Update of Epilepsy

Byung In Lee, MD
Department of Neurology, Yonsei University College of Medicine

Significant advances in epilepsy have been achieved in 2014. In the 2014 Round-up paper in Lancet Neurology, Dr. Schmidt introduced the paper by Fisher et al., a practical clinical definition of epilepsy, which has provided rational basis for earlier diagnosis of epilepsy in patients presenting with a single seizure. It also included the criteria for the diagnosis of "Epilepsy Resolved", which has never been existing before. This topic was already dealt in detail in my previous session of "Epilepsy Update" at the Fall Conference of KNA-2014. Other papers were related to "Familiar Endophenotypes" in idiopathic generalized epilepsy(IGE). IGE has long been held to have a genetic basis and assumed to involve large-scale brain networks. However, the mechanism of seizure expression is not fully known yet. One elegant way to show that IGE has a genetic cause is to detect familial endophenotypes in patients and their unaffected first-degree relatives. Endophenotypes are characterized by measurable biomarkers that correlate with an illness, at least in part because of shared underlying genetic factors. Chowdhury et al. (PLoS One 2014; 9:e110136) detected abnormal brain network properties in the 6-9Hz band of scalp electroencephalography in patients with IGE and in their unaffected first-degree relatives, which were proposed as an endophenotype of IGE. Wandschneider et al. (Brain 2014;137:2469-79), conducted fMRI study in first-degree relatives of patients with JME, which have shown abnormal activation of primary motor cortex and the supplementary motor area by increasing cognitive loads, a similar pattern to that of patients, which was proposed as another evidence of endophenotype of IGE. Apparently the proof of endophenotypes and their clinical utility may require further investigations in the future.

Another column for Epilepsy in 2014 by Perucca and O'Brien (Nat. Rev. Neurol. 2015;11:74-76) was titled as "Novel and large collaborations drive advances in epilepsy". They stressed that several large collaborative efforts and frameworks have led to significant conceptual innovations including a revision of the definition of epilepsy, and important discoveries regarding the etiology, pathophysiology and management of epilepsy. They also selected the definition paper by Fisher et al., as the first, which was followed by FEBSTAT study (by Lewis et al. Ann Neurol 2014;75:178-185), a landmark prospective multicenter study to investigate the causal relationship between hippocampal sclerosis (HS) and febrile status epilepticus (FSE). FSE precipitated acute hippocampal damage in 10% of patients, which was evolved to HS in the follow-up MRI in 10 of 13 patients with MRI evidence of acute hippocampal injury but none in 116 patients with FSE, an unequivocal evidence linking prolonged FSE with the development of HS.

Genetics in Epilepsy continued to make rapid progress in 2014. ILAE Consortium on Complex Epilepsies (Lancet Neurol 2014;13:893-903) undertook a meta-analysis of genome-wide studies in common epilepsies, combining 12 large phenotype-genotype data sets. The study identified two risk loci for all epilepsies. One locus was at 2q24.3, thereby implicating SCN1A gene, and the other was at 4p15, a region harbouring PCDH7, which encodes a protocadherin protein not previously implicated in epilepsy. The study also identified a risk locus for genetic generalized epilepsy at 2p16.1, thereby implicating VRK2 or FANCL, but no significant associations were found for epilepsy. Overall, these findings indicate that although epilepsies are a heterogeneous condition, certain loci can

broadly affect susceptibility to the development of epilepsy. Another advances in genetics of epilepsy is related to the "Somatic Mutations" of brain cortical malformations. Jamur et al. (N Engl J Med 2014;371:733-744) applied targeted high coverage sequencing to DNA samples from 158 patients with brain malformations. Causative mutations were found in 27 (17%) of participants and 6 of those (30%) were somatic mutations. Of note, five of the identified somatic mutations were undetectable by traditional Sanger sequencing and one was missed by whole-exome sequencing, highlighting the fact that these techniques are not optimized to detect mutations that are only present in a small proportion of cells. Apparently the importance of somatic mutations in neuropsychiatric disorders is increasingly recognized and advances in next generation sequencing (e.g., single-cell sequencing and high depth sequencing) may allow us to address the role of somatic mosaicism in many different types of focal epilepsies without obvisous pathologies.

Another important paper from international collaboration is the study on the effects of maternal antiepileptic drugs on the developing offspring by Meador et al. (JAMA Pediatr 2014;168: 729-736). They compared cognitive outcomes at age 6 years in breastfed versus nonbreastfed children born to women with epilepsy taking AED monotherapy. After adjustment for multiple confounding factors, breastfeeding was not found to be associated with adverse cognitive outcomes; on the contrary, breastfed children displayed higher IQ and enhanced verbal abilities compared with non-breastfed children, which was a remarkable finding to be discussed with mother with epilepsy for her nursing strategy.

In addition to these outstanding research, 2014 is marked as a year for the transition of treatment strategy from the use of anti-seizure drugs to targeted drugs for individual patient. Current AEDs have been criticized for their lack of effects on epileptogenesis and disease modification, which is largely related to our incomplete understanding about molecular mechanisms of epileptogenesis and disease progression. With rapid progress of genetics and basic neuroscience in this field, there is increasing possibilities for development of antiepileptogenic drugs and novel therapeutic measures including neuromodulation therapies, stem cell or gene therapies, etc. In fact, we have started to use repurpose drugs in epilepsy care, which has never been considered as drugs for epilepsy. They include rapamycin and related compounds, COX2-inhibitors, medical marijuanas, bumetanide, quinidine, etc. These drugs are increasingly tried in specific patient groups with severe refractory epilepsies for their relevant molecular mechanisms of action against epilepsy. As genetic analysis is more widely undertaken in patients not responding to current AEDs therapy, there has been increasing information about potential molecular defects linked to the drug resistance, which has precipitated the trial of novel therapeutic measures to compensate the molecular abnormalities rather than using conventional AEDs(agents for nonspecific seizure suppressants), i.e., ketogenic diet therapy in patients with SCL2A mutation, Quinidine for EIMFS (epilepsy of infancy with migrating focal seizure). In addition, there are increasing interests in combining second generation of antidepressants with AEDs for better management of DREs as well as prevention of SUDEP.

After two decades of New AEDs era, we are at the beginning of transitional stage from antiseizure drugs to antiepilepsy drugs. Future AEDs therapy will be further individualized and focused at specific targets to compensate disturbed molecular mechanisms precipitated by diverse genetic or environmental insults.