

A Patient with Interstitial 5q21 Deletion, Familial Adenomatous Polyposis, Dysmorphic Features, and Profound Neurologic Dysfunction

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Abstract

Familial adenomatous polyposis (FAP) is a hereditary autosomal dominant cancer syndrome, results from germ line mutation or deletion of the Adenomatous Polyposis Coli (APC) gene on chromosome 5q21. Patients with FAP suffer from multiple polyps mainly at the colorectal region as well as other parts of the gastrointestinal tract, which has propensity to transform into carcinoma. FAP has also been well described in association with various syndromic extra-gastrointestinal manifestations. Less commonly, patients with FAP present with varying degrees of cognitive dysfunction and developmental delay, though the reason for the association is unclear. Herein, we report the case of a male patient born with an interstitial deletion of chromosome 5q, 46,XY, del(5)(q14q23), presenting with familial adenomatous polyposis (FAP), profound developmental delay, cognitive dysfunction, and multiple congenital anomalies including talipes equinovarus, agenesis of the corpus callosum, and dysmorphic facial features.

Key words: Adenomatous Polyposis Coli, Child, Chromosome 5q21.

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1- INTRODUCTION

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant disease, which results in mutation of APC gene. Multiple adenomatous polyps develop in the epithelial lining of large intestine and rectum. These polyps tend to increase with age. These polyps develop as benign initially but later transform into malignant polyps if left untreated. The patient may present with mild to moderate anemia from bleeding polyps; weight loss from malignancy; constipation or diarrhea; congenital hypertrophy of the retinal pigment epithelium; jaw cysts; sebaceous cysts or osteoma.

2- CASE REPORT

The patient was born at 38 weeks gestation and weighed 3,639 grams. His Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. His mother was a 31 years old Caucasian G2P0 of Irish and English descent, the father was 35 years old and of German and Italian ancestry. The relationship was non consanguineous, and both parents are in good health. Our patient has no siblings and there is no history of congenital malformations or cognitive dysfunction in the extended family. The mother was not exposed to any known teratogens or toxins during this pregnancy. The pregnancy was complicated by decreased fetal movement and ultrasound discovered bilateral hydronephrosis and oligohydramnios. Soon after birth our patient required multiple surgical procedures for bilateral hydronephrosis, right hydrocele repair, and bilateral club foot correction and casting. He was found to have spontaneous nystagmus. Also, he has a high arched palate, anteverted nostrils, a broad forehead, and hypertelorism. At 28 months of age he was admitted to the hospital for complex febrile seizures. Magnetic resonance imaging (MRI) showed partial agenesis of the corpus callosum, grey

matter heterotopias, and delayed myelination of white matter. An electroencephalogram (EEG) at this time showed severe diffuse encephalopathy. As he aged, he demonstrated significant cognitive, gross and fine motor, social, and language delay, and later developed eustachian tube dysfunction and juvenile nasopharyngeal angiofibroma.

The patient began colonoscopy screening at the age of 5 years old. A positive fecal blood test prompted colonoscopy at age 11 and revealed multiple benign adenomatous polyps on the left side of the colon. Subsequent upper endoscopy uncovered multiple adenomatous polyps in the gastric mucosa, but sparing the small bowel. At age 14, colonoscopy revealed multiple (>100) benign appearing 26 mm adenomatous polyps in the rectum, sigmoid colon, descending colon, and splenic flexure. Endoscopy revealed multiple 28 mm pedunculated and sessile polyps in the stomach, 26 mm polyps throughout the duodenum, and diminutive pedunculated and sessile polyps in the jejunum. At present, our patient is twenty four years old and remains free of colon carcinoma. His family has opted against the use of medical treatment, opting instead for herbal remedies against the recommendations of his medical team.

3- DISCUSSION

Familial adenomatous polyposis (FAP) is an autosomal dominant disease that occurs in the population with an incidence of approximately 1 in 8,000. FAP is caused by germ line mutation or deletion of the tumor suppressor gene adenomatous polyposis coli (APC) located on chromosome 5q21 (1, 2). One study estimates that gene mutations comprise 85% of cases while deletions make up the remaining 15% (3). Approximately 75% of these cases are thought to be inherited while 25% are de novo mutations (4). FAP shows near complete penetrance (1) and

affected patients are predisposed to the development of hundreds to thousands of adenomatous polyps that most frequently involve the colon, but can be found throughout the gastrointestinal tract.

Polyps tend to develop in the second or third decade of life with a mean age of 16 years old (5). These polyps inevitably lead to the development of carcinoma following the well detailed adenoma to carcinoma sequence (6) and in accordance with Knudson's two hit hypothesis (7). If left untreated, the lesions progress to cancer by the third decade. In addition to the characteristic colonic lesions, patients with FAP frequently develop lesions in other sites along the gastrointestinal tract below the esophagus. Most commonly these lesions occur in the duodenum, but they can also be found in the stomach, pancreatic ampulla, and elsewhere.

A review of 20 studies between 1977 and 1996 found the incidence of duodenal adenomas in patients with FAP to be 61%, and gastric adenomas in these patients to be 41%. Gastric polyps are most commonly found in the fundus or the body and may number in the hundreds (8). Despite the high incidence of extra colonic lesions in patients with FAP, they rarely are found to be neoplastic (9).

In a study of 1,255 patients with FAP from 10 groups, the incidence of upper gastrointestinal cancer was 4.5% (57/1255) (10). The most common site was the duodenum (29/1255), followed by the ampulla (10), stomach (7), jejunum (5), pancreas (3), bile duct (2), and ileum (1). FAP should be suspected in any patient with >100 colonic polyps. Current American Gastrointestinal Association (AGA) guidelines (11) recommend genetic testing of an affected family member, and if conclusive, other at risk family members who may have inherited the mutation. Absence of a mutation must be considered inconclusive. Flexible sigmoidoscopy or colonoscopy should be offered every 12

months beginning at age 10 or 12. Upper gastrointestinal endoscopy for screening of gastric and duodenal polyps should be performed as well (12-13). Once polyps become too numerous to count, endoscopic surveillance becomes unreasonable, or high grade dysplasia or carcinoma is confirmed histologically, treatment involves colectomy with ileorectal anastomosis or total proctocolectomy with ileal pouch-anal anastomosis, depending on the involvement of the rectum (14).

Phenotypic variations of FAP were described to include the presence of polyposis and extra gastrointestinal involvement. Gardner syndrome was described in the 1950s to elucidate the association between chromosome 5q based colonic polyposis and osteomas, fibromas and epidermal cysts (15). Turcot's syndrome describes the findings of malignant tumors of the central nervous system in the context of FAP (16). Furthermore, there have been disorders associated with chromosome 5q deletion with no gastrointestinal involvement. For example, patients with the 5q variant of myelodysplastic syndrome are thought to have favorable outcomes due to the up regulation of p53 in the erythroid lineage (17-18). Also, there have been several case reports of 5q21 dysfunction and varying degrees of cognitive dysfunction and developmental delay (19-24).

We report the case of a male patient who was born with an interstitial deletion of chromosome 5q, 46, XY, del(5)(q14q23). The patient also reported colonic and upper gastrointestinal lesions, and had multiple dysmorphic features, multiple congenital defects, and profound cognitive dysfunction. The cause and effect of mutation or deletion of the APC gene on chromosome 5q21 has been well described. Less is known about the association between this genetic aberration and the extra gastrointestinal lesions found in FAP variants such as Gardner's

syndrome and Turcot's syndrome. Even more unclear is the link between 5q21 dysfunction and mental functioning. This patient demonstrates the characteristic colonic findings with additional, less common findings including dysmorphic features, agenesis of the corpus callosum, and cognitive dysfunction. This case underscores the possible association of chromosome 5q21 to other developmental anomalies. In summary, patients with known deletion or mutation of chromosome 5q should be surveilled closely for any signs of developmental delay or other neurologic deficits.

4- CONCLUSION

Prior to reaching to advance stages of colorectal cancer, any polyps in patients with FAP should be rule out for malignancy. It is very important that these patients with known deletion or mutation of chromosome 5q should also be closely monitor for the presence of any signs of developmental delay, cognitive dysfunction or other neurologic deficits.

5- CONFLICT OF INTEREST: None.

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