FACTORS CAUSING MENTAL RETARDATION

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ABSTRACT

Mental Retardation (MR) is a heterogeneous group of disorders characterized by a significant impairment of cognitive and development due to abnormalities in the structure or function of brain. Mentally Retarded persons have IQ less than 70. The worldwide prevalence of MR is 1-3%. A number of factors including environmental factors, genetic factors, malnutrition, maternal use of alcohol during pregnancy, drug and poverty are responsible for MR. The congenital dysfunction of brain and injury of brain can also cause MR. The leading cause of MR births include Fetal Alcohol Syndrome, Down's syndrome and metabolic disorders like PKU.

Keywords: Mental retardation, intellectual disability, intellectual quotient, malnutrition, birth trauma, chromosomal aberrations, karyotyping

INTRODUCTION

Mental Retardation (MR), also termed as Intellectual Disability (ID) or Developmental Delay (DD) is a heterogeneous group of disorders. It is characterized by a significant impairment of cognitive and development because of abnormalities in the structure or function of brain throughout the life (1). Mental ability of a person is determined by Intellectual Quotient (IQ). On the average IQ level of a mentally normal person is considered as 100. On IQ basis if a person has IQ less than 70 then he or she is considered as Mentally Retarded. From these mentally retarded people if they have IQ level in between the ranges from 49 to 70 they will be categorized in mild mentally retarded people. In moderate MR the person has IQ in ranges from 35 to 50. (1). In severe MR cases the affected ones have IQ 20 to 34. The last class on the basis of IQ level is of those people who have IQ level below 20, they are categorized to have profound MR (1). (2). This classification is very helpful to understand the severity of the disease (2). The MR person have impairments in adaptive skills and the onset of the disease is before the age of 18 year (3). In a meeting of The Board of American Association on Mental Retardation (AAMR) in the year 2001, the term MR was changed to Intellectual Disability after many discussions of AAMR members (4).

The prevalence of MR is 1-3% worldwide and this prevalence is expected to be high in under developing countries because of the non-genetic factors such as malnutrition, poor healthcare and environmental factors (5). On the basis of IQ level, MR is ranging 2-3% but the prevalence of MR is roughly reported to 1% (6). Actual prevalence varies considerably and with the range as high as 9.7 %. This difference in MR arises because of the variations in population studies, study design and case definition. Generally MR is more common in boys than girls and on the average the ratio is 1.4:1 (7).

There are many ways to classify MR. On the basis of appearance of MR, it is classified into Syndromic MR (SMR) and Non- Syndromic MR (NSMR). In SMR the affected individual

shows other functional or anatomical abnormalities along with MR. Whereas in NSMR, MR is the sole presentation and no other functional or anatomical defects are present (8).

NSMR is thought to arise because of the defects in neurons, their wiring or in communication. Therefore, the genes which are involved in specification and experience dependent remodeling of neuronal networks required for normal information processing in the brain are the prime candidates. The boundary between SMR and NSMR causing genes is not clear yet and the same gene may be involved in causing NSMR and SMR. For example, mutations in HUWE1 cause both SMR and Non-Syndromic X-linked MR. Number of genes involved in both types of MR is continuously increasing (9, 10).

Genetic factors responsible for MR include abnormalities in chromosome number and monogenic defects. These genetic factors are responsible for 25-50 % of all MR people (11). Out of these 25-50% affected individuals chromosomal abnormalities are present in 20 – 25 % (12). These chromosomal abnormalities arise because of the non-disjunctioning of chromosomes during meiosis, submicroscopic deletions and duplications. Non-disjunctioning of chromosomes cause SMR. For example, non-disjunctioning of 21st chromosome causes Down's syndrome or Monogolism. In Down's syndrome the affected individuals show other anatomical and functional abnormalities along with MR. Submicroscopic deletions and duplications accounts for approximately 15 % of the MR individuals (13,14).

MR is thought to be X- linked because of the previous observations that the male individuals were more affected as compared to females and the major focus of the researchers was on X-linked inheritance (15). Till now, 95 genes have been found to involve in X- linked MR (16). But the number of X-linked genes is thought to be much more greater because of the fact that nearly 40 % of X chromosome genes are expressed in brain So any mutation in these genes may become responsible for MR. These genes are involved in the production of proteins which are responsible for the regulation of actin cytoskeleton, chromatin remodeling, gene expression and gene regulation (17).

Although the number of genes involved in X linked MR has been reached to 95 (18), but the genetic basis of autosomal recessive mental retardation (ARMR) is still poorly understood. It is estimated that ARMR is present in nearly quarter of all individuals with NSMR (19). It is a big challenge in Western population to successfully map of ARMR genes because of high genetic heterogeneity, lack of consanguinity and insufficient family size (20). Countries like Pakistan where interfamily marriages are more common and the marriage rate between cousins is approximately 60 %. Out of all cousin marriages more than 80 % marriages are between first cousins. This socio cultural practice helps to understand the molecular and physiological basis of MR (21).

MR is not a simple mental illness but it is referred to a person's capability of thinking the reason. There are many factors responsible for MR. These factors may be genetic or different environmental factors such as prenatal exposure of the fetus to toxic substances (22).

Causes of MR

Approximately 3% of the whole population of the world has IQ level less than 70 (23). Although many genes that are involved in MR have been mapped yet the causes of MR in almost 50 % of MR cases are unknown (24). 5.1% of the MR patients are affected with fragile X syndrome (25). There are many factors which are responsible for MR. These factors include environmental factors, genetic factors, malnutrition, maternal use of alcohol during pregnancy, drug and poverty. These factors are categorized under the heading of behavioral or social factors (26).

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Congenital dysfunction of brain, injury of brain during the critical period of prenatal or postnatal development may also be responsible for MR. MR may also be the result of near drowning, traumatic brain injury and central nervous system malignancy. In industrial nations 1 to 7 in 1000 MR births is because of Foetal Alcohol Syndrome. It is the most common cause of MR in these nations (27). Second leading reason of MR is Down's syndrome. It is also termed as trisomy of chromosome number 21. The incident rate of Down's Syndrome is 1 in 700 births (28).

One of the important factors responsible for genetic disorders is consanguineous marriages. The study of genetic disorders like MR becomes very easy in the regions where the rate of cousin marriages is very high (29).

ENVIRONMENTAL FACTORS

Prenatal Problems

First trimester of the pregnancy is very important for the normal development of the foetus. Prolong fever of the mother during first trimester may affect normal development which may result MR in the baby (30). Infectious agents such as human immunodeficiency virus, Rubella, herpes, syphilis and cytomegalovirus may also cause MR if the mother is infected with any of these infectious agents during pregnancy (31). Abnormal developmental of the foetus may cause MR in the foetus. There are many prenatal factors responsible for MR. Postnatal exposure of infant to heavy metals such as lead can cause MR in infant. This postnatal exposure is very critical in the infants who have low birth weight (32). Phenylketonuria (PKU) which itself is a genetic disorder but if it is untreated in infectious mothers it may also results in MR in the foetus (33). Use of drugs such as alcohol by the pregnant mother may also cause MR in the baby (34). Illness of the mother because of rubella and cytomegalovirus can also cause MR in the baby. Environmental contaminants, which results in exposure to radiations may also be the reason of MR (35).

Neonatal Problems

Late pregnancy, during delivery and first four weeks of life are neonatal period. Any problem during these processes may result in MR. Complications of pregnancy, kidney disease, heart disease and diabetes in mother may result in MR in children. Birth asphyxia, birth trauma, complicated delivery, severe prematurity and very low birth weight are delivery perinatal problems, which may result in MR. Problems such as severe jaundice, hypoglycemia and septicemia during this neonatal period may result in MR (36).

Postnatal Problems

Infants and childhood period is postnatal period. Problems such as Japanese encephalitis, Bacterial meningitis, Tuberculosis, head injury, prolonged malnutrition and chronic lead exposure during this period may result in MR (3).

Exposure to Certain Types of Toxins or Diseases

Exposure to heavy metals like mercury and lead may also responsible for MR. On the other hand some infectious diseases such as meningitis, whooping cough, measles etc. if not treated properly may result in MR (37).

Iodine Deficiency

Iodine deficiency is affecting approximately two billion people in the world. This deficiency is more common in developing countries. Iodine deficiency in mother during pregnancy

restricts the growth of brain of the fetus which leads to hypothyroidism and as a result of this deficiency, affected fetus will be mentally retarded because of the restricted brain growth (38).

Malnutrition

Another very important cause of MR is malnutrition. This malnutrition affects the mental ability in the people of the areas affected by famine. As a result of these famines people face the problem of nutritional deficiency which ultimately results in mental retardation (39).

Metabolic Disorders

Metabolic disorders are arisen because of the missing of one or more key enzymes in the metabolism of different substances. These metabolic disorders along with other problems may also cause MR. For example, PKU is a metabolic disorder which is the result of point mutation. With the advancements in the field of molecular medicine metabolic disabilities can be prevented with early treatment (29).

GENETICS OF MR

There are many genes which are involved in the development of brain because of the complex structure and function of the brain. As a result of this there are many genetic causes of MR. In fact most of the cases are result of genetic disorders. Genetic causes are responsible in 60 % of severe MR cases and make it the most common cause of severe MR (40). Two most common genetically transmitted forms of MR are Down's syndrome and Fragile X syndrome. Down's syndrome is a chromosomal disorder and Fragile X syndrome is a monogenic disorder. Mild form of MR arises from malnutrition, exposure to chemicals, and other environmental factors (26).

Chromosomal Abnormalities

Change in chromosome number or chromosomal aberrations are a major cause of genetic diseases in humans. Spontaneous mutations are the result of this change in genetic material. These chromosomal abnormalities are result of spontaneous mutations so in such cases parents are not the carriers of the diseases. These chromosomal abnormalities vary from very large numerical chromosomal abnormalities, to very small microdeletions. Sometimes partial chromosomal abnormalities may also occur. These chromosomal abnormalities are responsible for MR in approximately 28% of all affected individuals (*12*).

If these chromosomal abnormalities are of more than four Mb can be seen by simple light microscope. Less than four Mb cryptic chromosomal aberrations are detected by Fluorescent In Situ Hybridization (FISH) techniques (*41*).

Numerical Chromosome Abnormalities

Numerical chromosome abnormalities include monosomy which is the result of missing of a chromosome and polyploidy in which addition of the chromosome takes place. In both of the conditions change in chromosome number takes place. In case of monosomy new cell will posses one chromosome less than normal cells. In polyploidy addition of more than two homologous set of chromosomes occurs in the new cell (42). These numeric changes in chromosome number result in syndromes. In most of these syndromes some degree of MR is present. For example, Down's syndrome which is also termed as mongolism is the result of trisomy of chromosome number 21. It results in the most common form of MR (43). Other trisomies are Edward's syndrome in which trisomy of chromosome number 18 takes place and Patau's syndrome which is the result of the trisomy of chromosome number 13. In all of the above syndromes new born child has severe form of MR. In Edward's syndrome and

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Patau's syndrome usually the new born individuals die in the first few weeks of their life. Although numeric sex chromosome abnormalities are more common then numeric autosomal abnormalities yet these abnormalities are not essentially associated with MR. For example, Klinefelter's syndrome which is the result of abnormality in sex chromosome number. Individuals having Klinefelter's syndrome do not have MR. However, if the number of X chromosomes exceeds two then in all the cases, the affected individuals will be mentally retarded e.g. triple X syndrome (44).

Partial Chromosome Abnormalities

Although the chromosome number abnormalities are most common cause of MR yet MR may also be the result of partial chromosome abnormalities. These partial chromosomal abnormalities may take place at any part of any chromosome. These abnormalities include the deletion of one or more than one base pair is called as deletions and addition of one or more than one base pair called as insertion may take place. Deletions in almost all cases result in MR. As the type and size of deletions vary so the phenotypes of the individuals having deletion mutations vary considerably (44).

CYTOGENETICALLY INVISIBLE MICRODELETIONS

Interstitial Microdeletions

It is very difficult to detect microdeletions and submicroscopic deletions under light microscope. The result of these deletions is the loss of particular chromosomal signals which results in the loss of function or abnormal function of the gene. These deletions are called contiguous deletions. The removal in the part of a gene takes place in the cluster of specific regions and does not occur randomly. For example, submicroscopic deletions of a segment on chromosome 7q11.23 results in MR along with other recognizable phenotypic features. This condition is known as William-Beuren syndrome (45). These microdeletions are also responsible for Smith Magenis syndrome and Velocardial syndrome. Smith Magenis syndrome arises from deletions of 17p11.2 portion. This deletion results in growth retardation along with other phenotypic abnormalities, such as behavior problems (46). Velocardiofcial syndrome is caused by the micro deletions of 22q11. In this syndrome patient along with learning disability also shows cleft palate, cardiac anomalies. FISH is used to detect these microscopic deletions (41).

Subtelomeric Deletions

Deletions of nucleotides may take place at any portions in the chromosome. If the deletions take place at the end of the chromosome, these deletions are called subtelomeric deletions (47). Teleomeres are the terminal ends of the chromosomes. They are TG rich region and have the repetitions of these simple repeats TTAGGG from many hundreds to thousands. Although the numbers varies yet these repeats are present in all vertebrates. Number of these repeats is variable in the different individuals of the same species. This variability is also present in the different levels of the age of same individual. Deletions in these subtelomeric regions are very critical as this region is extremely gene rich region. Because of this gene richness the deletions in these regions cause MR in many of the cases (48). Complex families of repetitive DNA are also present near to these repeats. The complex families of repetitive DNA may also be shared by several chromosomes. These repeats may extend up to few hundred kilo basis and may show the involvement in the chromosomal rearrangement. This phenomenon is called cross talk (49). For example Miller Dieker syndrome which is the result of deletions of the 17p telomere (50). Initially the frequency of MR people because of

these submicroscopic mutations was thought to be 5 % of all MR cases. But due to the fact that these subtelomeric deletions cannot be seen by karyotyping the exact frequency of these mutations is still unknown. Now a day FISH and comparative genomic hybridization are becoming the powerful tools for the detection of these types of mutation (51).

Monogenic Causes of MR

Mutation can take place at various positions in the genome. If these mutations take place in the gene it may alter the expression of the gene. These mutations may result in the description of the gene which results in MR or a variety of phenotypes associated with MR. This all depends upon the function of the gene and type of mutation which has taken place (52). Milder form of MR may remain hidden until the disorder is identified in a more severely affected family member that may lead to the complete diagnosis of milder forms (53).

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