

# Sotos Syndrome

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# What is Sotos Syndrome?

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# What is a Syndrome?

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- “A group of findings that occur in more than one organ system with a common etiology”
- A recognizable pattern of features (physical or behavioral)
  - David Smith



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## **Five cases from Sotos et al 1964 with four key (diagnostic) features**

- Overgrowth
- Advanced bone age
- Developmental delay
- Characteristic facial appearance



# 1. Different Growth Pattern

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- Skeletal “overgrowth”
  - Usually increased length at birth
  - Increased height, weight and head circumference in childhood
- Final adult height usually “normal”
- Normal onset of puberty
- Disproportionately large hands and feet

# Sotos Syndrome

## Final Height Predictions

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- Females
  - mean 8cm > predicted FH
- Males
  - mean 13.6cm > predicted FH



## 2. Advanced Bone Age

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- Comparison of how mature the bones are, compared to how old the child actually is
- Loose association with early tooth eruption



# 3. Developmental Characteristics

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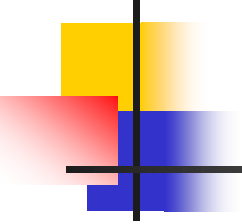
- Developmental delays (early)
- Hypotonia
- Speech and language delays (consistent and persistent)
- Cognition
  - Reported IQ 20 - 120
- Learning disabilities
- Poor fine motor control / dis-coordination



## 4. Characteristic Facial Features

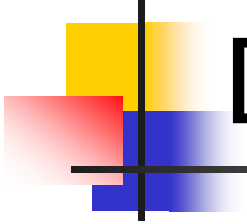
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- Frontal bossing
- Dolichocephaly
- Hypertelorism
- Down slanting palpebral fissures
- Tapering lower face
- Prominent jaw
- High arched palate

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- Children with Sotos syndrome tend to look more like each other than their siblings

# How is Sotos Syndrome Diagnosed?

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# Diagnostic Criteria

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- The "strict criteria" proposed for a diagnosis of Sotos syndrome requires that the individual have at least three of the following:
  - Typical facial appearance
  - Birth length above the 90th percentile
  - Bone age above the 90th percentile
  - Early verbal and motor delays
- Individuals who have some of these characteristics but insufficient to be classified as "typical" Sotos syndrome, are often said to be "Sotos-Like".
  - Confirmed by availability of DNA diagnostic test



# Other 'Overgrowth' Disorders

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- Fragile – X syndrome
  - Must exclude before confirming diagnosis
- Beckwith – Wiedeman syndrome
  - Recent reports intriguing
- Weaver syndrome
- Marshall – Smith syndrome
- 47 XYY, 47 XXY
- Nevo syndrome
- Perlman syndrome
- Unclassifiable



# Diagnostic Studies

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- Clinical evaluation (including family history)
- Bone Age
- Chromosomes
- Fragile X
- MRI Scan
- Other (potentially)
  - Endocrine tests
  - Metabolic tests



# Brain changes

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- “Macrocrania without megalencephaly”
- Increased sizes of fluid filled spaces in the brain
- Subtle markers of cerebral dysgenesis
- Hypoplasia of the cerebellar vermis
  - Non-specific
- Typical MRI changes seen in 146/150 scans of children with classic Sotos



# Macrocephaly

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- With very rare exceptions, children with Sotos syndrome do not have hydrocephalus
- Macrocephaly with enlarged fluid spaces may be interpreted as 'communicating hydrocephalus'

# The role of MRI in the diagnosis



- Though not one of the 4 key criteria, additional evidence can be provided by the brain MRI scan. Children with Sotos syndrome do not have severe brain malformations. However, they usually have extra fluid on the surface of the brain, enlarged ventricles and absence or reduced size of the corpus callosum. The brain itself is normal size. The extra fluid, which fills up the space inside the skull, is not "hydrocephalus, although some people have used that term. These findings are not unique to Sotos syndrome, but they are very common.
- MRI diagnosis criteria:
  - Excess fluid between the brain and skull
  - Generously sized ventricles - particularly in the "trigone" region
  - Small corpus callosum (particularly in the middle third)
  - Midline changes (absent corpus callosum, wide / cavum septum pellucidum, mega cisterna magna)
  - Small cerebellar vermis (especially lobules 6 & 7)
  - Normal sized brain in larger than average skull



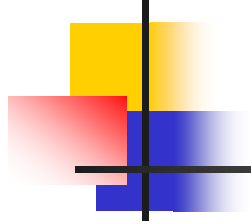
# Secondary Brain Effects

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- Higher incidence of periventricular leukomalacia
- Neonates with Sotos at higher risk for brain injury
  - large infants
  - macrocephaly
  - hypotonia

# What Causes Sotos Syndrome ?

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# The Cause of Sotos Syndrome

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- 85 - 90% of patients with classic Sotos syndrome have a change in a gene called NSD1
- NSD1 [Nuclear receptor-binding, su(var), enhancer-of-zeste and trithorax domain-containing protein 1]
  - 5q35



# The cause of Sotos syndrome

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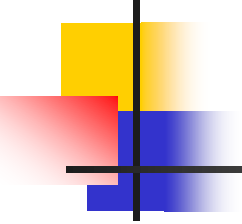
- 85 - 90% of patients with classic Sotos syndrome have a change in a gene called NSD1
  - 15% have a deletion detectable by FISH
  - 75% have a mutation (gene change)
  - 10% don't have a change in NSD1 that we can find



# NSD1 Gene and Other Conditions

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- Some patients with Weaver syndrome have changes in NSD1 gene
- Maybe 5 – 10% of patients with “Sotos like” syndrome have NSD1 changes
- Possible relationship to BWS



# Issue #1 : Behavioral Changes

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- Attention deficit disorder
- Psychiatric
  - phobias, obsessions
- Autism
  - “Autistiform behaviors”



# Issue #2 : Neurologic

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- Autonomic Nervous System
  - Excess sweating
  - Facial flushing
  - Poor temperature control
- Poor coordination / fine motor control



# Hypotonia

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- Tone versus strength
- Concept of fighting gravity
- AFO's oftentimes helpful in walking
- **PHYSICAL THERAPIST**



# Seizures

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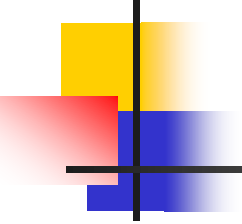
- Seizures can come in many forms
- Some forms are subtle
  - e.g. absence seizures
- Temperature control problems may exacerbate
- CHILD NEUROLOGIST



# Developmental Delay

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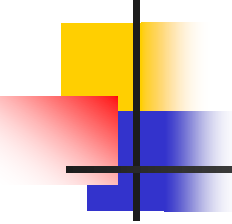
- Generally speaking, developmental progress is linear
- Speech and language delays are often disproportionate
  - Expressive language more affected
- Early developmental 'scores' have little predictive value
- As compared to most other conditions, children with Sotos syndrome may do some 'catch up'
- **EARLY INTERVENTION / DEVELOPMENTAL PEDIATRICIAN**



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A unique feature of Sotos syndrome lies in the “natural history” of this condition. In contrast to most other conditions with neuromotor impairments, the early developmental delays seen in patients with Sotos syndrome are poorly correlated with long term outcomes.

e.g. things often get better



# Issue #3 : Feeding

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- Hypotonia
- High arched palate
- Oro-motor dis-coordination
- Texture hypersensitivity
- OCCUPATIONAL THERAPIST



# Issue #4 Childhood Tumors

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- Rare
- Early reports inaccurate
- Series from Hersch et al 1991 <2%
- UK study 1/40 by age 24
- 3 cases out of over 300 (Trevor Cole)
- **NO SPECIAL SURVEILLANCE INDICATED**



# Issue #5

## Associated Medical Conditions

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- Scoliosis
- Developmental heart defects
- Frequent upper respiratory infections
- Neonatal hyperbilirubinemia (jaundice)
- Glucose intolerance
- Hyperthyroidism
- Hemihypertrophy
- Nystagmus/strabismus

# Issue # 6

## Resources for Persons with Sotos syndrome

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- SSSA
- Local clinical genetics program
- Pediatric neurologist
- Early intervention programs
- Pilot Parents, Parents Educating Parents, Association for Retarded Citizens
- State health department (state genetics coordinator)