Brains, Genes, And Puberty: Testosterone Replacement Therapy in Klinefelter Syndrome

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2019 AXYS Family Conference
Goals

- Introduce Klinefelter Syndrome (KS)
- Learn about differences in executive and psychosocial functioning as well as brain differences in KS
- Discuss how testosterone may play a role in KS phenotype
- Explore the ways in which testosterone replacement therapy may affect brain and behavior
- Describe current gaps in understanding and need for further research
- Introduce a new research study at Stanford (BGAP Study)
Klinefelter Syndrome (KS)

- Genetic disorder that consists of a sex chromosome aneuploidy
  - Due to atypical number of X chromosomes
- Majority born with 47, XXY karyotype
- Most common sex chromosome condition

Credit: Alila Medical; Media/Shutterstock.com

Davis, et al., 2016
Common physical, behavioral, and neurocognitive traits

- Tall stature
- Testicular failure, reduced testosterone, impaired spermatogenesis (creation of sperm)
- Gynecomastia (enlarged breast tissue)
- Delayed or incomplete puberty

Ross et al., 2008, 2017; Lee et al., 2011
Common physical, behavioral, and neurocognitive traits

- Increased behavior problems, social problems, and withdrawal (shyness, reduced self-esteem)
- Increased depression, anxiety, and social-emotional issues

Ross et al., 2008; 2017; Lee et al., 2011
Common physical, behavioral, and neurocognitive traits

- Motor dysfunction and impaired visual-motor integration
- Language based learning issues
- Deficits in executive functioning
  - Working memory
  - Sustained attention/inhibition

Ross et al., 2008; 2017; Lee et al., 2011
Impact of physical, behavioral, and neurocognitive traits
Brain differences in KS
Reduced volume in

- Hippocampus
  - Learning and memory

- Insular cortex
  - Interoception/emotion processing
  - Some aspects of executive function
  - Social cognition

- May be associated with verbal memory and mood disturbances

Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014
Reduced volume in:

- Social deficits and mood/behavior dysregulation

**Amygdala**

<table>
<thead>
<tr>
<th>Fear and anxiety</th>
<th>Processing of faces, emotions, and social stimuli</th>
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Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014
Reduced volume in temporal and frontal regions leads to language and executive function/attention deficits. 

- Language and verbal memory
- Decision making

Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014
Increased volume in Sensorimotor (precentral and postcentral gyri) and posterior-occipital regions (cuneus and precuneus) could explain the preservation of visuospatial abilities and/or may indicate compensatory neurodevelopment.

Patwardhan et al., 2000, 2002; Bryant et al., 2011; Hong et al., 2014; Oh et al., 2014
How can KS be treated?
Testosterone replacement therapy (TRT)
Puberty-associated neurodevelopment and the role of testosterone

- Two hormone-sensitive periods in brain development:
  - perinatal
  - peripubertal

- Adolescence is a developmental period where gonadal hormones (e.g. testosterone) organize brain and behavior

Testosterone changes through lifespan
Androgen receptors and low levels of testosterone

- Several areas of the brain have androgen receptors (hypothalamus, amygdala, hippocampus, cortex)

- Recent research has found low testosterone levels as early as infancy or early adolescence in KS

http://www.essapharma.com/our-work/androgen-receptor/

Ross et al., 2005
Influence of TRT on the brain and associated behavior?
TRT may increase temporal lobe size and improve verbal fluency in males with KS

• Retrospectively looked at testosterone effects in adults with KS

• 20 participants total (10 with KS 47, XXY; 5 with KS received TRT)

Patwardhan et al., 2000
• Temporal lobe volume was significantly larger in KS TRT+ compared to KS TRT-

• No significant difference in temporal lobe volume between KS TRT+ and TD group

• KS TRT+ had significantly higher verbal fluency scores than KS TRT-

• No difference is verbal memory scores between both KS groups

Patwardhan et al., 2000
KS boys treated with low doses of androgen (oxandrolone) showed improvement in visual-motor functioning, anxiety and social functioning

- 2 year clinical trial
- Included boys ages 4-12 years of age

Ross, et al., 2017
Low doses of oxandrolone might also cause increase in hippocampal size in boys with KS

- Subgroup of KS participants in oxandrolone clinical trial were scanned as well as TD controls

Foland-Ross, et al., 2018
Positive association between hippocampus volume and performance on spatial memory task

Larger hippocampal volumes with treatment in KS

Foland-Ross, et al., 2018
Testosterone treatment is associated with reduction in depressive symptoms

- Study broadly looking at the effects of testosterone in men without KS
- Adult participants, varied ages, hypogonadal and eugonadal

Walther et al., 2018
Early hormone therapy (EHT) during infancy in KS

- Positive treatment effects in the following domains:
  - Speech and language development
  - Reading skills
  - Verbal and non-verbal intellectual quotients
  - Neuromotor planning and execution

- Fewer behavioral problems:
  - Externalizing behavior problems
  - Aggressive behaviors
  - Schooling behavior
  - Affective problems

Samango-Sprouse et al., 2013, 2015
Current gaps in understanding

- Very little data available about the effect of hormone intervention in KS other than those studies discussed earlier.

- No studies have yet systematically assessed the influence of TRT on brain function or associated cognition in adolescent boys with KS.

- No disorder-specific treatments (other than TRT) for brain dysfunction in KS.
New NICHD-funded Study at Stanford and Nemours (Reiss & Ross)

- There are huge gaps in our understanding of the neural effects of testosterone supplementation on adolescents with KS

- The goal of the new project is to clarify the role of TRT on pubertal brain development and function and to test whether initiating this treatment in peri-pubertal males leads to improvements in executive and social-emotional functioning
  - What changes/improves, what does not change/improve
  - Does timing of TRT matter with respect to age or pubertal level make a difference
  - What cognitive-behavioral characteristics remain problematic after TRT – and how do we address these with additional interventions!

- Overarching goal to generate research findings that will lead to new, disorder-specific treatment approaches and improved clinical outcomes
So what’s wrong with current approaches to cognitive and behavioral challenges in KS?

- Actually, nothing
- Always use the best treatment modalities you have available at present (preferably evidence-based!)
- But current symptom-based treatments are always going to be limited in effectiveness because they were not developed for KS!
- Persistent problems with cognition (particularly executive function) can have long-term, significant effects on outcome
  - Vergunst et al.: Association between childhood behaviors and adult employment earnings in Canada JAMA Psychiatry, 2019
Methods

• Structural and functional magnetic resonance imaging (MRI)
• Diffusion-weighted imaging (DWI)
• Clinical interviews and questionnaires (CDI, MASC, KSADS, etc.)
• Computerized testing (Go/No-Go Tasks, AAT, etc.)
• Neurocognitive testing (WISC-V, NIH Toolbox, DKEFS, etc.)
• Assessment of hormone levels and physical exams
Accelerated Longitudinal Design
Naturalistic study design

Primary goal is to clarify brain and behavioral changes in KS associated with TRT as it is administered in typical clinical practice.
Innovation

- First-of-a-kind study
- Longitudinal design including up to 4 time points
- Multi-level approach (behavior, cognition, TRT, brain, environment)
- Impacts outside of KS
- Findings will help inform the development of more effective, disorder-specific treatments for KS
Building a more complete model of brain & behavioral development in KS

Environment

Prenatal Development

Early Development

Pubertal Development

Adult Outcome

47XXY

Hormonal Alterations
Building a precision medicine approach to KS

Yesterday
Symptom-Based
Intuition Medicine

Today
Cohort-Based
Evidence-based Medicine

Tomorrow
Algorithm-Based

Precision Medicine

- Brain development & function
- Genetic & molecular profile
- Physiological profile
- Treatment response
- Family environment
- Cognition and behavior

Big data analytics (TDA, ML)
Reference databases/algorithms

Precision Medicine for KS
Some initial ideas for a precision medicine approach to KS

- Optimize TRT treatment in light of a better understanding of brain, cognitive-behavioral and social-emotional development in KS
  - Assess dose, duration and timing (developmental windows)
  - Consider possibility of KS “subgroups” in terms of response

- Develop new cognitive-behavioral and social-emotional treatments that take advantage of, and target the specific profile or strengths and weaknesses in KS
  - Computer-based cognitive training to enhance specific executive functions

- Develop innovative, imaging-based interventions that have the potential to amplify hormone and cognitive-behavioral/social-emotional treatments to enhance outcome
  - fNIRS-based real-time feedback to enhance executive function
  - Hyperscanning to enhance social-emotional function
Functional Near-Infrared Spectroscopy (fNIRS): A method for obtaining functional brain imaging data in naturalistic settings
Potential Therapeutic Applications of fNIRS in KS

Hyperscanning

Neuro-feedback

reinforce

fNIRS signal

Hyperscanning + Neuro-feedback!
To learn more about the study, visit our website at:
- med.stanford.edu/BGAPstudy

Interested in being a part of our study? See if your son is eligible by visiting:
- is.gd/BGAPstudy
- Table at AXYS Meeting

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Thank you
And questions