U.S. FOOD & DRUG ADMINISTRATION

Pediatric Male Hypogonadism

current unmet need

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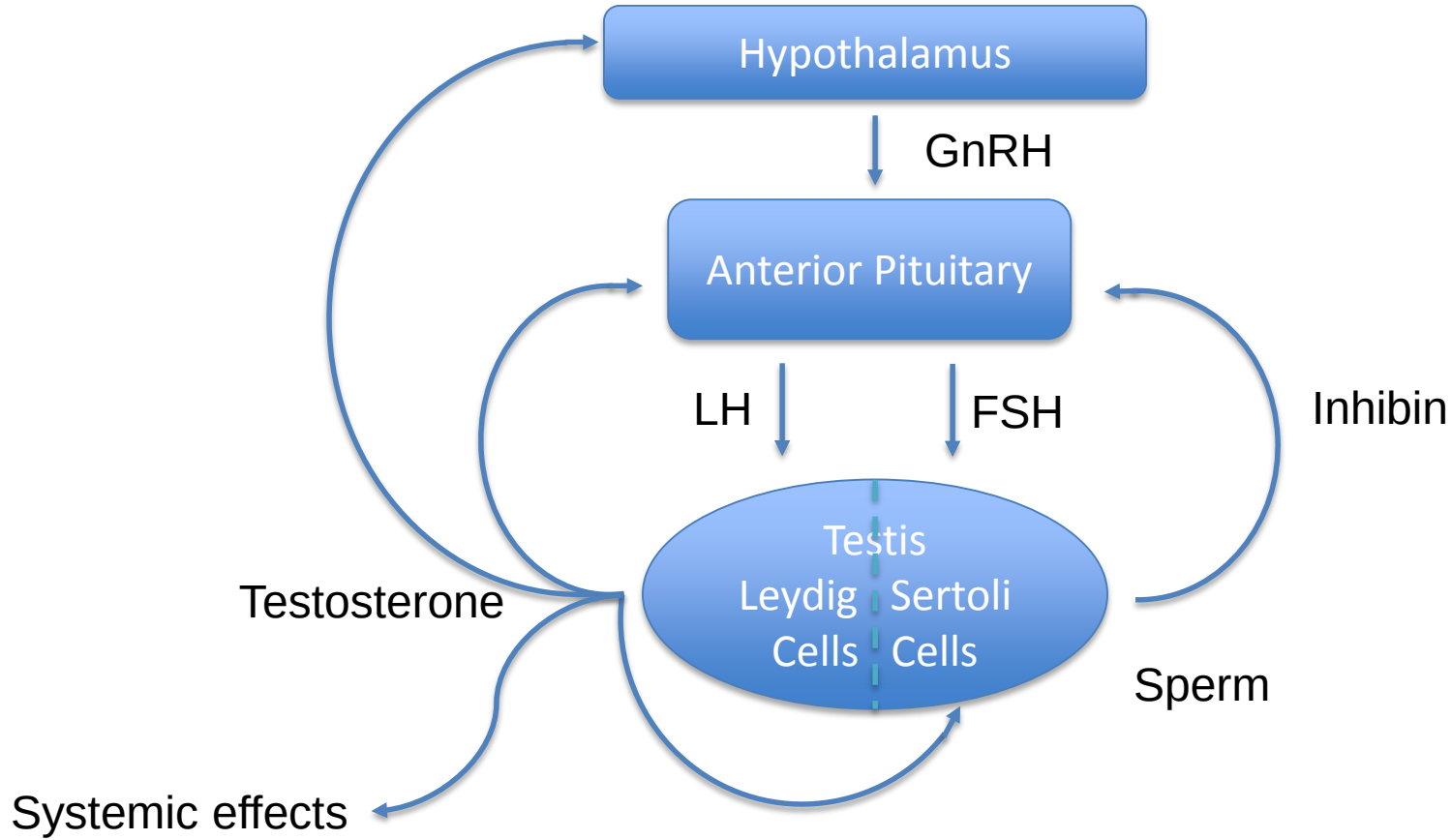
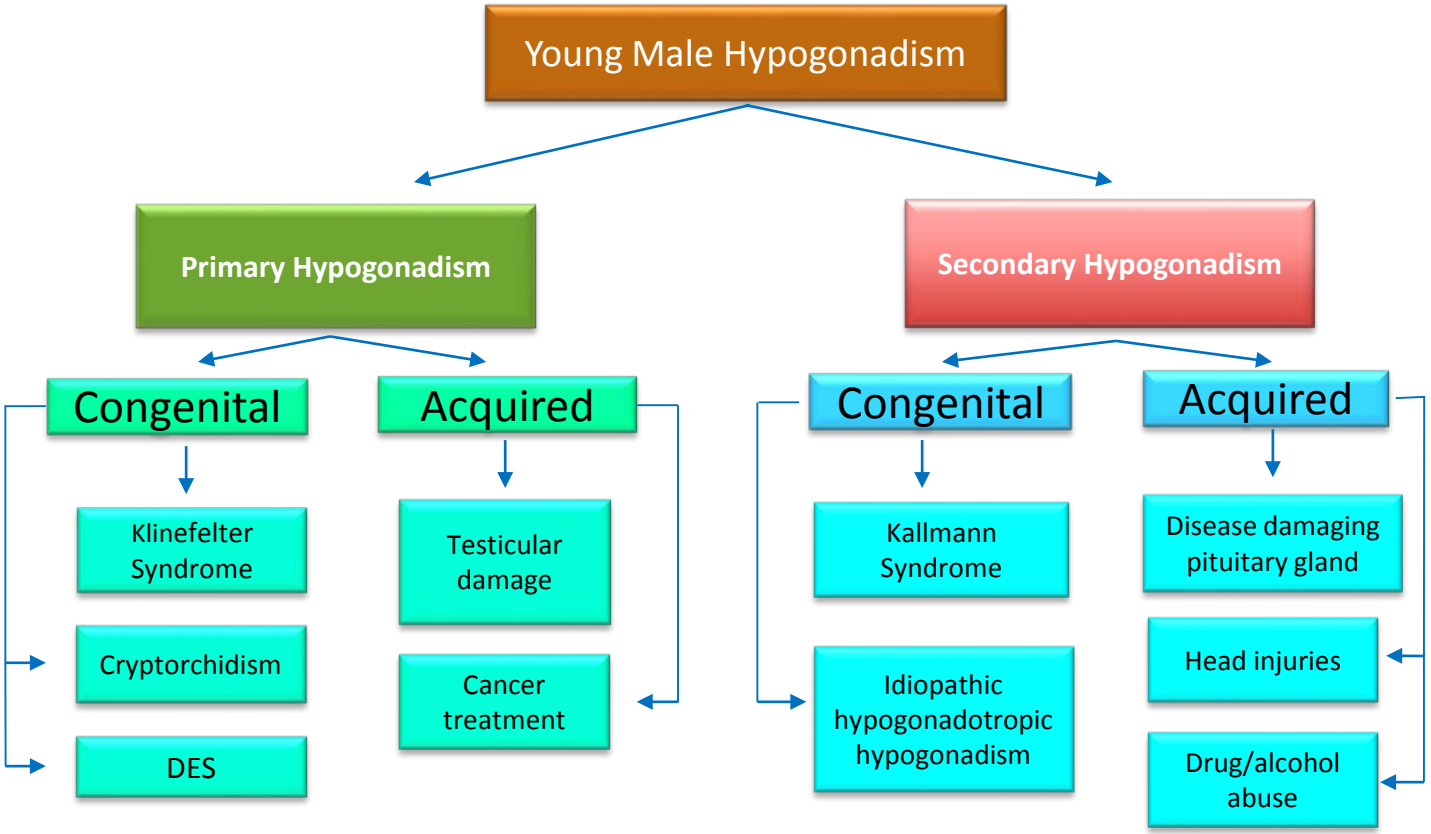
Division of Metabolism and Endocrinology Products

Hypothalamic-Pituitary-Gonadal Axis



Testosterone Effects

Anabolic Effects	Androgenic Effects
Muscle mass and strength	Maturation of sex organs and prostate
Bone growth and maturation	Erectile function, sex drive, and fertility
Red blood cell production	Enlargement of larynx (Adam's apple)
Regulation of platelet aggregation	Facial and axillary hair growth
Modulates mood, behavior, cognition, and memory	


Young Male Hypogonadism
Primary Hypogonadism
Secondary Hypogonadism
Congenital
Acquired
Congenital
Acquired
Klinefelter Syndrome
Cryptorchidism
DES
Testicular damage
Cancer treatment
Kallmann Syndrome
Idiopathic hypogonadotropic hypogonadism
Disease damaging pituitary gland
Head injuries
Drug/alcohol abuse

Primary Hypogonadism

- Klinefelter Syndrome
  - 47 XXY, 48XXXY…
  - Most common sex chromosome disorder
  - 1 : 500 live newborn males
- Approximately 250,000 men in the US have Klinefelter syndrome (in 2008)
  - Approximately 10% diagnosed in childhood.[1]

1. Groth, K.A., et al., Clinical review: Klinefelter syndrome--a clinical update. J Clin Endocrinol Metab, 2013. 98(1): p. 20-30.

Primary Hypogonadism

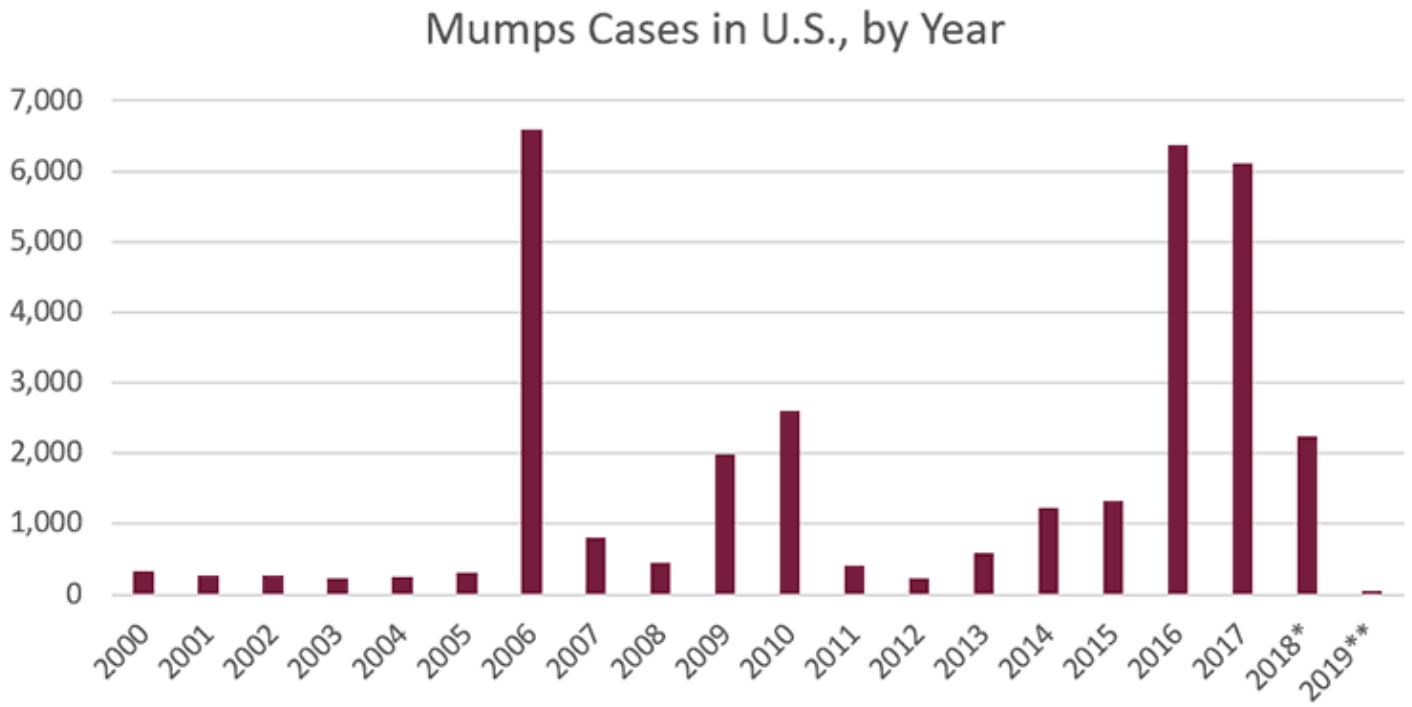
- Cryptorchidism
  - Occurs in 3% of full term neonates
  - 33% in premature infants[1]
- The prevalence decreases to 0.8% and 1.5% at 1 year of age[1]
- 1% risk per month of Leydig cell depletion[2]

1. Leissner J, Filipas D, Wolf HK. The undescended testes: consideration and impact on fertility. BJU Int. 1999;83:885–92
2. Tasian GE, Hittleman AB, Kim GE, et al. Age at orchidopexy and testis palpability predict germ cell and leydig cell loss: clinical predictors of adverse histological features of cryptorchidism. J Urol. 2009;182:704–9.

Primary Hypogonadism

- Structural damage to testis due to
  - Trauma
  - Cancer and cancer treatment
  - Viral Illness (mumps)
  - Autoimmune

Primary Hypogonadism



* Case count is preliminary and subject to change.
**Cases as of January 31, 2019. Case count is preliminary and subject to change.

https://www.cdc.gov/mumps/outbreaks.html

Pediatric cancer statistics

- In 2018, an estimated 15,590 children and adolescents ages 0 to 19 were diagnosed with cancer[1,2]
- 26-36% of male survivors have hypogonadism following treatment[3]

1.Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: A Cancer Journal for Clinicians 2018; 68(1):7-30.
2.https://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet#r1
3. Burney, Basil O and Jose M Garcia. “Hypogonadism in male cancer patients” Journal of cachexia, sarcopenia and muscle vol. 3,3 (2012): 149-55.

Pediatric cancer statistics

- Non-Hodgkin's Lymphoma
  - Over 70,000 cases annually (4.3% of all cancers)
  - 1.7% of patients < 20 years[1] (about 1,200 cases)
- Acute Lymphoblastic Leukemia
  - 0.4% of all cancers
  - Approximately 3,000 patients < 18 years[2]
- Up to 83% of ALL or NHL patients have hypogonadism after treatment

1.https://seer.cancer.gov/statfacts/html/nhl.html
2.Steffens, M., et al., Endocrine and metabolic disorders in young adult survivors of childhood acute lymphoblastic leukaemia (ALL) or non-Hodgkin lymphoma (NHL). Clin Endocrinol (Oxf), 2008. 69(5)

Secondary Hypogonadism

- Kallmann Syndrome
  - Delayed or absent puberty
  - Impaired sense of smell
  - Gene mutations affecting gonadotropins (LH,FSH)

- Prevalence: 1:8,000 – 1:30,000 males[1,2]

1.https://ghr.nlm.nih.gov/condition/kallmann-syndrome#statistics.

2. A. Vidal, L. Loidi, E. Colino, M.C. Miranda, R. Barrio Síndrome de Kallmann ligado al cromosoma X: heterogeneidad interfamiliar e intrafamiliar Med Clin (Barc), 128 (2007), pp. 777-779

Secondary Hypogonadism

- Other genetic causes of hypogonadotropic hypogonadism
  - "Idiopathic" prior to mutation discovery
  - Normal sense of smell

- Rare (1:10,000 combined)

Secondary Hypogonadism

- Central nervous system tumors
  - 5.6 /100,000/year ≤ 19 years of age[1]
- Hypogonadism
  - 13% prior to therapy[2-6]
  - 20-80% post therapy[2-6]

1. Ostrom, Q.T., et al., CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro-Oncology, 2015. 17(Suppl 4): p. iv1-iv62.
2. Merchant, T.E., et al., *Preirradiation endocrinopathies in pediatric brain tumor patients determined by dynamic tests of endocrine function.* Int J Radiat Oncol Biol Phys, 2002. **54**(1): p. 45-50.
3. Gonc, E.N., et al., *Endocrinological outcome of different treatment options in children with craniopharyngioma: a retrospective analysis of 66 cases.* Pediatr Neurosurg, 2004. **40**(3): p. 112-9.
4. Mills, J.L., et al., *Menarche in a cohort of 188 long-term survivors of acute lymphoblastic leukemia.* J Pediatr, 1997. **131**(4): p. 598-602.
5. Constine, L.S., et al., *Hypothalamic-pituitary dysfunction after radiation for brain tumors.* N Engl J Med, 1993. **328**(2): p. 87-94.
6. Rappaport, R., et al., *Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors.* J Clin Endocrinol Metab, 1982. **54**(6): p. 1164-8.

Secondary Hypogonadism

- Traumatic Brain Injury
  - 100 to 300 /100,000/year[1,2]
  - Male:female – 2:1 to 4:1[1]
- Hypogonadism
  - 41.6% in the acute phase[3]
  - 7.7% at 12 months → chronic[3]

1. Cassidy, J.D., et al., Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med, 2004(43 Suppl): p. 28-60.
2. McKinlay, A., et al., Prevalence of traumatic brain injury among children, adolescents and young adults: Prospective evidence from a birth cohort. Brain Injury, 2008. 22(2): p. 175-181.
3. Tanriverdi, F., et al., High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. J Clin Endocrinol Metab, 2006. 91(6): p. 2105-11.

Combined primary and secondary hypogonadism

- Prader-Willi Syndrome
  - Genetic syndrome
    - Obesity, short stature
    - Hyperphagia (intense hunger and overeating)
    - Behavioral problems, intellectual impairment
  - 1:15,000 births, 1:1 male:female
  - Males: nearly 100% hypogonadal

Combined primary and secondary hypogonadism

- Adrenal Hypoplasia Congenita[1]
  - Genetic disorder
    - Affects multiple endocrine tissues
      - Hypothalamus, pituitary, gonads
    - Delayed puberty and/or pubertal arrest
  - 1:12,500 live births[1]

1. Achermann JC, Vilain EJ. NR0B1-Related Adrenal Hypoplasia Congenita. 2001 Nov 20 [Updated 2018 Jan 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.

Estimates of cases

Condition	Prevalence	Boys in US
AHC	1/12,500	163
PWS	1/15,000	195
Kallmann Syndrome	1/30,000	391
TBI	100-300/100,000/year, 7.7% hypogonadal	904
IHH	1/10,000	1,175
Klinefelter Syndrome	1/500, 10% diagnosed	2,350
Cryptorchidism	0.8% of births at 1 year, 1%/month Leydig Cell failure	11,280
Pediatric cancer all causes	26% of male cancer survivors	32,750

Estimates of cases

- Total cases = 49,208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