The definition of refractory epilepsy is controversy. A patient is considered to have refractory epilepsy if any seizures occur while the person is documented as having an antiepileptic drug (AED) concentration of at least one standard medication in the usually effective range, and the definition holds until the patient has been seizure free for at least one year. Refractory epilepsy can also be defined as a chronic disorder requiring treatment with AEDs over the course of many years. The US National Association of Epilepsy Centers defines AED resistance as continuing seizures despite 12 months of care in an epilepsy center. There is also common agreement that failure of two monotherapy trials is the minimum criterion for declaring that someone has refractory epilepsy.

Besides, correct identification of the patient and the epilepsy syndrome is very important for proper selection of AEDs. Temporal lobe epilepsy (TLE), certain AEDs such as carbamazepine, lamotrigine, topiramate, oxcarbazepine, levetiracetam and zonisamide, become the drugs of choice. To date, none of the new AEDs has demonstrated a superior effectiveness over the older AEDs in the head to head monotherapy trials. There is no statistically significant difference in efficacy.
among the new AEDs by head to head or meta-
analyses(8-10). Despite new AED therapy, epilepsy remains
uncontrolled in a significant proportion of patients (11-14),
particularly refractory TLE.

In regard to the cause of refractory TLE, initial pre-
cipitating injury (IPI) of seizures may play a role in
refractory TLE. IPI is defined as any significant medical
event prior to seizure onset(15). They include febrile
seizures, status epilepticus, central nervous system infec-
tion, head trauma, or birth trauma. However, previous
prospective epidemiologic studies of children experienc-
ing either one seizure or status epilepticus and popula-
tion studies of children with febrile seizures suggest that
the majority of these children will not develop refractory
TLE(16). This suggests that IPI alone may not be the cause
of refractory TLE. A large study found that patients with
IPI related to either status epilepticus or febrile seizures
were found to have hippocampal sclerosis (HS). It
explained that prolonged febrile seizures might produce
hippocampal injury and thereby increase hippocampal
excitability leading to the gradual development of HS
and TLE(17). In addition, HS constituted the most frequent
neuropathologic finding in adult patients with medically
refractory TLE(18), but this does not mean that all patients
with HS have refractory TLE. A study used a 3D volumetric sequence, T2: relaxation times and proton MR
spectroscopy to predict seizure intractability. It was
found that refractory TLE had HS associated with signal
change in the anterior temporal white matter and the
reduction of N-acetylaspartate in the ipsilateral temporal
lobe(18). Additionally, HS patients with refractory TLE
often have extrahippocampal structural abnormali-
ties(19-22). Recent study provides a unique quantitative
assessment in patients with TLE and indicates that
regions of the brain remote from the temporal lobe of
seizure onset may be adversely affected with significant
changes in cerebral cortical structure(22). It is concluded
that refractory TLE may not be related simply to the
presence of HS.

It was also found that hippocampal atrophy might be
seen immediately after episodes of status epilepticus,
febrile seizure and other severe IPI(24-25). Additionally,
progressive hippocampal atrophy was correlated with
durations of TLE(26). Hippocampal atrophy was associat-
ed with a substantially higher risk of relapse after AED
withdrawal(27). Other lesion etiologies in the temporal
lobe may be additional risk factors in refractory TLE.
Stroke, vascular malformation or tumor seem to be much
more treatment responsive than those associated with
cortical dysplasia, hippocampal sclerosis or dual
pathologies(28). Cortical dysplasia is frequently associated
with medically refractory epilepsy(29,30). A Sprague-
Dawley rat embryo model that mimics human focal corti-
cal dysplasia shows early development of hippocampal
kindling. Cortical dysplasia is therefore associated with
vulnerability to epilepsy(31).

The mechanisms underlying the refractory TLE are
not known. One explanation for refractory TLE is
impairment of drug penetration into the brain by efflux
transporters(32). One of the members of efflux transporters
is P-glycoprotein (P-gp). P-gp is believed to act as an
active efflux pump by reducing intracellular drug accu-
mulation. P-gp belongs to a highly conserved protein
superfamily, the adenosine triphosphate (ATP)-binding
 cassette (ABC) proteins which has more than 100 mem-
bers and can be found in all kinds of organisms(33).
Human P-gp is encoded by a small gene family compris-
ing two genes, designated ABCB1 or multiple drug
resistance 1 (MDR1) and ABCB4 or multiple drug resis-
tance 2 (MDR2), located near each other on chromo-
some 7q21.1(34). But only human MDR1 genes encode
the drug transporter associated with multidrug resis-
tance(35). This is supported by another study that overex-
pression of MDR1 gene in brain of some patients with
medically refractory epilepsy contributed to their lack of
response to AED treatment(36). The role of P-gp in drug
resistance in epilepsy is further complicated by the pres-
ence of other efflux transporters in the brain such as
multidrug resistance protein (MRP) with at least 9 mem-
bers identified in humans(37,38). Some 20 other efflux
transporters belonging to protein familities such as
organic anion transporter and organic cation transporter
and monocarboxylic acid transporter also have been
found in a variety of tissues including the brain(38-40).
Whether these transporters contribute to the blood-brain
barrier and drug resistance is largely unknown. The role
of P-gp and other efflux transporters in drug resistance of refractory epilepsy is assessed in different studies. MDRs are upregulated in the hippocampus of patients with refractory TLE. P-gp and multiple drug resistance protein (MRP) are found in temporal lobe pathologies of patients with refractory temporal epilepsy who underwent temporal lobectomy. Current evidence suggests that an overexpression of P-glycoprotein (P-gp) encoded by MDR1 and other efflux transporters such as MRP in the cerebrovascular endothelium in or around the region of the epileptic focus may lead to drug resistance in epilepsy.

Another major theory for refractory TLE is the loss of antiepileptic drug sensitivity at certain target sites in the brain. Cumulative evidence suggested that there was reduced pharmacosensitivity to sodium channel-acting drugs in both epileptic rats and patients with refractory TLE. Carbamazepine produced a use-dependent blockade of sodium channel activity in normal rodent brain, characterized by a progressive increase in inhibition with higher frequencies of stimulation, but use-dependent block of sodium channel activity was absent in epileptic brain tissue. Loss of sodium channel sensitivity to carbamazepine was shown in tissue from temporal lobe surgery patients resistant to carbamazepine.

The sodium channel is just one of many possible AED targets that may be altered in refractory TLE. Alterations in gamma aminobutyric acid (GABA) receptor activity may be another target mechanism of pharmacoresistance to certain AEDs. Using an experimental model of TLE, the pharmacosensitivity of (GABA) receptor subunits was reduced in single dentate granule cells harvested from epileptic rats. Reorganization of (GABA) receptor subtypes was demonstrated in the hippocampus of human temporal lobe epilepsy, reducing potency of AEDs that enhanced GABAergic inhibition via (GABA) receptor.

Frequency, duration and severity of seizures may contribute to refractory TLE. Gowers first postulated the seizures beget seizures. In TLE, hippocampal volume as measured by MRI is inversely correlated with seizure frequency. Other studies found no relationship between frequency or duration and ipsilateral hippocampal volume, but rather a correlation between seizure frequency and contralateral hippocampal volume. The total estimated number of seizures, partial or generalized, as calculated from reported frequency times duration of epilepsy, also correlated with hippocampal atrophy. The above studies show that hippocampal and extrahippocampal neuronal damage or dysfunction increases with duration of TLE in patients who become intractable.

Recent extensive experimental data have provided sufficiently convincing evidence to suggest that seizures indeed do beget seizures by means of a cascade of events that include various types of neuronal damage, sprouting of neuronal axons and new synapse formations that establish aberrant glutamatergic synapses. Experimental studies showed that mossy fiber synapses, instrumental in TLE and enriched in kainate excitatory receptors, sprout in humans and in animal models; the mossy fiber synapses also establish novel functional synapses, including aberrant ones. The formation of aberrant kainate receptor-mediated synapses further contributes to the generation of additional seizures.

Additional studies showed that in some brain regions, there is a direct link between the severity of seizures and neuronal loss. The extent of the CA3 lesion is directly correlated with the severity of the seizures i.e., duration of the postictal depressions; duration and severity of the ictal events; lesions of the mossy fibers that innervate CA3 neurons reduce both the initial seizures triggered by kainate and the extent and the severity of the subsequent lesions; and neuronal damage is not seen at an early developmental stage when mossy fibers are not fully operative. It is concluded that seizure frequency and intensity is critical to epilepsy progression in refractory TLE.

Recent study showed that TLE may be a progressive neurological disorder that requires early and effective treatment. MRI study revealed that progressive neocortical atrophy occurred in patients with refractory TLE and was correlated with epilepsy duration. The prolonged period of refractory epilepsy may be associated with progressive psychosocial deprivation, and cognitive impairment. It is also evident that patients with med-
ically refractory TLE are physically and socially disabled\(^6\)\(^0\). Since epilepsy surgery is the most effective “curative” management for patients with refractory TLE\(^6\)\(^1\),\(^6\)\(^2\), early recognition of refractory TLE and referral for epilepsy surgery may prevent years of unnecessary seizure activity and its consequences\(^6\)\(^3\) and is recommended for refractory TLE under American Academy of Neurology practice guidelines\(^6\)\(^4\).

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