Polyps in Pediatrics: Roadblocks to Early Intervention
Sonal Desai, MD
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Grand Rounds

Conflict of Interest
• I have no disclosures to report at this time.

Goals of Presentation
• Understand 3 various Polyposis Syndromes
• Diagnosis, management, and surveillance
  - Familial Adenomatous Polyposis
  - Peutz-Jeghers Syndrome
  - Lynch Syndrome (HNPCC)
  - Juvenile Polyposis
• Identify factors inhibiting early intervention for potential FAP/AFAP families
• Strategize a plan to overcome roadblocks

Case 1
• 15½ 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 1
• Physical Exam: +FOBT, rest unremarkable
• Labs: normal CBC, FAP 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)
**Colonoscopy**

**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

**Age of Presentation**

<table>
<thead>
<tr>
<th>Hereditary Polyp Path</th>
<th># of polyps</th>
<th>Colorectal CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg age of onset in FAP (hereditary adenomatous polyposis)</td>
<td>16 yrs</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Avg age of onset in AFAP (adenomatous familial adenomatous polyposis)</td>
<td>20-25 yrs</td>
<td>&lt;100</td>
</tr>
<tr>
<td>MAP (adenomatous polyposis)</td>
<td>46 yrs</td>
<td>10-100</td>
</tr>
</tbody>
</table>

**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%

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

**Variants of FAP**

- **Gardner Syndrome**
- **Tartot Syndrome**
- **Hereditary Desmoid Disease**

**Management Options**

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

**Medical Interventions**

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

**Spigelman Staging**

**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, Tarkot Syndrome, Hereditary Desmoid Disease*
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 fetoprotein
  - Normal bilirubin, LFT, and thrombocytosis

↓ expression of APC gene is associated with ↑ expression of β catenin

<table>
<thead>
<tr>
<th>Study</th>
<th>Size of study (n)</th>
<th>APC mutation (n)</th>
<th>β catenin mutation (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurahasi et al</td>
<td>11</td>
<td>8</td>
<td>Not tested</td>
</tr>
<tr>
<td>Oda et al</td>
<td>13</td>
<td>8</td>
<td>Not tested</td>
</tr>
<tr>
<td>Koch et al</td>
<td>52</td>
<td>0</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Wei et al</td>
<td>12</td>
<td>12</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Jeng et al</td>
<td>9</td>
<td>8</td>
<td>8 (89%)</td>
</tr>
</tbody>
</table>

This review suggests the alterations in the APC/β catenin pathways contributes to the pathogenesis of hepatoblastoma.

Evaluation for Hepatoblastoma

- Family History for FAP
- Labs:
  - Alpha fetoprotein, LFT, bilirubin, CMP, CBC
- Imaging:
  - Abdominal ultrasound
- Further investigation and specialty referral

Peutz-Jeghers Syndrome (PJS)

- History:
  - 1921: Described by Dr. Jan Peutz
  - 1949: Dr. Harold Jeghers credited w/ definitive descriptive reports thru 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

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### Lynch Syndrome

**History:**
- 1966: characterized by Dr. Henry T. Lynch
- 1984: “Lynch syndrome” coined by colleagues
- 1985: “HNPPC” 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)

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### Surveillance I

**Familial Adenomatous Polyposis**
- Starting at age 10 yrs
- Yearly EGD/colonoscopy
- Annual thyroid palpation
- Hepatoblastoma:
  • Q.4-6 months: abdo exam
  • Yearly: AFP, u/s abdo
- Post colectomy:
  • Flex sigmoidoscopy/EGD
Surveillance II

<table>
<thead>
<tr>
<th>Lynch Syndrome</th>
<th>Peutz-Jeghers Syndrome</th>
</tr>
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<tbody>
<tr>
<td>Starting 10 yr earlier than youngest affected family member</td>
<td></td>
</tr>
<tr>
<td>Yearly EGD/colonoscopy</td>
<td></td>
</tr>
<tr>
<td>Evaluation of extra-intestinal manifestations</td>
<td></td>
</tr>
<tr>
<td>Starting at age 10 yrs</td>
<td></td>
</tr>
<tr>
<td>Capsule endoscopy or enteroscopy if available</td>
<td></td>
</tr>
<tr>
<td>Yearly pelvic u/s in females</td>
<td></td>
</tr>
<tr>
<td>Evaluation for extra-intestinal manifestations</td>
<td></td>
</tr>
<tr>
<td>Look out for signs of obstruction</td>
<td></td>
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</tbody>
</table>

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

GENETICS AND POLYPS

Adenomatous polyposis coli (APC) locus and leading to the development of colorectal adenomas.
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

American Society of Clinical Oncology (ASCO)

- Indications:
  - Individual has personal or family hx features suggestive of genetic cancer condition
  - Test can be adequately interpreted
  - Results will aid in dx or influence medical/surgical management of pt or family members at hereditary risk of cancer
- Testing Kids for Cancer Susceptibility
  - Consider availability of EBM 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

Goals of Presentation

- Understand 3 various Polyposis Syndromes
  - Familial Adenomatous Polyposis
  - Peutz-Jeghers Syndrome
  - Lynch Syndrome (HNPCC)
  - Juvenile Polyposis
- Identify factors inhibiting early intervention for potential FAP/AFAP families
- Strategize a plan to overcome roadblocks
Are We Asking the Right Questions?

Cancer Risk Assessment from family history: Gaps in primary care practice
Sifri et al. JFP online, October 2002. vol 51, no. 10.

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 +/- fmhx 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%) [1st (51%) 2nd (37%)]</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>76</td>
<td>87</td>
<td>P=0.014</td>
</tr>
<tr>
<td>A FHx of polyps in the GI tract?</td>
<td>26.7</td>
<td>18</td>
<td>61</td>
<td>P&lt;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
- Monetary constraints
  - No wanting to pay additional co-pay
  - Insurance reimbursement
  - No insurance

Physician’s Perspective

- Incomplete knowledge of family history
- Limited communication with family members
- Lack of understanding the consequences of noncompliance
- Time constraints in clinical practice

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- Identify factors inhibiting early intervention for potential FAP/AFAP families
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Summary

- Families affected with FAP/AFAP
- 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