

*Sotos Syndrome Support Association
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*G. Bradley Schaefer, MD
Founding Director, Medical Genetics
University of Arkansas for Medical Sciences*



Diagnosis of Sotos Syndrome

Accuracy from the beginning



Sotos Diagnostic Features:

- **Growth:** Increased length at birth. Increased height, weight, head circumference in childhood. Head size remains large, but height and weight tend to normalize. Sotos children do not become "giants".
- **Appearance:** Characteristic facial features including large head, elongated shape, high forehead, long chin, slightly wide-spaced eyes which tend to slant downward. Sotos kids look more like each other than their siblings.
- **Development:** Early development delay, especially gross motor due to hypotonia. Behaviour problems common.
- **Bone Age:** Advanced bone age (as determined by an X-ray).



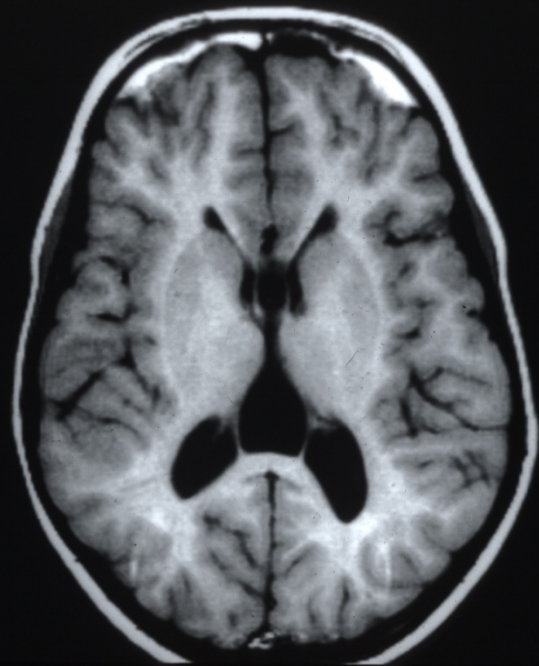
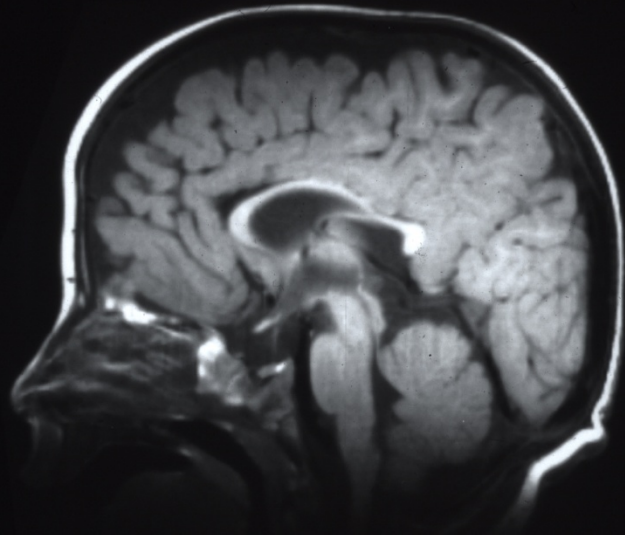
Making the diagnosis ...

- **MRI scan of the brain:**

- 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





Diagnosis of Sotos Syndrome

Characteristic Facial Features

- Children with Sotos syndrome tend to look more like each other than their family members
- The pattern of facial features seen in Sotos syndrome is the key distinguishing feature
 - Highest correlation with genetic testing



Making the diagnosis ...

- The "strict criteria" proposed for a diagnosis of Sotos syndrome requires that the individual have at least three of the following:
 - Facial appearance: large head, tall narrow skull, wide set down-slanting eyes, flat-bridged nose, high arched palate, early eruption of teeth (often by 3 months of age), thin hair, pointed chin, prominent forehead, and the appearance of a receding hairline.
 - 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".



“Sotos-like” Syndrome

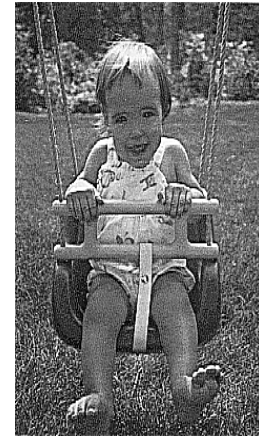
- Exactly as the name implies
- Many features of Sotos, but not enough to confidently confirm a diagnosis
- Gene testing now confirms what we previously suspected:
 - Some (5 – 8%) do have a change in the NSD1 gene (mild Sotos syndrome)
 - The rest probably have a different genetic cause with a similar clinical effect

Sotos syndrome testing:

Approximately 75% of patients with a clinical diagnosis of Sotos syndrome have an alteration in the *NSD1* gene.

In the European, white population:

- 5-10% have a deletion detected by FISH
- 70% have a mutation detected by DHPLC/sequencing



Photos from the Sotos Syndrome Support Association (need to get permission)

Figure 1. FISH analysis using *NSD1* probe shows deleted region (arrow).
Figure 2. DHPLC reveals alteration in pattern at arrow for exon 23.
Figure 3. Sequence analysis of exon 23 confirms missense mutation at arrow.

FIGURE 1.

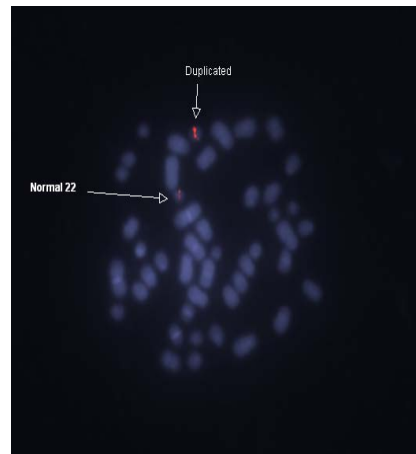


FIGURE 2.

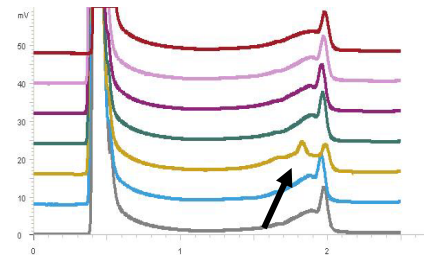
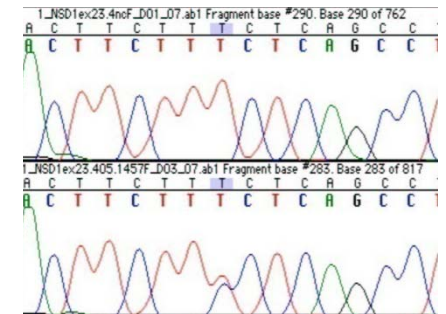


FIGURE 3.



7618T>C nucleotide change
S2540P amino acid change

Recent studies demonstrate that approximately 5% of Sotos syndrome patients have partial deletions, such as exonic deletions, of the *NSD1* gene [Douglas et al., J. Med. Genet. 2005,42(9):e56] that will not be detected by FISH or DHPLC/sequencing. Our laboratory is in the process of analyzing the *NSD1* gene for exon deletions using the multiplex ligation probe amplification (MLPA) technology for future clinical testing purposes.

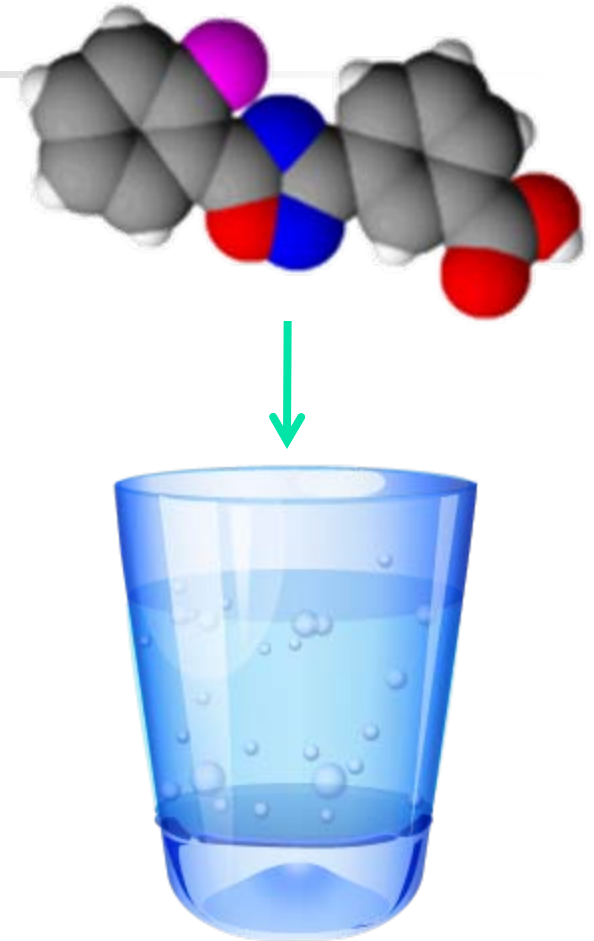


What's in a diagnosis?

- Etiology (cause)
- Pathophysiology (mechanism)
- Natural history (collective wisdom)
- Genetics (familial implications)
- Targeted treatments (current and future)

What is Ataluren?

- Potential therapy for nonsense mutation mediated genetic disease, currently in clinical trials for BMD/DMD and cystic fibrosis
- Taken orally as a powder that can be dissolved in liquid such as water or milk



We have a diagnosis – now what?



A big part of the journey that is Sotos syndrome is arriving at an accurate diagnosis. Once the diagnosis is made, there are many immediate activities that revolve around getting a diagnosis. Assimilating this information takes some time, but usually happens in a relatively short period of time. So what happens next? Are there things we should anticipate? What about the development? What about behaviors? What about autism? What about adult life? We'll explore these and many more long term thoughts about the life of a person with Sotos syndrome



Things not to worry about

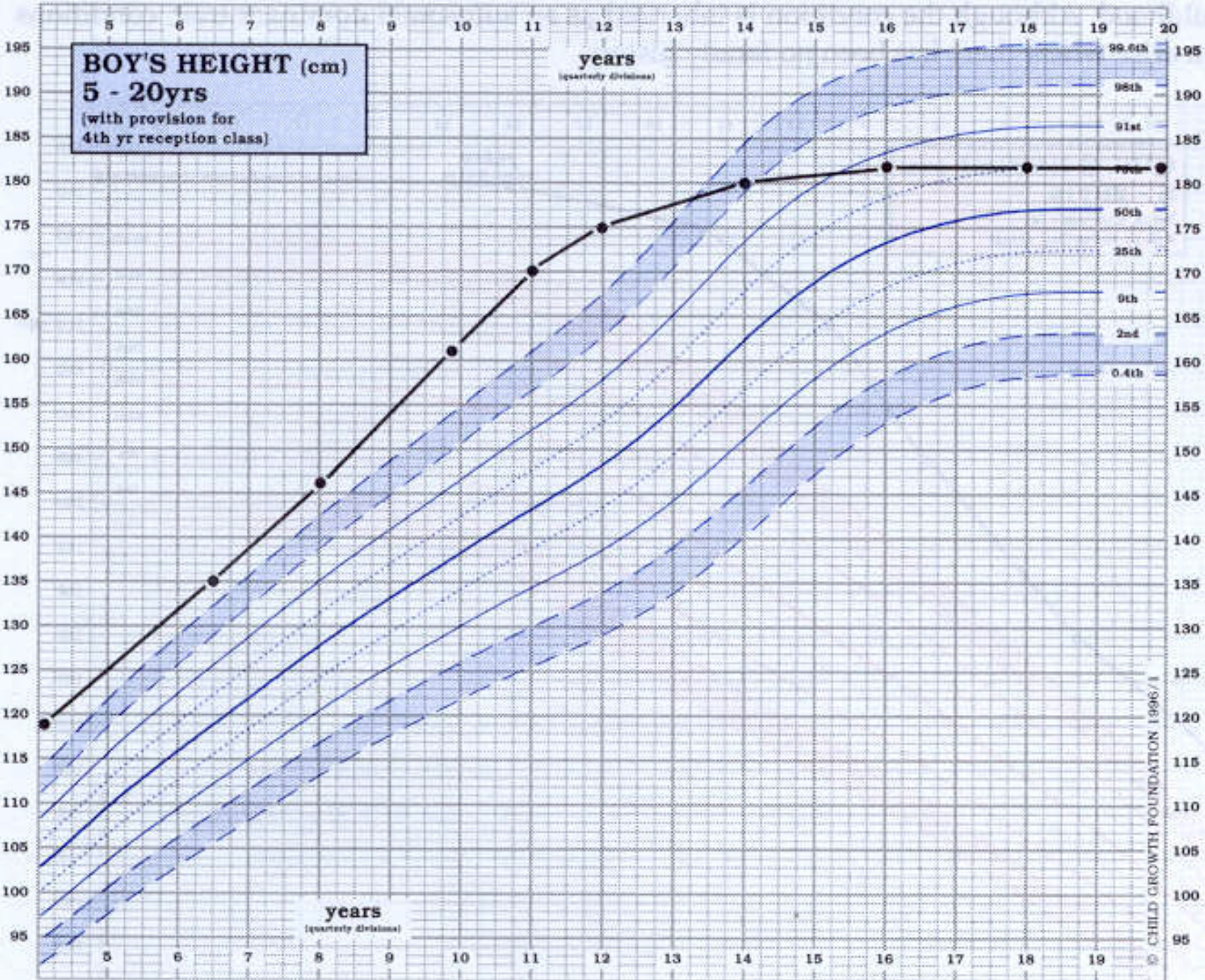
Sotos Syndrome

Final Height Predictions

- Females
 - mean 8 cm (3") greater than predicted FH

- Males
 - mean 13.6 cm (5 ¼") greater than predicted FH

BOY'S HEIGHT (cm)
5 - 20yrs
 (with provision for
 4th yr reception class)



77"

68"



Cancer Risk

- Series from Hersch et al 1991 (<2%)
- UK study 1/40 (2.5%) by age 24
- 3 cases out of over 300 (1%)
- Tumors occur in 1-3% of persons with Sotos syndrome
 - Reported sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia (ALL) and small cell lung cancer



The cancer incidence rate is:

- 60.4 per 100,000 in the 25- to 29-year-old population;
- 1/3 for a lifetime



Cancer Risk

- Rare
- Early reports inaccurate
- No special surveillance indicated



Longevity

- No evidence that person with Sotos syndrome have a shortened life expectancy
- I am aware of several individuals over 60 years old



Watch for 'stuff'



Does _____ occur with Sotos?

- Commonly reported associations (in handbook, articles)
- Other things not reported??
- Chance occurrence of 2 rare events



Seizures

- Seizures (30%)
 - can appear in many forms
- Some forms are subtle
 - e.g. absence seizures
- Temperature control problems may exacerbate seizures
 - “febrile seizures” 50%



Feeding and Swallowing

- Multiple contributors to feeding and swallowing problems
 - Hypotonia
 - High arched palate
 - Oro-motor dis-coordination
 - Texture hypersensitivity
 - Other esophageal dysfunction



Associated Medical Conditions

- Frequent upper respiratory infections and ear infections
- Gastro-esophageal reflux
- Scoliosis
- Thyroid disorders
- Mega-colon

What do I do with
developmental milestones?





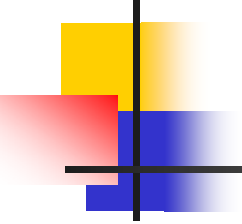
Monitoring Development

- Developmental quotient (DQ)
 - Compares skills to age matched peers
 - Little to no prognostic value
- Intelligence quotient (IQ)
 - A test that tries to assess learning potential
 - No perfect test



Key Principles

- Development is not a foot race
- Natural history of neuro-development in Sotos



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



Hypotonia

universal in Sotos syndrome

- Low muscle tone
- Not the same as strength
- Increases difficulty of tricking gravity
- Symptoms
 - Gross motor delays
 - “Loose joints”
 - Protruding tongue
 - Drooling
 - Problems with feeding / swallowing



Hypotonia

- Generally improves with time
- Probably never completely goes away
- Therapies
 - Physical therapy
 - Occupational / speech therapy
 - Orthotics
 - Sugeries



Speech and Language

- Expressive language impairments
 - Reduced variety of words
 - Shorter sentences
 - Simplified grammar
- Sound production impairments
 - Create their own linguistic 'rules'



Speech and Language

- Voice differences
 - Hoarseness, hypernasal, pitch changes
- Social – pragmatic differences
 - Monotone speech
- Stuttering
 - Later onset than typical (even into adolescence)



Pediatric Neuropsychology

A professional specialty
concerned with learning &
behavior in relationship to a
child's brain

-Division 40, APA



Pediatric Neuropsychology

Referrals:

Difficulties with learning, attention, behavior, socialization, or emotional control

A disease or inborn developmental problems that affects the brain in some way; or

A brain injury from an accident, birth trauma, or other physical stress -Division
40, APA



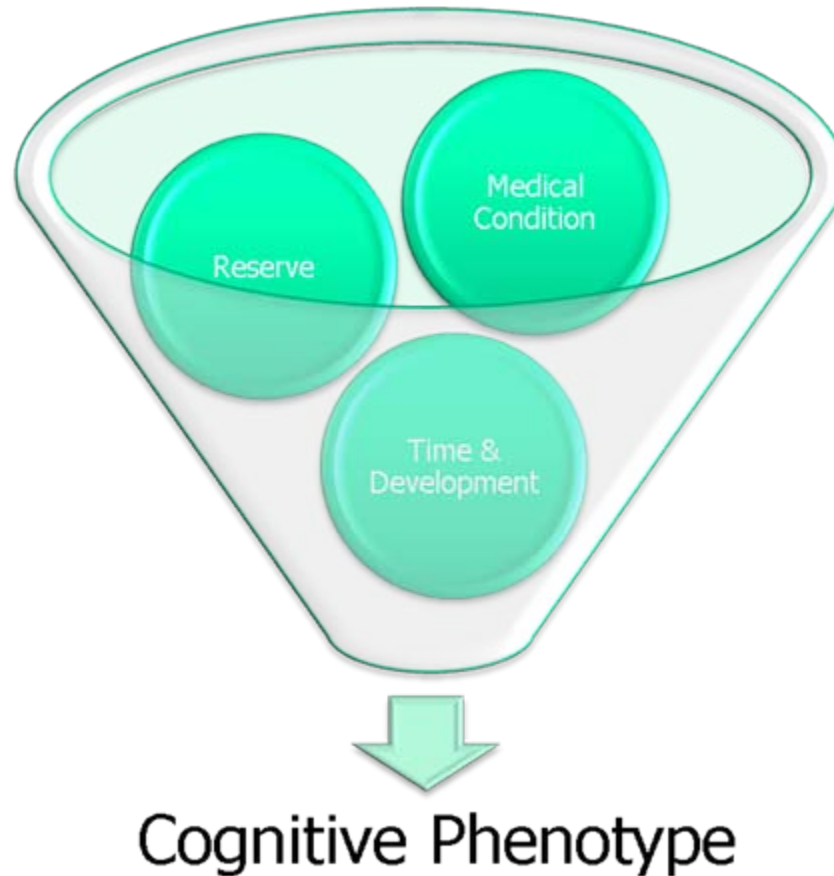
Pediatric Neuropsychology

What is assessed?

- Intelligence
- Achievement skills
- Attention / Executive Functioning
- Learning & Memory
- Language
- Sensory & Sensory Motor
- Motor
- Behavioral, Emotional, & Social Functioning



Why?





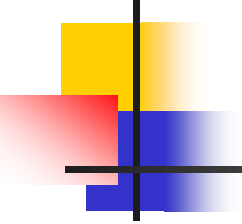
Toileting

- 50% resolve per year if uncomplicated
- Diagnostic evaluation after “too long”
 - UTI’s for wetting
 - Mega-colon for stooling
 - Tethered cord for one or both
- Behavioral interventions
 - Awareness training
 - Distractibility
- Medications as needed



Should I let them _____ ?

Graduated responsibilities

- 
-
- The key issue is the individual (cap)abilities of the person.
 - Reported IQ range in Sotos syndrome is 20 – 120
 - Strengths / weaknesses assessment
 - Parents insight
 - Quantitative tools



Drivers License

- Not age dependent, but skill readiness
 - Skills achievement check list
 - Co-pilot / navigator activities
 - Trial runs
 - Professional evaluations



Other major milestones

- Solo travel
 - Planes, trains and automobiles
- Employment
- College



Career Planning

- Some can accomplish independent living
- As in most things, must be individualized
- Must figure in
 - Cognition
 - Social skills
 - Temperament
- Personal preference
 - Many seem to have a great affinity for working with younger children



Behaviors



Behavioral Changes

- Attention deficit (hyperactivity) disorder
- Agression
- Phobias
- Obsessions / compulsions
 - Adherence to routines
- Impulsivity
- Tantrums
- Frustration behaviors



Autism

- "Autism" means a developmental disability significantly affecting verbal and non-verbal communication and social interaction, generally evident before age three, that adversely affects educational performance.



Autism

- Diagnostic Criteria
 - Impairment of reciprocal social interactions
 - Impairment of verbal and non-verbal communications
 - Restricted educational activities
 - Abnormal interests and stereotypic behaviors



Autism and Sotos

- Autism (some)
- Autistic behaviors (many)
- PDD nos (many)
- None of the above (some)



Autism and Sotos Syndrome

- You can safely assume if a child has Sotos syndrome and autism / autistic behaviors that the two are linked (no need to look for something else)
- The interventions are the same as for any other person with autism

Partial List of Genetic Syndromes with a Reported Association with Autism

<u>NO WORK-UP INDICATED</u>	<u>AUTISM EVALUATION INDICATED</u>
Fragile X syndrome	Apert syndrome
Rett syndrome	Williams syndrome
Angelman syndrome	De Lange syndrome
Prader-Willi syndrome,	Noonan syndrome
Smith-Lemli-Opitz syndrome	Down syndrome
Smith-Magenis syndrome	Turner syndrome
Tuberous sclerosis	Neurofibromatosis
CHARGE syndrome	Myotonic dystrophy, Duchenne dystrophy
Shprintzen syndrome (22q11 deletions)	Moebius anomalad
Sotos syndrome	Cohen syndrome
PTEN associated disorders	Oculo-auriculo-vertebral spectrum
Hypomelanosis of Ito	Joubert syndrome
Lujan-Fryns syndrome	



Common Autism Therapies

<http://autism.healingthresholds.com/therapy>

- Speech and language therapy (used by 70% of parents)
- Visual schedules (used by 43.2% of parents)
- Sensory integration therapy (used by 38.2% of parents)
- Applied behavior analysis therapy - ABA (used by 36.4% of parents)
- Social story therapy (used by 36.1% of parents)
- Vitamin C (used by 30.8% of parents)
- Vitamin B6 and magnesium (used by approximately 30% of parents)
- Essential fatty acids (used by 28.7% of parents)
- Picture exchange communication system - PECS (used by 27.6% of children)
- Casein-free diet (used by 26.8% of parents)
- Gluten-free diet (used by 23.1% of parents)
- Vitamin A (used by 22.0% of parents)



Other Autism Therapies

<http://autism.healingthresholds.com/therapy>

■ Behavioral Strategies

- Cognitive/behavioral therapy (used by 21.3% of parents)
- Discrete trial training (used by 18.7% of parents)
- TEACHH (used by 15.7% of parents)
- Augmentative and alternative communication (used by 12.6% of parents)
- Conductive education (used by 10% of parents)
- Gentle teaching (used by 10% of parents)
- Facilitated communication (used by 9.8% of parents)
- Auditory integration training (used by 9.1% of children)
- Rapid prompting (used by 7.0% of parents)
- Visual integration training (used by 6.5% of parents)
- Holding therapy (used by 4.3% of parents)
- Integrated movement therapy (used by 4.3% of parents)
- Multisensory environments – Snoezelen (used by 3.5% of parents)



Other Autism Therapies

<http://autism.healingthresholds.com/therapy>

■ **Alternate Behavioral Strategies (1)**

- Music therapy (used by 16.0% of parents)
- Floortime (used by 13% of parents)
- Weighted vest or blanket (used by 12.8% of parents)
- Craniosacral manipulations (used by 4.7% of parents)
- Infant massage (used by 4.1% of parents)
- Aromatherapy (used by 4.1% of parents)
- Transfer factor (used by 2.4% of parents)
- Dance therapy (used by 2.4% of parents)
- Joint action routines (used by 2.2% of parents)
- Bolles sensory learning method (used by 1.9% of parents)
- Neurofeedback (used by 1.8% of parents)
- Fast forward (used by 1.7% of parents)
- Irlen lenses (used by 1.6% of parents)
- Lindamood-Bell (used by 1.4% of parents)
- Interactive metronome (used by 1.4% of parents)



Other Autism Therapies

<http://autism.healingthresholds.com/therapy>

■ **Alternate Behavioral Strategies (2)**

- Azrin 24-h toilet training (used by 1.1% of parents)
- LEAP (used by 1.0% of parents)
- Osteopathy (used by 1.0% of parents)
- Self-injurious behavior inhibiting system – SIBIS (used by 1.0% of parents)
- Clathration (used by 0.8% of parents)
- Institute for human potential (used by 0.6% of parents)
- Rhythmic entrainment interventions (used by 0.6% of parents)
- Acupuncture (used by 0.6% of parents)
- Neural therapy (used by 0.4% of parents)
- Watsu (used by 0.4% of parents)
- Electro-aversive therapy – Faradic skin shock (used by 0.4% of parents)
- Eden program (used by 0.2% of parents)
- Baudhuin preschool (used by 0.2% or parents)



Other Autism Therapies

<http://autism.healingthresholds.com/therapy>

■ Prescribed Therapies (1)

- Risperdal (used by 10.2% of parents)
- Clonidine (used by 6% of parents)
- Prozac (used by 4.9% of parents)
- Ritalin (used by 4.6% of parents)
- Nystatin (used by 4.6% of parents)
- Zoloft (used by 3.9% of parents)
- Depakote (used by 3.6% of parents)
- Adderall (used by 3.2% of parents)
- Paxil (used by 2.8% of parents)
- Tegretol (used by 2.0% of parents)
- Secretin (used by 1.6% of parents)
- Bethanechol (used by 1.2% of parents)
- Klonopin (used by 1.0% of parents)
- Xanax (used by 1.0% of parents)
- Clozapine (used by 1.0% of parents)
- Tenex (used by 1.0% of parents)
- Buspar (used by 1.0% of parents)



Other Autism Therapies

<http://autism.healingthresholds.com/therapy>

■ Prescribed Therapies (2)

- Diflucan (used by 0.8% of parents)
- Vancomycin (used by 0.6% of parents)
- Lithium (used by 0.6% of parents)
- Sporanox (used by 0.6% of parents)
- Ativan (used by 0.4% of parents)
- Naltrexone (used by 0.4% of parents)
- Intravenous immunoglobulin (used by 0.4% of parents)
- Inderal (used by 0.2% of parents)
- Vagal nerve stimulation (0.2% of parents)
- Dilantin (used by 0.2% of parents)
- Tofranil (used by 0.2% of parents)
- Thorazine (used by 0.2% of parents)
- Haldol (used by 0.2% of parents)
- Valium (used by 0.2% of parents)



Other Autism Therapies

<http://autism.healingthresholds.com/therapy>

■ **OTC medications**

- Antihistamine (used as a sleep aid by 6.7% of parents)
- Dexedrine (used by 1.4% of parents)
- Pepcid (used by 1.2% of parents)



Other Autism Therapies

<http://autism.healingthresholds.com/therapy>

■ Homeopathic

- Probiotics (used by 20.5% of parents)
- Mega-vitamin therapy (used by 15.8% of parents)
- DMG (dimethylglycine) (used by 14.0% of parents)
- Melatonin (used by 10.8% of parents)
- Homeopathy (used by 10.2% of parents)
- L-Glutamine (used by 10.1% of parents)
- Yeast-free diet (used by 7.6% of parents)
- Chelation (used by 7.4% of parents)
- Reduced L-glutathione (used by 4.4% of parents)
- Feingold diet (used by 2.7% of parents)
- Extended breast feeding (used by 0.8% of parents)



Sotos Syndrome and Socialization

- Persistently socially naïve
- Struggle with unfamiliar settings
- Tendency towards social isolation
- Relate better to younger kids and adults than peers



Education



Educational Process for CSHCN (US)

- IEP
- IFSP
- Educational transition



Medical Transition



500,000 Children with Special
Health Care Needs turn 18
every year



Youth with Special Health Care Needs (YSHCN)

- 90% of YSHCN reach their 21st birthday
- 45% of YSHCN lack access to a physician familiar with their health condition
- 30% of all youth 18-24 years of age lack a payment source for health care
- 40% YSHCN demonstrate ER use annually (vs 25% of 'typical' youth)
- YSCHN experience increased school interruptions



Health Care Transition (HCT):

“The purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care system”

Transition from child-centered to adult health-care systems for adolescent with chronic conditions. A position paper of the Society for Adolescent Medicine. *J Adolesc Health*. 1993; 14:570-576



Policy Recommendations

1. Ensure all YSHCN have an identified health care professional who attends to the unique challenges of transition.
2. Identify knowledge and skills required to provide developmentally appropriate transition services, and include them in training for primary care residents and physicians.
3. Maintain a portable, accessible, and current medical summary.



Policy Recommendations

4. Create a written transition plan by age 14 with young person and family. Annually update.
5. Guidelines for primary and preventive care should be applied to all adolescents and young adults.
6. Ensure affordable, continuous health insurance throughout adolescence and adulthood, including
 - Health care transition planning
 - Care coordination



Sexuality



Puberty

- (Early) normal, not precocious
- Pre-signs
 - Girls = breast buds
 - Boys = testicular enlargement
- Preparation / anticipation



Sexuality Issues

- Self discovery
- Dating
- Sexual activity
- Protection
 - STDs
 - Abuse
- Reproduction



Planning for the Future



Career Planning

- Some can accomplish independent living
- As in most things, must be individualized
- Must figure in
 - Cognition
 - Social skills
 - Temperament
 - Anxiety
 - Personal preference
 - Many seem to have a great affinity for working with younger children



Life without mom and dad

- Residence
 - Group home options
 - Talk to siblings / other relatives
- Safe storage of important documents
- Wills / trusts



Most Importantly.....

Have fun