Disclosure Statement

• Speaker: J-F Lemay

Dr Lemay has documented that he has nothing to disclose.

Pathogenesis of Autism Spectrum Disorders

Main objective of the presentation

• Case presentation X 4 of medical genetic syndromes and autism

Autism and Genetic Syndrome

- Angelman syndrome
- Prader-Willi syndrome
- 15q11-q13 duplication
- Fragile X syndrome
- Fragile X premutation
- Deletion chromosome 2q
- XXY syndrome
- Smith-Lemli-Opiz
- Apert syndrome
- Mutations in the ARX gene
- De Lange syndrome
- Smith-Magenis syndrome
- CHARGE syndrome
- HEADD syndrome
- Lujan-Fryns syndrome
- Moebius syndrome
- Hypomelanosis of Ito
- Tourette syndrome
- Williams syndrome
- Reit syndrome
- Noonan syndrome
- Down syndrome
- Velo-cardio-facial
- Myotonic dystrophy
- Steinert disease
- Tuberous Sclerosis
- Duchenne
- Timothy syndrome
- 10p deletion
- Cowden syndrome
- Cohen syndrome
- Goldenhar syndrome
- Joubert syndrome
- Neurofibromatosis type 1
- Kabuki syndrome
- Turner syndrome

Case 1
### History at birth

<table>
<thead>
<tr>
<th></th>
<th>Twin A</th>
<th>Twin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>1848 g</td>
<td>2390 g</td>
</tr>
<tr>
<td>APGAR (1 and 5 min)</td>
<td>8,9</td>
<td>5,7</td>
</tr>
<tr>
<td>Umbilical cord</td>
<td>2-vessels</td>
<td>normal</td>
</tr>
<tr>
<td>Neonatal course</td>
<td>complicated</td>
<td>normal</td>
</tr>
<tr>
<td>Heart and renal issues</td>
<td>present</td>
<td>not present</td>
</tr>
<tr>
<td>Head CT-scan</td>
<td>normal</td>
<td>3rd ventricle and extraspaces more prominent</td>
</tr>
</tbody>
</table>

### History: brief description

- Described as easy babies in first year of life
- Due to late speech and developmental concerns—both kids started SLP therapy at 2 years of age
- Behavioral issues were present (age 1-3 y)
  - Self-injurious behavior ++++
- Disordered communication and social skills: possibility of PDD-NOS? (age 3 y)
- One blood test confirmed the diagnosis

### Case 1: Your choices ...

1. Fragile X
2. Fetal Alcohol Syndrome
3. Turner Syndrome
4. Smith Magenis Syndrome
5. Kabuki Syndrome
6. Noonan Syndrome
7. Williams Syndrome
8. Neurofibromatosis type 1
9. Tuberous Sclerosis
10. Smith-Lemli-Opitz syndrome

### Chromosominal Diagnosis

- Age: 3 years 4 months
- Chromosome testing confirmed for both children a 17p11.2 interstitial microdeletion
- Parental chromosomes studies were normal.

### Smith-Magenis Syndrome (SMS)

- SMS: Caused by a 17p11.2 interstitial microdeletion
Smith-Magenis Syndrome

- Common behavioral and developmental phenotype:
  - Developmental delay
  - Self-harm/ self injurious
  - Sleep disturbance (shift of their circadian rhythm of melatonin with a paradoxical diurnal secretion of the hormone).
  - Autism spectrum disorder features

Clinical Physical Features (SMS)

<table>
<thead>
<tr>
<th>System</th>
<th>Finding</th>
<th>Twin A</th>
<th>Twin B</th>
<th>Frequency in SMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniofacial</td>
<td>Normal/propionate</td>
<td>Yes</td>
<td>Yes</td>
<td>Required</td>
</tr>
<tr>
<td>ENT</td>
<td>Chronic ear infections</td>
<td></td>
<td></td>
<td>Very common</td>
</tr>
<tr>
<td>Ocular</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Common</td>
</tr>
<tr>
<td>Cardiac</td>
<td>ASD, VSD, Pulm Stenosis</td>
<td>Normal</td>
<td>Normal</td>
<td>Common</td>
</tr>
<tr>
<td>Hernia</td>
<td>Reflux, Hema +, Hyposcale</td>
<td>Hema +</td>
<td>Less common</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Ch. ENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency in SMS</td>
<td>Twin BTwin A SMS Finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological Assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Psychological Assessment

- ASD: ADOS + (score of 29), ADI-R + (above cut-off)
  - Both kids: limited communications, pointing and use of gestures- poorly modulated and inconsistent eye contact etc.
- BSID-II
  - Developmental age of 12 months (both kids)
- VABS
  - Composite score < 1st ile (both kids)

NB: PLS-4 (speech): Twin A: unde 1st ile
Twin B: 1st ile

Neurobehavioral features (SMS)

<table>
<thead>
<tr>
<th>Issues</th>
<th>Findings</th>
<th>Twin A</th>
<th>Twin B</th>
<th>Frequency in SMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>abnormal</td>
<td>negative</td>
<td>negative</td>
<td>Very common</td>
</tr>
<tr>
<td>Cognition</td>
<td>Cognitive impairment</td>
<td>+++</td>
<td>+++</td>
<td>Very common</td>
</tr>
<tr>
<td>ASD</td>
<td>Features ++</td>
<td>++</td>
<td>++</td>
<td>Very common</td>
</tr>
<tr>
<td>Verbal</td>
<td>Speech delay</td>
<td>+++</td>
<td>+++</td>
<td>Very common</td>
</tr>
<tr>
<td>Self-injurious behaviour</td>
<td>Present +++</td>
<td>++</td>
<td>+++</td>
<td>Very common</td>
</tr>
<tr>
<td>Adaptive behaviour</td>
<td>Delayed</td>
<td>+++</td>
<td>+++</td>
<td>Very common</td>
</tr>
<tr>
<td>Motor</td>
<td>FM Delay</td>
<td>+++</td>
<td>++</td>
<td>Very common</td>
</tr>
</tbody>
</table>

Discussion

- Same deletion: no clear genetic mechanism responsible for the differences with cardiac/renal/behavioral phenotype.
- Pre- and Postnatal environments were the same for these twins and cannot explain the observed difference in behavior.

SMS: few thoughts

- Examining the differences in behavioural/developmental and clinical phenotype in these monozygotic twins may lead to a better understanding of the etiology of the clinical variability seen in SMS, as well as the natural history of this syndrome.
- Further work is required to understand the variation in presentation of all individuals affected by SMS.
Case 2

History

- Normal pregnancy and delivery
- BW 2985 gm; height 51cm; HC 35 cm
- Siblings (2 brothers):
  - #1: Diabetes type 1
  - #2: Familial neurological tremors
- Parents: non-related
- Described as an easy baby
- Late with sitting (10 months)
- Walked at 20 months

- No words by 24 months
- Eye contact fluctuating
- Play-skills at 24 months: minimal
- However very active ++++
- Limited attention; impulsivity +
- Child described as different when compared to other siblings

Articles SMS


Blood Testing were done at 30 months

Social-Communication skills:
- Unusual eye contact
- Facial expressions directed to others
- Quality of social overtures: not the best

Evaluation done at 38 months
- ABAS-II: GCS score low extremely
- ADOS: positive ASD
- ADI-R: many elements + for ASD
Case 2: Your choices ...

1. Fragile X
2. Fetal Alcohol Syndrome
3. Turner Syndrome
4. Goldenhar Syndrome
5. Kabuki Syndrome
6. Noonan Syndrome
7. Williams Syndrome
8. Neurofibromatosis type 1
9. Tuberous Sclerosis
10. Smith-Lemli-Opitz Syndrome

Fragile X Syndrome:
- Leading inherited of MR and leading single gene associated with autism
- 1 in 3,600 with MR, also a cause of LD, anxiety disorders, mood instability.
- Also 30% with autism; 2-6% with autism have FXS

Expression of the Fragile X Gene is Increased in carriers

<table>
<thead>
<tr>
<th>Typical</th>
<th>Premutation</th>
<th>Full mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CGG) &lt; 45</td>
<td>(CGG) 55 - 200</td>
<td>(CGG) &gt; 200</td>
</tr>
</tbody>
</table>

mRNA
FMRP
Clinical normal

(Premutation-specific disorders) Fragile X
Premature ovarian failure (POF)
Tremor/ataxia syndrome (FXTAS)

The Fragile X Gene
A family affair

Fragile X as a model of autism

- Many children with FXS have autism (30%) and many children with autism (2-6%) have fragile X
- Both disorders have big heads and rapid brain growth early in childhood
- FXS has problems with hyperarousal and anxiety so it models this subtype of autism
- Both disorders have problems with facial processing (e.g., avoiding looking at the eyes which overactivates the amygdala)
- Both disorders have decreased AMPA receptors
- Those with FXS and autism have lower IQ than FXS alone. However level of FMRP does not correlate with autism once you control for IQ (Loesch et al 2007)
Articles Fragile X


Case 3

History

- Born (male) at term 36 weeks following concerns regarding kidney development
- BW 2800 gm
- Stayed 22 days NICU and Special Care nurseries
- Health concerns:
  - Breathing difficulties
  - Feeding concerns
  - Kidney failure

At 3 months of age: hospitalized due to further problems and food allergies
- Remained on oxygen for 20 months following his birth and continued to have difficulties with feeding and vomiting
- Few UTI
- Hearing: last test WNL
- Vision: mild esotropia
- Concerns with his social communication

A diagnosis of .... was discussed with the parents at the age of 3 months
Since then
  Socially:
  - Parents felt that he was experiencing the world differently than others
  - Needed prompting to engage in physical closeness
  - Eye contact sporadic but if present was very intense
  - Lack of interest in interactions
  - Strong preference for solitary play activities

May 2007:
  - Appropriate receptive language abilities with moderate expressive language delays
  - Severe fine motor delays
  - Variety of sensory concerns
  - Low trunk and extremity muscle tone
  - MRI Head: somewhat abnormal
• ABAS-II: GAC score extremely low range (0.2nd percentile)
• ADOS: positive for ASD
• ADI-R: positive for ASD
• Mullen Scales of Early Learning: not able to complete it

Case 3: Your choices ...

1. Angelman syndrome
2. Fetal Alcohol Syndrome
3. Turner Syndrome
4. Goldenbar Syndrome
5. Kabuki Syndrome
6. Noonan Syndrome
7. Williams Syndrome
8. Neurofibromatosis type 1
9. Tuberous Sclerosis
10. Smith-Lemli-Opitz Syndrome

Kabuki syndrome

• Gender: male to female ratio 1.16/1
• Craniofacial abnormality: peculiar facies (100%) with long palpebral fissures and partially everted lower eyelid
• Neurological abnormality: MR (92%) and hypotonia
• Stature (postnatal growth deficiency 83%)
• Visceral abnormality
• Other: speech delays, learning disabilities, ASD-like behavior

Kabuki Syndrome

• First case 1969 in Japan; recognized in 1981 (Nikawa-Kuroki syndrome)
• Name: reminiscent of the make-up of actors in Kabuki, the traditional form of Japanese theater (founded in 17th century)
• There have been no direct evidence or any clues to clarify the cause of the syndrome
• No clinically genetic test to confirm the diagnosis

Kabuki Syndrome

• Several patients have been found to have autism or autistic-like behavior- but why?
Articles on Kabuki Syndrome


Case 4

History

- Pregnancy:
  - mother had polyhydramnios
  - Fetal hydronephrosis (left side) detected at 20 wks
- Delivery: C-section secondary to fetal heart deceleration at 39 weeks gestation; APGAR 7,9
- BW: 3731 g Cord pH 7.30
- Perinatal period:
  - RDS; oxygen requirements; but normal echo heart
  - Surgeries for the left kidney
  - Surgery for small bowel rotation
  - Later Echo heart: Pulmonary stenosis
- Parents are non-related
- Siblings: normal
- Mild delays : motor skills
- The diagnosis of ... was made at one year-old.

More clinical info...

- Obstructive sleep apnea
- TAA with myringotomy tubes inserted Dec 1999
- Sleep issues: taking Melatonin
- Clinically euthyroid
- Small stature
- Allergic to dairy products (?)- on soy milk
- ADHD : dx 2007
  - Currently on Biphentin
  - Going Grade 4 Sept 2008
- IQ testing 2007: WISC-IV 71 (3rd ile)
- Social-communication:
  - Avoiding eye contact
  - Prefers to play alone
  - Engaging in parallel play
  - Difficulty with change in routines
  - Several stereotypic/ repetitive behavior
  - Obsession for pets
  Also :Sensitive to noise ; DCD +
History Summary

- PDD-NOS features
- ADHD
- Borderline Cognitive functioning
- Pulmonary Stenosis
- Obstructive Sleep Apnea
- Developmental Coordination Disorder
- Left hydronephrosis
- Intermittent exotropia

Case 4: Your choices …

1. Angelman syndrome
2. Fetal Alcohol Syndrome
3. Turner Syndrome
4. Goldenhar Syndrome
5. De Lange Syndrome
6. Noonan Syndrome
7. Williams Syndrome
8. Neurofibromatosis Type 1
9. Tuberous Sclerosis
10. Smith-Lemli-Opitz Syndrome

Noonan Syndrome

- Described in 1963 Dr. J. Noonan
- Cardinal symptoms:
  - Pulmonary stenosis
  - Short stature
  - Webbing of the neck
  - Inattentive symptoms
  - Language and communication difficulties
  - Motor coordination difficulties
  - Few cases with ASD reported in the literature

IQ scores Noonan syndrome

Articles on Noonan syndrome

- Autistic behaviors in a boy Cohen P Volkmar F J Autism Dev Disord 1983 Dec (13(4); 433-4
Conclusions:

- Although the strong correlation between autism and genetic factors has been long established, the exact genetic background of autism is still unclear.
- Many genetic syndromes have been described in children with pervasive developmental disorders / ASD.
- Important when a child is diagnosed with a genetic syndrome: verify Intellectual abilities but also ASD features.

Other interesting article


- Thank you and have a good day!