INTRACTABLE EPILEPSY, FROM BIOMOLECULAR ASPECTS TO SURGICAL TREATMENT

Moh. Hasan Machfoed * and Zaenal Muttaqein**

ABSTRACT

Epilepsy is one of the most common neurological disorders, affecting almost 1% of the population. The term of intractable epilepsy can be simply defined as epilepsy that is difficult to control medically or pharmacoresistant, because the majority of patients with intractable epilepsy are resistant to most of the standard antiepileptic drugs. Due to its complex biomolecular basis, intractable epilepsy is difficult to be treated pharmacologically. Although antiepileptic drug (AED) have optimally been given, about 30-40% of epileptic patients continue to have seizures, and half of these patients are potential candidates for surgical treatment. From clinical point of view, temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS) is one of the most common medically intractable epilepsies. The biomolecular aspects of temporal lobe epilepsy and the clinical experience of surgical treatment for intractable epileptic patients will be the focus of this paper. From July 1999 to July 2004, in Dr Kariadi and Telogorejo hospitals Semarang, surgery had been performed for 64 intractable epileptic patients, consisting of 56 patients with TLE, 2 with extra-temporal lobe epilepsy, and 6 with generalized tonic-clonic epilepsy with drop attack. All patients had MRI, and routine interictal EEG. In patients with partial or localized related epilepsy (n = 58), MRI examination revealed hippocampal sclerosis and/or atrophy in 49 cases, hemispheric atrophy in 1, hippocampal calcification in 1, temporal lobe tumor in 3, normal MRI in 2, and focal cortical dysplasia in two. Anterior temporal lobectomy were performed to 56 TLE cases, lesionectomy plus multiple subpial transection to 2 extra-TLE and callosotomy to 6 cases of generalized tonic-clonic epilepsy. The results of operation were evaluated both from seizure elimination rate (Engel's criteria), and their psychological improvement as reported by their family members. Among the TLE cases, 38 patients could be evaluated for 12-52 months after operation. Pre-operatively, these patient had seizure attack between 1-2 to 6-10 times monthly despite 2-4 antiepileptic drugs had been given in combination. Seizure free were seen in 26 cases, aura seen in 5, five cases had no more than 2 attacks a year, and seizure frequency decreased more than 75% in 2 cases. All patients were better socialized according to the family members, especially the younger and highly educated ones. 2 patient had post-operative depression, 1 had temporary contralateral hemiparesis which resolved completely in 3 months, and 2 others had wound infection which needed the bone flap removal. The patients who previously took two or more AEDs, could be seizure free by taking only one drug after operation. From 38 patients, 10 had stopped taking the drug. From this clinical experience, it can be concluded that surgery was useful in intractable epilepsy.

Keywords: intractable epilepsy, biomolecular aspects, temporal lobe epilepsy, surgical treatment

INTRODUCTION

Intractable epilepsy can be caused by many factors including: genetic and chromosomal abnormalities, malformations of cortical development, congenital infectious diseases, inborn errors of metabolism, hypoxic-ischaemic injury, central nervous system infection, neoplasm, etc. The bases of biomolecular mechanism underlying all of the above abnormalities differ significantly each other. Surgical treatment to abolish seizures is recommended for mesial TLE, which possibly the most common form of human epilepsy and the most refractory to AEDs (Schmidt et al, 2003). It is well known that approximately 65% of patients are seizure free after surgery with continued medical treatment, while 21% were improved, and 14% were not improved. It has been proved that surgery is superior than optimized medical therapy in TLE patients (Engel et al, 2003)

CLINICAL CONDITIONS ASSOCIATED WITH INTRACTABLE EPILEPSY

Cortical malformation

Cortical dysplasias or malformations due to abnormalities of cortical development are a well-recognized cause of intractable seizures. The study performed by Prayson found that: (1). cortical dysplasia was identified in 38.5% of extratemporal resections for epilepsy; (2). the common cortical dysplasia patterns observed included diffuse cortical disorganization, neuronal cytomegaly, and increased molecular layer neurons; (3). 10% of extratemporal cortical dysplasia was associated with tumors; (4). Improved seizure
control was obtained in approximately three fourths of patients after resection; and (5), seizures associated with balloon cell dysplasia were less successfully managed with surgery (Prayson et al, 2003).

**Infantile spasms**

Infantile spasms (IS) is a catastrophic form of epilepsy found only in infants and young toddlers. There are many causes of IS, including tuberous sclerosis, hypoxic-ischemic injury, congenital infectious diseases, inborn errors of metabolism, malformations of cortical development, genetic syndromes such as Aicardi's syndrome and chromosomal abnormalities (Zupanc, 2003). The majority of patients with IS have a poor prognosis with intractable epilepsy, severe developmental delays and/or significant cognitive impairments. Of all patients with IS, 70 - 90% have mental retardation. Furthermore, 20 - 50% of patients with IS develop Lennox-Gastaut syndrome with multiple seizure types, cognitive impairments and a markedly abnormal electroencephalogram, arguably one of the most difficult epilepsy syndromes to treat. IS are resistant to most of the standard antiepileptic drugs. Surgical resection may be the treatment of choice for those infants with focal cortical dysplasia and intractable infantile spasms (Zupanc, 2003).

**Neoplasma**

Luyken analyzed 207 consecutive patients with intractable epilepsy who had resection of supratentorial tumors. Histologic examination revealed 154 classic epilepsy-associated tumors (ganglioglioma, dysembryoplastic neuroepithelial tumor, pleomorphic xanthoastrocytoma, and pilocytic astrocytomas) and 53 others (astrocytomas and oligodendro gliomas). After surgery, 82% of the patients were seizure free. The study concluded that tumors associated with long-term epilepsy should be removed early for two different reasons: high rate of seizure freedom and rare but potential risk of malignant tumor progression (Luyken et al, 2003). In another study, Liu reported that non-neoplastic astrocytes (derived from brain tissues of patients with epilepsy) expressed interleukin 4 receptor alpha (IL-4Ralpha) and (derived from brain tissues of patients with epilepsy) expressed interleukin 4 receptor alpha (IL-4Ralpha) and responded to interleukin 4 (IL-4) in culture (Liu et al, 2000).

**Chronic focal encephalitis**

Chronic focal encephalitis (CFE) generally presents with seizures that increase in severity and frequency as the disease progresses. Malfunction of synaptic transmission through altered glutamate signaling has been proposed as a likely mechanism triggering CFE. Baranzini examined the expression of 52 genes by real time RT-PCR (kinetic RT-PCR or kRT-PCR) in a brain specimen from a CFE patient with active seizures. The CFE specimen displayed a dramatic increase in the expression of several inflammation-related genes (i.e. IL1 beta, IgVH, and IL2R gamma among others) and a striking down-regulation of several GluRs, in particular mGluR4 (Baranzini et al, 2003).

**TEMPORAL LOBE EPILEPSY (TLE)**

There are 2 separate types of TLE syndromes: the majority of patients suffer from seizure onset within and subsequent atrophy of mesio-temporal lobe structures. Neuropathological evaluation usually identifies Ammon's horn sclerosis as pathological substrate in these patients. In addition, the amygdala complex may be involved in seizure generation/propagation and neuronal damage can also be histopathologically detected, i.e., amygdala sclerosis. In these patients, TLE develop and prove to be pharmacoresistant after occurrence of febrile convulsions during the first 2 to 4 years in life and a subsequent latency period of several years without any clinical signs of seizures. The second type of TLE usually associates with focal lesions within the temporal lobe either close to or even within limbic structures. As a rule, patients suffering from such lesions also develop pharmacoresistant (intractable) TLE. However, the amygdala and hippocampus may not be necessarily involved in the pathogenetic/epileptogenic process, which is important to design very restricted resection strategies, i.e., tailored lesionectomies. Tailored resections are required to avoid substantial post-operative disturbances in the memory-emotional system of individual patients (Elger, 2002).

**Temporal Lobe Epilepsy and Fibrile Seizures**

Among suspected etiologies, febrile seizures have frequently been cited. This is due to the fact that retrospective analyses of adults with TLE have demonstrated a high prevalence (20-60%) of a history of prolonged febrile seizures during early childhood, suggesting an etiological role for these seizures in the development of TLE (Bender et al, 2004).

Specifically, neuronal damage induced by febrile seizures has been suggested as a mechanism for the development of mesial temporal sclerosis, the pathological hallmark of TLE. However, the statistical correlation between febrile seizures and TLE does not necessarily indicate a causal relationship. For example, preexisting (genetic or acquired) 'causes' that result
independently in febrile seizures and in TLE would also result in tight statistical correlation (Bender et al, 2004).

For obvious reasons, complex febrile seizures cannot be induced in the human, and studies of their mechanisms and of their consequences on brain molecules and circuits are severely limited. Therefore, an animal model was designed to study these seizures. The model reproduces the fundamental key elements of the human condition: the age specificity, the physiological temperatures seen in fevers of children, the length of the seizures and their lack of immediate morbidity. Neuroanatomical, molecular and functional methods have been used in this model to determine the consequences of prolonged febrile seizures on the survival and integrity of neurons, and on hyperexcitability in the hippocampal-limbic network. Experimental prolonged febrile seizures did not lead to death of any of the seizure-vulnerable populations in hippocampus, and the rate of neurogenesis was also unchanged. Neuronal function was altered sufficiently to promote synaptic reorganization of granule cells, and transient and long-term alterations in the expression of specific genes were observed (Bender et al, 2004)

**BIOMOLECULAR ASPECTS OF TEMPORAL LOBE EPILEPSY**

**Experimental Animal**

Symptomatic temporal lobe epilepsy typically develops in three phases: brain insult à latency period (epileptogenesis) à recurrent seizures (epilepsy). Lukasiuk et al hypothesized that remodeling of neuronal circuits underlying epilepsy is associated with altered gene expression during epileptogenesis. Epileptogenesis was induced by electrically triggered status epilepticus (SE) in rats. Animals were continuously monitored with video-EEG, and the hippocampus and temporal lobe were collected either during epileptogenesis (1, 4 and 14 days) or after the first spontaneous seizures (14 days) for cDNA array analysis. Altogether, 282 genes had altered expression, from which 87 were in the hippocampus and 208 in the temporal lobe (overlap in 13).

Assessment of hippocampal gene expression during epileptogenesis indicated that 37 genes were altered in the 1-day group, 12 in the 4-day group and 14 in the 14-day epileptogenesis group. There were 42 genes with altered expression in the 14-day epilepsy group. In the temporal lobe, the number of genes with altered expression was 29 in the 1-day group, 155 in the 4-day group, 32 in the 14-day epileptogenesis group and 62 in the 14-day epilepsy group. Products of the altered genes are involved in neuronal plasticity, gliosis, organization of the cytoskeleton or extracellular matrix, cell adhesion, signal transduction, regulation of cell cycle, and metabolism. As most of these genes have not previously been implicated in epileptogenesis or epilepsy, these data open new avenues for understanding the molecular basis of epileptogenesis and provide new targets for rational development of anti-epileptogenic treatments for patients with an elevated risk of epileptogenesis after brain injury (Lukasiuk et al, 2003).

Research into the molecular mechanisms of epileptic brain injury is hampered by the resistance of key mouse strains to seizure-induced neuronal death evoked by systemically administered excitotoxins such as kainic acid. Because C57BL/6 mice are extensively employed as the genetic background for transgenic/knockout modeling in cell death research while they are seizure resistant, Araki sought to develop a seizure model in this strain characterized by injury to the hippocampal CA subfields (Araki et al, 2002).

Adult male C57BL/6 mice that underwent focally evoked seizures induced by intraamygdalal microinjection of kainic acid, experienced ipsilateral CA3 pyramidal neuronal death. Damage was largely restricted to the ipsilateral CA3 subfield of the hippocampus, but injury was also consistent within CA1, suggesting that this mouse model better reflects the hippocampal neuropathology of human temporal lobe epilepsy than did the rat, in which CA1 is typically spared. Degenerating cells were > 95% neuronal and cells often exhibited the morphological features of apoptosis. These data establish a mouse model of focally evoked seizures in the C57BL/6 strain associated with a restricted pattern of apoptotic neurodegeneration within the hippocampal subfields that may be applied to research into the molecular basis of neuronal death after seizures (Araki et al, 2002).

**Febrile Seizures (FS)**

Patients with generalised epilepsy with febrile seizures plus (GEFS+) can have typical and isolated FS, FS lasting more beyond age 6 years, and subsequent afebrile (typically generalised) seizures. Mutations associated with GEFS+ were identified in genes for subunits of the voltage-gated sodium channel and the gamma2 subunit of the ligand-gated GABAA receptor. Screening for these genes in patients with severe myoclonic epilepsy in infancy showed de novo mutations of the alphal subunit of the voltage-gated sodium channel.
Antecedent FS are commonly observed in temporal-lobe epilepsy (TLE). In sporadic mesial TLE-characterised by the sequence of complex FS in childhood, hippocampal sclerosis, and refractory temporal-lobe seizures-association studies suggested the role of several susceptibility genes. Work on some large pedigrees also suggests that FS and temporal-lobe seizures may have a common genetic basis, whether hippocampal sclerosis is present or not. The molecular defects identified in the genetic associations of FS and epileptic seizures are very attractive models to aid the understanding of epileptogenesis and susceptibility to seizure-provoking factors, especially fever (Baulac et al, 2004).

Cytoarchitectural Abnormalities in Hippocampus

Hippocampal sclerosis (HS) is the most common pathological substrate for TLE with a characteristic pattern of loss of principle neurons primarily in CA1 and hilar subfields. Other cytoarchitectural abnormalities have been identified in human HS specimens, including dispersion of dentate granule cells and cytoskeletal abnormalities in residual hilar cells. The incidence of these features, their relationship to the severity of HS and potential indication of underlying hippocampal maldevelopment is unknown (Thom et al, 2002).

In a series of 183 hippocampectomies, Thom identified classical HS (grades 3 and 4) in 90% of specimens, granule cell disorganization or severe dispersion in 40% of cases with a bilaminar pattern in 10%, and cytoskeletal abnormalities in hilar cells in 55% of cases. The severity of granule cell disorganization correlated closely with the degree of hippocampal neuronal loss but not with the age at first seizure or a history of a precipitating event for epilepsy such as prolonged febrile seizures.

These findings suggest that granule cell disorganization is closely linked with the progression of HS rather than a hallmark of impaired hippocampal maturation. Furthermore, stereological quantitation of granule cells showed evidence of cell loss but greater numbers in regions of maximal dispersion, which may indicate enhanced neurogenesis of these cells. Quantitation of reelin-and calretinin-positive Cajal-Retzius cells in the dentate gyrus molecular layer in 26 cases showed no correlation between the number of these cells and the severity of granule cell dispersion, but increased numbers of these cells were present in HS with respect to control groups. Although a role for Cajal-Retzius cells is therefore not implicated in the mechanism of granule cell disorganization, their excess number may be indicative of underlying hippocampal maldevelopment in HS (Thom et al, 2002).

Genetic Factors

Molecular mechanisms underlying increased hippocampal excitability in human TLE are largely unknown. A disturbance of the imbalance between excitatory and inhibitory neurotransmission pathways in the epileptic hippocampus may contribute substantially to a decreased seizure threshold (Nader et al, 2002). Nader found that the ratio for the GAD/NMDAR1 transcripts was significantly higher in TLE cases when compared to the nonepileptic samples. Such findings are mainly a consequence of the increased amounts of GAD mRNA detected in the epileptic hippocampus. Compared with nonepileptic samples, and without correction for neuron losses, the amounts of NMDAR1 mRNA in HS are slightly reduced, and in the non-HS samples they are significantly increased, which is consistent with an increase of NMDAR1 in the hippocampal remaining neurons, as previously reported.

These results also contribute to the indication of GAD67 mRNA upregulation in human TLE. A possible functional implication for the increased GAD mRNA levels could be a mechanism to reduce neuronal hyperexcitability, synchronization, and/or the spread of seizure (Nader et al, 2002). TLE with hippocampal sclerosis (HS) is one of the most common medically intractable epilepsies. Although the pathogenesis of HS still remains highly controversial, genetics may play a role as a predisposing factor. Previous evidence in a Japanese population shows that the homozygotes for allele 2 at position -511 of the interleukin (IL)-1 beta gene promoter region (IL-1 beta -511/2) confers susceptibility to the development of HS. Jin found association between IL-1 beta -511 polymorphism and the development of HS in Chinese population (Jin et al, 2003).

Potschka used the novel MPSS (massively parallel signature sequencing) method for analysis of gene expression in the rat kindling model of TLE. Kindling by repeated electrical stimulation of the amygdala resulted in the differential expression of 264 genes in the hippocampus compared to the controls. The most strongly induced gene was Homer 1A, an immediate early gene involved in the modulation of glutamate receptor function. The overexpression of Homer 1A in the hippocampus of kindled rats was confirmed by RT-PCR. In order to evaluate the functional implications of Homer 1A overexpression for kindling, he used transgenic mice that permanently overexpress Homer 1A. Immunohistochemical characterization of these mice showed a marked Homer 1A overexpression in glutamatergic neurons of the hippocampus. Kindling of Homer 1A overexpressing mice resulted in a retardation
of seizure generalization compared to wild-type controls.

This data demonstrate that kindling-induced epileptogenesis leads to a striking overexpression of Homer 1A in the hippocampus, which may represent an intrinsic antiepileptogenic and anticonvulsant mechanism in the course of epileptogenesis that counteracts progression of the disease (Potschka et al, 2002).

Active program of cell death/ apoptosis

Experimental and human data suggest programmed (active) cell death may contribute to the progressive hippocampal atrophy seen in patients with refractory TLE. Death-associated protein (DAP) kinase is a novel calcium/calmodulin-activated kinase that functions in apoptosis mediated by death receptors. Because seizure-induced neuronal death involves both death receptor activation and calcium, Henshall examined DAP kinase expression, localization, and interactions in hippocampal resections from patients with intractable TLE (n = 10) and autopsy controls (n = 6). Expression and phosphorylation of DAP kinase was significantly increased in epilepsy brain compared with control. DAP kinase and DAP kinase-interacting protein 1 (DIP-1) localized to mitochondria in control brain, whereas levels of both were increased in the cytoplasm and microsomal (endoplasmic reticulum) fraction in epilepsy samples. Coimmunoprecipitation analysis showed increased DAP kinase binding to calmodulin, DIP-1, and the Fas-associated protein with death domain (FADD) in epilepsy samples. Finally, immunohistochemistry determined DAP kinase was coexpressed with DIP-1 in neurons. This study provides the first description of DAP kinase and DIP-1 in human brain and suggests DAP kinase is a novel molecular regulator of neuronal death in epilepsy (Henshall et al, 2004).

The genes that are mutated in the brain encode proteins that maintain basic cell function by: (1) supplying energy demands, (2) controlling proteolysis and (3) controlling normal cell death. The loss of neuronal cells in the hippocampus and the dentate gyrus in individuals who have temporal-lobe epilepsy is thought to promote further seizures, by the formation of mossy fibre sprouting (the formation of new excitatory synapses by axonal sprouting). In animal models of kindling-induced seizures, apoptotic cell death can account for some of this neuronal cell loss. The loss of a cytoprotective effect, leading to neuronal cell loss, might induce epilepsy in the Progressive Myoclonus Epilepsies (PMEs), and research is ongoing into the pathogenetic mechanisms involved in this group of disorders (Bate et, 2004)

Malfunctioning of the GABA-ergic System

Malfunctioning of the GABA-ergic system has been postulated as a possible cause of epilepsy. Furtinger investigated changes in the mRNA expression of the GABA(B) receptor subtypes GABA(B)-R1 and GABA(B)-R2 and of GABA(B) receptor binding in the hippocampus of patients with TLE compared with post-mortem controls.

In patients with Ammon's horn sclerosis, significant decreases in [3H]CG54626A binding were observed in subfields CA1 and CA3 of the hippocampus proper and the dentate hilus. On the other hand, both GABA(B) receptor mRNAs and receptor binding were enhanced after correction for neuronal loss in dentate granule cells and in the molecular layer, respectively, and the subiculum of patients with and without hippocampal sclerosis. These increases were even more pronounced when correcting the values for cell losses in the respective areas and indicated also increased expression of GABA(B)-R in the dentate hilus. Increased expression of both subtypes of GABA(B) receptors indicates augmented presynaptic inhibition of glutamate release as a possible protective mechanism in TLE (Furtinger et al, 2003). Bureau found that endogenous phosphorylation of distinct gamma-aminobutyric acid type A receptor polypeptides involved in the inhibition of epileptogenicity (Bureau et al, 1999)

Glutamate NMDA receptor subunit R1 and GAD mRNA expression

A disturbance of the imbalance between excitatory and inhibitory neuro-transmission pathways in the epileptic hippocampus may contribute substantially to a decreased seizure threshold. Neder have extended the investigation whether TLE is associated with changes in the expression of GAD67 and NMDAR1 by assessing the relative amounts of the mRNAs in human hippocampal samples by means of semiquantitative RT-PCR. The samples included 16 hippocampal slices obtained at surgery from intractable TLE (HS, n = 14; non-HS, n = 2) and 3 postmortem control hippocampi.

The ratio for the GAD/NMDAR1 transcripts was significantly higher in TLE cases when compared to the nonepileptic samples. Such findings are mainly a consequence of the increased amounts of GAD mRNA detected in the epileptic hippocampus. Compared with nonepileptic samples, and without correction for neuron losses, the amounts of NMDAR1 mRNA in HS are slightly reduced, and in the non-HS samples they are
significantly increased, which is consistent with an increase of NMDAR1 in the hippocampal remaining neurons, as previously reported. The results also contribute to the indication of GAD67 mRNA upregulation in human TLE. A possible functional implication for the increased GAD mRNA levels could be a mechanism to reduce neuronal hyperexcitability, synchronization, and/or the spread of seizure (Neder et al, 2002).

**Loss of Glutamine Synthetase**

High extracellular glutamate concentrations have been identified as a likely trigger of epileptic seizures in mesial TLE (MTLE), but the underlying mechanism remains unclear. Eid investigated whether a deficiency in glutamine synthetase, a key enzyme in catabolism of extracellular glutamate in the brain, could explain the perturbed glutamate homeostasis in MTLE (Eid et al, 2004).

The anteromedial temporal lobe is the focus of the seizures in MTLE, and surgical resection of this structure, including the hippocampus, leads to resolution of seizures in many cases. By means of immunohistochemistry, western blotting, and functional enzyme assays, Eid assessed the distribution, quantity, and activity of glutamine synthetase in the MTLE hippocampus.

The result was, in western blots, the expression of glutamine synthetase in the hippocampus was 40% lower in MTLE than in non-MTLE samples. The enzyme activity was lower by 38% in MTLE vs non-MTLE. Loss of glutamine synthetase was particularly pronounced in areas of the MTLE hippocampus with astroglial proliferation, even though astrocytes normally have high content of the enzyme. Quantitative immunoblotting showed no significant change in the amount of EAT2, the predominant glial glutamate transporter in the hippocampus.

The interpretation of the study was a deficiency in glutamine synthetase in astrocytes is a possible molecular basis for extracellular glutamate accumulation and seizure generation in MTLE. Further studies are needed to define the cause, but the loss of glutamine synthetase may provide a new focus for therapeutic interventions in MTLE (Eid et al, 2004).

**Loss of Kappa Receptors Activation**

The endogenous kappa receptor selective opioid peptide dynorphin has been shown to inhibit glutamate receptor-mediated neurotransmission and voltage-dependent Ca2+ channels. It is thought that dynorphin can be released from hippocampal dentate granule cells in an activity-dependent manner. Since actions of dynorphin may be important in limiting excitability in human epilepsy. Jeub investigated its effects on voltage-dependent Ca2+ channels in dentate granule cells isolated from hippocampi removed during epilepsy surgery. The result of the study suggest that a protective mechanism exerted by dynorphin release and activation of kappa receptors may be lost in hippocampi with recurrent mossy fiber sprouting (Jeub et al, 1999).

**CLINICAL EXPERIENCE OF SURGICAL TREATMENT FOR INTRACTABLE EPILEPTIC PATIENTS**

From July 1999 to July 2004, in Dr Kariadi and Telogorejo hospitals Semarang, surgery had been performed for 64 intractable epileptic patients, consisting of 56 patients with TLE receiving anterior temporal lobectomy, 2 with extra-temporal lobe epilepsy receiving lesionectomy plus multiple subpial transection, and 6 with generalized tonic-clonic epilepsy with drop attack receiving callosotomy.

All patients had MRI, and routine interictal EEG. Intracranial subdural grid EEG and sphenoidal EEG were performed in each patient. Wada test or intracarotic sodium amobarbital (amytal) injection were performed in about half of the patients with epileptogenic foci in the dominant temporal lobe. Psychological evaluation, including Standard Progressive Matrices (SPM) and Wechsler Adult Intelligence Scale (WAIS) tests were performed for patients operated during the last 2 years.

In patients with partial or localized related epilepsy (n=58), MRI examination revealed hippocampal sclerosis and/or atrophy in 49, hemispheric hemiatrophy in one, hippocampal calcification in one, temporal lobe tumor in three, normal MRI in two, and focal cortical dysplasia in two (all were extratemporal). The temporal lobe tumor were pleomorphic xantho-astrocytoma (PXA) of the hippocampus in one, and Disembryoblastic Neuroepithelial tumor (D-NET) of the temporal neocortex in two. So that the MRI pathology in 49 out of 56 TLE patients were hippocampal sclerosis and/or atrophy. The side of the epileptic temporal lobe or the operated side were based on the side of MRI lesion in 54 patients, sphenoidal lead EEG in one, and invasive subdural grid EEG in one.

Among the TLE cases, 38 patients had their post-operative 12-52 months, and their seizure elimination rate was reported here. Pre-operatively, these patients had seizure attack between 1-2 to 6-10 times monthly...
Intractable Epilepsy, from Biomolecular Aspects to Surgical Treatment

Despite 2-4 antiepileptic drugs had been given in combination. All of them received anterior temporal lobectomy with (36 cases) and without amygdalo-hippocampectomy (2 cases). The results were evaluated both from seizure elimination rate according to Engel's criteria, and their psychological improvement as reported by their family members.

Seizure free were seen in 26 cases (Engel's Ia), aura seen only in five cases (Engel's Ib), five cases had no more than 2 attacks a year (Engel's II), and seizure frequency decreased more than 75% in 2 cases (Engel's III). All patients were better socialized according to the family members, especially the younger and highly educated ones. Two patients had post-operative depression that needed psychiatric support for 3 months after operation, one person had temporary contralateral hemiparesis which resolved completely in 3 months, and two others had wound infection which needed the bone flap removal. Patients were asked to continue their AEDs as before, at least for a 6-month period of time and re-evaluation was performed thereafter. The patients who previously took two or more AEDs polytherapy with excellence post-operative course (Engel's I) could be seizure free by taking only one drug. These patients were asked to taper-off their AEDs 1 year after operation. From 38 patients, 10 had stopped taking the drug.

LITERATURE REVIEW RELATED WITH SURGERY IN TLE PATIENTS

Neurophysiological recordings, high-resolution brain imaging and neuropathological analysis of surgical brain specimens identify the hippocampus as the major target structure being affected in patients with TLE. Moreover, removal of this structure during epilepsy surgery is effective in controlling seizures in these patients (Elger, 2002).

Luyken analyzed 207 consecutive patients with intractable epilepsy who had resection of supratentorial for neuroepithelial tumors. After surgery, 82% of the patients were seizure free. The study concluded that tumors associated with long-term epilepsy should be removed early for two different reasons: high rate of seizure freedom and rare but potential rik of malignant tumor progression (Luyken et al, 2003).

CONCLUSIONS

1. Intractable epilepsy can be caused by many factors and the bases of biomolecular mechanism underlying all of the above abnormalities differ significantly each other.

2. Many clinical conditions are associated with intractable epilepsy including: neuronal migration disorders, cortical malformation, infantile spasms, neoplasma, chronic focal encephalitis, etc

3. TLE is one of the most common medically intractable epilepsies.

4. Although molecular mechanisms underlying the human TLE are largely unknown, there many factors have been identified, such as: cytoarchitectural abnormalities, gene mutations, mRNA upregulation, interleukin polymorphism, gene overexpression, cell apoptosis, malfunction of GABA system, etc.

5. The result of our clinical experience of surgical treatment for intractable epileptic patients showed that surgery was superior than optimized medical therapy in TLE patients

6. A greater understanding of basic disease mechanisms and developments in molecular biology have led to an increased number of effective drugs for patients with epilepsy whose condition is intractable.

REFERENCES


possible mechanism for raised extracellular glutamate in mesial TLE. Lancet 360(9402): 28-37.


