Angelman syndrome & 15q Duplication syndrome

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Ideogram of chromosome 15, showing genes located in the typical deletion region of Prader-Willi syndrome

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Disorders of 15q

- **Angelman syndrome** – loss of function of UBE3A from the maternal 15q region

- **Prader Willi syndrome** – loss of function of UBE3A from the paternal 15q region

- **15q duplication syndrome**
  - Isodicentric chromosome 15 – 2 extra copies of the maternal 15q region on a 47\(^{th}\) marker chromosome
  - Interstitial duplications – 1 extra copy of the maternal 15q region contained within the maternal chromosome 15 (46 XX or XY)
Angelman Syndrome (Angleman.org)
Angelman Genetic subtypes

- Maternal deletions (68%)
- UBE3A Mutation (13%)
- Imprinting Center Defect (6%)
- Uniparental Disomy (3%)
- Unknown (~10%)
Clinical Manifestations of Angelman syndrome

- Clinical manifestations of Angelman syndrome are mainly Neurological/Psychological
  - Developmental delays (expressive speech most affected); very happy disposition
  - Epilepsy (~80-90%)
  - Movement disorders (tremor, ataxia, myoclonus) ~100%
  - Sleep disturbance (>50%)
  - Anxiety and difficult behaviors
  - GI dysfunction (>80%)
  - Orthopedic and ophthalmologic issues
    - Scoliosis, strabismus, etc.
Isodicentric 15q (idic15) idic15.org
idic15
Clinical manifestations of idic15

- Clinical manifestation of idic15 are mainly Neurological/Psychological
  - Developmental delays (global) – with significant hypotonia
  - High incidence of autistic spectrum disorders (~80%)
  - Behavioral issues – impulsivity, self-injurious behavior, anxiety, hyperactivity, agitation
  - Epilepsy common (~50-60%)
  - Sleep disturbance (>50%)
  - GI dysfunction (70-80%)
  - Orthopedic and ophthalmologic issues
    - Scoliosis, strabismus, etc.
Interstitial duplications (Urraca et al. 2013)
Clinical manifestations of Interstitial duplications

- Clinical manifestations similar to idic15 but milder
  - Subtle dysmorphic features
  - ASD of varying degrees is most common presentation
  - Often behavioral issues with anxiety most common issue; also can have emotional lability and hyperactivity
  - Seizures reported but not common
  - Sleep dysfunction can be present
  - GI dysfunction common – can be as severe as idic15
  - Paternal duplications can be symptomatic but rare and not associated with ASD (sleep, GI, anxiety)
MGH Angelman Syndrome Clinic and Dup15q Center

- Neurology/Epilepsy
- Psychiatry
- Neuropsychology
- Sleep medicine
- GI
- Consults to Genetics
- Consults to Ortho/Physiatry and Ophthalmology
- Consults for PT, OT, speech, Aug. Comm.
Epilepsy in Angelman syndrome
Seizures in Angelman syndrome

- Epilepsy in Angelman syndrome is a generalized epilepsy
  - Generalized tonic-clonic
  - Atypical absence
  - Atonic
  - Myoclonic
  - Focal seizures present in ~30%
  - Tonic seizures and spasms rare if present at all
ASF Seizure Survey

- Seizure survey performed in 2006-07
  - On-line questionnaire through ASF

- 461 responses
  - 391 (86%) had seizures
  - 60% had multiple seizure types
  - ~30% reported focal seizures (typically along with generalized seizure types)

- Thibert et al., *Epilepsia* 2009
AS Seizure types

Seizure Types

- GTC
- Atonic
- Absence
- Focal
- Myoclonic
- Tonic
- Spasms
AS Seizures by subtype

Genetic Subtypes

- Deletion
- UPD
- UBE3A
- Imprinting
Seizures in AS - Age

Seizures in AS relative to age:

- Average onset approximately 2-3 yrs of age, typically beginning in childhood (rarely under 1 year of age)
- Seizures are usually most frequent and most intense in early childhood and tend to improve by puberty
- Seizures can then return and persist into adulthood but are typically much less frequent and less intense – a recent study of 110 adults with AS showed ~1/3 had seizures recur in adulthood but these were typically more mild and less frequent (Larson et al. 2015)
NCSE

- Non-convulsive status epilepticus (NCSE)
  - Occurs in >50% of those with AS; some studies report ~90% but in our clinic only ~20%
  - Episodes of decreased alertness lasting days to weeks often with loss of skills
  - Typical seizures usually lessen during NCSE
  - AS not progressive so always consider NCSE first if any regression
  - Frequent myoclonic jerks in this setting could be myoclonic status in non-progressive encephalopathies (MSNE) – rare but AS most common etiology
NCSE EEG
EEG in AS

- About 90-95% have abnormal EEG patterns with or without clinical seizures
- Normal EEG’s rare but have been reported in some with imprinting center defects
- 3 common patterns
  - Bi-frontal predominant slow spike and wave with a “triphasic” appearance
  - Rhythmic 4-6 Hz centrotemporal activity
  - Posterior “notched” delta activity
Frontal notched delta
Notched delta
Seizure treatment in AS

- Controlled with 1st AED: 77%
- Controlled with 2nd AED: 15%
- Refractory to at least 2 medications: 8%
Seizure treatment in AS

- Valproic acid
- Clonazepam
- Phenobarbital
- Topiramate
- Carbamazepine
- Lamotrigine
- Levetiracetam
- Phenytoin
- Zonisamide
- Ethosuxamide
- Gabapentin
- Felbamate
- Oxcarbazepine
- Tranxene
- Clobazam
- ACTH
- Nitrazepam
- Other
# Seizure Medications (Shaaya et al 2016)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No change</th>
<th>&lt;50% improved</th>
<th>50-90% improved</th>
<th>&gt;90% improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>0</td>
<td>0</td>
<td>8 (38.1%)</td>
<td>13 (61.9%)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>0</td>
<td>0</td>
<td>5 (14.3%)</td>
<td>30 (85.7%)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0</td>
<td>0</td>
<td>2 (11.8%)</td>
<td>15 (88.2%)</td>
</tr>
<tr>
<td>Clobazam</td>
<td>2 (7.1%)</td>
<td>0</td>
<td>2 (7.1%)</td>
<td>24 (85.7%)</td>
</tr>
<tr>
<td>LGIT</td>
<td>0</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>
## Seizure Medications

(Shaaya et al 2016)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average Dose (mg/kg/day)</th>
<th>Average course (months)</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>26.6 (8-60)</td>
<td>56</td>
<td>66.6%</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>60.4 (6-200)</td>
<td>36</td>
<td>20%</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>6.6 (2.5-12)</td>
<td>58</td>
<td>23.5%</td>
</tr>
<tr>
<td>Clobazam</td>
<td>1.0 (0.2-2.1)</td>
<td>13</td>
<td>32%</td>
</tr>
</tbody>
</table>
Seizure Medications

- Similar to the Seizure Survey of 2009, newer medications such as Levetiracetam (Keppra) and Lamotrigine (Lamictal) have similar efficacy to Valproic acid – in our clinic population the efficacy is a bit higher.

- Clobazam was not widely used in the 2009 study so sufficient data was not available. In our clinic, efficacy is similar to that of Levetiracetam and Lamotrigine.

- Also similar to the 2009 study, valproic acid had much higher rates of side effects, mainly tremor and decreased motor skills/ambulation.
Treatment of NCSE

- In progress case series at MGH

21 children with NCSE (26 total events) – all 21 treated with oral diazepam (Valium) as outpatients
  - Median duration of therapy – 6 days
  - Typical starting dose ~0.3 mg/kg/day divided into TID or BID
  - 5/26 needed 2 courses with 1/26 needing 3 courses
  - 22/26 (85%) treated successfully with Valium
  - 3/4 non-responsive episodes responded to prednisone; 1 was placed in burst suppression.
Low Glycemic Index Treatment

- Based on the “glycemic index” foods (raises blood glucose)
- Allows for 40-60 gm carbohydrates per day
  - 10% carbs; 20-30% protein; 60-70% fat
- No need for admission; monitoring less strict than ketogenic but still needed
- Meals based on percentages above and caloric needs
- Compliance better than ketogenic as less restrictive
- Efficacy not quite as good as ketogenic so can convert for better control
  - 1/3 not effective or not tolerated
  - 1/3 50-90% reduction in seizures
  - 1/3 >90% reduction in seizures or seizure free
  - Can take 2 weeks to 2-3 months to see effects
LGIT trial in AS

- LGIT prospective trial – 6 children with AS

  - After 4 months:
    - 4 children >90% seizure-free
    - 1 child 50-90% seizure-free
    - 1 child <50% seizure free

  - After 1 year (5 still on LGIT)
    - All 5 children >90% seizure-free
    - All 5 remain on LGIT 7-9 years later
      - Thibert et al., *Epilepsia* 2012
LGIT in AS (MGH – Grocott et al 2017 Ep and Behav)

- Overall – 23+ children/adults have been on the LGIT
  - Daily seizures (5) – all improved with 1 seizure-free except illness
  - Weekly seizures (3) – all improved with 1 seizure-free except illness
  - Monthly seizures (2) – both seizure-free, 1 except for illness
  - Seizures only when ill (3) – 2 were similar and 1 seizure-free
  - Only NCSE (1) – still had NCSE
  - Well controlled (1) – stayed well controlled and cut medications

- Overall themes
  - LGIT very effective in Angelman syndrome
  - Seizure control often achieved with >60 g per carbohydrates
  - Illness and NCSE are the 2 situations where diet is less effective
Non-epileptic Myoclonus

- **Myoclonic seizures**
  - Common in Angelman syndrome (~15-40%) and are often the first seizure type reported; onset in early childhood
  - Events are usually brief in duration – typically seconds but can last up to a minute
  - Children with myoclonic seizures typically have generalized spike and wave activity on interictal EEG and seizures captured on EEG are associated with spike and wave activity
- **MGH clinic:**
  - 17/185 (15%) had myoclonic seizures
  - Age of onset ~1-8 years (78% had onset before 5 years)
Non-epileptic Myoclonus

- Non-epileptic myoclonus
  - Age of onset is at puberty or later
  - Events last seconds to hours and can occur multiple times per day
  - There is no significant alteration of consciousness during the events and no post-ictal period
  - There is no associated regression or loss of skills
  - Events captured on EEG show no EEG changes
    - 12 individuals had prolonged EEG capturing events
    - 5 has inpatient video (3 MGH); 7 ambulatory (2 MGH)
    - All captured events and none had EEG correlate
Prevalence of NEM by age

Figure 1: Percent of patients in cohort with NEM by age group (n=185)
Epilepsy in 15q Duplication syndrome
Epilepsy in Dup15q

- Epilepsy appears to be multifocal
  - MRI’s show focal abnormalities
  - Pathology shows regions of focal abnormalities

- Some children have focal or multifocal seizures which typically respond well to medication

- Some children have secondarily generalized seizures which are typically much harder to treat, at times resulting in a Lennox-Gastaut type of epilepsy including epileptic spasms
MRI Findings

- 11 MRI’s – idic(15) – 9 and int dup(15) – 2
  - 8/11 children had hippocampal malformation with incomplete hippocampal inversion that was bilateral in 7 and right in 1
  - 2/11 children had unilateral mesial temporal sclerosis (both idic(15) with refractory seizures)
  - Hypoplasia of the corpus callosum, which is the most previous reported finding, was present in two children

- Boronat et al. 2015
MRI
Dup15q Seizure Survey

- Seizure survey performed in 2010 through the Dup15q Alliance
  - Same survey as used by the ASF
- 95 responses
- 83/95 with idic15
  - 63% have seizures
  - 50% have multiple seizure types
  - 26% have infantile spasms

- Conant et al., Epilepsia 2013
idic15 seizure types
idic15 – spasms
Treatment - Spasms

- ACTH
- Vigabatrin

Comparison chart showing the effectiveness of ACTH and Vigabatrin in treating spasms, with ACTH significantly more effective than Vigabatrin in reducing spasms by over 90%.
Response to 1st Medication

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-100%</td>
<td>24%</td>
</tr>
<tr>
<td>50-90%</td>
<td>21%</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>12%</td>
</tr>
<tr>
<td>No change</td>
<td>31%</td>
</tr>
<tr>
<td>Worse</td>
<td>12%</td>
</tr>
</tbody>
</table>
Treatments – non-spasms
Idic15 EEG (in progress)

- Nearly all EEG’s had a common finding
  - Excessive beta activity throughout

- A subset of children had very characteristic EEG patterns in sleep
  - Bursts of high-voltage, high-amplitude polyspikes
  - Alpha-delta sleep
  - Sleep activated discharges (ESES-type pattern)
Excessive beta activity
High voltage/high frequency spikes
Alpha-delta sleep
Int Dup15 Seizures

- Dup15q seizure survey
  - 3 reported seizures (1 had a single focal seizure)
  - 2 had epilepsy (16%)

- MGH Dup15q Center
  - 2/11 children with epilepsy (18%)
  - Both with focal seizures on monotherapy

- Urraca et al. 2013
  - 1/13 had focal epileptiform discharges and likely focal seizures (8%)
Sleep in AS

- Sleep problems are described in the AS diagnostic criteria as ‘abnormal sleep-wake cycles and diminished need for sleep’ - listed as 20-80% prevalence (Williams et al, 2005)

- Sleep problems in AS are likely multifactorial and may be related to abnormal GABA transmission

- Other factors that may play a role in sleep dysfunction
  - Epilepsy
  - Medications, especially seizure medications
  - GI symptoms – specifically constipation and reflux
  - Anxiety
Sleep in AS

- 58% report difficulties with sleep – difficulty falling asleep most common
  - Expressive sleep disorders
  - Sensitivity to the environment
  - Disoriented awakening
  - Apnea

- Significant correlation between sleep disturbance and epilepsy (P=0.005) and with multiple seizure types (P<0.005)
  - Conant et al.; Epilepsia, 2009
Sleep in AS

<table>
<thead>
<tr>
<th>Medications</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>80%</td>
</tr>
<tr>
<td>Trazadone</td>
<td>40%</td>
</tr>
<tr>
<td>Amitryptiline</td>
<td>20%</td>
</tr>
<tr>
<td>Melatonin</td>
<td>20%</td>
</tr>
<tr>
<td>Choral hydrate</td>
<td>10%</td>
</tr>
<tr>
<td>Benadryl</td>
<td>10%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>10%</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>10%</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>10%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>10%</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>10%</td>
</tr>
<tr>
<td>Ambien</td>
<td>10%</td>
</tr>
</tbody>
</table>
Sleep Medications

- Limited studies have assessed sleep medications in AS – this is an area that needs more exploration.

- Melatonin is typically first line medication and 2 small studies showed it to decrease sleep latency, decrease nighttime wakings, and lengthen overall sleep.

- Other medications that have been useful anecdotally:
  - Trazodone
  - Benzodiazepines such as clonazepam and clobazam
  - Gabapentin (Neurontin)
  - Clonidine
  - Hydroxyzine
Dup15q Sleep

Full Dup15q Cohort (67)
- No Sleep Issues (25)
  - Sleep Issues Mild/Untreated (6)
    - Uses Sleep Medication (18)
      - Melatonin Monotherapy Helpful (11)
      - Melatonin Partially Helpful (2)
      - Other Sleep Medications Trialed (5)
  - Does Not Sleep Well (36)
    - Dysfunction Caused by Other Issues (18)
      - Sleep Apnea (3)
      - Seizures (11)
- Has Sleep Issues (42)
Dup15q Sleep

- Types of Sleep Dysfunction (in MGH cohort)
  - 30-40% don’t have any form of sleep dysfunction
  - Trouble Falling Asleep
    - 13% idic(15)
    - 31% int dup(15)
  - Nighttime waking
    - 41% idic(15)
    - 54% int dup(15)
  - Early Waking
    - 9% idic(15)
    - 0% int dup(15)
GI Dysfunction
Etiology of GI issues

- GI issues in Angelman Syndrome and Dup15q are both likely multifactorial
  - Decreased gut motility due to abnormal neuronal input
  - Picky eaters with decreased intake in vegetables and fiber – often a sensory issue
  - Decreased fluid intake
  - Medications – some medications such as benzodiazepines can be constipating
Medical issues related to GI

- GI dysfunction often causes or exacerbates other issues in AS
  - GI pain and reflux can significantly worsen sleep as reflux is more severe when lying down
  - GI pain can cause or exacerbate aggressive behaviors and anxiety
  - Severe reflux can lead to medical issues such as aspiration pneumonia
  - Significant GI dysfunction can exacerbate seizures due to overall stress placed on the body in addition to the pain and anxiety
GI in Angelman  (Glassman et al 2017)

<table>
<thead>
<tr>
<th>GI Dysfunction</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of any GI symptoms</td>
<td>141/163 (86.5%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>116/163 (72%)</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>72/163 (44%)</td>
</tr>
<tr>
<td>Cyclic vomiting – type spells</td>
<td>16/163 (9.8%)</td>
</tr>
<tr>
<td>Eosinophilic Esophagitis</td>
<td>7/120 had endoscopy – 4/120 (3.3%) had EE</td>
</tr>
<tr>
<td>Swallowing difficulties</td>
<td>9/163 (5.5%) – trouble swallowing 10/120 (8.3 %) swallow study</td>
</tr>
</tbody>
</table>
GI issues by genetic subtype

- Constipation and reflux rates did not differ significantly amongst genetic subtypes
- Poor feeding as an infant was much more common in those with deletions and only those with deletions required g-tubes
- Only those with deletions or UPD reported:
  - Difficulty swallowing
  - Excessive swallowing
  - Swallow studies performed
  - Eosinophilic Esophagitis
Gl in Dup15q

- Prevalence of Gl symptoms – 30/38 (79%)
  - Idic15 – 23/30 (76%)
  - Int Dup15 – 7/8 (87.5%)
- Prevalence of Constipation – 18/38 (47%)
- Prevalence of Gl Reflux – 17/38 (45%)

Shaaya et al. 2015
Movement disorder in Angelman syndrome
Movement Disorders

- Classic AS Phenotype
  - Ataxic gait
  - Mild tremor
  - Spasticity of distal lower limbs
- Ataxia affects up to 88% of children
- Tremor can progress with age
- Hypotonia common in infancy (~51%); 22% have persistent hypotonia and 33% develop hypertonia
  - Hypotonia not nearly as severe as in Dup15q
Non-epileptic Myoclonus

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Autism and Anxiety
Autism Spectrum Disorders

- Autism spectrum disorders (ASD)
  - ASD are common in children with 15q duplications (~80%) and range from mild to severe
  - ASD in Dup15q is somewhat atypical and these children tend to show more desire to socialize than children with idiopathic autism
  - ASD is rare in Angelman syndrome but some children do meet criteria – most with larger deletions
  - Children with Angelman syndrome are very social and make excellent eye contact – often hypersocial
  - Further studies are needed to assess this in more detail for both syndromes
Anxiety

- Anxiety is very common in Angelman syndrome and can be severe, presenting a significant quality of life issue; it appears to worsen with age.

- Anxiety in AS can have an atypical presentation:
  - Excessive swallowing
  - Refusal to walk or leave the house
  - Excessive clinging to caregivers (can be aggressive)

- Anxiety also appears to be very common in children with 15q Duplications and can present more with agitation or aggression.

- Anxiety in both syndromes is a significant area of need in terms of further studies and better understanding.
References


References


