



DEVELOPMENTAL DELAY AND MENTAL RETARDATION IN PATIENTS WITH INHERITED METABOLIC DISORDERS

RAMADEVI.K^{1*} AND P.THIRUMALAIKOLUNDUSUBRAMANIAN²

¹*Institute of Biochemistry, Madras Medical College, Chennai*

²*Department of Internal Medicine, Chennai Medical College and Research Institute, Irungalur, Tiruchi Dist, Tamilnadu.*

ABSTRACT

Developmental delay and Mental retardation commonly refer to decreased intellectual and functional abilities and are associated with a wide spectrum of disorders. Identification of the condition is very important because it has implications regarding treatment (in potentially treatable disorders), prognosis, genetic counseling of families, and implementation of prevention programs.

KEY WORDS: Inherited metabolic disorder, Developmental Delay, Mental retardation,



RAMADEVI.K

Institute of Biochemistry, Madras Medical College, Chennai

INTRODUCTION

Developmental delay (DD) also referred as Developmental disability (DD), is common in pediatric practice and is observed in 5-10% of children¹. On careful evaluation, an Inherited Metabolic Disorder (IMD) can be identified in approximately 1% of patients with DD². The incidence of IMDs and the frequency of individual disorders vary depending on ethnicity. Mental retardation (MR) is a common disorder frequently of unknown origin. Although the terms developmental delay and mental retardation are commonly used to describe decreased intellectual and functional abilities they are not synonymous. The term developmental delay is more associated with motor and neurological functions that are expected to be attained for a corresponding age. Mental retardation is often used to denote decreased cognitive functions and impaired intellectual abilities and may be a consequence of a DD. Hence the two characteristics frequently coexist and overlap in many patients and the two terms are

frequently used interchangeably. The most recent American Association on Mental Retardation (AAMR) definition is that MR is a disability characterised by significant limitations both in intellectual functioning and in adaptive behaviour as expressed in conceptual, social and practical adaptive skills. The disability originates before age 18³. In patients younger than 5 years of age the term Developmental delay is preferred since abnormalities at early developmental stages do not necessarily predict the future condition of MR. Psychometric tests are necessary to establish the diagnosis and severity. MR is accepted if the intelligence quotient (IQ) is lower than 70 and is considered borderline from 70 to 85.⁴ Developmental delay and mental retardation are associated with a wide spectrum of disorders and it is very important that they are accurately identified because it has implications regarding treatment (in potentially treatable disorders), prognosis, genetic counselling of families, and implementation of prevention programs^{5,6}.

Causes of developmental delay

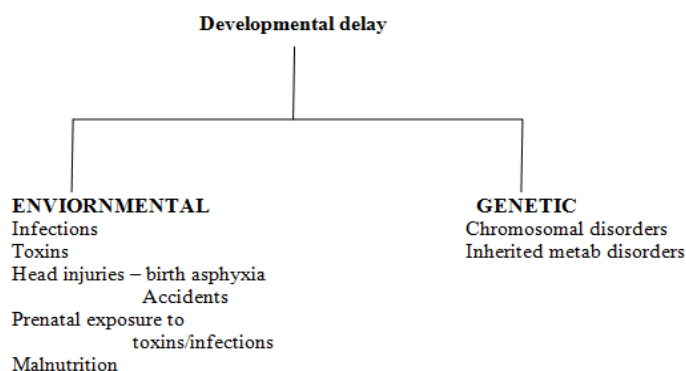


Figure 1
Developmental Delay

Among the genetic causes, Inherited Metabolic Disorders (IMD) remain responsible for only about 1% of MR, which is a very low proportion even compared with other causes, such as cytogenetic and sub-telomeric aberrations and fragile X disease (9.5%, 4.4%, and 5.4%, respectively). Only few inherited metabolic diseases actually cause isolated MR. Additional neurological signs such as regression, ataxia, seizures movement disorders or behavioural problems are commonly found. Van Karnebeek et al have reported that IMDs are responsible for 1- 5 % of unspecific MR.⁷

Conditions during neonatal period that may contribute to DD

- Hypoglycemia
- Hypocalcemia
- Hyperbilirubinemia
- CNS infections
- Respiratory distress syndrome
- Seizure disorders
- Traumatic injuries to the head, spine, hands, feet, or legs

- Degenerative diseases-conditions that affect the nervous system and cause gradual deterioration of it
- Metabolic and genetic disorders

Environmental Factors that May Place a Child at Risk for developmental delay are

- a. Living in families classified as dysfunctional;
- b. Living in families that are at lower socioeconomic levels
- c. Living in families with varied cultural backgrounds;
- d. Being born to teenage mothers or mothers more than forty years old;
- e. Being exposed prenatally to – Thyroid disorders, syphilis, or other viral infections. Viruses, drugs, or alcohol;
- f. Being born into families with other children who have developmental delays;
- g. Being born to mothers who were malnourished during pregnancy;
- h. Being born to mothers who have diabetes.

Genetic basis of brain dysfunction in MR

Two major groups of MR genes have been delineated⁸⁻¹¹:

- those leading to dysfunctional neurodevelopment programmes and brain malformations,
- those that lead to alterations in molecular synaptic organization and plasticity mechanisms.

Some IEMs appear to influence the expression of one or the other group of genes.¹² Metabolic insults will also have direct consequences that differ depending on the period (prenatal, early or late infancy, adolescence) in which the metabolic defect (energy defect, intoxication, storage of abnormal substances) becomes relevant. Defects in energy production (such as oxidative phosphorylation) sometimes lead to a wide spectrum of problems ranging from obvious abnormalities of brain formation to subtle clinical abnormalities. Disorders of

energy availability (such as creatine and glucose transport defects) do not cause brain malformations but mild to moderate MR (sometimes associated with autistic traits in creatine transport defects). Aberrant neurotransmission (glycine, serine, biogenic amine disorders) may produce severe mental and motor disturbances. Excess or unavailability of substrates (urea cycle disorders, organic acidurias) cause different degrees of mental disability depending on the level and duration of exposure to the toxin. In any case, and whatever the neurobiological mechanism, a crucial issue is that mental retardation can be prevented or reversed in some treatable IEMs.¹³

Table 1
IEMs in which mental retardation can be the leading sign

S.No.Disorder	
1	Creatine transporter deficiency
2	MCT8 (monocarboxylate transporter of thyroid hormones) dysfunction, or Allan–Herndon–Dudley syndrome (AHDS)
3	Occipital horn syndrome
4	4-Hydroxybutyric aciduria, or succinic semialdehyde dehydrogenase deficiency
5	L-2-Hydroxyglutaric aciduria
6	Adenylosuccinate lyase deficiency
7	Sanfilippo disease type B and A, or mucopolysaccharidosis type IIIB/A
8	Hartnup disease
9	Urea cycle disorders, late-onset presentations
10	Homocystinuria due to deficient cystathionine betasynthase
11	CDG type Ia
12	Beta-mannosidosis
13	Atypical mild forms of non-ketotic hyperglycinaemia
14	Cerebrotendinous xanthomatosis

Table 2
Laboratory tests in mental retardation focusing on IEMs

Laboratory tests in unspecific mental retardation without dysmorphic features

- Genetic analyses, e.g. high-resolution chromosomes, consider fragile-X syndrome
- Basic laboratory tests (blood glucose, lactate, ammonia, acid–base status, blood counts, liver function tests, creatine kinase levels, uric acid)
- Thyroid function including free T₃
- Consider maternal phenylalanine
- Creatine metabolites (urine creatine transporter deficiency)
- Glycosaminoglycans in urine (by electrophoresis Sanfilippo disease)
- Consider purines and pyrimidines (urine)

Additional laboratory tests in mental retardation with neurological abnormalities

- Consider additional genetic analyses, e.g. Rett syndrome, Angelman syndrome, FISH or microarray analysis
- Urine: Simple tests, organic acids, oligosaccharides, sialic acid
- Plasma/serum: Quantitative amino acids including homocysteine
- Biotinidase activity, if not included in neonatal screening (dried blood spots)
- Consider purines and pyrimidines (urine), glycosylation disorders (CDG)
- Consider thiamine deficiency

Additional laboratory tests in mental retardation with dysmorphic features

- Additional genetic analyses, e.g. microarray analysis
- Maternal phenylalanine
- Sterols, peroxisomal studies (very long-chain fatty acids, phytanic acids, plasmalogens)
- Transferrin isoelectric focusing for glycosylation studies (CDG)

Adapted from: Zschocke J, Hoffmann GF (2004).¹⁴

Diagnostic approach to mental retardation

Establishing an etiological diagnosis is a major challenge as the spectrum of possible causes is enormous and the range of diagnostic investigations is not only extensive but also expensive. The assessment of a person with MR must be multidisciplinary. Taking a good clinical history (including prenatal, birth history, family history with a pedigree of three generations), and performing a detailed clinical examination (including formal testing, neurological and dysmorphological assessments) by specialists trained in neuropaediatrics and clinical genetics as well as testing of hearing and vision remain the basis and must come before any laboratory or neuroimaging studies. In a detailed study undertaken by Sempere et al¹⁵ the urine of 944 patients with unexplained mental retardation was thoroughly investigated. In this study the urine samples for metabolites such as creatinine, creatine, guanidinoacetate, succinylamino-imidazole carboxamide riboside (SAICAr), succinyladenosine (S-Ado), orotic acid, urate, thymine, and uracil besides the screening for PKU, UCD, organic acidurias, MPS and purine/pyrimidine disorders were screened using HPLC, GC-MS and TMS. Following such elaborate studies

they identified that 0.8% of the cohort had an IEM-three with cerebral Cr deficiency syndromes (CCDS)], one with adenylosuccinate lyase (ADSL) deficiency, and three, with phenylketonuria (PKU).¹⁵ The availability and use of these sophisticated diagnostic facilities enabled the investigators to arrive at a confirmed diagnosis. Similarly D.J.Michelson et al have reported in a systematic review that genetic and metabolic screening tests are helpful in choosing the appropriate management of such children.¹⁶ Hence the most important principle is a rational and sequential evaluation. The treatable disorders should be considered first in the differential diagnoses. The key elements include the medical, family and developmental histories, clinical and neurological examinations, as well as appropriate use of laboratory and imaging tests.¹⁷ Guidelines and standard operating procedures for the evaluation of mental retardation should be developed and made available to all physicians treating these patients.

Declaration

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