Diagnostic Approach to a Child with Mental Retardation

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Mental retardation (MR) is diagnosed when an individual demonstrates significantly subaverage general intellectual function. Even though concurrent deficits in adaptive behavior are also required for this diagnosis as adopted by the American Association on Mental Retardation, less attention is paid to this aspect in practice and in many studies on the prevalence and etiology of MR(1,2). In a young child a developmental quotient (DQ) replaces the intelligence quotient (IQ) measurable by standardized tests while in newborns and young infants MR may be predictable on the basis of gross neurological malfunction. The diagnosis of MR has tremendous, lifelong impact on a child and his family and therefore great care must be exercised in making this diagnosis. The limitations of the methods available for assessment of intellectual function and their applicability across a wide range of socio-cultural, ethnic and geographically distinct groups are beyond the scope of this review. The focus of this paper will be the clinical and laboratory evaluation of a child already diagnosed with or considered to be at risk for MR.

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Prevalence and Classification and Mental Retardation

Genetic as well as environmental factors contribute to the development of human intellectual potential. Therefore, it follows that abnormalities of the same can impair intellectual development and cause MR. Mental retardation can result from a variety of genetic, developmental, infectious, teratogenic, perinatal and postnatal traumatic insults to the brain. *Table I* shows an orderly grouping of the major causes of MR. A child in Group B or C rarely needs a diagnostic work-up other than careful documentation of the event(s) that led to the brain damage. The pediatrician himself may have first hand knowledge of these events. In the majority of children in whom the cause of MR is not that obvious, the major challenge is to maximize the probability of placing the child in Group A rather than Group D without resorting to unnecessary diagnostic studies.

The prevalence of MR varies in different populations of children depending on the age, sex and the method of ascertainment. The highest prevalence rates are found in school age children reflecting the

TABLE I—*Classification of the Causes and Conditions Associated with Mental Retardation*

A. Prenatal onset
   1. Intrinsic to the fetus (developmental or morphogenetic)
      (*a*) Chromosomal abnormalities
      (*b*) Single gene syndromes
      (*c*) Unknown genesis syndromes
      (*d*) Multifactorial syndromes and assocaitions
   2. Extrinsic to the fetus (teratogenic)
      (*a*) Infections (syphilis, TORCH-infections)
      (*b*) Exposure to alochol, drugs, lead
      (*c*) Maternal PKU.

B. Perinatal
   1. Prematurity (poor nutrition, toxemia of pregnancy, multiple gestation *etc.*)
   2. Traumatic delivery
   3. Hypoxia

C. Postnatal
   1. Infections (meningitis, encephalitis)
   2. Trauma to the brain
   3. Lead poisoning
   4. Seizures

D. Unknown

fact that greatest demands on intellectual and adaptive behavior are placed on children in this age group. Males are found more frequently than females in many studies of mental retardation. Various explanations, biological as well as social, have been offered for this male excess which is most notable in the mildly retarded group(3-5). Mutations of X chromosomal genes that have greater detrimental impact on males may be responsible for a portion of this male excess(6). The prevalence of mental retardation and the incidence of specific causes of mental retardation may vary with time in the same geographic location because of changing socio-economic conditions or health care practices

Mental retardation may be classified into the physiologic or culturofamilial and the organic groups. The mildly retarded patients tend to be in the former group whereas those in the organic group generally have moderate, severe or profound MR and a demonstrable morphologic or metabolic abnormality. Mild MR is physiologic to the extent that the children who have it are in the tail end of the bell-shaped curve that represents the distribution of IQ scores in the general population. Parental IQ, home

and educational environment and other unknown psychosocial factors contribute to a significant proportion of mild MR(7). A child's cognitive development may also be impaired by discrete but difficult to detect noxious influences such as subclinical lead intoxication, fetal alcohol effects without stigmata of the fetal alcohol syndrome and child abuse or neglect. Genetic studies have documented recurrence of MR in families consistent with a polygenic inheritance pattern(8-10).

The subclassification of MR by degree of severity, *i.e.,* mild, moderate, severe and profound, is useful for rehabilitative management, prognostication and research into the causes of mental retardation. However, it has little impact on the diagnostic approach to the mentally retarded child proposed here. *Table II* lists several recent epidemiological surveys of the prevalence and etiology of MR in a wide range of populations. Only two groups are defined, severe (IQ less than 50) and mild (IQ between 50 and 70). A specific etiology for MR is established in 58 to 71%(11-15) of the severely retarded group versus 37 to 55%(3,12,16) of those that are mildly retarded. Even though more of the mildly retarded patients in these surveys have unknown causes for their condition relative to the severely retarded ones, it should be pointed out that some of these studies did not look at the relatively common and more recently recognized causes of mental retardation such as the Fragile X syndrome(17) and fetal alcohol effects(18). Finally, it is also important to recognize that the variability inherent in most of the syndromes or conditions that cause MR makes it difficult to exclude etiologic diagnoses solely on the basis of severity of MR. For example it is well known that the IQ score of a child with the Down syndrome may vary from the profoundly retarded to the normal range.

The diagnostic approach to a child with MR referred for evaluation of possible etiology must have a clearly defined purpose that meets the expectations of the family. Epidemiologic studies or research protocols that examine the cause of MR in a population may or may not meet those needs or lead to a diagnostic overkill. The parents must also be counselled as to the realistic goals of the investigations planned and the major benefits to be derived from a specific diagnosis before committing them to a large investment of time, effort and money. It must also be remembered that symptomatic treatment and rehabilitative therapies can usually proceed without a specific etiologic diagnosis. With these caveats the following scheme is presented for the evaluation of a child with mental retardation *(Fig. 1).* It relies heavily on the use of readily learned clinical skills and judicious use of laboratory tests in agreement with several investigators who believe that laboratory tests generally confirm a diagnosis rather than suggest a clinically unsuspected one(15,19,20). The evaluation is heavily biased towards the Recognition of a biomedical cause for the mental retardation consistent with the expected role of the clinician in a team approach to the management of an extremely complex issue that requires the expertise of a variety of specialists.

Medical and Family history

A look at *Table I* reveals that a meticulously documented history of a mentally retarded child's prenatal course dating from the time of conception offers a number of clues to the etiology of retardation. The factors that have a direct bearing on the etiology of MR include maternal ingestion

TABLE II–*Etiology and Mental Retardation

Study	Subject population (n)	Prenatal				Perinatal			Postnatal		
		Chromosomal	Single gene	Multifactorial	Environmental	Infections or other	Hypoxia	Prematurity or low birthweight	Trauma or neglect	Disease or other	Unknown
Severe (IQ <50)											
McQueen *et al.*, 1986 (Maritime Provinces)	7-10 year olds; (n=296)**	24.5	4.5	16.8	11.2	3.5	6.6	-	-	3.6	29
Einfeld, 1984 (Sudney, Australia)	0-21 year olds; (n=3, 208)	23.5		22.4	←	8.5	→	3.4	11	2.8	24.4
Willard *et al.*, 1982 (France)	3-17 year olds; institutionalized (n=124)	21	3.2	10	5.6		25		0.8		33
Elwood & Darragh, 1982 Northern Ireland	Born 1955-1976; (n=1,777)	38	5		1	2.5	3.7	5.1	0.6	2.8	40
Hunter, *et al.*, 1980 (Manitoba)	20 year olds; institutionalized before 1977; (n=406.)	13.5	12.6	1.7	4.9	5.6	4.2	3.2	3.7	8.8	41.9

Mild

Einfeld, 1984 (Sudney, Australia)	0-20 year olds; IQ=52-67 (n=344)	7.8		16.6	←	3.9	→	4.3	14.7	3.4	49
Hagberg *et al.*, 1981 (Gothenburg, Sweden)	Born 1966-1970; IQ=50-70 (n=91)	4.3	1	11	8.8	1	18.6	←	2	→	62.6
Blomquist *et al.*, 1981 (northern Sweden)	Born 1959-1970; IQ=50-69 (n=171)	7.6	8.2	23.4	8.2	1.2	5.3	0.6	2.3	2.3	45

*Modified from McLauren and Bryson (1987); numbers in columns represent percentage of population studied.
** IQ <55

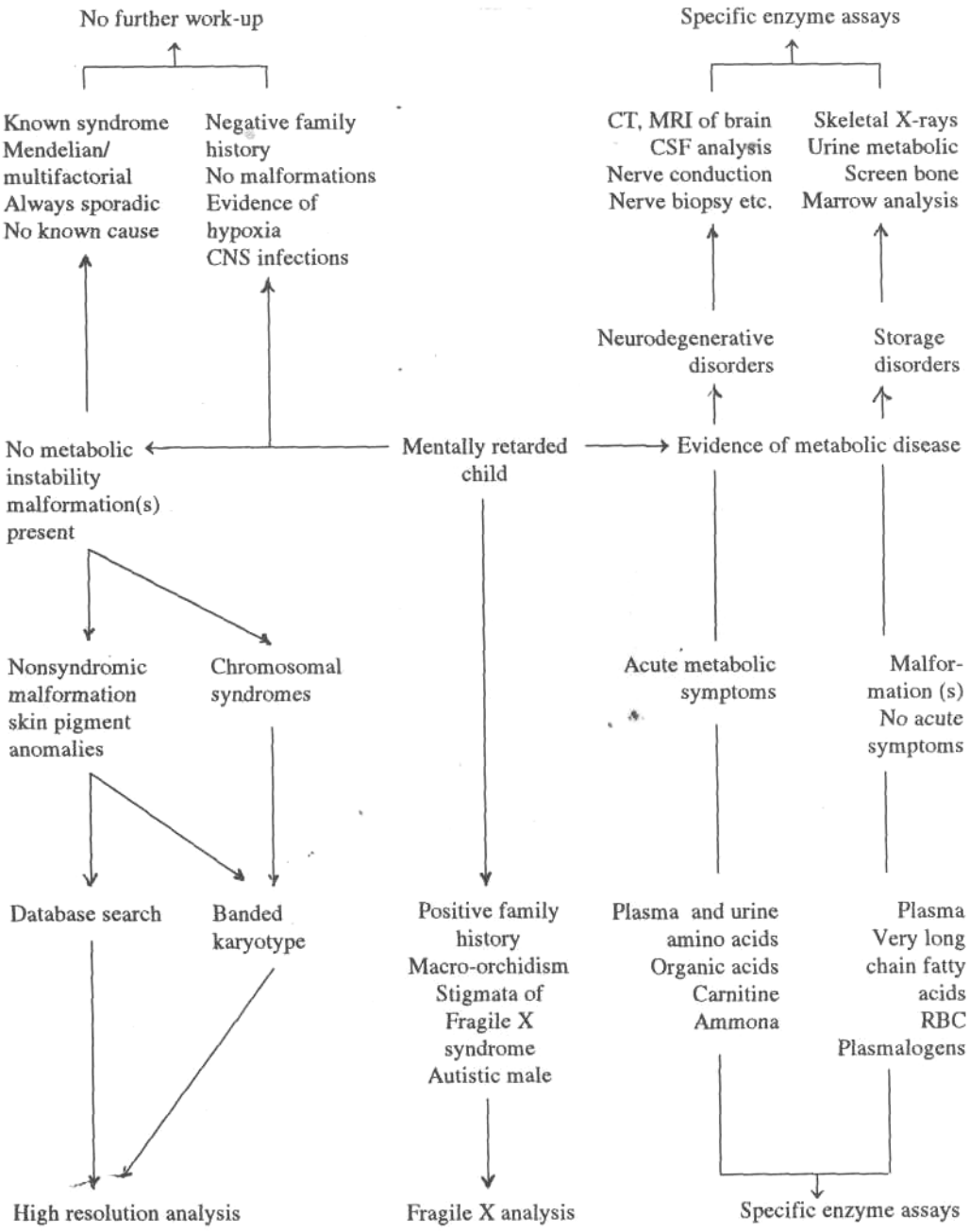

Fig. 1. A schematic representation of the diagnostic approach to the mentally retarded child (see text for details)

of alcohol or other teratogenic substances during pregnancy, maternal and fetal infections, premature or traumatic birth and low Apgar scores with poor response to resuscitative efforts. A number of nonspecific symptoms are reported more often by mothers of retarded children as compared to those who delivered only healthy infants. Signs and symptoms such as excessive nausea, periodic vaginal bleeding or spotting in the early months of gestation, poor weight gain, decreased fetal movement, oligohydramnios and polyhydramnios suggest but do not establish a prenatal onset of the process that led to MR. Premature onset of labor, prolonged labor and birth trauma indicate a perinatal or nongenetic environmental contribution to MR. Not too infrequently, multiple pathogenetic events, genetic as well as environmental, multiple pathogenetic events, genetic as well as environmental, contribute to brain damage and retardation in the same individual. Diseases such as myotonic dystrophy and Ehlers-Danlos syndrome in the mother may increase the risk of premature birth which may increase the risk of MR in her child. Another example is poorly controlled maternal diabetes mellitus which increases the risk of fetal neural tube closure defects, premature birth and neonatal hypoglycemia in their offspring which in turn may cause brain damage.

Family history of retardation, congenital malformation, neonatal death, stillbirths or other reproductive mishaps suggest chromosomal or dysmorphogenetic etiology for MR in a child whereas consanguinity between the parents of a retarded child points to a recessively inherited metabolic defect. The mildly retarded or even intellectually normal mother of a microcephalic mentally retarded child may have previously unrecognized phenylketonuria (PKU). Although rare, maternal PKU syndrome should be considered in a mentally retarded child when there are no healthy siblings and when the mother is retarded. The high risk of recurrence of mental retardation and the ease with which the diagnosis can be made justifies consideration of maternal PKU syndrome in such families.

The natural history of the disease associated with MR is another important historical clue. For example, a static course is more likely to be due to developmental defects, teratogenic or traumatic insults to the brain whereas a progressive loss of function, beginning after a period of normal development clearly indicates a neurodegenerative or storage disorder. Lysosomal enzyme deficiency states, peroxisomal disorders and mitochondrial fatty acid beta oxidation defects may present a bewildering variety of static, progressive or intermittent signs and symptoms(21). Physical examination with careful attention to details can often sort these from one another.

Physical Examination

Physical examination of the patient and his parents and siblings when needed, offers by far the most important clues to the diagnosis of syndromes of prenatal onset associated with MR. Many well established malformation syndromes such as the Williams syndrome or the Rubinstein-Taybi syndrome can be diagnosed solely on the basis of physical examination of the patient. Similarly, hypomelanotic macules, cafe-au-lait spots, port-wine stain over the face, skull or the eye, and linear sebaceous nevi point to neurocutaneous syndromes. Often one may recognize external clues to developmental anomalies of the brain. The link between hypotelorism, midline facial defects and the holoprosencephaly malformation sequence

provides such an example. It should be remembered, however, that malformations are not causally specific, *i.e.,* they may result from multiple pathogenetic mechanisms. Thus, holoprosencephaly may be associated with chromosomal imbalance (trisomy 13, deletion 18q *etc.),* single gene mutations or teratogenic insults (maternal diabetes mellitus). The autosomal dominant holoprosencephaly syndrome may have a widely variable phenotype the minimal expression of which may be a single central upper incisor(22). Therefore, the examination of the parents and other relatives of a malformed patient should not be ignored in the search for a cause for the mental retardation.

The Art and Science of Syndrome Identification

New syndromes and nonrandom associations of malformations, signs and symptoms are being identified and described with increasing frequency in mentally retarded children. Some of these new syndromes are seen only in a small number of families and reported in specialty journals that do not have wide circulation. Several clever strategies have been devised to assist the clinician who may feel somewhat overwhelmed by the explosion of new knowledge in syndromology. Text books such as "Smith's Recognizable Patterns of Human Malformation" by Jones(23) provide sign or symptom-based differential diagnoses of syndromes while other exhaustive reference texts(24) and encyclopedias(25) and catalogues^) provide ready reference material to assist diagnosis. Computerized data bases that provide both text and figures such as the London Dysmorphology Data Base, Online Mendelian Inheritance in Man and POSSOM are other resources that are currently coming into vogue. However, a motivated clinician remains the key to the successful application of any of these diagnostic aids. The recognition of the crucial sign or symptom must inevitably be the first step before any search for a syndrome diagnosis can begin. Many text books provide useful guidance to teach oneself the art of recognizing dysmorphic features in a patient(23,27).

Ancillary Studies

Roentgenographic examination of the skeleton and soft tissues is a simple, inexpensive and readily available tool for the diagnosis of a number of conditions associated with mental retardation(28). The intracranial calcification seen in fetal toxoplasmosis, tuberous slcerosis and Sturge-Weber syndrome, the dysostosis multiplex of the mucopolysaccharidoses are examples in which radiographs offer quick and useful diagnostic assistance.

Other imaging studies such as ultrasonography and computed tomography of the head or of other internal organs are of crucial importance in the diagnosis of mental retardation associated with developmental defects and/or progressive degeneration of the brain. These studies, while safer than the invasive methods such as pneumoencephalography, are expensive and not readily available. Their judicious use may be reserved for those patients in whom simpler methods have failed to yield an answer or in those who have a high potential to benefit from therapeutic intervention. Mentally retarded patients with recent onset of focal seizures or raised intracranial tension, infants with hypsarrhythmic EEG or hypomelanotic cutaneous macules suspected to be due to tuberous sclerosis are examples of patients who would clearly benefit from such studies.

It is standard practice to perform *chromosomal studies* on patients who are mentally retarded as well as malformed. The old rules of thumb that restricted such analysis to patients with one major and three or more minors malformation or two major malformations, *etc.* may be too rigid. The ability to detect small structural chromosomal anomalies with modern high resolution banding techniques, the great variability of phenotypic features associated with these subtle abnormalities which makes it impossible to exclude them on clinical basis are reasons for more liberal use of chromosome analysis in the evaluation of mental retardation. The laborious and time consuming high resolution analysis, however, should not be requested as an initial screening test. Such a study focussed on the analysis of a specific chromosome region is justifiable in those patients in whom a clinically suspected microdeletion syndrome needs cytogenetic confirmation *(Table III)*. In patients with the Down syndrome or other trisomies chromosome analysis is required to detect translocations even though it is not needed for the diagnosis of the syndrome itself. It has also been observed recently that streaky pigmentary anomalies along the lines of Blaschko serve as a marker for chromosomal mosaicism(29).

A very important recent discovery in mental retardation research is the development of reliable laboratory methods for the diagnosis of the fragile X syndrome(30). This syndrome which is believed to be the most common currently known cause of

TABLE III — *Indications for Chromosome Analysis in Mentally Retarded Children*

1. Routine banded karyotype analysis
   - Down syndrome, other trisomies or chromosomal syndromes
   - One or more congenital malformation or dysmorphic features
   - Pigmentary anomalies of the skin following lines of Blaschko
2. Fragile X analysis
   - Mental retardation, macro-orchidism, or other stigmata associated with the Fragile X syndrome.
   - Familial mental retardation consistent with X-linked inheritance including males and/or females
   - Infantile autism
3. High resolution or focussed analysis

Syndrome	*Known microdeletion site*
Prader-Willi syndrome	Paternally derived 15q11-13
Angelman syndrome	Maternally derived 15q11-13
Miller-Dieker syndrome	17p13
DiGeorge syndrome	22q11
WAGR syndrome	11p13

heritable mental retardation is associated with an unstained, constricted site at a fixed location on the long arm of the X chromosome (fragile site Xq27.3). The demonstration of this site requires special laboratory procedures. Since the demonstration of the fragile site at Xq27.3 is essential for the diagnosis of the fragile X syndrome, the clinician should not only be aware of its varying and subtle manifestations but also alert- the laboratory of his specific suspicion. The fragile X syndrome has been thoroughly reviewed for the clinician recently(31).

Metabolic screening studies are useful in those mentally retarded patients in whom the history and physical examination have provided the appropriate clues to the possibility of an inborn error of metabolism (IEM). Routine use of metabolic screening studies to detect aminoaciduria, mucopolysaccharidurias, phenylketonuria and homocystinuria are controversial because of their low yield. Prominent among the clues that might prompt one to ask for a battery of urine metabolic screening tests are a history of neonatal onset of seizures, hypotonia, poor suck, recurrent episodes of vomiting, lethargy or coma, or the detection of cataracts, hepatomegaly, cardiomegaly, hypotonia, or muscle weakness. Laboratory studies showing hypoglycemia, ketosis, acidosis or hyperammonemia are other common starting points. Major congenital malformations are conspicuously absent among this group of disorders with rare exceptions such as the cerebro-hepato-renal syndrome of Zellweger. Even though individually rare these disorders in aggregate are not too uncommon. Some IEMs such as PKU, biotinidase deficiency or medium chain fatty acid acyl co-A dehydrogenase (MCAD) deficiency are treatable(32). Furthermore, all IEMs have a genetic basis and a high risk of recurrence. Therefore, their recognition is of great value to the family.

DNA studies are of limited use at this time in the diagnosis of MR. However, the *molecular bases* are being defined of a rapidly increasing number of genetic diseases with or without MR. Prenatal or presymptomatic diagnosis and heterozygote detection are possible now for several diseases such as ornithine transcarbamylase deficiency, Duchenne muscular dystrophy, neurofibromatosis and the fragile X syndrome. Advances in molecular genetics will soon make it possible not only to diagnose diseases at the level of the gene but also to find novel pathogenetic mechanisms and treatment for established syndromes and diseases. An example may be offered of cytogenetically normal patients with Prader-Willi and Angelman syndromes in whom DNA studies have 'Shown uniparental disomy of maternal or paternal origin, respectively(33-35). These syndromes are the first examples of genomic imprinting disorders in humans(36). Currently, DNA diagnosis is based on the use of restriction fragment length polymorphism (RFLP) based linkage analysis or direct analysis of gene deletions and mutations on DNA amplified by the polymerase chain reaction(37).

Conclusions

In summary, a great many diagnoses come to mind when a clinician encounters a mentally retarded child. It is possible with some effort to sort out the genetic from the nongenetic and the treatable from the untreatable causes of mental retardation. Even though mental retardation itself may not be curable much can be offered to the child and his family by a compassionate and knowledgeable physician. Similarly, the prevention of the recurrence of heritable

causes of mental retardation, while not expected to have a great impact on the prevalence of the handicap anytime soon, is of immeasurable value to the individual family.

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