Malan Syndrome

Sotos -2

NFIX-related condition(s)
Sotos-like syndrome

- Patients with many features of Sotos syndrome but not classic
- About 8% will have an NSD1 mutation
- (?) Atypical cases of Weaver and Beckwith-Wiedeman syndromes
- Maybe 5% will have a change in a gene called NFIX (sometimes called Sotos-2 or Malan syndrome)
- Other reported genes: APC2 (Sotos-3) and SETD2 (Luscan-Lumishish Syndrome)
- Several others TBA
  - Dr. Fahrner’s research
Malan Syndrome
(Clinical Features)

- GROWTH
  - Height
    - Birth height above centile 95
    - Postnatal height above centile 98
  - Weight
    - Birth weight above centile 95
  - Other
    - Height-weight ratio below centile 25
Malan Syndrome (Clinical Features)

- Cardinal facial characteristics include:
  - long, narrow, triangular face
  - macrocephaly
  - prominent forehead
  - everted lower lip
  - prominent chin
Malan Syndrome (Clinical Features)

- HEAD & NECK
  - Head
    - Macrocephaly
    - High forehead
  - Eyes
    - Hypermetropia
    - Strabismus
    - Nystagmus
    - Astigmatism
    - Downslanting palpebral fissures
  - Mouth
    - Small mouth
    - Everted lower lip
    - Prognathism
  - Teeth
    - Premature eruption of teeth
Malan Syndrome (Clinical Features)

- SKELETAL
  - Advanced bone age
  - Chest
    - Pectus excavatum
  - Back
    - Scoliosis
  - Limbs
    - Coxa valga
  - Hands
    - Long fingers
Malan Syndrome
(Clinical Features)

- **ABDOMEN / GI**
  - Abdominal wall hypotonia
  - Vomiting,
  - Chronic diarrhea, constipation

- **SKIN, NAILS, & HAIR**
  - Livedo reticularis, generalized

- **Nails**
  - Malformed nails
Malan Syndrome (Clinical Features)

- **NEUROLOGIC**
  - Seizures
- **NEURO-DEVELOPMENT**
  - Cognitive impairment
  - Motor delay
  - Hypotonia
- **NEURO-SENSORY**
  - Speech delay / apraxia
  - Vision changes
    - Strabismus, nystagmus
    - Optic nerve hypoplasia
- **NEURO-IMAGING**
  - Ventricular dilatation
  - Hypoplasia corpus callosum
  - Ventricular dilatation
Malan Syndrome
(Clinical Features)

- BEHAVIORAL / PSYCHIATRIC MANIFESTATIONS
  - Autistic traits
  - Behavioral anomalies especially anxiety
<table>
<thead>
<tr>
<th>Development</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor retardation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Speech delay</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Mental deficiency</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Behavioral anomalies</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Autistic traits</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Craniofacial features</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long / narrow face</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Downslanting palpebral fissures</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Hypertelorism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proptosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epicanthal folds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thin upper lip</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Everted lower lip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognathia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small nose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short nose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anteverted nares</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low nasal bridge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High forehead</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Frontal bossing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex craniosynostosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat occiput</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eyes</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypermetropia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strabismus</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Nystagmus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astigmatism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic nerve hypoplasia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculo-skeletal abnormalities</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal wall hypotonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pectus excavatum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coxa valga</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Advanced bone age</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hand / foot abnormalities</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long fingers</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Clinodactyly of the 5th finger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overlapping toes</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brain MRI</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular dilatation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoplasia of the corpus callosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiari I malformation</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Seizures / EEG anomalies</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal EEG</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal abnormalities</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor feeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTT (G-tube)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other abnormalities</th>
<th>NM</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformed nails</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Premature eruption of teeth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized livedo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Malan Syndrome (GENETICS)

- NFIX gene
  - 19p13.13

- May be caused by a microdeletion or gene mutation

- Pathogenesis = haploinsufficiency

- Autosomal dominant inheritance
NFIX gene

- NFIX gene encodes a protein that functions as a transcription factor
  - Transcription factors turn specific genes "on" or "off" by binding to nearby DNA sequences.
- Very little is known about the genes regulated by NFIX and the role they play in causing Malan syndrome
- Different changes in the NFIX gene cause a different condition known as Marshall-Smith syndrome
Deletion Cases

- Involves genes other than NFIX
  - Ataxia
  - Migraines
    - One case had cyclical vomiting responsive to pizotifen (migraine medication)
Genotype does not define phenotype !!!!

That is, you can not predict what a particular person with NF1X gene changes is going to experience or not experience based on the genetic test results.
Pleiotropy

- Multiple clinical features all due to changes in the same gene
- For example people with NF1X gene changes can have:
  - Overgrowth
  - Macrocephaly
  - Vision problems
  - Hearing loss
  - Skeletal changes
  - Neurologic changes
    - Neurodevelopmental
    - Seizures
    - Structural brain changes (seen on MRI)
Important Clinical Genetic Concept

- Each person with Malan syndrome will not exhibit every reported trait.
- They have an increased threshold for developing certain problems, but everyone’s baseline threshold is different.
- It is sort of like a buffet line ....
What’s on the buffet line?

- Common features
  - Overgrowth
  - Macrocephaly
  - Low muscle tone
  - Speech /language problems
  - Facial changes
  - Developmental delays
  - Behavioral changes

- Less common features
  - Seizures
  - Skeletal changes
  - Gastrointestinal problems
  - Vision / hearing problems
Expanded Phenotype

- Often described as a spectrum
  - i.e. the spectrum of NF1X related features
- It has been suggested that at a minimum 100 cases of a condition need to be described before it can be assumed that the major part of the phenotypic spectrum has been identified
  - (2015) 20
  - (2018) 80
  - (2019) ~ 82
Important Clinical Genetic Concepts

- The NF1X is only one of 19,000 genes that a person has.
  - Even if it has a change, this does not ‘trump’ the way the other genes work.
- A person with Malan syndrome will still have all of the other genetic traits and predispositions that are inherited from the parents.
  - Malan syndrome does not define the child!
1. Hypotonia
Hypotonia

- Common in Malan syndrome
- Low muscle tone
  - Not the same as strength
Consequences of hypotonia

- ‘Floppy baby’
- Delayed motor development
  - Problems over-coming gravity
- Loose (hyperflexible) joints
  - Not a CTD
- Oro-motor problems
  - Protruding tongue
  - Drooling
  - Problems with feeding / swallowing
- Frequent infections (not immune deficiency)
  - Ear infections
  - Colds, bronchitis
Hypotonia

- Generally improves with time
- Probably never completely goes away
- Therapies (don’t have to know anything about Malan syndrome)
  - Physical therapy
  - Occupational / speech therapy
  - Orthotics
  - Surgeries
2. Neuro-developmental delays

Bell Curve of Approximate IQ Scores
as pertains to American Mensa's testing program

- Delayed
- Low average
- Average
- High average
- Gifted

68 percent of the population fall between 85 and 115
Key Principles of Development

- Development is not a foot race
- Few predictive tools
  - Neuropsychologic testing
Pediatric Neuropsychology

What is assessed?

- Intelligence
- Achievement skills
- Attention / Executive Functioning
- Learning & Memory
- Language
- Sensory & Sensory Motor
- Motor
- Behavioral, Emotional, & Social Functioning
3. Behavioral changes
Which therapies to use?

- Consider risks / side effects
- Look for reputable documentation of efficacy
- Seek input from trusted health care professionals
- Talk to other families
- If it isn’t working stop it
- Customize for your child
4. What about cancer?
Cancer and Malan syndrome

- Nothing reported to date

Secretary Carcinoma of the Skin: Report of 6 Cases, Including a Case With a Novel NFIX-PKN1 Translocation.
5. Seizures

- Seizures
  - can appear in many forms
- Some forms are subtle
  - e.g. absence seizures
- Temperature control problems may exacerbate seizures
  - “febrile seizures” (actually seizures associated with fevers)
Watch for ‘stuff’
If it ain’t broke, don’t fix it

The following are appropriate at times of clinical evaluations:

- Thorough history to identify known clinical sequelae of Malan syndrome
- Examination / monitoring for curvature of the spine
- Audiologic assessment
- Referral to a pediatric ophthalmologist. May want pediatric neuro-ophthalmologist. Referral to the appropriate clinical specialist if problems are identified.