WHEN CHROMOSOMES GO ASTRAY

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• 8 yrs male child/1st live born of non consanguinous marriage was referred to us with CHD & behavioural disorder

• H/O spontaneous abortion at 3 months in earlier pregnancy

• Conception at 35 yrs (10 yrs post marriage)

• Uneventful antenatal period

• H/O recurrent RTI from 1 month of age - evaluated and found to have CHD (large ASD)

• Dysmorphic facies (+)

• Behavioural abnormalities (+)

• No H/O seizures
• DEVELOPMENT HISTORY:
  – Social milestone delayed
  – Language - incomprehensible speech

• Partial eye contact
• Aggressive behaviour
• Hyperactivity (+)
• Impulsivity (+)
• Preoccupied behaviour
• PHYSICAL EXAMINATION:
  • Dysmorphic features
    – Bulbous nose
    – Large ears
    – Maloccluded teeth
    – Micrognathia
    – Small forehead
    – Epicanthal folds
SYSTEMIC EXAMINATION

• CVS:
  – S2 split (+) wide & fixed
  – MSM Gr 3/6 (+) in PA

• RS & P/A:
  – Normal

• CNS:
  – No cranial nr palsy
  – Vision & Hearing - N
  – Sleep disturbances (+)
  – Tone, power, reflexes - N
  – Bowel bladder - N
• **ROUTINE:**
  - Hematological inv - normal
  - Thyroid profile - normal

• **ECG:**
  - Incomplete RBBB

• **ECHO:**
  - Large ASD OS type 18-20 mm L→R shunt
  - Dilated RA/RV/PA

• **USG - abdomen:**
  - Normal study

• **MRI BRAIN:**
  - Normal study
• Psychiatrist opinion:
  - IQ - 64%
  - ADHD
  - Autistic disorder

Treatment given:
• Surgery for ASD
• Started on atomoxetine, clobazem
• Routine follow up
COMPLETE DIAGNOSIS

-- KEY WORDS:

- NET SEARCH
- DYSMORPHISM
- Autism
- ADHD
- CHD
- INTELLECTUAL IMPAIRMENT

CHROMOSOMAL ANOMALY
CHROMOSOMAL ANALYSIS:

- Referred to geneticist in Kolkata for further evaluation

- **MICRODELETION CHROMOSOME 1q21.1 REGION CONFIRMED BY FISH TECHNOLOGY**
DISCUSSION
• Chromosome 1 – largest chromosome
• Represents 8% of total DNA with approx 4316 genes
• 1q - long arm of chromosome 1
• 1q 21.1 → complex structure
• Only 25% of the structure is not duplicated
• Several gaps – 700 Kb
• **DELETION:**
  - A missing piece of DNA visible under microscope

• **MICRODELETION:**
  - A deletion so small that can be identified using molecular or DNA technology (Array CGH)
2 random processes:

- **MEIOSIS** - chromosome number is halved
- **Scrambling of DNA** - deletion, duplication, translocation, inversion

**COPY NUMBER VARIANTS:**

- Number of copies of a particular gene varies from one individual to next
- Due to non allelic homologous recombination
**CAUSES:**

- **De novo** – spontaneous deviation with a copy number variation - 75%

- From a **carrier parent** with CNV - 25%
CLASS I / DISTAL/ SMALLER

- closer to the tip of the long arm of the chromosome
- DNA is missing between 146 Mb and 147.8 Mb
- at least nine known genes

CLASS II / PROXIMAL/ LARGER

- larger deletion of around 1.35 to 2 Mb
- At least 25 genes
- Causes TAR syndrome
Genes in 1q21.1:

- PDE4DIP
- HYDIN2
- PRKAB2
- PDIA3P
- FMO5
- CHD1L
- BCL9
- ACP6
- GJA5
- GJA8
- NBPF10
- GPR89B
- GPR89C
- PDZK1P1
- NBPF11.

• HYDIN2:
  - only active in brain
  - Determines head size
  - Deletion - microcephaly
  - Duplication - macrocephaly

• GJA 5:
  - Expresses a protein called **CONNEXIN 40**
  - Expressed in atria of the heart

• GJA 8:
  - **CONNEXIN 50**
  - Keeps the lens in eye transparent
CLINICAL FEATURES

• SMALL HEAD
• MILD/MODERATE DEVELOPMENTAL DELAY
• UNUSUAL FACIAL FEATURES
• BEHAVIOURAL/ MENTAL HEALTH PROBLEMS
• CARDIAC PROBLEMS
• LOOSE JOINTS/ DOUBLE JOINTEDNESS
• SEIZURES
• CATARACT
• OTHER ANOMALIES
• **Unusual facial features:**
  – Prominent forehead
  – Deep set eyes
  – Bulbous nose

• **Cardiac problems:**
  – Duplication - TOF
  – Deletion - PDA, VSD, **ASD**, TGA, TA, Aortic valve and arch anomalies
• BEHAVIOURAL PROBLEMS:
  – ADHD
  – Antisocial behaviour
  – Aggressiveness
  – Autistic like behaviour - duplication
  – Anxiety
  – Depression
  – Hallucination
  – SCHIZOPHRENIA - deletion
• **Other anomalies:**
  
  – Missing ribs
  – Extra fingers/toes
  – Webbed/incurving toes
  – Clubfeet
  – Unusual brain structure
  – Hydrocephalus
• Diagnosis:

FISH TECHNIQUE

Screening of both the parents

Recurrence rate:

25% if one of the parent is affected
TREATMENT:

- Supportive management
- Address the cardiac, neurological and ophthalmological problems
- Routine pediatric care
- Routine developmental assessments

• RESULTS:

• We identified 25 persons with a recurrent 1.35-Mb deletion within 1q21.1 from screening 5218 patients. The microdeletions had arisen de novo in eight patients, were inherited from a mildly affected parent in three patients, were inherited from an apparently unaffected parent in six patients, and were of unknown inheritance in eight patients. The deletion was absent in a series of 4737 control persons (P=1.1×10^-7). We found considerable variability in the level of phenotypic expression of the microdeletion; phenotypes included mild-to-moderate mental retardation, microcephaly, cardiac abnormalities, and cataracts.
CONCLUSIONS:

We have identified recurrent molecular lesions that elude syndromic classification and whose disease manifestations must be considered in a broader context of development as opposed to being assigned to a specific disease. Clinical diagnosis in patients with these lesions may be most readily achieved on the basis of genotype rather than phenotype.
TAKE HOME MESSAGE

• To identify the chromosomal anomaly & prevent recurrences in subsequent pregnancies
• Holistic approach is needed for children with CHD associated with behavioural abnormalities
• Behavioral problems if unattended can make life of caregivers miserable
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