h (Kasteleijn-Nolst Trenité et al. 2013).

AMPA Receptors as Novel Targets for Antiepileptic Drugs

Alpha-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are key mediators of seizure spread in the CNS and represent promising targets for AEDs. There is emerging evidence that AMPA receptors may play a role in epileptogenesis and in seizure-induced brain damage (Russo et al. 2012). This evidence suggests that AMPA receptor antagonists could have broad utility in epilepsy therapy. Competitive and noncompetitive AMPA receptor antagonists are broad-spectrum anticonvulsants in animal seizure models. There is evidence that these antagonists can potentiate the antiseizure activity of NMDA receptor antagonists and conventional AEDs (Rogawski 2013). This evidence suggests that the preferred use of AMPA receptor antagonists may be in combination therapies. AMPA receptors are distributed widely in the CNS and are present in all areas relevant to epilepsy, including the cerebral cortex, amygdala, and thalamus. Although there are regional differences in the expression of the four subunits, GluA1, GluA2, and GluA3 are the most abundant subunits in the forebrain, with the exception of some thalamic nuclei, where GluA4 is also abundant. Approximately 80% of AMPA receptors at excitatory synapses on CA1 hippocampal pyramidal neurons are GluA1/GluA2 heteromers (Rogawski 2013).

BGG492 (Selurampanel), a Competitive AMPA/Kainate Antagonist in Clinical Development for the Treatment of Epilepsy

BGG492 shows anticonvulsant activity in several animal models of epilepsy, including electroshock and chemically-induced seizures in rodents, WAG/Rij rats (a genetic model of absence epilepsy), the rat amygdala kindling model (indicating a potential anti-epileptogenic effect), and in fully kindled rats (a model of therapy-resistant partial seizures in human) (Russo et al. 2012). It is well understood that properties required for high affinity at AMPA receptors are contrary to those required for oral bioavailability. As a compromise, BGG492 has moderate binding affinity for rat and human AMPA receptors, but >100-fold selectivity with regards to the glycine-binding site of NMDA receptors and no significant affinity in a 150-target safety panel (Russo et al. 2012). BGG492 is only metabolized to a limited extent, and does not inhibit CYP450 enzymes. Its very favourable safety profile is evidence by a lack of cardiovascular, phototoxic or teratogenic potential, as well as by results of in vivo toxicology studies in rats, dogs and monkeys, where only minor and reversible effects were observed. Dose-limiting adverse effects were related to the classical signs of exaggerated pharmacology for AMPA/kainate receptor antagonism, mostly ataxia and decreased locomotor activity. BGG492 is currently in Phase II development for epilepsy but clinical trials are ongoing also for migraine and pain.

A phase II study on the effect of BGG492 on PPR in patients with photosensitive epilepsy has been recently completed (ClinicalTrials.gov Identifier: NCT00784212).

NS-1209

NS-1209 is a water-soluble AMPA antagonist that shows high efficacy against status epilepticus induced by electrical stimulation of the amygdala or by subcutaneous administration of kainic acid in rats (Pitkanen et al. 2007). It also displayed some neuroprotective activity against status-induced hippocampal neurodegeneration (Perucca 2009). Clinical testing in the treatment of recurrent seizures has been initiated but no published data are available. Moreover, at the present time, no clinical trials in epilepsy are registered. Conversely, a Phase II controlled study in neuropathic pain has been published (Gormsen et al. 2009).

Perampanel: Pharmacokinetic Profile, Efficacy and Safety

Perampanel, a non-competitive selective antagonist of the AMPA glutamate receptors, exerts a direct influence on post-synaptic glutamatergic transmission (Rogawski 2011).

Investigation of this agent took place in two different neurological diseases: drug-resistant partial-onset epilepsies and Parkinson's disease (Rascol et al. 2012; Zaccara et al. 2013). The studies on patients with drug-resistant POS were carried out on little less than 1700 patients that were recruited in phase II and phase III (French et al. 2012; French et al. 2013; Krauss et al. 2012a).

After oral administration, absorption of perampanel is rapid and almost complete. Bioavailability was found to be complete with low systemic clearance after oral administration, consistent with a low first-pass metabolism. Fasting conditions do not affect the extent of absorption, but do slow drug absorption. After multiple oral dosing both the C_{max} and the AUC increase proportionally with dose. C_{max} of perampanel is reached within approximately 1 h. In humans, perampanel is 95 % bound to plasma proteins (Franco et al. 2013). The average $t_{1/2}$ of perampanel without concomitant inducer AEDs is approximately 105 h, the longest among the new generation AEDs, allowing once-daily dosing. Perampanel is extensively metabolised by primary oxidation mediated by CYP3A followed by glucuronidation. About 30 % of an orally administered dose of radio-labeled perampanel is found in the urine and 70 % in the faeces, primarily as a mixture of oxidative and conjugated metabolites (Franco et al. 2013). The pharmacokinetics of a single 1 mg dose of perampanel were examined in subjects with mild to moderate hepatic impairment. The mean apparent clearance of perampanel was lower in both mildly and moderately impaired subjects compared to demographically matched healthy subjects. In view of these pharmacokinetic properties of perampanel a dose reduction in hepatically impaired subjects should be considered. To date, no data have been reported on the perampanel pharmacokinetics in subjects with renal impairment (Franco et al. 2013).

The efficacy of perampanel was demonstrated in three phase III, randomized, placebo-controlled, double-blind, multicentre trials (studies 304, 305, and 306).

Studies 304 and 305 compared once-daily perampanel doses of 8 and 12 mg with placebo (French et al., 2012; 2013) and study 306 (Krauss et al. 2012a) compared once daily perampanel doses of 2, 4 and 8 mg with placebo. Design of trials scheduled a 6-week baseline, a starting dose of 2 mg/day and weekly increments of 2 mg/day to the target dose. The titration phase was followed by a 13 weeks maintenance period. In Study 304 patients were randomized to receive once daily treatment with perampanel 8 mg ($n=133$), perampanel 12 mg ($n=134$) or placebo ($n=121$), with a 19-week double-blind phase (6-week titration and 13-week maintenance period). The 50% responder rates compared to placebo for the intention-to-treat (ITT) population were 37.6% with 8 mg ($p=0.0760$), 36.1% with 12 mg ($p=0.0914$) versus 26.4% with placebo. The median percentage change in seizure frequency for the ITT population was: −26.3% with 8 mg ($p=0.0261$) and −34.5% with 12 mg ($p=0.0158$) versus −21.0% with placebo (French et al. 2012). In Study 305 patients on a stable regimen of 1–3 AEDs were randomized to receive once daily treatment with perampanel 8 mg ($n=129$), perampanel 12 mg ($n=121$) or placebo ($n=136$) in a 19-week double-blind treatment (6-week titration and 13-week maintenance period). The 50% responder rates compared to placebo for the ITT population were 33.3% with 8 mg ($p=0.0018$), 33.9% with 12 mg ($p<0.001$) versus 14.7% with placebo. The median percent change in seizure frequency for the ITT population were: −30.5% with 8 mg ($p<0.001$) and −17.6% with 12 mg ($p=0.011$) versus −9.7% with placebo (French et al. 2013). In Study 306 patients on a stable regimen of 1–3 AEDs were randomized to receive once daily treatment with perampanel 2 mg ($n=180$), perampanel 4 mg ($n=172$), perampanel 8 mg ($n=169$) or placebo ($n=185$) in a 19 week double-blind add-on treatment (6-week titration and 13-week maintenance period). The 50% responder rates of perampanel compared to placebo for the ITT population were 20.6% with 2 mg ($p=$ns), 28.5% with 4 mg ($p=0.013$) and 34.9% with 8 mg ($p<0.001$) versus 17.9% with placebo. The median percentage change in seizure frequency for the ITT population was −13.6% with perampanel 2 mg ($p=$ns), −23.3% with perampanel 4 mg ($p=0.003$) and −30.8% with perampanel 8 mg ($p<0.001$) versus −10.7% with placebo (Krauss et al. 2012a).

A good tolerability profile of perampanel emerges from a recent meta-analysis of randomized controlled trials which demonstrated that AEs were not significantly more frequent during perampanel treatment in respect to placebo (Krauss et al. 2012b). The two main AEs associated with perampanel were dizziness and ataxia. Moreover, perampanel has been associated with somnolence. Noteworthy, no AEs clearly related to cognition have been associated with the treatment with perampanel while the drug was associated to weight gain, the only non-neurological AE of this drug. Idiosyncratic AEs haven't been associated with perampanel since rash appeared in a number of patients so small that it was considered non-significant. Perampanel is metabolised partly by reactive metabolites and these are responsible of mediation of most immune-mediated idiosyncratic drug reactions (European Public Assessment Reports). These facts are reassuring but cannot exclude other rare idiosyncratic AEs because the number of subjects included in the RCTs was insufficient to detect them (Zaccara et al. 2007; 2013).

Perampanel is approved in Europe and the US as adjunctive therapy for adults with focal seizures with or without secondary generalization.

General Remarks and Conclusions

There is a remarkable array of new chemical entities in the current AED development pipeline. In some cases, the compounds were synthesized in an attempt improve upon the activity of marketed AEDs. In other cases, the discovery of antiepileptic potential was largely serendipitous. Entry into the pipeline begins with the demonstration of activity in one or more animal screening models. Results from testing in a panel of such models provide a basis to differentiate agents and may offer clues as to the mechanism. Target activity may then be defined through cell-based studies, often years after the initial identification of activity. Some pipeline compounds are believed to act through conventional targets, whereas others are structurally novel and may act by novel mechanisms. A variety of AEDs that may act through novel targets are also in clinical development. However, so far, the mechanism of action of an antiepileptic compound has been rarely useful to predict its efficacy. Moreover, some of the new agents have been already evaluated in various non-epileptic conditions, such as neuropathic pain, migraine, and Parkinson's disease and it is even more difficult to predict their impact of epilepsy treatment.

The ideal AED would be effective well-tolerated, easy to take, devoid of significant drug interactions. However, mechanisms underlying epileptogenesis are multiple and complex, and is probably a utopian ideal to realize "the gold standard" AED. Nevertheless, the challenge for new more efficacious, more specific, and better tolerated drugs is continuing and a better knowledge of mechanisms underlying epilepsy should represent the guide for future research. The ultimate goal of should be not only to render seizure-free the patients but also allow to improve quality of life of individuals and reduce costs of medical care. It remains to be demonstrated whether any of the AEDs in the pipeline will reach these objectives.

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Reproductive Hormones in Epilepsy Therapy: From Old Promises to New Hopes

Alberto Verrotti, Giovanni Prezioso, Claudia D'Egidio and Vincenzo Belcastro

Abstract A significant mutual interaction between sex hormones and the central nervous system has been reported by several studies in the past years.

This paper aims to discuss the genomic and electrophysiological effects of androgens, estrogens and progestogens on neurons, their influence on seizure frequency and antiepileptic drugs metabolism, and, conversely, the hormonal changes and reproductive dysfunction in patients with epilepsy.

In conclusion, the correlations between Polycystic Ovary Syndrome (PCOS), reduced effectiveness of contraceptives and antiepileptic drugs have also been mentioned.

Epilepsy represents one of the most frequent neurological diseases worldwide, affecting nearly 1 % of the population. It is characterized by the chronic recurrence of seizures in an unpredictable fashion. The prevention of seizures is the primary goal of epilepsy treatment. This requires the use of anti-epileptic drugs (AEDs) for the majority of patients.

Biological, experimental, and clinical studies for a number of years reported a noticeable interaction between epilepsy, AEDs and sex hormones.

Not only seizures and AEDs can induce significant changes in sex hormones regulation, sexual development, and reproductive functions, but also seizures and AEDs metabolism are strongly influenced by steroid hormones and their derivatives.

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Sex Hormones Role on CNS

Androgens, estrogens, and progestogens play a key role in shaping neural activity since prenatal life, moreover they exert a regulatory action on neurotransmitters and their receptors in neurons. Sex hormones interact with tissues, like the brain, by means of both receptor mediated and receptor-independent pathways. The first mechanism starts with nuclear receptor dimerization after hormone binding, thereafter the steroid-receptor complex in turn binds to and regulates the transcription of sex steroid responsive genes or post-transcriptional proteins. (Keefe 2002; Reddy 2009; Finocchi and Ferrari 2011) Each steroid receptor isoform is linked with different adapter protein and different response elements. Non-genomic effects of sex steroids have also been reported. (Keefe 2002) These effects are usually faster than nuclear receptor-mediated ones. Indeed, some steroids seem to conditioning electrophysiologic neuronal activity by interacting with high affinity on specific binding sites of the main neurotransmitter receptors, like GABA-A and NMDA receptors, effectively acting as neural stimulants or depressant. For instance, some of these hormones exert an agonist action on the GABA-A receptor even more potent than benzodiazepines and barbiturates, clearly affecting the epileptogenic activity. (Keefe 2002; Reddy 2009)

Estrogens show evident proconvulsant and epileptogenic properties, even if in sometimes they may exhert protective and anticonvulsant effects. Several studies have found estradiol (E2) both to enhance NMDA receptor activity and to temporarily decrease GABA inhibition. Moreover it appears to decrease GABA synthesis. There is also emerging evidence of hippocampus hyperexcitability due to estrogen and brain derived neurotrophic factor interactions (Foldvary-Schaefer et al. 2004; Erel and Guralp 2011; Finocchi and Ferrari 2011; Guille et al. 2008)

In contrast, clinical studies reported marked anticonvulsant qualities of progesterone, in particular of its 5α-reduced metabolites, like allopregnanolone. It has been demonstrated that glial and neuronal cells of the cerebral cortex and subcortical white matter are even able to synthesize by themselves from cholesterol these metabolites (neurosteroids). (Finocchi and Ferrari 2011; Reddy 2009; Guille et al. 2008). Neurosteroids activate the GABA receptor both directly, by binding two distinct sites different from the benzodiazepine or barbiturate sites, and indirectly, through a longer-term action on progesterone nuclear receptors. (Reddy 2009)

Nevertheless, proconvulsant neurosteroid acting as NMDA receptor agonists and GABA-A receptor antagonists have been identified (i.e. pregnenolone sulfate). (Reddy 2009)

In regards to androgens, testosterone affects neural activity depending on its conversion to androstanediol, which has anticonvulsant and GABA-A agonist property, and E2 with the aforementioned proconvulsant activity. (Reddy 2009; Keefe 2002; Hamed 2008)

Table 1 Three types of catamenial epilepsy. (modified from Reddy 2009)

Subcategories of catamenial epilepsy	Main characteristics
C1—perimenstrual	Due to the rapid decrease in anticonvulsant progesterone and neurosteroids blood level during days −3 to +3 which lead to descreased GABA inhibition
	Incidence: 71% of women with regular ovulatory cycles
C2—periovulatory	Due to the proconvulsant estrogen peak not balanced by an adequate level of neurosteroids in days 10–13. This requires a decrease in GABA inhibition and a marked excitation
	Incidence: 71% of women with regular ovulatory cycles
C3—inadequate luteal	Due to the insufficient brain levels of neurosteroids resulting from progesterone metabolism in anovulatory cycles. The final result is both a marked estradiol excitation and a persistent low GABA inhibition during days
	Incidence: 78% of women with anovulatory cycles (luteal phase)

Effects on Seizures-Catamenial Epilepsy

There is clinical evidence that interaction between steroid hormones and the CNS influences seizure susceptibility in epileptic patients. Being this especially evident in women, whose remarkable hormonal changes during puberty as well as pregnancy and menopause affect seizure frequency and AED metabolism. Moreover menopausal transition seems to have an effect on seizure susceptibility with a seizure increase of about 30% in women with epilepsy in perimenopause and a tendency to decrease after menopause, but there is no consensus on these findings (Erel and Guralp 2011; Røste et al. 2008).

Another clear proof of the role of sex hormones in seizure exacerbation is the catamenial epilepsy phenomenon in women. Catamenial epilepsy (CE) derives from the Greek word *katamenios*, which means "monthly", and it refers to a cyclical variation in seizures frequency in relation to menstrual cycle phases in women affected by epilepsy (genetic, structural, metabolic or of unknown cause), especially temporal-lobe epilepsy (Foldvary-Schaefer et al. 2004; Guille et al. 2008; Reddy and Rogawski, 2009; Pennell 2009; Pack 2010; Finocchi and Ferrari 2011). The incidence varies from 10 to 70% due to the lack of an unambiguous definition and to methodological differences among studies (Reddy 2009). A significant contribution to the study of CE was made by Herzog et al. (Herzog et al. 1997), who proposed the most accepted definition: a twofold increase in average daily frequency during a phase of menstrual cycle. They also described three subcategories of CE: C1 during the perimenstrual period, probably due to the withdrawal of allopregnanolone and other inibitory neurosteroids at the time of menstruation, C2 in the periovulatory phase, owing to an increase in estrogen concentration, defined above as proconvulsant, and C3, typical of the inadequate luteal phase of women with anovulatory cycles (see Table 1 and Fig. 1). A concurrent involvement in CE of AEDs blood level fluctuations and of the possible changes in water, pH, and electrolyte cannot

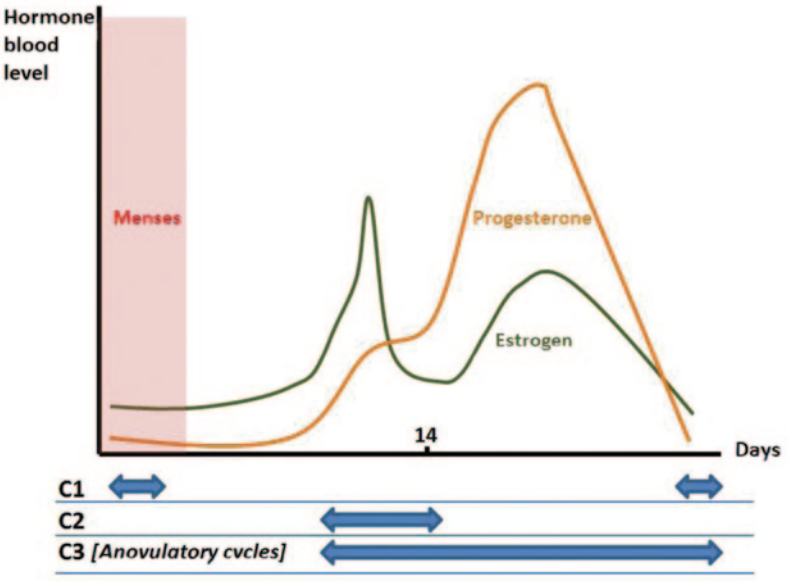

Fig. 1 Seizures distribution within the three patterns of catamenial epilepsy

be definitely ruled out, although hormonal oscillation maintains a key etiologic role (Pack 2010). A correct diagnosis of CE requires both careful compilation and evaluation of menstrual and seizure diaries as well as characterization of cycle type and duration (Reddy 2009; Foldvary-Schaefer et al. 2004). It is not rare to find women with CE presenting with state-dependant pharmacoresistance or intractable seizures (Reddy and Rogawski 2009). The first-line therapy includes the AEDs and usually requires cyclic dosage adjustments or supplement with other AEDs. Adjunctive hormonal treatment with progesterone or estrogen antagonists has been reported to augment seizure control in appropriate CE patients (Pack 2010; Herzog 1995, 1999). Natural progesterone, mainly converted to the anticonvulsant allopregnanolone, has been demonstrated to be effective in women with focal epilepsy and CE, even though it showed endocrine and CNS side effects (Herzog 1986, 1995, 1999; Pack 2010; Reddy 2009). Synthetic progestogen like Medroxyprogesterone is only partially converted to active neurosteroids, resulting in moderate improvement in seizure frequency (Zimmerman et al. 1973; Mattson et al. 1984). Nonetheless it provokes menses interruption and consequently reproductive disturbances in long-term therapy. On the contrary the use of combined oral contraceptives has a questionable effectiveness (Guille et al. 2008). Antiestrogens (clomiphene citrate), androgen, or synthetic gonadotropin-releasing hormone therapies have a limited utility as they show several adverse events (Foldvary-Schaefer et al. 2004). Great interest has been recently engendered about the use of Ganaxolone in CE. Ganaxolone is a synthetic analogue of allopregnanolone with potent positive action on GABA-A receptors resulting in anticonvulsant effect (Reddy 2009; Pack 2010; Guille et al.

2008; McAuley et al. 2001). Non-hormonal therapy of CE includes Acetazolamide, a carbonic anhydrase inhibitor with a broad spectrum of efficacy on seizures. The mechanism of action on seizure reduction is unclear, maybe a diuretic effect is implied. Since Acetazolamide is subject to tolerance as much as significant adverse events, it is usually administered intermittently (Reddy 2009; Ross 1958; Lim et al. 2001; Pack 2010).

Anyway, further investigation is needed in the matter of CE therapy given that data currently available largely belong to small non randomized studies and empirical evidence (Reddy 2009).

Effects of Seizures on Sex Functions

Epilepsy itself may directly influence the hypothalamic-pituitary axis (Herzog et al. 1986; Isojärvi et al. 2005; Scharfman et al. 2008) Preclinical investigations suggested that the involvement of medial temporal lobe regions in epilepsy may alter sex hormone secretion and reproductive functions. A dysregulation of GnRH pulsatility and therefore of LH/FSH ratio in epileptic women and of testosterone/LH ratio in epileptic men has been described (Verrotti et al. 2011; Drislane et al. 1994; Ciampani et al. 2005; Morell 2003; Herzog 2008; Hamed 2008; Fawley et al. 2006). Experimental studies reported an interesting correlation with laterality, even though datas are not univocal (Pack 2010; Quigg et al. 2009). Unilateral left-sided temporolimbic discharges seem to increase the pulse frequencies of GnRH secretion, resulting in a higher occurrence with PCOS, while right-sided temporolimbic discharges may decrease GnRH pulse frequency and are more commonly associated with sexual dysfunction (hypotalamic amenorrhea, functional hyperprolactinemia, infertility and premature menopause in women; decreased libido, abnormal semen analysis and reduced fertility in men with epilepsy) (Verrotti et al. 2011; Herzog et al. 1986; Morrell et al. 2005; Quigg et al. 2009; Harden 2008; Duncan et al. 2009).

Furthermore, some studies draw attention to the increased risk of premature ovarian failure and perimenopausal symptoms in women with epilepsy (Klein et al. 2001; Harden 2003).

Mutual Interactions Between Sex Hormones and AEDs

There is increasing evidence of AEDs contribution to sex dysfunction in epileptic patients. Indeed, studies suggest that AEDs may variably influence both the steroid hormones metabolism and their binding proteins (Hamed 2008; Bauer et al. 2002). Enzyme-inducing AEDs (EIAEDs)—such as phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ)—rather than non-EIAEDs (NEIAEDs) have been known to play a critical role in steroid hormones abnormalities (see Table 2). EIAEDs can

Table 2 EIAEDs and NEIAEDs. (modified from Reddy 2009)

EIAEDs	NEIAEDs
Carbamazepine	Clobazam
Oxcarbazepine	Clonazepam
Phenobaribatal	Ethosuximide
Methylphenobarbital	Mesuximide
Phenobarbital sodium	Valproic Acid[a]
Phenytoin	Lamotrigine
Fosphenytoin sodium	Gabapentin
Felbamate	Pregabalin
Topiramate	Vigabatrin
Primidone	Tiagabine
	Zonisamide
	Sultiame
	Beclamide
	Levetriacetam
	Rufinamide
	Stripentol

[a] weak CYP inducer

induce hepatic cytochrome P450 (CYP450), a system of mixed oxidative enzymes which metabolizes AEDs to a more water-soluble form. As the CYP450 is involved in steroids metabolism, its induction implies a faster hormone clearance (Isojärvi et al. 2005). In addition, EIAEDs were found to increase serum sex hormone-binding globulin (SHBG) levels in patients with epilepsy, reducing biologically active steroid hormones like DHEAS, T, free androgen index, and E2 (Pennell 2009; Erel and Guralp 2011; Verrotti et al. 2011). This may result in impotence and decreased fertility in men, hyperandrogenism and menstrual disorders in women. EIAEDs may also correlate with hypogonadotropic hypogonadism, by inhibiting LH secretion, and with decreasing libido and potency, by increasing the conversion of testosterone to E2 (Hamed 2008).

Anyway also NEIAEDs have been found to be involved in hormonal dysregulation. Valproate (VPA), in particular, seems to be associated with high serum concentrations of T, androstenedione and DHEAS, and with increase in levels of LH and LH/FSH ratio, leading to polycystic ovary syndrome, hyperandrogenism and amenorrhea in women, reduced feritlity and sperm abnormalities in morphology, count and motility in men (Verrotti et al. 2011; Isojärvi et al. 1993; Prabhakar et al. 2007; Rauchenzauner et al. 2010; Xiaotian et al. 2013; Morrell et al. 2005; Chen et al. 1992). Even if not yet clear, VPA may directly alter androgen production in ovaries or it may act indirectly, by inhibiting steroid hormones metabolism and thereby increasing serum androgen levels. It is noticeable that hyperandrogenism has been evidenced more frequently in women who have gained weight during VPA therapy and in those who started treatment before the age of twenty.

Low prevalence of reproductive disorders has been reported during therapy with new AEDs like oxcarbazepine and lamotrigine (LTG), but no data are available for a number of other new AEDs. Besides, women on LTG, previously treated with VPA, seems to show a marked improvement in reproductive dysfunction (Isojärvi et al. 1998).

PCOS and AEDs

Among reproductive dysfunctions, PCO and PCOS appears to be particularly common in epileptic women (10–25 versus 5–6% of health women) (Herzog et al. 2003). Even though PCOS has been detected in non-treated epileptic patients, several studies highlighted an increased incidence during AED treatment, in particular with VPA, but the evidence still remains controversial (Isojärvi et al. 1993, 1995, 1996, 2001; Morrell et al. 2002, 2008; Betts et al. 2003; Prabhakar et al. 2007). Special attention should be directed to weight gain and insulin resistance, which can be common adverse effects of vigabatrin, carbamazepine and gabapentin other than VPA, because they have been reported as important risk factors for PCOS (Verrotti et al. 2011). Elevated serum leptin, impaired adipokine regulation, and low serum IGFBP-1 levels have been linked to VPA-related obesity in women with epilepsy (Belcastro et al. 2013; Greco et al. 2005; Gungor et al. 2007; Verrotti et al. 2011, 1999; Rauchenzauner et al. 2008). Moreover, VPA seems also able to stimulate insulin secretion both indirectly, by increasing free fatty acids levels in blood through albumin binding competition and directly by stimulating pancreatic b-cells and inhibiting glucose transporter protein type 1 (GLUT-1) activity (Luef et al. 2002, 2009, 2003; Wong et al. 2005; Belcastro et al. 2013; Evans et al. 2003). Finally, the inhibition of sympathetic nervous system, the impairment of insulin signal transduction pathway and the direct influence on the ovary via aromatase inhibition are other proposed mechanism of action of VPA (Verrotti et al. 2011). It has been demonstrated that all of these metabolic abnormalities predispose also to metabolic syndrome, which is frequently detected among VPA overweight patients as a consequence of the excess fat mass (Belcastro et al. 2013; Verrotti et al. 2010; see Fig. 2).

On the other hand, EIAEDs like phenitoine and CBZ may prevent from the development of PCOS, by reducing free T levels.

Contraceptive and AEDs

EIAEDs may also interfere with oral contraceptive pills (OCPs) efficacy similarly by reducing the biological active hormone concentrations and allowing ovulations. In order to reduce the risk of unplanned pregnancies it is recommended to

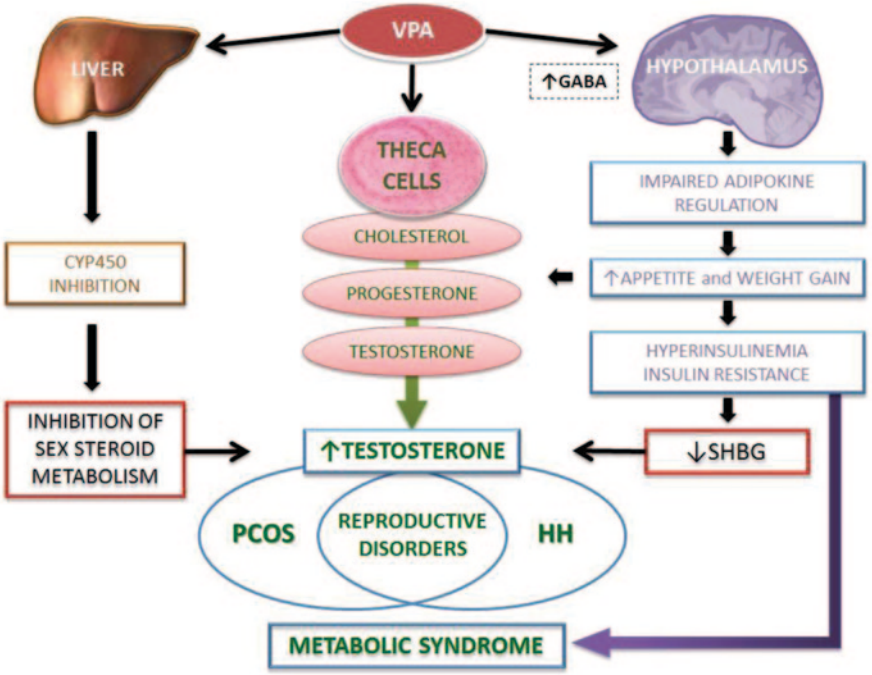

Fig. 2 Hormonal and metabolic alterations in VPA therapy. (modified from Verrotti et al.2011)

prescribe an OCP with higher doses of ethinyl estradiol (≥ 50 micrograms) and to use additional non-hormonal forms of contraception (Erel and Guralp 2011; Bartoli et al. 1997; Pennell 2009; Guberman 1999).

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Neuromodulation for the Treatment of Drug-Resistant Epilepsy

Pantaleo Romanelli and Alfredo Conti

Abstract Surgical neuromodulation for epilepsy refers to procedures involving the electrical stimulation of cortical, diencephalic, cerebellar and peripheral targets (such as the vagus nerve). Stereotactic radiosurgery also provides a neuromodulatory approach, affecting the discharging behavior of epileptic neurons in absence of evident target necrosis. Cortical transections or Multiple Subpial Transections (MST) are a non-resective technique useful to treat epileptogenic foci located in eloquent cortex. Electrical stimulation, stereotactic radiosurgery, and MST are emerging procedures for the treatment of medically refractory epilepsy in patients not amenable to resective surgery due to inability to map the focus, presence of multiple epileptogenic foci and/or involvement of eloquent cortex. Radiosurgery can also be offered to patients ineligible for invasive surgery for a variety of medical contraindications.

Introduction

Epilepsy is the most common chronic neurological disorder affecting approximately 1 % of the population worldwide. About one-third of the patients with epilepsy respond poorly to medical therapy with the initial response being highly predictive of long-term seizure control (Go and Snead 2008; Kuzniecky and Devinsky 2007). Patients who are poor responders to established medical treatments are exposed to the long-term medical and social sequelae of intractable seizures leading to multiple hospital admissions and chronic disability. Patients with uncontrolled generalized

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tonic-clonic seizures also have a substantially increased risk of death either due to trauma, sudden unexplained cardiorespiratory arrest, or sudden unexplained death in epilepsy (SUDEP) (Go and Snead 2008; Kuzniecky and Devinsky 2007; Cascino 2004; Tolstykh and Cavazos 2013).

Identification of the epileptic focus and subsequent surgical resection is the gold standard for the treatment of medically refractory seizures. Resective surgery can be performed when a concordant localization of the seizure focus is obtained based on seizure semiology, EEG and MRI, with further support provided by advanced techniques such as magnetic resonance spectroscopy (MRS), magnetoenecephalography (MEG), ictal and interictal SPECT, and PET.

Mesial temporal lobe resection provides excellent outcomes in terms of seizure freedom with rare serious complications while neocortical epilepsy has lower, but still appealing rates of post-surgical seizure freedom (Jette and Wiebe 2013).

However, a large number of refractory patients cannot be selected for resective surgery due to the inability to identify and localize the epileptogenic focus or to the overlap between the epileptogenic focus with eloquent neo-cortex (sensorimotor, speech areas) or archicortex (dominant hippocampus), which cannot be resected without inducing serious neurologic sequelae. Seizure foci located in close proximity to eloquent cortex can be safely resected but accurate cortical mapping is mandatory (Bauman et al. 2005; Devinsky et al. 2003). Detection of multiple independent seizure foci is generally considered a contraindication to resective surgery, but in highly selected cases, multiple resections guided by staged cortical mapping can still provide positive seizure control (Devinsky et al. 2003; Romanelli et al. 2001, 2002; Bauman et al. 2008).

Neuromodulation is an emerging surgical option employed to treat patients when resective surgery is contraindicated (Anderson et al. 2009; Romanelli et al. 2012; Saillet et al. 2009). It is commonly reserved for patients who are not candidates for resective surgery due to poor localization of the epileptic zone, spatial co-localization of ictal focus and eloquent cortex, presence of multiple independent ictal foci or seizure origin located in deep brain regions. In such circumstances surgical approaches to entirely and effectively remove the epileptogenic tissue carry a relevant risk of new neurological deficits (the typical case of Hypothalamic Hamartomas [HH]).

Neuromodulation is a non-resective approach to the treatment of epilepsy that has historically included the delivery of electrical stimulation to selected brain regions or to the vagus nerve. Other non-resective approaches such as stereotactic radiosurgery and multiple subpial transections, which affect the pathophysiology of an epileptic focus without removing it, can also be included in this definition. This paper provides a concise review of the following neuromodulatory treatments: vagus nerve stimulation (VNS), deep brain stimulation (DBS), the new responsive neurostimulation devices, stereotactic radiosurgery, and multiple subpial transections.

Vagus Nerve Stimulation

Vagus nerve stimulation is the most common neuromodulation procedure for the treatment of epilepsy. It is usually offered to patients with severe medically-refractory epilepsy who are not eligible for or not responsive to microsurgical resection. Vagus nerve stimulation is characterized by low surgical risk and lack of significant toxicity and has been approved for the treatment and prevention of refractory seizures in adults and adolescents by the European and US regulatory boards in 1994 and 1997, respectively.

According to Cyberonics, the manufacturer of the VNS, the device has been implanted in over 65,000 patients worldwide (http://eu.cyberonics.com/en/vns-therapy/healthcare-professionals/implanted-components). Despite the extensive clinical use, a satisfactory explanation of the mechanism of action of VNS in epilepsy is not yet available. Modulation of the brainstem, thalamic insular and limbic targets exerted by the afferent branches of the vagus nerve is involved in the anti-epileptic effect of VNS, but a coherent framework explaining why the patient's response is so widely unpredictable is still missing. The development of implant strategies based on improved patient response prediction is an essential step needed for the progress of VNS.

Vagus nerve stimulation placement requires a delicate but quick microsurgical procedure on the left vagus nerve (selected to minimize vegetative side-effects). The nerve is identified and dissected by spreading apart the carotid artery medially and the jugular vein laterally. Three coils are looped around the left vagus nerve in order to minimize vegetative side effects. From a patient perspective, VNS implant surgery is usually performed on an outpatient basis, or at times, patients may need to stay in the hospital for one day. Complication rates are usually minimal, but stimulation-induced side effects such as dysphonia (20–30 %) and cough (6 %) are relatively common. These side effects are usually transient and can be managed by the reduction of stimulation intensity (Ben-Menachem et al. 1999; Uthman et al. 2004). Other side effects such as sleep apnea or cardiopulmonary dysfunction are very rare (Papacostas et al. 2007).

The long term safety and efficacy of VNS in the adjunctive treatment of epilepsy have been widely reported over the years both in adults and children (Baaj et al. 2008; Ben-Menachem et al. 1999; Benifla et al. 2006; Uthman et al. 2004). Reduction of seizure frequency following VNS implantation occurs over time, with further improvement in seizure reduction recorded 1 year after VNS implantation (Mapstone 2008). The number of patients achieving complete seizure freedom after VNS is very small (≈2 %), while an approximate 40 % of patients achieving a substantial reduction (more than 50 %) of seizure frequency and intensity is commonly reported (Mapstone 2008). A noticeable improvement in social, affective and behavioral scores in association with the ability to reduce the medical therapy load has been reported in responsive patients (Baaj et al. 2008; Ben-Menachem et al. 1999; Benifla et al. 2006; Uthman et al. 2004). Overall, VNS is a safe and well-tolerated therapy providing improved seizure control to some patients. The

main shortcomings of VNS therapy are the unpredictability of response, cost of the device, and the need for additional minor surgeries to replace the battery. A better understanding of the mechanism of action of VNS is needed to pave the way for improved, targeted patient selection.

Deep Brain Stimulation

Deep brain stimulation (DBS) is a minimally invasive neuromodulation technique of proven efficacy in the treatment of movement disorders such as Parkinson's disease. Treatment of medically refractory epilepsy is one of the many emerging DBS applications. As for VNS, the DBS mechanism of action in the suppression of epileptic activity is not entirely clear. The insertion of a DBS lead within a neural network acts to modulate seizures either through direct electrical stimulation or by a microlesional effect, or some combination of both (Van Roost et al. 2007; Stacey and Litt 2008). The anterior or centromedian nucleus of the thalamus, subthalamic nucleus, caudate nucleus, hippocampus, hypothalamus, and cerebellum are among the DBS explored targets (Ellis and Stevens 2008). The cerebellum was one of the earliest structures studied for stimulation in epilepsy patients, though only modest efficacy has been reported with modulation of this target alone (Fountas et al. 2010; Davis and Emmonds 1992; Cooper et al. 1976). The caudate nucleus has been explored as well as a brain stimulation target to improve epilepsy (Chkhenkeli and Chkhenkeli 1997): low frequency stimulation induced some improvement in the frequency of generalized seizures, but this has not generalized to firm conclusions about the true overall efficacy of the treatment.

The anterior (ANT) nucleus of the thalamus is the most attractive and explored DBS target due to its central position within the limbic system. The main output pathway of the limbic system proceeds from the hippocampus to the mammillary body, which innervates the ANT through the mammillo-thalamic tract. Within the ANT, massive projections to the cingulate gyrus and to the frontal lobe justify its definition as the "pacemaker for the cortex" and its crucial role in the genesis of generalized seizures (Mirski and Ferrendelli 1986). Bilateral ANT DBS is a widely explored procedure that is facilitated by relatively easy surgical targeting. Widely different clinical indications and outcomes have been reported (Andrade et al. 2006; Hodaie et al. 2002; Kerrigan et al. 2004; Lee et al. 2006; Osorio et al. 2005; Upton et al. 1985; Velasco et al. 2001). Overall, the procedure has been found to be relatively safe and well-tolerated while the seizure control rate is quite variable. A large multicenter randomized double-blinded trial was performed on over 100 subjects, which demonstrated an efficacy on seizure control similar to that offered by VNS (Fisher et al. 2010). Median decline in seizures was 40.5 % in the stimulated group and 14.5 % in the control group, while seizure intensity was improved as well. After 2 years of chronic high-frequency and high-intensity stimulation, 54 % of patients noted seizure reductions while 14 patients (12.7 %) were seizure-free for at least 6 months. Overall, these are encouraging results; however, the cost of bilateral DBS

implantation and frequent changes of battery are known considerations. Relatively high stimulation intensities were needed, requiring frequent changes of battery, which is most likely related to the large volume of the ANT. Current DBS design was developed in order to stimulate relatively small neural volumes. ANT has an overwhelmingly larger volume than that of common DBS targets such as the subthalamic nucleus (STN), the ventrolateral thalamic nuclei or the Globus Pallidus pars interna. Insertion of multiple leads or new designs are likely to be necessary in order to provide an adequate ANT stimulation coverage.

The medial thalamus, namely the centromedian nucleus (CM), was explored as a DBS target by Velasco and colleagues (Velasco et al. 2001). This nucleus has a much smaller size than the ANT, though much larger than STN, and is likely to be more responsive to DBS than ANT. CM projects widely to the neocortex and research suggests that modulation of this nucleus exerts an antiepileptic effect mediated by cortical desynchronization (Velasco et al. 2001). There are mixed reports ranging from modest to significant improvements in seizure control for the treatment of focal epilepsy with secondary generalization (Velasco et al. 1987) and Lennox-Gastaut syndrome (Velasco et al. 2001; Shimizu and Maehara 2000) using DBS in the CM.

The subthalamic nucleus (STN) is the main DBS target for movement disorders. In addition, STN DBS has been explored also as treatment for refractory epilepsy. The antiepileptic effect of STN DBS is thought to be mediated by the inhibition of the excitatory effect of the substantia nigra pars reticulata (SNr) on gabaergic neurons in the dorsal midbrain anticonvulsant zone (DMAZ), placed in the deep layers of the superior culliculus (Gale 1986; Iadarola and Gale 1982).The extensive STN projections to sensorimotor cortex could also exert a crucial role on the control of tonic and clonic seizures. The first successful treatment of refractory epilepsy by DBS in a child with cortical dysplasia was reported by Benabid et al. (Benabid et al. 2001). Seizure reduction ranging between 60 % and 80 % in refractory focal epilepsies has been subsequently reported by various groups (Chabardes et al. 2002; Dinner et al. 2002; Vonck et al. 2003; Shon et al. 2005). A 50 % seizure reduction rate has also been observed in progressive myoclonic epilepsy (PME) (Vesper et al. 2007). Overall, similarly to CM DBS, the number of cases reported so far is small and heterogeneous and no prospective trials have been performed. On the other hand, STN is the most explored DBS target: DBS placement here is facilitated by the unique electrophysiological STN signature found when performing microelectrode recording. Therefore a precise assessment of DBS placement (usually done within the sensorimotor domain) is much easier here than in ANT or CM, where no electrophysiologic signatures are available. STN is likely to represent a useful target to treat seizures characterized by a predominant motor component. Further studies are clearly needed to assess the role of STN DBS in the treatment of refractory epilepsy but also to inform the process of DBS thalamic (ANT, CM) versus basal ganglia (STN) target selection in general.

The hippocampus and amygdala are two of the most epileptogenic areas of the brain, and thus are the most common origins of refractory epilepsy. Microsurgical resection of the amygdalo-hippocampal complex is also the most common surgical

procedure for epilepsy and is associated with post-operative resolution of seizures in up 75% of patients (Schramm 2008). DBS placement within the hippocampus has been used experimentally for poor candidates for resective surgery, such as those with bilateral ictal localization, or in whom preoperative neurophysiological findings (e.g., WADA test) predict a significant potential for memory loss. The elongated shape of the hippocampus fits very well with the insertion of DBS leads but the stimulation volume is rather large and the current DBS design is surely not optimized for this indication. Test stimulation is performed after DBS placement as continuous high-frequency square-wave pulses. A subclavicular internal pulse generator is then placed and connected via an extension cable to the implanted leads, providing chronic stimulation if a substantial reduction of interictal spike activity during a period of acute stimulation is witnessed (Boon et al. 2007; Van Roost et al. 2007). No major surgical complications have been reported, but high intensity stimulation may induce reversible memory deficts (Boex et al. 2011). A microlesional effect has been also described. Seizure outcomes are quite variable within and across the studies (Boon et al. 2007; Van Roost et al. 2007; Boex et al. 2011; McLachlan et al. 2010).

Hippocampal DBS is a procedure of great interest to treat mesiotemporal lobe epilepsy (MTLE), especially when resective surgery is not indicated. However, experience is limited, reported seizure outcomes are widely variable, and optimal stimulation protocols have not yet been defined. This is also true for other neuromodulation procedures for epilepsy: the field is promising but much more work is needed to assess the overall utility, role and impact of DBS, as well as the best criteria for patient selection.

Responsive Stimulation

The main limitation of current DBS is the inability to adapt the stimulation field and intensity to changing conditions such as those typical of an epileptic focus. Responsive stimulation aims to predict and respond to seizures, suppressing epileptiform activity by delivering stimulation in response to electrocorticographic activity (Litt 2003; Sun et al. 2008).

Responsive stimulation requires preliminary cortical mapping and then acts directly on the seizure focus. Stimulation is not continuous as is the case in DBS (closed-loop stimulation), but is provided only at specific times to abort oncoming seizures, thus potentially reducing the likelihood of functional disruption or habituation due to continuous treatment (Litt and Echauz 2002). The electrodes delivering open-loop stimulation can record the electrical activity of the target and stimulate "on demand", in a pacemaker-wise fashion. Electrocorticographic activity over the target region is continuously monitored: when abnormal activity is detected, electrical stimulation is delivered to abort the epileptic discharge and restore normal electrical rhythm. In essence, the device recognizes specific brain discharges indicating a high risk for evolution into clinical seizures and acts to abort their propagation.

A pilot trial of four patients with refractory seizures treated with responsive cortical stimulation showed suppression of clinical seizures with resolution of electrographic seizure activity (Kossoff et al. 2004). Responsive cortical stimulation using the RNS System (NeuroPace, Mountain View, CA), provides a continuous electrocorticographic analysis triggering the stimulation when ictal or pre-ictal activity is detected, was studied in patients with refractory partial-onset seizures (Morrell 2011). This large, prospective, multicenter, randomized double-blind trial has been performed on 191 adults undergoing placement of subdural or depth electrodes over 1 or 2 selected seizure foci. Overall, the procedure was safe and well-tolerated. A 37.9 % reduction in mean seizure frequency in the treatment group compared with a 17.3 % reduction in the sham group ($p = 0.012$) was found during a 12-week period. After 2 years follow-up, 46 % of patients had at least a 50 % reduction in their mean seizure frequency. Verbal functioning, visuospatial ability, and memory showed some improvement as well. These results again appear grossly comparable to those of VNS. Again, further work is needed in order to identify appropriate clinical and patient selection characteristics to ensure the best clinical outcomes.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) is a strikingly effective approach to treat a variety of brain tumors but is also an excellent tool to treat functional brain disorders such as trigeminal neuralgia. The attractiveness of a non-invasive treatment devoid of the risks and discomforts associated with open surgery and general anesthesia as well as the excellent results obtained explain the exponential growth of SRS over the last decade (Niranjan et al. 2012). Treatment of epilepsy is an emerging application of SRS: it was initially observed that secondary epilepsy improves after radiosurgical treatment of the underlying lesion. Following this observation, radiosurgery was proposed as a primary treatment for idiopathic localization-related epilepsy (Romanelli and Anschel 2006). Most reports focus on the treatment of secondary epilepsy, caused by intrinsic brain tumors, arteriovenous malformations (AVMs) or cavernomas, with a smaller number of recent papers describing the SRS in the treatment of epilepsy related to mesial temporal sclerosis or hypothalamic hamartoma (Regis et al. 2002b; Schrottner et al. 2002; Romanelli et al. 2008; Regis et al. 2004b). In most cases, no evident neuroradiologic or histologic changes can be appreciated over the epileptic region following treatment with SRS, which is in agreement with the fact that the doses received are usually too low to induce radionecrosis (Regis et al. 1996; Romanelli and Anschel 2006; Srikijvilaikul et al. 2004). Irradiation of epileptogenic cortex using non-necrotizing doses is associated with modulation of neurotransmitters and reduction of pathological discharges while normal neuronal activity is preserved (Regis et al. 2002a). As a non-invasive procedure, SRS provides an attractive treatment option for those cases where non-invasive seizure mapping can be achieved. Low-dose irradiation of seizure foci located in eloquent regions using magnetoencephalography (MEG)-guided SRS is

a good example of a thoroughly non-invasive mapping and treatment approach providing a safe and effective procedure for highly challenging or inoperable lesions (Kurita et al. 2001; Stefan et al. 1998). The refinement and availability of non-invasive mapping techiques for refractory epilepsy is clearly a condition sine qua non needed for the evaluation of radiosurgical treatments for epilepsy. The rapid evolution of MR imaging and the introduction of high density surface EEG (Ramon and Holmes 2013) are likely to provide the needed support for an increasing use of SRS in the treatment of epilepsy in future years.

Treatment of mesial temporal lobe epilepsy (MTLE) by stereotactic radiosurgery was first reported by Regis et al. (Regis et al. 2004b). In a recent prospective multicenter pilot trial, two different radiosurgery doses were compared and the overall seizure remission rate was 69 % during the third follow-up year after treatment, which is comparable to that reported for resective temporal lobectomy (Chang et al. 2010). The main shortcoming of SRS in the treatment of mesial temporal lobe epilepsy is the long delay to appreciate a visible effect on seizures.

Furthermore, SRS appears to be an excellent treatment option for hypothalamic hamartomas (HH), which are typically associated with severe medically-refractory epilepsy (Arita et al. 1998; Regis et al. 2004a; Rosenfeld 2011; Schulze-Bonhage et al. 2004; Selch et al. 2005). The efficacy of SRS for the treatment of severe epilepsy induced by HH is strictly bound to the delivery of adequate doses, with the best results obtained by prescribing a marginal dose of > 17 Gy. The post-operative course may be characterized by an increased number of seizures, sometimes with a large number over only several days. The duration of this period is brief, days or weeks, and rarely more than 1 month and it is followed by a gradual overall improvement (Regis et al. 2007; Romanelli et al. 2008). So far, no major neurological complications following SRS have been reported; this is of great importance considering the complexity and overall risks of open surgical approaches. Surgical and radiosurgical treatments can be easily integrated in patients with large HH. In such cases, a surgical debulking procedure could be followed by radiosurgery delivered to the unresectable epileptogenic intrahypothalamic component.

A large amount of retrospective data is available regarding seizure outcomes following the treatment of arteriovenous malformations (AMVs) with SRS. Pollock and coworkers (Pollock et al. 1994) retrospectively studied 67 patients with smaller AVMs (Spetzler-Martin Grade I or II) that were potentially resectable by surgery. All subjects had been first offered surgical resection, and had declined. Two patients were lost to follow-up, leaving 65 subjects who had data collected for a minimum of 24 months (mean 35 months). Thirty-one patients (47.7 %) had experienced symptomatic seizures prior to radiosurgery. Mean AVM volume was 3.1 cm^3, with a mean marginal dose of 21 Gy (maximum dose: 36 Gy). Sixteen patients (52 %) had seizure frequency reduced to < 1 seizure per year, while 15 had no change in seizure control. No patients developed new seizures following treatment. There was a 7.7 % hemorrhage rate and a 3 % mortality rate (due to hemorrhage) within 8 months following radiosurgery; however there was no risk of bleeding if there was total obliteration or subtotal obliteration with patency of early draining veins only.

A retrospective review of 40 pediatric cases of AVMs treated by a multimodality approach and followed for a mean of 38.7 months has been reported by Hoh et al. (Hoh et al. 2000). Ten patients with AVM-related seizures were treated with proton beam radiotherapy if lesions were located in eloquent areas or had a particular pattern of venous drainage. Mean dose was 15.9 Gy to a mean volume of 9.9 cm^3. Nine out of ten patients (90%) became seizure free following treatment. It should be noted that AVM embolization was also performed concurrently and seizure outcome was not analyzed in detail to assess the respective weight of radiosurgery versus embolization in the outcome of seizure freedom. The authors report no radiosurgery-related complications or morbidity. One patient had a hemorrhage after radiosurgery, before the AVM had been obliterated.

A further retrospective study published by the same group in 2002 reports on 141 patients with AVMs and seizures, representing 33% of 424 patients treated for AVM over an eight year period (Hoh et al. 2002). Follow-up data have been available for 110 patients out of 141.These patients were treated with a multimodality, multidisciplinary approach including various combinations of surgery, radiosurgery, and embolization. Mean follow-up period was 34.8 months. Those who received radiosurgery were treated with proton beam therapy with a mean dose of 15.5 Gy to a mean volume of 7.7 cm^3. These investigators identified the following pre-treatment risk factors for the development of symptomatic seizures with AVM: male gender, age <65 years, AVM size >3 cm, and temporal lobe AVM location. Of the 110 patients treated with the multiple modalities, 73 (66%) were seizure-free (Engel Class I), 11 (10%) were Class II, 1 (0.9%) was Class III, and 22 (20%) were Class IV. Treatment-specific analysis revealed that surgery had the highest number of patients with Class I outcome (81%), followed by embolization (50%), and then radiosurgery (43%). However, if the AVM was completely obliterated, then all treatments yielded the same percentage of patients with a Class I outcome. The following factors were associated with a Class I outcome: short seizure history, associated intracranial hemorrhage, generalized tonic-clonic seizure type, deep and posterior fossa AVM location, surgical resection, and complete AVM obliteration. In addition 5.7% of patients who did not have pre-treatment symptomatic seizures, subsequently developed seizures.

Hadjipanayis (Hadjipanayis et al. 2001) selected thirty-three patients with AVMs of the precentral gyrus for retrospective study out of a group of 770 patients treated Gamma Knife radiosurgery for AVMs. Median AVM volume was 3 cm^3 and the median dose to the margin was 20 Gy. Twenty-seven (87%) of the patients had initially presented with seizures. After a mean follow-up of 54 months, there was a 63% rate of seizure freedom. The remaining 37% continued to experience seizures. The following variables showed no relationship to seizure control: marginal dose, volume, Spetzler-Martin grade, gender, age, and perimotor versus motor cortex location. Two patients (6%) developed new bleeding at 12 and 23 months post-radiosurgery, resulting in one death (3%). Hand weakness occurred in one subject with an 8.4 cm^3 target volume and another patient developed subjective sensory, visual, and auditory deficits. This adverse effect profile compares favorably with most of the surgical resection series involving a similar population.

Schauble et al. (Schauble et al. 2004) identified 70 patients with AVM-associated seizures who had been treated by Gamma Knife radiosurgery. 10.3 cm^3 average tissue volume was treated with a prescription isodose average of 18 Gy. Patients were evaluated at 1, 2, and 3 years post treatment. However, a potentially significant bias was introduced by the fact that patients requiring retreatment before year 1, 2 or 3 were excluded from evaluation at all further time points. Therefore, the most poorly responding patients were excluded from long-term follow-up. Sixty-five patients were studied at the 1-year time point and 51 at the 3-year time point. At 1 and 3 years, 74 and 78 % respectively, had an excellent outcome (non-disabling seizures only). Seizure-free rates at years 1 and 3 were 45 % and 51 % respectively. Factors predictive of a favorable outcome included low seizure frequency before radiosurgery, presence of generalized tonic-clonic seizure, and smaller size AVM. There was a 5 % mortality rate from AVM-related hemorrhages post radiosurgery. In addition, one patient died due to "worsening edema." The total post-radiosurgery hemorrhage rate is not reported.

Seizure improvement has been also reported after SRS for cavernous malformations (CM). Over a 17-year period, 95 patients were treated for CMs by proton beam therapy at Massachusetts General Hospital. This group was retrospectively analyzed with an average follow-up of 5.4 years by Amin-Hanjani et al. (Amin-Hanjani et al. 1998). The patients had been treated with radiosurgery if there were symptomatic CMs in locations where the risk of surgical morbidity was deemed unacceptable or based on failed previous attempts at surgical resection. Median volume treated was 3.1 cm^3, with a median marginal dose of 16.5 Gy (90 % isodose). During the first 2 years after treatment, there was a 22.4 % per year per lesion hemorrhage rate (17.4 % pretreatment), however after 2 years, the rate decreased to 4.5 %. In addition to a 16.3 % rate of permanent neurological disability, there was a 3.2 % mortality rate due to hemorrhage within the first 2 years after radiosurgery. Eighteen of the subjects had seizures prior to treatment. There was a significant improvement in seizure control after treatment and no patients developed new onset seizures or intractable epilepsy after treatment. Although disability increased after radiotherapy overall, the greatest risk was in those patients with deep CMs. There were no deaths among those with lobar lesions. Since seizures were prominent in those with lobar CMs, the chance for neurological deterioration was lower in patients with seizures.

Regis et al. (Regis et al. 2000) published a retrospective multicenter report of 49 patients treated for CMs with Gamma Knife radiosurgery. All patients had drug-resistant epilepsy and were followed for greater than 12 months following treatment. Mean dose at the margin of the lesion and volume were 19.17 Gy and 2.4 cm^3 respectively. Fifty-three percent of the patients became seizure-free (Engel Class I) while 20 % experienced a significant decrease in number of seizures and 26 % had little or no improvement. The average time to seizure remission was 4 months. Five of the patients who failed to improve following radiosurgery were treated with microsurgery. Three of these later patients became seizure free, one has rare seizures, and one has "failed completely." One patient experienced a hemorrhage 3 months following radiosurgery. Seven patients developed severe radio-induced

edema. Better outcome was associated with simple partial seizures, compared with complex partial seizure type. Mesiotemporal location was also associated with a poor outcome while lateral-temporal location was associated with a good outcome.

The combination of non-invasive mapping and frameless radiosurgical treatment using the Cyberknife to treat selected cases of drug-refractory epilepsy has been recently described (Romanelli 2014).

Even if dedicated studies are rare, the selected studies discussed indicate that SRS can provide seizure improvement or freedom in selected patients with MTLE, HH, tumors, AVMs and CMs. Patients with seizure foci located near or over eloquent cortex can substantially benefit from SRS. An expanded use of SRS can be anticipated in parallel with the development of non-invasive seizure mapping techniques.

Multiple Subpial Transections

Multiple subpial transections (MST) refer to a microsurgical procedure aiming to cut the horizontal connections mediating epileptic activity diffusion from the ictal focus to adjacent and distant cortex (Blount et al. 2004; Devinsky et al. 1994; Dogali et al. 1993; Hashizume and Tanaka 1998). MST can be considered a neuromodulatory technique because the cortex generating seizures is not resected, but rather modified to prevent the development of synchronized pathological ictal discharges in the cortex (Morrell and Hanbery 1969; Sawhney et al. 1995). This procedure predates the introduction of electrical neuromodulation and radiosurgery in the treatment of epilepsy and was, for over two decades, the only surgical option to treat patients with medically-refractory epilepsy involving eloquent cortex (Blount et al. 2004; Devinsky et al. 1994; Dogali et al. 1993; Hashizume and Tanaka 1998; Morrell and Hanbery 1969; Mulligan et al. 2001; Sawhney et al. 1995; Schramm et al. 2002; Spencer et al. 2002).

The cerebral cortex is functionally organized in vertically oriented columns of neurons working as a homogeneous processing unit. The output of the columnar networks is mainly transmitted by vertical axons directed to near or far cortical regions, to the thalamus and basal ganglia, or to the brainstem and spinal cord while adjacent columns are interconnected by horizontal axons, providing the recruitment and synchronization of the critical mass of cortex needed to generate seizures (Chervin et al. 1988; Hubel and Wiesel 1962; Mountcastle 1957; Mountcastle 1997). The spread of epileptic activity follows a non-uniform horizontal spatial pattern involving the cortical layer V, which acts as the seizure trigger (Lueders et al. 1981; Telfeian and Connors 1998). MST provides a way to undercut the horizontal axons, mediating the spread of epileptogenic activity while sparing the vertically-oriented fibers subserving neurological function.

MST is generally reserved for patients undergoing extensive preoperative and intraoperative electrophysiological evaluation to map the epileptogenic foci and their precise spatial relationships with sensorimotor, language, or visual cortices. Once

a precise focus localization is achieved, multiple incisions through the epileptic cortex are placed to transect the horizontal axons responsible for the propagation of seizures, while preserving the vertical axons subserving neurological functions. The procedure aims to provide selective disconnection of cortical fibers without subcortical white matter and superficial pial injuries. Preservation of the pial blood supply to the cortex is a critical factor for the success of the procedure and is facilitated by the use of special hooks to penetrate the cortex through a puncture hole made in the pia mater. The cortical transections are spaced approximately 5 mm apart and oriented perpendicular to the long axis of the selected epileptic gyrus. Multiple parallel transections made at this distance over a cortical gyrus provide an effective disconnection and parcellization of the seizure focus without injury to or disruption of the basic functions of the columns (Morrell et al. 1999). The number of transections are estimated pre-operatively and then refined based upon electrocorticography recordings during the procedure.

MST is mostly used in conjunction with surgical resection of a preoperatively mapped epileptogenic area (Blount et al. 2004; Mulligan et al. 2001; Orbach et al. 2001a; Schramm et al. 2002; Shimizu and Maehara 2000; Spencer et al. 2002; Hufnagel et al. 1997). MST can be added to microsurgical resection of non-eloquent brain regions or used alone in severe epilepsy conditions, such as epilepsia partialis continua (EPC) and Rasmussen encephalitis (Irwin et al. 2001; Molyneux et al. 1998; Morrell et al. 1995; Morrell and Hanbery 1969). MST provides a unique tool for the treatment of Landau-Kleffner syndrome (LKS) in children, an epileptic disorder characterized by speech deterioration (Irwin et al. 2001). A literature review has identified 211 patients treated with MST (Spencer et al. 2002). Late seizure recurrence has been described, and is likely due to restoration of horizontal connections over time, provides a medium for the spreading of epileptogenic activity (Orbach et al. 2001b).

A novel way to generate cortical transections equivalent to MST has been recently described (Romanelli et al. 2013). Synchrotron-generated X-ray microplanar beams (microbeams) are characterized by the ability to deliver extremely high doses of radiation to spatially restricted volumes of tissue. The minimal dose spreading outside the beam path provides an exceptional degree of protection from radio-induced damage to the neurons and glia adjacent to the microscopic slices of tissue irradiated. The preservation of cortical architecture following high-dose microbeam irradiation and the ability to non-invasively induce the equivalent of a surgical cut over the cortex is of great interest for the development of novel experimental models in neurobiology and new treatment avenues for a variety of brain disorders (Romanelli and Bravin 2011).

When synchrotron-generated microbeams were used to replicate MST, cortical transections sized 100 and 600 μm were generated over the sensorimotor cortex of naïve and epileptic rats using incident doses of, 360 and 240 Gy, respectively. Histologically evident cortical transections were found immediately and after 7 months. No neurological injury was observed. Convulsive seizure duration was drastically reduced in rats receiving local infusion of kainic acid (Romanelli et al. 2013). This

novel approach combining SRS and MST holds great experimental and clinical potential, providing a non-invasive but powerful way to modulate cortical function.

Conclusions

The treatment of medically-refractory epilepsy is one of the greatest challenges of modern medicine. Microsurgical resection of the seizure focus provides the greatest chance to achieve seizure freedom, but is feasible only in patients in good medical condition with a single detectable seizure focus not involving eloquent cortex. Neuromodulation using electrical devices such as VNS or DBS, MST, and SRS provide precious adjunctive options to improve seizure control in patients with severe medically refractory epilepsy not eligible for resective surgery.

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New Radiosurgical Paradigms to Treat Epilepsy Using Synchrotron Radiation

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Abstract Synchrotron-generated X-ray microplanar beams (microbeams) are characterized by peculiar biological properties such as a remarkable tissue-sparing effect in healthy tissues including the central nervous system and, as a direct consequence, the ability to deliver extremely high doses without induction of radionecrosis. Growing experimental evidence is showing remarkable tolerance of brain and spinal cord to irradiation with microbeam arrays delivering doses up to 400 Gy with a beam width up to 0.7 mm. Submillimetric beams can be delivered following a stereotactic design bringing to the target doses in the range of hundreds of Gray without harm to the surrounding tissues. Microbeam arrays can be used to generate cortical transections or subcortical lesions, thus enabling the non-invasive modulation of brain networks. This novel microradiosurgical approach is of great interest for the treatment of a variety of brain disorders, including epilepsy.

As discussed in the neuromodulation chapter, epilepsy is the most common chronic neurological disorder affecting approximately 1 % of the population worldwide. Current estimates indicate that 20–30 % of patients with epilepsy are refractory to antiepileptic drugs (AED) (Go and Snead 2008; Kuzniecky and Devinsky 2007). These medically intractable patients are candidates for surgical treatment. The primary goal of epilepsy surgery is to resect the seizure focus without causing neurological sequelae. While mesial temporal sclerosis declares itself on neuroimaging studies, neocortical seizure foci cannot be localized precisely on the basis of surface EEG and neuroimaging, thus requiring invasive monitoring procedures. Subdural grids and strips or stereoencephalography are performed on selected patients to obtain a precise mapping of the seizure focus and of eloquent

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cortical regions. If the seizure focus does not involve eloquent cortex, then focus resection can be performed. The risk of significant morbidity is especially high when the epileptogenic zone overlaps eloquent cortex, such as speech or primary motor areas. The main limits of current resective epilepsy surgery is the needed to remove extensive parts of the brain and the inability to treat seizure foci involving eloquent cortex (Shorvon et al. 2012). Multiple subpial transections (MST) and stereotactic radiosurgery (SRS) are attractive non-resective alternative to treat seizure foci involving eloquent cortex (Romanelli et al. 2012).

Multiple subpial transections (MSTs) is a non-resective procedure developed to treat patients with severe medically-refractory seizures involving highly functional regions of the brain (Orbach et al. 2001; Mulligan et al. 2001; Mountcastle 1957; Morrell et al. 1995; Morrell et al. 1989; Morrell and Hanbery 1969). This approach has the merit to avoid the resection of the focus but there is limited experience using it to treat also seizure foci located in non-eloquent cortex or in the hippocampus (Patil and Andrews 2013; Patil et al. 2004). MSTs are usually performed by an open surgical procedure aiming to the placement of parallel cortical incisions spaced by intervals of 5 mm. Neuroanatomic studies show that the basic functional cortical unit is arranged vertically, while epileptic activity spreads horizontally. Vertical cortical incisions interrupt the horizontal axons carrying the spreading of seizure activity thus preventing seizure propagation while preserving the vertical columns subserving neuronal function. In essence, MSTs induce a selective disconnection leaving behind an intact functional cortex (Morrell et al. 1999; Telfeian and Connors 1998; Chervin et al. 1988). Stereotactic radiosurgery (SRS) is another emerging non-resective approach to treat epilepsy: narrow beams of radiation coming from different angles are directed with high precision and accuracy to a selected target, achieving a very high energy deposition within the target volume while sparing the surrounding normal tissue thanks to a rapid dose fall-off. SRS using the Gamma-Knife or the Cyberknife is an excellent tool to treat brain tumors and functional brain disorders such as trigeminal neuralgia. The attractiveness of a non-invasive treatment devoid of the risks and discomforts associated with open surgery and general anaesthesia as well as the excellent clinical outcomes explain the exponential growth of SRS over the last decade (Niranjan et al. 2012). Treatment of epilepsy is an emerging application of SRS: it was initially observed that secondary epilepsy improves after radiosurgical treatment of the underlying lesion. Following this observation, radiosurgery was proposed as a primary treatment for idiopathic localization-related epilepsy (Romanelli and Anschel 2006). The amount of energy which can be deposited by current radiosurgical techniques is limited by the size of the smallest collimator available (4 mm for the GammaKnife, 5 mm for the Cyberknife). Therefore the seizure focus can be selectively irradiated delivering doses up to 25 Gy in single session: time to achieve seizure control can be as long as 2 years. Figure 1 shows a Cyberknife treatment delivered to treat medically-refractory complex partial seizures induced by mesial temporal sclerosis. The entire hippocampus was irradiated with a prescribed dose of 23 Gy delivered to the 81 % isodose. The limits of current radiosurgical treatments for epilepsy include the long waiting time to achieve response and the possibility of complications such as radio-

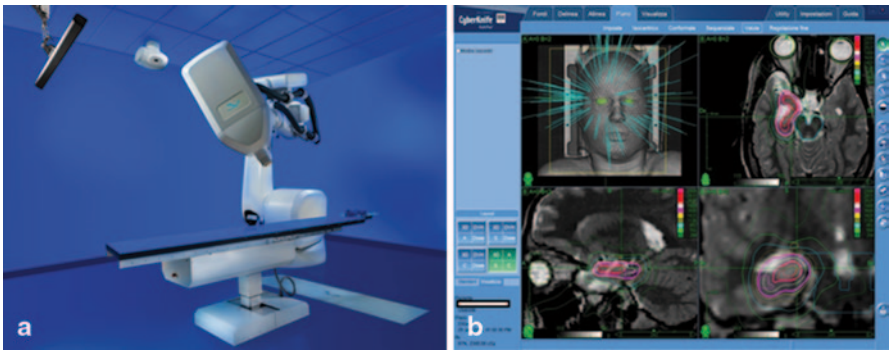

Fig. 1. **a** The Cyberknife is a robotic linac providing image-guided frameless non-isocentric beam delivery. **b** Cyberknife treatment planning for drug-refractory complex partial seizures induced by mesial temporal sclerosis. A prescribed dose of 23 Gy was delivered to the 81 % isodose

Fig. 2 European synchroton radiation facility of Grenoble. (Taken from www.esrf.eu)

induced edema and radionecrosis. Current SRS does not allow to generate in a non-invasive way the equivalent of cortical or hippocampal microsurgical transections. The delivery of higher doses to restricted tissue volumes allowing to transect the epileptogenic focus is a novel radiosurgical paradigm developed at the European Synchrotron Radiation Facility (ESRF) in Grenoble.

At the ESRF (Fig. 2), microscopic arrays of X-ray beams originating from a Synchrotron source can induce the equivalent of a microsurgical cut through the neocortex or hippocampus by delivering very intense doses of radiation (hundreds to thousands of Grays(Gy) to tissue slices of microscopic thickness (Brauer-Krisch et al. 2010; Slatkin et al. 2007; Romanelli and Bravin 2011). Synchrotron-generated microplanar beams (microbeams) are delivered as an array of parallel beam of the wanted thickness (going from 25 all the way up to 600 μm). Microbeam irradiation can deliver peak doses of several hundred Gy with doses in non-irradiated valleys limited to a few Gy. This unique irradiation modality slows, and sometimes ablates, malignant brain tumours in rodents (Laissue et al. 1998). Additionally to its high

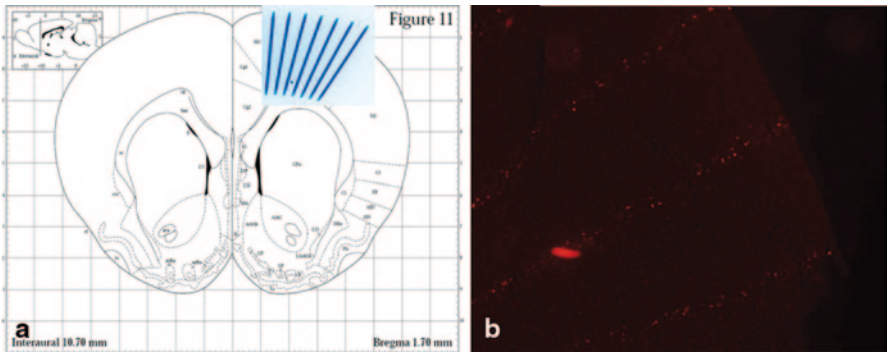

Fig. 3 **a** Representative picture of microbeam sensorimotor cortex transections. The brain sketch is extracted by Paxinos and Watson Atlas 1986 (Paxinos and Watson 1986). **b** Immunohistochemistry using pH2AX as marker to highlight immediate DNA double strand breaks and cell apoptosis

precision, the technique allows users to take advantage of the rapid regeneration of normal microvessels damaged in the direct paths of thin microbeams (Slatkin et al. 1995; Smilowitz et al. 2002; Blattmann et al. 2005; Van De Looij et al. 2006; Serduc et al. 2006). The preferential tumoricidal effects, or strong tumour palliation properties, are due, in part, to the lack of recovery of the tumour vasculature (Laissue et al. 1998; Zhong et al. 2003; Dilmanian et al. 2002), presumably because of structural differences between microvessels of tumour and those of the surrounding normal tissue (Denekamp et al. 1998). Microbeam radiosurgery offers great opportunities to modulate cortical function without neurological injury. An array of parallel or convergent microbeams can be used to transect epileptogenic cortex, disconnecting and parcellizing the focus through the severing of horizontal axons while maintaining the function subserved by the vertical columns (A and III B). Our group performed transections of the primary motor cortex delivering peak doses up to 360 Gy without evidence of neurological injury (Romanelli et al. 2013). The adjacent cortical columns exposed to much lower valley doses (less than 5 Gy) failed to show any histological evidence of evident tissue damage. No sign of motor deficit was found during a 6 months observation period through Rotarod® test. In a kainic-acid model of convulsive seizures originating from the sensory- motor cortex, cortical transetions over the focus induced immediate seizure control (Romanelli et al. 2013). Immunohistochemistry techniques have shown preliminary evidence of cortical neurogenesis together with the development of reactive gliosis (not visible by conventional histology) along the beam pathway (Fardone 2013). This interesting finding supports the controversial hypothesis that there is cortical neurogenesis after irradiation injury (Gould 1999; Kornack and Rakic 2001; Koketsu et al. 2003; Gould et al. 2001; Gould 2007) but also after other types of cortical injury such as ischemia (Parent et al. 2002; Kokaia et al. 2006; Thored et al. 2006), multiple sclerosis (Danilov et al. 2006), epilepsy (Scott et al. 1998; Parent et al. 2002; Zhang et al. 2014), and following focal apoptosis (Magavi et al. 2000). Further studies are ongoing to better characterise the neurogenesis process after microbeam transections both in hippocampus and neocortex before and after the exposure to microbeam irradiation (Fig. 3).

In conclusion, submillimetric transections, either placed over neocortical seizure foci or through the hippocampus, could prove to be an excellent tool to be added to the current techniques used to control seizures. The development of devices delivering submillimetric beams able to generate cortical transections might add a powerful new tool to the clinical treatment of epilepsy and, more in general, to modulate cortical functions in a wide variety of neuropsychiatric disorders.

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