CHAPTER II

LITERATURE REVIEW

When two diseases happen in one patient, this might indicate that both share the same genetic defect.[1, 2]History behind MR and epilepsy might help us understand these two conditions. In ancient times, patients with MR seem to be neglected by people in the society.[3] People think they are not fit enough to fulfill at least minimum requirement set from the environment, being at least to be independent. Being capable to work and improving knowledge for human kind benefit is the highest goal for people nowadays. If they couldn't fulfill those criteria, then they might not be accepted by the society to be joining them in a higher rank of group.[3]

People with epilepsy also have not always been accepted by society. They thought that epilepsy was caused by supranatural forces. The idea that MR and epilepsy are caused by dysfunction in the brain slowly progressed after the Hippocrates era **(**460-370 BC). Quran (619-623 M) stated how to treat people with mental disability in the Sura 4:5.[4] Starting later, people gradually have better understanding due to extensive researchsfocused on pathogenesis of MR and epilepsy.[5]

II.1 MENTAL RETARDATION

II.1.1 Definition

Mental retardation (MR) is described to substantial limitations either in cognitive or non-cognitive functioning. There are three most widely used criteria for defining MR for physicians. The first one is DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders) published by the American Psychiatric Association, which is explained as follows: (i) significant sub-average intellectual functioning, (ii) concurrent deficits or impairments in present adaptive functioning, and (iii) onset before 18 years old.[6-9]

Another common used definition comes from the American Association on Intellectual and Developmental Disabilities (AAIDD). Similarly, AAIDD defines MR as a disorder that has limitation in intellectual and adaptive behavioral functioning that is expressed in conceptual, social and practical adaptive skills before onset of 18 years old.[10, 11] The third one is explained by the World Health Organization (WHO) as International Classification of Disease (ICD-10), that MR is a condition of incomplete development of the mind, that can be shown by impairment of skills during the developmental period, skills that have effect on their intelligence like cognitive, language, motor, and social abilities.[12] These definitions are widely used and very important to distinguish MR patients with other similar mental illness for many MR researchers.[6, 13-16]

Diagnosing MR needs a proper and valid intelligence assessment. There are countless types of IQ (Intelligence Quotients) tests available, with varying amounts of validity. The main used is WISC-IV (Wechsler Intelligence Scale for

Children). For young children most clinicians are using Stanford-Binet-IV, Woodcock-Johnson-R and WPPSI (Wechsler Preschool and Primary Scale of Intelligence).[17] For children less than 5 years old before IQ test can be done, clinicians usually use Development Delay (DD) terms. Not all children with Developmental Delay develop MR, for example on cases with cerebral palsy, some of neuromuscular disruptions could lead to learning disturbance, but an IQ test performed later shows normal results.[18]

II.1.2 Classification of MR

Degree of severity on MR as mild, moderate, severe or profound can be seen from DSM-IV-TR and ICD-10.[7, 12] Also described in IQ score.

Table 2. Degree of MR based on IQ scores from DSM-IV-TR and ICD-10.[6]

	DSM-IV-TR		ICD-10	
Degree of MR	code	IQ level	code	IQ level
Mild	317	50-55 to 70	F70	50-69
Moderate	318.0	35-40 to 50-55	F71	35-49
Severe	318.1	20-25 to 35-40	F72	20-34
Profound	318.2	<20-25	F73	<20

Another classification of MR are syndromic and non syndromic cases. MR is classified as syndromic if it is related with dysmorphic or specific groups of features. Also if it is related to specific clinical, radiological, metabolic or biological features. While non syndromic MR is defined as a condition that only cognitive impairment is the only feature that manifested in that patient.[19]

II.1.3 Prevalence

It's generally known that the MR prevalence is around 1-3% of the population while males occupy a bigger proportion.[6, 14-16, 18, 20] Around 85% of

MR cases are in the mild group. Most of them remain classified as normal children until they reach the first or second grade of elementary school. Moderate MR comprises around 10% of all MR cases. Their language and communication skills start to have problems during their second grade of elementary school. Even during their adolescence they have also problems on socializing so that they become alienated. Next is severe MR, coping around 4% of MR cases. While profound MR happens on 1-2% MR cases. The more severe MR, the more causative factors can be identified.[20]

II.1.4 Etiology

Being able to know and understand the causes of MR has a huge impact for a lot of people. For the patient themselves, it can be a promising future in order to get the correct further management, early screening for various complications and protection from unnecessary tests. For their family and society, knowing the recurrence risk, possibility to perform prenatal diagnosis, more information of the diseases are important also.[21] Regrettably more than half of the cases still are unexplained.[6, 21, 22]

There are many factors causing MR; it could be genetic, non genetic, or unknown. For genetic factors, chromosomal abnormalities, single gene disorders (Mendelian disorders/ mitochondrial), multi-factorial, or other genetic causes disorders may be the causes. Non-genetic factors, could be environmental such as toxins and infections, or it might be developmental disturbances during prenatal, natal, or post natal period.[6, 15, 16, 23]

A nice overview of the distribution of MR causes, taken from 10.997 MR patients published by Stevenson et al. in 2003 (adapted from Koolen DA thesis on 2008) is depicted in this picture below.

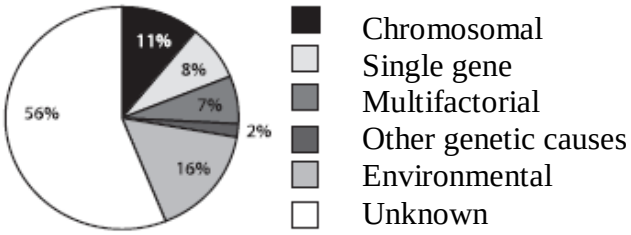


Figure 1. Causes of mental retardation.[6, 22]

From that figure, around 11% causes of MR are chromosomal, 8% single gene, 7 % multifactorial, 2% other genetic causes, 16% environmental, and 56% remain unknown.

There are three main periods of time that are very important to be evaluated in order to know the causes of MR in a patient, which are prenatal, perinatal and postnatal. During prenatal, genetic play roles for about 60-80% cases.[12]

MR is classified as prenatal if the causes are due to chromosomal aberration, single gene disorder, or environmental factors such as Iodine and/or folic acid deficiency, severe malnutrition during pregnancy, drug induced (alcohol, nicotine, cocaine), radiation, infection (rubella, syphilis, *toxoplasma*, cytomegalovirus, HIV) during pregnancy etc. It will be classified as perinatal when it comprises any causative agents during late pregnancy period, while giving birth and during neonatal period (first four weeks of infancy). A lot of risk factors could have an effect, such as diseases of the mother (heart failure, kidney failure, diabetes, etc), prematurity, very low birth weight, asphyxia, complication during

delivery. Another possibility is poor baby condition such as septicemia, hypoglycemia, icteric (yellow baby), etc. Postnatal category refers to condition that affect MR patient after 4 weeks old, such as brain infection, head trauma, chronic toxicity, severe malnutrition and lack of stimulation.[12] Nevertheless, genetic factors play a crucial role since approximately half of MR cases have a familial history.[24-27]

II.2 THE DEVELOPMENT OF GENETIC RESEARCH

Chromosomal abnormalities such as trisomies, monosomies, supernumary marker chromosomes, unbalanced translocations and large deletions and duplications are the most common genetic cause of MR. They occupy 7% of MR cases.[28] After new molecular techniques became more available and cheaper, many smaller cytogenetic rearrangements started to be revealed. Using FISH and MLPA scientist could find around 5% more of pathogenic chromosomal aberrations.[29, 30] But still, those two techniques are not enough to detect aberrations on a large genomewide scale. The latest technology used is genome wide array such as CGH (comparative genomic hybridization), then SNP (Single Nucleotide Polymorphism) arrays. That are hoped to be able to detect chromosomal aberrations in 5-10% more.[29-31]

The search for underlying genetic defect of mental retardation and epilepsy plays a very important role in the field of pediatrics and neurology. Detecting the molecular basis for the disorder may provide precise genetic counseling.[32-38]

Genetics diagnosis for MR and epilepsy individual is based on dysmorphology and additional examination assessments. Laboratory assessment,

neuro imaging, or many other advanced techniques are considered as the tool to confirm the genetics diagnosis. None of themhas the highest priority and have to perform first. On MR and epilepsy cases, all tools are necessary, because it is a very complex disorder. In order to get the exact diagnosis, complete and reliable data are needed.[24]

The Online Mendelian Inheritance in Man (OMIM) database for genetic conditions (http://www.ncbi.nlm.nih.gov/omim) contains 1684 entries for mental retardation and 284 for mental retardation epilepsy (October 2010). This data shows so many differential diagnose and other diseases that related to MR phenotype.[6] Sensory disturbances found in more than 10% of MR population, four times higher than in normal population. Seizures also often happen in MR patients.[20]

II.3 EPILEPSY

II.3.1 Definition

The fact that epilepsy is found in 10-25,5% of the MR population makes us more interested to get deeper information about it.[1, 20, 39] Starting with the definition, epilepsy is a brain disorder that is characterized by repeated events of epileptic seizures. It has neurobiologic, cognitive, psychological, and social consequences. Epilepsy is different with epileptic seizure. An epileptic seizure is a temporary incident of signs and/or symptoms due to abnormal extreme or synchronous neuronal activity in the brain.[40, 41] First the most important diagnostic test in epilepsy is a thorough and detailed history of the patients episodes. A physician will perform a physical and neurological test in order to look for the

cause and location of the seizure. For epilepsy, the history is usually more vital than the physical test and EEG.

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) have come to compromise definitions for the terms epileptic seizure and epilepsy. An epileptic seizure is a temporary occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a condition of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the manifestation of at least one epileptic seizure.[40]

II.3.2 Classification

Classification of syndromic epilepsy relied on seizures factors type (general or localized), etiology (symptomatic or idiopathic), age of onset and seizures related conditions. While classification that is based on seizures type can be defined from clinical assessment and electro encephalogram (EEG). Description based on seizures type shown in the next list.[40, 42]

I. Partial Seizures (Focal, start in one place)
- Simple (no loss of consciousness/ memory)
- Complex (loss of consciousness/ memory)
  With or without aura (warning)
  With or without automatisms
- Secondarily generalized (spreads)

II. Generalized
- Absence, typical or atypical (petit mal)
- Tonic-Clonic (grand mal)
- Myoclonic
- Atonic
- Tonic

III. Unclassifiable

The term of “epilepsy” also encompasses various different syndromes. Epilepsy syndromes fall into two broad categories: generalized and partial (or localization-related) syndromes. In generalized epilepsies, the major type of seizures begins at once in both cerebral hemispheres. Many forms of generalized epilepsy have a genetic basic. In most of them, the neurologic function is found to be normal. In partial epilepsies, seizures initiate in one or more localized foci, although they can spread to the whole brain.[40, 42]

II.3.3 Prevalence

Among all of the neurological problems, epilepsy is the most common one. It affects at least 50 million or approximately 1% of people worldwide. Complex partial seizures are reported for about 40% of all seizure types in adults. Simple partial seizures account for about 20%, primary generalized tonic-clonic seizures about 20%, absence around 10% and other seizure types for 10%. In a pediatric population, absence seizures engage a greater section.[2, 43, 44]

Studies conducted in India, show the prevalence between 4.6 and 8.5 per 1000, while in Sri Lanka they found 9.02 per 1000 rates. Jallon showed almost similar prevalence by several studies, Pakistan (9.99), China (4.4), and Japan (1.5).[45]China studies illustrated the rate was 1.54 per 1000 and 6.2 per 1000.[46, 47] The WHO conclusion from general studies is that estimation of the active epilepsy in developing country prevalence rates, range from 5 to 10 per 1000 people.[48]

II.3.4 Etiology

The most regular subject asked in every epilepsy patient is “Why do I have seizures”? In ancient period of time, people tended to relate epilepsy with

supernatural motive behind it. Not only in the past, even to these days in countries like Tanzania,epilepsy still being associated with possession ofgenie or spirits, witch, poison and is believed to be contagious[49]. Epilepsy actually has physical causes. The end result of many factors that could cause destruction of the brain may cause epilepsy. In order to make epilepsy understandable, based on epilepsy causes, it is divided into three categories: symptomatic, idiopathic and cryptogenic.[42]

Around 70% of epilepsy cases are caused by non-genetic factors like head trauma, congenital malformation of the brain, lack of oxygen during birth, a brain tumor, a stroke, a cerebral hemorrhage, alcoholism, brain infections (encephalitis or meningitis). In the remaining group (30%) the cause of the epilepsy is genetically inherited.[50, 51]

It is indeed difficult to interpret etiology of research patients without good history archives from each MR patient. That is the importance of this research, to search the genetic possibility as the cause of MR with epilepsy in Indonesia. It is indeed difficult to interpret etiology of MR epilepsy patients without good history archives from each patient.

II.3.5 Epilepsy pathogenesis

Seizures happen mostly due to imbalance of excitation and inhibition in a part of the brain. Or in other words, it is an electrochemical disorder. The etiology of seizures varies with the type of seizure, it depends whether it starts focally in one part of the brain or generalized all over the brain. Causes for focal seizures are head trauma, stroke, infection, vascular malformations, tumors (neoplasm),

dysplasia, mesial temporal sclerosis, etc. General seizures causes vary from metabolic, medication reactions, idiopathic until genetic.[33, 35, 41, 50-53]

One of the general epilepsy that has explainable mechanism is absence epilepsy. Having 3-8 years as age of onset, absence epilepsy also has specific clinical characteristics. The patients lose their consciousness for a moment in the middle of their activity and suddenly come back to consciousness and don't know what was happening. There are several hypotheses behind it. Some studies conclude that absence epilepsy happens due to circuit changes between thalamus and cerebral cortex. They suspect that the abnormal circuit is caused by disruption of T-type calcium channels or altered function of *g*-aminobutyric acid (GABA) receptor.[43]

II.3.6 Genetic research in epilepsy

New gene hunting techniques may allow recognition of some new genes in patients without family history of seizures. Those genes known to be related to the development of epilepsy were initially identified in a few rare families with multiple affected individuals. This is a quickly evolving field and the current concept is that the ''common'' epilepsies (the non-familial and the non-encephalopathic epilepsies) are complex diseases resulting from an interaction of multiple genetic and environmental factors.[35, 41]

As a complex disorder with multiple sub classifications and etiologies, it is a very challenging job to find genetic causes for epilepsy cases. Andrade CS et al (2009) explained in his study about epilepsy due to Malformation of Cortical Development (MCD). MCD usually happen because of abnormalities in genes

involved in neuronal proliferation, migration and cortical lamination during embryogenesis. For epilepsies with normal macroscopic appearance, most of their genetic defects caused by alterations in voltage-gated or ligand-gated channels.[2, 43, 44]

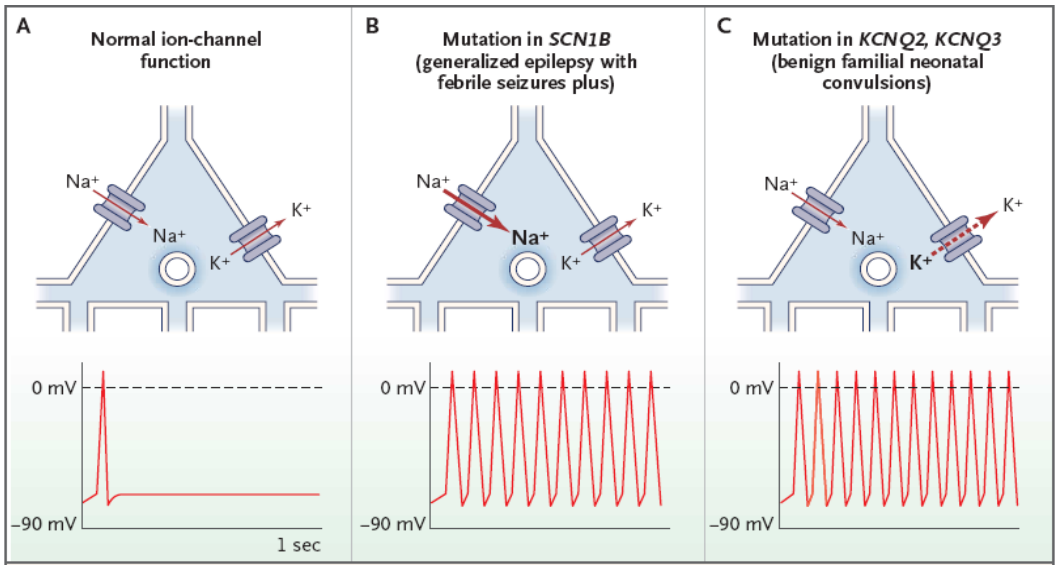


Figure 2. Ion-Channel Dysfunction Associated with Epilepsy

Section A illustrates neuronal-ion-channel in a normal function and the action potential. Section B shows the effect of mutations in *SCN1B*, which encodes a voltage-gated sodium-channel subunit. While section C describes the consequences if there are mutations in *KCNQ2* and *KCNQ3*, which both encode potassium channels happened. They both are associated with benign familial neonatal convulsions.[43]

Focal cortical dysplasia is said to be related with mutations in the *TSC1* gene.[54] Polymicrogyria related with mutations in *SPRX2*.[55]Lissencephaly is caused by mutations in *LIS1*and*ARX*.[56]*LGI1* and *ARX* genes are involved in cell migration during development.[57]

Genetic epilepsy with febrile seizures plus, mutations found in *SCN1B*[58]and*SCN1A*.[59, 60]Severe myoclonic epilepsy of infancy (SMEI) mutations founded in *SCN1A*[34]and*SCN2A* (later onset and no febrile seizures).[61]

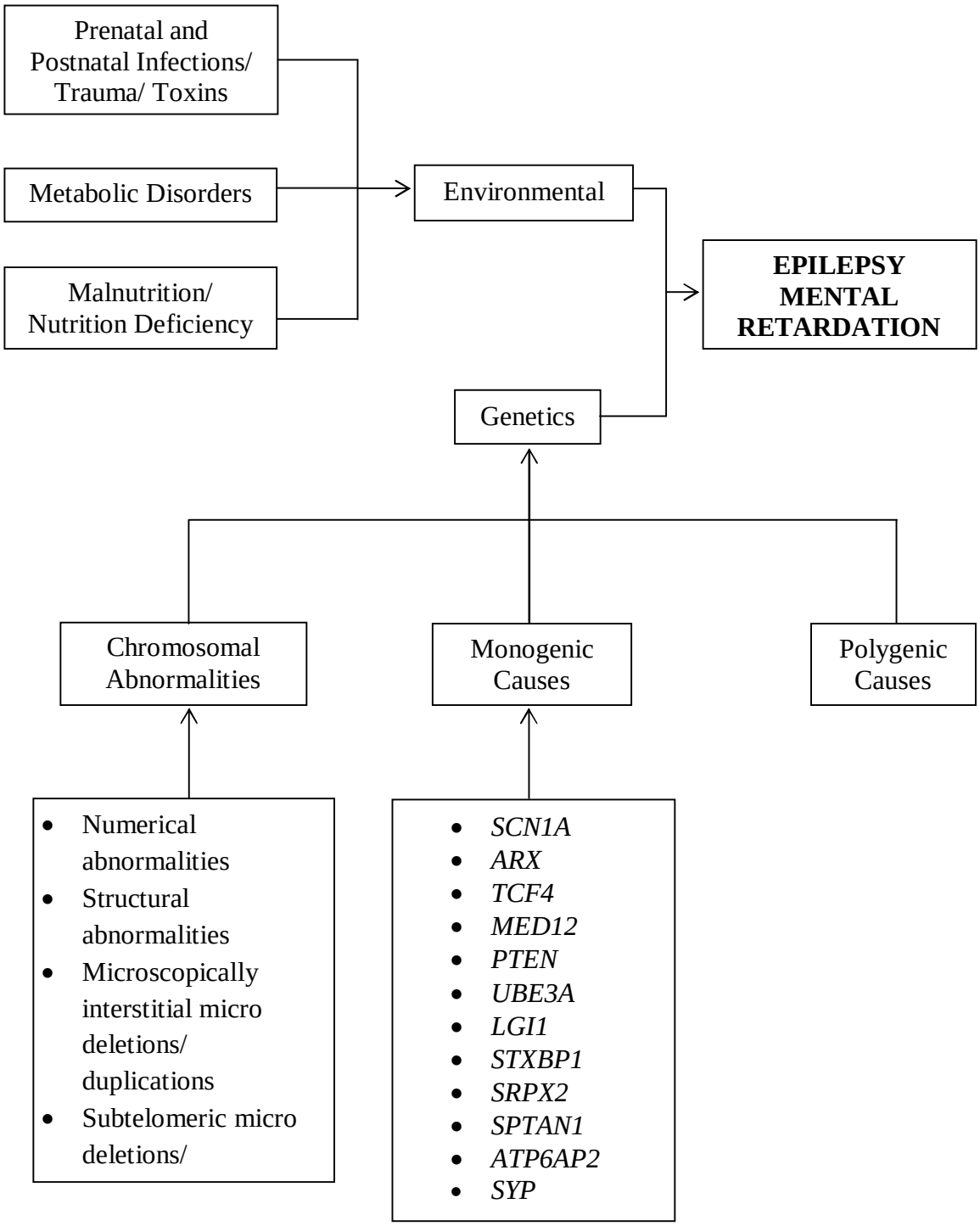
Autosomal dominant temporal lobe epilepsy with auditory features are related with mutations in *LGI1*.[50, 62] Other gene mutations have been identified in potassium channels (*KCNQ2* and *KCNQ3*) associated with benign neonatal familial convulsions, and in the nicotinic acetylcholine receptor (*CHRNA4* and *CHRNB2*) in autosomal dominant temporal lobe epilepsy.[57]

Although many patients meet the clinical criteria for a particular syndrome, not all of them have the same genetic abnormalities (for example only 30–50% of patients with Dravet's syndrome possess an abnormality of the sodium-channel gene). In general, epilepsy syndromes occur sporadically, and genetic analysis is not always easy. When genetic analysis became more accessible and cheaper, there were more hopes that it would clarify the mechanisms of epileptogenesis, seizure generation and transmission.[57]

II.4 MENTAL RETARDATION AND EPILEPSY

Genetic association between MR and epilepsy has been suggested in both syndromic and monogenic cases, which are completing each other. For syndromic, there are early infantile epileptic encephalopathy or known also as Ohtahara syndrome, severe myoclonic epilepsy in infancy (SMEI) or Dravet syndrome, Lennox–Gastaut syndrome, and West syndrome (WS). The studies where MR and epilepsy are present together provides convincing evidence for the relationship linking MR and epilepsy.[57]

II.5 THEORETICAL SCHEME



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