0021-7557/04/80-02-Suppl/S71
Jornal de Pediatria

Mental retardation

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Abstract

Objective: This paper describes recent advances in the neurobiology of mental retardation, emphasizing new diagnostic resources provided by cytogenetics, molecular testing, and neuroimaging.

Sources of data: MEDLINE (January 2000 through October 2003), using the following key words: mental retardation, developmental disability, child, and adolescent. Search of the *Pediatrics* and *New England Journal of Medicine* websites using the key word mental retardation. The *Online Mendelian Inheritance in Man* (OMIM) database was searched for information on clinical genetics.

Summary of the findings: In October 2003, the number of genetic syndromes associated with mental retardation reached 1,149. Considering the genetic or environmental and congenital or acquired causes of mental retardation, current diagnostic investigation is able to detect the etiology in 50 to 70% of cases.

Conclusions: Diagnostic evaluation should follow a stepwise approach in order to make rational use of the expensive tools of cytogenetics, molecular biology, and neuroimaging.

J Pediatr (Rio J). 2004;80(2 Suppl):S71-S82: Mental retardation, developmental delay, neurogenetics, cerebral plasticity.

Introduction

Mental retardation (MR) is one of the most commonly observed neuropsychiatric disorders among children and adolescents. Its prevalence among young individuals is of 1%,[1,2] however, some authors report rates of 2 to 3%,[3,4] with estimates of up to 10%.[5] It is commonly agreed that MR is more frequent in males, a finding that is attributed to numerous gene mutations in X chromosome.[6] The male/female ratio is 1.3 to 1.9:1.[3] When affected children visit the general pediatrician, they often present with speech delay, behavioral disorders, or low school performance.

The diagnosis of MR is established according to three criteria:[7] onset of symptoms before the age of 18 years; intellectual function significantly lower than average, with an IQ equal to or less than 70; and poor adaptive skills in at least two of the following areas: communication, self-care, social/interpersonal skills, self-guidance, school performance, work, leisure, health and safety. An IQ greater than 85 is considered normal, and individuals with an IQ between 71 and 84 are regarded as having a borderline IQ level.[8] IQ tests are more valid and reliable in children older than five years,[9] therefore, many authors prefer to use other names for MR, such as developmental delay,[9] learning disabilities,[8] developmental disorder,[10] or developmental deficiency.[11] Moreover, since IQ tests are not always available, there is a natural tendency towards the use of developmental delay and MR as synonyms, but we should bear in mind that not every young child with developmental delay will have MR when formally tested at a later age.[9]

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Despite recent improvements in investigation methods, the etiology of MR remains unclear in 30 to 50% of cases.[1,12] Different classifications are used to facilitate the clinical investigation of MR. It may be classified into prenatal, perinatal, or postnatal MR.[2] Classically, the intensity of RM is correlated with IQ scores. Thus, children with an IQ of 50-55 to 70 have mild MR; those with an IQ of 35-40 to 50-55, moderate MR; those with an IQ of 20-25 to 35-40, severe MR; and those with an IQ lower than 20-25, profound MR.[7] Mild MR is seven to ten times more common than moderate or severe MR.[12] A more practical classification subdivides MR into mild (IQ of 50-70) and severe (IQ< 50),[8] which is the classification adopted herein. Quite often, the chances to find the etiology of MR are higher in individuals with severe MR,[3,8] but as new genetic and molecular diagnostic techniques become available to clinicians, the probability of establishing a diagnosis does not rely on the intensity of MR.[5] The cause of MR may be genetic or environmental, and congenital (e.g.: fetal exposure to teratogenic agents, chromosome disorders), or acquired (e.g.: central nervous system infection, head trauma).[13] MR may be also classified into syndromic, that is, the child has dysmorphic characteristics that lead to the diagnosis of a genetic syndrome, or non-syndromic.[14] Newborn infants diagnosed with congenital structural defects have 27 times the chance to be diagnosed with MR at the age of seven years.[15]

Probably no other area has contributed so much to the understanding of MR as genetics. Nevertheless, this contribution has brought on a maze of diagnostic options. A search of the term *mental retardation* on the Internet Online Mendelian Inheritance in Man (*http://www3.ncbi.nlm.nih.gov/omim/*) in October 2003 resulted in 1,149 hits regarding distinct genetic syndromes associated with MR. In a recent review, Battaglia[16] admitted that physicians must be experiencing "virtual panic" due to the extensive diagnostic evaluation of MR, with a high emotional and financial burden for patients. The good news is that an etiologic diagnosis can be established in at least 50% of affected patients, and the best alternative consists of a logical stepwise approach, according to the findings of anamnesis and physical examination.[5,9]

The aim of the present review is to provide general pediatricians with an update on recent improvements regarding MR in children and adolescents, in light of neuroscience and new resources made available through cytogenetics, molecular diagnosis, and neuroradiology. Treatment strategies will also be discussed.

Neurobiology of mental retardation

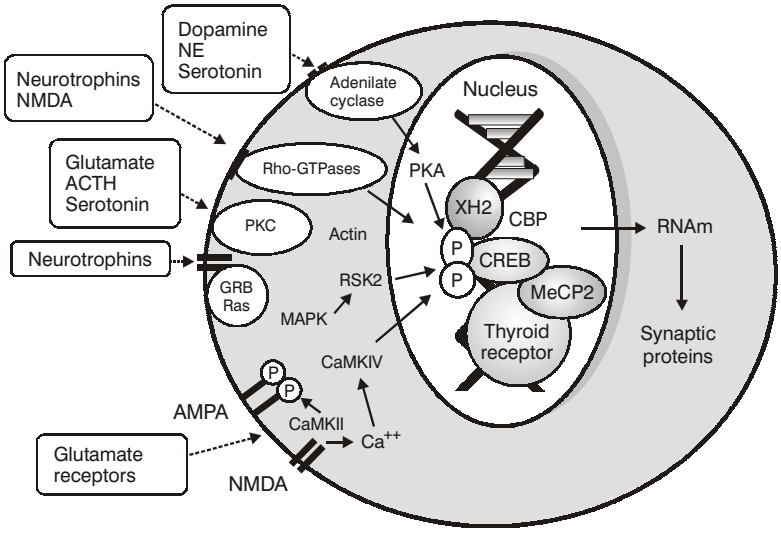
The human genome mapping project and gene knockout studies with laboratory animals allow determining specific intracellular changes in each gene mutation and the correlation of a deficient molecule with the resulting cognitive deficit, thus establishing the cellular bases of cognition.[13,17]

Neurons, which conduct nerve impulses, have two types of extensions: several short dendrites, which are branched and receive signals from other neurons, and a single long axon, which sends out the signals.[18] Dendritic spines are tiny protrusions found in postsynaptic regions of excitatory synapses;[19] serving as a bridge between axons and dendrites, they mediate the synaptic plasticity that determines learning, memory and cognition.[20] In other words, synapse remodeling and changes in dendritic spine shape and density underlie many brain functions such as learning and memory.[19] Furthermore, various proteins encoded by genes whose mutations produce X-linked MR activate the signaling paths that regulate the morphology of dendritic spines, release of neurotransmitters, growth of axons and actin cytoskeleton. The current theory is that MR originates from a defect in the structure and function of neuronal synapses.[19]

MR has been associated with changes in dendrites and dendritic spines for several decades.[13] Recently, studies on pyramidal neurons in the cerebral cortex and hippocampus of patients with Down's syndrome, Rett's syndrome and fragile X syndrome have confirmed changes in dendritic spine shape and density.[21]

Plasticity refers to the capacity of the brain to be molded by experience, learn, recollect, reorganize itself and recover after injury.[22] Plasticity develops from the interaction of excitatory and inhibitory synapses, especially excitatory ones, mediated by glutamate. The activation of glutamatergic NMDA and AMPA receptors causes synapses to form and stabilize.[22] Rho-GTPase activating proteins also are implicated, since they regulate the actin cytoskeleton,[13] which is essential to neuronal growth and differentiation.[19] Learning and memory are related to short-term changes in the strength or efficiency of synaptic neurotransmission, and long-term changes in the structure and number of synapses.[23] Gene transcription is required for the activity of long-term memories and construction of mature neuronal circuits in the developing brain.[22] Thus, plasticity involves the stimulation of receptors on the cell surface by neurotransmitters, activation of intracellular signaling cascades, gene transcription, and synthesis of new proteins that modify the physical shape and number of synapses (Figure 1).

The recent discovery that X-linked MR may originate from mutations in the genes that encode PAK3, OPHN1 and ARHGEF6 proteins, all of which interact with Rho-GTPases, underscores the importance of these cellular mechanisms to the cognitive function.[13,19] In 1999, Amir et al.[24] found that mutations in the MECP2 gene, which encodes methyl-CpG or MeCP2-binding protein 2, account for over 80% of cases of Rett's syndrome, a cause of MR in female individuals.[25] The human cerebral cortex exhibits an interesting pattern of MeCP2 expression: this protein is scarce or absent in immature neurons, but abundant in mature neurons throughout life.[26] On top of that, a



AMPA = alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; NMDA = N-methyl-D-aspartic; PKA and PKC = protein kinases; CaMKII and CaMKIV = calmodulin-dependent protein kinases; Rho-GTPases = Rho protein family of small guanosine triphosphatases; Ras = another GTP binding protein family; GRB = growth factor receptor-bound protein; MeCP2= transcription repression; XH2 = helicase; CREB = transcription activato.

Figure 1 - Neuronal plasticity mechanisms that mediate learning and memory (adapted with permission from Johnston[22])

reduction in the dendritic branching of pyramidal neurons was observed in certain regions of the cerebral cortex both in Rett's syndrome and in autism.[27]

The fragile X syndrome is a common inherited cause of MR.[28] This syndrome is almost always associated with the expansion of trinucleotide CGG repeats within the FMR1 gene at Xq27.3.[29] The FMR1 gene encodes protein FMRP, which binds to RNAm, and its regulatory transcription-translation action is important for the maturation and function of synapses.[8,17,22] In healthy individuals, CGG repeats have six to 54 units, whereas those with the fragile X syndrome have an expansion above 200 units, which indicates full mutation. A total of more than 200 CGG repeats result in hypermethylation, with transcriptional silencing of the FMR1 gene; so the FMRP protein is absent. Individuals with 55 to 200 repeats are in the premutation range, which is unstable and tends to expand during the first female meiotic division.[30] Mice that had their FMR1 gene knocked out showed macroorchidism and learning and memory disabilities, thus mimicking the human phenotype.[31] Pathological studies in patients with the fragile X syndrome and in genetically modified mice revealed abnormal dendritic spines, reinforcing the idea that dendritic spine dysgenesis is associated with MR.[28]

Inactivation of one of two alleles of each gene on X chromosome that occurs at the beginning of the embryonic period in girls[26] produces two cell populations. This genetic mechanism is responsible for the wide variety of phenotypes in recessive X-linked diseases in heterozygous girls, as the inactivation of the mutant allele occurs randomly.[6] In case of the fragile X syndrome, girls with the mutation tend to have milder clinical symptoms.[8]

Epidemiology of mental retardation

A study[1] assessed the epidemiological characteristics of MR in California between 1987 and 1994. After excluding children diagnosed with cerebral palsy, autism, chromosome aberrations, infections, endocrine or metabolic disorders, traumas or intoxications, brain malformations, and central nervous system diseases or neoplasms, the authors found 11,114 children with unclassified MR. They found out that a birthweight < 2.500 g was the strongest predictive factor for MR, and observed other risk factors associated with MR, such as low educational level, advanced maternal age at time of delivery, and multiple births.

The risk of MR is higher in children with congenital structural defects.[11,15] A study compared the presence of a congenital structural defect at the age of one year with the diagnosis of MR at 7 to 9 years.[15] The results showed that congenital structural defects, either involving

or not the central nervous system, increased the risk of MR by 27 times. Children with Down's syndrome and those with sex-linked chromosome disorders were at greater risk for RM, however, the presence of spina bifida had a relative prevalence of 91.2, compared to children without any congenital disorder; skin disorders showed a prevalence of 70.9; and musculoskeletal disorders had a prevalence of 47.1.

Another study assessed the increased risk of developmental disabilities — MR, cerebral palsy, hearing impairment and visual loss— in a group of 9,142 children born between 1981 and 1991 with significant congenital defects.[11] The authors defined prevalence ratios of MR for each congenital defect in comparison with children without congenital defect, and found the following values: chromosome disorders: 62.5; central nervous system disorders: 30.2; fetal alcohol syndrome: 29,1; TORCH infections: 24.3; ophthalmic disorders: 7.2. The association of MR with multiple disorders suggests that some cases are not caused directly by concurrent congenital defects, but instead, that they could be brought on by other factors found during embryonic development, which would be common causes of congenital defect and MR.[11]

There is a gradient of developmental sequelae inversely related to birthweight and gestational age. This means that the younger newborns are, the greater the risk for MR and other disorders such as cerebral palsy, epilepsy, behavioral disorders, and subtle cognitive deficits.[32] In a study conducted by the National Institute of Child Health and Human Development Neonatal Research Network,[33] the authors assessed 1,151 infants at 18 months with extremely low birthweight (401 to 1,000 g), and found a Bayley II mental scale score below 70 in 37% of individuals. Using logistic regression, the authors found the following factors to be associated with an increase in cognitive morbidity: male individuals, chronic lung disease, intraventricular hemorrhage grade 3 or 4, periventricular leukomalacia, use of steroids for chronic lung disease and necrotizing enterocolitis.

A meta-analysis of 80 studies[34] compared IQ scores of over 4,000 children with low birthweight and of 1,568 full-term controls with birthweight greater than 2,500 g and revealed a difference of 6.01 in favor of the latter ones. More recent analyses showed a reduction in IQ scores from 0.3 to 0.6 standard deviations in preterm infants.[32] On the other hand, a study with 144 children aged between 7 and 16 years[35] concluded that very low birthweight (< 1,500 g) was associated with severe MR only when the children also had cerebral palsy.

Parmeggiani et al.[36] studied 28 patients with cerebellar hypoplasia and, after finding out that 75% of them had MR, they concluded that cerebellar hypoplasia is an important risk factor for MR. Nordin & Gillberg[37] studied 177 individuals with MR or motor deficiency and observed that the prevalence of autistic spectrum disorders in 101 children with MR was of 19.8%. The authors highlighted that many children with severe MR have autistic spectrum disorders, but not the majority of them.

Causes of mental retardation

The discovery of phenylketonuria in 1934 quickly led to the conclusion that a low- phenylalanine diet could prevent MR associated with the disease,[38] and this model of diagnostic definition, which clarified the physiopathology of the disease and indicated possible treatment, encouraged further studies about MR. In fact, there are many reasons for establishing the etiology of MR:[5] the family wants to elucidate the problem, and the definition of its cause helps determine the risk of recurrence, request appropriate lab exams, implement proper treatment whenever available, predict the prognosis, and refer patients and family to support groups.

Nowadays, a careful clinical evaluation can identify the etiology of MR in up to 50 to 70% of cases,[1,12] a percentage value that is far better than that observed in older case series. For instance, in 715 cases investigated from 1985 to 1987,[2] the etiology of MR could be identified in only 22% of children. The most prevalent causes, in decreasing order of frequency, were the following: perinatal asphyxia, Down's syndrome, neonatal or postnatal CNS infection and fetal alcohol syndrome. In a more recent study[39] including 99 children younger than five years with global developmental delay, 44 (44%) had a definite diagnosis. Seventy seven percent of the cases with known etiology included only four diagnoses— cerebral dysgenesis, hypoxic-ischemic encephalopathy, intrauterine exposure to toxins, and chromosome aberrations. Inborn errors of metabolism were not included in the diagnoses because they had already been identified by universal neonatal screening. Using logistic regression, the authors detected clinical characteristics associated with a greater probability of determining the etiology of MR: prenatal exposure to toxins, microcephaly, focal motor symptoms, and absence of autistic behavior.

A diagnostic survey carried out in southern Brazil included 202 individuals with MR from the Association of Parents and Friends of the Mentally Handicapped (APAE).[40] The authors conducted a careful clinical examination and laboratory investigation to define the diagnosis in 132 patients (65.3%). Down's syndrome was detected in 32.2% of cases, followed by Mendelian inheritance disorders in 12.4%, acquired conditions including infections in 10.4%, and CNS malformations in 4.0%. The high percentage of Down's syndrome probably shows a selection bias.

The conclusion that etiology is more often defined in severe MR is no longer valid with the advent of new diagnostic methods, such as high-resolution karyotyping, fluorescence in situ hybridization (FISH), subtelomeric screening, chromosome microdissection, and nuclear magnetic resonance spectroscopy.[5]

Table 1 shows some clinical and laboratory signs with possible etiologies of MR. In the subsequent sections, we will discuss some of the most prevalent causes.

Down's syndrome

Down's syndrome, or trisomy 21, is the most frequent cause of MR,[8] with an incidence of approximately 1:800 live births.[3] More than 90% of cases result from maternal nondisjunction, but some cases originate from translocation or mosaicism. Some studies reveal that up to 20% of children with MR suffer from Down's syndrome.[41] Affected children have an average IQ of 50,[8] and diagnosis often is based on clinical findings, such as simian crease, hypotonia, epicanthal folds, flat occiput, macroglossia, upslanting palpebral fissure, absence of startle reflex in the neonatal period, increased space between the great toe and second toe, and congenital heart diseases, such as endocardial cushion defect and ventricular septal defect.[3,8] Karyotyping is essential for confirming the diagnosis and determining the underlying genetic mechanism.

Fetal alcohol syndrome

The fetal alcohol syndrome consists of a group of physical, behavioral and cognitive disorders observed in children exposed to alcohol while still *in utero.*[42] It is one of the most common causes of MR in industrialized countries, with up to 8% of MR cases being affected.[41] Clinical features of this syndrome include typical facies, thin upper lip, flat and long philtrum (Figure 2), short palpebral fissures, ptosis, upturned nose and flat midface.[42] Additional characteristics are cleft palate, prenatal and postnatal growth delay, microcephaly, agenesis of the corpus callosum, congenital heart disease and behavioral disorders. Exposure during the first trimester of pregnancy interferes with organ formation and craniofacial development, whereas the development of the central nervous system is influenced throughout pregnancy due to continued neuronal maturation. The pathophysiology of this syndrome is not fully understood yet, but it seems to be related to the formation of free radicals with consequent cellular injury to developing tissues.[42]

It should be underscored that fetal alcohol syndrome is one of the major preventable causes of MR; therefore, women who are planning to get pregnant and those who already are must abstain completely from alcoholic beverages. In addition, evidence shows that early diagnosis and intervention may reduce the occurrence of secondary deficiencies.[43]

Lead poisoning

Childhood lead poisoning results in persistent cognitive deficit.[44] Several factors expose children to lead toxicity, among which are dust, paint chips, and leaded gasoline.[22,45] Children with blood lead concentration equal to or greater than 10 µg/dl are considered to be at risk of intoxication.[45] Studies with animal models revealed that lead influences several stages of neuronal plasticity by reducing the release of neurotransmitters, binding to NMDA receptor, and interfering with protein kinases.[22]

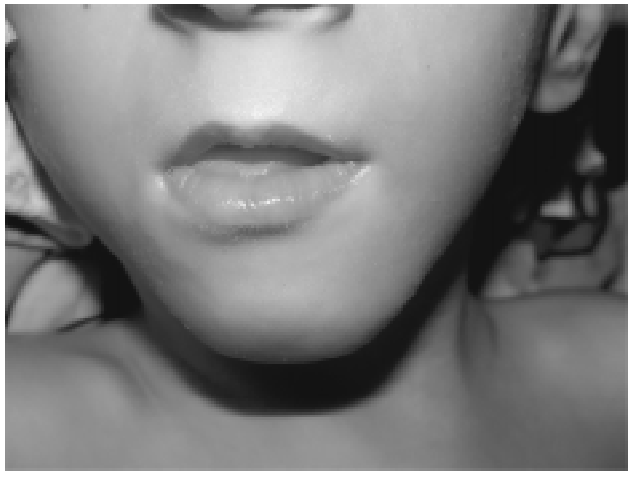


Figure 2 - A eight-year-old boy with fetal alcohol syndrome (note his thin upper lip and flat and long philtrum)

In Brazil, there are no published data on the prevalence of lead poisoning, but in the USA, the CDC has reported a blood lead concentration as high as 10% among preschool children.[45]

Congenital infections

Among 715 ten-year-old children with MR studied by Yeargin-Allsopp et al.,[2] only six cases (0.8%) were associated with congenital infection; however, as the etiology was detected in only 22% of the cases, congenital infections accounted for 3.8%. Despite the efficiency of vaccines and other preventive measures, TORCH infections are still responsible for some cases of MR among children, especially in developing countries. In congenital syphilis, for instance, MR results from the propensity of *Treponema pallidum* to infect the meninges and cerebral blood vessels, where inflammatory response seems to contribute to neurosensory hearing loss.[46]

Neurocutaneous disorders

Neurofibromatosis type 1 (NF1) (Table 1) is characterized by six or more café-au-lait spots, affecting 1 in every 4,000 individuals, of whom 4 to 8% have an IQ < 70.[47] Other cognitive deficits that have been described include impaired visuospatial skills, inattention and executive dysfunction, but there seems to be no specific cognitive pattern for NF1.[47] A recent study assessed attention deficit hyperactivity disorder (ADHD) in children with NF1.[48] The authors found a prevalence of ADHD of 50% in 93 children with NF1 and concluded that the coexistence of this disorder decreased the IQ score and increased the cognitive deficit. NF1 is caused by mutations

Table 1 - Correlation of some clinic and laboratory indexes with the etiology of mental retardation

Indice	Diagnostic suspicion	Locus and inheritance*	Additional findings
Macrocephaly	Proteus syndrome	I	Partial gigantism of the hands and/or feet, hemihypertrophy, subcutaneous tumors, nevi
	Macrocephaly-autism syndrome	AD	Clinical evaluation
	Soto's syndrome	Various, AD	Dolicocephaly, hypnotia, advanced bone age
Microcephaly	Miller-Dieker syndrome	17p13.3, AD	Lissencephaly, prominent retardation and epileptic crisis
	Wolf-Hirschhorn syndrome	4p16.3, I	'Greek helmet' facies, cleft lip and palate
Luxation of the crystalline lens	Homocystinuria	21, AR	Marphanoid habitus, high plasmatic homocysteine
Gynecomastia	Klinefelter's syndrome	XXY	Sparse facial hair, tall stature, eunuchoid habitus
Aniridia	WAGR syndrome	11p13, AD	Wilms' tumor, aniridia, genitourinary abnormalities and mental retardation
Cafe-au-lait spots	Neurofibromatosis type 1	17q11.2, AD	At least 6 spots > 5 mm in children and > 15 mm in adolescents, neurofibromes, bone lesions, benign and malign tumors
Ash-leaf shaped hypopigmented spots	Tuberous sclerosis	9q34 ou 16p13, AD	Hypochromic spots and epileptic crisis (infantile spasms)
Outbursts of laughter	Angelman syndrome	15q11, I	Absence of speech, epileptic crisis, delayed psychomotor development, tongue protrusion
Obesity	Prader-Willi syndrome	15q11, I	Hypotonia, small hands and feet, micropenis and cryptorchidism
Elfin-facies	Williams syndrome	7q11.23, AD	Short stature, supravalvar aortic stenosis, hypercalcemia, hypercalciuria
Grotesque facies	Mucopolysaccharidosis type I	4p16.3, AR	Delayed growth, hepathomegaly, blurred cornea, gibbus
	Mucopolysaccharidosis type II	Xq27-28, RX	Idem; without blurred cornea and gibbus
Large thumb and/or halux	Rubinstein-Taybi syndrome	16p13.3, AD	Microcephaly, speech difficulties, prominent nose, cryptorchidism, short stature
Self-Mutilation	Smith-Magenis syndrome	17p11, I	Cupid bowed upper lip, prominente forehead, insertion of foreign objects into body orifices
	Lesch-Nyhan syndrome	Xq26-27, RX	Hyperuricemia, hipotoyia, dystonia, lip and hand bitting
Hypocalcemia	DiGeorge's syndrome/ Velocardiofacial syndrome	22q11, AD	Congenital cardiopathy, hypoplasia of the thymus, absence of parathyroid gland
Megaloblastic Anemi	Serine deficit	1q12, AR	CSF with low serine levels, congenital cataracts
	Defficiency of methyl cobalamin	1q43, AR	Lack of motor coordination, reduced plasmatic methionine
	Abnormal folate metabolism	AR	Basal nucleus calcification, low seric level of folate
Alpha-thalassemia	S. ATR-16	16p13.3, AD	Microcephaly, H hemoglobin in the erytrocytes
	S. ATR-X	Xq13, DX	Idem, more dismorphic characteristics
Reduced cholesterol seric level	Smith-Lemli-Opitz syndrome	AR	Microcephaly, cataractss, ptos is, low set ears, micrognathia, genital hypoplasia in boys
	Congenital glicosilation disorders	16p13.3-p13.2, AR	Isoelectric focalization of seric transferences

* Abbreviatures: AD = autossomic dominant; AR = autossomic recessive ; DX = dominante binding-X; RX = recessive binding-X; I = isolated cases; CSF = cerebrospinal fluid.

in the gene that encodes neurofibromin, whose function is to regulate GTPases; possibly, tumor susceptibility and cognitive deficits associated with the mutations are caused by problems with intracellular GTPase signaling.[22]

Tuberous sclerosis (Table 1) is a multisystemic syndrome whose clinical characteristics include hypopigmented macules (Figure 3), forehead plaques, adenoma sebaceum and subungual fibromas.[8] Cranial

computed tomography shows calcified periventricular nodules, which may appear only at the age of 3-4 years, and cortical tubers.[49] There are two mutations associated with tuberous sclerosis: TSC1 gene on chromosome 9 encodes a protein known as hamartin, and TSC2 gene on chromosome 16 produces tuberin, which also is a GTPase activating protein.[22] These proteins are believed to regulate cellular proliferation.[8] MR is present in 47% of affected children, but develops only in those individuals who had epileptic seizures in their first years of life.[8]

Hypomelanosis of Ito is characterized by hypopigmented lesions (whirled and streaked areas) along Blaschko's lines, macrocephaly, and epileptic seizures. In a series of 34 cases, MR was detected in 64.7%.[50]

Rett's syndrome and other MECP2 mutations

Rett's syndrome is a common cause of MR in girls, with a prevalence in Sweden of 1:10,000 to 1:15,000.[26] The first symptoms appear after 6 to 18 months of normal development, when the child presents with speech impairment, stereotyped hand wringing, epileptic seizures, respiratory disorders, and autonomic instability, evolving into late motor deterioration.[25,26] After the genetic etiology of this syndrome was defined by Amir et al. in 1999,[24] the location of MECP2 gene was confirmed to be on chromosome X. Affected girls are heterozygous for the allele in question. Since then, more than 70 MECP2 gene mutations have been described to cause Rett's syndrome.[51] The affected boys, who are hemizygous, succumb to intrauterine death or have fatal neonatal encephalopathy.[26] Affected girls have a lag in brain and head growth after symptom onset, with acquired microcephaly.[25] Controversy still exists over the precise function of MeCP2 (Figure 1). Some authors believe that it represses gene transcription,[22] while others state that Rett's syndrome is a presynaptic signal transduction disorder.[26]

Studies with genetically modified animals demonstrated that Rett's syndrome is a neuronal disease; however, whether this syndrome is a cerebral developmental disorder or a deficiency in the cellular maintenance of neurons is still unknown.[26] Huppke et al.[51] developed a symptom score to help define when to indicate the investigation of MECP2 mutations.

Other MECP2 gene mutations are not necessarily lethal in males. Affected boys may have severe MR with progressive neurological symptoms, nonfatal static encephalopathy, childhood schizophrenia, or a phenotype that is similar to that of Angelman's syndrome.[5,26,52]

Fragile X syndrome

Fragile X syndrome is the most common inherited cause of MR in males,[8] with an estimated prevalence of 1:4,000 boys and 1:6,000 girls.[29] Physical examination shows prominent ears and a long thin face (Figure 4), relative macrocephaly, hyperextensible joints and, usually after puberty, macroorchidism.[53,54] Other symptoms also include hyperactivity, hand flapping and autistic behavior,[29] the latter of which affects 25% of patients.[8]

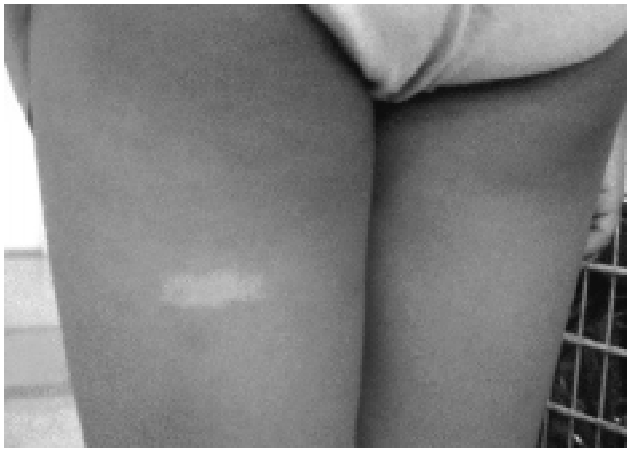


Figure 3 - A six-year-old boy with tuberous sclerosis (diagnosis was suspected based on the leaf-shaped hypopigmented macules on the posterior surface of his thigh).

Figure 4 - A boy (arrow) with Fragile X characteristic facies (note that his two sisters and his mother present a less evident but suggestive phenotype of the syndrome; photograph courtesy of Dr. Juan Llerena, Genetics Department, Fernandes Figueira Institute, RJ; displayed with the mother's permission)

Besides the afore-mentioned FMR1 gene mutation, researchers found a similar expansion with over 200 CGG repeats in another fragile site distal to the first one, where the FMR2 gene, whose mutation causes MR, is located, in addition to a phenotype that is mistaken for the fragile X syndrome due to FMR1 gene mutations.[55] FMR2 mutation is less prevalent than that of FMR1 and is associated with a milder phenotype, sometimes with only MR-associated speech delay.[56] A British study including 534 preschool children with speech delay revealed full FMR1 mutation in three children (0.6%) and full FMR2 mutation in none of the children.[56] Nevertheless, three other children had very small FMR2 alleles suggesting deletions. The authors concluded that the investigation of these mutations is justified in preschool children with speech delay, especially if there is family history of MR.

The laboratory diagnosis of the fragile X syndrome may be defined by cytogenetics, or more appropriately by two molecular DNA tests used to determine the size of CGG repeats —Southern blot and polymerase chain reaction.[29] A list of six items was made to select the patients who should be submitted to the tests, with scores from 0 to 2 for each of the items: MR, family history of psychiatric disorders or MR, long thin face, prominent ears, attention deficit hyperactivity disorder and autistic behavior.[54] Patients with a score $\geq$ 5 should be tested.

Brain malformations

A series of brain malformations have been described in children with MR, including cerebral cortical dysplasia, dysplasia of the corpus callosum, ventriculomegaly and minor cerebral and cerebellar disorders.[4] In some cases, brain malformation is associated with a syndrome of multiple congenital defects, such as congenital muscular dystrophies[57] and X-linked lissencephaly and heterotopy syndromes.[58] Some authors consider certain minor brain disorders to be risk factors for developmental delay, among which are cavum septum pellucidum, hypoplasia of the corpus callosum and megacisterna magna.[4]

The presence of microcephaly or macrocephaly should raise suspicion as to central nervous system malformation.[5] Several genetic syndromes with cerebral cortical malformations associated with microcephaly have been reported.[59]

Inborn errors of metabolism

Inborn errors of metabolism are well known causes of MR,[5] and their early detection and treatment can prevent MR, as occurs with phenylketonuria, galactosemia and hypothyroidism,[60] which were included in the universal neonatal screening.

The list of metabolic causes of MR is extensive and includes lysosomal storage disorders, nonketotic hyperglycinemia, urea cycle defects, oxidative phosphorylation disorders or mitochondriopathies, deficient biosynthesis of cholesterol, deficient synthesis of serine, congenital disorders of glycosylation and creatine deficiency[60] and the new group of metabolic disorders called pediatric neurotransmitter diseases, among which we have succinic semialdehyde dehydrogenase deficiency.[61]

Creatine deficiency is a new metabolic disease that has been described thanks to nuclear magnetic resonance spectroscopy, which revealed creatine depletion in the brain.[62] Oral creatine supplementation improved the cognitive deficit in two of the patients.[63]

Protein-energy malnutrition

Experimental studies with lab animals showed that malnutrition soon after birth reduces the growth rate of the central nervous system and the number of neurons, producing a thinner cerebral cortex, deficient myelination, poor dendritic branching and several dendritic spine abnormalities.[64] Infants who suffered from severe malnutrition have neurointegrative defects and varying degrees of MR documented some years after recovery.[65] Maternal protein-energy malnutrition does not cause permanent neurological or intellectual deficit in the fetus as brain growth is not affected.[66] However, within the first 24 months of postnatal life, malnutrition causes more severe brain damage.[67] A recent study assessed dendritic spine density and morphology in cortical neurons of 13

infants who died from severe malnutrition, compared to seven well-nourished infants who died of other causes.[64] The authors reported remarkable findings regarding spine density on apical dendrites, similar to those described in MR due to other causes, and they concluded that, although they could not demonstrate that such findings are the cause and not a coincidental association with MR, they could represent the basis for synaptic dysfunction associated with severe malnutrition at young age.

How to investigate mental retardation

The first and foremost step in addressing a child or adolescent with evidence of MR consists of a thorough anamnesis and physical examination. Anamnesis should include the family history of neurological diseases and MR, consanguinity, parental educational level; detailed gestational history, including exposure to toxins, drugs and infections; delivery and childbirth history; and pedigree of the last three generations.[5] Physical examination should necessarily include measurement and classification of head circumference, careful inspection of the skin, with Wood's lamp (if possible), thorough neurological examination and extensive investigation of congenital defects, bearing in mind that these defects could be very subtle.[8] Review of photographs or videotapes may be useful, the latter of which are valuable in documenting movement disorders and behavioral disorders.[5]

Pediatricians should carry out the physical examination on a child with MR bearing in mind that neuromuscular disorders— e.g.: spasticity, ataxia, athetosis, tremors and hypotonia — are the most prevalent physical findings in X-linked MR syndromes.[14]

Laboratory investigation of MR varies according to patient's age, index of suspicion of treatable etiologies and parents' concern with the recurrence of MR in future gestations. A sensible practice (Table 2) that increases the possibilities of establishing a diagnosis consists of serial reassessments of patients over a regular period of time.[5] Since not many metabolic diseases cause isolated MR without other associated symptoms[60] and due to its prevalence of only 0-5% in children with MR,[5] metabolic investigation should not be included in the initial screening.[9] Nonetheless, homocystinuria, easily detected by elevated homocysteine serum levels, and urea cycle defects, revealed by hyperammonemia, may produce a mild phenotype, therefore homocysteine and ammonia serum levels could be included in initial exams.[60]

Poplawski et al.[68] proposed that urine metabolic screening of amino acids and organic acids should be included in the initial investigation of all children with isolated MR. They assessed 1,447 individuals with developmental delay without other clinical signs, and found inborn errors of metabolism in 16 of them (1.1%).

In children with yet undiagnosed MR and microcephaly, the possibility of maternal hyperphenylalaninemia should be considered.[60] Metabolic investigation of these children will yield normal results; only the measurement of maternal phenylalanine serum levels will confirm the diagnosis.[8]

Given the frequency of 4 to 34.1% of chromosome aberrations in MR patients,[12] it has been commonly agreed that initial evaluation should include karyotyping at the 500 band level.[5] Some authors recommend molecular analysis of the fragile X syndrome in all cases of MR,[9] whereas some others propose an initial clinical screening so as to increase the number of positive

Table 2 - Phases of mental retardation screening*

Phase 1
Anamnesis
Physical and neurologic examination, including head circumference and investigation of dysmorphic characteristics
Heredogram including three generations
Review of the results of the heel prick test
Phase 2
Screening for autism
Complete blood test, serum levels of electrolytes, iron, calcium, magnesium, phosphor and alkaline phosphatase
Screening of the auditive and visual impairments
Review of photographs and video tapes
Phase 3
Neuroimaging exam (CT and/or MR with protons spectroscopy)
Serum levels of homocysteine and amonia
Endocrinal tests (e.g., tests of thyreiod function)
Tests for TORCH†, if necessary
Karyotype
Investigation of the Fragile-X, if necessary
Ophtalmological exam
Neuropsychological tests, including IQ†
Phase 4
Arterial gasometry
Detailed metabolic research (e.g., aminoacids and urinary organic acids, lactatus and piruvate in the serum and in the cerebrospinal fluid)
Blood level of plumbum
Serum level of creatinokinase
Genetic and neuropediatric tests
Electroencephalogram, in case of epilepsy
Phase 5
Biopsies and hystopathological exam of the limbs
FISH† technique for specific microdeletions
Chromosomal subtelomeric studies
Mother's serum level of phenylalanin, if the child presents microcephaly
DNA probes for specific mutations (e.g., MECP2†)
Spectroscopy through MR, if not performed yet

* Source: suggestions partialy based on the references 5 and 9.
† IQ = intelligence quotient; FISH = fluorescence in situ hybridization; MECP2 = gene of Rett's syndrome; TORCH = congenital infections such as toxoplasmosis, syphilis, rubella, cytomegalovirus and herpes.

results.[54] Genetic and molecular exams that should be requested in certain cases include the FISH technique for the detection of microdeletions, investigation of chromosomal rearrangements and subtelomeric deletions, and the use of DNA probes for specific mutations such as MECP2 and other genes implicated in X-linked MR.[5]

A consensus conference[69] proposed that neuroradiological exams should be conducted to assess MR especially in patients with microcephaly or macrocephaly, spasticity, epileptic seizures, or loss of acquired abilities. Since then, improvements in neuroradiological methods, such as nuclear magnetic resonance spectroscopy, and their capacity to detect treatable causes of MR,[63] and the detection of cerebral cortical malformations in an increasing number of children with MR, led to the recent suggestion that neuroimaging exams be initially performed in the investigation of MR, even in children without any other neurological findings.[5,62] Computed tomography is still the exam of choice for patients with abnormal cranial shape, that is, craniosynostosis, or in those suspected of having intracranial calcifications, caused by tuberous sclerosis or by congenital infections.[62] However, magnetic resonance provides more information on changes in white and gray matter and myelination as well as on skull base and posterior fossa.[62]

Caution is urged in the use of neuropsychological tests. Although they are essential, the interpretation of results should take into account the ethnical and cultural context, level of education, motivation, cooperation, and associated deficiencies of patients.[5] An example is the interference of attention deficit hyperactivity disorders with the results of IQ tests. A child with ADHD may have an artificially low performance in some subitems, thus falsely reducing the IQ score. A review of the subitems in search of significant discrepancy between partial scores helps clarify this interference.[70]

How to treat mental retardation

Most of the causes of MR have no available cure,[8] but the definition of the etiology often helps the family to understand the prognosis and estimate the risk of recurrence.[3] In this regard, an accurate diagnosis is inestimable to genetic counseling of patients and family, allowing for the prediction of future medical problems. For instance, 21% of women who have the fragile X syndrome premutation will have premature ovarian failure.[71]

The fact that a certain etiology of MR has no cure does not prevent pediatricians from providing affected children with comfort and quality of life by indicating early stimulation programs,[72] treating associated disorders[73] and defending patients' rights in the community. For example, when ADHD is associated with MR, the use of methylphenidate can improve children's attention and behavior, although it does not improve learning.[74] Epilepsy is another disorder often associated with MR, and special attention should be paid to the cognitive and behavioral adverse effects of antiepileptic drugs.[75] Pediatricians should also bear in mind that children and adolescents with MR belong to a group at high risk for child maltreatment.[76]

An extremely common problem in MR patients concerns their self-injurious behavior.[77] This behavior is expressed differently in distinct disorders, such as in the fragile X syndrome, Lesch-Nyhan syndrome, Smith-Magenis syndrome, Rett's syndrome and Prader-Willi syndrome. A study revealed a prevalence of 2 to 50% for self-injurious behavior in children with severe MR and investigated its occurrence in relation to chronic pain.[78] The authors concluded that there are two forms of self-injurious behavior: one that is associated with pain and directed towards the site of origin of the pain, and another one, which is more frequent, that is not associated with pain and is directed towards the hands and head. The management of this problem can include changes in behavior and functional communication training,[77] as well as drug therapy with selective serotonin reuptake inhibitors, trazodone, or buspirone.[79]

A recent study has proposed the use of melatonin in the daily dose of 0.3 mg before bedtime to treat insomnia in adolescents with MR.[80]

Gene therapy of MR secondary to monogenic disorders is still a possible alternative.[81]

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