Polyps in Pediatrics
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Division of Pediatric Gastroenterology
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Pediatric Grand Rounds

Disclosure
• I have no relationships with commercial companies to disclose.

Learning Objectives
• Understand 4 various Polyposis Syndromes
  • Diagnosis, management, and surveillance
    • Familial Adenomatous Polyposis
    • Peutz-Jeghers Syndrome
    • Lynch Syndrome (HNPCC)
    • Juvenile Polyposis

• Identify factors inhibiting early intervention for potentially affected families

• Strategize a plan to overcome roadblocks

Case Presentation I
• 15 y/o Caucasian male with PMHx of hematochezia attributed to constipation and anal fissure 2 yrs ago, presents for evaluation of rectal bleeding. Symptoms were present about 5-6 months prior to evaluation, which progressively worsened in past 2-3 months. The blood was bright red and mixed in the stool. The patient was scheduled for EGD/colonoscopy for further evaluation.

Case Presentation II
• Physical Exam: +FOBT, rest unremarkable
• Labs: normal CBC, FAP genetic testing ordered

• Family Hx:
  – Paternal Grandfather: Colon Cancer and Polyps
  – Maternal Grandmother: Breast cancer — Diagnosed at age 70
  – Mother: Colon Cancer w/ mets to liver on chemo tx — Diagnosed at age 46 yr
  – Maternal Uncle: 60 polyps removed
  – Brother: 6 polyps removed (21 y/o)
Patient Presentation of Polyp Evaluation

- Clinical symptoms requiring further evaluation
  - Referral to a specialist
- Request of family member due to concern of a new diagnosis in a relative
- Incidental Finding

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Familial Adenomatous Polyposis (FAP)

- Most common adenomatous polyposis syndrome
- Autosomal dominant inherited disorder
- 2nd most common genetic CRC syndrome
- Germline mutation in the adenomatous polyposis coli (APC) gene
- Frequency: 1 in 6,850 to 1 in 31,250
- Malignancy risks:
  - Colon 100% by 39 years; Small bowel 4-12%

Age of Presentation

<table>
<thead>
<tr>
<th>Hereditary Polyposis</th>
<th># of polyps</th>
<th>Colorectal CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg age of onset in FAP (familial adenomatous polyposis)</td>
<td>16 yrs</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Avg age of onset in AFAP (attenuated familial adenomatous polyposis)</td>
<td>20-25 yrs</td>
<td>&lt;100</td>
</tr>
<tr>
<td>MAP (MHY associated polyposis)</td>
<td>46 yrs</td>
<td>10-100</td>
</tr>
<tr>
<td>Juvenile Polyposis</td>
<td>15 yrs</td>
<td>&gt;3-10</td>
</tr>
</tbody>
</table>

Colonoscopy

Sessile Polyps

A: the endoscopic appearance of early FAP and the difficulty in identifying adenomas
B: endoscopic appearance after spraying with dilute Indian ink contrast chromoendoscopy

P Rozen, F Macrae, Familial adenomatous polyposis: The practical applications of clinical and molecular screening. Familial Cancer, 2006; 5:227-335
**Gastric Polyps**

- **Fundic gland polyps**
  - Most common type in FAP patients
  - Incidence: 26-61% (FAP pts) vs 0.8-1.9% (general pop.)
  - Occur at younger age, more numerous
  - Increased frequency of dysplasia
  - Associated with:
    - FAP, AFAP, and Cowden’s syndrome

**Duodenal Polyps**

- **Duodenum**
  - >90% adenomatous polyps
  - 5-10% cancer
  - Cumulative risk of periampullary cancer 10% by age 60

**Ophthalmology**

- **Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE)**
  - Occurs in 70-80% of all FAP pts
  - Usually present at birth
  - CHRPE(+): 4 small or 1 large pigmented lesion via a bilateral lens fundoscopic exam
  - No malignancy potential

**Study**

- **Austrian Pedigree (1990-1996)**
  - 39 people (20 FAP, 19 relatives)
  - 75% (15/21 FAP), 31.6% (6/19 at risk) = CHRPE +

**Conclusion:**
- Index pt w/ FAP is CHRPE +, then ophthalmologic predictive dx for at risk pt is possible
- CHRPE – members of CHRPE + family should not be excluded from scope or genetic testing
- Lesions seem to be specific to FAP
- CHRPE +/- status aid in locating mutation

**Variants of FAP**

- **Gardner Syndrome**
- **Hereditary Desmoid Disease**
- **Turcot Syndrome**

**Management Options**

- **Education**
- **Genetics Evaluation**
- **Endoscopy/Colonoscopy**
  - Baseline: Polypectomy
  - Scheduled intervals
- **Capsule Endoscopy**: small bowel polyps
- **Surgery**: prophylaxis colectomy
- **Labs**
- **Observation for extra-colonic manifestations**
Medical Interventions

- **Suldinac**
  - Non-steroidal anti-inflammatory
  - Aids in regression of polyps
  - Short term benefit
- **COX-2 inhibitors**
  - Not favorable after reports of cardiac issues with use

Surgical Intervention

- **Colectomy**
  - Treatment to reduce risk of colorectal cancer in FAP or at risk patients with adenomatosis

Extracolonic Cancer Risks in FAP

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Relative Risk</th>
<th>Absolute Lifetime Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmoid</td>
<td>852</td>
<td>15</td>
</tr>
<tr>
<td>Duodenum</td>
<td>330.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Thyroid(adult)</td>
<td>7.6</td>
<td>2</td>
</tr>
<tr>
<td>Brain</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Ampullary</td>
<td>123.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Hepatoblastoma (kid)</td>
<td>847</td>
<td>1.6</td>
</tr>
<tr>
<td>Gastric</td>
<td>-</td>
<td>0.6</td>
</tr>
</tbody>
</table>


Hepatoblastoma in FAP

- Most common primary liver tumor in kids
  - Children age 5 years or younger
- First association noted in 1983
- Incidence in kids of FAP families: 1 in 235
  - 1 in 100,000 in general population
- Clinical Presentation:
  - Enlarging abdominal mass>anorexia, wt loss, pain
  - Rt lobe (3x) > lt lobe affected
- Labs: elevated alpha feto-protein
  - Normal bilirubin, LFT, and thrombocytosis

Goals of Presentation

- Understand 4 various Polyposis Syndromes
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    - Perutz- Jeghers Syndrome
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Peutz-Jeghers Syndrome (PJS)

- **History:**
  - 1921: Described by Dr. Jan Peutz
  - 1949: Dr. Harold Jeghers credited with definitive descriptive reports through his publication
  - 1954: Dr. Andre Bruwer introduced the eponym
- **Inheritance:** autosomal dominant
  - Variable phenotypic manifestations
- **Cause:** germline mutation in tumor suppressor serine/threonine kinase (STK11/LKB1) gene
  - Chromosome 19 p13.3

- **Incidence:** 1:8300 – 200,000 live births
- **Presentation:** adolescence to early adulthood
- **Characteristics:**
  - Polyp type: Hamartomatous
  - Mucocutaneous involvement: in 95% of cases
    - Perioral region (crosses the vermilion border, 94%)
    - Buccal mucosa (66%)

- **Evaluation:**
  - Labs: CBC, iron study, FOBT, cancer antigen
  - Imaging/studies: CT, EGD/colon, capsule endoscopy
  - Referral to specialists

<table>
<thead>
<tr>
<th>Organ affected</th>
<th>Relative Risk (RR) compared to public</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine</td>
<td>520</td>
</tr>
<tr>
<td>Stomach</td>
<td>96</td>
</tr>
<tr>
<td>Pancreas</td>
<td>132</td>
</tr>
<tr>
<td>Colon</td>
<td>84</td>
</tr>
<tr>
<td>Esophagus</td>
<td>57</td>
</tr>
<tr>
<td>Ovary/breast</td>
<td>27/15.2</td>
</tr>
</tbody>
</table>

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Lynch Syndrome

- **History:**
  - 1966: characterized by Dr. Henry T. Lynch
  - 1984: “Lynch syndrome” coined by colleagues
  - 1985: “HNPCC” coined by Dr. Lynch
- **Inheritance:** Autosomal dominant trait
- **Cause:** DNA mismatch repair of genes
  - MLH1, MSH2, MSH6, or PMS2
- **Characteristic:**
  - Accelerated cancer progression (2-3 yr vs 8-10 yr)

Pedigree

- Lynch Family Pedigree
  - MLH1 L55SR
  - Variance of Unknown Significance
  - Amsterdam II Criteria
    - THREE cases with cancer, one 1st degree relative, two generations involved
    - CHILD syndrome: child born < 45 yr
Lynch Syndrome

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Juvenile Polyposis Syndrome

- Most common type of pediatric GI polyp
- Inheritance: Autosomal dominant
  - BMPR1A, SMAD4/DPC4, or PTEN genes
- Presentation: rectal bleeding
- Diagnostic Criteria:
  - Multiple (>3-10) juvenile colorectal polyps
  - Juvenile polyps throughout the GI tract
  - Any # of juvenile polyps with a family hx of juvenile polyposis
- Pathology: hamartomatous polyp

Genetics and Polyps

Adenomatous polyposis coli (APC) Gene

- Tumor suppressor gene
- Located on chromosome 5q21
- Localized in 1987...cloned in 1991
- Functions:
  - Scaffolding protein (affects cell adhesion/migration)
  - Inhibits progression of cells from G0/G1 to S phase
  - Promotes chromosomal stability
- Mutation results in a truncated/nonfunctional protein
MYH associated polyposis (MAP)

- Also known as MUTYH
- Autosomal recessive
- Base excision repair gene
- MUTYH encodes DNA repair enzyme MYH glycosylase
- Located on chromosome 1p34.3-p32.1
- No multigenerational family hx of polyps/colon cancer

American Gastroenterological Association (AGA)

Indications:
- Confirm FAP dx
- Presymptomatic testing for at risk members (10 yr or older)
- Confirm dx of AFAP in pt w/ >20 adenomas
- Test pt older than 10 yr at risk for AFAP

**POLICY STATEMENTS FOR HEREDITARY CRC AND GENETIC TESTING**
American Society of Clinical Oncology (ASCO)

Indications:
- Individual has personal or family history features suggestive of genetic cancer condition
- Test can be adequately interpreted
- Results will aid in diagnosis or influence medical/surgical management of patient or family members at hereditary risk of cancer

Testing Kids for Cancer Susceptibility
- Consider availability of evidence-based risk reduction strategies and probability of developing malignancy in childhood
- Scope of parental authority encompasses right to decide for/against testing
- Geneticist should be child's advocate

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Are We Asking the Right Questions?

Cancer Risk Assessment from family history: Gaps in primary care practice

- Objective: Determine if adequate amount of family history is collected/recorded by FP to appropriately identify pts at increased risk for cancer
- Study Design: retrospective chart review
  - 500 charts (pt 40-60 yrs old)
- Outcomes measured:
  - Family hx taking: initial/date, updated data, +/- genogram
  - Cancer features: state +/- famhx cancer, colon polyps (+: note relative affected, site, age of dx/death)

Results

<table>
<thead>
<tr>
<th>Documentation in charts reviewed for each question n=500</th>
<th>Findings n= (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Record of family hx of cancer (+/-)</td>
<td>276 (55%)</td>
</tr>
<tr>
<td>+ family hx of cancer</td>
<td>215 (43%)</td>
</tr>
<tr>
<td>Site of cancer</td>
<td>440 (88%)</td>
</tr>
<tr>
<td>Specific relative identified</td>
<td>460 (92%)</td>
</tr>
<tr>
<td>[1st (51%) 2nd (37%)]</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>40 (8%)</td>
</tr>
<tr>
<td>Age at death</td>
<td>95 (19%)</td>
</tr>
<tr>
<td>Mention of family hx of polyps</td>
<td>7 (1.4%)</td>
</tr>
<tr>
<td>Positive for polyps</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Age at diagnosis of polyps</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Updated family history information</td>
<td>175 (35%)</td>
</tr>
</tbody>
</table>

Conclusion: Quantity and type of family hx recorded is not adequate to fully assess familial risk.

Survey: 2011 American Society of Clinical Oncology Gastrointestinal Cancer Symposium

<table>
<thead>
<tr>
<th>How Frequently do you ask new pts to provide</th>
<th>Entire Cohort (%)</th>
<th>Oncologists (%)</th>
<th>GI (%)</th>
<th>Onc vs GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A medical history?</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>Not significant</td>
</tr>
<tr>
<td>A FHX of cancer among 1st degree relatives?</td>
<td>89.5</td>
<td>92</td>
<td>96</td>
<td>P=0.913</td>
</tr>
<tr>
<td>A FHX of cancer among 2nd degree relatives?</td>
<td>45.3</td>
<td>50</td>
<td>43</td>
<td>P=0.790</td>
</tr>
<tr>
<td>Age @ dx of relatives w/ cancer?</td>
<td>69.8</td>
<td>58</td>
<td>67</td>
<td>P=0.014</td>
</tr>
<tr>
<td>A FHX of polyps in the GI tract?</td>
<td>26.7</td>
<td>16</td>
<td>61</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

Table: Percentage of Physicians Who “Very Frequently” Ask New Patients to Provide a Family Hx of Cancer and Polyps in GI Tract
Survey Conclusions

• 264 MDs from University of Pennsylvania School of Medicine
• Gastroenterologists outperform Oncologists:
  – in assessing pt risk for inherited colorectal cancer syndromes
  – refer pt for genetic counseling 73.9% vs 36.8 % (P=0.008)
• No detailed 3 generation FHX obtained
• EDUCATION about disease and resources

Colorectal Cancer Surveillance Behaviors Among Members of Typical and Attenuated FAP Families

• Cross Sectional Study (1/2000-12/2003)
• Participants: enrolled in University of Utah based hereditary CRC registry or 1st degree relative
• Study Size: 150 participated from 429 potentially eligible
• Procedure: 45 min computer assisted telephone interview

Measures

• Sociodemographics:
  – Age, sex, health insurance status, reimbursement for CRC surveillance
• Psychosocial Factors:
  – Recall on advise of getting regular screening
  – Perceived relative risk for CRC
• Clinical Factors:
  – Disease status, prior genetic counseling, APC mutation status
• Colonoscopy Utilization
  – Primary outcome was endoscope surveillance

Outcomes

• Risk Perception:
  – Pt believed avg or low risk of CRC less likely to have scope (p=0.01)
• Dxed FAP/AFAP pts more likely to report genetic counseling vs at-risk FAP/AFAP
  – 50%/58% vs 31%/37%
• Use of CRC surveillance test low
  – FAP: affected 52% and at risk 46%
  – AFAP: affected 58% and at risk 33%

Roadblocks from a Family Perspective

• Insufficient knowledge of respective family’s history
• Incorrect risk status perception
• Lack of interest in meeting more MDs
• Clinics out of town
• Monetary constraints
  – Not wanting to pay additional co-pay
  – Insurance reimbursement
  – No insurance

Physician’s Perspective

• Incomplete information of patient family history
• Limited communication among family members
• Lack of patient understanding the consequences of noncompliance
• Time constraints of a clinical practice
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Summary

- Families affected with polyposis syndromes
- Onset of communication is variable
  - Primary care
  - Specialty
- Resources: Utilized correctly and timely manner
- Registry
- Education to the families and updates to medical colleagues

THANK YOU