REVIEW ARTICLE

APPROACH TO MENTAL RETARDATION AND GLOBAL DEVELOPMENTAL DELAY

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Abstract

Objective

Mental Retardation (MR) or Intellectual Disability is one of three chronic and disabling neurological disorders of children and adolescents. Its prevalence is estimated 1-3% of the population. MR is defined as significant sub-average intellectual functioning and adaptive behavior that become detectable before the age of 18. MR may come into view before 5 years as delay in at least two developmental domains which is called Global Developmental Delay (GDD). The causes of mental retardation can be considered under the titles of prenatal, perinatal and postnatal factors. Prenatal causes account for approximately 60 -80 % of the etiological factors. All patients with GDD / MR should undergo a stepwise diagnostic approach, because a specific diagnosis leads to opportunity for treatment, future planning and genetic counseling. History, physical examination and neurodevelopmental examinations are the most important parts of the approach. Recent advances in cytogenetic investigations and neuroimaging studies have led to recognition of new disorders and improvement of the diagnostic yield.

Keywords: Mental retardation ; global developmental delay; diagnostic yield.

Introduction

Definitions and classifications

Developmental disabilities are a group of interrelated, static neurologic disorders occurring in childhood and are expected to affect 5 % to 10 % of the children (1). Development can be divided into three major domains or skill areas (cognitive, motor, social and adaptive). Mental retardation (MR) is one of developmental disabilities at cognitive domains. Other terminologies that have been used instead of mental retardation are Mental Deficiency, Cognitive Deficiency, Mental Subnormality, Feeble-Mindedness, Mental Handicap, Oligophrenia, Idiocy, Amentia and Intellectual Disability. More recently, intellectual disability has been suggested to replace mental retardation (2).

Tredgold has defined mental deficiency as a state of arrested or incomplete development of the mind. World Health Organization (WHO) defines mental retardation as an incomplete or insufficient general development of mental capacities (3).

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), has defined mental retardation as "significantly sub-average intellectual function, existing concurrently with deficits in adaptive behavior and manifest during the developmental period" (4).

The American Association on Mental retardation (AAMR) defines mental retardation as follows: "Mental retardation refers to substantial limitations in present functioning. It is characterized by significantly sub-average intellectual functioning, existing concurrently with related limitations in two or more of the following applicable adaptive skill areas: communication, self-care, home living, social skills, community use, self direction, health and safety, functional academics, leisure and work "(5). These findings must be evident before the age of 18 years (5). Significantly sub-average intellectual functioning means an Intelligence Quotient (IQ) score of 2 or more standard deviation below the mean (less than 68 on the Stanford-Binet or less than 70 on the Wechsler test).

Global Developmental Delay (GDD) is a subset of developmental disabilities defined as "a significant delay in two or more of the following developmental domains: gross/fine motor, speech/language, cognition, social/personal and activities of daily living" (6). The term GDD is usually reserved for children younger than five years old whereas the term MR is usually applied to older children when IQ testing is more valid and reliable (1).

The degrees of mental retardation are expressed in various terms. DSMIV presents four types of MR, according to the degree of IQ level as mild (IQ:50-70), moderate (IQ:36-50), severe (20-35) and profound (less than 20) (7). American Association on Mental Retardation focuses on the pattern or intensity of supports needed as intermittent, limited, extensive and pervasive or complete (8). When discussing the etiology and likelihood of a specific etiology, it is convenient to divide MR into mild and severe categories:

Mild mental retardation (IQ:50–70) occurs in 30/1000 persons with an identifiable cause found in up to 50% while severe mental retardation (IQ:<50) occurs in 3-4/1000 persons with an identifiable cause detected in 70–80 % of the cases .

Epidemiology of mental retardation

The prevalence of mental retardation at any time is estimated to be about 1 percent of the population (9), although cohorts defined only by IQ range from 2% to 3%.

As mentioned earlier, mild mental retardations is 10-12 times more common than severe mental retardation.

Mental retardation is found more commonly in boys than girls in a 1.4:1 ratio (10), but ranges from 1.3 to 1.9: 1 (11). This difference may be due to the presence of X-linked mental retardations. Severe to profound mental retardation presents as developmental delay before 5 years of age, but mild mental retardation presents as academic dysfunction.

Etiology

Hereditary and environmental factors may have a role in the etiology of mental retardation. Parents seek to know the etiology of their child's developmental disabilities. In many cases of mental retardation, especially in mild cases, etiological diagnosis cannot be confirmed even after complete investigations. Etiological diagnosis is important because in some patients, a treatable cause may be present or genetic factors assist parents for further pregnancy or prediction. The causes of mental retardation can be considered under the headings of prenatal, perinatal and postnatal factors.

Prenatal causes account for approximately 60-80 % of the etiological factors and may be genetic or non-genetic (12). Genetic causes can be divided into chromosomal disorders and non-chromosomal genetic conditions. Dysmorphic features and presence of other malformations such as eyes, nose, mouth, heart, lung, genitourinary and skeleton, in addition to mental retardation, suggest chromosomal disorders .

Down syndrome, with an incidence of 1 in 600 newborns, is the most common identifiable genetic cause of mental retardation and constitutes 4-7 % of all cases (13). Other chromosomal aberrations are various forms of trisomy, deletion syndromes (Cat-cry, Prader-willi, Angelman), X chromosome abnormalities and Fragile X Syndrome. Fragile X Syndrome is the most common inherited cause of mental retardation. Fragile X Syndrome is widespread in humans and its frequency may be higher in some ethnic groups, such as Tunisian Jews and African- Americans (14;15). Speech delay, autistic like behavior and hyperactivity are often the presenting symptoms. Long facies, large ears and macroorchidism are suggestive signs.

Non-chromosomal genetic conditions can be divided

as phakomatosis or neurocutaneous syndromes, Inborn Errors of Metabolism (IEM) and some structural brain abnormalities. The neurocutaneous syndromes such as tuberous sclerosis and neurofibromatosis are autosomal dominant. Other inheritance patterns and sporadic cases are present in the phakomatosis. Many IEMs including aminoacidopathies, organic acidemias, urea cycle disorders and lysosomal storage diseases are associated with intellectual disability. Newer IEMs are serine defects, creatine deficiency and glucose transporter deficiency (16). Many structural brain abnormalities are associated with mental retardation and sometimes other congenital anomalies.

Non-genetic prenatal conditions consist of conditions such as environmental factors, maternal infections, antepartum hemorrhage and toxemia of pregnancy.

Perinatal causes have been responsible for 10- 20 % of cases and includes neonatal asphyxia, prematurity and birth trauma (12).

Postnatal causes such as meningitis and encephalitis, trauma, malnutrition, poverty, psychosocial deprivation and lead poisoning account for up to 10 percent of the cases (12).

Diagnostic categories of mental retardation are showed in Table 1 (17;18).

Table 1: Causes of mental retardation by diagnostic category (17, 18)

Chromosomal abnormalities	4-28 %
Recognizable Syndromes	3-9 %
Structural brain abnormalities	3-17 %
Complications of prematurity	2-10 %
Perinatal conditions	8-13 %
Environmental / Teratogenic causes	5-13 %
Cultural / Familial mental retardation	3-12 %
Metabolic / Endocrine Causes	1-5 %
Unknown	30-50 %

Diagnostic evaluation of GDD / MR

"There is consensus that the history and the physical examination are the most important aspects of the investigation. An accurate prenatal/birth and hereditary/familial history, in addition to a three-generation pedigree, is an essential step in the diagnostic evaluation of GDD / MR" (19). A detailed family history including mother's previous gestational history, intrauterine problems, intrauterine toxin or radiation exposure, neonatal birth weight and head circumference, Apgar score, and the duration of hospital stay and the timing of the developmental milestones should be recorded. Head holding, rolling, crawling, sitting, standing, walking, babbling, first distinct words, two-word phrases and use of sentence are among the most important motor and language skills that must be recorded (20). The possibility of any loss or regression of previously acquired skills must be addressed as well as the age and reason for initial parental concern (20).

A thorough physical examination including skin, abdomen for organomegaly, spine, minor anomalies and neurodevelopmental assessment can help either in making a diagnosis or in directing laboratory testing. The head shape, fontanels status and the current head circumference should be plotted. Amelanotic nevi, adenoma sebaceum , café au lait spots, diffuse dermal melanocytosis and ichthyosis are some examples of skin findings that suggest a specific diagnosis. Extensive Mongolian spots or diffuse dermal melanocytosis may be a clue to some neurometabolic disorders such as Hurler, GM1 gangliosidosis and Niemann-pick disease (21). Congenital ichthyosis may be associated with Sjogren-Larsson syndrome (22). Shaefer and Bodensteiner state that the association of intellectual disability and congenital malformations has long been recognized and that a necessary component of the evaluation of a child with idiopathic intellectual disability is a comprehensive dysmorphologic examination (23).

Van Karnebeek, in a prospective study of the diagnostic evaluation of the developmental delay or intellectual disability of 281 children, found an etiologic diagnosis in 150 cases. One third of these diagnoses were made on the basis of the history and examination alone; in another one third, the history and examination provided essential clues to the diagnosis, and laboratory studies alone provided diagnosis in the remaining one third (24). This study found that based on clinical history alone, a diagnosis could be established in 1 of 20 patients, and based on physical examination alone, 1 in 30 patients could be diagnosed. Based on the combination of history

and examination together, 1 in 3 patients were diagnosed (24). Diagnostic yield of neurologic examination in the evaluation of intellectual disability is reported as 42.9 % (6,24).

Intellectual assessment, adaptive evaluation, audiometry, vision testing, psychiatric and behavioral assessment are essential for diagnosis and evaluation of GDD/MR.

Recent technological advances in cytogenetic analysis and imaging have increased the potential for diagnostic yield.

Cytogenetics: "The yield of cytogenetic testing has been enhanced by recent advances including higher resolution banding, fluorescent in situ hybridization (FISH) and chromosome painting" (20). Chromosomal abnormalities are reported in 4-34 % of the patients with GDD / MR and cytogenetic analysis is regarded as a mainstay in the diagnostic process (19). In a retrospective review from Montreal Children's Hospital, the laboratory test with the highest yield of abnormal results was chromosome analysis (25). Van Karnebeek et al believe that routine karyotype is a valuable technique in the diagnostic evaluation of GDD/MR (24). They state that there is a relationship between the number of minor anomalies and the likelihood of a chromosome abnormality; a higher number of anomalies (>6) indicates a significantly higher likelihood to find a chromosome abnormality (24). Shevell et al believe that routine cytogenetic analysis is indicated in the evaluation of GDD even in the absence of dysmorphic features (26). Curry recommends that "Fragile X testing be strongly considered in both males and females with unexplained intellectual disability especially in the presence of a positive family history, a consistent physical and behavioral phenotype and absence of major structural abnormalities" (27). Van Karnebeek recommends that all boys with an unexplained intellectual disability have molecular genetic testing for Fragile X syndrome but that routine testing of girls is not warranted unless there is a positive family history (24). With the identification of an expanded trinucleotide repeat in the FMR-1 gene at Xq27, the standard diagnostic test for Fragile X Syndrome is now the quantification of the size of the trinucleotide repeat by DNA techniques, such as PCR and southern blot. Four forms of the CGG trinucleotide repeat have been described: normal (6-40 repeats), intermediate (41-60 repeats), permutation (61-200 repeats) and full mutation (>200-230 repeats) (28). A small expansion or premutation is usually not associated with cognitive deficits. A larger expansion or full mutation is associated with Fragile X syndrome and is associated with typical features.

The consensus conference in 1997 suggested that whenever there is a temporary diagnosis of microdeletion syndrome, a focused FISH analysis may be the first step (27).

About 50% of all structural chromosome abnormalities include the telomeric region. Many deletions of the telomeres are evident by standard techniques, and the syndromes caused by such deletions are often clinically identifiable; for example, cri du chat syndrome, which is caused by the deletion of the telomere of the short arm of chromosome 5 (29). FISH techniques have been applied to examine the subtelomeric regions of each chromosome for abnormalities that are known to cause intellectual disability (19). FISH studies make it possible to localize specific DNA sequences by fluorescent labeling metaphase or prometaphase chromosomes, thereby providing numerous new markers, such as Williams Syndrome (7q11.23), Prader-willi syndrome (15q 11-13), Angelman syndrome (15q 11-13) and Miller-Dieker (17p 13.3) .

Hidden chromosomal rearrangements involving the telomeric portions have been described as being responsible for a significant proportion of unexplained MR and other congenital anomalies. Submicroscopic subtelomeric chromosome defects have been found in 6.5-7.4 % of children with moderate to severe MR (30,31).

Specific subtelomeric FISH probes have been developed for each of the 42 telomeric regions in the human genome. Subtelomeric probes are expensive and must be requested only when there is strong suspicion of chromosomal rearrangements according to clinical findings and/or the pattern of transmission in the family. De Vries et al concluded that "good indicators for subtelomeric defects are a family history of MR, prenatal onset growth retardation, postnatal poor growth or over growth, two or more facial dysmorphic features and one or more nonfacial dysmorphic features or congenital abnormalities" (19,32).

Rett syndrome is one of the leading causes of GDD/ MR in females and is caused by mutations in the X-linked gene encoding methyl-CpG- binding protein 2 (MECP2) (33-35). About 80% of the patients with Rett syndrome have MECP2 mutations, but this mutation may result in progressive neurological manifestations (36,37), nonprogressive encephalopathy in males (38), or even an Angelman-like phenotype (39), without the manifestations of Rett syndrome . In other words, MECP2 mutation is not necessarily lethal in males.

Neuroimaging: The diagnostic yield of neuroimaging for the evaluation of GDD / MR has a wide variation from 9% to 80%, depending on the practice of newer techniques and additional clinical findings. With high resolution Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI), positive findings can be found in 30-60 % of patients (40). When imaging is done for screening of GDD under 5 years of age, abnormal findings may be found in 13.9 %, but 3 times higher if there are focal neurologic signs or head growth abnormalities (28). CT contributes to the etiologic diagnosis of GDD in approximately 30% of children and MRI will reveal abnormalities in 48.6 to 65.5 % of children with GDD (28). Abnormal neurologic findings, an abnormal head size, unexpected changes in behavior and seizure disorder in addition to GDD/ MR significantly increase the diagnostic yield (26,40). Finding of the congenital brain malformations can help with etiologic diagnosis, prognosis and genetic counseling. The radiological findings of GDD/ MR include cerebral injury (periventricular leukomalacia, ventriculomegaly, hemorrhagic sequels, and congenital infections), cerebral malformations (corpus callosum agenesis, septooptic dysplasia, migrational abnormalities) and cerebral dysgenesis (40). Some minor cerebral dysgenesis that can be found with neuroimaging are cavum septum pellucidum, megacysterna magna and corpus callosum dysgenesis. In one study, cerebral dysgenesis was the most common identified cause of developmental delay (6). Cerebral cortical malformations are a major cause of developmental delay and epilepsy (41,42). Finding cerebral malformations on neuroimaging is not necessarily accompanied by GDD / MR; for example, we reported a case of subcortical band heterotopia associated with corpus callosum agenesis but without GDD (43). Although CT scan remains the study of choice in intracranial calcification and craniosynostosis, MRI allows sensitive assessment of gray and white matter and cerebral posterior fossa contents. Proton MR Spectroscopy (MRS) is a newer technique that is proved to be useful in the diagnosis of some metabolic disorders presenting with GDD / MR (44).

"The diagnostic yield of metabolic studies, electroencephalogram, thyroid function testing and lead screening in children with isolated mild mental retardation (those without abnormalities on examination or diagnostic red flags in the history) is low" (28). Routine metabolic screening tests are not recommended in the evaluation of GDD/ MR because of its low diagnostic yield (45). Routine screening for IEM in children with GDD has a yield of about 1% and when screening is performed, the yield may increase to about 14% (28). There was consensus that such tests should be selective and targeted. Parental consanguinity, affected sibling, congenital ataxia or dysequilibrium, epilepsy, developmental regression, prominent feeding difficulties, organomegaly and coarse facial feature merit metabolic testing including blood gas, serum lactate and ammonia, serum aminoacid, carnitine, homocysteine and very long chain fatty acids and urine organic acids, orotic acid, glycosaminoglycans and oligasaccharides (6).

Phenylketonuria (PKU) is one of the inborn errors of metabolism (IEM) that needs early diagnosis to prevent mental retardation, although even early diagnosis and treatment cannot prevent executive dysfunction (46,47). Biotinidase deficiency is a treatable IEM that may present with GDD without other symptoms or signs. Early diagnosis and treatment of Biotinidase deficiency improves outcome; therefore, in many countries, this disorder is screened routinely in the neonatal period (48). Electroencephalography (EEG) is useful in the evaluation of developmental delay, principally in association with seizure disorder or speech regression suggestive of Landau-Kleffner syndrome (6,17,28,42). An EEG is recommended when a child with GDD/ MR has a history of epilepsy, epileptic syndrome or speech regression (28).

There is evidence that children with developmental delay may have significantly higher blood Lead concentration than normal children (49); therefore, some investigators

recommend Lead level testing as the first line screening tests (50). The North American Recommendations suggest that Lead screening should be targeted for those with risk factors for lead exposure (28). Approximately 10 % of the children with developmental delay and identifiable risk factors for excessive environmental Lead exposure may have an elevated Lead level (28).

McDonald et al also recommend thyroid function tests (TFT) as first line screening tests due to the importance of early treatment and its accompaniment to some chromosomal abnormalities such as Down syndrome and Turner syndrome (50). In the absence of newborn screening, congenital hypothyroidism may be responsible for approximately 4 % of cases of developmental delay (28).

Furthermore, the North American Recommendations suggest TFT only if there are systemic features of hypothyroidism (28).

Calcium assay will assist in the diagnosis and management of conditions like DiGeorge syndrome, Williams's syndrome and pseudohypoparathyroidism (51). Iron deficiency can be associated with developmental delay, and therefore its measurement is recommended (52). Diagnostic yield of investigations in children with developmental delay are shown in Table 2 (28).

Clinical Pitfalls in the diagnosis of mental retardation: Variations of normal development and pseudo-retardation are the main pitfalls in the diagnosis of mental retardation. Variations of normal development and the wide range of its achievement may cause diagnostic errors, if the physician is not familiar with them. For example, Bottom-shufflers are a group of normal children that show delay in weight-bearing and walking and replace crawling. Excessive reliance on gross motor milestones may cause missing of mental retardation diagnosis in children with normal motor milestones. Lack of opportunity and stimulation in a normal child, children with severe medical illnesses, deafness or poor vision, severe physical handicap and infantile autism are main causes of pseudo-retardation.

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Table 2: Diagnostic yield of tests in children with global developmental delay(39)

	Test	Diagnostic yield %
Neuroimaging	MRI	55.3
	CT scan	39
Genetic Studies	Routine cytogenetic studies	3.7
	Subtelomeric deletion	6.6
	Fragile X screen	2.6
	MECP2	Unknown
	Metabolic testing	1
	Thyroid screen (T4, TSH)	4
Without Newborn Screening	Serum Lead level	Unknown
	EEG	1

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