16-year-old female with a 2 month h/o of increasing polyuria and polydipsia

- Blood sugar done by PCP was WNL
- Random urine showed a low specific gravity
- Diabetes insipidus suspected and referred to endocrinology
H&P
- History- as mentioned
  - ROS- amenorrhea for 4 months

- Examination
  - Well appearing teenager
  - Normal height, normal BMI
  - Normal visual fields
  - Normal exam

16y
Brief period of water deprivation
- Serum osm-304 mOsm/kg
- Urine Osm-54 mOsm/kg
  =DIABETES INSIPIDUS

- After DDAVP- urine osm-726 mOsm/kg
  CENTRAL DIABETES INSIPIDUS (CDI)

Initial Work up of CDI
- Imaging
- Rule out anterior pituitary deficiency

16y- anterior pituitary function
- Cortisol was low- ACTH stimulation test-peak-5.3 mcg/dL
- Thyroid normal
- LH, FSH and estradiol normal follicular range
- Growth factors- IGF1 low, IGFBP3 WNL
- Prolactin-55 ng/mL
Posterior pituitary bright spot absent

6 x 7 x 8 mm enhancement involving the pituitary infundibulum
- Normal pituitary stalk measurement <2.6 mm

Barkovich and Raybaud; Pediatric Neuroimaging: 2012; Lippincott Williams and Wilkins

Compression of the pituitary stalk
Impairment of the inhibitory effect of dopamine on lactotropes

Elevated prolactin

2 issues
- Pituitary stalk thickening
- Anterior pituitary involvement
ETIOLOGY

Pediatric causes of CDI

- Congenital midline CNS malformations
- Genetic defects in vasopressin synthesis
- Post trauma
- Post surgical
- Post infectious
- Tumors- craniopharyngiomas
- Germinoma
- Langerhans cell histiocytosis (LCH)
- Autoimmune
- Idiopathic


1997 UCSF- 9 children with idiopathic CDI aged 2 yr -18 yr , follow up MRI
- Biopsy done with progression of pituitary stalk thickening over 3-14 months
- Biopsy 7/9- germinoma in 6 patients and inflammatory cells in 1
- “Idiopathic” central diabetes insipidus warrants close follow-up

------------------------------------------------------------------------------------------------------

2000 French study-Natural history of 25 ‘idiopathic’ central DI with PST
- In the first 3 years of follow-up- 4 had germinoma


?Idiopathic central diabetes insipidus

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- 2000 French study-Natural history of 25 ‘idiopathic’ central DI with PST
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Long term study

- 85 patients with DI
- Median age 7.5 years
- Endocrine tests and neuroimaging
  - 6 mo x2 years
  - Annually for 3 years
  - Reassessed after adult height achievement ~10 years

Diagnosis initial

- Twenty-four patients (28.2%) at the time of presentation
  - 8 LCH
  - 2 germinomas
  - 6 craniopharyngiomas
  - 3 midline defects
  - 3 familial autosomal dominant DI
  - 2 had post-traumatic CDI


Within 2.5 years

- 61 (71.8%) patients with idiopathic DI
  - 11 (13.0%) received a specific diagnosis
    - 7 - germinoma
    - 4 - LCH


Long term follow up

The remaining 43 patients (50.2%) ‘idiopathic CDI’ patients followed for a median 10 years

- Normal (1.0–3.0 mm)
- Minimal increases (3.1–3.9 mm)
- With moderate enlargement (4.0–6.5 mm).
  - 3 (2 minimal, 1 moderate PST) developed LCH
  - 1 (minimal PST) developed Hodgkin’s Lymphoma


ANTERIOR PITUITARY HORMONE DEFICIENCIES
Anterior pituitary hormone deficiency in children with DI

- 79 children with CDI, median age 7.0 years and median duration of follow-up was 7.6 years
- 61% had anterior pituitary hormone deficits, even higher with LCH
- Most frequent abnormality was GHD
- Followed by hypothyroidism, hypogonadism and adrenal insufficiency


FURTHER EVALUATION OF CENTRAL DIABETES INSIPIDUS WITH PITUITARY STALK THICKENING

Pituitary stalk thickening

- Germ cell tumors
- Langerhan cell histiocytosis
- Autoimmune - lymphocytic infundibulo hypophysitis
- Idiopathic

Autoimmune antibodies

- Vasopressin-cell autoantibodies (AVPc-Abs)
- AVPc-Abs were found in 15 patients (75%),
  - 9 with idiopathic CDI
  - 4 with LCH
  - 2 with germinoma
- AVPc-Abs - not specific
- Not available, not done

**Further Work up for DI+PST**

- **LCH**
  - Skeletal survey/bone scans

- **Germ cell tumors- tumor markers**
  - Serum and CSF
    - human chorionic gonadotropin
    - alpha-fetoprotein

**Biopsy?**

- **CONSIDER**
  - MRI criteria
    - Enlargement of the pituitary stalk lesion (>4 mm) (>6.5 mm)
    - Progressive enlargement of pituitary stalk
    - Enlargement of the anterior pituitary gland
    - Third ventricle involvement
    - Anterior pituitary involvement

- **RISK**
  - Cause further anterior pituitary deficits
  - Rarely an earl gland can be misdiagnosed as hypophysitis – inflammatory lymphocytic reaction


**If no biopsy- follow up**

- Imaging every 6 months during the first 2 years (with high suspicion of germinoma, can be ~3 months)

- Annual imaging for another year

- Year 3-5 and longer, continue clinical follow up

Di Iorgi N, Morana G, Maghnie M. Pituitary stalk thickening on MRI when is the best time to re-scan and how long should we continue rescanning for? Clin Endocrinol (Oxf). 2015 Oct;83(4):449

**16y**

- PST >6.5 mm
- Tumor markers serum and CSF were negative
- Skeletal survey was normal
- Anterior pituitary
  - Hypoadrenalism
  - GH insufficiency
  - Secondary amenorrhea-most likely hypogonadism
Hormone replacement
- Desmopressin
- Hydrocortisone
- Birth control pills

Right endonasal transphenoidal biopsy
pituitary stalk

Pituitary stalk biopsy results:
- ‘Section show a mixed chronic inflammatory infiltrate comprised of small lymphocytes, macrophages, and numerous eosinophils. A subset of the cells show crescent shaped nuclei with open chromatin and prominent nuclear folds. Immunohistochemical stains show that the atypical cells are positive for CD1a, S-100, and CD68. The findings confirm the diagnosis of Langerhans’ cell histiocytosis.’

Previously cell of origin was thought to be epidermal
Langerhans cells

Cell-specific gene expression profiling suggest that
LCH arises from bone marrow–derived immature
myeloid dendritic cells

Precursor myeloid cells acquire somatic mutations that
activate the MAPK pathway

Multi system disorder

Recurrent otitis media, skin lesions, bone lesions,
pulmonary involvement, or liver disease

LCH-related CDI can occur as a single organ localization
at the level of pituitary/pituitary stalk

Growth hormone deficiency (GHD) is the most frequent
additional deficit

Marchand E, Boucher MA, Couru C, Pelletier, Brunel-Bombardier I, Pfeifer L, committee. Central diabetes insipidus as the
inaugural manifestation of Langerhans cell histiocytosis: natural history and medical evaluation of 26 children and
adolescents. J Clin Endocrinol Metab. 2011 Sep;96(9):E1352-60

Langerhans cell histiocytosis
16 y

- Antineoplastic chemotherapy for LCH
  - vinblastine/prednisone
  - completed

- Panhypopituitarism
  - Multiple hormone replacement
2 patients
- 4 year old and a 7-year-old female
- Breast development, otherwise normal
- Any onset of pubertal changes prior to the age of 8 years in a girl is considered precocious
- Both girls had precocious onset of puberty

4 year old
- Tanner 3 breasts
- Tanner 2 pubic hair
- Bone age advanced
- GnRH stimulation test
  - LH elevated
  - Estradiol elevated
7 year old

- Tanner 3 breasts
- Tanner 2 pubic hair
- Baseline LH and estradiol were prepubertal
- Patient lost to follow-up for 2 years
- Came back at age 9 years
- Puberty had progressed, patient was also seeing neurology for migraines
- Hormonal profile – pubertal LH and FSH
- Advanced bone age

**Physiological Basis of Puberty**

- Advanced bone age
- Increased GnRH pulsatility
- Rise in sex steroids
- What initiates this process?
- It has been proposed that a ‘pulse generator’ stimulates GnRH neurons

**Transition from child to adolescence**

- GnRH secretory activity is low
- Gradual increase in GnRH pulsatility
- Rise in sex steroids
- What initiates this process?

**?Pulse Generator**

- Kisspeptin is a hypothalamic neuropeptide
- Acts via GPR54, a G-protein coupled receptor located on GnRH neurons
- Kisspeptin and its receptor GPR54 play key roles in establishing the onset, tempo and pace of puberty

The kiss1 gene was originally identified by scientists in Hershey, PA.

It was dubbed kiss1 in honor of another product of Hershey...

**Normal timing of puberty**

- **Multifactorial**
  - Genetically determined
  - Ethnicity
  - The growth hormone/insulin-like growth factor system, thyroid hormones
- **Nutrition**

**Timing of the onset of puberty?**

GONADARCHE: GONAD+ (GREEK) ARKHĒ, BEGINNING (FROM ARKHĒN, TO BEGIN)

**Leptin**

- Leptin appears to be an important link between nutrition and reproductive competence
- The attainment of a critical threshold appears to signal that nutritional stores are sufficient
- Permissive effect on the GnRH pulse generator


Complex interplay of numerous neural signals

CRCT1: the creb1-regulated transcription coactivator-1 (crct1) mediates leptin effects on the kiss1 system at the hypothalamus

MTOR: recent evidence also that another hypothalamic signal through MTOR (mammalian target of rapamycin) is also involved in the control of puberty onset, at least partially, via modulation of kiss1 expression


A functional or anatomical disruption of this complex signaling cascade may result in an early and precocious onset of puberty

GONADOTROPIN-DEPENDENT PUBERTY (CENTRAL PREOCIOUS PUBERTY)

- Children with neurological disorders
- Hydrocephalus, myelomeningocele
- Tumors

Work up of CPP requires CNS imaging

- Idiopathic

CNS Tumors that cause CPP

- Hypothalamic hamartomas
- Tumors located in the vicinity of the hypothalamus or optic nerves
  - Low grade gliomas, juvenile pilocytic astrocytomas
  - Gliomas in the optic pathway associated with NF1
- Tumors that cause obstructive hydrocephalus
  - Ependymomas
  - Pineal tumors
- Craniopharyngiomas
Non neoplastic developmental lesion

Histologically normal, neuron and glial cell mass is present in an ectopic location—at the base of the 3rd ventricle

Isointense on MRI

Triggers puberty
- ectopic production of GnRH
- secretion of glial factors such as transforming growth factor-β which stimulates GnRH

For CPP—no surgical intervention is needed


Mechanism of treatment
- (The pubertal process needs pulsatile GnRH release)
- ‘Continuous’ or non pulsatile GnRH is inhibitory
Long acting GnRH analogues

- Leuprolide- IM inj Q month or Q 3 months
- Histrelin implants –last for 1 year
  - Treated till reaches pubertal age

Further work up - Normal!

- Headaches
- No other symptoms or signs
- Formal vision evaluation normal
- Prolactin, thyroid, growth factors and cortisol were all normal
Craniopharyngioma

- 3-6% of all brain tumors in children
- It is diagnosed most often between the ages of 5 and 14 yrs, (2nd peak ~ 5th and 6th decades)
- Suprasellar tumor arising from ectodermal remnants of Rathke cleft
- Solid epithelial cells and cystic component
- Dark, oily fluid

Symptoms and Signs

- Raised ICP
  - Headaches, vomiting
- Vision changes
- Hypopituitarism
  - DI
  - Growth failure
  - Delayed puberty
- Precocious puberty

Prognosis

- 'Benign' histological appearance
- 10-year overall survival rates of 90%
- Traditionally, surgical excision is the treatment of choice
- Unfavorable long term prognosis with significant QUALITY OF LIFE ISSUES
- Due to tumor but also due to the treatment

Treatment- goal is to minimize morbidity

- There is no consensus on the optimal treatment for newly diagnosed craniopharyngioma
- Treatment is individualized on the basis of factors that include the following:
  - Tumor size
  - Tumor location
  - Potential short-term and long-term toxicity of treatment
Newly diagnosed
1. Radical surgery with or without radiation therapy
2. Subtotal resection with radiation therapy
3. Primary cyst drainage

Radical surgery - challenges
Gross-total resection is technically challenging because the tumor is surrounded by vital structures:
- optic nerves and chiasm
- the carotid artery and its branches
- 3rd cranial nerve
- the hypothalamus
- Attached to the pituitary stalk


Endocrine disorders accompanying resection are considered inevitable.
Further vision loss.
Hypothalamic involvement:
- loss of neurovegetative homeostasis
- hyperphagia/obesity
- behavioral disorders
- impairment in cognition, memory and executive functioning

Sequelae of Resection
- Endocrine disorders accompanying resection are considered inevitable.
- Further vision loss.
- Hypothalamic involvement:
  - loss of neurovegetative homeostasis
  - hyperphagia/obesity
  - behavioral disorders
  - impairment in cognition, memory and executive functioning


Subtotal resection with radiation
- The goal of limited surgery is to:
  - establish a diagnosis
  - drain any cysts
  - and decompress the optic nerves
- No attempt is made to remove tumor from the pituitary stalk or hypothalamus.
- The surgical procedure is often followed by radiation therapy.
- A systematic review of 109 studies found that subtotal resection plus radiation therapy had tumor control similar to those for gross-total resection.

Radiation - late effects

- Endocrine effects
- Vasculopathies
- Neurocognitive side effects (<7 years of age and with larger tumors)
- Subsequent neoplasms


Recurrence of craniopharyngioma occurs in approximately 35% of patients regardless of primary therapy

Treatment options
1. Surgery
2. Radiation therapy
3. Intracavitary instillation of
   - radioactive P-32, Yttrium-99, bleomycin
   - interferon-α
4. Systemic interferon α


Interferon α

- Has an effect on squamous cells which line the cysts
- Mechanism may be through FAS-mediated apoptotic pathway
- A number of series have been published on its use, with reduction in cyst size in up to 80% of patients
- Side effects consist of arthralgia, fatigue, fevers and occasionally new endocrine deficits


9 yr

- Large cysts encroaching on very vital structures
- Various options discussed with family
- Decided on initial trial of systemic interferon, to be followed by surgery/radiation
- Pegylated interferon-α-2b weekly injections
Follow up

- Not yet 3 months – no follow up MRI yet
- So far minimal side effects with injections
- No new endocrine problems
- Visual fields normal
- Headaches have resolved
References

1. Barkovich and Raybaud. Pediatric Neuroimaging 2012: Published by Lippincott Williams and Wilkins

References


References

20