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Southern Pediatric Endocrine Society

Pediatric Endocrinology: Our Short but Remarkable History

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THE HISTORY OF AUTOIMMUNITY (AID) AND ITS RELATION TO PEDIATRIC ENDOCRINE DISEASE

Robert M. Blizzard, M.D.
Professor Emeritus
University of Virginia Medical School
Charlottesville, Virginia

Autoimmunity is classified as Organ Specific (e.g. thyroiditis) and Non-Organ Specific (e.g. rheumatoid arthritis). Most endocrine diseases attributable to AID result from Organ Specific AID. The focus of this presentation will be primarily, therefore, on Organ Specific AID. However, a new type of classification is developing, and it is important that we realize this and the reasons for it. Specifically Davidson and Diamond presented in 2001 a review article entitled Advances in Immunology: Autoimmune Diseases\(^{51}\). They define an autoimmune disease as A Clinical Syndrome Caused By The Activation Of T Cells, Or B Cells Or Both, In The Absence Of An Ongoing Infection Or Other Discernible Cause. They promote this new definition and classification as they believe it uses "causation of disease" as the defining parameter(s) which makes the classification useful in deciding on therapy which may differ according to the pathogenic mechanism.

We in this review will adhere to utilization of the Organ vs Non-Organ Specific definition and classification. Recent reviews of major importance include those by Betterle\(^{55}\), Anderson\(^{56}\), Perheentupa\(^{53}\), Halonen\(^{57}\), Collin\(^{59}\), and Fierabracci and Bottazzo\(^{52}\).

In 1957 two groups (Deborah Doniach with Ivan Roitt\(^{30}\) in England and Witebsky and his group\(^{33}\) in the US), on the basis of demonstrating antibodies versus thyroglobulin in the sera of humans with lymphocytic thyroiditis, first called attention to the possibility that some thyroid disease may be due to an autoimmune etiology. In 1957 when Doniach presented her findings in Baltimore she and I had opportunity to meet together in my office for an hour. I suggested that many atrophic endocrine diseases were probably of the same origin, including some cases of Addison's disease and some cases of insulin dependant diabetes. Her response: "I'll bet you are correct. Why don't you explore the possibility?". I accepted the challenge and my colleagues (fellows) and Dr. Robert Chandler, Ph.D., in the next 25 years (1957-1982) published 29 papers in peer review journals on the topic of endocrine disease and autoimmunity\(^{1-29}\).

In 2003 autoimmunity accounts for at least 50% of all true (i.e. not variations of normal development) endocrine disease with which pediatric endocrinologists deal. Autoimmune disease of the thyroid, the pancreatic islets, and the adrenal cortex together make up more than 50% of all forms of organ specific autoimmunity. In the 30 minute presentation today I will spend approximately 50% of the time on the historical presentation dealing with what I learned and taught about autoimmunity between 1957 and 1983, at which time I was an active participant in investigative autoimmunity. The other 50% of time will be
spent succinctly covering what has been learned in the subsequent 21 years (1983-2003) while I have been only an interested bystander in this fascinating field. As will be evident at the conclusion there are still many questions to be answered.

Following Dr. Doniach's challenge in 1957 my group focused on studying and reporting between 1958-1960 that thyroid antibodies served as a potential etiological mechanism in multiple thyroid diseases.\textsuperscript{1,2,3} Between 1960 and 1962 we suggested that maternal autoimmunization to thyroid antigens might be a causative factor of congenital hypothyroidism.\textsuperscript{4-6} These studies were the basis for extensive and continuing investigation by multiple investigators\textsuperscript{9,26-40} in respect to maternal AID as a possible cause of congenital hypothyroidism (CH).

It is accepted in 2003 that TSH binding inhibiting immunoglobulin antibodies (TBI1), one of several types of TSH receptor blocking antibodies (TRB), account for most cases of transient hypothyroidism in the newborn\textsuperscript{33,35-42}, which is discussed below. This entity occurs in at least 2-4% of the newborns who appear by thyroid screening to be congenitally hypothyroid. We now believe that probably no placentally transferred immunoglobulins versus thyroid antigens account for failure of the gland to develop in congenitally aplastic hypothyroid infants. However, cytotoxic antibodies or thyroid growth-inhibiting antibodies directed against the TSH receptor have been demonstrated in tissue culture. Whether these may play an etiological role in thyroid agenesis remains inconclusive. Most cases of congenital aplastic or dysgenetic hypothyroidism, however, probably result from phenomena other than transplacental transfer of immunoglobulins directed against thyroid antigens.

Important considerations reported in the last seven years by different groups includes a report by Brown et al (1996)\textsuperscript{43} concerning the incidence of transient congenital hypothyroidism due to maternal TBI1 in over one million newborns. The conclusion in this paper was that only 2% of babies with congenital hypothyroidism had transient hypothyroidism due to TBI1. However, Dussault and Fisher (1999)\textsuperscript{36} reported that 12.5% of 523 hypothyroid infants had transient CH. Of course drugs such as propylthiouracil, iodide, and others also can produce transient congenital hypothyroidism and may account for some of these 12.5%.

Pediatricians need to be aware that at least one type of congenital hypothyroidism (transient) is related to autoimmunity and that pregnant women with thyroid AID are candidates to deliver infants with transient hypothyroidism. All these infants need to be identified and treated quickly following birth, and continued for the first few months with thyroxine until thyroid antibodies are no longer demonstrable in the infant’s serum. This will prevent mental retardation which occurs in an increased incidence in untreated patients with transient hypothyroidism, although not to the severe extent that occurs in patients who have untreated permanent CH. Of particular interest is that at least six reports \textsuperscript{4,11,33,36,39,44} of transient hypothyroidism have been described in more than one
affected offspring in mothers with a history of thyroid autoimmune disease. In one report\textsuperscript{41} one infant of an affected mother had transient hypothyroidism and a sibling had neonatal thyrotoxicosis, demonstrating that a female with chronic thyroiditis at different times of life may have a preponderance of TSI antibodies and, at another, TBII antibodies with different consequences for the neonatal offspring. Screening during pregnancy of all pregnant women who have a history of thyroid disease for thyroid antibodies is recommended. Ultrasound studies of the suspect thyroid are indicated as patients with transient CH will usually have normally appearing glands.

In 2002 in an editorial in JCE&M entitled “The Etiology of Thyroid Dysgenesis - Still An Enigma After all These Years”, Drs. Brown and Demmer\textsuperscript{69}, the investigators, discussed the complexities still present (gene mutations, autoimmune disease, other) that may be contributing causes of thyroid agenesis. The role of autoimmunity in producing thyroid agenesis remains inconclusive.

In 1962 our group seeking therapy other than T\textsubscript{4} replacement for patients with Hashimoto’s thyroiditis studied the clinical and laboratory effects of prolonged cortisone therapy\textsuperscript{8}. Antibody titers fell markedly and goiters dissipated with prolonged therapy using pharmacological doses of cortisone over a period of six months. Hypothyroidism was converted to euthyroidism. However, the dosage of cortisone required induced Cushing’s syndrome, and with reduction of the steroid dose the disease relapsed. We and others subsequently have confirmed that glucocorticoids can allay various autoimmune diseases such as alopecia, but not cure them, and that the treatment is often worse than the disease itself. In addition, no chemotherapeutic or immunological therapies have been successful. Consequently, thyroid hormone replacement remains the treatment of choice in patients with chronic lymphocytic thyroiditis.

Historically our group was the first in the U.S. to report the presence of adrenal antibodies in the serums of Addisonian patients\textsuperscript{7} and to extend those studies by identifying various adrenal antigens and antibodies in Addison’s disease\textsuperscript{9}. The association of adrenal and thyroid disease was elucidated in other publications by our group\textsuperscript{11,14,15,17}. Current thinking regarding autoimmune adrenal insufficiency is presented in Betterle’s reference\textsuperscript{55}.

Historically it became quite apparent in the early 1960s that insulin dependent diabetes mellitus also was a candidate to be an autoimmune disease as there was a strong association of autoimmune thyroid disease in patients with type 1-IDDM\textsuperscript{29}. Because of these associations it became apparent that there were different types of polyglandular autoimmune disease (PGAD) associations. Therefore in 1980 we developed a classification of polyglandular autoimmune diseases\textsuperscript{22,23,24}. In 2003 this classification continues particularly in relation to polyglandular autoimmune disease (PGA) type I and PGA-type II. The former deals with an autosomally recessively inherited syndrome where the patient to be so classified must have at least two of the most common characteristics of a triad of Addison’s disease, hypoparathyroidism and susceptibility to candidiasis. Polyglandular
autoimmune disease type II must have at least two of its characteristic triad of Addison’s disease, autoimmune thyroid disease, and insulin dependent diabetes mellitus. These two triads (PGA1 and 2) have much in common and yet are quite different in the age of clinical onset, other associated autoimmune diseases, and genetical inheritance. We have learned much in the past 20 years (1983-2003) to clarify the etiology of these organ specific autoimmune diseases. Particularly has the genome project enhanced our knowledge concerning the complexity of autoimmune endocrine diseases.

Among the multiple genes identified with autoimmunity, one in particular has received more attention than most of the others.\textsuperscript{53,54,57,58} This is the autoimmune regulatory gene which encodes a specific protein (AIRE protein) which is shown to have DNA binding activity and transcriptional transactivation potential. This protein has a pattern of expression that suggests a potential role in shaping the cell repertoire, particularly in the thymus and particularly in thymic medullary epithelial cells (MECs). These cells have been increasingly implicated in the clinical deletion of inactivation of semi-mature self-reactive thymocytes. Some very suggestive correlations exist between antigen expression levels in the thymus and disease susceptibility in humans and rodents. A vast number of papers have appeared in the literature since the AIRE gene and its mutations was extensively characterized in 1997. This gene has turned out to be of such tremendous importance because of its unique role in PGA type I. Further elucidation in the function of this gene and how the central autoimmunity of the thymus and the peripheral autoimmunity in affected organs relate will be quite revealing and helpful in our understanding of at least one discrete type (PGA1) of autoimmune etiological mechanism.

In summary, this presentation endeavors to be historical and current. Understanding the history of medical events enhances both the investigation and therapy which we pursue. Much thought has gone into assembling pertinent references from the past and from current times. Therefore, a desired goal of this presentation is to stimulate interest and supply the best appropriate references for those who wish to quickly broaden their perspectives.
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B. Diabetes (1960-1999)


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C. Adrenal and Parathyroid (See Section II. D)


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D. References 2000-2003


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Hypogonadism: A Case for Fertile Eunuch Syndrome
SPES 2003

I. David Schwartz, MD
University of South Carolina
School of Medicine

Fertile Eunuch Syndrome (?)

- Idiopathic Hypogonadotropic Hypogonadism:
  - A clinical disorder defined as:
  - "Selective failure of the neuroendocrine components of the reproductive system in the absence of an anatomic or functional cause."
  - In males, microphallus and/or cryptorchidism attest to deficiency of androgens in-utero.
  - Wide clinical heterogeneity
    - X-linked Kallmann Syndrome (KAL-1 gene mutation)
    - X-linked adrenal hypoplasia congenita (DAX-1 gene mutation)
    - Fertile eunuch syndrome: decreased GnRH, eunuchoid proportions, hypogonadal testosterone levels despite normal testicular size and preserved spermatogenesis

Fertile Eunuch Syndrome (?)

- CASE REPORT:
  - 16 3 y/o adopted, Caucasian male referred for delayed pubertal development.
  - Pubic and Axillary hair x 3 years; deodorant for 5 years
  - No voice changes.
  - No acne.
  - Tall.
  - Hx of depression, headaches, and GER.
  - Meds: paroxetine (Paxil), amitriptyline (Elavil), and mazdazine (Avad)
  - Severe myopia; no auditory or olfactory complaints
  - 10th grade, advanced classes
Fertile Eunuch Syndrome (?)

• CASE REPORT (cont'd):
  - CNS imaging in previous year for evaluation of headaches → ? Mild vascular “irregularity” no apparent follow up.

Fertile Eunuch Syndrome (?)

• CASE REPORT (cont'd):
  - BP 130/90, HR 90
  - Height 180.3 cm (+3.2 SD)
  - Weight 120.2 kg
  - BMI 37.0
  - TRH, TSH, FE 0.97
  - Arm Span 129.1 cm
  - (-1)5 to (-2)0 diopters, full visual fields, normal color vision;
  - of fraction
  - Circumcised penis, > 5.5 cm, buried in prepubic fat;
  > 10% (beard); testes 2.7-2.9 cm; Tanner IV pubic hair; moderate axillary hair, lipomastia with a barrel gynecomastia

Fertile Eunuch Syndrome (?)

• CASE REPORT (cont'd):
  - Lab:
    - T4 6.9 ug/dL; TSH 3.31 uU/ml
    - LH 2.8 mU/mL; FSH 11.0 mU/mL
    - Testosterone 6.0 ng/dL
    - Normal lipid and chemistry profiles
  - Karyotype 46, XY
Fertile Eunuch Syndrome (?)

- CASE REPORT (cont'd):
  - Clinical Course:
    - 16.5 years: Rx with Testosterone cypionate 100 mg IM monthly x 3 injections
    - 16.75 years: phallic > 7 cm; testes 3 x 3 x 5 cm; PH 17/
      - LH 8.0, FSH 21.7; Testosterone 190
    - Restart Depo-T 100 mg/month
    - 17.25 years: testes 4 x 4 x 3 cm; PH 27; BMI 56.4
    - erections/erected
      - LH 13.3; FSH 11.3; Testosterone 41
      - MII 2.4 ng/ml (3.0-5.4)
    - HOLD Testosterone.

Endocrine Reviews 2001; 22:657-674
Fertile Eunuch Syndrome (?)

• CASE REPORT (cont'd):
  - Clinical Course (cont'd):
    - 17.25 years: testosterone 4.2-4.4 ng/ml, BMI 37.3
    - LH 2.9, FSH 8.5, Testosterone 40
    - Inhibin B 16 pg/ml (normal men < 400)
    - 17.0 PI < 5 ng/ml, DHEAS 37 ug/dl
    - 17.25 years: BMI 38.6 (begin metformin)
    - LH 3.0, FSH 9.0, Testosterone 74, DHEAS 133
    - Inhibin B 64
    - 18.9 years: BMI 37.6
    - LH 2.7, FSH 6.5, Testosterone 54
    - Begin Androgel 5 gm daily

Fertile Eunuch Syndrome (?)

• Serum Inhibin B concentrations in adult males with hypogonadotropic hypogonadism:
  (JCEM 2002;87:152-160)

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>nHII</th>
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<th>nHII</th>
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<tr>
<td>n</td>
<td>36</td>
<td>10</td>
<td>30</td>
<td>42</td>
<td>6 (of 42)</td>
<td>5</td>
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<tr>
<td>Inhibin B (ng/mL)</td>
<td>170±40</td>
<td>70±38</td>
<td>46±4</td>
<td>85±12</td>
<td>23±24</td>
<td>35±15</td>
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</table>

Fertile Eunuch Syndrome (?)

• Testicular Volume in adult males with hypogonadotropic hypogonadism:
  (JCEM 2002;87:152-160)

<table>
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<tr>
<th></th>
<th>KS</th>
<th>nHII</th>
<th>(PES)</th>
<th>AHI</th>
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<tr>
<td>n</td>
<td>30</td>
<td>42</td>
<td>(6 of 42)</td>
<td>6</td>
</tr>
<tr>
<td>Testicular Volume (mL)</td>
<td>3.6±0.5</td>
<td>6.6±0.5</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
Fertile Eunuch Syndrome (?)

- Nomenclature "FES" initiated
  - Normal random LH/FSH ratio
  - Rise in LH but not FSH after HCG
- Makker A, Glinoer M. Menopause 1997; 4:110
  - No rise in LH and FSH after clomiphene
  - Proposed that FES and HVL were along a spectrum
  - FSH with premature oocyte maturation in GSI patients
Fertile Eunuch Syndrome

- Summary:
  - Teenage male with virilization but microcephalus
  - Delayed, but spontaneously normal Tanner growth
  - Mildly elevated FSH but non-elevated LH
  - 46, XY
  - Low testosterone
  - No evidence of CAH
  - "Low" MIS levels
  - "Normal" (?) inhibin B levels

Fertile Eunuch Syndrome

- Further evaluation (?)
  - hCG stimulation
  - Semen analysis
  - GnRH/somatolide (?)
  - Anyone interested in DNA?
Adiponectin in cord blood

Frank B. Diamond, Jr. M.D.
University of South Florida College of Medicine

Adiponectin

- 264 amino acid protein expressed abundantly in white adipose tissue
- Anti-inflammatory and anti-atherogenic
- Concentrations correlate with insulin sensitivity state...protects insulin action by accelerating fatty acid oxidation
- Low in obese adults, T2D, CAD, men compared to women; rises with weight loss

Adiponectin in cord blood

- Lindsay RS et al (Diabetes Care 26:8,2244-2249, 2003):
  134 ODM; 45 control infants
  33-42 weeks gestation
  specimens from umbilical vein
  auxologic and hormonal parameters
Lindsay et al: Principal findings

- Adiponectin present in cord blood at concentrations of 4.6-34.7 ug/ml
- Adiponectin levels lower in ODM vs. control subjects (19.7 +/- 0.1 vs. 21.8 +/- 5.3, ug/ml, p<.05)
- No significant relation of adiponectin to anthropometric or hormonal values (insulin, leptin) at birth
- Unrelated to mode of delivery

Adiponectin in cord blood: USF findings

- 102 cord blood specimens previously collected and frozen at -70; RIA using kit from Linco, Inc.
  24-29 wks n=36
  30-36 wks n=36
  >/=37 wks n=30

Adiponectin in cord blood: USF findings

- Results +/- SD in ug/mL:
  24-29 wks 7.28 +/- 6.5*
  30-36 wks 14.4 +/- 10.8
  >/=37 wks 17.1 +/- 8.9
  p<0.05
Unanswered questions

- Why does adiponectin vary directly with BMI in cord blood, but inversely to BMI in postnatal life?
- How does fetal/cord adiponectin correlate with maternal body composition?
- What might be potential roles of adiponectin in utero and in the perinatal period?

Thank you!

- Dr. Duane Eichler, Division of Biochemistry, University of South Florida College of Medicine
- Suzan Hanna, Research Asst. USF Diabetes Center
Gitelman syndrome masquerading as short stature

Ambika Ashraf MD, Kenneth McCormick MD
Children's hospital, Birmingham, Alabama

The patient was a 14 year old white female was evaluated for short stature. She was at the 5th centile for height all her life until 10 years of age and then declined to below 3rd centile. Mid parental target height is at the 50th centile. History was negative for intrauterine growth retardation, chronic illnesses or intake of medication. The patient denied licorice or laxative abuse, diuretic use, persistent vomiting or diarrhea, pyelonephritis, or dehydration. She had a history of constipation and mild polyuria.

On general inspection, she had no dysmorphic features but was lank and withdrawn. Chronological age 14.29 yrs, weight 27.3 kg, height 142.5 cm, (both weight and height below 3rd centile), blood pressure 115/72(normal), pulse 87/minute. Examination was normal except for delayed puberty: Tanner stages 2 breast and 1 pubic hair. Lab evaluation disclosed hypokalemia, hypochloremia, hypomagnesaemia, alkalosis, with normal BUN and serum creatinine. Other labs: freeT4 1.32 ng/dl, TSH 3.32 UIU/ml, IGF- 1 150 ng/ml, bone age 138 months (Chronological age 171 months, 3.4 standard deviations below the mean).

Fractional excretion studies were consistent with hypocalciuria, hyperkaliuria, and hyper magnesium, particularly given her circulating levels. Her renin was markedly elevated and aldosterone was, unexpectedly, found to be low. Renal ultrasound did not show evidence of nephrocalcinosis. Sweat chloride was negative.

She was started on indomethacin, spironolactone and potassium chloride supplements. After one month her serum electrolytes were normal and aldosterone had increased.

<table>
<thead>
<tr>
<th></th>
<th>Labs prior to Rx (weeks apart)</th>
<th>Labs after Rx</th>
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<tr>
<td>Na mmol/L</td>
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<tr>
<td>K mmol/L</td>
<td>2.6</td>
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<tr>
<td>Cl mmol/L</td>
<td>93</td>
<td>93</td>
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<tr>
<td>CO₂ mmol/L</td>
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<td>36</td>
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<tr>
<td>AG mmol/L</td>
<td>15</td>
<td>12</td>
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<tr>
<td>BUN mg/dl</td>
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<tr>
<td>Creatinine</td>
<td>0.5</td>
<td>0.6</td>
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<tr>
<td>Parameter</td>
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<td>Value 2</td>
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<tr>
<td>---------------------------</td>
<td>---------</td>
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<tr>
<td>Calcium mg/dl</td>
<td>9.4</td>
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<td>Phosphorous mg/dl</td>
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<tr>
<td>Magnesium mg/dl</td>
<td>1.5</td>
<td></td>
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<tr>
<td>Renin ng/ml/hr</td>
<td>2859</td>
<td>1529</td>
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<tr>
<td>Aldosterone ng/dl</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Urine calcium to urine creatinine ratio</td>
<td>less than 0.2 (0.16)</td>
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<tr>
<td>Prostaglandin E2 in urine</td>
<td>443ng/24hrs (normal 400-620 ng/24hrs varies with BSA)</td>
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</tbody>
</table>

**Discussion:**

The patient’s biochemical profile of metabolic alkalosis, hypokalemia and hypochloremia was suggestive of diuretic abuse, cystic fibrosis, recurrent vomiting, or Bartter’s or Gitelman’s syndromes: in short, any disorder resulting in chronic augmented salt loss. However, these disorders are typically characterized by elevated plasma renin and aldosterone. Bartter’s and Gitelman’s syndromes, both autosomal recessive, are prototypical congenital conditions of salt wasting, both representing primary renal tubular hypokalemic metabolic alkalosis. Bartter syndrome is a heterogeneous disorder characterized by deficient tubular reabsorption of sodium and chloride due to several known mutations in ion transporters and channels. In Bartter syndrome as a consequence of disturbed salt absorption in the thick ascending limb loop of Henle the activity of renin, angiotensin, and aldosterone increases. Prostaglandins increase as a consequence of volume contraction and elevated angiotensin levels, and this per se may stimulate renin secretion. Originally described by Bartter and colleagues in 1962 as a new syndrome of hypokalemic alkalosis associated with hyperaldosteronism, juxtaglomerular hyperplasia, a pitressin resistant urine concentration defect, growth and mental delay, hyperreninemia and normal blood pressure. The elevated fractional excretion of potassium is usually attributed to hyperaldosteronism in concert with enhanced sodium delivery to the distal tubules.
Based on the aberrant cation excretion, our patient’s ailment was consistent with Gitelman’s syndrome. Urinary calcium levels will discriminate patients with classic Bartter syndrome (normocalciuria or hypercalciuria) and Gitelman’s syndrome (hypocalciuria and magnesium deficiency). Gitelman disorder is a variant of Bartter syndrome and due to mutations in the thiazide sensitive co-transporter of the distal convoluted tubule.

What distinguishes our case is the low plasma aldosterone concentration in the face of elevated plasma renin activity. The precise explanation for the unanticipated low plasma aldosterone is unclear. In a large series of Bartter syndrome cases in which this infrequent occurrence was noted, it was suggested that the direct effect of hypokalemia may indeed outbalance the elevated circulating renin activity in the regulation of adrenal aldosterone production.

This report underscores the necessity of routine electrolyte determination in the evaluation of a supposedly healthy short child with normal physical findings. Furthermore, as previously described in a few patients, a normal serum aldosterone level does not exclude the diagnosis of chronic salt wasting as seen in Bartter’s or Gitelman’s syndromes.

Bibliography:

Case Presentation

Keecha A. LynShue, M.D.
Department of Endocrinology
Children’s Hospital of Pittsburgh

Case Presentation

- HPI
  - 10 year old WF with a history of:
    - 12 pound weight loss over 2 months
    - Polyuria, polydipsia and nocturia

- Presented to PCP
- U/A obtained and significant for 4+ glucose with trace ketones
- Glucose meter not available and patient subsequently sent to CHP ED.
In ED

- BS: 167
- Na: 138
- K: 3.8
- Cl: 104
- Bicarbonate: 27
- BUN: 7 Creatinine: 0.6
- Serum Osm: 293
- VBG: 7.37/48/37/27/2
- Urine: 500 glucose, trace ketones

PE

- Wt 39.4 kg

- General- Alert, well-nourished, well appearing WF in NAD

- Tanner 2 for breast development and pubic hair

Family History
Family History cont..

- Patient's 14 y.o first cousin-
  - Diagnosed with DM, age 12 after routine PE
  - Initial HgbA1C: 8.0%
  - Since diagnosis: HgbA1C range: 4-6%
  - Insulin dose: 0.5-0.6 units/kg/day

Family History cont..

- Patient's paternal grandfather:
  - Diagnosed with DM, age 18
  - Initially placed on insulin
  - Switched to oral agents in his 50's

Laboratory Data

Hemoglobin A1C = 13.5%
Insulin antibodies = Negative
Islet Cell antibodies = Negative
GAD antibodies = Positive
(10.9 U/mL, NI ≤1 U/mL)
Follow Up

- One month after diagnosis, pt had gained 4.5 kg
- Repeat HgA1C: 8.5%
- Insulin requirement: 0.27 units/kg/day

What kind of diabetes does the patient have?

Classification of Diabetes

- Type 1 Diabetes (IDDM)
  - Usually occurs in childhood
  - Characterized by severe insulinopenia
  - Associated with certain HLA types (HLA- DR3/DR6)
  - Autoantibodies usually are present

- Type 2 Diabetes (NIDDM)
  - Usually occurs in adults (less true)
  - Physical signs: obesity, acanthosis nigricans
  - Insulin may be increased, decreased or normal
  - Strong familial component
Maturity Onset Diabetes of the Young (MODY)

- Term: "MODY" was coined in the 1960's to identify children and young adults with non-insulin dependent, "maturity-onset" diabetes that was inherited in an autosomal dominant pattern.

Criteria for Diagnosis

- Diabetes onset before age 25 in the proband
- Correction of fasting hyperglycemia without insulin for at least 2 years following diagnosis
- Non-ketotic disease
- Inheritance is autosomal dominant

Molecular Etiologies-MODY

- MODY 1: HNF-4α
- MODY 2: Glucokinase
- MODY 3: HNF-1α
- MODY 4: IPF-1
- MODY 5: HNF-1β
- MODY 6: Neuro D1 gene

*All forms except for MODY2 are caused by transcription factor genes involved in the regulation of insulin gene transcription. MODY 3 and 4 are the most common cases of MODY.*
History of MODY

- **MODY 1**
  - Identified in 1972
  - John T. Sherrill, M.D.
  - University of Texas Medical Branch

- **MODY 2**
  - Identified in 1983
  - Investigators: P. Falini, et al.
  - National Human Genome Research Institute

- **MODY 3**
  - Identified in 1994
  - Chromosome 7q
  - Dennis R. Young, M.D.
  - University of Michigan

- **MODY 4**
  - Identified in 1995
  - Dr. Robert G. (Ogilvie) and
  - Barbara Yangden, M.D., Ph.D., of
  -RoutingModule

- **MODY 5**
  - Identified in 1997
  - Dr. Yuh-Ching Hsiao, Department of
  - Endocrinology and
  - Physiology, The University of
  - California, San Francisco

- **MODY 6**
  - Identified in 1999
  - Dr. Adachi

---

**MODY 1**

- Transcription factor expressed in liver,
  kidney, intestine and pancreatic islets
- 30-40% of MODY 1 subjects will require
  insulin
- Usually have hyperglycemia on OGTT
- Deficient glucagon secretion after AITT (?)
  Pan-islet lesion
MODY 2

- Glucokinase deficiency
- Glucose
- Glucose-6-P
- Prenatal period: Max be 500 g lighter than unaffected siblings
- About half of women with GCK mutations develop diabetes during pregnancy
- Homozygosity for GCK mutation can cause severe permanent insulin-dependent neonatal diabetes
- MODY 2 is a common cause of MODY worldwide and is the most common cause of MODY in France where it has been studied extensively.

Insulin Secretion

MODY-3

- Hepatocyte nuclear factor-1α mutation
- More than 130 HNF-1α mutations have been recognized
- HNF-1α is expressed in hepatocytes and beta cells
- Progressive insulin deficiency with increasing age
- One-third of MODY3 patients will require insulin treatment
- By age 40, diabetes can be seen in MODY3 carriers (and MODY1 carriers) as much or more than 80% of the time.
- MODY 3 is the most common form of MODY in the United Kingdom
MODY 4
- Mutation in Insulin Promoter factor-1 (IPF1)
- Homozygous mutation can lead to pancreatic agenesis
- Very rare

MODY 5
- Hepatocyte Nuclear Factor-1β mutation
- Renal cysts, proteinuria and renal failure
- Female carriers may have vaginal aplasia or bicornuate uterus
MODY 6
- NeuroD1/beta2 mutations
- Expressed in pancreatic endocrine cells, intestine and brain
- Secretin and cholecystokinin expression dependent on NeuroD1
- Important for normal pancreatic development

When to suspect MODY
- Strong family history to suggest an autosomal dominant mutation
- Mild hyperglycemia without tendency for ketosis
- No autoimmunity present
- Parent of a child with mildly elevated fasting blood glucose
- History of macrosomic children and gestational diabetes
- Glycosuria with normal blood sugars (MODY 3)

Why Make the Diagnosis?
- Hyperglycemia may vary
  - In 2/3 of MODY 2 cases require no glycemic medication and diet therapy may satisfactorily control blood glucose levels
  - Patients with MODY 3 are extremely sensitive to sulfonylureas
- Prognosis
  - Pros with MODY 2 usu. have mild elevations in HbA1c and rarely suffer from microvascular complications
  - Pros with MODY 3 usu. become diabetic in adolescence or young adulthood and have a marked decline in beta cell function. Therefore, may develop severe microvascular complications
Why Make the Diagnosis?

- Genetic counseling
  - Identify family members
  - Advise patients on the natural course/progression of their disease
Psychologic Adaptation in Idiopathic Short Stature During GH or Placebo

Susan R. Rose
Cincinnati Children's Hospital Medical Center

Study Collaborative Group
- JL Ross
- DE Sandberg
- J Baran
- JJ Chomman
- BJ Crowe
- DS Bernstein
- SC Hill
- MA Bach
- JD Jacobson
- BL Linder
- S Markowski
- SB Nuehl
- PS Thomas
- GB Cutler, Jr
- EW Leischek
- FG Cassoria
- CA Dupin
- K Roberts
- JC Jones
- G Heasner
- HL Dick
- KO Klein
- GM Leong
- G Sarn
- DG Scott
- KK Winter

Psychosocial Adaptation in SS

- Teasing
- Juvenilization
- Academic underachievement
- Negative stereotypes
- In one community-based study in the UK, only 12% of short healthy children were satisfied with their height
Purpose

- Assess the psychosocial adjustment & self-concept of children with ISS prior to initiation of GH therapy, &
- Evaluate prospectively whether GH treatment affects these outcomes

Study Design

- Randomized, double-blind, placebo-controlled trial of GH to near adult height (growth velocity ≤ 1.5 cm/y)
- GH 0.074 mg/kg/d (or placebo) sc 3 times (0.22 mg/kg/wk)
- Psychologic questionnaires baseline & yearly

Eligibility

- Inclusion criteria
  - Idiopathic short stature
  - Height or predicted height ≤ -2.5 SD
  - Girls 9-15 y, Boys 10-16 y
  - Prepubertal or stage 2 of puberty
  - Bone age ≤ 11 y (girls), ≤ 13 y (boys)
- Exclusion criteria
  - Chronic illness
  - Genetic syndrome
  - Prior GH, estrogen, or androgen treatment
  - Receiving restraint or similar stimulants
Subjects

- 71 children were recruited (1988-1999)
- 3 withdrew before receiving study drug
- 68 children were treated (53M, 15F)

Baseline characteristics

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<th>GH</th>
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<tr>
<td>Number</td>
<td>37 (29 male)</td>
<td>31 (24 male)</td>
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<tr>
<td>CA (y)</td>
<td>12.5 ± 1.6</td>
<td>12.2 ± 1.4</td>
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<tr>
<td>Bone age (y)</td>
<td>10.9 ± 1.7</td>
<td>10.9 ± 1.7</td>
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<tr>
<td>Ht SDS</td>
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<td>-2.8 ± 0.5</td>
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<tr>
<td>Wt SDS</td>
<td>-2.3 ± 0.7</td>
<td>-2.9 ± 0.9</td>
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<td>(Mean ± SD)</td>
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Psychologic questionnaires

- Children
  - Self-Perception Profile (SPP)
  - Silhouette Apperception Technique (SAT)
- Parents
  - Child Behavior Checklist (CBCL)
Self-Perception Profile

- SPP assesses
  - judgment of personal competence
  - perception of self worth or esteem
- "Some children do this (have several friends), others do that (keep to themselves)"

Silhouette Apperception Test

- SAT assesses
  - self-concept of size
  - expectations for therapy response
- Child picks one of five silhouettes representing the 3rd, 25th, 50th, 75th, & 97th %ile

Child Behavior Checklist

- CBCL assesses
- Competencies (higher = better)
- Behavioral problems (higher = worse)
  - Total behavior problems
  - Internalizing (fearful, inhibited, & over-controlled) versus
  - Externalizing (aggressive, antisocial, & under-controlled)
Results

- In June 2000, Data & Safety Monitoring Board ended study: slow accrual of remaining data did not warrant continuing placebo injections in control group.

Growth Results

- Duration of therapy 4.6±1.6y
- Near adult height
  - 3.7cm (0.5 SD) (p=0.02) taller in GH-treated than in placebo-treated
  - 5.0cm (0.7 SD) (p<0.001) with inclusion of those not yet at near adult height (by linear models, repeated measures)
- No adverse medical effects
Questionnaire Results

- At baseline in both treatment groups
  - CBCL & SPP scores were within one SD of normative population
  - Scores had no correlation with height
  - SAT = height between 3rd & 25th %ile
CBCL Results

- By 3rd & 4th yr
  - placebo group had increased behavioral problems
  - GH group showed a decline in problems
SPP Results

- No significant differences between GH & placebo groups at any follow-up point

SAT Results

- By 4th yr
  - placebo group perceived relative size as at baseline
  - GH group viewed selves as taller
Summary

- Baseline adjustment & self-concept in peripubertal short children were similar to the general population.
- Parents noted decline in behavior problems during yrs 3 & 4 of GH therapy.
- GH treatment of ISS did not result in deterioration in psychological functioning.

Conclusion

- GH treatment for ISS may optimize opportunities, but should not be rationalized on presumed psychological distress.
- Psychosocial impact of the short stature & adaptive coping strategies should be part of clinical assessment of a child with short stature.
Gross Intermittent Hematuria in a 9 year old boy

Samar K. Bhowmick, M.D., FACE
Professor of Pediatrics
University of South Alabama
College of Medicine

Case History

- 9-year-4-month old male with gross painless intermittent hematuria of 3 - 4 months duration
- Hematuria usually occurs after a soccer game
- Gross hematuria persists up to 4 - 6 hours
- No H/O weight loss, polyuria, polydipsia, chronic UTI or renal diseases
- Family History: Father had Kidney stones in his mid-30s

Physical Examination

- Healthy child, completely normal exam
- Ht and Wt at 10th and 5th percentile
- Serial BP measurement – normal
- No evidence of pubertal development
Laboratory Evaluation

- U/A - microscopic hematuria (50-100 RBC)
- Urine culture - negative x2
- Normal CBC, TFT, Lytes, BUN, Creatinine, Albumin
- Calcium: 12.9, 13.1, 13.7, mg/dl (8-10.8)
- Ionized Calcium: 6.45, 6.97, mg/dl (4.5-5.5)
- Serum PO₄: 2.8, 3.1, 3.0 mg/dl

Laboratory Evaluation

- 25O HD, Gastrin, Calcitonin - Normal
- 24-hr urine VMA, Catechol - Normal
- Spot urine ca: Cr-0.35, 0.32 (<0.2)
- 24 hrs urine calcium -136 mg (high)
- Intact PTH, 90.7, 101.98 pg/ml (10-60)

Radiological Evaluation

- Hand Films - Questionable Osteoporotic
- Renal sonogram - Normal
- Neck Sonogram - Negative
- Dual Thallium Technetium digital subtraction scan of neck - inconclusive
Patient was taken to surgery for Neck Exploration

Fig 1 – Macroscopic Findings – Light brown encapsulated, 200 mg nodule, measures 9 x 6 x 4 mm

Fig 2 – Low power view – Arrow on the capsule, inside the capsule "Adenoma Cells"
Fig 3 – Higher magnification – Large, uniform polygonal chief cells, arrow is on atrophic parenchyma

Discussion

Incident of Primary Hyperparathyroidism

- Adult: 25-30 cases/100,000
- Rare in children - <16 yrs of age
- Extremely uncommon in prepubertal age group
- Adult – female predominance 3:1
- Children – male/female (3:2) in most series

Clinical Presentation

- Adult – mostly asymptomatic, hypercalcemia, detected by routine chemistry profile
- Children: usually symptomatic, polyuria, wt loss, fatigue, poor appetite, abd pain, gross or microscopic hematuria, nephrocalcinosis
- Bone demineralization, fracture, cysts
- PHP in children account only for 1% of all hypercalcemia
Treatment

- Cervical exploration with or without preoperative localization
- 95% success without pre-operative localization
- IV methylene blue may facilitate localization during surgery
- Visualization of all glands if possible

Conclusion

- Our patient had convincing lab findings
- Pre-operative localization – inconclusive
- Cervical exploration revealed a right superior parathyroid adenoma
- Normal calcium, PTH and no hematuria 2 years post-surgery

Questions/Answers

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<tr>
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</tr>
<tr>
<td>Dumb look</td>
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Thank You
Southern Pediatric Endocrine Society  
Charlotte, North Carolina  
November 9, 2003

PRECOCIOUS PUBERTY: AN HISTORICAL PERSPECTIVE

Allen W. Root, M.D.

Departments of Pediatrics, Biochemistry and Molecular Biology, University of South Florida  
College of Medicine, Tampa, and the All Children's Hospital, St. Petersburg.

In this discussion, we shall review in an historical context, the definition, diagnosis, and  
management of isosexual precocity in infants and children. Precocious puberty was described in  
reports from ancient Greece and Rome. Craterus (300-200 BCE) reported a patient who was  
“child, youth, old man, begot a child, and died, all within seven years” (Thamdrup 1961).  
However, it is unlikely that this subject had the classical form of central precious puberty with  
which we are more commonly acquainted. By 1816, 20 children with sexual precocity had been  
identified, and by 1961 the number of reported children with precocious puberty grew to more  
than 1000.

Normal pubertal development - The definition of sexual precocity

Tanner and colleagues were among the first to codify the maturational stages of male genital  
development, female breast development, and pubic hair growth, the mean ages of onset of each  
pubertal stage, and the wide age ranges that each stage occupied (Tables 1, 2) (Marshall &  
Tanner 1969, 1970). The validity of these observations has stood the test of time, but in the past  
several years studies in the United States suggested that pubertal onset may be occurring at  
earlier ages, specifically in females. As we know, breast budding (thelarche) is usually the first  
manifestation of puberty in girls; in 15 percent of girls pubic hair growth (pubarche) is the initial  
pubertal sign. Menarche occurs on average two years after thelarche (range <1-5 years); the  
earlier the onset of thelarche the longer the interval between thelarche and menarche but the  
younger is the age of menarche; the later the onset of thelarche the shorter is the interval between  
theplarche and menarche but the older is the age of menarche (Marti-Hennberg & Vizmanos  
1997). Peak height velocity (PHV) is achieved at 12 years in girls - immediately prior to  
menarche. Pelvic ultrasonography demonstrates progressive increase in uterine length and  
ovidian volume during sexual maturation, both measurements correlating with breast growth and  
serum estradiol concentrations, although there is substantial overlap between stages. In addition  
to increase in volume, ovarian echogenic pattern varies with advancing puberty as multiple,  
initially small and then somewhat larger, follicular cysts appear and regress; in the late adolescent  
female a multicystic ovarian sonographic pattern is common.

Spurred by the findings of a survey of pubertal development in American females suggesting that
females) classifying them into those with true (central) precocious puberty (38 were “constitutional” of whom 4 were males and 18 had CNS insults), the adrenogenital syndrome (N=17), gonadal tumors (N=2), premature pubarche (N=17), premature thelarche (N=6), and drug-induced. Today the causes of sexual precocity (Table 4) and our understanding of their pathophysiology has increased substantially, but our present classification represents expansion of previously defined basic central and peripheral disorders.

Isosexual precocious puberty occurs more commonly in girls than boys (10:1). In children with true and complete, central isosexual precocious puberty (CPP), pubertal development is driven by gonadotropin releasing hormone (GnRH) but the "restraint" placed on the hypothalamic-pituitary-gonadal (HPG) axis by higher CNS centers has been lost at a prematurely early age. CPP may be due to congenital anomalies, infectious, neoplastic, or traumatic insults to the CNS, or it may follow treatment of disorders in which there has been long-standing non-centrally regulated sex hormone secretion, i.e., pseudoisosexual precocity (vide infra). In females, CPP is most often (60-70%) idiopathic, albeit asymptomatic hypothalamic hamartomas with GnRH synthesizing neurons may be identified by CNS imaging in perhaps as many as 10% of girls, particularly those less than 4 years of age at presentation. Other neurogenic abnormalities detected in girls with CPP include congenital malformations, empty sella turcica, hydrocephalus, myelomeningocele, benign arachnoid cysts and neoplastic tumors (Cisterno et al 2000). Both septo-optic dysplasia and cranial x-ray therapy lead to deficiencies of multiple anterior pituitary hormones including GH, but, paradoxically, in many of these children the HPG axis remains intact and begins to function at a prematurely young age. Early puberty has been observed in subjects with intrauterine growth retardation (IUGR) associated with maternal uniparental disomy for chromosome 14 (Fokstuen et al 1999). In boys with CPP, a CNS insult or structural abnormality may often be found in more than 90%, although in an Italian series, 60% of 45 boys with CPP did not have a demonstrable CNS lesion (De Sanctis et al 2000). Many children adopted from a foreign country also have early pubertal onset.

Pseudoisosexual precocious puberty (PPP) develops independently of GnRH and pituitary gonadotropins. Intracranial and mediastinal germinomas secrete human chorionic gonadotropin (hCG) and tumor derived ectopic secretion of luteinizing hormone (LH) stimulate Leydig cell secretion of testosterone in boys. However, in most instances PPP is gonadotropin-independent. Familial male-limited precocious puberty (FMPP, testotoxicosis, Leydig cell hyperplasia) is due to a germ-line mutation in the 7-transmembrane LH receptor that renders it constitutively active, i.e., functional in the absence of its ligand - thus "turning on" Leydig cell testosterone synthesis. Somatic mutations of the LH receptor are associated with nodular Leydig cell hyperplasia. The McCune-Albright syndrome (MAS) is due to an activating germ-line mutation in the Go subunit of G-protein, the membrane bound signaling molecule linked to the LH receptor, resulting in either granulosa cell production of estradiol or Leydig cell synthesis of testosterone. Ovarian cysts and granulosa and Leydig cell gonadal tumors secrete sex hormones independently of gonadotropin control and are at times due to somatic tissue-specific mutations in the LH receptor or the Go subunit of G protein. The syndrome of aromatase excess has been associated with premature thelarche in girls and gynecomastia in boys. It has been described in boys with
calcifying Sertoli cell tumors of the testis and the Peutz-Jehgers syndrome of hamartomatous intestinal polyposis and oral pigmentation. Although generalized increase in aromatase expression has been found in these subjects, mutations in the aromatase gene itself (CYP19A1, chromosome 15q21.2) have seldom been described. In two families with familial gynecomastia, overexpression of aromatase activity in many extra-gonadal tissues (fat, skin fibroblasts) was attributed to heterozygous inversions in a region of chromosome 15q21.1 in which two constitutively active and widely expressed genes are located; the inversions led to the juxtaposition of the promoters of these genes to CYP19A1 and consequently its constitutive activation (Shozu et al 2003). Hyperandrogenism due to congenital adrenal hyperplasia (CAH) associated with deficiency of either 21- or 11β-hydroxylase and consequent excessive secretion of testosterone leads to PPP in males. In children with primary hypothyroidism, thelarche, uterine bleeding, and ovarian cysts may occur in girls and macroorchidism in boys. In these children, PPP may be due to prolonged LH and FSH biologic activity or to thyroid stimulating hormone (TSH) binding to LH and FSH receptors. Primary hypothyroidism is occasionally accompanied by hyperprolactinemia and galactorrhea in both sexes.

Incomplete forms of isosexual precocious puberty are relatively benign. Since the HPG axis is active throughout infancy and childhood in girls, if an ovarian follicle secretes sufficient estrogen, breast and uterine endometrial growth may occur leading to premature thelarche or less commonly premature menarche, both self-limited and non-progressive states. However, perhaps 10% of little girls who appear to have isolated premature thelarche when first evaluated (normal linear growth and bone age, prepubertal gonadotropin and estrogen values), evolve into subjects with CPP. In general, the latter group is >2 years of age at onset of thelarche and breast development is persistent (Stanhope 2000). In infant boys, scrotal hair growth may reflect the surge in testosterone secretion that peaks at 3 months of age. Postnatally, in utero breast development usually disappears within several weeks after birth, but it may persist for as long as 8 months. Premature pubarche, which is most often due to early increase in adrenal androgen secretion (precocious adrenarche), is followed by functional ovarian hyperandrogenism in 20% of affected young women (Ibanez et al 2000). Premature adrenarche progressing to long-term hyperandrogenism occurs relatively commonly in girls with intrauterine growth retardation.

Evaluation of the child with precocious puberty

The history and physical examination remain the primary diagnostic tools for evaluation of the child with sexual precocity (Figures 1,2). Earlier bioassays for gonadotropins and sex hormones were cumbersome and insensitive. Development of sensitive assays for measurement of gonadotropins and sex hormones in serum and urine truly revolutionized the diagnostic evaluation of children with sexual precocity as has the evolution of imaging techniques enabling us to examine structures previously secreted within the abdomen, pelvis, and skull. Thus, in 1961 gonadotropin secretion was determined by “...injection of urine precipitated with tannic acid into infantile female rats...”, “...biological determination of androgens was carried out by the capon-comb method...” and “...estrogen excretion was carried out by the Allen-Doisy test...” (estimation of vaginal cornification in oophorectomised rats after injection of a urine extract)
(Thamdrup 1961). For evaluation of children with precocious puberty, Wilkins (1960) relied upon the measurement of urinary gonadotropins by their effect on the uterine weight of immature mice or the ovarian weight of immature rats, while estrogen effects were estimated by the vaginal smear and urinary estrogens measured by a chemical reaction after organic solvent extraction, washing of the extract with an aqueous alkaline solution and isolation by column or paper chromatography, an extremely labor intensive procedure.

The advent of radioimmunoassays for gonadotropins and sex steroids and the later development of ultrasensitive of immunofluorometric and immunochemiluminometric assays radically altered evaluation of the sexually precocious child. Thus, employing an ultrasensitive assay for luteinizing hormone (LH), a single basal LH value in excess of 0.3 mIU/mL is consistent with central precocious puberty. The utility of GnRH-induced secretion of LH and FSH in distinguishing between peripheral and central forms of precocious puberty and intermediate stages of hypothalamic-pituitary-gonadal maturation has been of major benefit, although the increasingly limited supplies of this material raise concern. An ultrasensitive biomolecular assay for estrogen involving the transformation of a yeast with human estrogen receptor complementary DNA and an estrogen response element upstream of a marker gene has permitted a detection limit of 0.02 pg/mL and afforded new insights into the regulation of estrogen secretion in infants and children (Klein et al 1994).

Plain roentgenograms of the abdomen and skull and extremely uncomfortable pneumoencephalograms were once the only procedures available permitting visualization of the interior of occult body compartments. Ultrasonographic examination of the pelvis and abdomen and computed tomographic (CT) and magnetic resonance imaging (MRI) of the abdomen and skull now permit unprecedented views of these regions. We visualize ovarian cysts and hypothalamic hamartomas with relative ease.

Treatment of precocious puberty

From expectant observation and intervention only in patients with the most apparent of mass lesions, the treatment of the sexually precocious child has evolved through attempts to inhibit gonadotropin secretion, initially with a variety of progestational agents including medroxyprogesterone, cyproterone, and danazol, then with short-, long-, and presently ultra-long acting agonists of GnRH with paradoxical inhibitory effects on gonadotropin secretion, to inhibitors of aromatase activity and androgen and estrogen receptor antagonists. The availability of GnRH antagonists may be anticipated shortly.

In most girls with premature thelarche, breast growth regresses within 2-4 years after it first develops; however, approximately 10% of children with presumed premature thelarche evolve into CPP. Thus, monitoring of girls with premature thelarche is essential. The girl with premature menarche may have several monthly menstrual periods before menses disappear. In general, the parents of girls with premature thelarche or menarche may be reassured and the child observed. Most boys and many girls with premature adrenarche have no long-term adverse
effects; however, because of the high frequency (20%) of functional ovarian hyperandrogenism, all girls with premature adrenarche require follow-up into young adulthood (Ibanez et al 2000).

In patients with PPP, the primary disease must be treated: gonadotropin-secreting, gonadal, and adrenal tumors are removed; patients with CAH receive cortisol, those with hypothyroidism thyroxine. Most isolated estrogen-secreting ovarian cysts may be managed expectantly as the cyst will often regress spontaneously. In boys with FMPP or MAS, testosterone synthesis may be decreased by ketoconazole (an inhibitor of 17α-hydroxylase/17-20 lyase) or its action blocked by flutamide (an androgen receptor antagonist). Anastrozole, an aromatase inhibitor, has proven variably effective in girls with hyperestrogenemia due to MAS (Kunz et al 2003); tamoxifen, an estrogen receptor antagonist, decreases the frequency of vaginal bleeding, growth velocity, and rate of skeletal maturation in girls with MAS (Eugster et al 2002). After suppression of gonadotropin-independent sex hormone secretion, some patients with PPP evolve into subjects with CPP, particularly if their bone ages are in the pubertal range when initially identified; these children may then be treated effectively with GnRHa.

In children with CPP due to a specifically treatable anatomic abnormality of the CNS, primary attention is focused on management of the underlying disorder; the effect of its successful treatment on the course of CPP is then monitored as this process may either regress, remain static, or progress. In subjects with idiopathic CPP or that associated with a hypothalamic hamartoma or other form of CPP for which primary therapy is not available (e.g., the child with PPP who during/after treatment has evolved into one with CPP), the pubertal HPG axis may be inhibited by the administration of a GnRH receptor agonist (GnRHa) (Comite et al 1981; Mansfield et al 1983); long-acting forms of GnRHa are more effective than are short-acting GnRHa forms administered several times daily by intranasal inhalation or subcutaneous injection. One of the most commonly employed long-acting agonists is depot-leuprolide (0.3 mg/kg intramuscularly every 3-4 weeks). (In GnRHa, the decapptide GnRH has been modified by replacement of the sixth amino acid glycine by a D-amino acid and the tenth amino acid (glycine) has usually been substituted.) A subcutaneous formulation of 11.25 mg of depot leuprolide provides three months of effective HPG suppression in children with CPP, thus reducing the number of yearly injection to four (Carel et al 2002). At present, a clinical study evaluating the usefulness of a GnRHa preparation that can be administered once yearly is underway, although the sagacity of administering such a product to children in whom rapid change is the norm might be questioned. At first, the use of a GnRH agonist (a stimulus to LH and FSH secretion) in children with CPP may seem paradoxical. Experimental studies in primates revealed that when GnRH is administered as a constant intravenous infusion over several hours, gonadotropin secretion is initially stimulated and then depressed; the latter is attributable to down-regulation of GnRH receptors and alteration in gonadotroph synthesis of gonadotropin subunits (Belchetz et al 1978). Similarly, when long-acting GnRHa is administered, gonadotropin secretion is initially stimulated and then inhibited. In some girls with CPP, vaginal bleeding occurs two weeks after the first injection of GnRHa but usually not thereafter. In most children with CPP, there is complete suppression of HPG function within 4-8 weeks after initiation of therapy. Continued efficacy of GnRHa therapy is monitored clinically
(decline in growth rate, regression or lack of progression of physical signs of sexual maturation, amenorrhea), radiographically (decreased rate or even arrest of bone age advancement), and hormonally (suppressed basal and stimulated estradiol or testosterone and gonadotropin values). The development of GnRH receptor antagonists for use in children with CPP may be anticipated (Huine & Lambalk 2001).

Although GnRHa effectively suppresses HPG function in children with CPP, the basic question that must be answered is how to identify that child in whom treatment is necessary and appropriate? The majority of boys with CPP merit therapy with GnRHa as bone age is usually markedly advanced and pubertal development progressive in these subjects. However, in many girls with CPP, sexual maturation progresses slowly; their bone age is not greatly in advance of chronologic age, the change in the height age/bone age ratio is <0.9 year per year, growth rate is normal, and predicted adult height remains compatible with genetic potential. In such children, reassurance and observation as they fade into early-normal puberty are appropriate measures. Clearly, it is essential to follow all girls with CPP as, on occasion, a child with the apparently slowly progressive form of CPP may experience rapid acceleration of skeletal maturation and develop criteria for treatment with GnRHa. Thus, several criteria should be fulfilled before placing the girl with CPP on GnRHa (Table 5). If the majority of the criteria are met, then treatment with GnRHa may be initiated. Depending on the age, skeletal maturation, and hormonal data, it is often reasonable to follow the girl with idiopathic CPP for 6 months without therapeutic intervention in order to document the rate of pubertal progression before deciding whether GnRHa therapy is appropriate.

Administration of GnRHa leads to cessation of menses in girls and regression or halt in progression of sexual characteristics in both sexes. The rates of linear growth and skeletal maturation decline. Prior to the availability of GnRHa, the adult stature of girls with CPP averaged 153 cm and that of boys 156 cm. Although the predicted adult height upon completion of GnRHa treatment is not realized, the adult height of children with CPP is now 8-12 cm taller than that reached prior to its use (Klein et al 2001). The adult height of girls with CPP treated both with GnRHa and recombinant human growth hormone (rhGH) has been reported to exceed the target height and to be 6 cm greater than that of girls receiving GnRHa alone (Pucarelli et al 2003). However, inasmuch girls receiving only GnRHa achieve their target heights, the merits of such therapy must be questioned. Therapy with GnRHa is usually discontinued between 11-12 years in girls (bone age 12-12.5 years) and 12-13 years in boys as age peers progress into pubertal development. After discontinuing GnRHa, linear growth rate accelerates and the HPG rapidly returns to the pubertal state; menses usually occur within 6-18 months after halting GnRHa.

Bone mineralization doubles during puberty; but treatment with GnRHa depresses the rate of bone calcium accrual. Supplementation of GnRHa-treated CPP girls with calcium (1 g/day) significantly increases lumbar spine volumetric bone mineral density compared to girls receiving GnRHa alone, although most GnRHa-treated girls have normal bone density at the completion of therapy (Antoniazzi et al 2003).

**Conclusions**
Children with sexual precocity have traveled a long journey - from fascinating oddity to the realization of active and effective intervention. In several genetic disorders associated with precocious puberty, we may even anticipate more aggressive approaches to the repair of the primary underlying abnormality by gene transfer or protein engineering.

Selected references


Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: A study from the Pediatric Research in Office
<table>
<thead>
<tr>
<th>Stage</th>
<th>Age: W</th>
<th>AA</th>
<th>Mex-Amer</th>
<th>Uterine length - cm</th>
<th>Right ovarian volume - mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepubertal, papilla</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elevation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9.96*</td>
<td>10.3</td>
<td>8.87*</td>
<td>9.5*</td>
<td>9.8*</td>
</tr>
<tr>
<td>Breast bud</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diameter &lt; areolar</td>
<td>±1.82</td>
<td>(10-10.5)</td>
<td>1.93</td>
<td>(9.3-9.8)</td>
<td>(9.4-9.9)</td>
</tr>
<tr>
<td>width</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>11.30</td>
<td>10.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; areolar width</td>
<td>±1.42</td>
<td>1.42</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Peak height</td>
<td>12.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>velocity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menarche</td>
<td>12.88</td>
<td>12.7</td>
<td>12.16</td>
<td>12.1</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>±1.20</td>
<td>(12.4-12.8)</td>
<td>1.21</td>
<td>(12-12.4)</td>
<td>(12-12.5)</td>
</tr>
<tr>
<td>IV</td>
<td>12.9+</td>
<td>12.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mounding of areola</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>above plane of breast</td>
<td>(10.4-15.3)</td>
<td>0.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>14.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritic hair</td>
<td>Age:W</td>
<td>AA</td>
<td>Mex-Amer</td>
<td></td>
<td></td>
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<tr>
<td>--------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10.31* 10.5!</td>
<td>8.78*</td>
<td>9.5! 10.3!</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slightly pigmented over mons or labia</td>
<td>±1.67 (10.4-10.9)</td>
<td>2.00 (9.2-9.8)</td>
<td>(10.1-10.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark, coarse on mons</td>
<td>11.53</td>
<td>10.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult in character confined to mons</td>
<td>12.6+ (10.4-14.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult - spread to medial thigh</td>
<td>14.6 (12.4-16.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**W.** White  AA - African-American  Mex-Amer - Mexican American  
Age - years  
Uterus - cm  
Ovary - mL (calculated as an ellipse - length x width x depth x 0.5233)  
± - Standard deviation (Range or Confidence interval)
<table>
<thead>
<tr>
<th>Germinalia</th>
<th>Age:W</th>
<th>AA</th>
<th>Mex-Amer</th>
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<tbody>
<tr>
<td>I. Prepubeirtal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis &lt;2.4 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III Testis ≥2.5-3.3 cm, &gt;4 mL</td>
<td>11.9**</td>
<td>11.08!</td>
<td>10.79!</td>
</tr>
<tr>
<td>IIII Testis &gt;3.3-4.0 cm, &gt;6 mL; phallus has grown in length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.0</td>
<td>12.55</td>
<td>12.03</td>
</tr>
<tr>
<td></td>
<td>±0.8</td>
<td>2.30</td>
<td>2.98</td>
</tr>
<tr>
<td>Peak height velocity</td>
<td>13.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11.5-16.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Testis &gt;4 cm, &gt;10 mL; phallus has grown in breadth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.3</td>
<td>15.29</td>
<td>15.07</td>
</tr>
<tr>
<td></td>
<td>±0.8</td>
<td>1.81</td>
<td>3.27</td>
</tr>
<tr>
<td>V. Adult</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis &gt;5 cm, &gt;15 mL</td>
<td>15.1</td>
<td>16.64</td>
<td>16.42</td>
</tr>
<tr>
<td></td>
<td>±1.1</td>
<td>1.64</td>
<td>1.43</td>
</tr>
<tr>
<td>Pubic hair</td>
<td>Age: W</td>
<td>AA</td>
<td>Mex-Amer</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>None</td>
<td>12.3</td>
<td>11.81!</td>
<td>11.48!</td>
</tr>
<tr>
<td>Slightly pigmented</td>
<td>±0.8</td>
<td>1.04</td>
<td>1.34</td>
</tr>
<tr>
<td>pigmented, at base of phallus or scrotum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark, coarse at base of phallus</td>
<td>±0.9</td>
<td>1.69</td>
<td>1.76</td>
</tr>
<tr>
<td>Adult in character confined to suprapubic region</td>
<td>14.7</td>
<td>14.89</td>
<td>15.21</td>
</tr>
<tr>
<td>±0.9</td>
<td>1.56</td>
<td>2.52</td>
<td>1.54</td>
</tr>
<tr>
<td>Adult - spread to medial thigh</td>
<td>15.3</td>
<td>16.84</td>
<td>16.67</td>
</tr>
<tr>
<td>±0.8</td>
<td>1.50</td>
<td>0.92</td>
<td>1.54</td>
</tr>
</tbody>
</table>


White: AA - African-American Mex-Amer - Mexican American

Age: years
(Range) ± Standard deviation
Table 3. Median age (range - years) of transition between stages of sexual maturation in males.

<table>
<thead>
<tr>
<th>Genitalia/</th>
<th>White</th>
<th>AA</th>
<th>Mex-Amer</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>10.1</td>
<td>9.5</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>(9.6-10.6)</td>
<td>(8.9-10.0)</td>
<td>(9.6-11.1)</td>
</tr>
<tr>
<td>IIII</td>
<td>12.4</td>
<td>11.8</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>(12.0-12.7)</td>
<td>(11.3-12.3)</td>
<td>(12.2-12.8)</td>
</tr>
<tr>
<td>IV</td>
<td>13.5</td>
<td>13.4</td>
<td>13.7</td>
</tr>
<tr>
<td></td>
<td>(13.2-13.8)</td>
<td>(13.1-13.6)</td>
<td>(13.4-14.1)</td>
</tr>
<tr>
<td>V</td>
<td>15.9</td>
<td>14.9</td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td>(15.3-16.4)</td>
<td>(14.4-15.5)</td>
<td>(15.3-16.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pubic hair:</th>
<th>White</th>
<th>AA</th>
<th>Mex-Amer</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>12.0</td>
<td>11.2</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>(11.7-12.3)</td>
<td>(10.9-11.4)</td>
<td>(12.1-12.6)</td>
</tr>
<tr>
<td>IIII</td>
<td>12.6</td>
<td>12.5</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>(12.3-13.0)</td>
<td>(12.3-12.8)</td>
<td>(12.9-13.3)</td>
</tr>
<tr>
<td>IV</td>
<td>13.5</td>
<td>13.7</td>
<td>14.1</td>
</tr>
<tr>
<td></td>
<td>(13.2-13.8)</td>
<td>(13.5-13.9)</td>
<td>(13.8-14.4)</td>
</tr>
<tr>
<td>V</td>
<td>15.7</td>
<td>15.4</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td>(15.3-16.0)</td>
<td>(14.9-15.9)</td>
<td>(15.5-16.2)</td>
</tr>
</tbody>
</table>


(Confidence interval)
Table 4. Causes of isosexual precocious puberty.

I. True and complete (central) precocious puberty

A. Idiopathic
   1. With/without hypothalamic hamartoma
   2. Adoption
B. Secondary
   1. Congenital anomalies: hamartoma, hydrocephalus, arachnoid or ventricular cyst, septo-optic dysplasia, empty sella syndrome, myelomeningoceles
   2. Post inflammatory: encephalitis, meningitis, abscess, granulomatous disease
   3. Radiation therapy
   4. Trauma
   5. Neoplasms: hypothalamic hamartoma, astrocytoma, ependymoma, glioma (neurofibromatosis), craniopharyngioma
   6. Following effective treatment of long-standing pseudoisosexual precocious puberty

II. Pseudoisosexual precocious puberty

A. Familial male-limited precocious puberty (LHR)
B. McCune-Albright syndrome (GNAS1)
C. Gonadal/extra-gonadal sex hormones
   1. Estrogen secreting: ovarian cyst, granulosa cell tumor, aromatase excess syndrome: familial, calcifying Sertoli cell tumors, aromatase excess
   2. Testosterone secreting: Leydig cell tumor, Leydig cell nodular hyperplasia, teratoma
   3. Human chorionic gonadotropin secreting: hepatoblastoma, germinoma, choriocarcinoma
D. Adrenal
   1. Congenital adrenal hyperplasia: 21-hydroxylase, 11β-hydroxylase deficiency
   2. 11β-Hydroxysteroid dehydrogenase type 1 deficiency
   2. Adenoma, carcinoma
   a. Luteinizing hormone secreting (ectopic)
   3. Glucocorticoid resistance
E. Exogenous sex hormones
F. Primary hypothyroidism

III. Incomplete precocious puberty

A. Premature thelarche
B. Premature menarche
C. Premature pubarche/adrenarche
Table 5. Criteria for treating the girls with precocious puberty with an agonist of gonadotropin releasing hormone.

1. The child has central precocious puberty.
2. Puberty is significantly premature (<6 years of age).
3. The physical signs of puberty are progressing rapidly (growth rate accelerated, menses present or anticipated).
4. The rate of advancement of skeletal maturation is more rapid than is the growth velocity, thus potentially compromising adult height (predicted adult height more than 2 SD below population mean or mid-parental target height).
5. The psychosocial health of the child is being compromised.
6. Interruption of pubertal progression is likely to improve the child’s quality of life.
7. The anticipated gains of treatment are worth the potential complications (local reactions, decreased bone mineralization) of GnRHa therapy.

Figure 1

History, Physical Examination, Bone Age

- Thelarche/Menarche
  - BA>CA
    - Basal LH
    - Gonadotropin-Releasing Hormone (GnRH)
  - BA<CA
    - Pubertal
      - Estradiol
      - Pelvic US
      - CPP
      - MRI
    - Prepubertal
      - Pelvic US
      - Ovarian cyst, neoplasm if +, exogenous estrogen if -

- Pubic Hair
  - BA=CA
    - 170HP
    - DHEAS
    - DHAS
  - BA<CA
    - 170HP
    - DHEAS
    - Adrenarche

- CAH
- Adrenal tumor if CT +
- Premature adrenarche
- Observe

BA = bone age, CA = chronologic age, LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone; AMH = anti-müllerian hormone; 17OHP = 17 alpha-hydroxyprogesterone; CPP = central precocious puberty; MRI = magnetic resonance imaging; US = ultrasonography; DHEAS = dehydroepiandrosterone sulfate; CAH = congenital adrenal hyperplasia (nonclassical form); CT = computed tomography.
**Figure 2**

**History, Physical Examination, Bone Age**

- **Testes**
  - Testosterone
    - Symmetric
      - Basal LH
      - GnRH
    - Prepubertal
      - CPP
      - MRI
    - Pubertal
      - FMPP
- **Phallus**
  - Symmetric
    - hCG
  - Asymmetric
    - Testicular US
      - Mass
        - Leydig cell, adrenal rest tumor
          - 17OHP
      - CAH
    - DHEAS
    - DHAS
    - Adrenarchal
      - Adrenal tumor
        - Premature adrenarche
        - Abdominal CT/US

**Abbreviations:**
- BA = bone age; CA = chronologic age; LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone; CPP = central precocious puberty; MRI = magnetic resonance imaging; US = ultrasonography; FMPP = familial male-limited precocious puberty; hCG = human chorionic gonadotropin; 17OHP = 17 alpha-hydroxypregesterone; CAH = congenital adrenal hyperplasia (nonclassical form); DHEAS = dehydroepiandrosterone sulfate; CT = computed tomography
Congenital Adrenal Hyperplasia: 50 yrs of Treatment

Claude J. Migeon, M.D.
Professor of Pediatrics
The Johns Hopkins School of Medicine

The Harriet Lane House for Invalid Children
1911 - 1963

Harriet Lane - Johnston
1830 - 1903
THE SUPPRESSION OF ANDROGEN SECRETION BY CORTISONE IN A CASE OF CONGENITAL ADRENAL HYPERPLASIA

PRELIMINARY REPORT

Lawson Wilkins, Roger A. Leibel, Robert Klein, and Eugenia Moshenberg

With the technical assistance of Harriet Schrager and Mary Ellen Chapman

Department of Pediatrics, Johns Hopkins University School of Medicine,
and the Serum Lab. House of the Johns Hopkins Hospital

Revised for publication February 13, 1932
FURTHER STUDIES ON THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA WITH CORTISONE

1. COMPARISON OF ORAL AND INTRAMUSCULAR ADMINISTRATION OF CORTISONE WITH A NOTE ON THE SUPPRESSIVE ACTION OF COMPOUNDS F AND E ON THE ADRENAL

LAWSON WILKINS, M.D., LYTT L. GARDNER, M.D., JOHN F. CRIGLER, Jr., M.D., SAMUEL H. SILVERMAN, M.D.

AND CLAUDE J. MIKEN, M.D.

FURTHER STUDIES ON THE TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA WITH CORTISONE

2. THE EFFECTS OF CORTISONE ON SEXUAL AND SOMATIC DEVELOPMENT, WITH AN HYPOTHESIS CONCERNING THE MECHANISM OF FEMINIZATION

LAWSON WILKINS, M.D., JOHN F. CRIGLER, Jr., M.D., SAMUEL H. SILVERMAN, M.D., LYTT L. GARDNER, M.D.

AND CLAUDE J. MIKEN, M.D.
Reprinted from Pediatrics, Vol 10, No 4
October, 1952

FURTHER STUDIES ON THE TREATMENT OF
CONGENITAL ADRENAL HYPERPLASIA
WITH CORTISONE

IV. Effect of Cortisone and Compound B in Infants
with Disturbed Electrolyte Metabolism

By John E. C slogans, Jr., M.D., Samuel H. Silverman, M.D.,
and Lawson Wilkins, M.D.
Early Reports of CAH Cases

- DeCrecchio, Il Morgani (1865)
- Flibiger & Virchow (1905)
- Debre-Semelaigne (1925)

Pathophysiology

- Jailer, Gold, Van de Wiele & Lieberman (1955)
- Bangiovanni, Eberlein & Root (1963)
- Kowarski, Finkelstein & Spaulding (1965)

Various Forms of CAH

1. Salt-Losing form
   1940 = Macroglossia precox associated with hyperplasia of androgenic tissue of the adrenals and death from corticoidrenal insuff.
   Wilkins, Fleischman & Howard

2. Simple-Virilizing form

3. Attenuated (Non-Classical) form
   1988 = Allelic form of CAH due to 21-OH deficiency
   Miljone, Rosenthal, Let et al.
Simple-Virilizing CAH

a. Normal or near normal cortisol
b. Increased cortisol precursors (17-hydroxyprogesterone)
c. Increased aldosterone to compensate for salt losing tendency
d. Increased androgens = masculinization
Salt-Losing CAH

a. No cortisol = hypoglycemia
b. No aldosterone = salt and water loss
c. Increased cortisol precursors (17-hydroxyprogesterone) = salt-losing tendency
d. Increased androgens = masculinization
Molecular Biology

1. Linkage of 21-OH genes and HLA genes
   - Dupont et al (1977)
2. Linkage of two 21-OH genes and two C4 complements
   - Carroll et al (1985)
   - White et al (1985)
3. Sequencing of 21-OH genes
   - Higashi et al (1986)
   - White et al (1986)

Mutations of the 21-OH Gene

1. Deletion
   - White, Neu, Dupont (1984)
2. Conversion
   - Donohue, Von Duy, McLenn, White, Jospe & Mignon (1986)
3. Point Mutations
   - non-sense/normal splicing/frameshift
   - Wedell et al (1994)
Treatment of CAH due to 21-OH Deficiency

1. Glucocorticoid replacement
   - oral Cortisol: 12 – 20 mg/AF/24 h
   - oral Prednisone (1/6) 2 – 3.3 mg/AF/24 h
   - oral Prednisolone (1/7) 1.7 – 3 mg/AF/24 h
2. Mineralocorticoid replacement
   - oral Florinef: .05 - .15 mg/24 h
3. In Stress = glucocorticoids x 2 or 3
4. Vomiting = Solucortef and visit ER

Clinical Monitoring of Treatment

- Growth
  - mid-parental height
  - growth %
- Bone Age
  - maintain at ±1 SD
- Blood Pressure
Hormonal Monitoring of Treatment

- Plasma 17-Hydroxyprogesterone
  - between 500 – 1,000 ng/dl
- Plasma Androstenedione
  - between 20 – 50 ng/dl
- Serum Electrolytes
- Plasma Renin
Long-Range Results

Men
1. height = 164 ± 7.4 cm
2. normal fertility (10/20 patients)
3. normal psychosexual development

Women
1. height = 157 ± 7.3 cm
2. delayed menarche/irregular menses
3. low fertility
4. atypical psychosexual development
   - tomboys
   - less heterosexual activity

Diagram: Adult height in cyan males vs. non-salt losers vs. salt losers.
Can Adult Height Be Improved?

1. Appropriate dose of glucocorticoids
2. ↓ glucocorticoids and ↑ mineralcorticoids
3. Anti-androgen
   - block androgen → estrogen conversion
4. Adrenalectomy
5. Growth hormone

GENDER

= The private and public experience of being male or female, including but not restricted to sexual behavior.

Money & Ehrhardt, 1972
Gender Role in 46,XX Patients Reared Female

Sexual Orientation in 46,XX Patients Reared Female

Can Gynecologic Function Be Improved In CAH?
- Prenatal therapy
- Improve surgery
- Better compliance
- Pre-pregnancy treatment
Future Improvements

- Improve compliance for life-time therapy
- Adjust treatment to the life-cycle of patients
- Long-term follow-up (25-30 yrs) to evaluate efficacy of new therapies

Acknowledgement

- The many Fellows of the Pediatric Endocrinology Clinic over the past 50 yrs
- Recently
  - Amy Wisniewski, Ph.D.
  - John Gearhart, M.D.
  - Howard Zazur, M.D., Ph.D.
  - Peter Lee, M.D., Ph.D.
  - Gary Berkowitz, M.D.
  - Matthew Malouf, B.A.
Pentose Cycle
Links
Carbohydrate Metabolism and
Glucocorticoid Production
in Adipocytes

A novel mechanism to explain nutrient-based fat expansion and insulin resistance

Kenneth McCormick
Gail Mick
Xudong Wang
University of Alabama at
Birmingham

Overview
• Hypothesis
  • Background
    – Pentose cycle
    – 11-β hydroxysteroid dehydrogenase
    – Paracrine effects of glucocorticoids
• Experimental Data
• Conclusions
Hypothesis

We propose:

11β-HSD1 oxo-reductase activity
(and, hence, local cortisol formation)
is determined by Pentose flux
(via NADPH production)

---

Pentose Cycle

- Generates NADPH -
  - a reducing agent for biosynthetic reactions e.g.
    fatty acid and steroid synthesis.
- Generates ribose 5-phosphate
  - for nucleotide and nucleic acid synthesis.
- Active in cells that:
  - make fatty acids (e.g. adipose, mammary)
  - undergo rapid division (ribose 5-phosphate is
    needed for DNA replication).
Pentose Cycle

- Oxidative:
  - Irreversible
  - Glucose-6-phosphate dehydrogenase (G6PD)
  - Generates 2 NADPH
  - Inhibited by DHEA
- Non-oxidative:
  - Ribose phosphate production
  - Glycolytic intermediates

Oxidative Pentose Pathway

11β-Hydroxysteroid dehydrogenase
(11β-HSD)
11 β-Hydroxysteroid dehydrogenase isoenzymes

11 β-HSD 1
- Oxo-reductase
- Cofactor: NADPH
- Tissue: liver, brain, adipose, muscle....
- Chromosome 1
- 34 kDa

11 β-HSD2
- Dehydrogenase
- Cofactor: NAD⁺
- Tissue: kidney, sweat gland, placenta....
- Chromosome 16
- 40 kDa

11 β-hydroxysteroid dehydrogenase (11 β-HSD2)

Human Kidney

Cortisol → 11 β-HSD2 → Cortisone

11 β-hydroxysteroid dehydrogenase (11 β-HSD1)

Liver and other tissues

Cortisol → 11 β-HSD1 → Cortisone
11-\(\beta\) hydroxysteroid dehydrogenase
Cortisone (inert) \(\Leftrightarrow\) Cortisol (active)

- Oxo-reductase:
  - Cortisone (inert) \(\Leftrightarrow\) Cortisol (active)
  - NADPH dependent
  - Promotes fat cell differentiation
- Dehydrogenase:
  - Cortisone (inert) \(\Leftrightarrow\) Cortisol (active)

Cellular NADP/NADPH

Key metabolic determinates:
- Production:
  - Oxidative pentose pathway
    - Glucose-6-phosphate dehydrogenase
- Consumption:
  - Fatty acid synthesis
  - 11 \(\beta\)-HSD oxo-reductase
  - Cellular redox state
Paracrine Effects of Increased Adipocyte Glucocorticoids

- Pre-adipocyte differentiation
- Insulin resistance
- Obesity

Experimental Methods

- Adipocytes:
  - Rat collagenase isolated epididymal fat cells
- Metabolic assays:
  - Pentose pathway
    - $[1-^{13}C] \text{ glucose oxidation}$
    - Corrected for $[6-^{13}C] \text{ glucose oxidation}$
  - $11 \beta\text{-HSD1 oxid-reductase}$
  - Dihydrocorticosterone (DHC) $\rightarrow$ Corticosterone (C)
  - Radioimmune detection of $[^{3}H] \text{ Corticosterone}$

Adipose tissue
White Adipocyte

Pentose Pathway Assay
Calculation of Pentose Cycle

\[
\frac{G_1\text{CO}_2 - G_6\text{CO}_2}{1 - G_6\text{CO}_2} = \frac{3 \ PC}{1 + 2 \ PC}
\]

\(G = \) Specific yield from radiolabeled glucose

\(PC = \) Pentose Cycle

Experimental Data

11 \(\beta\)-HSD1 oxo-reductase assay

Time curve  Effect of 11-DHC conc.
CENTRAL DIABETES INSIPIDUS & HISTIOCYTOSIS X (ANOTHER LANGERHANS CELL DISCOVERY)

George W. Moll, Jr., M.D., Ph.D., FAAP, FACE
Director of PEDIATRIC ENDOCRINOLOGY
Christina Lee Moll, B.A.
Summer Research Technologist
Department of PEDIATRICS
University of Mississippi Medical Center
Jackson, MS

LEARNING OBJECTIVES

1. Appreciate the contributions to medicine made by Paul Langerhans (1847-1888) German Anatoomist & Physiologist.

2. Understand an effective clinical approach to the patient with polyuria.

3. Understand the basic tests for diagnosis of Central Diabetes Insipidus (DI) and its etiologies.

4. Appreciate the diagnostic features of Langerhans' Cell Histiocytosis (LCH) and its prognosis with therapy.

I. Paul Langerhans and his cells

II. Central Diabetes Insipidus (DI)
   A. Polyuria & Work-up of DI
   B. Anatomic locations of Vasopressin production & secretion
   C. DI testing – partial DI consideration
   D. Vasopressin and Analogues

III. Patients with Symptoms of DI and Work-up

IV. Langerhans' Cell Histiocytosis (LCH)
   A. What is a Langerhans' cell?
   B. Clinical & Systemic features
   C. LCH diagnosis
   D. LCH treatment & prognosis
CENTRAL DIABETES INSIPIDUS & HISTIOCYTOSIS X –
GW Moll, Jr. & CL Moll (SPES 11/7-9/2003)

Paul Langerhans & his Cells
German Anatomist/Pathologist, 1847-1888

- Langerhans' main scientific achievements involved his descriptions of human & animal microscopic anatomy; one of first to succeed with novel methods & staining techniques in Virchow's laboratory
- His inaugural Dissertation (1865) described cell islands in pancreas
- Beiträge zur mikroskopischen Anatomie der Bauchspeicheldrüse
- He used gold chloride stain to study the skin & discovered cells with branching processes & characteristic fibrillar bodies in the Malpighian layer later called Langerhans' cells "Über die Nerven der menschlichen Haut", in Virchow Archiv für pathologische Anatomie, 44 (1888)

Differential Central DI and Work-up of POLYURIA

- Polyuria may involve renal or central (CHS) causes:
  Genetic: Familiar autosomal dominant with variable severity (22 mutations described in vasopressin gene), DMD/ADPKD or Weill-Marchesani syndrome
  Psychogenic Polydipsia
  Organic Polyuria: hypothalamic/pituitary malformation, injury or disease
  Drug-induced Polyuria: thiazide, tetracycline
  Assess & compare plasma chemistries with simultaneous urine osmolality
  Hyperglycemia > 200 mg/dl. Diabetes Mellitus
  Hypokalemia: prolonged results in nephropathy
  Elevated Creatinine without ketosis: renal disease
  Hypercalcermia: interferes with ADH & renal tubule
  Po2 > 300 mmHg & low Uosm (Richman & Morgen et al, AJDC 135, 1981):
  Diabetes Insipidus (DI) is likely
  Dehydration test 6-12 hours & Po2 < 290 mmHg: Compliance? Or
  Psychogenic Polydipsia, Dipspastic DI, Sarcoidosis

Differential Diagnosis and Work-up of DI

- End Dehydration Test with Pitressin SQ (1U/m2) or Desmopressin (DDAVP) IV (0.3 ug/kg) or SQ (0.08 ug/kg)
- Uosm increase of greater than 20% is a normal response:
  Central Diabetes Insipidus
  Osmolality Test (Hickey-Hare) up to 310 mOsm/kg
  Uosm unchanged: Pituitary DI
  Decreased thirst at high Osmolality:
  Essential Hyposthenuria
  Uosm > 300 but < 800 mOsm/kg:
  Partial Diabetes Insipidus
- Uosm unchanged with DDAVP: Nephrogenic DI
  Drugs, X-linked (V2 mutant), Autosomal-loc (Aquaporin-2)
CENTRAL DIABETES INSIPIDUS & HISTIOCYTOSIS X –
GW Moll, Jr. & CL Moll    (SPES 11/7-9/2003)

C.T. - 4 y/o Male

- 3 month history of progressive polyuria/ polydypsia to point of emesis
- Incomplete outside urine collections & vassopressin levels
- Reported crusty scalp lesions reviewed by a dermatologist as non-specific and not biopsied

<table>
<thead>
<tr>
<th>Glu</th>
<th>Na</th>
<th>K</th>
<th>Ca</th>
<th>Creat</th>
<th>BUN</th>
<th>Urine Osm</th>
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<tbody>
<tr>
<td>9/10 8am</td>
<td>94</td>
<td>140</td>
<td>4.1</td>
<td>&lt;3</td>
<td></td>
<td>30-44</td>
</tr>
<tr>
<td>9/10 5pm</td>
<td>87</td>
<td>156</td>
<td>4.1</td>
<td>10.1</td>
<td>0.4</td>
<td>3</td>
</tr>
<tr>
<td>DDAVP 0.08 mcg/kg injection sq</td>
<td></td>
<td></td>
<td></td>
<td>157-526</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sent home on 0.2 mg DDAVP po q12 h</td>
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<td>Head MRI ± contrast indicated infundibular mass, later rib</td>
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<tr>
<td>Histiocytosis X with liver involvement- Velbani/pred/Mtx</td>
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</table>

A.A. - 17 month Female

- Noted large R-inguinal & L-inguinal nodes, R-submandible mass, scaly dry skin eruptions over trunk
- Node biopsy confirmed Histiocytosis X with S100 positive Langerhan's cell disease
- 24 weeks of Velbani/Methylpred ending in progressive polyuria/polydypsia but head MRI reported normal
- Mother reported intake 101 1/2 ounces
  - output 129 ounces
- Gluc 91, Na 140, K 4.3, BUN 6, Creat 0.4, serum osm 280 for urine osm 371 with spot urine Na 107 mEq/L, start Diapid IN
- Currently using DDAVP 0.2 mg po 6-8am, 2pm, and DDAVP intranasal 2 puffs 8:30 pm

Focus On LCH: Biologically
What is a Langerhans' Cell?

<table>
<thead>
<tr>
<th>Class I</th>
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<tbody>
<tr>
<td>Disease Included</td>
</tr>
<tr>
<td>Histiosis (Antigen- Present)</td>
</tr>
<tr>
<td>Cellular Characteristics of the Lesions</td>
</tr>
<tr>
<td>Cloned Neutrophil</td>
</tr>
<tr>
<td>Dendritic Granules</td>
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<tr>
<td>Antigenic Expression</td>
</tr>
<tr>
<td>CD68</td>
</tr>
<tr>
<td>S100</td>
</tr>
<tr>
<td>Galactocyte (Frequently Meets in)</td>
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<tr>
<td>Proposed Pathophysiological Mechanisms</td>
</tr>
</tbody>
</table>
CENTRAL DIABETES INSIPIDUS & HISTIOCYTOSIS X –
GW Moll, Jr. & CL Moll (SPES 11/7-9/2003)

LANGERHANS’ CELL (LCH)
HISTIOCYTOSIS X

- LCH has several modes of presentation: mild solitary eosinophilic granuloma of bone to severe disseminated
- Typically 1st decade of life, est. 0.05-0.5 cases per 10^5
- Males more often than females, rare in Afro-Americans
- CNS manifestations occur in 10-50% & most are multi-system with rare solely CNS disease at presentation
- Common CNS sites include skull, spinal bones, hypothalamus and pituitary infundibulum
- Less common other CNS areas & rare isolated hemisphere

LANGERHANS’ CELL (LCH)
HISTIOCYTOSIS X

- Common histopathology is proliferation of an antigen-presenting dendritic cell (S100+) of bone marrow origin with unique Birbeck granules
- LCH appears likely due to immune system dysfunction
- Clinical: Symptoms vary with Site
  DI in 5% at presentation and up to 30% in review
  Calvarial mass lesions, Temporal hearing loss & chronic draining ear, Orbital present with proptosis
  Dural lesions may associate with headaches
  Parenchymal lesions vary with location, cerebellar frequently associate with dysmetria and ataxia

LANGERHANS’ CELL (LCH)
HISTIOCYTOSIS X

- Systemic manifestations include hematopoietic, hepatic, and pulmonary dysfunction
- Hand-Christian-Schuller disease (15% of LCH) classic triad of DI, exophthalmos, and destructive bone lesions
  Usually affects children 1 - 5 y/o
- Letterer-Siwe disease (10% of LCH) an acute disseminated form with high mortality, presenting with fever, anemia, thrombocytopenia, hepatosplenomegaly, and skin rash
  Usually affects children less than 2 y/o

It is not known whether the above outlined diseases are manifestations of a single population of cells, or whether the diseases are manifestations of multiple sub-populations of cells.
LANGERHANS' CELL (LCH) HISTIOCYTOSIS X

- Treatment - Surgery for tissue diagnosis, relieve mass effects, and complete microcirculation excision of CNS lesions if possible with preserved quality of life
- Radiotherapy and Chemotherapy (Veban/Steroid/Mtx)
- Prognosis - younger & greater extent of disease at presentation, the worse the prognosis
- Survival - overall at 5 yr 88%, 10 yr 88%, 15 yr 77%
  Estimated event-free rate of only 30% at 15 years

References
- University of California - Davis (www.histiocytosis.ucdavis.edu/linesers.html).
- Histiocytosis Association of America (www.histi.org/association/library).
THE GROWTH HORMONE RECEPTOR CHRONICLES

Arlan L Rosenbloom MD
Annual Meeting of the Southern Pediatric Endocrine Society
Charlotte North Carolina
November 7–9 2003

*Distinguished Service Professor Emeritus of Pediatrics
University of Florida College of Medicine
Address: Children's Medical Services Center
1701 SW 16th Ave., Building B
Gainesville, FL 32608–1153
e-mail: rosenal@peds.ufl.edu

Objective: To elucidate the history of understanding of the GH receptor and defects in its function.

Outline: I. The Pre-molecular Era
II. The Molecular Era
III. Continuing Conundrums
I. The Pre-Molecular Era

Highlights from the Yearbook of Endocrinology for calendar year 1961 included:

- studies of an immunologic assay of GH using hemagglutination inhibition of tanned and GH tagged red blood cells in acromegaly and with hypophysectomy
- examination of sulfation factor activity (which had been originally described by Salmon and Daughaday in 1957) before and after treatment with radiation for acromegaly
- growth promotion with administration of human pituitary GH extract in healthy prematures

Reviews in the volumes covering 1962 and 1963 included:

- two reports using the tagged red cell assay
- a study of GH like activity in rats (sulfation factor)
- the report of decreased GH concentrations in serum with severe malnutrition
- the treatment of "pituitary dwarfism" for 9-14 months in four children

The 1964 and 1965 editions contained:

- studies of GH release from rat pituitaries stimulated by a hypothalamic extract
- description of remarkable overlap in GH concentrations in human serum between those with hypopituitarism, with non-hypopituitary short stature and normals using the new radioimmunoassay
- the metabolic effects of partially hydrolyzed bovine GH in an ongoing attempt to get past the species specificity by defining a core of active nonhuman GH
- a report of 35 patients treated with GH extracted by Raben’s method
- the description of acquired resistance to hGH caused by specific antibodies
- a report that insulin induced hypoglycemia produced a greater GH response in full term and premature newborns than in normal adults.

The comprehension of the basis for hormone unresponsiveness is reflected in the 1965, third edition, of Lawson Wilkins’ classic, The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. In the chapter Endocrine Relationships and their Influences upon Growth, the section titled Responsiveness of Peripheral Tissues to Hormonal Action reads:

> There are a number of disorders in which endocrine symptoms are due to irresponsiveness of the tissues ("end organs") to normal amounts of hormone. Examples are nephrogenic diabetes insipidus, pseudohypoparathyroidism, and the inability of some male pseudohermaphrodites with feminizing testes to develop sexual hair even when androgen is administered. These are probably due to genetically determined defects of intracellular enzyme systems.

The 1966 Yearbook included:

- reports of the diurnal pattern of plasma GH concentration in children and adolescents
- the effect of arginine on serum levels of GH
- studies of the metabolic effects in man of bovine GH digested with trypsin
Most important to our discussion, was the report of a paper published in the Israel Journal of Medical Sciences [1].

**GENETIC PITUITARY DWARFISM WITH HIGH SERUM CONCENTRATION OF GROWTH HORMONE A NEW INBORN ERROR OF METABOLISM?**

ZVI LARON, M.D., ATHALIA PERTZELAN, M.D. and SHOSHANA MANNHEIMER

Department of Pediatrics, Tel Aviv University Medical School and Rogoff-Wellcome Trust Medical Research Laboratories, Beilinson Medical Center, Petah Tiqva, Israel

**ABSTRACT**

A description is given of three siblings with hypoglycemia and other clinical and laboratory signs of growth hormone deficiency but with abnormally high concentrations of immunoreactive serum growth hormone. Since exogenous growth hormone was active in these patients, the endogenous secretion of an abnormal growth hormone molecule is postulated.

- Discovered while doing radioimmunoassays of GH in children with classic features of GH deficiency.
- Yemenite Jewish family with three affected siblings
- The administration of exogenous GH led to a marked rise in plasma free fatty acids, indicating that the growth retardation was not due to tissue unresponsiveness.

By 1968, the Israeli investigators had accumulated 20 patients, exclusively Oriental Jews with high rates of consanguinity and frequent affected siblings [2]. They also reported that same year on 22 patients from 14 families and noted a response to GH therapy, including free fatty acid mobilization, nitrogen retention, and improved growth [3]. These effects may have been due to other pituitary hormones in the crude extracts administered or to nutritional changes in the investigative setting. It was noteworthy that adults and adolescents had normal GH levels, in contrast to the elevated levels in children. The first patient reported from outside Israel, also in 1968, was a 30-year-old man who demonstrated no metabolic response to exogenous GH, leading to the prescient hypothesis that the defect lay in peripheral receptor sites for GH [4].

Defective sulfation factor activation by GH was reported in 6 patients with Laron syndrome from Israel in 1969 [5]. The second and third patients reported from outside Israel were Arab siblings from a consanguineous union who failed to show short-term metabolic or long-term responses to exogenous GH [6]. That same year (1971), however, the Israeli group again described definite but less dramatic metabolic responses to GH in Laron syndrome patients than...
in those with GH deficiency and further demonstrated a lack of sulfation factor response to GH [7]. The editor of the Yearbook opined,

"Here, for the first time somatomedin enters the clinical arena."

At least part of these patients' resistance to exogenous GH was considered to be saturation of peripheral GH receptors by an abnormal GH molecule and it was thought that experimental findings supported the notion of competition at the peripheral receptor sites.

By 1973 it had become clear that the first step in the action of polypeptide hormones is binding to specific sites on the plasma membrane [8], reflected in the development of a radioreceptor assay for GH that year. Of great interest at that time was the function of insulin receptors which were being identified and studied in various tissues [9-11].

Biochemical studies had failed to illuminate the cause of Laron syndrome.

- Serum fractionation of GH from two Canadian patients was found to be normal [12].
- Binding to various antisera used for radioimmunoassay of GH was also found to be normal for 22 Israeli patients in 1973 [13]. Three years later it was demonstrated that GH from 7 patients with Laron syndrome behaved normally in a radioreceptor assay [14].

A generalized cellular unresponsiveness in Laron syndrome was indicated by failure of response to GH of erythroid progenitor cells from the peripheral blood of two patients with Laron syndrome, reported in 1980 by Golde et al. [15].

II. The Molecular Era

The initial direct evidence for receptor failure was the demonstration in 1984 that hepatocytes obtained by liver biopsy from two patients failed to bind radioactive GH, whereas control hepatic cells from kidney donors bound 8-24% of the radioactive ligand [16]. Studying the same patients as had Golde et al. 7 years earlier, Geffner et al. [17] reported in 1987 that transformed T-cells of Laron syndrome patients did not have mitogenic response to GH but did to IGF-I.

The similarity between mammalian (rabbit) specific GH binding protein (GHBP) in serum and GHBP in liver cytosol was initially demonstrated in 1985 [18]. Two years later simultaneous reports appeared showing that GHBP was absent from the sera of patients with Laron syndrome [19, 20]. That same year, the purification and protein sequencing of serum GHBP demonstrated that it was structurally identical to the extracellular hormone binding domain of the membrane bound GH receptor [21].

The GHR was the first to be cloned of a family of receptors that includes the receptor for prolactin and numerous cytokine receptors. Members of this family share ligand and receptor structure similarities, in particular the requirement that the ligand bind to two or more receptors or receptor subunits and interact with signal transducer proteins to activate tyrosine kinases [22].

Mutations of the GHR have provided insight into its physiology; nearly 40 distinct mutations in the extracellular and transmembrane domains produce a clinical picture of severe GH/IGF-I deficiency in the homozygous state or as compound heterozygotes, whereas 2 dominant
negative mutations of the intracellular domain result in a milder clinical syndrome. Some individuals described with features of GH resistance appear to have defective signal transduction by the GH-GHR complex. Knowledge of the biology and signaling of the GHR is important because GH is a powerful regulator of somatic growth, mitogenesis, and metabolism, with a wide variety of effects on target cells, all mediated by the GHR, which is expressed in 40 different tissues.

The GHR Gene and its Mutations

![Diagram showing the structure of the GHR gene](image)

Representation of the growth hormone receptor gene. The black horizontal line represents intron sequence, diagonal breaks in the lines indicate uncloned portions of the intron and the boxes represent exons, which are enlarged for clarity. Exons with horizontal stripes designate untranslated regions of the transcripts, the vertical striped exon the signal sequence, open exons the hormone binding domain, the diagonal striped exon the transmembrane domain, and the solid exons the intracellular domain. Reproduced from [23].

The structure of the human GHR gene is depicted in the figure above. There are 8 variants (V1-V8) contributing to the 5' untranslated region (UTR), followed by 9 coding exons (exons 2-10). Exon 2 encodes the last 11 base pairs of the 5'-UTR sequence, an 18 amino acid signal sequence, and the initial 5 amino acids of the extracellular hormone binding domain. Exons 3 to 7 encode the extracellular hormone binding domain, except for the terminal 3 amino acids of his domain, which are encoded by exon 8. Exon 8 further encodes the 24 amino acid hydrophobic transmembrane domain and the initial 4 amino acids of the intracellular domain. Exons 9 and 10 encode the large intracellular domain. Exon 10 also encodes the 2 kb 3'-UTR.

Four of the alternative 5'-UTRs of the human gene have been cloned from genomic DNA indicating that each was encoded by a separate exon. It has been suggested that this variability serves to regulate translational efficiency of the mRNAs [23]. The human GHR is unique in existing in an alternative splice isoform that excludes exon 3; this deletion has no demonstrable effect on GHR function [24].

The report of the characterization of the GHR gene included the first description of a genetic defect of the GHR, a deletion of exons 3, 5, and 6 [25]; recognition that the exon 3 deletion represented an alternatively spliced variant without functional significance resolved the dilemma of explaining deletion of nonconsecutive exons. No other exon deletions have been described in patients with GHI, but over 40 additional defects of the GHR gene have been described in association with GHI, including nonsense mutations, missense mutations, frame shift.
mutations, splice mutations, and a unique intronic mutation resulting in insertion of a pseudo-
exon [26]. Although normal functional isoforms lacking exon 3 occur naturally, typical Laron
syndrome has recently been described in a child who has compound heterozygosity for a
mutation in exon 3 and a common nonsense mutation at a hot spot in exon 4 (C38X) [27]. A
number of other mutations have been described which are either polymorphisms or have not
occurred in the homozygous or compound heterozygous state.

Protein Chemistry
The primary structure of the GHR deduced from the nucleotide sequence comprises 620 amino
acid residues, 46 in the extracellular domain, 24 in the transmembrane region, and 350 residues
in the long cytoplasmic domain. The extracellular domain includes 7 cysteine residues and 5
glycosylation sites. Analysis of the three-dimensional crystal structure of human GHR in
complex with GH revealed a homodimer consisting of one molecule of GH encompassed by two
molecules of receptor [28]. The subdomain containing 3 pairs of cysteine residues is the major
binding interface with GH. Another subdomain is involved in dimerization. Thus, the
extracellular domain of the GHR contains two binding sites, one involved in GH binding, the
other located close to the membrane spanning region and responsible for homodimerization.
The intact receptor lacks intrinsic tyrosine kinase activity or ATP binding motifs, but is closely
associated with JAK2, a member of the Janus kinase family. Two regions of the cytoplasmic
domain close to the transmembrane domain are important for signal transduction, by binding
JAK2. These are Box 1 (residues 280-287), a proline-rich sequence and Box 2 (23 amino acid
residues downstream) rich in serine, consisting of hydrophobic and charged residues [29].

Two mechanisms exist for the formation of GHRP, by proteolytic cleavage of the intact
membrane receptor in man and other non-rodent species, and by alternative splicing of a single
primary transcript in the rat and mouse. GH bound to soluble GHRP accounts for approximately
50% of circulating GH. The sites for antibody binding in the GH radioligand assay are not
affected by the GHRP, one reason why it was over 20 years after the development of the
radioligand assay for GH before this binding was recognized. The other main reason was
the conventional wisdom that polypeptide hormones were not supposed to circulate in the
bound state.

Formation of the ligand-receptor complex occurs sequentially. One receptor molecule binds to
site 1 on the GH molecule followed by binding to site 2 and subsequent linking of the two
receptor molecules to form the homodimer complex [28].

Abnormality of the GHR [29, 30]
All but 4 of the defects associated with GHI in the homozygous or compound heterozygous
state result in absent or extremely low levels of GHRP; these exceptions are the D152H, G223G,
R274T, and intron 6 insertion mutations. The D152H missense mutation affects the
dimerization site, thus permitting the production of the extracellular domain in normal
quantities, but with failure of dimerization at the cell surface. The two defects that are close to
[G223G] or within [R274T] the transmembrane domain result in extremely high levels of GHB.
These defects interfere with the normal splicing of exon 8, with the mature GHR transcript
being translated into a truncated protein that retains GH binding activity, but cannot be
anchored to the cell surface. The intronic heterozygous splice mutation preceding exon 9
results in an extensively attenuated, virtually absent intracellular domain and relatively mild
GHI. A similar heterozygous point mutation of the donor splice site in intron 9 has been
reported with normal to slightly elevated circulating levels of GHBP. These heterozygote GHR mutants transfected into permanent cell lines have demonstrated increased affinity for GH compared to the wild type full-length GHR, with markedly increased production of GHBP. When co-transfected with full-length GHR the dominant negative effect is demonstrated as overexpression of the mutant GHR and inhibition of GH-induced tyrosine phosphorylation and transcription activation. Naturally occurring truncated isoforms have also shown this dominant negative effect in vitro. Only one homozygous mutation involving the intracytoplasmic domain has been described, affecting the JAK2 binding site and abolishing STAT5 activity; unlike the mutations in or near the transmembrane region, GHBP concentrations are markedly reduced [Milward A, et al. Growth hormone insensitivity syndrome due to a growth hormone receptor truncated after box 1 resulting in isolated failure of STAT 5 signal transduction. JCEM, in press].

A novel intronic point mutation was discovered in a highly consanguineous family with two pairs of affected cousins with GHBP-positive GHI. This mutation resulted in a 108bp insertion of a pseudocodon between exons 6 and 7, predicting an in-frame, 36 residue amino acid sequence. This is a region critically involved in receptor dimerization [26].

There is only one mutation of the GHR that has been found in more than a few individuals, the E180 splice mutation in the South American cohort that accounts for half of the ~140 patients with GHI who have had their mutations identified. Other defects are family specific, with a few exceptions. The nonsense mutations R43X, C38X, and R217X, and the intron 4 splice mutation, each have been described in geographically dispersed populations, and on different genetic backgrounds. They are thought to represent mutational hotspots. For example, R43X mutation involves a CpG dinucleotide, considered to be the most common site of methylation in mammalian DNA; deamination of 5-methylcytosine leads to C→G transition, developing a potential mutational hotspot. Only one-third of reported patients with GHI outside of the South American cohort have been genetically characterized [31]. Thus, it is likely that many more mutations will be described.

**Signaling**

Binding of GH with the GHR dimer recruits and activates 2 receptor-associated JAK2 molecules, which results in self-phosphorylation of tyrosines of the JAK2 and of the receptor, and a cascade of phosphorylation of cellular proteins. These tyrosines form binding sites for several other signaling proteins. These include members of the family of signal transducers and activators of transcription (STATs), which couple ligand binding to the activation of gene expression, mitogen activated protein kinases (MAPK), phosphatidylinositol 3'-phosphate kinase, and protein kinase C. Negative regulation of GHR/JAK2 signaling has been suggested via phosphorylation of receptor-like transmembrane proteins [29].

GH independent dimerization and constitutive activation of the GHR has been demonstrated by replacing the extracellular domain with a leucine zipper sequence and transfecting GHR expressing cells. Activity was equivalent to fully activated wild type GHR, indicating that proximity of JAK2 kinases is an essential element in signaling [32].

Abnormality in the signaling pathway resulting in growth failure has been demonstrated in studies of cultured fibroblasts from GHBP-positive patients with GHI who have intact GHR. One patient was found to have a defect in activation of MAPK, but not the STAT pathway. In
another unrelated patient with severe GHI, the signaling defect was thought to be close to the GHR, preventing activation of both the STAT and MAPK pathways. The first mutation in the STAT pathway has just been described, a homozygous missense mutation in the gene for STAT5b that results in hyperphosphorylation of STAT1 and STAT3 in a patient with typical biochemical and clinical features of GH insensitivity [33].

III. Current and Continuing Conundrums

A. Why does severe IGF-I deficiency due to GHRHR mutation result in a different clinical and biochemical phenotype than that due to GH mutation or GHR mutation despite comparable severity of IGF-I deficiency?

- GHRHR insensitivity is not associated with hypoglycemia, micropenis, or facial dysmorphology as are severe GHD and GHI [34].
- With GHRHR insensitivity, IGF-I and IGFBP-3 concentrations are not greater in affected adults than in children, whereas levels are significantly higher in Laron syndrome patients in adolescence and adulthood than in childhood, for reasons that are unknown [35].

B. What are the environmental factors involved in the wide phenotypic variation with GHR mutation within families or inbred populations?

- French patient stimulated to grow with parenteral nutrition
- Growth equivalent to IGF-I treated patients in three placebo-controlled patients during 6-month trial in Ecuador [36]
- Better nourished patients grew better during 4 years of treatment with recombinant IGF-I

<table>
<thead>
<tr>
<th></th>
<th>Δ ht in cm</th>
<th>Δ ht age-yrs</th>
<th>Δ ht SDS</th>
<th>Δ ht vel cm/yr</th>
<th>Δ wt in kg</th>
<th>Δ lean mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet 1 (11)</td>
<td>+27.5</td>
<td>+3.7</td>
<td>+2.4</td>
<td>+2.1</td>
<td>+13.9</td>
<td>+8.2</td>
</tr>
<tr>
<td>Diet 2 (10)</td>
<td>+19.7</td>
<td>+2.2</td>
<td>+1.3</td>
<td>-0.3</td>
<td>+6.9</td>
<td>+4.2</td>
</tr>
<tr>
<td>All (21)</td>
<td>+23.8</td>
<td>+3.0</td>
<td>+1.8</td>
<td>+0.9</td>
<td>+10.6</td>
<td>+6.5</td>
</tr>
</tbody>
</table>

C. What is the role of IGF-I in bone? Studies of bone mineral and histomorphometry in Ecuadorian adults with GHR deficiency found normal bone structure and mineral content when appropriate adjustments made for the small size of the bones [37]. These results have recently been confirmed in studies from Israel reported at the 2003 annual Endocrine Society meeting.
D. What stimulates intrauterine IGF-I production in the absence of GH or GH action?
A single case of defective IGF-I synthesis due to a gene deletion resulted in profound intrauterine growth failure, sensorineural deafness and mental retardation, whereas GHD, GHR deficiency, and GHRHR deficiency have none of these features. IGF-I knockout mice have defective neurological development as well as growth failure [38]. Thus, IGF-I production in utero does not appear to be GH-GHR dependent.

E. What is the contribution of direct effects of GH, IGFBP-3 and other IGFBPs to growth?
Comparison of the growth responses of the 22 IGF-I treated GHRD patients to those of 11 GH treated GHD subjects in the same setting demonstrated GV increments in those with GHRD to be 63% of those achieved with GH treatment of GHD in the first year and less than 50% in the second and third years of IGF-I treatment. The GHRD group, however, did not differ from those with GHD in the change in bone age or in the ratio of height age to bone age changes over the 2 year period. There was a greater change in % MBWH in the GHRD group treated with IGF-I which might reflect the insulin like action of the levels of IGF-I, contrasting with the lipolytic effect of GH replacement therapy. The difference in growth response between IGF-I treated GHRD and GH treated GHD was consistent with the hypothesis that 20% or more of GHD influenced growth is due to the direct effects of GH on bone [39].

F. Why doesn't IGF-I replacement adequately correct the growth problem in GHRD?

<table>
<thead>
<tr>
<th>#</th>
<th>age-yrs</th>
<th>dose ug/k</th>
<th>Start*</th>
<th>1 year*</th>
<th>2 year*</th>
<th>Source</th>
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<td>26</td>
<td>3.7-19.6</td>
<td>40-120 bid</td>
<td>-6.8 (1.6)</td>
<td>-6.1 (1.5)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>3.7-16.7</td>
<td>40-120 bid</td>
<td>-6.4 (1.7)</td>
<td>-5.6 (1.6)</td>
<td>-5.2 (1.9)</td>
<td>Europe</td>
</tr>
<tr>
<td>2</td>
<td>18/17.5</td>
<td>120 bid</td>
<td>-8.0/-9.1</td>
<td>-7.1/-7.9</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4.7-17.1</td>
<td>120 bid</td>
<td>-8.5 (1.3)</td>
<td>-7.5 (1)</td>
<td>-7.0 (1.2)</td>
<td>Ecuador</td>
</tr>
<tr>
<td>7</td>
<td>3.1-15.2</td>
<td>80 bid</td>
<td>-8.0 (1.8)</td>
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<td>9</td>
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<td></td>
</tr>
<tr>
<td>6</td>
<td>0.5-14.6</td>
<td>150-200/d</td>
<td>-6.2 (1.5)</td>
<td>-6.0 (1.6)</td>
<td>-5.8 (1.2)</td>
<td>Israel</td>
</tr>
<tr>
<td>8</td>
<td>2.3-11</td>
<td>80-120 bid</td>
<td>-5.6 (1.1)</td>
<td>NA</td>
<td>-4.5 (1.3)</td>
<td>N Carolina</td>
</tr>
</tbody>
</table>

Parentheses in the number column indicate that this is part of the previous cohort.
* standard deviation score for stature (SD in parentheses)

G. How important is partial GH insensitivity?
GH resistance might be expected to occur in an incomplete form, analogous to insulin resistance, androgen insensitivity, or thyroid hormone resistance. Affected children might have growth failure with normal or slightly increased GH secretion, variable but usually decreased GHBP levels, decreased IGF-I concentrations, but not as severely reduced as in GHD or GHRD.
and might respond to supraphysiologic doses of GH. It might also be expected, given the need for dimerization of the GHR for signal transduction, that certain mutations could have a dominant negative effect in the heterozygous state.

Credibility for a heterozygous defect as a cause of short stature requires the demonstration of functional significance, not only by transfection of the mutant allele, but by co-transfection with wild-type GHR gene, to approximate the circumstance in vivo. Goddard et al. [40] have identified 6 mutations in 8 children with short stature (SDS for height -5.1 to -2.0) and normal or increased stimulated GH levels. One patient had compound heterozygosity involving a novel mutation in exon 4 (E44K) and a mutation in exon 6 previously associated with GHRD in the homozygous state (R161C). Two other patients were heterozygous for this mutation. The other 5 patients included 2 who were heterozygous for the same novel mutation in exon 7 (R211H), and one each with novel mutations of exon 5 (C122X), exons 7 (E224D), and exon 10 (A478T). Expression in vitro of these four novel mutations involving the extracellular domain has shown functional effects, although co-transfection studies have not yet been reported. The defect involving exon 10 has not been expressed in vitro. Other defects without demonstrable significance have been described involving exon 10 [41-42]. None of these putative partial GHI patients had the clinical phenotype of GHD. Five of the 8 patients were treated with GH with variable improvement in growth velocity, from slight to dramatic, in the first year. This variable response could be due to GH resistance or to the fact that the patients were not GH/IGF-I deficient.

The subjects studied by Goddard et al were selected from the large Genentech National Cooperative Growth Study database in pursuit of the question raised by the observation that GHB concentrations are low in children with idiopathic short stature (ISS, i.e. short children without a recognizable syndrome or GHD). Using a ligand mediated immunofunction assay Carlson et al. [43] studied a large number of short children with known causes of growth failure such as GHD and Turner syndrome, or ISS, and compared their GHB concentrations in serum to those of normal controls. Ninety percent of the children with ISS had GHB concentrations below the control mean and nearly 20% had concentrations that were 2 standard deviations or more below the normal mean for age and sex. Whether the distribution of GHB concentrations in unexplained short stature indicates that partial GH resistance is a common cause of short stature remains to be demonstrated.

If heterozygous mutations of the GHR ultimately prove to be one cause of partial GH resistance, this would explain only a very small proportion of idiopathic short stature. This impression is supported by a review of 37 patients who had relatively high GH responses to insulin and failure to increase IGF-I concentrations in the serum after several days of GH administration. GHB concentrations were normal. Only one patient of this group failed to demonstrate a growth response to exogenous GH. The authors concluded that partial GH insensitivity was likely to be a rare cause of unexplained short stature [44]. Similar results have been reported from the study of Brazilian youngsters with idiopathic short stature and low IGF-I and IGFBP-3 levels [45].

The possibility of an effect of heterozygosity for a mutation known to cause GHRD in the homozygous state was able to be explored in the unique Ecuadorian cohort with GHRD, which comprises a large population with a single mutation, permitting genotyping of numerous first degree relatives. There were no significant differences in stature between carrier and
homozygous normal relatives, indicating a lack of influence of heterozygosity for the E180 splice mutation of the GHR [46]. A more general indication of the lack of influence of heterozygosity for GHR mutations involving the extracellular domain on growth comes from studies of the large multicenter European based GHI study. In both the European and Ecuadorian populations the stature of parents and of unaffected siblings does not correlate with statural deviation of affected individuals [46, 47], while expected high correlation exists between parents and unaffected offspring [46]. If the mutations that cause growth failure in the homozygous state also affected growth in heterozygotes, heterozygous parents and predominantly heterozygous siblings would have height SDS values which correlated with those of affected family members. In the Ecuadorian families, there was no difference in height correlations with parents between carriers and homozygous normal offspring.

Conclusions

During the past four decades, pediatric endocrinologists have gone from inferring GH deficiency from indirect tests such as recovery from insulin induced hypoglycemia to accurate measurement of circulating GH, which led to the discovery of GH insensitivity, cause for which was not appreciated until 20 years after its recognition. Cloning and characterization of the GHR gene has led to identification of numerous functional mutations and a broad understanding of structure-function relationships of the membrane receptor and its activation through GH-induced homodimerization of receptor molecules. GH has myriad metabolic, mitogenic, and growth effects in the various tissues in which the GHR is expressed. Some of these effects involve local or paracrine roles, consistent with the appreciation of the GHR as a member of the cytokine receptor family. Although most attention has been paid to the stimulation of endocrine and auto- or paracrine IGF-I production, GH may induce a wide variety of growth factors, their receptors, and binding proteins, depending on tissue type, health and nutritional status, and developmental stage. The signaling pathways that have been described are used by many ligands, and explanations for either the specificity of the GH-GHR responses relative to other ligands, or in specific tissues or circumstances, remain to be determined.

REFERENCES

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**FOOTNOTE**

From the outset of our studies in Ecuador, we have emphasized the importance of avoiding the terms "dwarf" and "dwarfism" which have pejorative connotation in Spanish ("enano" "enanismo") as they do in English. Our advocacy for this effort was dramatically demonstrated by the effect of our participation in the 1992 conference in Lisbon, billed as "Lessons from Laron-Type Dwarfism (1966-1992)" but published as "Lessons from Laron Syndrome (LS) 1966-1992" [Rosenblom AL, Guevara-Aguirre J, Fielder PJ, Gargosky S, Rosenfeld RG, Diamond FB Jr, Vaccarello MA. Growth hormone receptor deficiency/Laron syndrome in Ecuador: Clinical and biochemical characteristics. In: Laron Z, Parks JS (eds) Lessons from Laron Syndrome (LS) 1966-1992. Pediatr Adolesc Endocrinol Vol 24. Basel: Karger, pp 34-52 1993]
Granulosa Cell Tumor of the Ovary in a 3-Year-Old Girl

Aishah I. Rana, PGY3
Fereydoun Zaageneh, MD
West Virginia University – Charleston Division
Department of Pediatrics

Introduction
- Exceedingly rare in children
- Common ovarian cause of precocious pseudopuberty; 10% of all reported cases
- Classic presentation of abdominal mass and rapid precocious sexual development due to excess sex steroid hormone production
- Aim to improve awareness and clinical appreciation for early diagnosis and optimal outcome

Case Report
- Previously healthy 3 ½-year-old AA female with 4 day h/o abdominal distension; no abdominal pain or fever
- Recent development of breast and pubic hair
- No GI or urinary symptoms
Case Report cont...

- No vaginal bleeding
- Recent whitish vaginal discharge
- PMH and FH non-contributory
- HT and wt >95%
- VSS; active, alert, in no apparent distress

Case Report cont...

- Hyperpigmented areola with prominent nipples and palpable breast tissue (Tanner Stage II)
- Minimal axillary fuzz present; no hirsutism, acne, or change of voice
- Marked abdominal distension

Case Report cont...

- Abdominal exam revealed large pyriform palpable midline mass, firm in consistency; extending above the pelvis and umbilicus
- Abd nontender and moderately distended; normal bowel sounds
Case Report cont...

- Estrogen effects on external genitalia (hyperpigmented labia)
- GI exam reveals estrogenized vaginal mucosa; pale pinkish hue, clear to whitish secretions; no clitoral enlargement
- Pubic hair present with sparse, downy strands over labia and pubic area (Tanner Stage II)

Work-Up

- Bone age was estimated to be 4 years and 2 months
- Pelvic US revealed large solid non-cystic mass
- Abdominal CT confirmed left-sided pelvic mass extending up out of pelvis and displacing bladder superiorly
- Liver, kidneys, adrenals, gallbladder were normal; uterus was enlarged

Laboratory Data (Pre-op)

- ↑ Serum Progesterone 104 ng/dl (nl 3-24); ↑ 17α-Hydroxyprogesterone 247 (nl 3-90)
- Markedly ↑ serum Total Estrogens 78 ng/dl (nl <2.5); ↑ Estradiol 86 (nl <1)
- Normal DHEA-S 26 ng/dl (nl 5-57); ↑ 279 (nl 20-150); ↑ Androstenedione 264 (nl 8-50); ↑ Total Testosterone 238 (nl 3-10)
- ↓ FSH <1 mIU/ml (nl 1-5); Normal LH 3.0 mIU/ml (nl 1-4)
- CBC, blood cts. blood chemistries, UA, urine cts., T4, TSH, stool guaC were all normal
Treatment: Exploratory Laparotomy and Left Salpingo-oophorectomy

- Tumor size (14.5 cm x 11.5 cm x 6.5 cm); wt 630 grams
- Tumor confined to left ovary with smooth surface and intact capsule
- Peritoneal fluid with no malignant cells
- Rt ovary was normal

Tumor (Mid-Cut Section)

- Whitish yellow hue due to lipid content
- Patchy areas of hemorrhage
- Nongranulating and lobulated in appearance

Histology: Granulosa Cell Tumor

- Granulosa cells are rounded and hyperchromatic; spindle shaped Thea cells are admixed
- Solid cellular neoplasm with focal follicle formation
- Marked nuclear atypia and mitoses
Histology cont...

- Follicles vary in size with eosinophilic and basophilic secretions
- Granulosa cells rounded with clear and abundant cytoplasm; occasional rosette formation

Post-op Course

- Benign hospital course
- Post-op hormone levels normalized
- Estrogen effects resolved within 6 months post-op
- Follow-up maintained at regular intervals with no recurrence noted during the 5 year follow-up, serum estrogen levels remained normal

Discussion

- Granulosa cell tumors are rare, particularly in children
- Sex-Cord Stromal tumors 5-8% of all ovarian tumors
- Granulosa cell tumors 2% of all Sex-Cord Stromal tumors
- 95% adult type; 5% juvenile type
- Multifactorial etiology
Granulosa Cell Tumors are Functional in Nature
- Mostly estrogen producing
- Common ovarian cause of precocious pseudopuberty; accounts for <10% cases
- Increased levels sex steroids; low levels gonadotropins (FSH/LH)
- Signs/Symptoms develop rapidly
- Tumor grows fast and its size does not correlate with degree of pubertal changes

Prognosis of Granulosa Cell Tumors is Excellent
- Tumor stage is the most significant prognostic factor; >90% cases are stage I at presentation (confined to single ovary with an intact capsule)
- Most granulosa cell tumors in the pediatric age group are benign; therefore, a conservative unilateral salpingo-oophorectomy is recommended
- Literature concludes a high overall cure rate in children

Conclusion
- **Granulosa cell tumor should be** considered in the differential diagnosis of any pediatric female patient with an abdominal mass and precocious pseudopuberty
- Excellent prognosis with early diagnosis and management is expected
Thyroid and Corticoid

Hussein Abdullatif, M.D
University of Alabama at Birmingham

Patient 1

- 13 and 9/12 year old male presents because of slowing growth and lack of progress in puberty. Review of systems is positive for Asthma, and use of occasional inhaled steroids, otherwise negative. There is family history of delayed puberty in the mother, other wise history is negative.

Patient 1 Exam

- Wt at the 10th percentile, Height at the 50th percentile. Looked skinny but healthy. His exam was normal except for Tanner I-II in pubic hair and Testes 3-4 cc in size. There was no Gynecomastia.
Patient 1 labs

- Testosterone 23 ng/dl
- LH 35 MIU/ml, FSH 15 MIU/ml
- Free T4 1.32 ng/dl, TSH 6.61 UIU/ml
- Chromosomes 46 XY
- Electrolytes were normal as well as the CBC and Sed rate.

Patient 1 followup I

- Several tests including Beta HCG stim test suggested Gonadal Failure. Chromosome test on skin biopsy revealed 4 out of 500 cells to have 47XXY pattern. No testicular biopsy was obtained. Patient was started on Testosterone injections.

Patient 1 Thyroid labs

<table>
<thead>
<tr>
<th>Date</th>
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<th>TSH</th>
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<tbody>
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<td>1.32</td>
<td>6.16 (High)</td>
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<tr>
<td>12-18-2000</td>
<td>1.03</td>
<td>7.77 (High)</td>
</tr>
<tr>
<td>08-06-2001</td>
<td>0.83 (Low)</td>
<td>6.00 (High)</td>
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</table>
Cortrosyn Stim test

<table>
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<tr>
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<th>After</th>
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<tr>
<td>ACTH</td>
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<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>&lt; 1.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Renin</td>
<td>934 ng/dl/hr</td>
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</table>

After Prednisone and Florinef

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<th>TSH</th>
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<tbody>
<tr>
<td>10-17-2001</td>
<td>1.32</td>
<td>4.4</td>
</tr>
<tr>
<td>7-26-2002</td>
<td>1.25</td>
<td>1.56</td>
</tr>
<tr>
<td>10-10-2003</td>
<td>1.18</td>
<td>1.45</td>
</tr>
</tbody>
</table>

Patient 2

- A 12 year old female comes for followup of DM type I. She was doing well with no problems. Diabetes Control was fine. The patient was not seen by us for a while because of distance and an available local pediatrician.
Patient 2

- Physical exam was fine with Growth parameters around the 25th %. Tanner stage II for pubic hair and Breasts. No Lipohypertrophy and no evidence of neuropathy nor nephropathy.

Patient 2 labs

- HBA1C 7.3
- Free T4 0.79 (low)
- TSH 7.7 (high)

Patient 2 additional labs

- Anti TPO antibodies positive
- Anti adrenal antibodies Positive
- AM Cortisol 1.8, ACTH 2429
- Na 139, K 4.3
- Renin 701
Patient 2 six months later

- Patient is on Prednisone and Florinef, but not thyroid hormone. She is doing well but having higher blood sugars. HBA1C 8.1 Free T4 1.05 and TSH 2.21

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Literature search

- Hossein Gharib discussed a few patients with Hypothyroidism at the time of the diagnosis with Addison disease. He suggested that Hypothyroidism treatment be postponed a few months after Steroid replacement therapy.

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Literature search 2

- JCEM 1980 Topliss et al.
- Presented 10 patients with Addison disease, 3 of them had High TSH and low Free T4 index and 3 had high TSH but normal Free T4 index. All but one corrected with Steroid replacement therapy.
Literature 3

- Study of 33 patients with Addison disease, 14 had clinical or subclinical Hypothyroidism and 16 had increase thyroid antibody titres. bTSH stimulations revealed a decreased response in free T4, and Free T3 when compared to normals or Addison Disease but no Thyroid antibodies nor evidence of Hypothyroidism.

Literature 4

- JCEM 1996 Vol 81 no 7: 2602
- In patients with Addison disease but no Thyroid Autoantibodies and no evidence of Hypothyroidism, TSH levels increase in times of Glucocorticoid deficiency and decrease in times of Glucocorticoid excess.

Conclusions

- Mildly elevated TSH or Subclinical Hypothyroidism can be the first presenting sign of Addison disease.
- Treatment of Addison disease can reverse this finding at least for a while.
- Whether those patients will end up Hypothyroid or not remains to be seen.
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3β-Hydroxy Dehydrogenase Deficiency

Peter A. Lee, M.D., Ph.D.
Penn State College of Medicine
Milton S. Hershey Medical Center
Hershey, PA

3β Hydroxysteroid Dehydrogenase Deficiency

- Diminished steroids in all 3 pathways
- Elevated 17-hydroxypregnonolone and DHEA
- Ambiguous genitalia in both sexes
  - Elevated DHEA may virilize the females
  - Enzyme deficiency in testis as well as adrenal results in androgen deficiency and inadequate virilization of males

3β-Hydroxysteroid Dehydrogenase

- Catalyzes rearrangement of the double bond in ring A and conversion of a hydroxyl group at the 3 position to a keto group
- Deficiency of enzyme leads to decreased synthesis of cortisol, aldosterone, and sex steroids in turn leading to increased ACTH secretion
3β-Hydroxysteroid Dehydrogenase

- Increased ACTH stimulation leads to accumulation of excessive amounts of steroid precursors with the Δ⁵-3-hydroxy configuration, e.g.:
  - Δ⁵-pregnenolone
  - 17α-hydroxyprogrenolone
  - dehydroepiandrosterone (DHEA)
  - DHEAS

3β-Hydroxysteroid dehydrogenase deficiency

- Severely affected individuals present as neonates or in early infancy with evidence of cortisol and aldosterone deficiency, such as poor feeding, vomiting, dehydration, hyponatremia and hyperkalemia
- Thus, presentation may be with adrenal insufficiency
3β-hydroxysteroid dehydrogenase deficiency

- Associated with mild virilization of female ascribed to increased peripheral conversion of excessive DHEA and inadequate virilization of male
- Associated with partial virilization of male external genitalia ranging from clear genital ambiguity, mild to severe hypospadias, to minimal virilization

Genetics of 3β-hydroxysteroid dehydrogenase deficiency

- Decreased enzyme activity a result of mutations in the 3β-hydroxysteroid dehydrogenase II gene
- The altered enzyme function resulting in severe, salt-wasting forms is associated with mutations resulting in stop codons, insertions or deletions resulting in frameshifts, and point mutations

Genetics of 3β-hydroxysteroid dehydrogenase deficiency

- The 3β-hydroxysteroid dehydrogenase I gene is expressed in placenta and peripheral tissues
- Since expression of this gene is intact among these patients, it may explain why Δ4 steroids (17α-hydroxyprogesterone and androstenedione) levels may be normal or elevated.
First Report

Unusual Steroid Pattern in Congenital Adrenal Hyperplasia: Deficiency of 3\(\beta\)-HydroxyDehydrogenase

Alfred M. Bongiovanni
The Children's Hospital of Philadelphia

First Report: Deficiency of 3\(\beta\)-Hydroxy Dehydrogenase

- Urinary steroid profiles in 3 infants
  - Predominance of 3-\(\beta\)-hydroxy-\(\Delta^5\) steroids
  - Absence of urinary pregnanetriolone, pregnanetriolone & 17\(\beta\)-hydroxypregnanolone
- All 3 infants of died
  - 2 females with masculinization of external genitalia studied at 1 and 2 weeks of age
  - A male with hypospadias studied at 8 wks.
- Hydrocortisone suppressed urinary 17-KS

Type II 3\(\beta\)-hydroxysteroid dehydrogenase (HSD3B2) and Premature Pubarche

- Among 30 girls with premature pubarche, 9 who had 17\(\beta\)-hydroxypregnenolone >6 SD were screened for HSD3B gene mutations, the 3 girls with the highest levels were found to have mutations
  - One girl had a homozygous T259M mutation and 2 sisters had a new compound heterozygous G129R/P22H mutations
Old Order Amish Kindred

- Sisters with genetically verified 3β-hydroxysteroid dehydrogenase deficiency
- A paternal cousin (once removed) who never developed normally at puberty and had minimal stamina
- A maternal distant female relative with the same diagnosis
- A infant male newborn (kindred of father) found by newborn screening

Old Order Amish Kindred

- [Diagram showing family tree]

Old Order Amish Kindred: Older Sister

- Neonatal presentation with hyponatremia, shock, hyperpigmentation, and mildly virilized genitalia
- Treated with cortisol and flornidom
### Old Order Amish Kindred: Older Sister

<table>
<thead>
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<td>&gt;720 ng/mL (25-350)</td>
</tr>
<tr>
<td>17-OHprogesterone</td>
<td>&gt;2000 ng/mL (&lt;7.3)</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>119 ng/mL (6-68)</td>
</tr>
<tr>
<td>Sodium</td>
<td>116 mmol/L (135-145)</td>
</tr>
<tr>
<td>K</td>
<td>6.8 mmol/L (3.5-5.0)</td>
</tr>
<tr>
<td>Glucose</td>
<td>85 mg/dL (70-120)</td>
</tr>
</tbody>
</table>

### Old Order Amish Kindred: Older Sister

- Length decelerated to below the 5%ile by 2 years of age
- Height %ile gradually increased from age 2 to 7 years from >5 to 30%
- Marked growth acceleration from 7.5 to 8.5 years to the 75%ile, 10 cm/yr
- Current height is at the 50%ile

### Old Order Amish Kindred: Older Sister

- Presented at 8 years and 9 months
  - Complaints of recurrent headaches and vomiting
    - Symptoms did not improve with increase glucocorticoid therapy
  - Growth acceleration over the previous 12 months from the 30th to 70th percentile
  - Breast development was Tanner stage 3
Old Order Amish Kindred: Older Sister

- Subsequent worsening of symptoms of headaches, with fatigue, bloating, and lower abdominal pain
- Reported to be in a cyclic pattern at 4 week intervals
- Skeletal age normal for age
- LH 0.2, FSH 1.5 and estradiol < 20
- DHEAS 110 µg/ml (< 95)

Old Order Amish Kindred: Older Sister

- Pelvic ultrasound showed asymmetrically enlarged ovaries bilaterally, with numerous "prominent follicles"
- Repeated estradiols 29 to 55 pg/mL
- Response to GnRH stimulation included a rise of LH to 7.8 mIU/ml and FSH to 4.0 mIU/ml

Old Order Amish Kindred: Older Sister

- Treated for 12 months with GnRH analogue
  - Resolution of symptoms of headaches and abdominal bloating and discomfort
  - Change in ovaries on ultrasound to more normal appearance
  - Deceleration of growth rate
Ovarian Sonography before and during GnRHα therapy

Old Order Amish Kindred: Older Sister
- Trial off therapy after 2
- Reoccurrence of symptoms of headaches and abdominal bloating and discomfort
- Estrogen/progesterone combination therapy as been begun

Old Order Amish Kindred: Younger Sister
- Diagnosed at 4 4/12 years after older sister's presentation
- Baseline steroid characteristic and mutations verified
- Treated with 18 mg hydrocortisone/M²
- Continued to grow at an accelerated rate
- Noted at 5 years to have Tanner 2 breasts and progression of pubic hair
Old Order Amish Kindred: Younger Sister (cont)
- Rapid subsequent progression of breast development
- Equivocal LH and FSH response to GnRH stimulation
- Estradiol level of 43 ng/dL
- Enlarged polycystic ovaries on ultrasound
- Begun on GnRHa therapy (DepoLupron)

Old Order Amish Kindred: Younger Sister (cont)
- Suppression verified with peak LH of 0.65 and FSH of 0.85 after GnRH stimulation
- Estradiol levels fell to < 10 pg/mL
- Growth continued at 10 cm and 15 kg/year
- Ovarian volume diminished and fewer large cysts were observed

Old Order Amish Kindred: Paternal distant relative
- Female child who presented with mild clitoromegaly
- Hormonal profiles included elevated 17-OH-prog, androstenedione and DHEA
- Originally misdiagnosed as 21-hydroxylase deficiency
- Treatment has continued with only hydrocortisone with reasonable control
Old Order Amish Kindred: Male Infant-Mother's Kin

- Had elevated 17-hydroxyprogesterone on state screening examination
- Youngest of 4 siblings
- Began on therapy at 7 days of life
- Found to have same mutation as sisters
- One hospitalization for dehydration
- Thriving well at one year of age

Old Order Amish Kindred: Father's First Cousin

- Married for almost 40 years without children
- Had no maturation at marriage, did not grow a beard until 10 years later
- Complained of weakness, diminishing stamina, dizziness upon rising, and lean stature

Old Order Amish Kindred: Father's First Cousin

- Androstenedione: 0.89 ng/ml (0.5-2.0)
- Testosterone: <15 ng/dL (250-900)
- DHEA: 187 ng/dL (180-1250)
- DHEAS: 332 ng/ml (1500-4500)
- 17-OH-pregnenediolone: 86 ng/dL (20-450)
- 17-OH-progesterone: 0.2 ng/ml (0.3-2.1)
- Progesterone: 0.4 ng/ml (0.1-0.3)
- LH: 24.5 u/mL (1.0-8.4)
- FSH: 105.0 u/L (1.0-10.5)
Old Order Amish Kindred: Father's First Cousin

DNA analysis found no deletion of 3-β-hydroxysteroid dehydrogenase II gene
Hypopituitarism and Longevity

John S. Parke, M.D., Ph.D.
Emory University School of Medicine
Atlanta, GA, USA

A General Theme Across Evolution

Larger species live longer,
But within a species,
Disruption of glucose/insulin/IGF-I signaling pathways leads to:
1. Smaller size
2. Longer lifespan


C. elegans

- Dauer formation (Daf)
  - Nonfeeding, stress-resistant, larval stage
- DAF-2
  - Insulin-like receptor
  - Mutants bypass Daf and live 60% longer
- DAF-16 localizes to nucleus
  - Increased stress resistance
  - Decreased central metabolism
  - Decreased reproduction
Drosophila

- Juvenile hormone inhibits adult diapause, a state with arrested reproductive development
- Insulin-like receptor (InR) activation promotes JH production
- InR mutants and InR substrate (Chico) mutants have a 100% increase in adult longevity

Dwarf Mice

- Model
- Ames
- Snell
- Little
- Knockout
- Partial KO

<table>
<thead>
<tr>
<th>Gene</th>
<th>Increase</th>
</tr>
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<tr>
<td>Prop1</td>
<td>50 %</td>
</tr>
<tr>
<td>Pit1</td>
<td>40 %</td>
</tr>
<tr>
<td>GHRIIR</td>
<td>40 %</td>
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<tr>
<td>GHIR</td>
<td>40%</td>
</tr>
<tr>
<td>IGF-I</td>
<td>33 % (Females)</td>
</tr>
</tbody>
</table>

Additive effects with caloric restriction

Dwarf Humans

- Gene
- PROPI
- PIT1
- GHRIIR
- GHR
- GHI

- Evidence for Greater Longevity
- You will see the raw data
- Very little data, smaller clusters
- Brazilian cluster N= 105 in 4 gen
- Several in their 60's
- Equadorian cluster N=79
- Deaths at 55 & 56 of MI
- Oldest now 68 & 67
- Important new paper from them
The Case

- Born in 1930
- Born as a twin
- Heights
  - 92 cm @ 9
  - 130 cm @ 42
  - 135 cm @ 58
- On T4 treatment
- GH 0.5, IGF-1 <10, PRL 5,
  Cortisol 26.3 ug/dl
- PROPL 150ng/ml
  homocysteine

Krizsik and Laron Visit in 1990

The Context
Mother, Aunts, Uncles and Grandparents

The Raw Data on Longevity

- Males: N = 14
  - 1804: 52 D
  - 1805: 55 D
  - 1906: 8 D
  - 1907: 42 D
  - 1908: 48 D
  - 1909: 47 D
  - 1910: 44 D
  - 1911: 13 D
  - 1912: 32 97
  - 1913: 15 D
  - 1914: 18 D

- Females: N = 10
  - 1805: 38 D
  - 1806: 38 D
  - 1807: 43 D
  - 1808: 56 L
  - 1809: 57 L
  - 1810: 23 L
  - 1811: 14 L

Swiss Cohort with GH1 Deletion

- Males: N Lifespan Range
  - Affected: 5 57.4 41-77
  - Sibs: 11 70.9 40-87
  - Controls: 100 70.2 23-91

- Females: N Lifespan Range
  - Affected: 6 47.4 29-63
  - Sibs: 14 74.2 22-89
  - Controls: 100 75.3 21-90

Benson et al. JCBM, 2003
Different Clusters and Different Conclusions

- Croatia – PROPI deletion patients can live to a ripe old age (but not 120 years)
- Switzerland – GH deletion patients die young and the women die before the men
- Why would humans provide an exception to the rule of increased longevity with impaired GH signaling?

Acquired Hypopituitarism

- More common than congenital disorders
- Usually caused by tumors or their treatment
- There is an increased mortality
- It occurs at a fairly young age and is more strongly related to the disease than to hormone deficiency
- It does not provide a good model for interactions between GH and aging

Size does matter

- Median Lifespans
- Saint Bernards – 6 years
- Chihuahuas – 16 years
The Samaras Slope

Age at Death
Extrapolated from current US longevity and average male and female heights

Experimental Approaches
- MILs more mortality data from known clusters of genetic disorders
- Set up a registry and wait for people to die
- Develop a panel to assess biological markers of aging and compare affected with sibs
  - Telomeres
  - Oxidative stress
  - Cardiovascular
  - Cognitive
- Normative studies for preliminary data
  - Human
  - Rhinos
  - Other
A Challenge

- If you had access to a study population of 60 persons of all ages with PRO1 deficiency ...
- How would you determine whether they were aging more or less rapidly than their siblings?
Treatment of Graves’ Thyroiditis

Mark S. Rappaport, M.D., Ph.D.
Pediatric Endocrine Associates, P.C.
Atlanta, GA

Southern Pediatric Endocrine Society
2003 Annual Meeting
Charlotte, NC

Reference texts indicate that propylthiouracil (PTU) and methimazole (MMI) should be dosed multiple times daily in the treatment of Graves’ thyroiditis. These suggestions are based on limited pharmacokinetic data. Proper dosing of these medications in pediatrics and adolescence has even less supportive data, and likely is an extrapolation of adult dosing on a mg per kg basis. There is some support in the literature for the adequacy of once daily dosing of MMI for Graves’ treatment, mostly from assay studies following thyroidectomy which show long tissue half lives of this drug. Once daily dosing would likely have great benefit for treatment by increasing patient compliance with the prescribed treatment plan.

Graves’ thyroiditis is a moderately common condition in our pediatric endocrine practice. Treatment outcomes are variable, and many patients take several weeks longer than expected to respond to treatment, or have clinical courses characterized by dips and swells in T4 and T3 levels. In our three physician practice, both PTU and MMI are used with differing dosing and frequency regimens, on a case-by-case basis. The optimum treatment regimen for this patient population is not known. In this study, the treatment of Graves’ disease in our practice is reviewed, including medications selected, doses chosen, frequency of administration, and the initial clinical response to treatment.

How long does it take for patients to respond to treatment?

![Graph showing response time to treatment](image)

Is dose chosen critical?

![Graph showing dose vs. treatment outcome](image)

References:

Treatment of Graves Thyroiditis

Mark S. Rappaport, M.D., Ph.D.
Pediatric Endocrine Associates, P.C.
Atlanta, GA
Curious case

- 11 year old girl presented with a goiter of 6 months duration.
- PE:
  - P 124-140, BP 122/68
  - thyroid 7 cm lobes
  - no lid lag or proptosis
- Labs:
  - T4 = 21.2 µg/dl, T3 = 639 ng/dl, TSH < 0.1

Curious case

- Treatment:
  - MMI 5 mg tid (0.4 mg/kg/day)
  - propranolol

Curious case

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Treatment goals

- allow patient to become euthyroid
- eliminate cardiovascular effects
- eliminate effects on nervous system
- reverse eye disease
- minimize adverse effects of treatment

Treatment goals

want to accomplish these goals IMMEDIATELY !!
(or at least as soon as possible)

Questions ...

- What medications are available for treatment?
- Which is the best medication?
- How should it be used to provide the quickest resolution of hyperthyroidism?
Choice of medications

- PTU (propylthiouracil)
- MMI (methimazole)
- Other types of drugs can assist in management, but none have the potency of the thioumarilides

Choosing PTU

- Advantages:
  - Effective at inhibiting organification of iodine
  - Can block conversion of T4 to T3
- Disadvantages:
  - Short half life requires frequent dosing
  - Poorer compliance on tid or more frequent plan
  - Effects on T4 to T3 conversion require high doses

Choosing MMI

- Advantages:
  - Effective at inhibiting organification of iodine
  - Longer half life allows dosing less often
  - Probably better patient compliance
- Disadvantages:
  - Doesn't block conversion of T4 to T3
What dose?

- PTU 5 - 10 mg/kg/day (tid)
- MMI 0.5 - 1.0 mg/kg/day (q day or bid)
  - S. Reisner et al., JCEM Vol. 80, No. 11: 2767-2778 (1995)
- adult text: PTU - 8.5 mg/kg/day, MMI 0.6 mg/kg/day

Rationale for PTU
block of T4 to T3 conversion

- Study in athyreotic people
  (given 250 mg PTU q 6 hrs x 8 days)
  - T3 120 → 80 → 113 µg/dl
  - TSH increased 195 %
  - TRH 64 → 101


Rationale for PTU
block of T4 to T3 conversion

- Study in Graves patients
  (prior to any other treatment)
  - with 200 mg, effect lasts just a few hours
  - with 800 mg, effect lasts 9 hours
  (T3 decreases 65 %)

Rationale for MMI
Long persistence in thyroid gland

- MMI is concentrated in the thyroid gland
  tissue content greatly exceeds plasma concentration
- thyroid tissue content doesn't vary after 3-24 hours of
dosing, regardless of administration q.d. bid. or tid.
  - measured at thyroidectomy in adolescents with Graves'


Rationale for MMI
Long persistence in thyroid gland

- dosing above 15 mg/day seems to saturate thyroid
  binding
  - tissue content doesn't vary at 15-40 mg/day
- dosing saturates regardless of frequency of
  administration
  - once-a-day as effective as multiple dosing

> Chung-Hao Houch Tao Chih (Chinese Medical Journal)
73:6, 347, X: 22, 1994

Dosing interval: MMI
Can once daily dosing work?

<table>
<thead>
<tr>
<th>n</th>
<th>dosing</th>
<th>response in 3 months</th>
<th>avg time to response</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>15 mg q day</td>
<td>93%</td>
<td>5.3 weeks</td>
</tr>
<tr>
<td>32</td>
<td>30 mg q day</td>
<td>91%</td>
<td>6.3 weeks</td>
</tr>
<tr>
<td>50</td>
<td>10 mg tid</td>
<td>86%</td>
<td>6.0 weeks</td>
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</table>
Dosing interval: MMI

Can once daily dosing work?

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Response in 3 months</th>
</tr>
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<tbody>
<tr>
<td>PTU</td>
<td>10 mg q 12 h</td>
</tr>
<tr>
<td>0.25 mg q 6 h</td>
<td>100 mg q 8 h</td>
</tr>
<tr>
<td>0.5 mg q 6 h</td>
<td>100 mg q 8 h</td>
</tr>
<tr>
<td>MMI</td>
<td>10 mg q 12 h</td>
</tr>
<tr>
<td>0.25 mg q 6 h</td>
<td>100 mg q 8 h</td>
</tr>
<tr>
<td>0.5 mg q 6 h</td>
<td>100 mg q 8 h</td>
</tr>
</tbody>
</table>


Curious case

<table>
<thead>
<tr>
<th>Weeks</th>
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<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>30</td>
</tr>
</tbody>
</table>

Suspicions

- Compliance in adolescents with Graves' disease is likely poor
- Simplified regimen of MMI once daily might provide best compliance, and best control of hyperthyroidism
How long does it take for patients to respond to treatment?

Is PTU or MMI more effective?

Days to euthyroidism

<table>
<thead>
<tr>
<th></th>
<th>PTU</th>
<th>MMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>71.4</td>
<td>68.1</td>
</tr>
<tr>
<td>median</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>daily dose (mg/kg/day)</td>
<td>5.5 ±/-.2.7</td>
<td>0.63 ±/.30</td>
</tr>
</tbody>
</table>
Is initial T3 predictive of response?

Is thyroid size predictive of response?

Does dosing frequency make a difference?

MMI data
Conclusions
Based on the data from our practice:

- PTU and MMI were equally effective
- "lower" dosing is as effective as "higher" dosing
- severity of presentation (gland size or thyroxine level) should not be a factor in choosing treatment

Supplemental treatments

- carnitine
  - decreases clinical and biochemical effects of thyroid hormone
  - low cost, adverse event free
  - works at 2 g/day dosing


Supplemental treatments

- Lugol's solution
- bile sequestrants
- other drugs which inhibit thyroid hormone transport or nuclear receptors

Graves' remission
Does dosing affect duration?

- Inconsistent results
  - higher dosing prolongs remission.
  - Might be able to stop treatment as soon as euthyroid
McCune-Albright Syndrome


McCune DJ, Britton L. Osseous fibrous dysplasia, report of a case in which the condition was confirmed with precocious puberty, pathologic pigmentation of the skin and hyperthyroidism, with a review of the literature. J Pediatr. 1946;29:352-365.


McCune-Albright Syndrome

Donovan James McCune (1902-1976)

Qualified in Medicine at the Johns Hopkins Hospital, Baltimore in 1928

At the time of his death he was a pediatrician at Columbia University, New York.

McCune-Albright Syndrome

Polyostotic fibrous dysplasia
Café-au-lait skin pigmentation
Autonomous endocrine hyperfunction
McCune-Albright Syndrome

Sporadic
Somatic post-zygotic missense
mutations of GNAS1 gene
GNAS1: chromosome 20q
Exons 1-13 of GNAS1 code for Gsα
Gsα: intrinsic GTPase activity
(GTP→GDP)
Mutations: Constitutive activation
McCUNE-ALBRIGHT SYNDROME

Long-term follow-up of combined treatment with aromatase inhibition and an anti-estrogen

3.19 y.o. white Latin girl with a 3-day history of vaginal bleeding and a 4-month history of progressive breast enlargement who was seen on 7-20-95. There was no family history of precocious puberty, although the mother had menarche at 9.5 years (maternal grandmother had menarche at 13 years). Initial evaluation by a family physician was "inconclusive"; pediatrician at a local clinic saw her 1-2 months later and referred the girl for evaluation. There was no sexual hair, apocrine body odor or history of trauma. There was no use of systemic or topical medications. The girl was always tall with a height over the 97%.

The parents were divorced. The mother was 28 years old, 164 cms tall and healthy; menarche occurred at 9.5 years. The father was 31 years old, 5'8", healthy. The PGF was 5'7" and PGM 5'5". The MGF was 5'8" and the MGM 5'4". An 8 year-old sister was healthy.

Physical examination: 3.19 years; HA = 4.2 yrs; WA = 4.35 yrs; HT = 102.9 cms; WT = 16.6 kgs; P = 78/min; R = 14/min; BP = 80/40.

General examination was negative. The breasts were at stage II+, there was estrogenization of the labia minora and vagina, and the clitoris was normal. There was no sexual hair. The neurological examination was normal.

Laboratory evaluation: Bone age = 4.2/12; Pelvic US = post-pubertal uterus with endometrial echo. Post-pubertal left ovary. Large right ovary with a cyst that measured 4.5 x 4 cms. Well-defined vaginal outline. LH = < 0.02 mIU/ml; FSH = 0.44 mIU/ml; Estradiol = 140 pg/ml; Estrone = 28 pg/ml; SHBG = 3.5 mcg/dl; Androstenedione = 14 ng/dl; T < 3 ng/dl; IGF-I = 111 ng/dl; T4 = 8.8 mcg/dl; TSH = 1.82 mcIU/ml. LH-RH stimulation test = prepubertal (see table).

Repeat pelvic US one month later: cyst of right ovary = 3.7 x 2.2 cms. All other findings unchanged.

The girl was followed with frequent observation but no therapy. Presumptive diagnosis was isolated, dominant right ovarian cyst. There were periodic pelvic US's and laboratory studies (see attached). The physical examination on 7-8-96, at a chronological age of 4.16 years, showed complete regression of breast development and no other evidence of puberty (no sexual hair, no apocrine body odor). Vaginal bleeding occurred on 7-20-95 at presentation, on 10-1-95, middle November 1995, and on 10-30-96.

On pelvic US of 10-31-96 (following vaginal bleeding on 10-30-96), the uterus was described as post-pubertal and "prominent", the left ovary as large and containing several follicular cysts, and the right ovary was described as large (4.8 x 3.6 cms) with decreased blood flow on color Doppler, suggesting the possibility of a torsion. Examination by surgery and endocrinology was completely unremarkable without signs of an acute abdomen; there was estrogensation of the labia and vagina, the breasts were at stage II+, and there was no sexual hair. The child was observed without intervention and repeat pelvic US on 11-7-96 showed a "normal" right ovary comparable in size to the left ovary, and blood flow was completely normal.

Physical examination on 12-10-96 was described as showing no breast development (stage I) and no estrogensation of the labia or vagina.

*On 2-12-97 I see her for breast tenderness, further breast enlargement, and vaginal bleeding. She had been seen at the emergency room in the previous 24 hours for periumbilical abdominal discomfort, vomiting, and mild fever. She was treated with Tylenol rectal suppository. A pelvic US (2-11-97) showed a pubertal uterus, normal right ovary (1.6 cms) and a cystic lesion of the left ovary measuring 2.5 cms. There was no mention of an endometrial echo.
On **physical examination**, at a chronological age of 4.76 years, her HA was 7.26 yrs; HT = 122.0 cms; WT = 27.4 kgs; P = 78/min; R = 20/min; BP = 98/60. Her general examination was negative, with a completely benign abdominal exam. There was no sexual hair or apocrine body odor, the breasts were enlarged at 4.8 x 4.8 cms (III - III+), there was engorgement of the areolas and there was modest estrogenization of the labia minora and vagina. There were no pigmented changes of the skin. A 10 y.o. sister had begun to have 2y. sexual characteristics at 8.5 years and was “ready to menstruate”.

**Laboratory studies:** LH < 0.02 mcui/ml; FSH < 0.02 mcui/ml; estradiol = 52 pg/ml; estrone = 24 ng/dl; SHBG = 2.4 mcg/dl; androstenedione = 12 ng/dl; testosterone < 3ng/dl; DHEA-S < 10 mcg/dl. A bone age was 8-8.25 years.

On 5-13-97, the LH was 0.04 mcui/ml, the FSH was 1.4 mcui/ml; the estradiol was <5 pg/ml, the estrone was 14 pg/ml, the IGF-I was 152 ng/ml, the T4 was 9 mcg/dl and the TSH was 2.2 mciu/ml.

On 5-16-97, a bone scan showed multiple areas of isotope concentration in the occipital region, the diaphysis of the right humerus and proximal right radius, left femur and proximal right femur, the diaphysis of both tibias and the left fibula, and the left iliac bone. The bone survey was much less informative. A Wood’s lamp examination was negative for skin pigmentation.

On 8-28-97, at a CA of 5.30 yrs., treatment was started with testolactone (40 mg/kg/day) and continued until 9-16-98 (CA = 6.35 yrs). Because of the number of tablets to be taken (24 tablets per day) and less than adequate compliance with four-times-per-day regimen, treatment was changed to anastrozole, 1 mg per day once daily, shortly after 9-16-98. On 10-16-98, (CA = 6.41 yrs) treatment with tamoxifen was added at 10 mg per day.

The girl was seen every 4-to-6 months for the next 3 years (see attached tables for repeat laboratory studies and pelvic ultrasounds). After the episode of vaginal bleeding of 2-10-97 pre-treatment, bleeding recurred on 4-22-98 and July of 1998 (both while on testolactone) and on 10-6-98, 6-21-99, and mid-October of 2001 (while on combination therapy with anastrozole and tamoxifen). The breasts remained at stage III with relatively pubertal areolae and nipples. There was cyclical estrogenization of the labia and vagina. At 7.92 years, pubic hair was at stage III and axillary hair at stage II.

Treatment with a combination of anastrozole and tamoxifen was continued until 11-7-2001 when, at a chronological age of 9.49 years and a bone age of 12 years, both medications were discontinued and puberty allowed to progress spontaneously.

The patient was lost to follow up because of insurance reasons, but contact was re-established on 9-23-03 when she came to visit socially. On that day, at a chronological age of 11.37 years, she was 159 cms and 74 kgs. She was menstruating every 4 to 6 weeks and was in good health.

**Addendum.**

**Before treatment:** \( \Delta BA = 3.75 \) years; \( \Delta CA = 1.57 \) years; \( \Delta BA/\Delta CA = 2.39 \)

**After treatment:** \( \Delta BA = 4.20 \) years; \( \Delta CA = 4.16 \) years; \( \Delta BA/\Delta CA = 1.01 \)
McCUNE-ALBRIGHT SYNDROME
Summary of laboratory and radiological data

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<th>60'</th>
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<td>0.42</td>
<td>1.5</td>
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Pelvic Ultrasound.

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Laboratory studies.

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McCUNE-ALBRIGHT SYNDROME

Bibliography

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    To block estrogen's synthesis or action: that is the question
    Santen RJ

    McCune-Albright syndrome: new insights
    Collins MT, Shenker A
Case Report: Insulinoma presenting as a seizure disorder

9 y/o WF who presented to her pediatrician’s office after a 5 minute major motor seizure. In his office, a fingerstick glucose was 47, urine ketones were negative, and serum beta hydroxybutyrate was negative. She had had a three year history of “spells” that were interpreted as seizures and treated with a series of anticonvulsants. They were more frequent with exercise, although could not definitely be associated with periods of fasting. She would typically become aple, incoherent, and had been noted on occasion to have brief periods of tonic clonic generalized movements, followed by a postictal state of confusion and lethargy. She had been treated with a series of anticonvulsants, none of which afforded relief. Multiple EEGs, were normal until the one after her most recent seizure. She was referred to DUMC for continuous video/EEG monitoring as she completed a wean of her anticonvulsants and in the hospital had no seizure activity, nor signs or symptoms of hypoglycemia. She was hospitalized for observation and given a glucose meter to check multiple blood sugars while her anticonvulsants were reinstated. At home, parents documented several blood sugars in the 20’s associated with symptoms, relieved with food.

She was admitted for a provocative fast. In 24 hours, she became clinically hypoglycemic with a blood sugar of 26. She was given glucagon 1 mg IM and pre and post blood was drawn. Her blood sugar 30 minutes after the glucagon rose to 134 with resolution of symptoms. An abdominal MRI showed a 1.2 x 1 cm enhancing lesion in the anterior inferior aspect of the pancreatic head. Laparoscopic surgery at Emory has cured her. Subsequent genetic testing for MEN-1 was negative. She is not a straight A student.

<table>
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<td>Alanine</td>
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GAD-65, insulin autoantibodies, ICA antibodies were negative.