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Arto Immonen

Surgical Treatment of Refractory Temporal Lobe Epilepsy:

Preoperative Evaluation and Seizure Outcome

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ARTO IMMONEN

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ABSTRACT

Temporal lobe epilepsy (TLE) is the most frequent type of focal refractory epilepsy in adults. Surgical treatment of drug-resistant TLE has been shown to be superior to prolonged medical therapy. The purpose of this study was to investigate the long-term results of TLE surgery, the value of preoperative intracranial EEG and the complications related to diagnostic and therapeutic procedures in adult patients in a national epilepsy centre in Finland serving of a population of 4 million inhabitants.

In a longitudinal follow-up study the long-term seizure outcome was assessed with 140 consecutive adult TLE patients operated between 1988 and 1999. The seizure outcome was also analysed before and after the introduction of a standardised MR imaging protocol for epilepsy. The Engel classification was used for the post-operative outcome. The role of 3-D reconstruction MR-imaging in localisation of subdural electrodes was evaluated with one TLE patient. The complications of the diagnostic invasive procedures (146 patients) and temporal lobe resections (229 patients) were analysed from 1988 to 2006. The long-term seizure outcome was assessed among the 38 TLE patients without any focal findings in diagnostic MR imaging, all of whom underwent invasive EEG evaluation.

In patients with unilateral temporal lobe epilepsy, on the latest available follow-up date (5.4 ± 2.6 years) 46% were seizure free and 10% had only postoperative auras (Engel Class I). Rare seizures (Engel Class II) were identified in 15% of the patients. Engel I-II outcome was thus observed in 71% of these patients. In addition, 13% of the patients had a worthwhile reduction in seizures (Engel Class III), while 16% did not benefit from surgery (Engel Class IV). 86% of all seizure relapses occurred within one year of the operation. After the introduction of a standardised MR imaging protocol for epilepsy, 76% (41/54) of patients with unilateral TLE achieved Engel I-II outcome in the long-term follow-up compared to 63 % (31/49) before standardised MRI and, in particular, the rate of seizure-free patients increased. Among the 146 patients with intracranial EEG evaluation, 36 patients (25%) showed transient complications related to the invasive monitoring itself. Among the 229 operated patients, the total rate of major surgical and neurological complications lasting more than three months was 2% (5/229). The rate of transient (minor) complications was 10% (23/229). In operated patients with normal MRI who were studied with invasive EEG, 40% were seizure-free or had auras (Engel class I) and 5% had rare seizures (Engel class II) at the latest follow-up, whereas 26% were Engel class III and 29% were Engel class IV.

The postoperative long-term seizure outcome in a Finnish national referral centre for epilepsy surgery with adult TLE patients is comparable to reported results from other established epilepsy centres internationally. Outcome at one-year postoperatively was predictive of the long-term outcome. Preoperative evaluation with intracranial electrodes is a safe procedure. Surgical and neurological complications related to invasive monitoring were all transient, causing no permanent morbidity. Resective surgery in TLE can be performed with an acceptably low rate of morbidity, and there was no mortality related directly to the surgical procedures. The patients with no focal abnormality in preoperative MRI usually require chronic intracranial EEG evaluation to define the epileptogenic area. Epilepsy surgery is beneficial in MRI-negative TLE patients even though the outcome is not as favourable as for patients with a focal abnormality. In general, focal MRI abnormalities correlate positively with the outcome of TLE surgery. Therefore patients who have previously had unremarkable MRI scans could eventually be candidates for surgical treatment and should be rescanned now when more advanced MRI equipment and methods have become available.

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Medical Subject Headings (MeSH): Epilepsy, Temporal Lobe/surgery; Follow-Up Studies, Finland; Humans; Magnetic Resonance Imaging; Neurosurgical Procedures/adverse effects; Treatment Outcome

TIIVISTELMÄ

Lääkehoidolle reagoimattoman ohimolohkoepilepsian kirurginen hoito: leikkausta edeltävät selvittelyt ja hoidon tulokset

Ohimolohkoepilepsia on aikuisilla yleisin lääkehoidolle reagoimattoman epilepsian muoto. Hoitoresistentin ohimolohkoepilepsian kirurgisen hoidon tulokset ovat pelkkää lääkehoitoa parempia. Tämän tutkimuksen tarkoituksena oli selvittää ohimolohkoepilepsiaa sairastavien aikuispotilaiden leikkaushoidon pitkäaikaisseurannan tuloksia valtakunnallisessa Kuopion Epilepsiakeskuksessa. Leikkausta edeltävien kajoavien tutkimusten merkitys epilepsiapesäkkeen paikantamisessa ja myös tähän liittyvät komplikaatiot arvioitiin varsinaisen kirurgisen hoidon komplikaatioiden lisäksi.

Väitöskirjatutkimus tehtiin neljänä erillisenä osatutkimuksena vuosina 1988–2006 hoidetuille potilaille. Ohimolohkoleikkaus tehtiin 229 potilaalle ja 146 potilasta tarvitsi leikkaustoimenpidettä edellyttävän kallonsisäisen EEG-rekisteröinnin. Seurantatutkimuksessa oli mukana 140 ohimolohkoepilepsian vuoksi vuosina 1988–1999 leikattua aikuispotilasta, joiden epilepsiakohtausten esiintymistä arvioitiin leikkauksen jälkeen n.s. Engelin luokituksella. Lisäksi arvioitiin kolmiulotteisen magneetti- rekonstruktio kuvauksen merkitystä kallonsisäiseen EEG-rekisteröintiin liittyvien elektrodien paikannuksessa. Kallonsisäiseen rekisteröintiin ja ohimolohkoleikkausiin liittyvät komplikaatiot selvitettiin vuosina 1988 – 2006 leikatuilla potilailla. Lisäksi seurattiin vuosina 1990-2006 leikattua 38 potilasta, joilla ei leikkausta edeltävissä selvittelyissä todettu korkeakenttä-magneettitutkimuksessa poikkeavia muutoksia (MRI-negatiiviset) ja joille kaikille potilaille tehtiin epilepsiapesäkkeen paikantamiseksi kallonsisäinen EEG- rekisteröinti.

Toispuoleista ohimolohkoepilepsiaa sairastavista potilaista oli 46 % leikkauksen jälkeen pitkäaikaisseurannassa (5.4 ± 2.6 vuotta) kohtauksettomia ja 10 % sai lyhyitä kohtauksen alkuoireita ilman tajunnan menetystä (auroja) (Engelin luokka I). 15 %:lla potilaista todettiin vain harvoja yksittäisiä kohtauksia seurannan aikana (Engelin luokka II), näin hyvän leikkaustuloksen saavutti 71 % potilaista (Engel luokat I-II). Merkittävä kohtausten vähenemä todettiin 13 %:lla potilaista (Engelin luokka III) ja 16 % potilaista ei hyötynyt leikkauksesta (Engelin luokka IV). 86 % kohtausrelapseista tapahtui ensimmäisen postoperatiivisen vuoden aikana. Ennen vuotta 1993 leikatuista potilaista 63 % saavutti hyvän hoitotuloksen (Engelin luokka I-II), mutta kun erityinen epilepsia MRI protokolla tuli käyttöön vuonna 1993, hyvä hoitotulos saaavutettiin 76 %:lla potilaista. Myös täysin kohtauksettomien potilaiden osuus kasvoi. MRI- negatiivisista potilaista oli leikkauksen jälkeisessä pitkäaikaisseurannassa 40 % kohtauksettomia tai heillä esiintyi auroja (Engelin luokka I). Viidellä %:lla potilaista todettiin vain harvoja kohtausoireita (Engelin luokka II), 26 %:lla kohtausten vähentyminen oli merkittävää (Engelin luokka III) ja 29 % ei hyötynyt leikkauksesta (Engelin luokka IV). Kallonsisäisiin rekisteröinteihin liittyi ohimeneviä komplikaatioita 25 %:lla potilaista (36/146). Vakavia kirurgisia ja neurologisia puutosoireita aiheuttavia komplikaatioita, jotka olivat todettavissa vielä kolme kuukautta ohimolohkoleikkauksen jälkeen, havaittiin vain kahdella %:lla (5/229) potilaista. Ohimeneviä komplikaatioita esiintyi 10 %:lla (23/229) potilaista.

Aikuisten ohimolohkoepilepsian leikkaushoidon pitkäaikaisseurannan tulokset Kuopion Epilepsiakeskuksessa ovat kansainvälisesti vertailukelpoisia muiden epilepsian hoitoon keskittyvien keskusten tulosten kanssa. Hoidon hyvä vaste säilyy myös pitkällä aikavälillä ja tulos jo ensimmäisen vuoden kohdalla leikkauksesta ennustaa hyvin pitkäaikaisseurannan tuloksia. Kallonsisäinen EEG-rekisteröinti osoittautui turvalliseksi menetelmäksi eikä siihen liittynyt pysyviä haittoja aiheuttavia komplikaatioita. Ohimolohkoepilepsian kirurgiseen hoitoon ei liittynyt kuolleisuutta ja suhteutettuna siitä saatuun hyötyyn, leikkaushoidosta aiheutuvat komplikaatiot ovat hyväksyttävissä. Ohimolohkoepilepsian kirurginen hoito todettiin kannattavaksi myös niillä potilailla, joilla leikkausta edeltävissä selvittelyissä ei aivojen magneettitutkimuksessa todettu poikkeavia löydöksiä. Leikkaushoidon tulokset ovat kuitenkin paremmat niillä potilailla, joilla magneettikuvauksessa todetaan aivoissa paikallinen poikkeava löydös. Siten niitä potilaita, joilla aiemmat aivojen magneettitutkimukset on aikanaan tulkittu normaaleiksi, olisi suositeltavaa arvioida vielä uudelleen kehittyneempien magneettikuvantamisen menetelmien ollessa nyt saatavilla.

Luokitus: WL 385, WN 185, WO 179

Yleinen suomalainen asiasanasto (YSA): epilepsia – leikkaushoito – komplikaatiot; kuvantaminen – lääketiede; magneettitutkimus – aivot

To Johanna, Santeri, Verneri and Kasperi

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LIST OF ORIGINAL PUBLICATIONS

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I Jutila L, Immonen A, Mervaala E, Partanen J, Partanen K, Puranen M, Kälviäinen R, Alafuzoff I, Hurskainen H, Vapalahti M, Ylinen A. Long-term outcome of temporal lobe epilepsy surgery: analyses of 140 consecutive patients. J Neurol Neurosurg Psychiatry 2002;73(5):486-94.

II Immonen A, Jutila L, Könönen M, Mervaala E, Partanen J, Puranen M, Rinne J, Ylinen A, Vapalahti M. 3-D reconstructed magnetic resonance imaging in localization of subdural EEG electrodes. Case illustration. Epilepsy Res 2003;54:59-62.

III Immonen A, Jutila L, Kälviäinen R, Mervaala E, Partanen K, Partanen J, Vanninen R, Ylinen A, Alafuzoff I, Paljärvi L, Hurskainen H, Rinne J, Puranen M, Vapalahti M. Preoperative clinical evaluation, outline of surgical technique and outcome in temporal lobe epilepsy. Adv Tech Stand Neurosurg 2004;29:87-132.

IV Immonen A, Jutila L, Muraja- Murro A, Mervaala E, Äikiä M, Lamusuo S, Kuikka J, Vanninen E, Alafuzoff I, Ikonen A, Vanninen R, Vapalahti M and Kälviäinen R. Long-term epilepsy surgery outcomes in patients with MRI-negative temporal lobe epilepsy. Submitted.

The publishers of the original publications have kindly granted permission to reprint the articles in this dissertation.

CONTENTS

TABLES

FIGURES

ABBREVIATIONS

AEDs	Antiepileptic drugs
AMT	α-[^{11}C]methyl-L-tryptophan
ATL	Anterior temporal lobe
CA	Cornu ammonis
CNS	Central nervous system
CT	Computer tomography
DBS	Deep brain stimulation
DIR	Double inversion recovery
DNET	Dysembryoplastic neuroepithelial tumour
DTI	Diffusion tensor imaging
ECD	^{99m}Tc-ethyl cysteinate dimer
ECoG	Electrocorticography
EEG	Electroencephalography
FCD	Focal cortical dysplasia
[^{18}F-FCWAY]	Selective 5-HT$_{1A}$ receptor antagonist
[^{18}F]FDG	^{18}F-fluorodeoxyglucose
FLAIR	Fluid attenuated inversion recovery sequence
fMRI	Functional magnetic resonance imaging
FOV	Field of view
GABA	Gamma-aminobutyric acid
HMPAO	^{99m}Tc-hexamethylpropyleneamine oxime
^{1}H-MRS	Proton magnetic resonance spectroscopy
IAT	Intracarotid amobarbital test
IBE	International Bureau for Epilepsy
ILAE	International League Against Epilepsy
IQ	Intelligence quotient
IR	Inversion recovery
Lac	Lactate
MCD	Malformation of cortical development
MEG	Magnetoencephalography
MP-RAGE	Magnetization prepared, rapid acquisition gradient echo

MRI	Magnetic resonance imaging
MTLE	Mesial temporal lobe epilepsy
MTS	Mesial temporal sclerosis
NAA	N-acetyl aspartate
[^{123}I]NNC-13-8241	(123)I-labelled specific benzodiazepine receptor radioligand
NTLE	Neocortical temporal lobe epilepsy
PET	Positron emission tomography
SAH	Selective amygdalohippocampectomy
SISCOM	Subtraction of ictal and interictal single photon emission computed tomography scans co-registered with MRI
SPECT	Single photon emission computed tomography
SUDEP	Sudden unexpected death in epilepsy
3T	Three Tesla
TLE	Temporal lobe epilepsy
TE	Echo time
TR	Repetition time
VNS	Vagal nerve stimulation

1 INTRODUCTION

Epilepsies are one of the most common chronic neurological diseases, with a prevalence of 0.5 -1 % in the general population. It has been estimated that one third of newly diagnosed epilepsies will become refractory to medical therapy over time (Andermann 2002). Temporal lobe epilepsy (TLE) is the most frequent type of focal refractory epilepsy, accounting for two thirds of localisation-related epilepsies (Wieser and ILAE Commission on Neurosurgery of Epilepsy 2004). Surgical treatment of medically refractory epilepsy aims at reducing the number and intensity of seizures, minimising neurological morbidity and antiepileptic drug toxicity and finally, improving the patient's quality of life.

Preoperative evaluation in epilepsy surgery requires a multidisciplinary team approach including structural and molecular imaging, video-EEG monitoring, neuropsychological and psychiatric assessment. Recent advances in imaging technology, in particular, have enabled more patients to benefit from resective epilepsy surgery. In a randomised controlled trial the seizure outcome of epilepsy surgery in refractory TLE has been shown to be superior to prolonged medical therapy, and the patients in the surgical group also showed improvement in quality of life parameters (Wiebe et al. 2001). TLE patients with uncontrolled seizures are prone to sudden unexpected death in epilepsy (SUDEP), which is the most important epilepsy-related cause of death. Research during the past two to three decades has shown that incidence varies substantially depending on the epilepsy population studied, ranging from 0.09 per 1000 patient-years in newly diagnosed patients to 9 per 1000 patient-years in candidates for epilepsy surgery (Tomson et al. 2008). Some studies have shown that the excess mortality associated with refractory epilepsy is eliminated in patients who are seizure-free after surgery (Sperling et al. 2005), but these results are still controversial (Tomson et al. 2008).

At Kuopio University Hospital, which serves as a Finnish national centre for epilepsy surgery referral for a population of 4 million inhabitants, systematic evaluation for and treatment with epilepsy surgery started in 1988. Especially during the early years, the work concentrated mainly on surgery for TLE. The main objective of this study

was to evaluate the experience of a single centre in preoperative work-up and long-term seizure outcome in TLE patients from a defined geographical area.

2 REVIEW OF THE LITERATURE

2.1 Definition and impact of temporal lobe epilepsy (TLE)

According to definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005). Epilepsy is a disorder of the brain characterised by 1) an enduring predisposition to generate epileptic seizures and by 2) the neurobiologic, cognitive, psychological, and social consequences of this condition. Epilepsy itself increases the risk of accidents and sudden unexpected death (SUDEP) (Tomson et al. 2008).

The definition of epilepsy requires the occurrence of at least one non-provoked epileptic seizure. Epilepsy is not a specific disease or a single syndrome but rather a broad category of symptom complexes arising from disordered brain functions that themselves may be secondary to a variety of pathologic processes. In temporal lobe epilepsy (TLE), the most common syndrome of all epilepsies, the seizures originate from mesial and/or neocortical temporal lobe structures.

2.2 Epidemiology of epilepsy and TLE

In the Nordic countries the rates of prevalence for epilepsy vary from 3.6 to 5.3/1000 in children and 5.5 to 6.3/1000 in adults (Keränen et al. 1989, Forsgren 1992, Eriksson and Koivikko 1997, Forsgren et al. 2005). Similar results have been reported in other European countries (Forsgren et al. 2005). In 60 % of all cases the onset of the seizures is of focal origin. Of these focal epilepsies, in about 80% of the patients the seizures are initiated within the temporal lobes, which is the most epileptogenic region of the brain (Luby et al. 1995, Jeong et al. 1999).

In epilepsy, three prognostic groups are generally considered: (1) spontaneous remission (20-30%) as seen, e.g. in benign epilepsy with centrotemporal spikes or childhood absences; (2) seizure remission achieved with antiepileptic drugs (AEDs)

(20-30%), which occurs in most focal epilepsies and juvenile myoclonic epilepsy syndromes; (3) persistent clinical seizures despite AEDs (30-40%), i.e. refractory epilepsy (Kwan and Sander 2004). It has been estimated that half of these patients with refractory epilepsy, making up about 5% of all epilepsy patients, would eventually benefit from epilepsy surgery (Engel 1993). Of all epilepsy surgery procedures, TLE surgery has been performed most often.

2.3 Subtypes of TLE

2.3.1 Mesial temporal lobe epilepsy (MTLE)

Mesial temporal lobe epilepsy (MTLE) is the most common localisation-related epilepsy in adults and is often associated with mesial temporal sclerosis (MTS). Mesial temporal sclerosis is characterised by segmental pyramidal cell loss in the CA1, CA3 and CA4 regions (Blumcke 2008). Onset of the seizures typically occurs in the latter half of the first decade of life, with increased incidence of complex partial seizures. The characteristic clinical semiology of the seizures is comprised of abdominal, autonomic or emotional auras. The lateralising clinical signs can be attributed to the typical spreading of seizures from mesial temporal structures with expression of, e.g. automatism, contralateral hand dystonia and postictal aphasia on the dominant-side speech functions (Lüders 2008).

Apart from the most common pathology, hippocampal sclerosis, MTLE can be caused by other mesial pathologies like gliosis or tumours. The term ‘dual pathology’ is used in the presence of a neocortical lesion involving temporal or extratemporal areas (e.g. low-grade tumour or cortical dysplasia) and coexistent ipsi- or contralateral hippocampal sclerosis.

2.3.2 Neocortical temporal lobe epilepsy (NTLE)

The clinical semiology of neocortical or lateral temporal lobe epilepsy (NTLE) is more heterogeneous than in MTLE because the seizures can arise from many different and more widespread cortical foci. Visual and auditory hallucinations occur more commonly from discharges arising from the lateral temporal lobe than from the

mesio-basal temporal lobe. Consciousness may even be preserved, as in elementary seizures, or at least preserved for a longer time than in temporomesial seizures.

The aetiology of NTLE consists of various possible pathologies including, e.g malformation of developmental origin, vascular or neoplastic lesions. Due to the development of the MRI techniques, focal cortical dysplasias (FCD) are increasingly diagnosed as a cause of focal epilepsy and are thus identified in about one fourth of the operated patients (Tassi et al. 2002). In their series of 120 patients with cortical dysplasias, Fauser et al. found 55 patients with FCD localization in the temporal lobe. In addition, they described 48 out of 55 of their TLE patients as being assoaciated with dual pathology (i.e. FCD located in the temporal lobe or temporo-occipitally and additional hippocampal sclerosis) (Fauser et al. 2006). In 2004 Palmini et al. proposed the now widely used classification of the cortical dysplasias for clinical and research purposes; mild malformation of cortical development (MCD) with ectopically placed neurons in or adjacent to cortical layer I are classified as type I and microscopic neuronal heterotopia outside layer I as type II. These cannot be detected by current MRI techniques. Focal cortical dysplasias (FCD) were classified according to whether there are only architectural abnormalities of the cortical layer (FCD type Ia: cortical dyslamination or type Ib: cortical dyslamination with giant or immature neurons) or whether, in addition to architectural abnormalities, they appear with dysmorphic neurons or balloon cells (FCD Taylor type IIa: dysmorphic neurons but without balloon cells or IIb: dysmorphic neurons and balloon cells) (Palmini et al. 2004).

Dysplastic tumours such as dysembryoplastic neuroepithelial tumours (DNET) and gangliogliomas are a common pathology associated with focal epilepsies and from the oncological standpoint are considered to be benign lesions. Sharma et al. reported thirty two patients with operated DNETs, the majority of them (94%) located in the temporal lobe (Sharma et al. 2009). According to the recent report of Ruban et al. with 38 patients, gangliogliomas are the most frequent tumours occurring in TLE, followed by DNETs (Ruban et al. 2009). Both gangliogliomas and DNETs are frequently associated with focal cortical dysplasia (50% and 83%, respectively), which may require rather radical resection of the pathological area to achieve a good seizure control (Prayson et al. 1995, Takahashi et al. 2005). Low-grade tumours of

glial origin (pilocytic astrocytoma, grade I-II astrocytomas and olidendrogliomas) and cavernous hemangiomas are also a recognized pathological entity related to chronic TLE.

2.4 The course of TLE

TLE patients have an increased incidence of family history of epilepsy, suggesting a genetic predisposition (Currie et al. 1971, Helbig et al.2008). After a presumed initial insult, such as prolonged complex febrile convulsions, status epilepticus, CNS infection or trauma, TLE patients may initially have a long seizure-free interval or latency period of years before the unprovoked recurrent seizures develop (French et al. 1993). In TLE habitual seizures usually begin during the first 10-15 years of life (French et al. 1993, Engel 1996).

The drug of choice for the first-line monotherapy in TLE is carbamazepine or oxcarbazepine. Other monotherapy options are lamotrigine, levetiracetam, valproate and topiramate. Moreover, there are currently over 20 AEDs that can be used in different combinations. Some patients reach complete remission of seizures after the antiepileptic treatment has been started. Other patients who develop intractable TLE have a seizure-free interval initially. However, seizures may recur during adolescence or later; and often they then become intractable (Engel 1996). There are also patients with intractable epilepsy who have an evolutionary pattern of TLE, with seizures becoming progressively more elaborate over time (French et al. 1993). Of all TLE patients treated with antiepileptic medication, 60 to 70% are not satisfactorily controlled (Currie et al. 1971, Lindsay et al. 1979). If temporal lobe seizures persist, the disorder may lead to neuronal damage (Salmenperä et al. 2001) followed by impaired cognitive performance and behavioural disturbances (Oyegbile et al. 2004). Therefore, when the clinical situation of TLE points to a progression of the disorder, despite appropriate antiepileptic medication, the patient should be evaluated for resective surgical treatment. In particular, in TLE associated with hippocampal sclerosis, early surgery should be considered because seizures are almost always refractory (Semah et al. 1998) and surgery has been proven to be highly effective.

2.5 Temporal lobe epilepsy surgery

2.5.1 History of epilepsy surgery

The history of epilepsy surgery is presumed have begun in 1886 in London, when Victor Horsley operated a 22-year-old man with focal motor seizures caused by a depressed skull fracture (Horsley 1886). Thereafter, there was significant interest in surgical treatment by removing probable epileptogenic lesions, partly due to the fact that no effective antiepileptic drugs were available before the introduction of phenobarbital in 1912. After the first human EEG was introduced by Berger, the understanding and diagnostics of epilepsy was revolutionised (Berger 1929). In particular, this helped researchers to discover the role of the temporal lobe as an important localisation of pharmaco-resistant epilepsy. The pioneer work of Jasper and Penfield in Montreal and Bailey and Gibbs in Boston introduced the anterior temporal lobe (ATL) resection (Jasper and Kershmann 1941, Penfield and Flanigin 1950, Bailey and Gibbs 1951). Murray Falconer from the UK introduced a standard en-bloc ATL resection, which routinely included removal of the temporomesial structures (Falconer 1953). His work profoundly influenced our understanding of the role of hippocampal sclerosis in the pathogenesis of mesial temporal lobe epilepsy (MTLE) (Falconer and Taylor 1968).

2.5.2 Indications for epilepsy surgery candidacy

First, the seizures need to be drug-refractory. Recently, drug-refractory epilepsy has been defined as the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained freedom from seizures (Kwan and Sperling 2009). Patients with refractory epilepsy should be referred to epilepsy centres for comprehensive evaluation and presurgical work-up. Second, the informed patient must declare his wish to undergo presurgical evaluation. Third, for the resective approach, the clinical diagnosis must be focal epilepsy.

Alhough higher age (over 50 years) is not a contraindication for TLE surgery, it has been shown in several reports that seizure outcome is more favourable in younger

patients (Sirven et al. 2000, Boling et al. 2001, Grivas et al. 2006). For older patients the risks for surgical and neurological complications are, as expected, somewhat higher than in series of younger patients (Rydenhag and Silander 2001, Grivas et al. 2006).

Whereas normal intelligence is not a prequisite for surgical consideration, cognitive deficit raises the possibility of multifocal and multilobar epileptogenicity. However, it has been shown that patients with low IQ can benefit from epilepsy surgery, in particular, with lesional TLE, although the seizure outcome at the lowest IQ level was not found to be as satisfactory. In this latter group of patients, in order to make final recommendations, the cognitive effects of epilepsy surgery and psychosocial outcome should be studied further in details (Malmgren et al. 2008).

Patients with chronic psychiatric diseases are usually not excluded from surgical evaluation, but preoperative counselling with a psychiatrist familiar with epilepsy surgery is mandatory. However, patients with active psychosis, depression or a significant personality disorder would preclude surgery because of the inability of the patient to cooperate in the evaluation and difficulty in post-operative rehabilitation. Cardiorespiratory diseases, coagulopathies and other internal risk factors may require further preoperative consultation, particularly with older patients, and may consequently prevent surgical intervention.

2.5.3 Preoperative evaluation

A general aim of the presurgical evaluation in TLE is to verify unifocal ictal onset of habitual seizures with video-EEG monitoring, which should also be in concordance with clinical seizure semiology and not contradict a possible focal lesion detected by high resolution MRI. Neuropsychological testing, molecular imaging and magnetoencephalography (MEG) are additional tools for localising the seizure onset zone. In cases of non-lesional TLE or dual pathology, further evaluation with intracranial EEG electrodes is usually warranted (Figure 1).

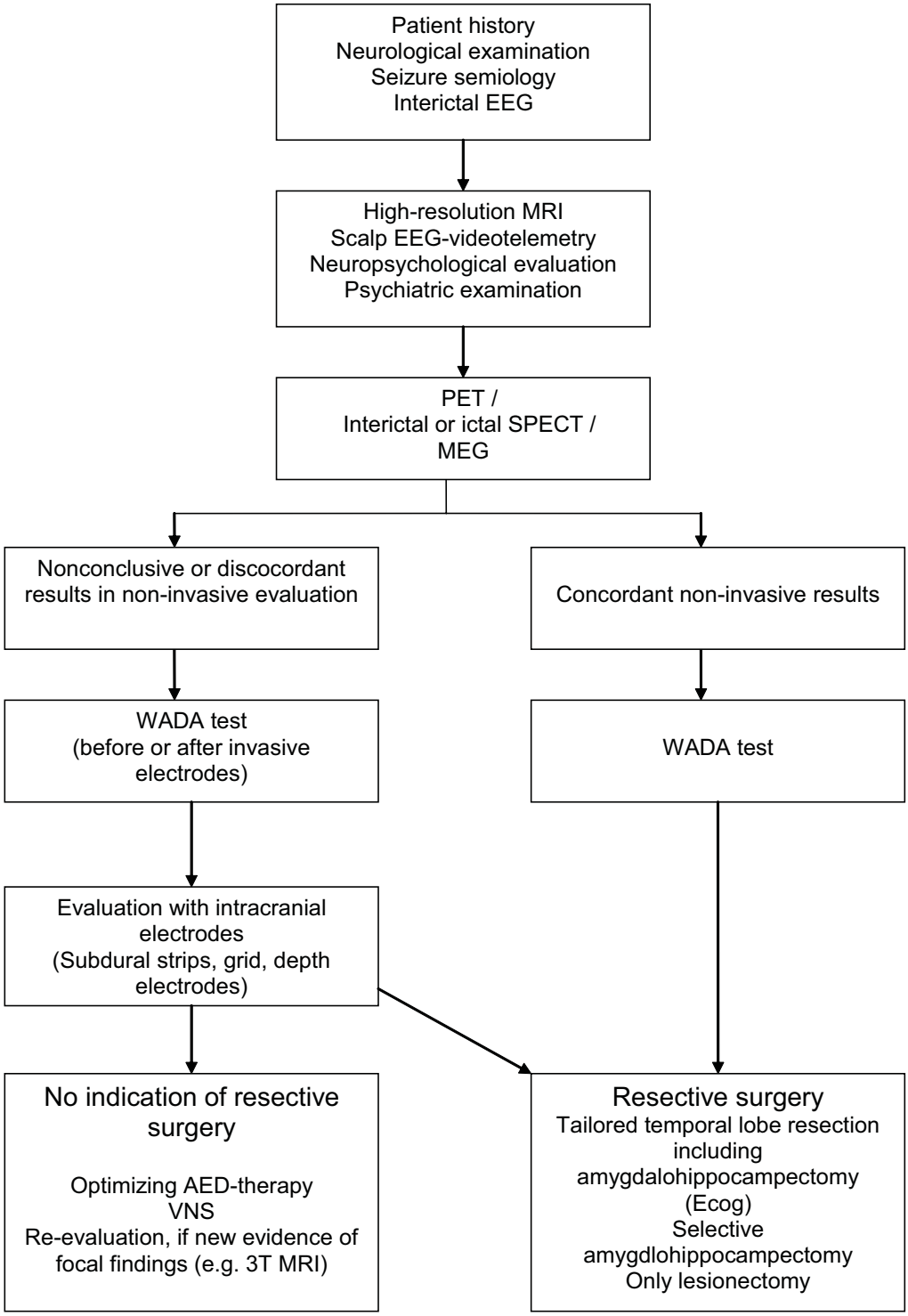

Figure1. The scheme for preoperative evaluation in TLE

2.5.3.1 Noninvasive evaluations

2.5.3.1.1 Seizure semiology and neurological examination

The clinical history of the patient with regard to, e.g. seizure semiology, past history of medication, family history and his/her neurological examinations, are the clinical basis for further preoperative evaluation. Careful analysis of the clinical manifestations allows a hypothesis to be made as to the localisation and lateralisation of the epileptogenic zone. This hypothesis will require the support of other tests; the epileptogenic zone cannot be localised by seizure semiology alone.

2.5.3.1.2 Scalp (surface) EEG

Interictal EEG provides information about the irritative zone of the epileptogenic areas but is never alone sufficient for localisation of the epileptogenic zone for surgical treatment, since the interictal EEG abnormalities seen in a significant proportion of TLE patients are often multilobar or bilateral.

Ictal scalp EEG with simultaneous video recording (video-EEG monitoring) of the typical seizures of a given patient is a mainstay for defining the exact type and origin of the seizure in order to proceed to resective surgery. To increase the possibility for ictal recordings, antiepileptic medication is significantly reduced or even withdrawn during video-EEG. Additional semi-invasive sphenoidal or foramen ovale electrodes may be helpful for localising and lateraling the epileptic focus in TLE (Velasco et al. 2006, Guangming et al. 2009). In a majority of adult patients with TLE, surface ictal EEG combined with other non-invasive methods provides accurate estimation of the epileptogenic zone for clinical decision-making for surgery (Kilpatrick et al. 1997, Foldvary et al. 2001).

2.5.3.1.3 Magnetic resonance imaging (MRI)

2.5.3.1.3.1 Structural imaging

The development of magnetic resonance imaging (MRI) has played the most important role in selection of patients for surgical treatment of epilepsy. To demonstrate structural lesions associated with TLE, MRI provides the best anatomical detail of any imaging modality. It is highly sensitive and specific in detecting mesial temporal lobe sclerosis (MTS), which is the most frequent structural abnormality observed in TLE (Duncan 1997). Typical features of MTS are hippocampal atrophy, loss of internal architecture, increased signal in T2-weighted images and decreased signal in T1-weighted images (Figure 2). Other commonly seen pathologic conditions related to the aetiology of TLE are malformations in cortical development (cortical dysplasias), low-grade astrocytic tumours, developmental tumours (e.g. ganglioglioma, dysembryoplastic neuroepithelial tumour (DNET) and vascular malformations.

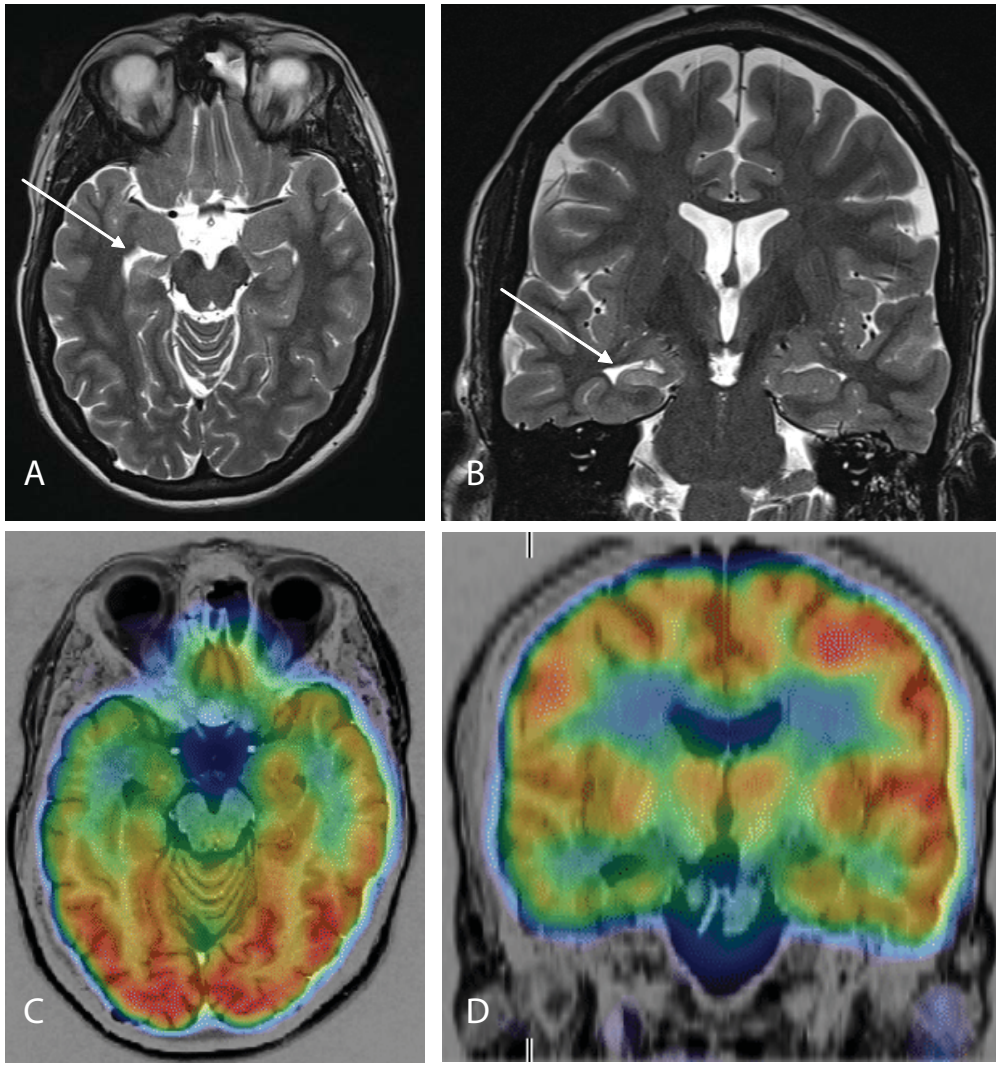

Figure 2. Typical imaging findings in hippocampal sclerosis. A 41-year-old woman with a 23-year history of TLE. Three Tesla MRI reveals a right-sided hippocampal sclerosis (white arrow) and the seizure onset is from the right temporal lobe according to the ictal EEG recording (Axial and coronal T2 images, A-B). FDG-PET image is fused with MR-imaging and it shows wide hypometabolism in right temporomesial and temporal neocortical areas (C-D).

High resolution MRI (i.e., 1.5 to 3T or more) is usually performed according to a specific imaging protocol, which is tailored to evaluate the pathological conditions commonly seen in drug-resistant TLE patients. Transaxial T2- weighted fast spin echo imaging with 3-5 mm thick sections covers the whole brain and is used for efficient screening of any space-occupying lesion. Coronal T2- weighted fast spin echo images are necessary for precise anatomic localisation within the temporal lobe and are mandatory for adequate evaluation of MTS. A coronal or sagittal three-dimensional (3D) T1- weighted gradient echo volume aquisition with isotropic voxels covers the whole brain with 1.2- 2 mm partitions, allows reformatting in any orientation and enables estimation of hippocampal volumetry. Fluid attenuated inversion recovery sequence (FLAIR) is also induced in the protocol, usually in both transaxial and coronal orientations and preferably with rather thin slices. Inversion recovery (IR) sequence provides a good contrast between the gray and white matter, and double inversion recovery (DIR) sequence has been reported to increase detection of subtle alterations in gray matter (Rugg-Gunn et al. 2006). T2*-weighted or susceptibility-weighted sequences may be used to detect traces of hemosiderin in, for example, cavernomas or after trauma. The coronal sequences are best oriented at a right angle to the long axis of the hippocampus. Such studies are monitored by an experienced neuroradiologist, and contrast material is administered for further characterisation only if a space-occupying lesion (tumour or cavernoma) is identified.

Patients with no evident lesion on MRI, despite conventional epilepsy imaging protocol, remain a challenging subgroup of TLE patients. Development of 3T MRI techniques can improve the presurgical evaluation of patients with focal epilepsy who were previously considered MRI negative with 1.5 T MRI (Knake et al. 2005) (Figure 3). Strandberg et al. showed that MRI at 3T could identify abnormalities in 20 % of patients with previously unremarkable pathology, above all, malformations of cortical development (MCD) (Strandberg et al. 2008). Recently, encouraging results have been reported on statistical methods, such as statistical parametric mapping, which allows comparisons of individual 3D imaging data to a group of healthy control individuals and may increase the sensitivity of interpretation (Rugg-Gunn et al. 2006).

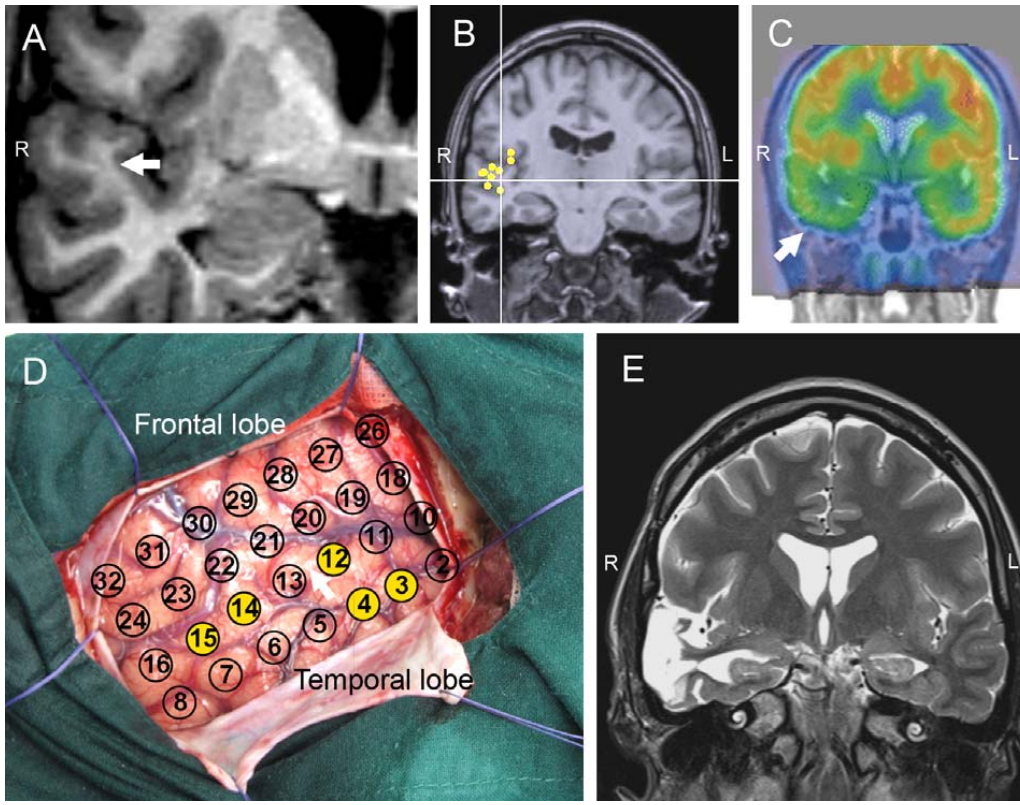

Figure 3. Preoperative multimodal evaluation. A 31-year-old female with partial epilepsy since the age of four and nowadays having seizures almost daily. Preoperative MRI with 1.5 Tesla did not show any abnormalities, but imaging with the 3 Tesla MRI revealed blurring of the white matter in the right upper temporal gyrus (arrow) (T1 coronal image) indicating possible focal cortical dysplasia (A). The MEG study detected interictal spikes at the same localisation (B) and FDG-PET showed hypometabolism in the lateral temporal cortical area (arrow) (C). The area of ictal onset was localised to contacts 3, 4, 12, 14 and 15 with subdurally implanted GRID-electrode (D) and the neocortical resection of temporal lobe tailored according to the ictal intracranial EEG-findings was performed in November 2009 (Arrow indicates the site of cortical dysplasia). The patient was seizure-free (Engel 1A) at the three months follow-up, and the pathological examination confirmed focal cortical dysplasia (Taylor type IIB). The postoperative MRI (T2 coronal image) showed the resection of temporal lateral cortex including the cortical dysplasia (E).

Diffusion tensor imaging (DTI) is a relatively new technique, which provides three-dimensional information about water diffusion in tissues. It is sensitive to the molecular movement of water, which indicates cellular integrity and pathology. Some reports have shown that DTI could help to localise epileptogenic areas in patients with refractory epilepsy but whose results with conventional MRI are normal (Rugg-Gunn et al. 2001, Thivard et al. 2006, Chen et al. 2008).

2.5.3.1.3.2 Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy is the only non-invasive method of measuring metabolites in brain tissue in vivo. Proton magnetic resonance spectroscopy (^{1}H-MRS) can detect a decrease of N-acetyl aspartate (NAA) and unilateral presence of a lactate (Lac) peak in mesial temporal lobe structures, thus lateralising the epileptogenic focus (Chernov et al. 2009). The role of spectroscopy in clinical workup remains controversial, because the reported results are based on retrospective series with a small number of patients.

2.5.3.1.3.3 Functional MRI (fMRI)

Functional MRI (fMRI) provides non-invasive measurements of neural activity by means of a signal dependent on the oxygen level in the blood, which is well-established in evaluation of motor functions. Delineation of the primary motor areas does not play an important role in TLE, but fMRI has been used to define language dominance and to predict possible memory decline after temporal lobe resection (Binder et al. 2008, Powell et al. 2008). Studies comparing the correlation between the Wada test and fMRI in determination of language dominance still provide only cautious recommendations for replacing the Wada test with non-invasive fMRI, particularly in left-sided temporal or extratemporal epilepsy or in cases of mixed speech dominance (Woermann et al. 2003, Benke et al. 2006, Arora et al. 2009).

2.5.3.1.3.4 Volumetry

MRI-based hippocampal volumetry has been used for quantitative identification of uni- or bilateral hippocampal damage, which could be missed by visual inspection. The hippocampal volumes have usually been measured manually, but a method for using estimations of hippocampal grey matter content, an automated MRI analysis of hippocampal atrophy, is under development (Bonilha et al. 2009). Hippocampal T2 time also reflects the pathology of the tissue. As water content is often higher in tissue with a pathological change than in the surrounding normal tissue, the change results in longer T2 relaxation time. Van Paesschen et al. (1997) found a positive correlation between hippocampal T2 time and the ratio of glial to neuronal density in the hippocampus of TLE patients. Moreover, prolongation of hippocampal T2 time correlated with the severity of loss of hippocampal volume in TLE (Van Paesschen et al. 1995, Pitkänen et al. 1996, Van Paesschen et al. 1997). Both volumetry and T2-relaxometry are, however, currently used more in research than in individual preoperative evaluations.

2.5.3.1.4 Molecular imaging

2.5.3.1.4.1 Positron Emission Tomography, PET

Positron emission tomography (PET) is widely used as an additional diagnostic tool for defining the epileptogenic areas of the brain. Interictal (rarely ictal) ^{18}F-fluorodeoxyglucose PET ([^{18}F]FDG-PET) is the method most commonly used to visualize the glucose metabolism of the brain, which is often characterized by regional reduction in glucose uptake (interictal hypometabolism) (Figure 2). Other PET tracers have also been developed during recent years to visualise a wide variety of specific receptor systems: [^{11}C]flumazenil PET for GABA-receptors, [^{11}C]carfentanil PET for opioid receptors, [^{18}F-FCWAY] PET (selective 5-HT$_{1A}$ receptor antagonist) for serotonin receptors and AMT (α-[^{11}C]methyl-L-tryptophan) PET for imaging the synthesis of serotonin. The lack of larger clinical studies has

limited the use of these receptors over [^{18}F]FDG-PET imaging in epilepsy (Goffin et al. 2008).

A recent meta-analysis by Willman et al. showed that ipsilateral [^{18}F]FDG-PET hypometabolism may be an indicator for good postoperative outcome. Moreover, if the ictal scalp EEG and MRI are concordant, the PET does not appear to be necessary (Willmann et al. 2007). On the other hand, if the MRI and scalp-EEG results are nonlocalising, it has been shown that the PET is also cost-effective in presurgical evaluation (O'Brien et al. 2008).

2.5.3.1.4.2 Single Photon Emission Computed Tomography, SPECT

Single photon emission computed tomography (SPECT) is a non-invasive method for estimating the regional flow of blood in the brain ictally or interictally. It is used as commonly as PET studies as an additional diagnostic aid in localizing the zone of seizure onset. ^{99m}Tc-labeled compounds are generally used to show acute ictal hyperperfusion of the seizure-onset zone (or interictal hypoperfusion), such as ^{99m}Tc-ethyl cysteinate dimer (ECD) or ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO). [^{123}I]Iomazenil or [^{123}I]NNC-13-8241 has been used for benzodiazepine receptor studies.

In temporal lobe epilepsy, the superiority of ictal SPECT studies compared to interictal studies has been clearly shown, indicating sensitivities of 84-97% for ictal SPECT studies but only 44-55% for interictal SPECT with regard to the localisation of seizure origin (Devous et al. 1998, Zaknun et al. 2008). Injection of the tracer as early as possible during the seizure is extremely important, since the switch from ictal hyperperfusion to postictal hypoperfusion and the propagation of the seizure may confuse interpretation of the ictal onset zone (Van Paesschen 2004). Digital subtraction of ictal and interictal SPECT scans co-registered with MRI (SISCOM) is a technique that combines structural and functional imaging, thus improving delineation of the epileptogenic zone. The predictive value of SISCOM with respect to good surgical outcome has also been shown (O'Brien et al. 1998, Matsuda et al. 2009).

2.5.3.1.5 Magnetoencephalography, MEG

Magnetoencephalography (MEG) is a non-invasive method of defining the cortical seizure focus based on localisation of magnetic dipoles, indicating synchronous electrical activity of a larger number of cells (Figure 3). It has also been used to localise the eloquent cortical functions near the epileptogenic focus and to determine the language dominant hemisphere (Papanicolaou et al. 1999, Hirata et al. 2004). It has been shown that MEG can detect interictal spikes more precisely than video-EEG does (Knake et al. 2006); but on the other hand, to obtain ictal recording by MEG is limited and technically is very demanding. Analysis of the MEG source analysis can provide additional information for localising the seizure onset zone in temporal lobe epilepsy, for predicting the outcome and possibly for planning limited surgical resections (Assaf et al. 2004). Due to the relatively high cost of MEG installation, it is available in only a few epilepsy surgery centres. Thus far the only MEG establishment in Finland was launched in Helsinki in 1994 (BioMag Laboratory, Helsinki, Finland), providing presurgical localisation of the eloquent cortex and epileptic foci.

2.5.3.1.6 Neuropsychological evaluation

Neuropsychological assessment in TLE plays a pivotal role both in preoperative evaluation and in post-operative follow-up. Comprehensive evaluation of cognitive functioning associated with frontal-lobe functions includes, e.g intelligence, attention, language, visuospatial and frontal ‘executive’ skills. The learning and memory dysfunction associated with TLE is well recognized and may provide useful information about the localisation and lateralisation of the epileptogenic area (Jones-Gotman et al. 2000). In the dominant temporal lobe, the deficits typically involve verbal memory and word-retrieval skills; and in the nondominant lobe, impairments on measures of visuospatial functioning and visual memory are recognized, but the neuropsychological test for the latter provides less accuracy mainly due to the lack of adequate test methods. It has been shown that presurgical neuropsychological evaluation is a useful tool for predicting the patient’s postoperative cognitive outcome

and even the seizure outcome (Stroup et al. 2003, Baxendale et al. 2006, Potter et al. 2009).

The classical WADA (intracarotid amobarbital test, IAT) test was first introduced 1960 in order to lateralise the speech dominance by injecting sodium amobarbital into each carotid artery (Wada 1949, Wada and Rasmussen 1960). Assessment of memory function in the WADA test, which is based on the hypothesis that pharmacologic inactivation of a single temporal lobe should not create global amnesia if the awake temporal lobe is healthy, was first reported by Brenda Milner (Milner et al. 1962, Milner 1997). There is currently a large discrepancy between epilepsy surgery centres in how they use the Wada test for presurgical evaluation of TLE patients. The large study of Haag et al. examined 1421 Wada procedures with regard to its role in presurgical evaluation conducted in 16 European centres between the years 2000 and 2006. The overall frequency of the Wada test compared to the number of surgeries was 38%, varying among centres from 8% to 110% (including re-evaluation of some patients); and the number of Wada tests performed at centres has been decreasing since 2000. The reliability and validity of language determination was rated as good but its prognostic value in memory decline was questioned (Haag et al. 2008). In an international survey (92 epilepsy surgery centres in 31 countries) by Baxendale et al. only 12 % of the centres indicated that every candidate for TLE surgery should undergo a Wada test prior to surgery, and one-third of the centres never or very rarely (in less than 5% of cases) performed a Wada procedure (Baxendale et al. 2008). The emerging functional MRI paradigms in preoperative evaluation of language dominance and verbal memory may further reduce the role of Wada test in coming years.

2.5.3.2 Invasive EEG evaluation

2.5.3.2.1 Indications

In the majority of TLE cases, the patients have MR imaging that suggests unilateral mesial temporal sclerosis and concordant interictal and ictal scalp-EEG recordings, functional imaging and clinical findings, hence allowing straightforward surgical

treatment. When non-invasive studies remain non-concordant or inconclusive with regard to localisation of seizure onset zone, video-EEG with intracranial EEG electrodes is warranted. In general, the indications for invasive EEG evaluation in TLE are: non-lesional focal epilepsy (normal high resolution MRI), lesional but disconcordant scalp-EEG or other non-invasive findings, bitemporal or frontotemporal differential diagnostics and, rarely in TLE, delineation of eloquent areas (Wernicke) with a grid electrode (Diehl and Lüders 2000, Sinha et al. 2008).

The main advantages of intracranial EEG electodes are improved spatial resolution and sensitivity to record, in particular, the higher EEG frequencies, which are attenuated in scalp EEG. With the invasive electrodes it is also possible to evaluate the deep structures of the brain, such as basal and mesial temporal structures, or interhemispheric areas. On the other hand, the disadvantage of subdural EEG electrodes is their limited coverage of the whole brain; and with intracerebral depth electrodes this recording coverage is even more restricted. If the actual seizure focus is outside of the area covered by electrodes, the electrodes are recording seizure spread instead of the initial onset of seizure. Siegel et al. reported a failure rate of 12 % (13/110 patients) in localising the seizure origin with the invasive EEG methods used in their series. After re-evaluation of nine patients with intracranial EEG electrodes, satisfactory localisation of seizure onset could be achieved with seven patients, six of whom were seizure-free after surgical treatment (Siegel et al. 2000). The additional costs and possible complications related to these invasive procedures should always be taken into account, when the intracranial EEG evaluations with individual patients are considered.

2.5.3.2.2 Intracranial electrodes

Subdural strip electrodes are the devices most commonly used in invasive preoperative EEG evaluation of TLE patients. The strip electrodes consist of 4-10 platinum or stainless steel contacts in a single row, which are placed directly on the cortex into the subdural space through burr holes. Placement of the electrodes is individually tailored according to the assumption of the seizure onset area suggested by previous non-invasive evaluation. The subdural strips are most commonly

introduced bilaterally, covering the temporobasal and temporal lateral lobes as well as a part of the frontal lobe, including the orbitofrontal cortex. Of course, the preferred setting varies among centres according to their established practise and indication for invasive electrodes.

Intracerebral depth electrodes can be useful in cases of strictly mesial temporal epilepsy, e.g. bilateral hippocampal sclerosis, to define the side of seizure origin. Spencer et al. reported that using both depth and subdural electrodes simultaneously, the subdural electrodes were 20% less sensitive than depth electrodes for detection of seizures beginning in the hippocampus (Spencer et al. 1990). Eisenschenk et al. showed that suboptimal placement of the subtemporal subdural strip electrode compared to the depth electrode recording may result in false localisation. When the subtemporal subdural electrode covers the parahippocampal area medially to the collateral sulcus, the seizures are definitely localised, congruent with the results from depth electrode recording (Eisenschenk et al. 2001). Accurate implantation of depth electrodes requires a sterotactic device using either the occipital route, implanting one electrode on each side along the axis of the hippocampus and finally entering the amygdala, or two electrodes through the lateral temporal cortex separately to the hippocampus and amygdala. The use of depth electrodes carries a higher risk of intracerebral haematomas, as it is being more invasive than subdurally placed electrodes.

A grid electrode consists of multiple contacts embedded in a flexible sheet of silicone, which can be implanted in an open craniotomy to cover large areas of the cortex. In addition, to localise the zone of seizure onset, it can be used to delineate eloquent areas by cortical stimulation. Grid electrodes are primarily used to evaluate patients with extratemporal epilepsy. In cases of lateral neocortical temporal epilepsy or an associated temporal cortical lesion, the grid electrode may provide more definite information about the demarcation of the zone of seizure onset and allows stimulation of the Wernicke area on the dominant side during surgery.

2.5.3.2.3 Imaging of the electrodes

After implantation of the electrodes, for detailed EEG analyses it is mandatory to visualise the position of the electrode contacts in relation to the cortical anatomy. This allows accurate delineation of the zone of seizure onset and is helpful in planning the surgical resection. Traditionally, the antero-posterior and lateral skull X-ray films (two-dimensional, 2D) have been used for localising the subdural electrodes (Lesser et al. 1987), but development of the three-dimensional (3D) reconstructed MRI has allowed better interpretation of the position of the electrodes (Winkler et al. 2000, Schulze-Bonhage et al. 2002). In this method, the preimplantation MRI is used to produce a 3D reconstruction of the anatomy of the cortical surface. The image is then registered with postoperative CT or MRI scan to localise the implanted subdural electrodes (Figure 4). Peroperative digital photography co-registered with 3D MRI data pinpoints the exact location of the grid and details the cortical anatomy underlying the subdural grid electrode (Wellmer et al. 2002, Mahvash et al. 2007). This can be applied only in open craniotomies, but it helps the surgeon to orient in resecting the area of epileptic focus and to avoid the eloquent cortical areas defined by video-EEG and extraoperative cortical stimulation.

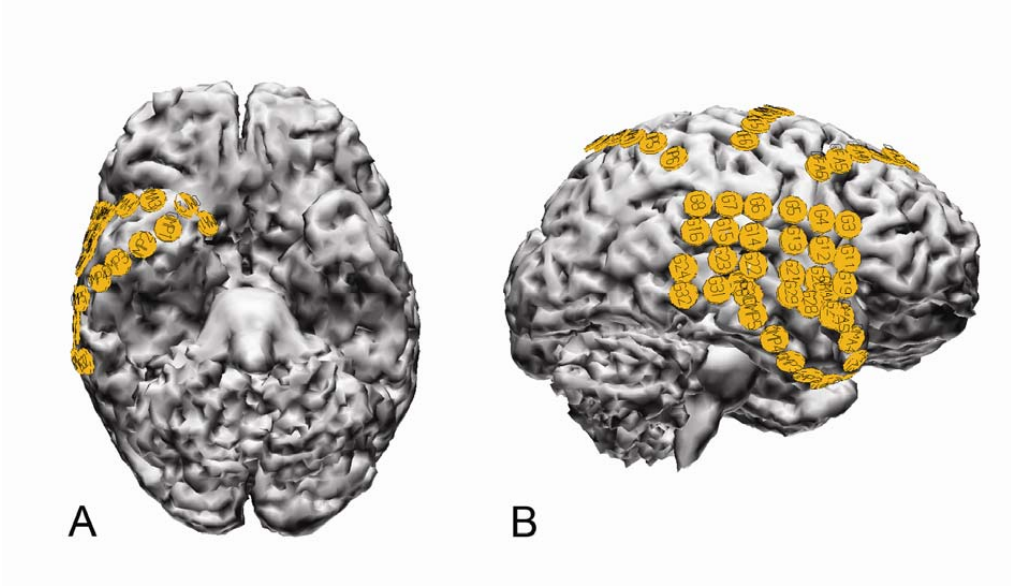

Figure 4. 3-D reconstructed MR images of the subdural grid and five strip electrodes. The patient had a low grade tumour in the right middle temporal gyrus and a history

of refractory daily seizures. The resection was tailored according to the findings in ictal video-EEG and the patient became seizure free. (A; inferior view, B; lateral view from right)

2.5.3.2.4 Complications

The proportion of patients requiring invasive EEG evaluation in epilepsy centres is diminishing due to development of non-invasive methods. There still remains a subgroup of patients for whom intracranial EEG evaluation is mandatory, and the risks and benefits must be weighed for each individual patient. Prospective studies by Swartz et al. and by Wiggins et al. showed that subdural electrodes are a safe and effective way of localising the epileptic focus (Swartz et al. 1996, Wiggins et al. 1999). Since then, several retrospective series of complications related to invasive evaluation have been reported; and the rate of major adverse events causing permanent deficits appears to be low (Behrens et al. 1997, Rydenhag and Silander 2001, Burneo et al. 2006, Tanriverdi et al. 2009). The most common complications reported in the literature are infections and haematomas. Invasive monitoring with grid electrodes is associated with most serious complications (Hamer et al. 2002, Burneo et al. 2006, Fountas and Smith 2007, Van Gompel et al. 2008, Wong et al. 2009). In three of these articles, five deaths have been reported associated mainly with uncontrollable brain oedema. Most of the complications were, however, transient; and their occurrence was associated, e.g. with the larger and greater number of grids, longer duration of evaluation and older age of the patient. Subdural grid implantation seems to be better tolerated in children than in adults (Johnston et al. 2006, Musleh et al. 2006). It has been suggested that greater plasticity of paediatric brain tissue and veins, as well as greater tolerance for foreign bodies, could explain the lower rate of complications in the paediatric population.

2.5.4 Operative treatment

Epilepsy surgery requires multidisciplinary collaboration, and all patients who are being considered as candidates for surgery should undergo evaluation at the patient management conference. The core of the team should include, at minimum, an

epileptologist, a neurosurgeon, a clinical neurophysiologist, a neuroradiologist, a psychiatrist and a neuropsychologist. The main task of the team is to facilitate a consensus decision on whether the patient is a candidate for epilepsy surgery and whether there is enough evidence in the preoperative evaluation to proceed to surgical treatment. The need for intracranial EEG evaluation, surgical approaches and overall risks related to the selected treatment are discussed (Carreno and Lüders 2008).

The primary data for the decision-making are obtained from structural MRI and recordings of ictal VTM-EEG. In patients with TLE if the MRI reveals a discrete structural abnormality in concordance with ictal EEG data, supportive data from the neuropsychological evaluation exist and molecular and functional imaging is congruent, the decision for curative surgery is justified. In the case of conflicting findings, palliative resective surgery may be considered, assuming that the expected outcome is thoroughly discussed at the patient management conference and the patient and his family are also counselled.

2.5.4.1 Strategies for operative treatment

Since the pioneer work by neurosurgeons Penfield, Bailey and Falconer on TLE surgery, many modifications of tailored and anatomical temporal lobe resections have been adopted. The variability seen even in classic anterior two-thirds lobectomies (ATL), including amygdalohippocampectomy, was reviewed for 47 epilepsy centres participating in the second Palm Desert Conference. The median length of resection from the temporal tip was 5.5 cm in the nondominant lateral temporal cortex (range 2-6.5 cm), 4.5 cm on the dominant side (range 2-6 cm) and 3 cm of the hippocampus (range 1-3.5 cm) (Spencer and Ojemann 1996).

Ideally, removal of the epileptogenic zone leads to seizure control without any negative impact on cognitive functions, in particular, no adverse effects on postsurgical memory. In several studies classical anterior temporal lobe resection, including amygdalohippocampectomy vs. selective amygdalohippocampectomy (SAH), has been evaluated to determine its impact on the seizure outcome. Most of

the retrospective analyses have concluded that these different strategies for surgical approaches result in equally good seizure outcomes (Arruda et al. 1996, Clusmann et al. 2002, Paglioli et al. 2006). There are reports of worse outcome with paediatric patients undergoing SAH, which casts into doubt the existence of purely mesial juvenile TLE (Clusmann et al. 2004, Datta et al. 2009). In their retrospective study Bate et al. compared the seizure outcome in 82 patients with ATL and 32 patients with SAH and reported significantly better outcomes in the ATL group (Bate et al. 2007).

The impact of the extent of mesial or neocortical resection in TLE on the seizure outcome is controversial. Some studies show better seizure outcomes with extensive resection of the hippocampus or the entorhinal cortex (Wyler et al. 1995, Bonilha et al. 2007). Shamim et al. used postoperative MRI scans to calculate the resection volume after temporal lobectomy and concluded that the larger resection volume was associated with improved seizure control (Shamim et al. 2009). On the other hand, other reports indicate no benefit of more extensive resections with respect to seizure control (Wolf et al. 1993, Arruda et al. 1996, van Rijckevorsel et al. 2005). In their postoperative MRI controlled series, Joo et al. reported that greater resection of the hippocampus may predict better outcome, but this was not associated with the extent of resection of the lateral temporal gyri (Joo et al. 2005).

In summary, there is marked variation among epilepsy centres in the extent and types of resection in temporal lobe surgery for epilepsy. Neither more selective types of resection nor larger extent of resection have ultimately proven to be better for achieving better seizure outcome.

Many epilepsy centres have for decades used intraoperative electrocorticography (ECoG) to define the extent of both mesial and lateral temporal lobe resections. However, the use of intraoperative ECoG as a guide for resectioning in order to achieve better seizure outcome is controversial. The presence of spikes outside the boundaries of neocortical temporal resection areas guided by ECoG have not correlated with outcome (McBride et al. 1991, Cascino et al. 1995, Schwartz et al. 1997). The recorded post-resection epileptic discharge did not correlate with the

outcome, nor did recorded post-resection discharge predict clinical seizures (Schwartz et al. 2000).

Intraoperative hippocampal ECoG has also been used in guiding the tailored resection of the hippocampus, which may potentially allow the functionally important hippocampus to be left behind. In their series of 140 TLE patients, McKhann et al. found that hippocampal ECoG predicted how much hippocampus should be removed in order to maximise seizure-free outcome (McKhann et al. 2000). Intraoperative ECoG has also been used in predicting seizure outcome in selective amygdalohippocampectomies. Chen et al. reported that patients with spikes restricted to the mesiobasal temporal lobe more frequently remained seizure-free compared to patients with spikes laterally in the temporal lobe (Chen et al. 2006). ECoG has also been used to guide the extent of resection for removing lesions like the cavernous haemangiomas associated with temporal lobe epilepsy. The critical question is whether to remove only the lesion or to perform more aggressive resection in order to achieve better seizure control. In their series of 61 patients with temporal lobe cavernomas, Van Gompel et al. recently demonstrated that the use of intraoperative ECoG was associated with larger resection and improved the seizure outcome (Van Gompel et al. 2009).

2.5.4.2 Surgical and neurological complications

Resective surgery for TLE is associated with a broad variety of complications related to the complex anatomy and functions of the temporal lobe (Sasaki-Adams and Hadar 2008). Partial visual field defects (contralateral upper quadrantanopsia) are very common after temporal lobe resection, affecting about half of the patients (Manji and Plant 2000, Wiebe et al. 2001). However, most patients are unaware of this and these defects can be diagnosed only with detailed routine testing of the visual field (Egan et al. 2000).

The surgical and neurological complications related to epilepsy surgery have been reported in a large multicentre study in Sweden (Rydenhag and Silander 2001). These researchers defined the complication as minor if it resolves within three

months and major if it affects activities of daily life and lasts longer than three months. Among the 449 therapeutic procedures reported, the most common minor surgical complication was infection, followed by hydrocephalus, cerebrospinal fluid leakage, haematoma and deep vein thrombosis/pulmonary embolism. Minor neurological complications included dysphasia and cranial nerve dysfunction, which affect the oculomotor or trochlear nerves. Major surgical complications affected one patient with infection and one patient with haematoma; the neurological deficits included hemiparesis (10 patients) and hemianopia (2 patients). The overall reported rate of minor complication was 8.9% and for major complications 3.1%. Another large single-centre study by Behrens et al. from Germany reported surgical complications in 7.8% of 429 therapeutic procedures, none of them resulting in permanent morbidity (Behrens et al. 1997). The total rate of neurological complications was 5.4%, with 3.0% causing transient morbidity and 2.3% causing permanent morbidity. Neither of the above mentioned series reported mortality related to the surgical procedures.

In a study involving only surgery for epilepsy of the temporal lobe (215 patients), Salanova et al reported one patient with hemianopia, two patients with mild hemiparesis, seven patients with transient cranial nerve palsies and eight with transient language difficulties (Salanova et al. 2002). Sindou et al. reported the complications in a consecutive series of 100 patients with temporo-mesial epilepsy surgery; three patients had a haematoma, three patients had meningitis, two patients required shunt insertion and two patients had mild permanent hemiparesis (Sindou et al. 2006). No surgical mortality was reported in these series either.

A recent study by Tanriverdi et al. reported the morbidity from a unique series of epilepsy surgery at a single institution in Montreal, Canada, involving 1905 patients who underwent 2449 therapeutic procedures performed by a single neurosurgeon (André Olivier) (Tanriverdi et al. 2009). No major surgical complications were reported, and infections (1.0%) and intracranial haematomas (0.7%) were the most common minor surgical complications. The rate of overall neurological morbidity was 3.3% (minor 2.7%, major 0.5%) with hemiparesis being the most frequent neurological complication. No deaths were reported. However, in historical series before 1973 prior to the era of modern microneurosurgery, the mortality related to

epilepsy surgery has been reported to be 0.8 % -1.2% (Jensen 1975, Pilcher et al. 1996).

In summary, epilepsy surgery can be performed with an acceptably low rate of morbidity and is highly efficacious in treatment of refractory epilepsy.

2.5.5 Seizure outcome of resective surgery

The most widely used classification system for postoperative seizure outcome is adapted from Engel (Table 1) (Engel 1993). However, the category of patients free of disabling seizures (Class I) does not separate those patients with postoperative auras, and the outcome measure '≥50% seizure reduction' is missing from the classification, which is typically used in antiepileptic drug trials (=Engel IVA). Taking into account these issues, the International League Against Epilepsy (ILAE) issued a commission report proposing a new outcome classification (Table 2), which also counts seizure days rather than total number of postoperative seizures (Wieser et al. 2001).

Table 1. Engel's classification of postoperative outcome (Engel 1993)

Class I: Free of disabling seizures	
A	Completely seizure free since surgery
B	Nondisabling simple partial seizures only since surgery
C	Some disabling seizures after surgery but free of disabling seizures for at least 2 years
D	Generalized convulsions with antiepileptic drug withdrawal only
Class II: Rare disabling seizures	
A	Initially free of disabling seizures but has rare seizures now
B	Rare disabling seizures since surgery
C	More than rare disabling seizures after surgery, but rare seizures for at least 2 years
D	Nocturnal seizures only
Class III: Worthwhile improvement	
A	Worthwhile seizure reduction
B	Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years
Class IV: No worthwhile improvement	
A	Significant seizure reduction
B	No appreciable change
C	Seizures worse

Table 2. Classification of outcome with respect to seizures according to the International League Against Epilepsy (ILAE 2001)

Outcome classification	Definition
1	Completely seizure free, no auras
2	Only auras, no other seizures
3	One to three seizures days per year; ± auras
4	Four seizure days per year to 50% reduction of baseline seizure days; ± auras
5	Less than 50% reduction of baseline seizure days to 100 % increase of baseline seizure days; ± auras
6	More than 100% increase of baseline seizure days; ± auras

In a systematic review of 126 articles from 1991 to 2000 concerning the outcome of TLE surgery, McIntosh et al. showed a wide range of freedom from seizures, from 33% to 93% with a median of 70%. The major restrictions of this study were the short follow-up time, small sample sizes, dominance of cross-sectional methods and the heterogeneous definition of seizure outcome (McIntosh et al. 2001).

The only randomised, controlled trial of surgery for TLE compared to AED treatment was conducted between 1996 and 2000 in Canada by Wiebe et al. At the one-year follow-up the proportion of seizure-free patients was 58% in the surgical group and 8% in the medical trated group; and the quality of life, rates of employment and school attendance were better for patients who had undergone surgery (Wiebe et al. 2001).

Studies reporting the short-term seizure outcome for TLE show excellent results, but there is less information available on long-term seizure outcomes. The meta-analysis of 40 studies concerning TLE by Tellez-Zenteno et al. showed a 66% rate of seizure-freedom with a follow-up time of over five years (Tellez-Zenteno et al. 2005). Elsharkawy et al. recently reported that the rate of Engel I class outcome was 69 %

of 102 TLE patients monitored 16 years postoperatively (Elsharkawy et al. 2009). The long-term seizure outcome following selective amygdalo-hippocampectomy with 369 patients reported by Wieser et al. showed an Engel class I outcome of 66.9 % for these patients (median follow-up time 7.4 years) (Wieser et al. 2003). The rate of freedom from seizures after TLE surgery remains satisfactory also in long-term follow-up, and the outcome at one year postoperatively seems to be a reliable indicator of the long-term Engel class I outcome (Cohen-Gadol et al. 2006).

The seizure outcome in patients without any focal abnormalities in MRI has been reported to be significantly worse than in patients with hippocampal sclerosis or foreign tissue lesion on preoperative MRI. The study of Berkovic et al. showed that the postoperative rate of seizure freedom was only 21% in TLE patients with normal MRI (mean follow-up time 45 months); therefore the physicians may have been reluctant to consider surgery with these patients (Berkovic et al. 1995). Since then, several reports have shown better seizure outcomes in patients with normal MRI, but the patient series have been heterogeneous as have the preoperative evaluations. The rate of seizure-free patients varied from 41% to 60% in studies, that included only patients with temporal lobe epilepsy (Holmes et al. 2000, Sylaja et al. 2004, Bell et al. 2009). In studies that included both temporal and extratemporal origin of seizures, the rate of freedom from seizures was reported to be 45% to 63% (Engel class I) (Siegel et al. 2001, Alarcon et al. 2006, Bien et al. 2009) and 37% (ILAE class1) (Chapman et al. 2005). The overall conclusion drawn from results of recent studies supports the use of surgery in patients without any evident focal abnormalities in neuroimaging.

2.6 Other treatment possibilities

2.6.1 Gamma-knife surgery

The idea of Gamma-knife surgery is to achieve seizure control similar to that with conventional resective epilepsy surgery in mesial temporal lobe sclerosis without the surgical risks related to open surgery and possibly minimising the neurocognitive defects after treatment. The disadvantage of radiosurgery is the delayed response up to three years for the seizure control. In addition, some patients may require

prolonged steroid treatment for the extensive oedema caused by radiosurgery. The first gamma-knife treatment for mesial temporal lobe epilepsy was performed in France in 1993 (Regis et al. 1995), and since then prospective multicentre studies have shown seizure-remission rates comparable to those reported previously for open surgery (Regis et al. 2004, Barbaro et al. 2009). It has also been shown that the satisfactory seizure outcome is maintained in the long-term follow-up as well, with seizure-freedom rates of 47% to 60%. In both studies, however, the number of the patients was only 15 (Bartolomei et al. 2008, Rheims et al. 2008). On the other hand, other studies show no benefit from radiosurgery and a majority of those patients later had open surgery with excellent seizure outcome (Kawai et al. 2001, Srikijvilaikul et al. 2004, Vojtech et al. 2009). A prospective randomised study with a larger number of patients would reveal the possible advantages of radiosurgery over open surgery, but on the other hand, randomisation would be difficult due to the known delayed response of radiosurgery (Abou-Khalil 2004).

2.6.2 Stimulation

Neurostimulation is a novel treatment option, mainly for those epilepsy patients who cannot benefit from resective surgery. It has the advantage of reversibility and adjustability; but, on average, the effect of the treatment is considered to be palliative. Vagal nerve stimulation (VNS) is the only approved stimulation therapy in clinical use so far and shows a median reduction in seizures of 35-45% (Morris and Mueller 1999). The role of deep brain stimulation (DBS) is currently under intensive clinical research; and different targets such as the thalamus (Andrade et al. 2006), the subthalamic nucleus (Chabardes et al. 2002) and direct stimulation of the epileptic focus are being evaluated. In small clinical series, direct stimulation of the hippocampus in TLE has demonstrated potential efficacy in controlling seizures without memory deterioration (Boon et al. 2007, Velasco et al. 2007).

3 AIMS OF THE STUDY

The general aim of this study was to evaluate the effect of presurgical, especially invasive, methods on seizure outcome of patients after TLE surgery.

The more specific aims were:

1. To evaluate the overall long-term seizure outcome in patients after TLE surgery.
2. To evaluate the value of 3-D reconstructed MRI in localisation of subdural EEG electrodes.
3. To evaluate a single centre strategy for preoperative evaluation and surgical treatment of TLE, in particular, the rate of complications after resective surgery and use of intracranial EEG electrodes.
4. To evaluate the value of subdural EEG evaluation and surgical outcome in TLE patients without any focal abnormalities in MRI.

4 SUBJECTS AND METHODS

4.1 Patients

4.1.1 Patient population at Kuopio Epilepsy Center 1988- 2006

The Kuopio Epilepsy Center in Kuopio University Hospital is a comprehensive centre for epilepsy surgery, serving an adult population of 4 million inhabitants in Finland and children from its own catchment area (~900,000 inhabitants). Between 1988 and 2006, 229 adult patients underwent temporal lobe resection including amygdalohippocampectomy. During the same period, intracranial diagnostic evaluations were performed for 146 patients who had, according to the preoperative non-invasive evaluation, presumed temporal lobe epilepsy. One hundred and four of these 146 invasively evaluated patients for suspected temporal lobe epilepsy ended up having resective surgery.

4.1.2 Patient population in Study I

One hundred forty consecutive patients operated for TLE between 1988 and 1999 were included. Patients with temporal lesionectomies only but without amygdalohippocampectomy and those for whom any extra-temporal cortical excisions had been carried out were excluded from the study.

4.1.3 Patient population in Study II

A 41-year-old female patient with a 35-year history of partial secondary generalised epilepsy without structural abnormalities in MRI was evaluated with intracranial subdural electrodes and operated on in the year 2000.

4.1.4 Patient population in Study III

Between 1990 and 1999, 80 consecutive TLE patients with 84 intracranial EEG-evaluations were included. In all of these patients TLE was suspected based on the results of non-invasive evaluation.

Analysis of the complications was extended to cover all 146 invasively evaluated patients with suspected TLE between 1990 and 2006 and are thus reported in this thesis. During the same period the surgical and neurological complications of operated 229 adult patients with TLE were evaluated. Patients with any extratemporal resection were excluded as were patients with temporal lesionectomies without amygdalohippocampectomy.

4.1.5 Patient population in Study IV

Between January 1990 and December 2006, 146 patients with suspected TLE were evaluated with intracranial EEG-electrodes. Of these patients, 70 initially had MRIs that were interpreted as normal. After careful re-evaluation of the images, three patients turned out to have focal abnormalities in MRI and two others were excluded from the study due to the suboptimal quality of MRI (only low-field MRI available). In addition to temporal resection, one patient also had extratemporal surgery and was not included in this study. Thus after re-evaluation, 64 patients with normal high-resolution MRI were included in Study IV. After invasive video-EEG evaluation, resective surgery was performed on 38 patients. According to our agreed clinical protocol, patients with normal preoperative high Tesla MRI were not operated on without an invasive evaluation.

4.2 Methods

4.2.1 Preoperative evaluation

In Study I the pre-surgical evaluation included MRI and ictal video-EEG recording (136 recordings with scalp-video-EEG with sphenoidal electrodes, of whom 50 were

evaluated with invasive intracranial EEG-electrodes), neuropsychological evaluation (n=135) and psychiatric evaluation (n=118). The surgical procedure was classified as “curative” if preoperative assessment indicated unilateral TLE. If the patient had evidence of bitemporal or multifocal epilepsy or if for some other reason, the epileptic focus could not be removed, the aim of surgery was classified as “palliative”. Some patients with dual pathology (i.e. hippocampal atrophy in combination with an extrahippocampal structural lesion in MR imaging), combined temporal and extratemporal abnormality (temporal lobe lesion other than hippocampal atrophy in association with an extratemporal lesion in MR imaging), bitemporal MR imaging abnormality, or temporal foreign-tissue lesion without ictal EEG were also classified as palliative.

In Study IV all patients had been evaluated with ictal scalp- and intracranial video-EEG, high Tesla MRI and psychiatric and neuropsychological testing. In the case of bitemporal seizure onsets in invasive EEG, patients with strong unilateral predominance (80% or more of the seizures originating from one temporal lobe) and very difficult symptoms were, however, considered to benefit from resective surgery.

4.2.2 MRI

In Studies I and IV, before February 1993 the preoperative MR imaging was performed with various kinds of scanners and imaging protocols available. In February 1993 high-resolution MR imaging with a standardised protocol for epilepsy became available at Kuopio University Hospital for presurgical evaluation. Since then all candidates for epilepsy surgery have been systematically scanned with a 1.5 - T Magnetom MRI device (Siemens: Erlangen, Germany). The brain was imaged with transaxial T2- and proton density-weighted and coronal T2-weighted sequences and a coronal 3D T1-weighted sequence (magnetization prepared, rapid acquisition gradient echo, MP-RAGE) 10/41/1 (TR, TE, excitations), inversion time 250 ms, flip angle 12° ; FOV 250 mm, matrix 256x192) tilted against the long axis of the hippocampus. In both studies the MR images were re-evaluated independently by two experienced neuroradiologists, who did not know the clinical details of the patients.

In Study II, anatomical T1-weighted MR images were acquired before implantation of the subdural strip electrodes. MR imaging was performed on a Siemens Vision 1.5 T scanner (Siemens: Erlangen, Germany) with a circular polarized head coil. Anatomical images were obtained using the 3D-MPRAGE sequence (repetition time = 9.7 ms; echo time = 4 ms; inverse time = 20 ms; flip angle = 12 degrees; 128 sagittal slices; slice thickness 1.41 mm; field of view, FOV = 250 mm, matrix size 256 x 256). For localisation of electrodes, computer tomography (CT) images were acquired after implantation of the subdural strip electrodes. CT imaging was performed on a Siemens Somatom Plus (Erlangen, Germany): 44 axial slices, slice thickness 3.0 mm, FOV = 205 mm, matrix size 512 x 512. Both MR and CT images were loaded to Curry 4.0 software (Neuro Scan, Inc., Sterling, Virginia). Four unequivocal landmarks (nasion, inion, left ear, right ear) were used for matching the internal coordinate systems of MRI and CT. The coordinates of subdural electrodes were digitized from CT images electrode by electrode and visualized on the cortical surface segmented from MRI.

4.2.3 Invasive video-EEG (Study IV)

The indications for invasive EEG evaluation with MR-negative patients were in the majority of cases bitemporal or unilateral frontotemporal differential diagnosis. Therefore, the electrodes were implanted according to a prejudged and individual plan to cover the frontal and temporal neocortical and temporal and orbitofrontal basal areas. The strip electrodes (ranging from four to eight contact electrodes) were introduced into the subdural space through two frontal and two temporal burr holes under general anaesthesia. For two patients, after failure in localisation of the ictal onset zone with subdural strip electrodes, intracerebral depth electrodes were later introduced. For one of these patients two electrodes were stereotactically (Leksell Stereotactic System, Elekta Corporate, Stockholm, Sweden) implanted on both sides, with target points on the hippocampus and the amygdala, using the lateral temporal approach. For the other patient, the occipital route was used, one electrode implanted to the hippocampus and the amygdala on each side.

The ictal subdural EEG data were re-evaluated by two experienced specialists in clinical neurophysiology. When the first ictal electrographic onset appeared only on

the mesial electrode strip contacts, the seizure onsets were classified as ”unitemporal mesial”. Accordingly, if the ictal onset occurred in temporal neocortical strips, or was seen simultaneously in mesial and neocortical temporal contacts, but not in other strips, seizures were judged as ”unitemporal neocortical +/- mesial”. ”Bitemporal onset” refers to definite independent ictal onsets from both temporal lobes (either mesial or neocortical). For these seizures a unilateral predominance in seizure onsets was also evaluated by using the 80% cut-off point. Based on ictal onsets outside the temporal lobe strips, all other seizures were judged to be ”fronto-temporal”, ”extratemporal” or ”multifocal” onset. Temporal EEG findings were further considered to be ipsilateral or contralateral to the operation side.

4.2.4 Molecular imaging (Study IV)

Interictal [^{18}F] FDG-PET studies were performed at Turku PET Centre on 30 of 64 patients (17/38 for operated patients) according to previously published methods (Lamusuo, et al. 2001). Interictal and/or ictal SPECT studies were performed at Kuopio University Hospital on 28 of 64 patients, for whom data from 22/64 patients were available for re-evaluation (13/38 for operated patients). Ictal and/or interictal SPECT- perfusion or benzodiazepine receptor studies were performed using a Siemens MultiSPECT3 gamma camera with fan-beam collimators (Kuikka et al. 1993). [^{99m}TC]ECD was used as a tracer for perfusion studies (Kuikka and Berkovic 1994) and [^{123}I]Iiomazenil or [^{123}I]NNC-13-8241 for benzodiazepine receptor studies (Kuikka et al. 1996).The PET and SPECT studies were re-evaluated and graded as unilateral temporal or other (e.g. multifocal or contralateral). Furthermore, the findings in isotope imaging studies were graded as ipsilateral to the operated side or other (e.g. multifocal or contralateral).

4.2.5 Resective surgery and complications

In Studies I and IV, all operated patients underwent peroperative electrocorticography (EcoG) using two acutely implanted four-contact depth electrodes, inserted into the hippocampus and the amygdala separately, and 16 neocortically placed surface EEG-electrodes. Intravenous methohexital (a single 40

m.g. bolus) and since 2005, propofol were used to enhance the possible occurrence of focal epileptic discharge in ECoG, while inhalation anaesthesia was withdrawn during ECoG registration. According to the ECoG findings, the final extent of anterior temporal neocortical resection was tailored, but never exceeded 3.5 cm on the dominant and 4.0 cm on the nondominant side measured from the tip of the temporal pole. In Study IV, since 2001 the temporal neocortical resection was modified according to Spencer, leaving the upper temporal gyrus intact (Kim and Spencer 2000). If the earlier video-EEG and acute ECoG showed no independent neocortical epileptiform activity, selective amygdalohippocampectomy was performed, including resection of the paparahippocampal gyrus. In that case the temporomesial structures were approached through the medial temporal gyrus.

A complication was classified as major if it affected activities of daily living, lasted more than three months or included any significant neurological deficit. Minor complications resolved within three months. Information on causes of death was acquired from the Finnish National Registry of Mortality (Statistics Finland).

4.2.6 Histopathology

In studies I and IV the histopathological diagnosis was collected retrospectively from the medical records, and the interpretation of surgical specimens was re-evaluated by an experienced neuropathologist. The surgical specimens were taken from three defined neuroanatomical regions, i.e. hippocampal formation, amygdala and temporal pole. Each tissue sample was grossly inspected, measured and cut in coronal slices. A selection of these slices were fixed in buffered formalin and embedded in paraffin for histological examination. Seven-micron thick sections were prepared and stained with a hematoxylin-eosin stain. Each section was evaluated under light microscopy for its representativeness. Lesions, such as gliosis in the molecular layer, satellitosis, gliosis in white matter, developmental alterations related to migration of neurons, hippocampal sclerosis or other pathological lesions, were searched for and recorded.

4.2.7 Seizure outcome and statistical analysis

In Studies I and IV the seizure outcome was assessed according to a modified classification adapted from Engel using the complete classification with different subclasses (Engel 1993). Neighbourhood seizures (seizures occurring within one month postoperatively) were excluded from the analyses. Routine postoperative follow-up visits were scheduled for all patients at 3 months, 1 year and 3 years after the operation. Thereafter patients were either followed up at the center with clinic visits or contacted by telephone for additional historical details and up-to-date follow-up. In problematic cases, medical records were obtained from other hospitals or community health centres. Whenever possible, the original prospectively collected seizure calendars were obtained.

In Study I, seizure freedom was determined using the different Engel's subclasses (Table 1). Seizure freedom refers to Engel's subclass IA (patients who have been completely seizure free since surgery) at three months, one year and two years postoperatively. However, during long term follow-up (from 3 years onwards) seizure freedom refers to Engel's subclasses IA, IC and ID. In Engel's subclass IC patients may have some seizures after surgery, but they must have been free of disabling seizures for at least two years at the time of assessment. In Engel's class ID, patients may have atypical generalized convulsions after antiepileptic drug withdrawal, but no other seizures. Patients with postoperative auras only (Engel's subclass IB) were displayed separately at all time points, following the suggestions of the new ILAE classification (Wieser et al. 2001). In the subgroup analyses, patients who did not have seizures at three month follow-up (Engel IA) were considered initially seizure-free. In the subgroup analyses of seizure-relapses, patients with Engel's subclasses IC and ID were not re-considered to be seizure-free after the first postoperative seizure. In Study IV, Engel's main class I (including Engel's subclasses IA- D) was used to describe postoperative freedom from disabling seizures.

In Studies I and IV, Engel's class II refers to all patients who have rare seizures (fewer than 3 per year) postoperatively (Engel's subclasses IIA- C). In subclass IIA patients were originally seizure-free, but have rare seizures at the time of the assessment. In subclass IIB patients have rare seizures after surgery. In subclass IIC

patients may originally have more than rare postoperative seizures, but they must have had only rare seizures for at least 2 years at the time of assessment. Engel's class III refers to a reduction in seizure frequency of at least 80% postoperatively (worthwhile seizure reduction). Engel's class IV refers to a less than 80% seizure reduction postoperatively (no worthwhile improvement in seizure frequency, Engel's subclasses IVA- C). This includes patients with a seizure reduction of at least 50% (subclass IVA), patients with no change from preoperative seizure frequency and severity of seizures (subclass IVB), or patients with more frequent (an increase in seizure frequency of at least 50% postoperatively) or more severe seizures than preoperatively (subclass IVC). According to the Engel's classification during long-term follow-up, the seizure outcome data from preceding last two years is used for the assessment.

In Study IV, Engel's classes I and II were considered to be "favourable outcome" and Engel's classes III and IV "poor outcome".

In Study I, the statistical software SPSS WIN 9.0 software (SPSS Inc., Chicago, IL, USA) and in Study IV the version of SPSS for Windows 16.0 were used for statistical analysis. In Study I, the postoperative outcome was analysed using the Chi-square test for comparisons between patient groups. The existence of significant differences was defined as a probability value (p) < 0.05, and in Study IV the two-tailed Fisher's exact test was used.

5 RESULTS

5.1 Patient demographics

5.1.1 Study I

The median age of the patients at the time of the operation was 32 years (range 14 to 54 years). The median age at onset of epilepsy was 12 years (range 0.1 to 43 years), and median duration of epilepsy at the time of operation was 19 years (range 2 to 47 years). During the year preceding the operation, the preoperative frequency of seizures varied from 10 to 1655 seizures per year (median 78).

On the basis of the preoperative assessment, 103 patients (74% of all patients) had concurrent evidence of unilateral TLE. For them, the aim of surgery was judged preoperatively as “curative”. For an additional 37 patients the surgery was palliative. These 37 patients had bitemporal onset of seizure (n=18), unitemporal but extratemporally extending onset of seizure (n=6), multifocal epilepsy (n=2), dual pathology (n=2), combined temporal and extratemporal abnormality (n=2), bitemporal MR imaging abnormality (n=2), or posterior neocortical onset of seizure in the dominant temporal lobe together with ipsilateral speech dominance (n=2). Furthermore, three patients with temporal foreign-tissue lesion without ictal EEG were classified as palliative.

5.1.2 Study IV

The mean age at the time of intracranial EEG electrode implantation was 31 years (range 15-51 years). Mean age at the onset of seizures was 16 years (range 1-40 years) and the mean duration of epilepsy was 15 years (range 2-43 years).

Sixty-six intracranial recordings were performed for 64 patients. Two patients of the 64 had a combination of subdural and intracerebral depth electrodes, and in two patients a second invasive EEG-recording was performed only with depth electrodes. Finally, for 26 patients it was not possible to identify the area of seizure onset, thus

preventing us from proceeding to the resective surgery. For 16 patients the onsets of seizures were probable extratemporal or multifocal, 2 patients had a seizure onset near or at the eloquent area and 4 had independent bitemporal seizures. Finally, in 20 patients no further surgical evaluation was recommended, and the antiepileptic medication was optimised. In two patients a vagus nerve stimulator was implanted. Two patients were seizure-free after the EEG evaluation, and two patients experienced no seizures even during a prolonged (21 days) period of invasive EEG-registration.

During the same period we operated 126 MRI-positive TLE patients without invasive recordings and 63 MRI-positive patients with invasive EEG recordings. In addition, two patients with low-field MRI and one patient with larger than only temporal resection were operated after intracranial EEG-evaluation. The MRI-negative operated group (N= 38) constitutes 17% of all adult TLE-patients (N= 229) operated in our hospital during the same period.

5.2 MRI

5.2.1 Unilateral TLE (Study I)

Qualitative MR imaging demonstrated unilateral structural abnormality in the temporal lobe in 53% (n=55) of the patients with unilateral TLE. This included hippocampal atrophy with (n=9), or without (n=24) temporal cortical atrophy, and other unilateral structural lesions of the temporal lobe (n=22). MR imaging showed other abnormalities in 13% (n=13) of patients and it was judged as normal in 34% of the patients with unilateral TLE (n=35). The MR-imaging data were also evaluated in subgroups of patients imaged before or after introduction of a standardised MR-imaging protocol for epilepsy (operated on between December 1988 and January 1993 or February 1993 and December 1999, respectively). In the earlier group (1988 - 1993) MRI demonstrated structural abnormalities in 35% (n=17) of patients and in the later group (1993 - 1999) in 70% (n=38, $p<0.001$). The difference in the rate of abnormal findings probably reflects the improved MRI protocol.

5.2.2 Patients with palliative operations (Study I)

The largest subgroup among the palliatively operated TLE patients were those with normal qualitative MR imaging (n=13). When the MR-imaging data in subgroups of patients imaged before or after the introduction of a standardised MR-imaging protocol for epilepsy were evaluated, the changes were similar to those observed in unilateral TLE ($p<0.05$). Between December 1988 and January 1993, a unilateral structural abnormality of the temporal lobe was found in 8% (n=1), and the MR-imaging was interpreted as normal in 62% (n=8) of palliative patients. Thirty-one % (n=4) had dual pathology or concomitant temporal and extratemporal abnormality. In the later group (between February 1993 and December 1999) MRI demonstrated structural abnormality in 38% (n=9) and normal MR imaging in 21% (n=5). An additional 25% (n=6) of patients had dual pathology, concomitant temporal and extratemporal abnormality or extratemporal pathology, leaving 17% (n=4) for other aetiologies.

5.2.3 3-D reconstructed MR imaging (Study II)

In Study II the locations of the EEG electrodes were visualised on the segmented cortex of the 3-D reconstructed MR-images. Unexpectedly, the tips of both orbitofrontal and temporal strip electrodes were lying close to each other in the area of the right mesial temporal lobe, thus verifying that both of the electrodes involved in seizure onset were localised in the right temporal lobe.

5.3 Intracranial EEG (Study IV)

Among the 38 operated patients, according to the invasive ictal video-EEG monitoring the onset of the seizure could be defined in the unilateral temporal mesial area in 25 patients (66%). The ictal onset was unilateral neocortical +/- mesial in 29 of the patients (76%), bitemporal in 6 patients (16%) and frontotemporal or multifocal in 3 patients (8%). In bitemporal cases, unilateral predominance of 80% or more was found in all 6 patients.

5.4 Molecular imaging (Study IV)

PET showed an area of ipsilateral temporal hypometabolism in 10 patients, which was in concordance with ictal onset in invasive EEG recording; and extratemporal changes were seen in 7 patients. Interictal or ictal SPECT showed an ipsilateral temporal finding in 4 patients and other extratemporal locations in 9 patients.

5.5 Surgical procedures

In Study I, the operative procedures included anterior temporal resection and amygdalohippocampectomy, alone (n=113) or combined with lesionectomy (n=9), and selective amygdalohippocampectomy (n=18).

In Study IV, based on the peroperative electrocorticography findings, anterior temporal resection and amygdalohippocampectomy was performed in 30 patients and selective amygdalohippocampectomy in eight patients (21%). Twenty-three patients (61%) were operated on the left side and 15 (39%) patients on the right side.

5.6 Complications related to the surgical procedures and the rate of mortality

5.6.1 Resective surgery

Major complications related to resective surgery included prolonged dysphasia in one patient, homonymous hemianopia in three patients, and subarachnoidal haemorrhage caused by an intraoperative depth electrode in one patient. This last patient experienced prolonged dysphasia, which resolved completely within one year.

The most frequent minor complications included chronic subdural haematoma in 5 patients, who were treated with trephination and drainage. Two patients had subdural effusion, which resolved without further operative treatment. Six patients had postoperative probable aseptic meningitis without microbiological verification, one patient needed shunt insertion due to the hydrocephalus, and in one patient a bone lambeau infection was noted. One patient experienced deep vein thrombosis, and

one had to be reoperated within a week due to cerebrospinal leakage through mastoid cells. Six patients experienced dysphasia, which resolved completely within three months. The total rate of major complication was 2% (5/229) and for minor complications 10% (23/229) (Table 3).

Table 3. Surgical and neurological complications related to temporal resection in 229 operated patients.

Complication	Minor	Major
Surgical		
Haemorrhage, peroperative		1
Chronic subdural haematoma/hygroma	7 [a]	
Aseptic meningitis	6 [b]	
Hydrocephalus	1	
Lambeau infection	1	
Deep vein thrombosis	1 [c]	
Cerebrospinal fluid leak from the nose, reoperation	1	
Neurological		
Homonyme hemianopia		3
Dysphasia	6	1
Total number of complications	**23**	**5**
Total number of patients with complications	**21**	**5**

[a] Five chronic subdural haematomas evacuated and two subdural effusions treated conservatively.
[b] One patients with transient dysphasia had also aseptic meningitis.
[c] One patient with transient dysphasia had also deep venous trombosis.

5.6.2 Intracranial EEG-evaluation

Among the 146 patients with intracranial EEG-monitoring, 36 (25%) showed transient complications related to invasive evaluation: 24 patients experienced cerebrospinal fluid leakage from the wound, four patients had suspected meningitis with fever but without bacteriological verification. Two patients had transient third cranial nerve palsy, which was probably due to direct compression of the oculomotor nerve by a subtemporal strip electrode, which resolved within days after the electrode was pulled out about one centimetre. Two patients experienced transient diplopia; and one had an asymptomatic subdural haematoma, which was revealed by the postoperative CT imaging used for localising the electrodes. One patient had an asymptomatic subdural haematoma near the subtemporal strip electrode, which prevented proper recording from those contacts; and a new intracerebral electrode was therefore inserted through the same burr hole to the ipsilateral hippocampus. The invasive EEG evaluation could be completed, but later the patient developed temporal lobe encephalitis without microbiological verification. This patient was treated with antibiotics and corticosteroids and recovered without neurological or neuropsychological deficits. One patient experienced a middle ear infection, treated with antibiotics, and one had transient hyponatremia (Table 4). Despite the complications described above, for all patients the invasive EEG evaluation could be completed as planned; and no complications causing permanent neurological deficits were noted.

Table 4. Surgical and neurological complications related to intracranial EEG evaluation during 1990-2006 in 146 patients with suspected TLE.

Cerebrospinal fluid leak from the wound	24 (16%)
Suspected meningitis, no microbiological verification	4 (3%)
Transient paresis of third cranial nerve	2 (1%)
Diplopia, transient	2 (1%)
Subdural hematoma, asymptomatic	1
Subdural hematoma and postoperative encephalitis	1
Middle ear infection	1
Hyponatremia	1
	36/146 (25%)

5.6.3 Mortality

In Study I, six patients died during the follow-up. Two of these patients had been completely free of seizures postoperatively (14 and 27 months), and four had an unfavourable surgical outcome. The causes of death related to epilepsy (4 out of 6) were sudden unexpected death in epilepsy, suicide (depression related to poor seizure control), and prolonged epileptic seizure (n=2). No mortality was directly attributable to the surgical procedures.

5.7 Histopathology

In Study I, the pathologic examination of resected tissue displayed three different entities: patients with hippocampal sclerosis or gliosis (n=60), patients with tumour or cystic lesion (n=18), and patients with cortical microdysgenesis (n=17). Hippocampal

sclerosis was confirmed in 41 of 46 symptomatic patients with hippocampal atrophy in the preoperative MR imaging. Focal cortical dysplasia was observed in one patient, and benign or low-grade tumour (dysplastic neuroepithelial tumour, ganglioglioma, hamartoma, or oligodendroglioma) in six patients, who were evaluated preoperatively as suffering from probable symptomatic focal epilepsy.

In Study IV, 26 subjects (68%) did not display any definite pathological findings in any of their surgical specimens. In two subjects, only a microscopically identifiable tumour was observed, one defined as an oligodendroglioma and one as a dysembryoplastic neuroepithelial tumour. In two patients migrational alteration, i.e. cortical microdysgeneses, was observed. Only two patients displayed definite hippocampal sclerosis, i.e. neuronal loss and gliosis, within the CA1 region; and in six patients prominent gliosis without neuronal loss was seen.

5.8 Seizure outcome (Engel´s Classification)

5.8.1 One year outcome (Study I)

In patients with unilateral temporal lobe epilepsy 45% (n= 46) were completely seizure free and 12% (n=12) had only postoperative auras one year after the operation. Rare seizures (Engel II) were identified in 12% of the patients (n=12). Engel I-II outcome was thus observed in 68% of these patients. In addition, 13% of the patients (n=13) had a worthwhile reduction in seizures (Engel III), while 19% (n= 19) did not benefit from surgery (Engel IV). One patient died due to a prolonged epileptic seizure three months after the operation.

In patients with palliative operations 27% (n= 10) were free of seizures, 3% (n=1) had only postoperative auras, and 8% (n=3) had rare seizures. In addition, 24% (n=9) achieved a worthwhile reduction in seizures. A minimum of 80% reduction in seizures was therefore achieved by 62 % of these patients.

5.8.2 Long-term outcome (Study I)

In patients with unilateral TLE, the results of the long-term follow-up did not differ from those of the one-year follow-up ($p>0.05$ between groups). On the latest available follow-up date (mean follow-up 5.4 ± 2.6 y, range 3 months –10.5 y) 46% (n= 47) of the patients were seizure free; 10% (n=10) had only postoperative auras, and 15% (n=15) had rare seizures. In addition, 13% of the patients (n=14) achieved a worthwhile reduction in seizures and 16% (n= 17) did not benefit from surgery (Engel IV).

In patients with palliative surgery, on the latest available follow-up date 35% (n= 13) of patients became seizure free, 5% (n=2) had rare seizures and 22% (n=8) achieved a worthwhile reduction in seizures. The mean follow-up was 4.4 ± 2.2 years (range 1.0 -9.0 years). Also in palliative patients the results of long-term follow-up did not differ from those of one-year follow-up ($p>0.05$ between groups,).

5.8.3 Analysis of outcome before and after standardised MR imaging protocol for epilepsy (Study I)

The results were independently evaluated in patients operated on with or without a standardised preoperative MR-imaging protocol for epilepsy. There was a significant difference in the postoperative outcome between these two groups ($p\leq0.001$ for one-year outcome). Forty-nine patients with unilateral TLE were operated on before the introduction of a standardised MR imaging protocol for epilepsy (between December 1988 and January 1993). One year after the operation 61% (n= 30) of the patients achieved Engel I-II outcome, with only 27% (n=13) being seizure free. In the long-term follow-up (latest available follow-up data, median 7.7 years, range 1.0 - 10.5 years) 39% (n=19) of the patients became seizure free, 12% (n=6) had only postoperative auras, and 12% (n=6) had rare seizures. In addition, 19% (n=9) of the patients achieved a worthwhile reduction in seizures, while 18% (n=9) had no worthwhile reduction in seizures. A total of 54 patients with unilateral TLE were operated on after the introduction of a standardised MR-imaging protocol for epilepsy (from February 1993 to December 1999). One year after the operation 61% (n=33) of them were free of seizures, 11% (n=6) had only postoperative auras, and 2% (n=1)

had rare seizures. Moreover, 11% (n=6) achieved a worthwhile reduction in seizures. On the latest available follow-up date (median follow-up 3.8 years, range 3 months - 6.5 years) 52% (n=28) of the patients were seizure free, 7% (n=4) had only postoperative auras, and 17 % (n=9) had rare seizures. Nine percent (n=5) of the patients achieved a worthwhile reduction in seizures. Taken together, after the introduction of a standardised MR-imaging protocol for epilepsy, 74% of patients with unilateral TLE achieved Engel I-II outcome in the one-year follow-up and 76 % of patients in the long-term follow-up (Figure 5).

When the outcome was analysed in subgroups of palliative TLE patients operated on before or after the introduction of a standardised preoperative MR imaging protocol for epilepsy, trends of improved outcome similar to those in patients with unilateral TLE were observed ($p>0.05$). Twenty-four patients were operated on after the introduction of a standardised MR imaging protocol for epilepsy (between February 1993 and December 1999). On the latest available follow-up date (median follow-up 3.1 years, range 1.1 -6.8) 42% (n=10) of these patients were free of seizures, 4 % (n=1) had rare seizures, and 25% (n=6) achieved a worthwhile reduction in seizures. An at least 80% reduction in seizures (Engel I-III outcome) was therefore achieved by 71% (n= 17) of the palliative patients operated on after the introduction of a standardised MR-imaging protocol for epilepsy in the long-term follow-up (Figure 5).

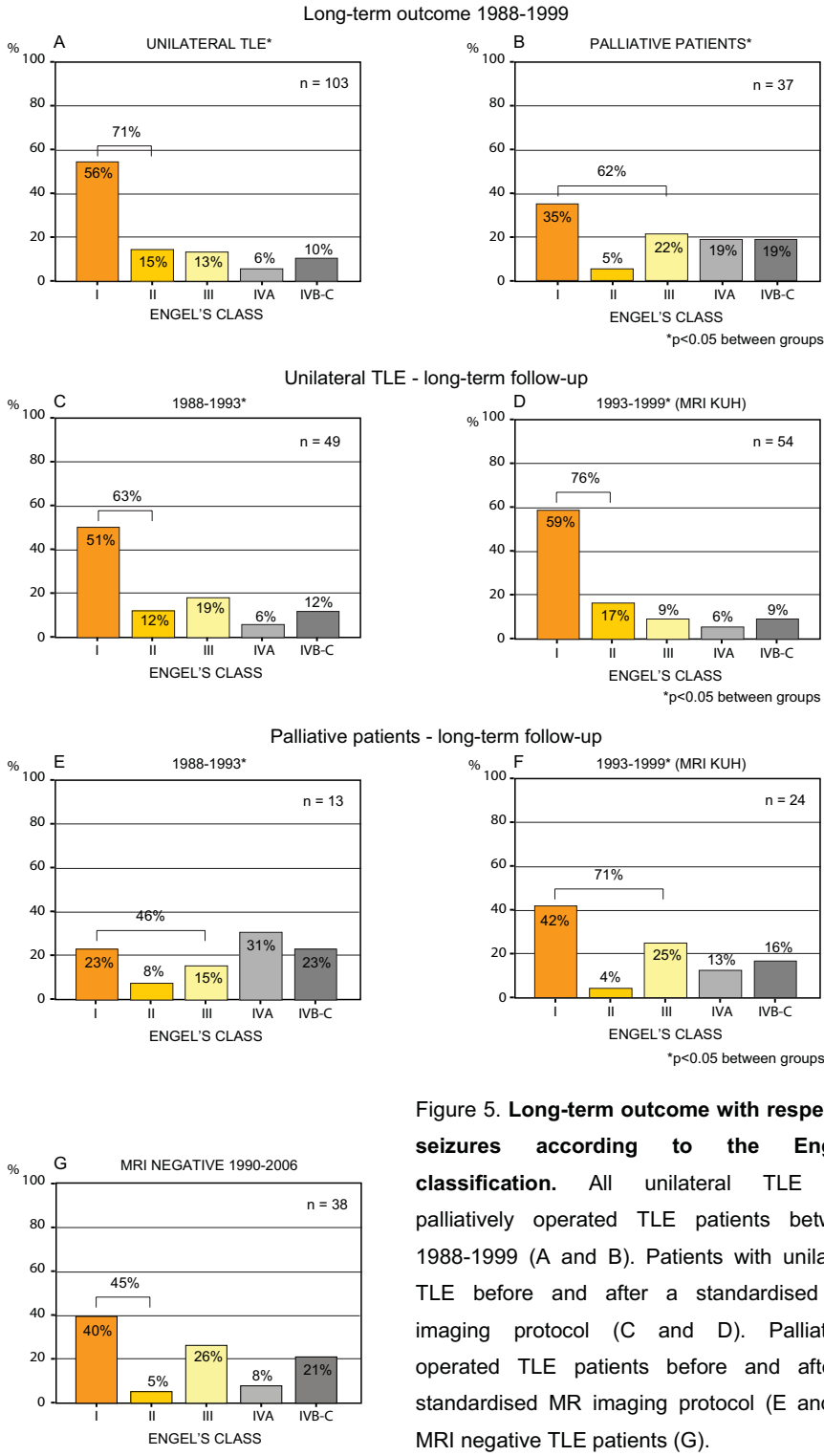

Figure 5. **Long-term outcome with respect to seizures according to the Engel's classification.** All unilateral TLE and palliatively operated TLE patients between 1988-1999 (A and B). Patients with unilateral TLE before and after a standardised MR imaging protocol (C and D). Palliatively operated TLE patients before and after a standardised MR imaging protocol (E and F). MRI negative TLE patients (G).

5.8.4 Late seizure relapse (Study I)

Eighty-six percent (71 of 83) of all seizure relapses occurred within one year after the operation. Late relapses were often preceded by a specific explanatory factor such as withdrawal of antiepileptic medication (n=3) or hyponatremia (n=1), and in none of the patients did this lead to subsequent persistent intractability during the follow-up.

Initially, 63% (88 of 140) of all patients were seizure free or had only postoperative auras at the first postoperative control visit (three months postoperatively). Of these, 53% (47 of 88) remained completely free of seizures also in the long-term follow-up (mean 5.2 ± 2.6 years, range 1.0-10.5 years), whereas 5% (4 of 88) experienced some seizures but again became seizure free (for at least two years). In addition, 11% (10 of 88) had only postoperative auras and 15% (13 of 88) had rare seizures.

5.8.5 Outcome with respect to seizures and predictive factors (Study IV)

In Study IV after one-year follow-up, 45% (17 of 38) of the patients had favourable outcome; 40% (n=15) had Engel class I and 5% (n=2) had Engel class II. Of the patients, 55% (21 of 38) had poor outcome after 12 months follow-up; 21% (n=8) had Engel class III and 34% (n=13) had Engel class IV.

The latest follow-up lasted mean 5.8 years (median 4.8 years, range 1.1-14.3 years). In addition, one patient died due to SUDEP three months after the operation with an outcome of Engel class IV at that time. His outcome has been taken into account in the analysis by carrying the last observation forward. At the latest follow-up 45% (17 of 38) of the patients had favourable outcome (40% (n=15) had Engel class I and 5% (n=2) had Engel class II). Twenty-one patients out of 38 had poor outcome (10 Engel class III and 11 Engel class IV). The outcome did not change between the 12-month follow-up and the latest follow-up (Figure 5).

Eight predictive factors were selected prospectively and evaluated as potential predictors of postoperative seizure outcome. Patients with noncongruent PET results

had the worst outcome (p=0.044); none of the other factors evaluated were statistically significant (Table 5).

Table 5. Analysis of predictive factors for seizure outcome at the latest postoperative follow-up in MR-negative temporal lobe epilepsy patients.

	n	Engel I-II	Engel III-IV	F, p
All	38	17 (45%)	21 (55%)	
Gender				
Female	23	13 (57%)	10 (43%)	p=0.100
Male	15	4 (27%)	11 (73%)	
Duration of epilepsy				
≤ 10 years	15	8 (53%)	7 (47%)	-
11-20 years	9	0 (0%)	9 (100%)	
≥ 21 years	14	9 (64%)	5 (36%)	
Invasive ictal EEG onset				
Ipsilateral to operated side	29	13 (45%)	16 (55%)	p=1.000
Other	9	4 (44%)	5 (56%)	
SPECT				
Ipsilateral to operated side	4	3 (75%)	1 (25%)	p=0.266
Other	9	3 (33%)	6 (67%)	
PET				
Ipsilateral to operated side	10	5 (50%)	5 (50%)	p=0.044
Other	7	0 (0%)	7 (100%)	
Surgery				
ATL + AH	30	13 (43%)	17 (57%)	p=1.000
Selective AH	8	4 (50%)	4 (50%)	
Side of surgery				
Right	15	6 (40%)	9 (60%)	p=0.744
Left	23	11 (48%)	12 (52%)	
Pathology				
Focal pathology	12	6 (50%)	6 (50%)	p=0.734
No focal pathology	26	11 (42%)	15 (58%)	

F,p = Fisher's exact test, p-value
ATL = anterior temporal lobe resection
AH = amygdalohippocampectomy
SPECT = single photon emission computed tomography
PET = positron emission tomography

6 DISCUSSION

In Finland, a comprehensive programme of epilepsy surgery was first established at Kuopio University Hospital, and the evaluation and surgical treatment of refractory epilepsy patients started in 1988. Before that the multidisciplinary epilepsy surgery team was trained at one of the most advanced epilepsy surgery centres, Montreal Neurological Institute in Montreal, Canada. In Finland, the first invasive intracranial EEG evaluations were performed in 1990. A majority of the operated patients have been adults with refractory TLE from a defined geographical area in Finland having a population of 4 million inhabitants. The present series of studies were based on the preoperative evaluation, surgical treatment and systematic follow-up of adult TLE patients treated at Kuopio University Hospital between 1988 and 2006.

6.1 Methodological considerations

Study I is a comprehensive analysis of the longitudinal follow-up of refractory TLE patients from consecutive series between 1988 and 1999. The strength of the study is that it has a long-term follow up from a relatively well-defined population. Nearly all adult TLE operations in a population of 4 million inhabitants in Finland were performed at Kuopio Epilepsy Center. The new preoperative MRI protocol seems to detect structural abnormalities more accurately than was the case before January 1993. Had the new protocol been in use during the the whole study period it might have had a beneficial impact on the results.

In Study IV, all patients without any focal abnormalities in high resolution MRI were systematically evaluated with intracranial EEG electrodes in a consecutive series between 1990 and 2006. During these years the MRI methods had developed considerably, which leads to the fact that some previously MRI-negative patients might now be MRI positive if scanned with current MRI methods. Moreover, molecular imaging (SPECT, PET) studies were not applied systematically, and therefore no firm conclusions can be made concerning their role in preoperative work-up. On the other hand, the operative techniques related to resective surgery and intracranial EEG evaluation remained uniform throughout the study period.

In both studies (I, IV) the mean follow-up was about five years, which is meaningful for assessment of the long-term outcome of epilepsy surgery.

6.2 Seizure outcome

The data obtained in Study I demonstrated that 57% of the unilateral TLE patients achieved Engel I outcome at one-year follow-up compared to 30% in the subgroup of palliative patients. In long-term follow-up the rate of Engel class I outcome was observed in 56% of patients with unilateral TLE and in 35% of palliatively operated patients. Our findings are in line with reported results of long-term seizure outcome after temporal lobectomy in a series of 325 patients (McIntosh et al. 2004).

Not surprisingly, the seizure outcome in a subgroup of palliative patients was worse than that for patients with unilateral temporal seizure focus. Surgical treatment of bitemporal epilepsy after invasive EEG evaluation is, however, also beneficial, even if the total freedom from seizures is not achieved (Boling et al. 2009). In Study I, 54% of our palliatively operated patients had bitemporal seizure onset or bitemporal MRI pathology.

It was shown in the present study that 86% (71/83) of seizure relapses occurred within the first postoperative year, thus indicating that the outcome at one-year follow-up was predictive of long-term outcome. Cohen-Gadol et al. reported similar results at the 1st year follow-up, this being a reliable indicator also of the long-term Engel class I outcome (Cohen-Gadol et al. 2006). The large meta-analysis of long-term seizure outcome by Tellez-Zenteno et al. showed the long-term outcome in TLE to be similar to the outcome in short-term controlled studies (Tellez-Zenteno et al. 2005). According to the two long-term follow-up studies, the likelihood of remaining seizure free after the two first years of freedom from seizures was 90% (Elsharkawy et al. 2009) and 86% (Foldvary et al. 2000).

Our data indicate that 53% of the initially seizure-free patients remained completely seizure-free (Engel class 1A) on long-term follow-up (mean 5.2 years). Yoon et al. reported that with patients who were seizure-free at one-year follow-up after

resective surgery, the likelihood of remaining seizure free declined to 56% over ten years; but half of the patients who relapsed had at most one seizure per year. In their series the longer duration of epilepsy before surgery and normal pathological findings were predictive factors for poorer outcome (Yoon et al. 2003).

Our results also demonstrate that epilepsy surgery can be beneficial for patients with TLE and nonlesional MRI. At the latest follow-up (mean 5.8 years) 40 % of our patients achieved Engel class I outcome, and the outcome did not change between the one-year and the latest follow-up.

6.3 The role of MRI

Standard MRI protocols fail to detect up to 50% of the lesions in epilepsy patients with refractory epilepsy (Von Oertzen et al. 2002). Therefore it has been suggested that a specific, pre-planned epilepsy protocol should be used. This was also shown here in the present Study I, when after introducing a standardised epilepsy imaging protocol in February 1993, the rate of unilateral structural abnormalities discovered in preoperative MRI increased from 35% to 70% in patients with unilateral TLE. Of course, improvement in MRI techniques from the early 1990's onward is likely to have facilitated detection of abnormalities. The seizure outcome was analysed before and after a standardised imaging protocol for epilepsy was introduced, and improved outcome trends were seen in unilateral TLE as well as in a subgroup of palliative patients operated after February 1993.

The diagnosis of unilateral HS on MRI has a positive predictive value for seizure outcome after surgery (Berkovic et al. 1995, Gilliam et al. 2000). Patients are often less likely to be operated on when no hippocampal anomalies are detected on MRI, which further underlines the impact of specific MRI protocol on patient management and emphasizes the importance of adequate imaging.

Earlier it was thought that mild MCDs and type I FCDs could not be detected in MRI, but recently MRI abnormalities have also been described for these pathologies (Krsek et al. 2008, Widjaja et al. 2008). The FCDs most frequently identified on MRI

are type II or Taylor-type FCDs; however, MRI still can be normal in FCD found in subsequent pathological samples (Bronen et al. 1997, Chan et al. 1998, Lee et al. 1998).

In our study, 44% of patients with suspected TLE and evaluated with intracranial EEG electrodes had normal MRI scans. Possible reasons include (a) a subtle form of MTS that is not apparent on MRI; (b) other pathology of the medial temporal lobe, such as microdysgenesis, not visible on MRI; or (c) temporal neocortical pathology, such as mild forms of cortical dysplasia, not detected by MRI. In Study IV, 68% of the operated patients with MRI-negative TLE did not display pathological alteration in any of their surgical specimens. Subtle pathology may not have been detected, especially when present in neocortical areas.

The development of 3T MR-imaging has enabled neuroradiologists to detect relevant abnormalities related to focal epilepsy with previously unremarkable 1.5 T scans (Knake et al. 2005, Strandberg et al. 2008). Focal temporal MRI findings correlate positively with the seizure outcome of TLE surgery. Therefore, patients who could be candidates for surgical treatment based on their clinical results, and who have had previously unremarkable MRI scans, should be rescanned when more advanced equipment and methods become available. However, high-sensitivity MRI will detect even subtle lesions, which may not be in concordance with other findings in preoperative evaluation, thus also being, at least theoretically, misleading. This stresses the importance of having a multidisciplinary team for epilepsy surgery. The MRI findings should thus be interpreted against all other data available at the presurgical evaluation work-up.

Since 1999, 3-D reconstructed MR-imaging was implemented for visualisation of the intracranial EEG electrodes after their implantation; before that, only a skull X-ray was used for localising the electrodes. We demonstrated the crucial role of the 3-D reconstructed MRI with one MRI-negative TLE patient who showed ictal onset from both frontal and temporal subdural strip electrodes. According to the 3-D MRI images, the frontal electrode was actually recording the temporopolar ictal activity; and a selective amygdalohippocampectomy was performed based on the results of the intraoperative EcoG, which showed no temporal neocortical epileptiform

discharge. Postoperatively, the patient was seizure free (Engel class IA). Without the exact information provided by the 3D imaging the patient would have been considered inoperable (i.e., seizures misinterpreted as arising simultaneously from the basal temporal and frontal areas).

6.4 The role of intracranial EEG electrodes in TLE

In the present Study I, 36% (50/140) of the patients underwent invasive preoperative EEG-evaluation with subdural strip electrodes in order to confirm the area of seizure onset. According to our agreed upon clinical protocol, none of the patients in Study IV who had normal high-field preoperative MRI was operated on without intracranial EEG- recording. The role of the ictal EEG findings is emphasized in the preoperative work-up when the structural imaging studies do not aid in defining the epileptogenic areas. However, the spatial resolution of invasive intracranial EEG in a complex three-dimensional cerebral cortex is limited and it may also result in false localisation (Eisenschenk et al. 2001, Knowlton et al. 2008). Of 29 patients (Study IV) with even unilateral temporal seizure onset, only 13 (45%) patients had good outcome and 16 (55%) patients had poor outcome. In these patients the surgical failure is probably due to insufficient excision of epileptogenic tissue. Patients may have more remote areas of epileptogenicity or diffuse epileptogenicity in the residual temporal lobe. A satisfactory resection of one epileptogenic region may still result in failure when another site, such as the opposite medial temporal area, begins or continues to initiate seizures.

After failed initial invasive monitoring, some patients may benefit from re-evaluation with intracranial electrodes (Siegel et al. 2000). In Study IV, two patients were re-evaluated with intracerebral depth electrodes inserted into the hippocampus and amygdala. For one of them the site of seizure origin could be identified, and the patient became seizure-free. To entitle the patient to a second invasive procedure, the practical benefit of such second implantations should certainly be judged to be very high.

6.5 Strategies for surgical resections in TLE

Classical resection of the anterior temporal lobe, including amygdalohippocampectomy, was applied in majority of the patients. Resection of the temporal neocortex could have been tailored according to the intraoperative ECoG findings, but it never exceeded 3.5 cm on the dominant side and 4.5 cm on the non-dominant side measured from the tip of the temporal lobe. Since 2001, a more sparing neocortical resection was adopted, leaving the upper temporal gyrus intact. In Study I, selective amygdalohippocampectomy was performed in 13% of the patients and in Study IV in 21% of the patients. In Study IV, the type of resection had no impact on seizure outcome regardless of whether a selective amygdalohippocampectomy or classical ATL including amygdalohippocampectomy was performed. The impact of the resection type was not analysed separately in Study I. Most retrospective analyses have concluded that there is no significant difference in seizure outcome between more selective and classical ATL types of resection (Arruda et al. 1996, Clusmann et al. 2002, Paglioli et al. 2006).

6.6 Complications and mortality

In the present study the total rate of major complications related to resective surgery was 2% and for minor complications 10%. Our results are in line with the rate of complications reported in a large single-centre study in Germany (Behrens et al. 1997) and a multicentre study in Sweden (Rydenhag and Silander 2001). Behrens et al. reported that the total rate of complications causing permanent morbidity was 2%, and the Swedish survey reported major complications in 3.3% for all resective procedures and 2.8% for temporal lobe resections. In our Finnish series no permanent hemiparesis was noted. On the other hand, the present series did not include any extratemporal surgery, which probably carries a higher risk for injury of the e.g. primary motor cortex and associated descending pathways.

Twenty-five percent of the evaluated patients showed transient complications related to intracranial EEG, but for all patients the EEG evaluation could be finished as

planned. The overall rate of major complications related to invasive EEG evaluation has been reported to be low (Swartz et al. 1996, Behrens et al. 1997, Wiggins et al. 1999, Rydenhag and Silander 2001, Burneo et al. 2006). This applies especially to the subdural strip electrodes, which were used with a majority of the patients in the present studies.

In Study I, six patients died during follow-up, of whom four had evidence of poor postoperative control of seizures. Sperling et al. evaluated and followed up prospectively a cohort of 583 patients who had had epilepsy surgery. They reported 19 deaths in their series, 18 of which were observed in patients with recurrent seizures. They concluded that successful epilepsy surgery reduces the risk of epilepsy-associated death (Sperling et al. 2005). Salanova et al. showed that the late mortality in 215 operated TLE patients occurred predominantly in patients with persistent seizures. In those patients who became seizure free, the mortality rate was similar to that of the general population (Salanova et al. 2002).

6.7 Clinical impact

The findings of the present series of studies support the concept that TLE surgery is beneficial, especially in MRI-positive patients, but also in selected patients with normal MRI. The evolution of MRI techniques and other non-invasive investigations will probably reduce the need for invasive EEG-evaluation. This study emphasises the importance of a multidisciplinary team in the complex presurgical evaluation of candidates for surgery. To maximise the benefit for the patient, epilepsy surgery should be performed in centres with multidisciplinary expertise and experience.

7 CONCLUSIONS

1. The postoperative long-term seizure outcome in a Finnish national referral centre for epilepsy surgery with adult TLE patients is comparable to reported results from established and recognised epilepsy centres worldwide. Outcome at one-year postoperatively was predictive of long-term outcome. Surgical treatment was also beneficial in a group of palliatively treated TLE patients, who in the preoperative evaluation did not have unilateral onset of seizure.

2. When refractory epilepsy patients with intracranial EEG-electrodes are evaluated, the 3-D reconstructed MRI imaging is superior to skull X-ray films for visualising the position of the electrodes in relation to the detailed cortical anatomy. This helps to delineate the area of seizure onset and helps to plan surgical resection.

3. Preoperative evaluation with intracranial EEG electrodes is safe. Surgical complications related to the invasive evaluation were all transient and cause no permanent morbidity. Resective surgery in TLE can be performed with an acceptably low rate of morbidity, and there was no mortality related directly to the surgical procedures.

4. Patients with no focal abnormality in preoperative MRI usually require chronic intracranial EEG studies to define the epileptogenic area. Epilepsy surgery is beneficial in these MRI-negative TLE patients even though the outcome is not as favourable as in patients with focal pathological findings in MRI. MRI findings correlate positively with the outcome of TLE surgery. Therefore patients who could be candidates for surgical treatment, but who have previously had unremarkable MRI scans, should be rescanned and re-evaluated for possible surgery when more advanced equipment and methods are available.

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Arto Immonen

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