Approach to Mental Retardation and Developmental Delay

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Objectives

- Definition of MR and DD
- Classification
- Epidemiology (prevalence, recurrence risk, …)
- Etiology
- Importance of diagnosis
Higher Cerebral Development Dysfunction

• Mental retardation

• Cerebral palsy
  – Abnormal motor actions and postural mechanisms
  – Non-progressive abnormalities of the developing brain
  – limited, stereotypic, and uncoordinated voluntary movements

• Autism
  – A behaviorally defined syndrome characterized by
    • Atypical social interaction
    • Disordered verbal and nonverbal communication
    • Restricted areas of interest
    • Limited imaginative play
    • A need for sameness
Mental retardation

Mental retardation is a serious and lifelong disability that places heavy demands on society and the health system.
mental retardation is not something you have, like blue eyes or a bad heart, nor is it something you are, like short or thin. It is not a medical disorder or a mental disorder… mental retardation reflects the “fit” between the capabilities of individuals and the structure and expectations of their environment. “
Definition

MR is accepted as having three components:

1) Significantly abnormal intellectual performance, generally determined by a test of intelligence
2) Onset during development before the age of 18
3) Impairment of the ability to adapt to the environment
Global developmental delay

- Reserved for children five years of age or younger
Global developmental delay (DD) describes significant delay in two or more of the following areas:

- Cognition
- Speech/language
- Gross/fine motor skills
- Social/personal skills
- Daily living
Prevalence

• Prevalence: 1% - 3%

• Mild MR occurring 7-10 times more frequently than moderate or severe MR.
  – Mild MR: 29.8/1000
  – Mod-severe MR: 3.8/1000

• In Iranian population: 1.8 – 2.7%
Why diagnosis?

- Estimating the recurrence risk in future pregnancies
- Prenatal diagnosis
- Minimizing the number of diagnostic procedures
- Short-term and long-term prognosis
- Treatment options
Recurrence risk

• Variable depending on the etiology

• From very low (the same as normal population) to 50% and even in rare situations to 75-100%

• Irrespective of etiology, empiric risk: 8.4%
### Recurrence Risks for Severe MR

<table>
<thead>
<tr>
<th>Study</th>
<th>Brothers</th>
<th>Sisters</th>
<th>All Sibs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male index case</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herbst and Baird (1982)</td>
<td>1 in 12</td>
<td>1 in 33</td>
<td>1 in 18</td>
</tr>
<tr>
<td>Bundey et al. (1985)</td>
<td>1 in 10</td>
<td>1 in 20</td>
<td>1 in 13</td>
</tr>
<tr>
<td><strong>Female index case</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herbst and Baird (1982)</td>
<td>1 in 22</td>
<td>1 in 17</td>
<td>1 in 19</td>
</tr>
</tbody>
</table>
**Classification**

- **Severity:**
  - **Mild**  
    - (IQ : 50-70)
  - **Moderate**  
    - (IQ : 35-50)
  - **Severe**  
    - (IQ : 20-35)
  - **Profound**  
    - (IQ < 20)
Classification

Pedigree analysis:

- Sporadic
- Familial
Etiology

Genetic

Non-genetic

- Prenatal and perinatal events
- Infections
- Environmental factors
Genetic causes

• Cytogenetically visible abnormalities
• Fragile-X syndrome
• Submicroscopic chromosomal abnormalities
• Single gene disorders
Objectives

• Contribution of different genetic disorders to MR/DD
• Cytogenetically visible abnormalities
• Fragile-X syndrome
• X-liked MR/DD
• Subtelomeric rearrangements
• Copy number variation of other genomic regions
• Inborn errors of metabolism: 1% of MR/DD patients
• De novo dominant mutations
• Autosomal recessive MR/DD
Genetic causes of sporadic MR

- Microscopic aberrations
- Submicroscopic aberrations
- Fragile-X syndrome
- X-linked MR
- Inborn errors of metabolism
- De novo dominant mutations

55%
Cytogenetically visible abnormalities

- Prevalence among MR/DD patients: 9%

- Aneuploidies
  - Trisomy (Down syndrome)
  - Monosomy

- Structural abnormalities
  - Deletions
  - Duplications
Cytogenetically visible abnormalities

- Often associated with
  - Dysmorphism
  - Multiple congenital anomalies
  - Prenatal onset
- IUGR
- Abnormal ultrasound findings
Fragile-X syndrome

- The most common cause of inherited MR/DD
- Prevalence: 1/4000 (males)
- Prevalence among MR/DD patients: 3-5%
- Both males and females are affected
Fragile-X syndrome

- Major clinical features
  - Speech delay
  - Dysmorphic features
    - Long face
    - Large ears
    - Macrocephaly
  - Psychologic disorders
    - Autism
    - Behavioral disorders
  - Macro-orchidism
Submicroscopic chromosomal abnormalities

- Subtelomeric rearrangements
- Common microdeletion/duplication syndromes
- Copy number variation of other genomic regions
Submicroscopic Cromosomal Abnormalities

Subtelomeric Rearrangements
0.5-15% •
Unselected patients: 5% •

Common Microdeletion and Microduplication (CMMSs) Syndromes
5.8-9.5% •

Genomic Copy Number Variations (CNVs)
10-17% •
Subtelomeric rearrangements

• Prevalence among MR/DD patients:
  – 0.5-15%
  – Unselected patients: 5%

• Major clinical features
  – Prenatal onset growth retardation
  – Multiple congenital anomalies
  – Dysmorphism
  – Moderate to severe MR
Common microdeletion/duplication syndromes (CMMSs)

• Prevalence among MR/DD patients: 5.8-9.5%
• CMMSs: 50% of total interstitial Microdeletion and Microduplication syndromes
• Overlapping clinical features
Microdeletion syndromes

- DiGeorge syndrome
- Williams-Beuren syndrome
- Prader-Willi syndrome
- Angelman syndrome
- Miller-Dieker syndrome
- Smith-Magenis syndrome
- Wolf-Hirschhorn syndrome
- Cri du Chat syndrome
- Langer-Giedion syndrome
- DiGeorge Syndrome 2

OVERALL – occurs 1/1600 deliveries
Genomic copy number variations

• Prevalence among MR/DD patients: 10-17%
Single gene disorders

- Inborn errors of metabolism: 1% of MR/DD patients
- X-liked MR/DD: 9-10%
- De novo dominant mutations
  - Recently proposed
  - Estimated prevalence: 50-60%
- Autosomal recessive MR/DD
  - Mostly in familial MR/DD
Autosomal dominant single gene disorders

• 2009-2011, Hamdan et al.
  – Investigation of 197 synaptic genes (glutamate receptor, …) in 95 patients: 11 new mutations found

  – Exome sequencing of 10 patients with sporadic MR: 6 pathogenic mutations found (60%)
  – More than all of the previous investigations

*New paradigm of de novo dominant mutations in MR*
Familial MR/DD
Genetic causes of familial MR/DD

- Low contribution of chromosomal abnormalities
- Single gene disorders:
  - Fragile X syndrome
  - Other X-linked disorders
  - Autosomal recessive MR/DD
  - Autosomal dominant MR/DD
Diagnostic Methods

- Karyotype
- Assessment of fragile-X syndrome
- FISH
- MLPA
- Array-based techniques
  - Array-CGH
  - SNP Array
- Exome sequencing
- Next-generation sequencing
Third Session
Diagnostic Techniques
Objectives

• Advantages and disadvantages of different diagnostic techniques
  – Karyotype
  – PCR screening of Fragile-X syndrome
  – FISH
  – MLPA
  – Array based techniques
  – Next generation sequencing
  – Exome sequencing
Karyotype

- The first technique for studying chromosomal abnormalities
- **Diagnostic yield:** 9%

**Advantages:**
- Genomic
- Detection of balanced abnormalities

**Disadvantages:**
- Low resolution (3-5 Mb)
- Labor intensive
Fragile-X syndrome

- Cytogenetic studies:
  - Replaced by molecular studies

- PCR screening:
  - Determining CGG repeat expansion of FMR1 gene

- Triplet-primed PCR:
  - Determining pre-mutations and full mutations

- Diagnostic yield: 3-5%
Diagnostic techniques of subtelomeric aberrations

- FISH
  - Costly
  - Labor intensive
- MLPA
- Array-CGH
  - costly
FISH

- The first molecular cytogenetic technique

- Advantages:
  - Higher resolution

- Disadvantages:
  - Limited targets

♫ You must know what you are looking for
MLPA

1. Denaturation and Hybridization
   - PCR primer sequence X
   - Hybridization sequence (left)
   - PCR primer sequence Y
   - Hybridization sequence (right)
   - Stuffer sequence

2. Ligation
   - Arrow indicating ligation

3. PCR with universal primers X and Y
   - Exponential amplification of ligated probes only
   - Diagram showing amplification

4. Fragment analysis
   - Chart showing fragment analysis results
Diagnostic techniques of CMMSs

• In the past:
  – “Phenotype -first approach”
  – One genetic test (FISH) for one syndrome
  – Screening was not feasible

• At present:
  – “Genotype -first approach”
  – One genetic test for all of the known and even unknown syndromes
  • MLPA
  • Array-based techniques
  – Screening rather than targeted diagnosis
Other genomic CNVs

- Prevalence: 10-17%
- Diagnosis: array-based techniques

First tier test for:
- Developmental delay/intellectual disability (DD/ID)
- Multiple congenital anomalies (MCA)
- Autistic spectrum disorder (ASD)
Platforms

• Selected probes:
  – Targeted CMA
  – Whole genome CMA

• Resolution:
  – BAC array (probe size: 75-150 Kb)
  – Oligonucleotide array: (50-60 bp)
    • SNP array
    • Non-SNP array
Oligonucleotide array
SNP arrays

- SNP ARRAYS
- A Single nucleotide polymorphism is a DNA sequence variation occurring when a single nucleotide in the genome differs between members of a species (or between paired chromosomes in an individual).
SNP array

- Advantages:
  - Very high resolution (>1000000 probes)
  - Detection of LOH
Next-generation sequencing

Exome sequencing

- Promising technique in detecting novel genetic changes (CNVs, single gene disorders)
- Technique of choice in near future
Objectives

• Different steps of any proposed diagnostic approach
• Limitations of each diagnostic approach
• How to select an appropriate diagnostic approach
Diagnostic approach to sporadic MR

• Guidelines based on the assessment of
  1. Chromosomal abnormalities
     • Microscopic
     • Submicroscopic
  2. Fragile-X syndrome
Diagnostic approach to sporadic MR

1. Karyotype
2. Assessment of Fragile-X syndrome
3. Assessment of DNA copy number differences (Array-CGH, MLPA, ...
Stepwise approach to sporadic MR

• Guidelines based on the assessment of
  1. Chromosomal abnormalities
     • Microscopic
     • Submicroscopic

2. Fragile-X syndrome

- Karyotype
- Assessment of Fragile-X syndrome
- Assessment of subtelomeric rearrangements (MLPA)
- Assessment of CMMSs (MLPA)
- Array-CGH
- SNP Array
Karyotype

Numerical or Structural Chromosomal Abnormality

Assessment of Fragile-X syndrome

Fragile-X syndrome

No CGG repeat expansion

Availability of array-based techniques + cost

Available

array-CGH or SNP array

Pathogenic Copy Number Variation

No pathogenic change

Exome Sequencing (de novo dominant mutations)

Not Available

MLPA (Subtelomeric Rearrangements)

Subtelomeric Aberration CMMSs

No pathogenic change
Diagnostic approach to familial MR/DD
Low contribution of chromosomal abnormalities to “Familial” MR

High contribution of single gene disorders
Familial MR/DD

- An extremely heterogenous disorder
- More than 10000 genes involved
- New genomic approach
  - Exome sequencing
Diagnostic approach

- Pedigree analysis
- The presence of dysmorphism and/or multiple congenital anomalies
Diagnostic approach

- Familial MR/DD with dysmorphism and/or MCA:
  - The same as sporadic MR/DD

- Familial MR/DD without dysmorphism and/or MCA:
  - Focusing on single gene disorders

Fafati 
5/30/13
65
Pedigree Analysis

Autosomal Recessive
- Assessment of Known
  - Mutation Detected
    - Exome Sequencing
      - Next-generation Sequencing
  - No Mutation Detected

X-linked
- Assessment of Fragile-X
  - No CGG repeat expansion
    - Mutation Detected
      - Exome Sequencing
        - Next-generation Sequencing
  - No Mutation Detected

Autosomal Dominant
- Dysmorphisms
  - Yes
    - Karyotype
      - Numerical or Structural Abnormalities
        - Available
          - array-CGH or SNP array
  - No
    - Exome Sequencing
      - No pathogenic change
      - Exome Sequencing
        (de novo dominant mutations)

Unknown
- Assessment of Fragile-X
  - No CGG repeat expansion

Fragile-X Syndrome
- Assessment of Known
  - No Mutation Detected

Fragile-X Syndrome
- Assessment of Known
  - No Mutation Detected

Fragile-X Syndrome
- Assessment of Known
  - No Mutation Detected

Exome Sequencing

MLPA (Subtelomeric Rearrangements + CMMSs)
- No pathogenic change

Array-CGH
- Numerical or Structural Abnormalities
  - Available
    - array-CGH or SNP array
  - Not Available
  - MLPA (Subtelomeric Rearrangements + CMMSs)
    - No pathogenic change
Conclusion

Genetic Counseling Issues
با تشکر از توجه شما