

Health and Development in XYY Syndrome

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Outline

- Medical Problems in XYY
- Development and Neurodevelopmental Disorders in XYY

XYY Syndrome

- 1 in 1000 live-born boys
- 85% or more males with XYY are never diagnosed
 - No dysmorphic facial features, normal IQ range
- Biased early studies of males in prisons or had psychiatric diagnoses
- Lack of large scale studies
- Ascertainment bias
 - Clinic based sample
 - No newborn screening

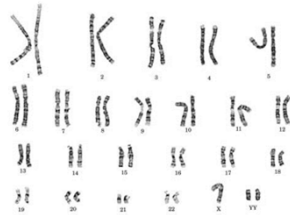
Sources...

- Medical Literature
 - Prospective cohort studies 1970's & 80's
 - Genetics Textbooks
 - Journal Articles
- Parents & Patients

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES
47,XXY Syndrome: Clinical Phenotype and Timing of Ascertainment
 Martha Zager Bartsley, MD¹, Karen Kowal, FAC², Carly Levy, MD³, Anja Cook, BA⁴, Natalie Ajayi, BA⁴,
 Heidi Tarajko, MD⁵, Melissa Laffin, MD⁶, Shanna Weller, PhD⁷, Shannon Dennis, BA¹, and Judith L. Ross, MD^{1*}
 Objective: To describe sociologic, physical, and behavioral features in a large cohort of males with 47,XXY (XXY),
 ages newborn to young adult.
 Study design: This is a cross-sectional descriptive study of male subjects with XXY who were evaluated at 1 of 2
 specialized academic sites. Subjects underwent a history, physical examination, laboratory testing, and cognitive/
 behavioral evaluation.
 Results: In 92 males with XXY (mean age 9.6 ± 5.3 years [range 0.5–36.5]), mean height SD was above average (1.0
 ± 1.2 SD). Macrocephaly (head circumference > 2 SD) was noted in 20.6% (20%), hypotonia in 33.0% (33%),
 cribriformity in 47.9% (52%), and hyperreflexia in 53.9% (58%). There was testicular enlargement for age (> 2 SD)
 in 41.9% (50%), but no increase in genital anomalies. No physical phenotypic differences were seen in boys diag-
 nosed prenatally vs postnatally. Testosterone, luteinizing hormone, and follicle stimulating hormone levels were in

XXY (Bartsley, 2013)

- Age range (n=90)
 - 6 months-36.5 years
 - Mean = 9.6 years
- Diagnosis
 - 35 Prenatal
 - 55 Postnatal
 - 5 hypotonia
 - 7 language delay
 - 17 behavior
 - 26 Other (dysmorphic,
parent's request)



Medical Care in XXY

- Growth
- Bones and Joints
- Acne
- Tics and Tremors
- Motor Tone and Coordination
- Puberty, Testosterone, Fertility
- Other

Growth in XYY

- Tall stature
 - Mean height above average
 - Height < 6 years average, but above average > 6 years
 - Taller than fathers by 4-5 inches
 - XYY 6 feet vs. XYY 6 ft 3 inches
- Puberty usually slightly delayed
 - Pubic hair 13.8 yrs vs. 12.4 years in male siblings
 - Growth spurt later but longer duration than siblings

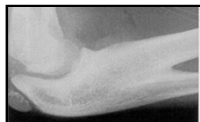
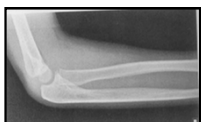
Bones and Joints

- Flat Feet
 - Pes Planus
 - Treatment controversial in mild cases
 - Arch supports vs. no arch supports
 - Moderate to severe cases
 - Orthopedic Evaluation
 - Orthotics



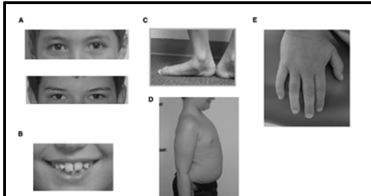
Bones and Joints

- Elbows
 - Radioulnar synostosis
 - 2 reported cases in literature
 - 1 case in our sample
 - Inability to pronate and supinate forearm
 - Limited range of motion can interfere with fine motor skills
 - X-ray if limited range of motion
 - But, usually no treatment...



Other Medical Findings

- 52% with Clinodactyly
- 59% with Hypertelorism
- 22% Dental problems
 - Prognathic jaw with underbite and macrodontia
- 63% Hypotonia
 - Decreased strength, tone, coordination
- 52% Flat Feet



Acne

- Literature
 - 4 reports from 1970's
 - Nodulocystic acne
 - 7/36 age 13+ (19.4%) with Mild-Moderate Acne (same as general population)
 - 0 with Severe, Cystic Acne
- Consider impact on self-esteem & peer relationships
- Treatments:
 - OTC preparations
 - Pediatricians / Dermatology
 - MANY EFFECTIVE MEDICATION TREATMENTS!

Co-Morbid Diagnoses

- 39% Asthma vs 9.6% general population
 - Asthma improves with age
 - Consider asthma diagnosis if your child has frequent respiratory infections
- 13% Seizures vs 1% general population
- Treatment is the same as the general population

Tics

- Literature
 - Geerts et al. (2003) – 5/38 XYY males (13%)
 - Reports of Tourette's Syndrome
- Prelim study 6/27 (22%)
- Tics
 - Motor vs. vocal
 - Occur in up to 10% of children during childhood
 - Treatment when impacting social development and self-esteem
 - No medications
 - Medications to target tics
 - Management of anxiety
 - Can be side effect of stimulant (ADHD medications)

Tremor



- Literature
 - Multiple reports of hand tremors
- Prelim study 7/27 (22%)
- Most likely to present >8-9 years, increases in adolescence
- Intention Tremor of hands
- Impacts writing and fine motor skills (self-care skills)
- Treatment:
 - Supports in school (keyboarding)
 - Weighted pens, cups, eating utensils can decrease tremors
 - Medications can be helpful if severe

Motor Tone & Coordination

- Low Muscle Tone / Hypotonia (63% cases)
 - Multiple reports in the literature
 - Consider physical therapy or activities to help with tone, coordination, and strength
- Salbenblatt et al (1987)
 - 4 males with XYY
 - Hypotonia (low muscle tone)
 - Motor planning dysfunction / dyspraxia
 - Problems with bilateral coordination
 - Problems with visual-motor integration

Motor Tone & Coordination

- MIND Institute Patients
 - Visual-Motor Coordination
 - 67% had motor coordination scores in the delayed range
- Recommendations:
 - Occupational/Physical therapy evaluations and treatments
 - Keyboarding/Assistive technology

Puberty, Testosterone, Fertility

- XYY is NOT XXY
- Most cases have normal puberty and are not infertile!!
- It is important to be aware of risks in these areas...
- PUBERTY –

Puberty, Testosterone, Fertility

- Testosterone levels in XYY – Many studies
 - Too high? Too low? Normal?
 - 39/43 normal testosterone level for age, 1 high testosterone, 1 low testosterone and delayed puberty (*Barkley et al, 2013*)
- Low testosterone production = hypogonadism
 - Clinical Signs of hypogonadism
 - Fatigue, Poor endurance
 - Low body hair, decreased sexual development
 - Small penis, testicles
 - Mood instability, depression
 - Concerns?? Evaluation by endocrinologist (doctor specializing in growth and hormones)

Puberty, Testosterone, Fertility

- Fertility
 - Survey of 1,007 males with infertility
 - Yoshida et. al (1997)
 - 3 with XYY (0.3%)
 - 28 with XXY (3%) (Other studies 2-18%)
 - XYY males are at higher risk for:
 - X&Y variations in their sperm
 - Children with XXY, XYY (and others??)
 - Genetic counseling prior to childbearing to discuss risks

Other Medical Problems

	Prenatal	Postnatal
Hypotonia	51%	71%
Clinodactyly	46%	57%
Dental Problems	29%	18%
Flat feet	44%	59%
Scoliosis	9%	16%
Motor Delay/dyspraxia	23%	18%
Low musculature	20%	20%

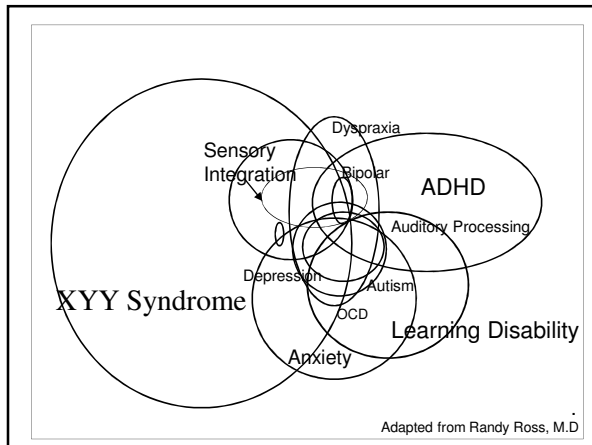
Outline

- Medical Problems in XYY
- Development and Neurodevelopmental Disorders in XYY

XYY and Development

AT RISK FOR:

- Speech and Motor delays
- Learning Disabilities
 - Verbal
 - Reading
- Short attention span
- Impulsivity
- Social Skills problems
- Sensory Integration Problems
- Anxiety, Depression, Mood Disorders



XYY Syndrome

(2003) Geerts et al, Genetic Counseling

	PRENATAL DX (n=12)	POSTNATAL DX (n=26)
Normal IQ	100%	92%
FSIQ	95.8	89.9
Special Ed	8%	50%
Speech delay	50%	77%
Motor delay	25%	85%
PDD	0%	19%

XYY Syndrome *(Bardsley, 2013)*

	PRENATAL DX (n=36)	POSTNATAL DX (n=44)
Full Scale IQ	102	85
Verbal IQ	101	82
Performance IQ	107	90
Special education	23%	52%
OT or PT	59%	70%
Speech therapy	64%	94%

XYY Syndrome

	PRENATAL DX (n=15)	POSTNATAL DX (n=25)
CBCL behavior total	63	66
Internalizing total	61	62
Externalizing total	57	60

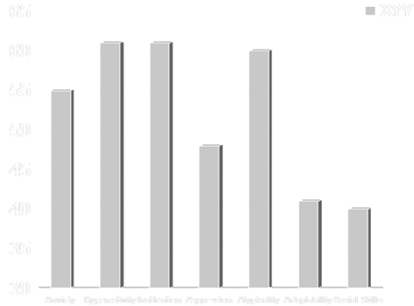
Most severe behavioral issues for both groups-
Internalizing behaviors (withdrawn, somatic complaints,
anxiety/depressed, social problems, thought, attention

XYY Syndrome

	PRENATAL DX (n=35)	POSTNATAL DX (n=55)
ADD or ADHD	40%	60%
Verbal and motor tic	18%	18%
Oppositional defiant	6%	5%
Depression	11%	15%
Anxiety	17%	31%
Autism/Pervasive Developmental	11%	40%

Behavioral Profiles - BASC

■ Behavioral Assessment System for Children (n=31)



Sensory Integration Dysfunction

- Difficulty processing information from the senses (touch, movement, smell, taste, vision, and hearing) and responding appropriately to that information.
- One or more senses that either over- or underreact to stimulation.
- Sensory processing disorder can cause problems with a child's development and behavior
 - Withdraw when touched.
 - Refuse to eat certain foods because of how the foods feel when chewed.
 - Oversensitive to odors.
 - Hypersensitive to certain clothes
 - Dislike getting his or her hands dirty.

Autistic Features

- Pervasive Developmental Disorders or Autism Spectrum Disorders
 - Autistic Disorder
 - Impaired Communication
 - Impaired Social-Emotional Reciprocity
 - Restricted Interests or Stereotyped Routines
 - Asperger's Syndrome
 - PDD-Not Otherwise Specified (PDD-NOS)

Autism Spectrum Disorders

	XXY	XYY	XXYY
N	20	21	20
Mean Age	9.13	9.45	12.19*
Diagnosis	XXY	XYY	XXYY
Prenatal	8	9	0
Postnatal	12	12	20
VIQ	102.3	90.4	76.75
PIQ	104.3	102.5	89.1
FSIQ	103.6	95.2	81.2

	XXY	XYY	XXYY
Overall ASD	5% (1/20)	38.0% (8/21)	45.0% (9/20)
% PDD	5% (1/20)	33.3% (7/21)	30.0% (6/20)
% AUT	0%	4.7% (1/21)	15.0% (3/20)

No PDD
 PDD
 AUT



ADHD

Attention-Deficit Hyperactivity Disorder Symptoms in Children and Adolescents with Sex Chromosome Aneuploidy: XXY, XYY, and XXYY

Nicole R. Tartaglia, MD,* Natalie Ayari, BA,* Christa Haruff-Lee, PhD,* Richard Boada, PhD†

- 33 males age 6-20 with XYY
 - 76% of males with XYY Syndrome met DSM-IV diagnostic criteria for ADHD.
 - 49% Predominantly Inattentive Symptoms
 - 24% Combined Inattentive and Hyperactive/Impulsive Symptoms
 - 3% Predominantly Hyperactive – Impulsive symptoms
- Prenatal 64% vs. Postnatal 82%

Table 4. Proportion of Children Within Each Trisomy Group Diagnosed with ADHD (Any Subtype) by Prenatal vs Postnatal Diagnostic Status

	47, XXY	47, XYY	47, XXX
Prenatal diagnosis	n = 25	n = 11	n = 14
No. with ADHD	5 (20%)	7 (64%)	6 (43%)
Postnatal Diagnosis	n = 31	n = 22	n = 11
No. with ADHD	15 (48%)	18 (82%)	7 (64%)

ADHD: attention-deficit/hyperactivity disorder.

Attentional Problems

- Not all attentional problems are AD/HD
- Main features of Attention Deficit/Hyperactivity Disorder
 - Inattention
 - Hyperactivity
 - Impulsivity



ADHD Symptoms in Children

- Inattention
 - Difficulty sustaining attention in tasks or play activities
 - Difficulty organizing tasks or activities
 - Distracted by extraneous stimuli
 - Loses things necessary for activities (toys, school assignments, pencils)
 - Does not follow through on instructions

ADHD Symptoms in Children

- Hyperactivity & Impulsivity
 - Fidgets with hands or feet, squirms in seat
 - Is “on the go” or “driven by a motor”
 - Blurts out answers
 - Has difficulty awaiting turn, butts into conversations/games
 - Often runs around, climbs excessively when inappropriate



ADHD in Children

3-8% of children,
Male:female 3:1



- ADHD – Combined Type
- ADHD – Predominantly Inattentive Type
- ADHD – Predominantly Hyperactive Type

It's not always ADHD...

- All complaints of Inattention or Hyperactivity are NOT necessarily ADHD
- Other considerations:
 - Learning Disability
 - Dyslexia
 - Auditory Processing Disorder
 - Anxiety
 - Sensory reactivity/Sensory Integration Disorder
 - Seizures
 - Sleep Disorder, Obstructive Sleep Apnea
 - Mental Retardation
- Diagnosis of ADHD by professional

Treatments for ADHD symptoms

- Behavioral Interventions
 - Strategies to support ADHD symptoms
 - Strategies to improve executive function
 - School accommodations
- Medications

Medications for psychological or behavioral problems in X&Y chromosome variations

- Not everyone will need medications
- Medical treatment of abnormality in brain development caused by genetic condition
- Medication treatment should always accompany behavioral therapies
- Criteria to consider treatments: (Only 1 needed)
 - Child expresses distress about symptoms
 - Interferes with learning, academic progress
 - Interferes with social development
 - Interferes with overall home life/general functioning
- If your child seems “drugged,” it is the wrong medication

Positive Response to ADHD Medications (n=101)

XXY	73%
YYY	79%
XXX	75%

Medications

- ADHD Medications:
 - Stimulants
 - Methylphenidate (Ritalin, Concerta, Metadate, Focalin, Daytrana, etc)
 - Adderall
 - Side effects: decreased appetite, sleep disturbance, tics, agitation
 - Benefits: They work the day you give them, can use as needed
 - Nonstimulants - Effects generally not as strong as stimulants, but can also help with anxiety in some children
 - Strattera (atomoxetine)
 - Side effects: sedation, agitation
 - Alpha Agonists:
 - Guanfacine: Intuniv (long acting), Tenex (twice per day)
 - Clonidine: Kapvay (long acting)
 - Side effects: sedation

Other Medications in XYY

- Medications to target Anxiety, Mood Swings, Outbursts, Tantrums
 - Anxiety / Depression
 - SSRIs (Zoloft, Celexa, Prozac)
 - Atypical Neuroleptics
 - Abilify, Risperdal
 - Can also help with atypical thoughts, paranoia, psychotic symptoms
 - Sleep (Melatonin, Trazodone)

Questions???

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