Overview of Williams syndrome

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Conflicts of Interest

- WSA supports the WS Registry ([www.williams-syndrome.org/registry](http://www.williams-syndrome.org/registry))
  - housed at MGH and run under my supervision
  - I receive no salary support from the WSA
Williams syndrome (WS)
OMIM # 194050

- Unique multi system developmental disorder
  - Characteristic physical features & medical problems
  - Distinctive cognitive, personality, & behavioral profile

- ~1/10,000 individuals
<table>
<thead>
<tr>
<th>Category</th>
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<tbody>
<tr>
<td>Auditory, ENT</td>
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<tr>
<td>Cardiovascular</td>
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<td>Development, Cognitive</td>
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<td>Personality, Behavior, Emotional well-being</td>
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<tr>
<td>Skin, Integument</td>
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Lengthy list of POTENTIAL Problems

- No single individual with WS develops all these problems!
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Auditory, ENT</td>
<td>“Hyperacusis” / Mild to moderate high tone SNHL / Ear wax</td>
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<tr>
<td>Cardiovascular</td>
<td>Vascular stenoses / Hypertension / Valve abnormalities / QTc prolongation / Stroke / Sudden death, anesthesia concerns</td>
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<tr>
<td>Development, Cognitive</td>
<td>Global cognitive impairment / Characteristic pattern of strengths &amp; weaknesses (“WBS cognitive profile”)</td>
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<tr>
<td>Dental</td>
<td>Poor dental hygiene / Abn shaped teeth / Malocclusion / Hypodontia</td>
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<tr>
<td>Endocrine</td>
<td>IGT, diabetes mellitus / Osteopenia &amp; osteoporosis / (Subclinical) Hypothyroidism / Hypercalcemia</td>
</tr>
<tr>
<td>Gastrointestinal, Weight</td>
<td>Weight gain / Constipation / GER / Abdominal pain of ?etiology / Diverticular disease / Celiac disease</td>
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<tr>
<td>Genitourinary</td>
<td>Voiding frequency, urgency, enuresis / Structural renal anomalies / Bladder diverticuli / Nephrocalcinosis / Recurrent UTI</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Short stature / Sleep dysregulation</td>
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<tr>
<td>Musculoskeletal</td>
<td>Joint laxity / Joint contractures / Spinal curvatures</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Hypotonia / Hyperreflexia / Cerebellar findings / Chiari, type 1</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Altered visual acuity / Reduced stereopsis / Cataract / Glaucoma</td>
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</tbody>
</table>
| Personality, Behavior, Emotional well-being | Impulsivity/short attention span (“ADHD”) / Anxiety + Phobias / Obsessive compulsive traits / Dysthymia / Friendly personality  
→ vulnerable to inappropriate advances or sexual abuse / “Psychosis” |
| Skin, Integument               | Soft skin with ?premature aging / Premature graying of hair / Inguinal & other hernias                                                      |
Supravalvar Aortic Stenosis (SVAS)
Glucose status in WS

- Majority (50-60%) of adults have abnormal glucose tolerance on standard oral glucose tolerance testing
  - Prediabetes
  - mild Diabetes Mellitus (DM)
Behavioral Features

- Engaging, Charming
- Empathic, Sensitive, Affectionate
- Musical
- Hyper/sociability - Outgoing, Disinhibited
- Attention problems, Hyperactivity
- Phobias
- Perseverative
- Anxiety, anxiety, anxiety
- Dysthymic / Depressed
- Socially isolated
WS Cognitive Profile

- Global cognitive impairment
- Mean Full Scale IQ = 55 - 65
- Most function in mild-moderate intellectual disability range
• AND WHAT AN ELEPHANT IS. It is one of the animals. And what the elephant does, it lives in the jungle. It can also live in the zoo. And what it has, it has long grey ears, fan ears, ears that can blow in the wind. It has a long trunk that can pick up grass or pick up hay... If they’re in a bad mood it can be terrible...If the elephant gets mad, it could stomp; it could charge. Sometimes elephants can charge like a bull can charge. They have big long tusks. They can damage a car. It could be dangerous. You don’t want an elephant as a pet. You want a cat or a dog or a bird.
What causes WS?

Is it a genetic disorder?
Normal chromosomes in WS
WS: microdeletion disorder w/ loss
26-28 genes
Mechanism of Underlying SVAS or DM

- Due to deletion of a chromosome 7 gene
- Deletion of elastin (ELN) gene → SVAS
- Deletion of MLXIPL (ChREBP) may → DM

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Impact of Williams syndrome

• Present at birth and lasts a lifetime
  – Never “outgrow” Williams syndrome
  – (Misconception that WS is a childhood or pediatric disorder)

• Likely to develop various medical problems over the lifespan
  – More medications, surgeries, doctor’s visits
  – (Huge financial + emotional burden to family)

• Intellectual and emotional disability
  – Unable to navigate medical system, manage own health care, live independently, hold a competitive job

• Treatment is supportive, not curative
Challenges Transitioning from Pediatric to Adult Medical Providers

- Pediatricians may hand over care adult providers unfamiliar with the special healthcare needs of these patients.

- This can result in over-referral to many different medical specialists which, in turn, → fragmentation of care.

- Poor transition results in decreased quality health care.
Possible Solutions Transitioning from Pediatric to Adult Medical Providers

The Maastricht model

° “a special outpatient clinic has been developed at the academic hospital in Maastricht, the Netherlands.

° …clinic is primarily aimed at providing quality healthcare for adult patients with ID and/or genetic syndromes in general.

° (The clinic is run by a) clinical geneticist and a medical doctor specialized in treating persons with ID.”

Create Centers of Expertise [CE] - “Regional or national multidisciplinary facilities specialized in groups of Rare Diseases and housed in University-based or tertiary care hospitals…… thus overcoming the limited experience of professionals confronted with very rare conditions”
### TABLE III. Requirements for Meeting the Healthcare Needs of RD-Affected Patients at Transition

- Expert multidisciplinary team
- Availability of dedicated areas
- Availability and accessibility of social worker, psychologist, vocational counselor, legal assistance, interpreter, trained nurses, and administrative personnel
- Training and education of the transition team
- Partnership/joint meetings with adult multispecialist team
- Dedicated care/transition coordinator acting as a link to the community
- Coordination and information sharing with primary care providers
- Telephone time/dedicated lines for patients, families, and primary care providers
- Links and collaboration with patient associations
- Links and collaboration with other national and international CEs
- Capacity to produce and adhere to good practice evidence-based guidelines for RD care in children and adults
- Capacity of implementing outcome measures and quality control

CEs, centers of expertise.
Suggested Strategies

- "continuing medical education (CME) programs"
  - needs of adults with Rare Diseases (RDs), with or without developmental and intellectual disabilities, how to communicate with them....."

- "group discussions between medical students & RD pts and their families"

- "training of adult psychologists & psychiatrists [AND MDs!] in life-span developmental psychology and the management of psychiatric problems"

- "financial support to individual CEs allocated on the basis of quality of care evaluations"

- "questionnaires asking patients and their families to evaluate their degree of satisfaction and make suggestions for improvement"
SUMMARY

- Williams syndrome as an example of a rare disorder with ID
  - Medical & Genetic aspects

- Impact of having Williams syndrome
  - Transition from pediatric to adult medical care

- Shared suggestions from two European groups on how to provide better care for adults with rare disorders.
  - Support advanced training in CT for a healthcare provider to specialize in treating persons with ID/RD?