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Safe Preparation and Administration of Intravitreal Bevacizumab Injections

TO THE EDITOR: The study by the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) research group (May 19 issue)[1] supports off-label use of bevacizumab (Avastin) for neovascular age-related macular degeneration, marking a more affordable treatment than ranibizumab (Lucentis) for preventing blindness. Because bevacizumab is supplied in 100-mg and 400-mg vials, it must be compounded into individual doses for intravitreal injections. Contamination can occur during preparation or administration.

In Tennessee, we are aware of three recent clusters of endophthalmitis secondary to alpha-hemolytic streptococcus, after intravitreal injections of bevacizumab in nine patients. Four patients (44%) lost eyesight; one also had meningitis and encephalitis, although we have not received confirmation that the encephalitis and meningitis were caused by the same strain of alpha-hemolytic streptococcus as that causing the endophthalmitis. Two completed investigations have implicated the same compounding pharmacy.[2] We observed noncompliance with face-mask usage as outlined in the standards for sterile compounding developed by the U.S. Pharmacopeia, known as USP 797.[3] Tennessee has product-preparation rules that pertain to the compounding and dispensing of sterile products but does not require adherence to USP 797. The rules of the Tennessee Board of Pharmacy require the wearing of a mask only if no laminar-flow hood is used or if the pharmacist or technician has a respiratory condition that may result in contamination of sterile products. We observed that the pharmacist at the implicated pharmacy compounded bevacizumab under a laminar-flow cabinet with no vertical barrier; the pharmacist wore no mask and spoke during the procedure. We hypothesize that this resulted in contamination by oral flora (alpha-hemolytic streptococcus) of the bevacizumab.

Because endophthalmitis can have severe consequences, it should be considered a "never event." It is also a sentinel event to identify breaches in infection control during compounding and injection procedures,[3,4] because small inocula may cause devastating infections in immune-protected sites (e.g., vitreous fluid). Bevacizumab provides a more economical alternative to ranibizumab to prevent blindness; it is critical that we ensure the safe use of this drug.

Beth Anne Frost, M.P.H.
Marion A. Kainer, M.B., B.S., M.P.H.
Tennessee Department of Health
Nashville, TN
marion.kainer@tn.gov

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Drug-Resistant Epilepsy

TO THE EDITOR: Kwan et al. (Sept. 8 issue)[1] provide a comprehensive review of the importance of drug-resistant epilepsy. The most serious related problem is catastrophic epilepsy in childhood,[2] which results in uncontrollable and devastating seizures that commence in early childhood; the prognosis for development in children with this condition is grim. Epileptic encephalopathy, which is a major part of catastrophic epilepsy, includes disorders in which the epileptic activity itself contributes to severe cognitive and behavioral impairments (e.g., West's syndrome).[3] Many children with catastrophic epilepsy have structural brain abnormalities that may be alleviated by neurosurgery.[4] Although such surgical procedures can be drastic,[1] young children often have good recovery of function after surgery as a result of neural plasticity.

A standard-of-care treatment for catastrophic epilepsy remains to be developed. The child's

pain and that of his or her family need to be handled better both medically and socially. The size of the population of children with catastrophic epilepsy remains to be determined, although there are epidemiologic studies of individual epileptic encephalopathies.[4,5]

Katsuhiro Kobayashi, M.D.
Harumi Yoshinaga, M.D.
Yoko Ohtsuka, M.D.

Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
Okayama, Japan
k_koba@md.okayama-u.ac.jp

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TO THE EDITOR: The review of drug-resistant epilepsy by Kwan et al. could have mentioned the role of allopurinol as an effective adjunct to antiepileptic drugs.[1] Allopurinol is considered to work as an adenosine agonist, which inhibits glutamate release from excitatory neurons[2] without changing the plasma concentrations of concomitant antiepileptic drugs.[3] The efficacy and tolerability of add-on allopurinol were confirmed by at least three double-blind, placebo-controlled trials.[2-4] Although allopurinol is not free of rare but serious adverse effects involving the skin, its low cost is advantageous.

Hideta Sakemi, M.D.

Rakuwakai Otowa Hospital
Kyoto, Japan
rakuwadr073@rakuwadr.com

No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The ketogenic diet, an effective treatment for intractable childhood epilepsy, has been in use since 1921.[1] According to the consensus statement of the International Ketogenic Diet Study Group, the ketogenic diet should be strongly considered after no more than two anticonvulsants have been tried.[2] A retrospective multicenter study involving 216 patients in Argentina showed that 20.5% patients became seizure-free and 36% had a 75 to 99% decrease in seizures.[3]

In another study, 76 patients with refractory childhood epilepsy were randomly assigned to one of two groups and began to receive a ketogenic diet with ratios of lipids to nonlipids of either 3:1 or 4:1. A total of 22 of 40 patients receiving the 4:1 diet (55%) and 11 of 36 receiving the 3:1 diet (31%) became seizure-free.[4]

Interestingly, some authors are recommending the ketogenic diet as first-line therapy in very select situations, such as infantile spasms and epilepsy with myoclonic astatic seizures.[5]

Commercial products are now available to prepare a formula-based ketogenic diet, which can help to improve compliance and efficacy. I should add that my 1-year-old daughter has intractable epilepsy and is receiving a formula-based ketogenic diet.

Javier J. Ricart, M.D.

Hospital de Enfermedades Infecciosas F.J. Muñiz
Buenos Aires, Argentina
javier_ricart@yahoo.com

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We thank Kobayashi et al. for stressing the devastating nature of catastroph-

ic epileptic encephalopathies and the magnitude of their impact on infants and young children as well as their families. Because a large number of antiepileptic drugs are typically tried unsuccessfully over a relatively short period in these patients, applying the proposed International League Against Epilepsy definition of drug-resistant epilepsy will allow their early and prompt identification as candidates for nondrug therapies. Indeed, as pointed out by Kobayashi et al., surgery can be very effective in such children with resectable lesions and perhaps can even enable development to "catch up," although this requires further study. Success with the ketogenic diet[1] and vagus-nerve stimulation[2] has also been reported in case series.

Sakemi refers to pilot studies that suggest potential benefits from allopurinol. Although these data are interesting, they are preliminary and hence were not included in our review, which focuses on antiepileptic drugs that have already been approved or are in clinical development.

We thank Ricart for supplementing the discussion on ketogenic diet with data from observational studies and expert opinion.

Patrick Kwan, M.D., Ph.D.

University of Melbourne
Melbourne, VIC, Australia
patrick.kwan@unimelb.edu.au

Steve C. Schachter, M.D.

Beth Israel Deaconess Medical Center
Boston, MA

Martin J. Brodie, M.D.

Western Infirmary
Glasgow, Scotland

Since publication of their article, the authors report no further potential conflict of interest.

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Thrombopoietin-Receptor Agonists for Immune Thrombocytopenia

TO THE EDITOR: In response to the review by Imbach and Crowther (Aug. 25 issue)[1] of thrombopoietin-receptor agonists for primary immune thrombocytopenia: we would like to draw attention to the fact that a substantial percentage of patients with immune thrombocytopenia have antiphospholipid antibodies and are at risk for thrombosis.[2] We report here the case of a 19-year-old woman with severe immune thrombocytopenia (platelet count, 7000 per cubic millimeter) and antiphospholipid antibodies and no prior thrombotic events. She had not had a response to prednisone and rituximab and had declined splenectomy. After 1 week of treatment with eltrombopag at a dose of 50 mg daily, she had acute kidney injury (peak level of serum creatinine, 7.2 mg per deciliter [636.5 μmol per liter]) and eltrombopag was discontinued (platelet count, 50,000 per cubic millimeter). A kidney biopsy showed acute thrombotic microangiopathy and acute tubular injury (Fig. 1). After the patient was treated with anticoagulation, plasmapheresis, prednisone, and rituximab, renal function and platelet count recovered partially. In contrast to the findings in another report,[3] the mechanism of eltrombopag nephrotoxicity appeared to be related to thrombotic microangiopathy with acute tubular injury. Caution is required in treating patients with immune thrombocytopenia and anti-

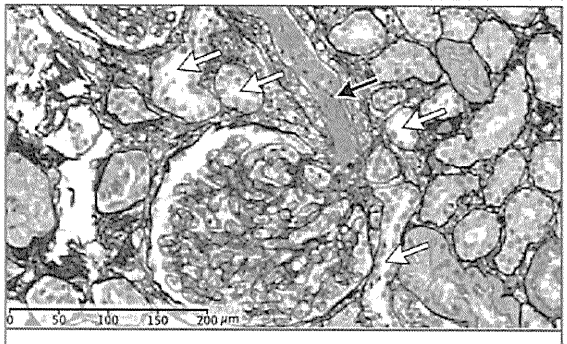

Figure 1. **Thrombotic Microangiopathy in the Renal Cortex.**
A light micrograph of the renal cortex shows acute thrombosis of an afferent arteriole (black arrow), associated with swelling of glomerular endothelial cells and capillary congestion. The adjacent cortical tubules (white arrows) display acute epithelial injury. (Light micrograph courtesy of Prof. Jan J. Weening, Erasmus Medical Center, Rotterdam, the Netherlands.)

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Review

Current challenges in the practice of epilepsy surgery ☆

Joanne M. Wrench [a], Riki Matsumoto [b], Yushi Inoue [c], Sarah J. Wilson [a,d,*]

[a] Psychological Sciences, University of Melbourne, Melbourne, Australia
[b] Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[c] Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan
[d] Comprehensive Epilepsy Program, Austin Health, Melbourne, Australia

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ABSTRACT

The accurate prediction of individual outcomes after epilepsy surgery represents a key challenge facing clinicians. It requires a precise understanding of surgical candidacy and the optimal timing of surgery to maximize a range of outcomes, including medical, psychosocial, cognitive, and psychiatric outcomes. We promote careful consideration of how epilepsy has affected an individual's developmental trajectory as key to constructing more differentiated profiles of postsurgical risk or resilience across multiple outcome measures. This life span approach conceives surgery as a crucial "turning point" in an individual's development from which varied outcome trajectories may follow. This helps clinicians understand the expectations patients and families bring to surgery, and emphasizes the interplay of factors that determine a patient's outcome. It also promotes comprehensive, longitudinal assessment of outcome using data analytical techniques that capture individual differences and identify subgroups with similar trajectories. An ongoing challenge facing clinicians is the development of an outcome classification system that incorporates outcomes other than seizures. We illustrate two emerging areas of research shaping how we define surgical candidacy and predict outcome: (1) using cortico-cortical evoked potentials to identify pathways of seizure propagation and cortico-cortical networks mediating cortical functions, and (2) predicting postoperative depression using a model that incorporates psychosocial and neurobiological factors. The latter research points to the importance of routine follow-up and postoperative psychosocial rehabilitation, particularly in patients deemed at "high risk" for poor outcomes so that early treatment interventions can be implemented. Significantly more research is needed to characterize those patients with poor outcomes who may require re-surgery.

1. Introduction

Of all its lessons, the history of epilepsy surgery teaches us most about the challenges and pitfalls of accurately predicting the individual outcomes of our patients after surgery. Advances in technology, first encompassing the era of electroencephalography and then neuroimaging, have without doubt increased our capability for accurately localizing the seizure focus [1]. These advances, however, have brought their own challenges, with increasing sophistication of our approach promoting the use of surgery in patients with more difficult-to-localize seizures. It is also the case that patient outcomes occur within the broader context of each individual's life history, and that this history may bring psychological and social complexity to the epilepsy surgery setting. Our challenge as we move forward is to improve our ability to systematically account for the complex interplay of factors that occurs in each individual as we endeavor to identify "suitable" surgery candidates, and then predict and assess the clinical outcomes of these individuals. In this respect, ongoing development of clinical skills in both the medical and psychosocial domains of epilepsy surgery is essential.

2. The modern-day practice of epilepsy surgery

It is generally accepted that the goal of epilepsy surgery is to treat or manage intractable seizures by maximizing seizure relief, minimizing adverse effects, and improving patient "quality of life" [2]. Prerequisites for consideration of surgery typically include proven intractability to conventional antiepileptic drugs, identification of the site of the epileptogenic region and ideally a causative lesion, documentation of possible neurological or cognitive deficits resulting from proposed procedures, evaluation of the psychosocial and psychiatric status of the patient, and consent for the surgical intervention and medicosocial treatment thereafter [3].

The undertaking of epilepsy surgery invokes a series of processes, each of which requires careful consideration, as they give rise to some

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* Corresponding author at: Psychological Sciences, University of Melbourne, Melbourne, VIC 3010, Australia. Fax: +61 3 9347 6618.
E-mail address: sarahw@unimelb.edu.au (S.J. Wilson).

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of the key challenges in the modern day practice of epilepsy surgery. These processes include: (1) determination of surgical candidacy and the timing (medical and personal) of surgery based on the completion of a comprehensive presurgical evaluation; (2) consideration of the most appropriate surgical method and approach; (3) preparation for the provision of postsurgical treatment including rehabilitation; (4) comprehensive evaluation of outcome; and (5) in some patients, consideration for re-surgery. Management of these processes is crucial to ensure that the surgical program progresses smoothly for each patient. The program starts when there is medical intractability and should include all medical and psychosocial interventions from the beginning. This means that the surgery program requires an interdisciplinary approach for the provision of comprehensive management and care [4].

3. Current challenges in the practice of epilepsy surgery

3.1. The challenge of more precisely defining "surgical candidacy"

Ideally, consideration of surgical candidacy should be based on the findings of a comprehensive presurgical evaluation that includes seizure diagnosis; neurophysiological, neuroimaging, and neurocognitive investigations, and psychiatric and psychosocial assessments, as well as counseling to address expectations of surgical outcome and the requirements of postoperative rehabilitation [5,6]. Each aspect of this evaluation may pose challenges for the treating surgical team, as it necessitates a breadth of technological and clinical expertise, as well as team cohesion to reach a consensus about the weight assigned to specific findings and the net result for a given patient. Considerable variability currently exists across centers in the type of presurgical investigations routinely undertaken to determine surgical candidacy. This is evident, for example, in the use of invasive presurgical techniques, such as intracranial EEG recordings and the Wada test to precisely delineate zones to be resected and spared, although there is an increasing trend to use less invasive functional imaging techniques where possible [5,7,8]. Variability in routine presurgical investigations across centers poses a significant challenge for interpreting the outcomes of studies as the influence of this variability has not been systematically addressed in research to date. Similarly, the presurgical evaluation informs the most suitable surgical methods and approach to be employed, with variability in surgical techniques across centers leading to increased reports of pathology- and resection-specific outcomes [9].

Even more fundamental to these issues are the differing levels of stringency used to define "medical intractability" across studies [10], with adequate trials of at least two antiepileptic drugs (AEDs) now serving a minimum requirement [11]. However, if our aim is to perform a more precise risk–benefit analysis of surgery versus medical treatment for a given patient, we still require greater understanding of the natural history of epilepsy and its treatment. This is best derived from community-based outcome studies that follow individuals over the long term, which are currently lacking in the literature [12]. As noted by Langfitt and Wiebe, the risk–benefit balance "differs across syndromes, patients, and within patients over time" [10]. The key clinical challenge is to improve our ability to identify those patients whose seizures will ultimately prove to be intractable versus those whose seizures will be controlled on medical treatment, thereby precluding the need for surgery in some patients while optimizing the timing of surgery for others.

For those patients deemed to have intractable seizures, also fundamental is the need to define the purpose of the surgical procedure, be it resective or palliative, as this primes expectations of postsurgical outcome in the surgery team, patient, and family [6]. To maximize patient recovery, consensus about what constitutes a reasonable set of expectations is required [13] and should canvass the notion of surgical "cure" versus "control," with the former invoking the more stringent outcomes of complete seizure freedom and cessation of all AEDs after surgery [14]. These notions should be considered relative to what constitutes becoming "well" in the daily life of the patient and what changes that might invoke for the patient and family after surgery [15].

This latter point highlights a dominant focus in the research literature to identify predictors of seizure outcome, with less attention to factors that predict other outcomes, such as AED cessation, mortality, and cognitive, psychiatric, or psychosocial functioning [14]. Ideally, we should aim for more differentiated profiles of surgical candidacy that identify patients at varying levels of risk across a range of outcomes, including patients at "high risk" for poor outcomes across multiple measures. This view promotes a broader search for the range of preoperative neurobiological and psychosocial markers of postsurgical risk or resilience. It requires knowledge of the interplay of factors that create the greatest or least risk for a given patient, promising a more sophisticated clinical understanding of "surgical candidacy" and the differing trajectories of outcome that may follow.

3.2. Promising Areas of Research and Young Investigators

Riki Matsumoto

Refining our understanding of surgical candidacy: In vivo investigation of cortico-cortical networks

The recording of cortico-cortical evoked potentials (CCEPs) using an in vivo electrical tract tracing method is an exciting new presurgical technique developed by Dr. Riki Matsumoto and colleagues at Cleveland Clinic and Kyoto University. It promises to refine our understanding of surgical candidacy, first through a more precise and tailored evaluation of the seizure network in each individual patient, and second through greater understanding of the functional systems of the brain involved. Both are important for improving our ability to identify patients at high risk for poor surgical outcomes across multiple outcome measures.

3.2.1. Cortico-cortical evoked potentials

A better understanding of seizure networks as well as the mechanisms involved in human higher cortical functions requires a detailed knowledge of neuronal connectivity. Little progress, however, has been made in the understanding of the neuronal connectivity of the human brain until very recently. The majority of knowledge of cortico-cortical connectivity has come from extrapolation from invasive trace-tracking studies performed in nonhuman primates. As it relates to the higher cortical functions of humans such as language, studies performed in nonhuman primates are less relevant. In vivo connectivity studies in humans have only recently begun using noninvasive methods, such as diffusion tensor tractography (DTT). This technique enables visualization of the "in vivo dissections" of association and commissural fibers, and has confirmed the presence of major white matter fasciculi in the living human brain [16,17]. These pathways, however, are determined solely by mathematical calculations of anisotropy of water molecules. Thus, further work is needed to understand the anatomical organization of cortico-cortical networks using different modalities, including CCEPs [18,19].

By means of subdural electrodes implanted for presurgical evaluation, Matsumoto and colleagues [18,19] applied electrical pulses (0.3-ms duration, frequency of 1 Hz, alternating polarity, 1–12 mA) directly to the cortex, and obtained evoked cortical potentials from adjacent and remote cortical regions by averaging the electrocorticogram time-locked to the stimulus onset (20–30×2 trials). In contrast to diffusion tractography, the CCEP technique has the advantage of tracking the inter-areal connectivity physiologically, providing directional as well as temporal information. Clinically, the CCEP method is highly practical because it can be done (1) easily with an online

averaging technique in a short time (less than a minute or two for each stimulus site), (2) without the cooperation of patients, and (3) with minimal chance of provoking seizures. Reflecting this high practicality, although originally developed for extraoperative evaluation, CCEPs can now also be used in the intraoperative setting.

3.2.2. Exploring the functional systems of the brain

Matsumoto and colleagues explored the language system in eight patients with intractable focal seizures [20]. After the cortical language areas were mapped by conventional high-frequency electrical stimulation, CCEPs were obtained by stimulating the anterior and posterior language areas. Stimulation of the anterior language area elicited CCEPs (7/8 patients) in the lateral temporoparietal area in the middle and posterior parts of the superior temporal gyrus, the adjacent part of the middle temporal gyrus, and the supramarginal gyrus. CCEPs were recorded at or around the core region of the posterior language area defined by conventional cortical stimulation. The connections between the anterior and posterior language areas were eletrophysiologically bidirectional as CCEPs were recorded at the anterior language area (3/4) on stimulation of the posterior language area. CCEPs were also recorded in the basal temporal area by stimulation of both the anterior (3/3) and posterior (1/2) perisylvian language areas. Different from the classic Wernicke–Geschwind model, this study revealed a bidirectional connection between Broca's and Wernicke's areas likely through the arcuate fasciculus. A distribution of CCEPs larger than that of the posterior language area identified by conventional electrical stimulation suggests the existence of a rather broad network surrounding the previously recognized core region of this area. This broad distribution is consistent with the recent DTT study that demonstrated the connection of the anterior language area (Broca's territory) to the lateral temporal area (Wernicke's territory) and the inferior parietal area (Geschwind's territory) [21]. As evidence in the nonhuman primate brain points to more extensive parietal than temporal projections to the ventral premotor area, a presumed homolog of Broca's area [22,23], it can be speculated that increased connectivity demonstrated between Broca's and Wernicke's territories in humans is the result of the evolution and acquisition of language function. This hypothesis is supported by a DTT study showing that only the frontotemporal tract, but not the frontoparietal tract, predominated in volume in the language-dominant hemisphere in patients with unilateral language dominance, as defined by the Wada test [24]. The functional connectivity demonstrated by CCEPs supports contemporary concepts of language organization, namely that neuronal groups participate as components of a network by means of feedforward and feedback projections [25].

To understand the rapid spread of epileptic discharges through the cortico-cortical networks involved in ictal motor manifestation, Matsumoto and colleagues used CCEPs to study cortico-cortical connections between the lateral and medial motor cortex [26]. As shown in Fig. 1, this demonstrated a human cortico-cortical network connecting (1) anatomical homologous areas of the lateral and medial motor cortex along the rostrocaudal cognitive–motor gradient (e.g., supplementary motor area [SMA] to the caudal lateral premotor/primary motor [MI] area, pre-SMA to the rostral lateral premotor area), and (2) the somatotopically homologous regions in the lateral and medial motor cortex (e.g., the hand SMA to the precentral hand motor area) in a reciprocal manner. These circuits could account for the propagation of epileptic discharges from and into the SMA [27,28], as well as the atypical motor responses infrequently seen in conventional cortical stimulation, namely, tonic and clonic responses in MI and SMA, respectively [29].

Detailed knowledge of the parietofrontal network is important for understanding spike propagation from the parietal to the frontal lobe in parieto-occipital lobe epilepsy. From the viewpoint of behavioral neurology, this network is essential in sensorimotor integration for various complex behaviors, and its disruption is associated with the pathophysiology of apraxia. CCEP investigation of this network by Matsumoto and colleagues revealed (1) mirror symmetry across the central sulcus (the more caudal parietal area connected to the more rostral premotor area and vice versa); (2) preserved dorsoventral organization (the inferior parietal lobule to the ventral premotor area and the superior parietal lobule to the dorsal premotor area); and (3) projections to more than one frontal cortical site in ~60% of explored connections (data reported in abstract form [30]). These findings provide an anatomical blueprint for the lateral parietofrontal network, and demonstrate that a connectivity pattern similar to that of nonhuman primates applies to the more recently developed inferior parietal lobule in humans.

Focal cortical dysplasia (FCD) is one of the common causes of intractable focal seizures. Although functional reorganization is presumed to occur at and around FCD, cortical functions can colocalize at "MRI-negative" FCD where cortical dyslamination and columnar disorganization are noted in the absence of balloon cells [31]. CCEP investigation successfully delineated the presence of the motor and language networks within "MRI-negative" FCD, whereas CCEPs were occasionally recorded partly within "MRI-positive" FCD [20,26]. Thus, when altered functional configuration is presumed at and around the focus, CCEP investigation can complement conventional electrical cortical mapping by delineating the cortico-cortical network involved in the related function.

3.2.3. Exploring the pathophysiology of epilepsy

By stimulating the seizure focus, Matsumoto and colleagues have shown that CCEPs may be useful for delineating the pathway involved in the propagation of seizure activity and in secondary epileptogenesis [32]. In particular, a preliminary case study suggested that a strong reciprocal connection between the primary and a secondary focus underlies secondary epileptogenesis [32].

Although intensive studies using animal models and human FCD tissue point to a high degree of intrinsic epileptogenicity as a result of an imbalance between increased excitatory and decreased inhibitory mechanisms, little is known about in vivo epileptogenicity, especially the transition from the interictal to ictal state. By analogy to the motor evoked potential elicited by transcranial magnetic stimulation of the motor cortex, CCEPs could be used to evaluate regional cortical or "cortico-cortical" excitability in and around the seizure focus by electrically stimulating the focus [33]. In two patients with FCD in whom peri-ictal CCEPs were incidentally investigated, cortico-cortical excitability at and around the focus increased during the transition from the interictal to ictal state, as judged from increased CCEP amplitude. This increased cortico-cortical excitability then diminished as the initial ictal phase progressed to a state of EEG desynchronization (preliminary data reported in abstract form [34]).

3.2.4. Future perspectives

Cortico-cortical evoked potentials provide us with a new way to explore inter-areal connectivity in vivo in humans. In addition to its impact on basic systems neuroscience, this method, in combination with conventional cortical mapping, could clinically map functional brain systems by tracking cortico-cortical connections among cortical regions in individual patients. This approach may help identify the cortico-cortical network of a given function within the context of pathology and any resultant plasticity of brain systems. In relation to epileptogenicity, as CCEPs can be used as a measure of regional cortical excitability, stimulating the focus and recording CCEPs in the adjacent area may help to evaluate cortical excitability at and around the focus [35]. When CCEPs are recorded in remote cortical areas on stimulation of the focus, this may be used to define the circuit involved in seizure propagation.

For future studies, although limited to patients undergoing invasive presurgical evaluation, a combined CCEP and diffusion

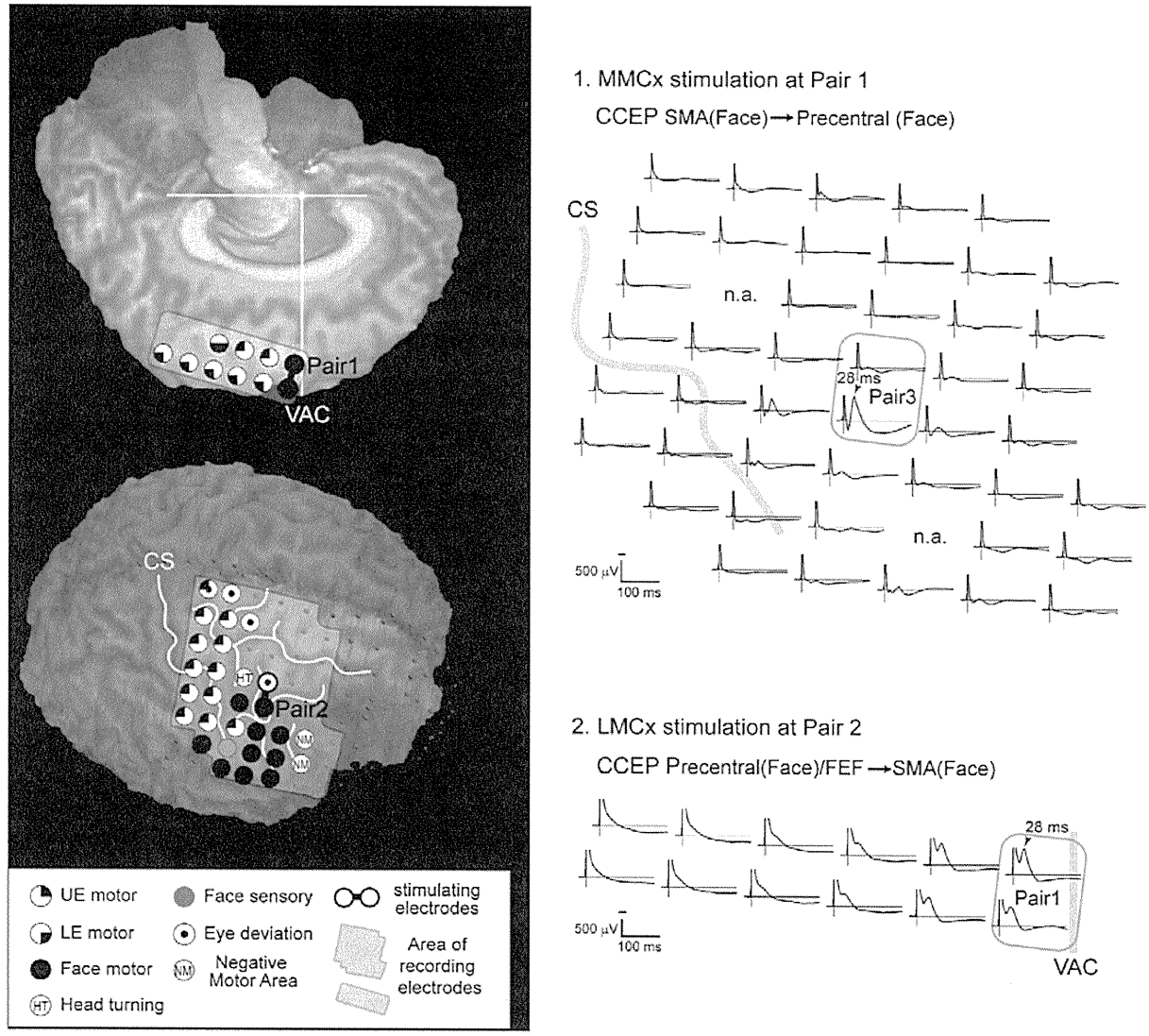

Fig. 1. CCEP investigation of the cortical motor system. Reciprocal connections were observed between the somatotopically homologous regions in the lateral (LMCx) and medial (MMCx) motor cortices. Stimulation of the face SMA (pair 1) elicited CCEPs in the lateral frontal area, with the maximum CCEP at the precentral face motor area (a lower electrode of pair 2). Stimulation of pair 2 (the precentral face motor area/FEF), in return, gave rise to CCEPs in the rostral part of SMA, being maximum at the initial stimulation pair (pair 1: face SMA) in the medial frontal area. VAC, vertical anterior commissural line; CS, central sulcus; UE, upper extremity ; LE, lower extremity. Modified from Matsumoto et al. [26].

tractography study would provide a rare yet valuable opportunity to further develop a contemporary framework of the organization of brain systems. Recently developed elaborate algorithms, such as probabilistic diffusion tractography, that incorporate multiple-fiber estimation will be of significant benefit for delineating subcortical pathways linking the two interconnected cortical areas revealed by CCEPs [36,37]. So far, functional connectivity has been evaluated in the resting condition, and thus the CCEP findings could be regarded as "blueprints" of the networks. With their excellent temporal resolution, CCEPs could also assess dynamic alteration of cortico-cortical connectivity during physiological activities by evaluating CCEP changes during tasks. This would help identify the cortico-cortical network essential for a particular task and contribute to the comprehensive mapping of brain systems, both of which are relevant to the characterization of suitable surgical candidates.

3.3. The dynamics of epilepsy and the timing of surgery: When is it best to operate?

From a broad perspective, the question of when to operate requires consideration of a patient's development across the life span and the extent to which epilepsy has influenced this. Conceptually, the influence of epilepsy can be viewed at three levels: its influence on the brain, its influence on physical health, and its influence on the patient's life more generally. Considered at the level of the brain, epilepsy may be static or dynamic. It may affect only a localized area, without any influence on other regions, in which case surgery may be considered at any time during the disease course. As demonstrated by CCEP research, however, it is often the case that epilepsy has dynamic effects on other regions or functions of the brain. These effects may be already apparent before the start of medical treatment [38] or may occur subsequent to it [39], with some epilepsies progressively affecting an individual's neurological and cognitive development [40]. This is especially seen in young children, in whom seizures may be associated with developmental arrest or regression; here catastrophic epilepsy is a devastating example [41]. Such effects are not restricted to childhood, however, with deterioration in cognition also described in adolescents and adults [42].

In terms of physical health, there can be adverse effects of seizures, AEDs, or other epilepsy-related factors on other organs of the body, such as reproductive dysfunction, osteoporosis, cardiovascular disease, or, in some cases, sudden unexpected death in epilepsy (SUDEP),

as well as accidents that can cause physical injury or death [5,43]. More generally, intractable epilepsy has been associated with a wide range of psychosocial difficulties that detract from a patient's life quality. These include poor self-image and perceived stigma, disrupted family, social, and sexual relationships, reduced school or employment opportunities, and limited recreational activities, including the inability to drive [44]. Higher rates of psychopathology have also been reported [45,46], leading to the view that poor psychosocial adjustment is as disabling as the seizures themselves.

It has been shown that active treatment may help prevent or modify these detrimental or adverse effects, with the best outcomes usually accompanying complete seizure freedom [47]. Coupled with rapid advancement of diagnostic techniques, this has allowed an increasing number of surgical candidates to be identified, often at an earlier age [48], although a substantive treatment gap still exists in countries with limited resources [49]. Clinically, it has been assumed that earlier surgery produces better functional, neurological, and cognitive outcomes, in part because the brain is in an earlier stage of development (i.e., greater plasticity) [50] and partly because the disease process (i.e., recurrent seizures) and its treatment with AEDs have had less time to exert detrimental, secondary effects on the brain [9]. Psychosocially, it has been assumed that earlier surgery minimizes the disruption to normal patterns of development and psychosocial functioning typically associated with chronic, intractable seizures. Within the research field, however, very few studies have directly tested these assumptions [10,51], and thus we still have limited empirical data on the key clinical issue "When is it best to operate?"

In this sense, timing combined with candidacy forms the most essential step in considering surgery. Like candidacy, however, timing factors still require a greater understanding of the natural history of intractability [10] to allow us to determine the optimal timing to alter this natural history for a given individual. From a life span perspective, surgery can be viewed as a crucial "turning point" in a patient's developmental trajectory. This perspective leads us to consider where an individual "began" and how the epilepsy has shaped the patient's development, both medically and as a person. This naturally brings the interaction of factors to the forefront, including how the epilepsy has affected the individual's neurobiological, physical, psychological, and social development, including the extent to which it has formed part of self-identity and dictated the functioning of the family system. These interactive processes underlie the expectations, risk, and protective factors a patient (and family) brings to the point of surgery, and ultimately determine whether this turning point leads to an upward, variable, or downward outcome trajectory. In other words, a life span perspective allows us to capture the complexity of issues necessary for considering surgical candidacy and to identify individual differences for postsurgical risk. It leads to a view of "poor" and "good" outcomes as downward and upward trajectories that encompass multiple interacting factors. At any point along this trajectory the clinical significance and relative contribution of specific factors may vary for a given patient, providing the possibility for outcomes to change, and opening the way for more targeted treatment interventions that serve to alter the course of the patient's trajectory. In this sense, a life span perspective promotes a detailed analysis of postsurgical outcomes.

3.4. Capturing individual differences in clinical and research outcomes

In line with presurgical evaluation, a comprehensive assessment of outcome should canvass a range of markers, including seizure, neurological, and cognitive outcomes, psychiatric and psychosocial functioning, and the patient's perceived quality of life [52]. This means that a comprehensive evaluation of outcome is patient oriented, taking the "whole person" into account, and involves regular follow-up and longitudinal assessment of each individual patient. Yet despite this, our approach to reporting outcomes in the literature using key metrics remains group based. This is true for seizure outcome, which is typically classified according to Engel or ILAE criteria [53,54] that capture change in an individual's seizure frequency, but are typically reported as group percentages across criteria. Similarly, psychosocial outcome is commonly reported as group-based (averaged) health-related quality of life (HRQOL) scores, which correlate with seizure outcome among other things [55]. This highlights a key challenge for the surgical team; to interpret and apply group-based outcome data to predict individual patient outcomes after surgery. For example, how should we translate mean HRQOL scores to predict a given patient's psychosocial functioning after surgery? Stated another way, how does well-being (broadly conceived) relate to a patient's ability to benefit from seizure freedom on a day-to-day basis postsurgery? Similarly for seizure outcome, how does an approximate 70% group statistic of seizure freedom after surgery (such as anterior temporal lobectomy) really translate into an individual's predicted seizure outcome?

Viewing these issues from a life span perspective indicates the need for greater understanding of individual differences in outcome. The goal of the surgical team is to identify the preoperative characteristics within each patient most likely to render a given outcome. For seizure outcome, this is often considered in terms of key neurobiological factors, such as a lesion on MRI, and concordance of preoperative neuroimaging and electrophysiological findings [9]. However, other factors are often not taken into account, for example, depressive symptoms within the patient or a lifetime psychiatric history, which have also been shown to predict seizure outcome [56,57]. Basic psychosocial issues can also be overlooked, such as the patient's willingness to adhere to any treatment after surgery, perhaps reflecting unrealistic preoperative expectations.

Related to this, a key and as yet unaddressed challenge is to develop an outcome classification system that routinely incorporates outcomes other than seizures. It is well established that in addition to seizures, cognitive impairment, psychiatric disturbance (e.g., anxiety, depression), and psychosocial adjustment difficulties can be equally important to patients in impacting their quality of life after surgery [46,58,59]. But how should these outcome variables be captured alongside seizure outcome? Should we adopt one combined metric or remain with the current practice of using many? And should a combined outcome classification system be defined solely by the clinical team or somehow weighted to reflect the needs and priorities of individual patients? Presumably an individually weighted, combined metric would move us closer to more accurate prediction of individual patient outcomes, and ultimately it should be possible to develop and test "algorithms" that take multiple predictors and outcome variables into account that can be effectively applied at an individual level. As yet, however, these issues have received limited research attention and represent important areas for discussion in future research.

By identifying these issues, we see the continued need to increase the sophistication of our clinical research approach. In the first instance, to capture individual differences in outcome a step forward is to begin to employ person-oriented as well as variable-oriented data analytical techniques. Person-oriented techniques enable us to identify trajectories of outcome at the individual and subgroup levels [60]. Methods used to identify differing psychosocial trajectories and their predictors include profile-focused clustering techniques or mixture modeling, combined with multivariate approaches such as discriminant function analysis [60–62]. For seizure outcome, actuarial methods, such as survival analysis, have proved vital for identifying factors that place subgroups of patients at greater risk for seizure recurrence [63]. By identifying trajectories, we increase our understanding of the way specific outcome variables may interact in a given individual or subgroup of patients, providing clues for the best predictors of individual outcomes that take these interactions into

account. In other words, trajectories move us closer to developing a more integrated account of research findings across the surgical outcome literature. A current challenge for the treating team is to draw this literature together and translate it into the clinical care of a patient. In the literature at present there is a tendency toward 'pockets' of research that examine seizure, cognitive, psychiatric, or psychosocial outcome relatively independently, with few studies examining their complex interactions. In a given individual, however, all of these variables are "at play," and a key goal is to understand how they interact over time to produce a poor, variable, or good outcome trajectory for a given patient. Understanding these interactions is crucial in predicting patients at risk of poor outcomes so that these can be minimized.

3.5. Promising Areas of Research and Young Investigators

Joanne M. Wrench

Modeling mood in epilepsy to predict patients at risk of poor outcomes

Dr. Joanne Wrench and colleagues at the University of Melbourne have been undertaking research aimed at identifying patients at risk of depression pre- and postsurgery as this continues to present a significant challenge for epilepsy clinicians. Depression is considered to result from complex interactions between psychosocial and neurobiological mechanisms, and thus it provides an important model for investigating the complex interplay of factors that determine surgical outcome. To date, Wrench and colleagues have identified some key predictors of pre- and postoperative depression that may help guide clinicians in identifying patients "at risk," so that appropriate treatments may be implemented.

3.5.1. Preoperative mood

To understand postoperative mood outcome, it is important to examine patients vulnerable to depression before they undergo surgery. There have been numerous studies examining the prevalence and clinical correlates of depression in patients with epilepsy. The bulk of this research has focused on temporal lobe epilepsy (TLE), perhaps reflecting the frequency with which these patients are seen in tertiary epilepsy centers and the relatively homogeneous nature of this clinical group. The prevalence of depression in TLE varies greatly, from as little as 3% to around 50% [64–67]. This group is also the most commonly considered for epilepsy surgery.

Research into the possible correlates of depression presurgically has provided mixed results. Although there is no consensus on the exact predictors of preoperative depression, mood disturbance is certainly multidetermined and is likely to include neurobiological, psychological, and sociodemographic factors. Fig. 2 summarizes the predictors of depression pre- and postsurgery as identified by Wrench and colleagues in their research to date.

3.5.2. Psychological and sociodemographic predictors of preoperative depression

As noted above, the negative psychosocial effects of chronic epilepsy on vocational, family, social, and sexual well-being have been well documented [44,68]. Some of these factors have been linked to preoperative depression, most notably lack of employment and financial burden or dependence [67,69,70]. A recent study by Wrench et al. [67] of 60 patients undergoing either temporal or extratemporal epilepsy surgery found two contributors to preoperative depression: financial dependence on others, and a family history of psychiatric illness. The relationship between a family history of psychiatric disturbance and depression suggests that depression cannot be attributed simply to the psychosocial effects of having a chronic illness. Rather, it supports the notion that depression in epilepsy, like depression in the general population, is linked to a genetic or "innate" risk. Related to this, certain personality traits have been shown to increase the risk of depression in intractable epilepsy, notably high neuroticism and low extraversion, with high neuroticism also associated with poor family adjustment before and after surgery [71,72]. This points to a complex interaction between innate risk and psychosocial factors, with the former likely exacerbated by the psychosocial stress of having intractable seizures and the restrictions they impose.

3.5.3. Neurobiological predictors of preoperative depression

Many of the brain structures associated with clinical depression in the general population are also involved in the pathogenesis of epilepsy. Prominent among these is the so-called "limbic system" and its connections. Structural neuroimaging studies in the general population have found evidence of volume differences between the

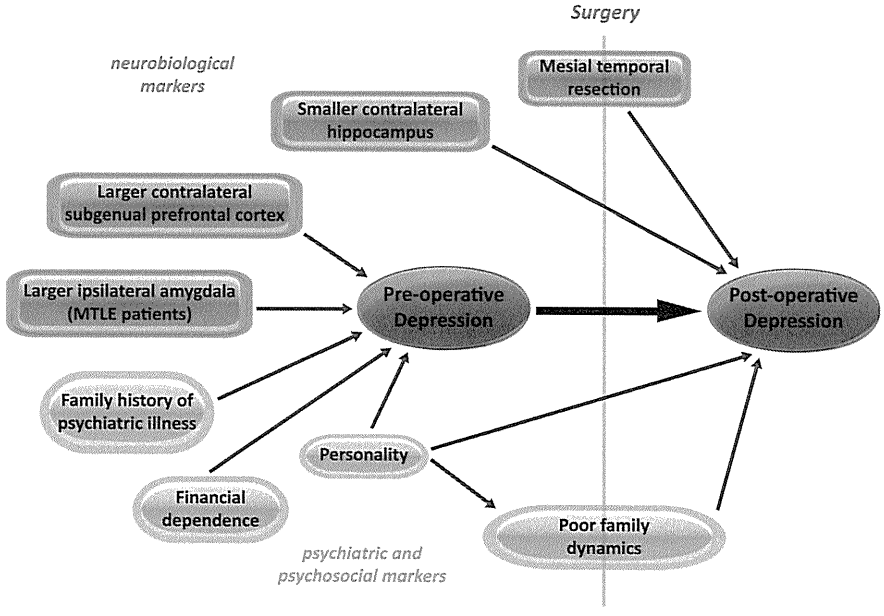

Fig. 2. Neurobiological, psychiatric, and psychosocial markers of depression before and after epilepsy surgery for medically refractory seizures. MTLE, mesial temporal lobe epilepsy.

prefrontal cortex, hippocampus, and amygdala in patients with depression compared with healthy controls [73–75]. In epilepsy, the relationship between depression and these structures remains poorly understood. Wrench and colleagues conducted a series of studies using voxel-based morphometry (VBM) to explore the links between these structures and the comorbidity of depression in patients with intractable epilepsy. In a sample of 42 presurgical candidates, patients with a history of depression had significantly larger volumes of the contralateral subgenual prefrontal cortex ($n=18$, $M=377.6$ mm^3, SD = 155.5 mm^3) than patients with no history of depression ($n=24$, $M=274.6$ mm^3, SD = 108.03 mm^3) ($F[1,40]=6.43$, $P=0.02$). This represents a 27% increase in the volume of the contralateral subgenual prefrontal cortex. A subset of this same sample with a mesial temporal lobe seizure focus ($n=26$) also had an enlarged ipsilateral amygdala volume when associated with a history of depression (history of depression: $M=30.5$ mm^3, SD = 4.1 mm^3; no history of depression: $M=24.8$ mm^3, SD = 3.3 mm^3, $t[24]=3.93$, $P=0.001$). There was no difference in the seizure frequency of patients with or without a history of depression, suggesting these results were not mediated by seizure occurrence.

Although preliminary, these findings suggest that patients with focal seizures and depression have structural changes to their mood network that can be identified before surgery. Whether these changes predispose patients to developing depression in the first instance or are a consequence of previous depressive episodes remains unclear. The underlying functional mechanism of these changes also requires elucidation, but monoamine deficits common to both depression and epilepsy may be one possible mechanism [76]. In particular, deficits in serotonin (5-HT1A) receptor binding have been demonstrated in both patients with TLE and patients with depression alone [76].

3.5.4. Postoperative mood outcome

For many patients, relief from intractable seizures afforded by epilepsy surgery is met with an improvement in mood. Other patients, however, may experience deterioration in their mood despite a positive seizure outcome. This may include the exacerbation of a preexisting mood disturbance or development of depression de novo after surgery [66,67]. Recent research suggests that around a third of patients experience a diagnosable depression in the year following anterior temporal lobectomy (ATL) [66,67,77,78]. This increased prevalence is not trivial as depression after surgery has been consistently shown to negatively affect quality of life [79], to have significant effects on health care utilization and cost [80], and to contribute to increased mortality rates via suicide [81]. Thus, identifying patients most likely to develop postoperative mood disturbances has the potential to significantly improve surgical outcome across a range of measures, and allows early psychological intervention or prophylactic antidepressant treatment to be implemented.

One approach is to view all patients who have a history of depression as being at risk of depression postsurgery. Certainly, having a history of depression is a strong predictor of postoperative depression, with a recent study indicating that 75% of patients experiencing depression in the 12 months after surgery had a previous history of depression [67]. The remaining 25%, however, developed de novo depression. It is this de novo group that presents a significant clinical challenge to the epilepsy surgery team, as these individuals often appear resilient presurgery, with minimal psychosocial sequelae of their epilepsy. Closer inspection of a case series of de novo patients by Wrench and colleagues [81] however, revealed considerable perceived stigma before surgery and significant family conflict after surgery, both of which preceded the onset of de novo depression following mesial temporal resection. This highlights the value of in-depth case analyses to identify factors important in determining individual patient trajectories and offering timely treatment. It also points to two possible mechanisms suggested to underpin the occurrence of depression postsurgery, including deleterious psychosocial consequences of surgery and disruption to key mood structures targeted by the surgical procedure. Recent research by Wrench and colleagues characterizing depression after epilepsy surgery has shed some light on the impact of these two mechanisms (see Fig. 2).

3.5.5. Psychosocial predictors of postoperative depression

From a psychosocial perspective, it has been well documented that many patients struggle to cope with a life free of disabling seizures, which may be fraught with new challenges and expectations [82,83]. This adjustment process, aptly named the *burden of normality* affects not only the patient, but also family members and social networks. Previous research has indicated that family conflict following surgery is common, as patients assert their independence and explore new vocational and social horizons [15]. Importantly, poor family dynamics postsurgery was the strongest predictor of postoperative depression in a multivariate study [67]. Poor family dynamics early after surgery is also influenced by the patient's personality traits, particularly high neuroticism. This, in turn, is associated with longer-term difficulties adjusting to a seizure-free life, as evident from increased report of psychological features of the burden of normality [71]. In addition to these indirect effects on postoperative depression, high levels of neuroticism coupled with low levels of extraversion have been directly linked to increased depression after surgery [71]. These findings again highlight the complex interplay of factors in individual patients after surgery, as well as the significance of providing ongoing support, not only to patients, but also to their families.

3.5.6. Neurobiological predictors of postoperative depression

The removal or deafferentation of limbic system structures central to mood by mesial temporal resection has been proposed as a possible mechanism of postoperative depression [67,83]. Supporting this, Wrench and colleagues found that de novo depression is significantly more common in patients undergoing surgery on the mesial temporal lobe than in patients undergoing surgery outside of this region [66,67,81]. Furthermore, they found that patients who underwent mesial temporal resection and had postoperative depression had significantly smaller hippocampal volumes before surgery on the side contralateral to the resection than patients with no postoperative depression [83]. This suggests that a smaller contralateral hippocampus may provide a structural marker of dysfunction of the mood network prior to surgery, which, following mesial temporal resection, elevates the risk of depression. It would be interesting to explore whether the volumetric differences found pre- and postsurgery in depressed patients translate into functional neurobiological deficits. Functional neuroimaging research, perhaps focusing on monoamines such as serotonin, would be a natural follow-up to this research.

3.5.7. Mechanisms of depression: Stress vulnerability?

Recent studies examining the pathogenesis of depression in the general population have explored the links between genetics, stress, and structural brain changes involving the mesial temporal lobes [84,85]. These have suggested gene by environment interactions, whereby people with a particular gene (such as polymorphism in the 5-HTT gene) are more vulnerable to depression in the face of significant life stress. On the basis of the data reviewed here, a similar model of biological predisposition and life stress may apply to depression in epilepsy. For example, genetic factors may be captured via a family history of psychiatric illness, structural brain changes include volumetric differences in the limbic network underpinning mood, and psychosocial stress plays out most saliently in the family in terms of financial dependence and disrupted family relationships. In other words, the psychosocial stress of poor family relationships may be seen as a catalyst for depression in the face of genetic and neurobiological risk [81]. One such neurobiological risk may be the

compromise of structures central to normal mood functioning following mesial temporal resection, highlighting the importance of routine postoperative follow-up and rehabilitation.

3.6. Implementing routine postoperative follow-up and rehabilitation

Apart from resource issues, a challenge to implementing routine follow-up and rehabilitation is the recognition that rehabilitation is essentially psychosocial in nature, as compared with more traditional physical and cognitively based models of rehabilitation that follow acquired neurological injury, such as stroke [82]. This type of rehabilitation is not routinely practiced in neurological settings, and is specific to treatments that render the patient suddenly "well" following chronic disability, such as epilepsy surgery. In addition to medical treatment, this model of rehabilitation requires a focus on the process of psychological change in the patient's sense of self (from "sick" to "well"), as well as translation of this change to real-life gains for the patient and family [82]. Patients deemed at "high risk" prior to surgery are likely to benefit from additional preventative and early interventions to minimize postoperative difficulties, for example, combining pharmacotherapy with cognitive-behavioral techniques to treat depressive symptoms and adjustment difficulties prior to or early after surgery, to improve seizure, psychiatric, cognitive, and psychosocial outcomes.

A current challenge for medical treatment after surgery is the lack of guiding principles surrounding medication withdrawal. This means that the timing of medication withdrawal is usually based on experience or determined by individual patient preferences [86]. Also underresearched are the effects of cortical reorganization after surgery, which are especially relevant to assessing cognitive outcome and determining patient suitability for rehabilitative techniques such as cognitive retraining [58,87]. Related to this, we require greater investigation of the links between the results of formal neuropsychological assessment and the patient's cognitive functioning in everyday life [88]. Importantly, all of these issues would benefit from a greater understanding of the natural history of cognitive change associated with epilepsy, including decline that may be halted by surgery as opposed to deficits that may arise following resection of eloquent cortex.

More generally, addressing the psychological and social complexities of surgical outcome means that we need to employ routine psychiatric, cognitive, and psychosocial assessments of all patients before surgery, accompanied by longitudinal follow-up and the provision of a psychosocial rehabilitation program after surgery [46,82]. From a life span perspective we need to really "know" our patients, not just medically (neurobiologically), but also psychologically, and socially. This includes treating the patient as part of a family system that exists within a broader cultural context, in an attempt to improve our understanding of family dynamics and cultural differences that may influence adjustment after surgery [82,89]. Although challenging to achieve, we propose that this comprehensive approach provides a benchmark of best clinical practice for tertiary epilepsy centers to move toward.

Also intrinsic to improving the surgical program for future patients with epilepsy is the need for careful assessment of patients with poor outcomes. This involves detailed analysis of their long-term follow-up data, and may contribute to discussions of re-surgery [89]. An evaluation for re-surgery is as important as the presurgical evaluation in preventing deterioration in a patient's quality of life, although there have been few discussions and rare reports of re-surgery outcomes, and there is limited understanding of the psychosocial issues involved [91]. A life span perspective allows us to think of the interplay between the patient and the epilepsy, rather than viewing the patient as "afflicted" or "not afflicted" with epilepsy. Although we know that the unpredictable nature of seizures can push patients toward learned helplessness [44], clinically there are many who remain resilient in the face of this. Factors that support resilience despite seizure recurrence after surgery are particularly important to identify, but reflect a research area that has been neglected to date. In general, the trajectories of patients experiencing seizure recurrence, surgical comorbidities, or re-surgery have not been well characterized and represent a pressing area for future research. This future promises the identification of new treatment options to help maximize positive outcome trajectories for patients and families after surgery.

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Original article

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Temporal changes in brain MRI findings in Rasmussen syndrome

Etsuko Yamazaki [1], Yukitoshi Takahashi [1,2], Noriyuki Akasaka [3], Tateki Fujiwara [1], Yushi Inoue [1]

[1] National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka
[2] Department of Pediatrics, Gifu University School of Medicine, Shizuoka
[3] Department of Pediatrics, National Nishi-Niigata Central Hospital, Niigata, Japan

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ABSTRACT – *Introduction.* MRI data is essential for early diagnosis and evaluation of surgical indication in patients with Rasmussen syndrome (RS). In the present study, we examined the status and evolutionary changes in MRI lesions to identify the MRI characteristics of RS. *Methods.* MRI of 15 RS patients was examined regarding frequency and distribution of atrophic lesions on T1-weighted images and high intensity lesions on FLAIR or T2-weighted images. *Results.* In 13 patients, atrophic lesions were observed predominantly in the frontal lobes with various extent of involvement. High intensity lesions were also observed in 13 patients. High intensity lesions were significantly more prevalent in the cortex of patients with later onset and were present in the insula in 37.5% of epilepsia partialis continua (EPC) type patients and in 57.1% of non-EPC type. Early MRI showed various combinations of atrophic lesions or high intensity lesions in seven of nine patients who underwent MRI examinations within one year of their first seizure. Serial MRI revealed high intensity lesions with characteristic features of regression (20.0% of patients), fluctuation (regression followed by reappearance; 33.3%) and expansion (46.7%). Appearance and reappearance of high intensity lesions in the cortex and/or subcortical white matter were associated with aggravation of seizures. Bilateral high intensity lesions were observed in three patients with unilateral epileptogenic foci, who were successfully treated by surgical intervention. *Conclusion.* Dynamic evolutionary changes in lesions (regression, fluctuation and expansion of high intensity lesions), as observed on MRI, may be a diagnostic feature of Rasmussen syndrome.

Key words: Rasmussen syndrome, magnetic resonance imaging, hemispherectomy

Correspondence:
E. Yamazaki
National Epilepsy Center,
Shizuoka Institute of Epilepsy
and Neurological Disorders,
886 Urushiyama, Aoi-ku,
Shizuoka 420-8688, Japan
<yama@szec.hosp.go.jp>

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Rasmussen syndrome (RS) is considered to be an autoimmune disease, and almost half of RS patients have preceding factors such as infection (38.2%) and vaccinations (5.9%). (Rasmussen *et al.*, 1958; Anderman and Rasmussen, 1991; Oguni *et al.*, 1991; Bien *et al.*, 2005; Takahashi, 2006). Our previous study showed that RS patients exhibit onset of epilepsy 13.3±16.9 days following infection and develop various degrees

of CNS dysfunction, including motor dysfunction (70.0% of patients), mental retardation (58.3%), psychiatric symptoms (7.4%) and aphasia (11.8%). These symptoms indicate a diagnosis of RS (Bien *et al.*, 2005). Early diagnosis of RS is essential to improve prognosis. From a clinical perspective, epilepsia partialis continua (EPC) is the most important diagnostic marker for RS patients. However, EPC develops 1.6±2.5 years after the onset of the first seizure (unpublished data) and also occurs in patients with epilepsies other than RS (Oguni *et al.*, 1991). Therefore, EPC is inadequate for specific and early diagnosis of RS. Furthermore, in RS patients without EPC, a definitive clinical diagnosis is difficult even at the advanced stage of RS.

Various autoantibodies against neural molecules (Rogers *et al.*, 1994; Takahashi *et al.*, 2003; Watson *et al.*, 2001; Yang *et al.*, 2000) are found in the serum and cerebrospinal fluid (CSF) of RS patients. Autoantibodies against GluR3 have been studied as an appropriate biomarker, but these autoantibodies are also detected in patients with epilepsies other than RS, and measurement of autoantibodies against GluR3 by ELISA has been suggested to be unreliable (Wiendl *et al.*, 2001; Watson *et al.*, 2004). Therefore, although autoantibodies against CNS molecules may support a diagnosis of RS, they do not serve as hallmarks for this disease.

Due to the difficulties in clinical and laboratory diagnoses of RS, neuroimaging studies have been used to improve clinical diagnosis. Previous MRI studies revealed characteristic hemispheric atrophic lesions with slow progression, and hyperintense lesions on fluid-attenuated inversion recovery (FLAIR) or T2-weighted images (Aguilar and Rasmussen, 1960). Studies on serial MRI changes suggest a unidirectional MRI staging (stages 0-4) system according to volume changes (swelling or atrophic lesions) and signal changes on FLAIR or T2-weighted images. However, we have found more complicated MRI patterns than those encompassed by simple unidirectional staging (Bien *et al.*, 2002a). In the present study, we examined MRI lesions and their evolutionary changes in order to identify the MRI characteristics of RS and thus facilitate early definitive clinical diagnosis.

Materials and methods

Patients

Subjects comprised 15 RS patients at the National Epilepsy Center (Shizuoka City, Japan) and Nishi Niigata Epilepsy Center (Niigata City, Japan), for whom serial MRI images were available *(tables 1, 2A)*. RS was diagnosed based on published diagnostic criteria (Bien *et al.*, 2005), as either fulfilling all three criteria of Part A or two of three criteria of Part B. Part A consisted of clinical findings of focal seizures (with or without EPC) and unilateral cortical deficit; EEG findings of unihemispheric slowing with or without epileptiform activity and unilateral seizure onset, and MRI findings of unihemispheric focal cortical atrophy and either grey or white matter abnormality or ipsilateral caudate head abnormality. Part B consisted of clinical findings of EPC or progressive unilateral cortical deficit; MRI findings of progressive unihemispheric focal cortical atrophy, and histopathological findings of T cell dominated encephalitis and absence of parenchymal infiltration or viral inclusion bodies. Patients were classified as either EPC type (n=8,) or non-EPC type (n=7). Surgical intervention was performed in four EPC and four non-EPC type patients *(table 3)*.

Methods

Axial and coronal MRI images were used to evaluate atrophic lesions (ALs) and high signal intensity lesions (HILs) in all patients, and sagittal MRI images were also examined in some cases. Gadolinium enhancement was not performed in any of the patients. ALs were evaluated primarily on T1-weighted images, while FLAIR or T2-weighted images were also used for the evaluation of HILs. Evolutionary changes in ALs and HILs were studied in all patients. In each patient, MRI was repeated upon the decision of the attending doctor when the patient's seizure condition changed. ALs were classified into three categories according to distribution: focal *(figure 1A)*, unilateral *(figure 1B)* and bilateral *(figure 1C)*. Focal ALs were defined as the presence of ALs in one lobe, and unilateral as ALs in multiple lobes in one hemisphere and bilateral as ALs in both hemispheres, either in one or multiple lobes. HILs were classified into three types by predominant location: white matter dominant *(figure 1D)*, subcortical white matter dominant *(figure 1E)*, and cortex dominant *(figure 1F)*.

Results

Atrophic lesions (ALs)

Atrophic lesions were observed in 13 of the 15 patients (EPC type, n=7; non-EPC type, n=6) *(table 2B)*. Of these, five (EPC type, n=3; non-EPC type, n=2) had focal ALs, four showed unilateral ALs (EPC type, n=3; non-EPC type, n=1), and four showed bilateral ALs (EPC type, n=1; non-EPC type, n=3) at the last examination. Focal and unilateral ALs were observed in the hemisphere with epileptogenic foci. All four patients with bilateral ALs (EPC type: Patient 8; non-EPC type: Patients 9, 13 and 15) had unilateral epileptogenic foci causing

Table 1. Patient characteristics at initial and final examinations.

Pts	Type	Age atseizure onset	Clinical symptoms	EEG	MRI (CT)	Surgery	Final examination			
							Age	Motor status	Seizure status	Mental status
1	EPC	2 Y 8 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right HILs	NP	24 Y	Left HP	Daily	MR+++
2	EPC	3 Y 8 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+bilateral HILs	Right FH	8 Y	Left HP	Free	MR+
3	EPC	3 Y 8 M	UCD+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+right HILs	Right temporal R	9 Y	Normal	Daily	MR+
4	EPC	3 Y 10 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs	Right FH	14 Y	Left HP	Free	MR+
5	EPC	3 Y 11 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+right HILs	Right FH	9 Y	Left HP	Free	Normal
6	EPC	4 Y 1 M	UCD+FS+EPC	Left UHS with epileptiform activity, USO → BHS, BSO	Left progressive ALs	NP	21 Y	Right HP	Daily	MR++
7	EPC	6 Y 2 M	Progressive UCDs+FS+EPC	Right UHS with epileptiform activity, USO	Right progressive ALs+right HILs	NP	10 Y	Left HP	Daily	MR+
8	EPC	8 Y 10 M	Progressive UCDs+FS+EPC	Left UHS with epileptiform activity, USO	Left progressive ALs → SE → bilateral ALs + left HILs	NP	18 Y	Right HP	Daily	MR++
9	Non-EPC	0 Y 2 M	Progressive UCDs+FS	Right UHS with epileptiform activity, USO	SE → Bilateral progressive ALs + Bilateral HILs	Right FH	4 Y	Left HP	Free	MR++

Table 1. (*Continued*)

Pts	Type	Age atseizure onset	Clinical symptoms	EEG	MRI (CT)	Surgery	Final examination			
							Age	Motor status	Seizure status	Mental status
10	Non-EPC	2 Y 7 M	Progressive UCDs+FS	Right UHS with bilateral epileptiform activity, USO	Bilateral HILs	Right frontal R	19 Y	Normal	Free	Normal
11	Non-EPC	6 Y 5M	Progressive UCDs+FS	Right UHS with epileptiform activity, USO	Right progressive ALs+HILs	NP	10 Y	Left HP	Daily	Normal
12	Non-EPC	9 Y 0 M	Progressive UCDs+FS	Left UHS with epileptiform activity, USO	Left progressive ALs+HILs	NP	12 Y	Right HP	Weekly	MR++
13	Non-EPC	15 Y 9 M	UCD+FS	Left UHS with epileptiform activity, USO	Bilateral progressive ALs+left HILs	Left frontal R	32 Y	Normal	Weekly	Normal
14	Non-EPC	25 Y 9 M	Progressive UCD+FS	Left UHS with epileptiform activity, USO	Left ALs+HILs	Biopsy	29 Y	normal	Daily	Normal
15	Non-EPC	27 Y 2 M	Progressive UCDs+FS	Right UHS with epileptiform activity, USO	Right progressive ALs+HILs → bilateral progressive ALs	Right front-temporal R	38 Y	Left HP	Weekly	MR+

EPC: epilepsia partialis continua; UCD: unilateral cortical deficit; FS: focal seizure; UHS: unihemispheric slowing; USO: unilateral seizure onset; BHS: bilateral hemispheric slowing; BSO: bilateral seizure onset; ALs: atrophic lesions; HILs: high signal lesions; SE: status epilepticus; FH: functional hemispherectomy; R: resection; HP: hemiparesis; MR: mental retardation; NP: not performed; Y: year; M: month; CT: computed tomography; →: change to; +: mild; ++: moderate; +++: severe.

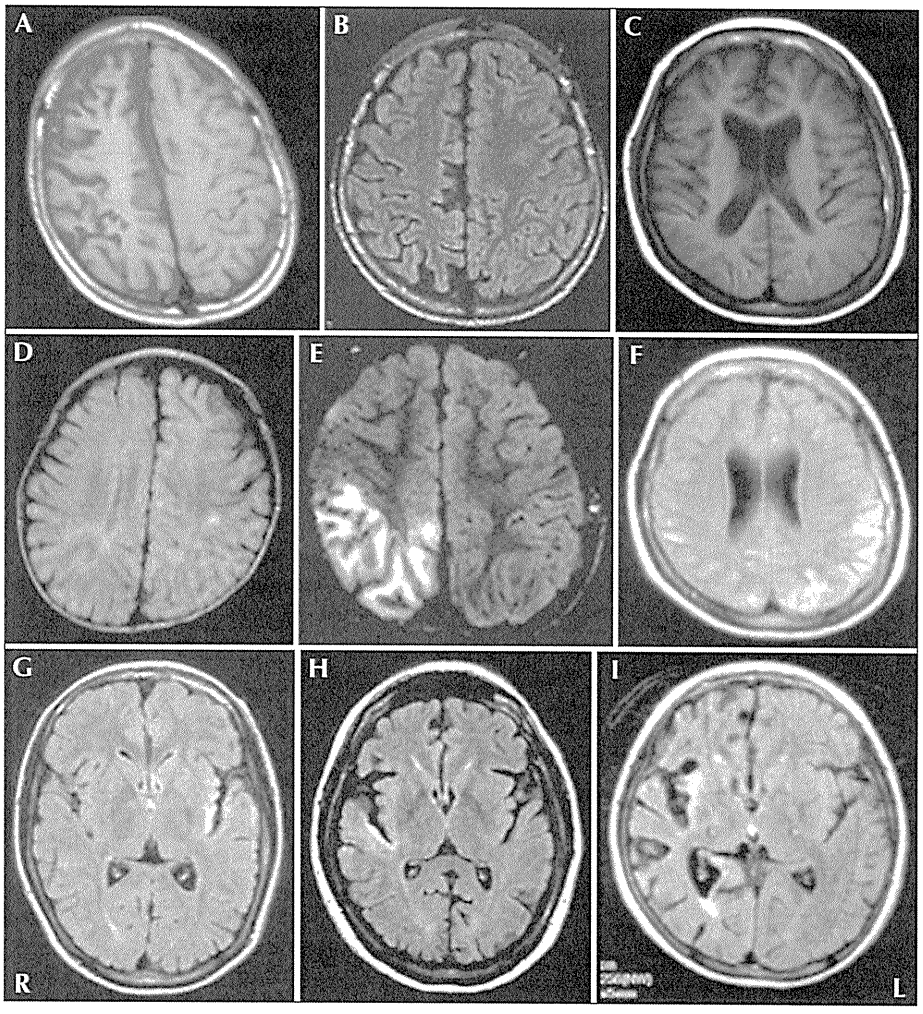

Figure 1. Typical MRI demonstrating atrophic lesions (ALs) and high intensity lesions (HILs).
A) Focal ALs in the right frontal lobe on T1-weighted image.
B) Unilateral ALs on axial fluid-attenuated inversion-recovery (FLAIR) MRI.
C) Bilateral ALs on T1-weighted image.
D) HILs in white matter detected by FLAIR MRI.
E) HILs in subcortical white matter on FLAIR MRI.
F) HILs in cortex on FLAIR MRI.
G) Left insular HILs detected by FLAIR MRI.
H) Right insular HILs on FLAIR MRI.
I) Right insular HILs on FLAIR image.

clinical seizures; two had infantile seizure onset and convulsive status epileptics, while two had seizure onset at age 15 or later and CPS status epileptics, and developed bilateral ALs after surgical intervention which failed to control seizures. Of the three EPC type patients with focal ALs, two had dominant ALs in the frontal lobe (Patients 4 and 8), and one in the temporal lobe (Patient 3). The two non-EPC type patients with focal atrophy both had dominant ALs in the frontal lobe (Patients 12 and 14). Both EPC and non-EPC types exhibited ALs predominantly in the frontal lobe.

High signal intensity lesions (HILs)

High signal intensity lesions were observed in 13 of 15 patients (EPC type, n=6; non-EPC type, n=7), and lesion distribution was variable *(table 2C)*. HILs were localised in the white matter in three patients (Patients 2, 5 and 9), white matter and cortex in one (Patient 10), subcortical white matter and cortex in four (Patients 1, 3, 7 and 11), and cortex only in five (Patients 8, 12, 13, 14 and 15). No significant differences in frequency and distribution of HILs were observed between EPC and non-EPC type patients.

Table 2. Patient background characteristics and lesion frequency on MRI.

	EPC type	Non-EPC type	Total
A. Patient background			
Number of patients examined	8	7	15
Sex (M/F)	7 / 1	2 /5	9 / 6
Seizure onset age (mean±SD, years)	4.6 ± 2.0	12.4 ± 10.8	8.2 ± 8.3
Focal hemisphere (R/L)	7 / 1	5 / 2	12 / 3
Observation period (mean±SD, years)	8.7 ± 7.4	18.1 ± 11.8	13.1 ± 10.5
B. ALs on T1-weighted images at final examination			
Number of patients with ALs	7	6	13
- Focal	3	2	5
- Unilateral	3	1	4
- Bilateral	1	3	4
C. Distribution of HILs on FLAIR or T2-weighted images at final examination			
Number of patients with HILs	6	7	13
Distribution pattern of HILs			
- White matter	2	1	3
- White matter+cortex	0	1	1
- Subcortical white matter+cortex	3	1	4
- Cortex	1	4	5
Insular HILs	3	4	7
Bilateral HILs	1	2	3
D. Early findings of ALs and HILs on MRI			
Number of patients examined	6	3	9
- No lesions	1	1	2
- HILs	2	0	2
- ALs and HILs	2	2	4
- ALs	1	0	1
E. Evolutionary changes of HILs on FLAIR or T2-weighted images			
E-1. Temporal evolution			
Patients without HILs at initial examination	3	3	6
No HIL throughout study	2	0	2

Table 2. (*Continued*)

	EPC type	Non-EPC type	Total
Appearance	1	3	4
- Persistence	1	0	1
- Regression	0	1	1
- Fluctuation	0	2	2
Patients with HILs at initial examination	5	4	9
- Persistence	3	1	4
- Regression	0	2	2
- Fluctuation	2	1	3
E-2. Spatial expansion			
U change to U	3	4	7
U change to B	0	0	0

Onset age: age of seizure onset; side of foci: side of original epileptogenic foci; observation period: period from initial to final MRI examination; EPC: epilepsia partialis continua; ALs: atrophic lesions; HILs: high signal intensity lesions; appearance: number of patients without HILs at the first examinations but with HILs at follow-up examinations; persistence: number of patients with HILs who showed repeatedly no change at follow-up examinations; regression: number of patients with HILs who showed reduction in intensity disappearance at subsequent follow-up examinations; fluctuation: number of patients with HILs showing repeated aggravation and reduction at follow-up examinations; expansion: number of patients with HILs at the first examination, which expanded spatially in follow-up examinations; U: unilateral expansion; B: bilateral expansion.

White matter and subcortical white matter dominant lesions were observed in six of eight (75%) patients with seizure onset before six years or younger and in two of seven (29%) patients with seizure onset at age six years or older. Conversely, cortical lesions were observed in three of eight (38%) patients with seizure onset before six, and in all seven (100%) patients with seizure onset at six or older; a higher rate of cortical lesions was significantly associated with later onset (Fisher exact probability test, p=0.01). Of 13 RS patients with HILs, ten had HILs ipsilateral to the epileptogenic focus, while the remaining three had bilateral lesions (Patients 2, 9 and 10). All three patients with bilateral HILs were diagnosed with unilateral epileptogenic foci based on seizure manifestation and ictal discharges on long-term EEG monitoring. All three patients were treated successfully by surgical intervention.

Early findings

We examined the initial MRI findings in nine patients who underwent MRI examinations in our hospital within one year of seizure onset (mean±SD: 4.7±4.4 months). ALs or HILs were observed in seven of nine patients *(table 2D)*. Two patients (Patients 3 and 8) showed HILs only, four had ALs combined with HILs (Patients 2, 7, 9 and 11), and one (Patient 5) had ALs only. In the patient with ALs only, the initial MRI was taken at three months after seizure onset, and subsequent FLAIR MRI revealed the appearance of HILs.

Evolutionary changes

Serial MRI was conducted in all patients at various intervals depending on clinical progression *(table 2E)*. Many patients showed evolutionary changes in HILs with respect to signal intensity or spatial distribution, independent of immunological therapy. In the six patients without HILs at initial examination, HILs appeared in four patients (66.7%) at 10.8±7.4 months after seizure onset. This suggests that observation of HILs can be anticipated in follow-up MRI, even if HILs are absent in early examinations. On follow-up MRI in these four patients, HILs appeared and persisted in one (Patient 5), appeared then regressed in another (Patient 14), and appeared, regressed and reappeared in two (Patients 13 and 15) *(table 2E-1)*.

Regression (disappearance or decrease in signal intensity) was found in three of 15 patients (20.0%; one without HILs at initial examination [Patient 14] and two with HILs at initial examination [Patients 10 and 11]) at 56.0 ± 56.3 months after onset of seizures. All regression cases were non-EPC type *(figure 2A)*.

Fluctuation (regression followed by reappearance) was found in five of 15 patients (33.3 %; two without HILs at initial examination [Patients 13 and 15] and three with HILs at initial examination [Patients 3, 8 and 12]), and reappearance was found at 70.8 ± 38.0 months after seizure onset *(figure 2B-F)*. The interval from seizure onset to reappearance was not significantly different between EPC type (88.5±51.6 months) and non-EPC type (59.0±32.2 months). Appearance