Complexities in Genetic Counseling: Testing Minors for Adult-onset Cancers and Unusual Findings

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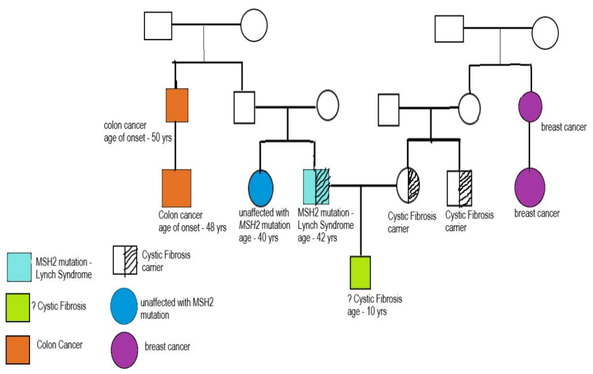
ABSTRACT

- **Background**: Lynch syndrome is a hereditary disorder caused by the DNA mismatch repair (*MLH1, MSH2, MSH6, PMS2,* and *EPCAM*) genes, considerably elevating the risk of developing various cancers, especially colorectal cancer.
- **Case Presentation**: A 42-year-old male with a known case of colon cancer and a family history of the same disease underwent pre-test genetic counseling. Immunohistochemistry showed loss of *MSH2* and *MSH6* expression. Lynch syndrome gene panel test revealed a pathogenic variant in *MSH2* (c.1216 C>T; p.Arg406Ter) gene.
- **Genetic counseling and family testing**: During the pre-test counseling, a detailed family pedigree and medical history were evaluated, emphasizing the importance of informed decision-making regarding genetic testing. The patient consented to the Lynch syndrome panel testing, which confirmed a heterozygous pathogenic variant in *MSH2* (c.1216 C>T; p.Arg406Ter) gene. Concerns later were raised regarding the potential cancer risk to his 10-year-old child, especially given the unusual findings of abdominal migraine. However, challenges were present in testing asymptomatic minors for adult-onset cancer. With consideration of few reported cases in pediatric lynch syndrome and a family history of cystic fibrosis, whole exome sequencing (WES) was offered, which did not report the *MSH2* gene variant. However, WES identified compound heterozygous mutations in the *CFTR* gene (c.1521_1523del; p.Phe508del and c.1291A>G; p.Ser431Gly). The identification of cystic fibrosis in child, with possible association to the unique presentation of abdominal migraine, underscores the need for regular follow-ups. During the subsequent session, at-risk family members were offered testing for Lynch syndrome. Also, the patient's wife underwent Hereditary Breast and Ovarian Cancer (HBOC) gene panel testing due to a family history of cancer on her side, which was negative.
- **Conclusion**: The case highlights the difficulties and intricacies of conducting genetic testing for hereditary cancers in minors. An analysis using whole exome sequencing discovered a potential link between abdominal migraine and cystic fibrosis stemming from atypical observations.



BACKGROUND

- Lynch syndrome is an autosomal dominant condition caused by a heterozygous variation in one of the DNA mismatch repair (MMR) genes that pre-disposes individuals to early onset colorectal cancers and other malignancies. [4]
- Lynch syndrome is generally considered an adult-onset disorder, with malignancy rarely manifesting in childhood.
- About 2-4% of colorectal cancers and 0.8-1.4% of endometrial cancers can be attributed to Lynch syndrome.

Cancer Type	General population risk	Lynch syndrome (MLH1 and MSH2 heterozygotes)	
		Risk	Mean age of onset
Colon	5.5%	52-82%	44-61 years
Endometrium	2.7%	25-60%	48-62 years
Stomach	< 1%	6-13%	56 years
Ovary	1.6%	4-12%	42.5 years
Hepatobiliary tract	< 1%	1.4-4%%	Not reported
Urinary tract	< 1%	1-4%	~55 years
Small bowel	< 1%	3-6%	49 years
Brain/central nervous system	< 1%	1-3%	~50 years
Sebaceous neoplasms	< 1%	1-9%	Not reported

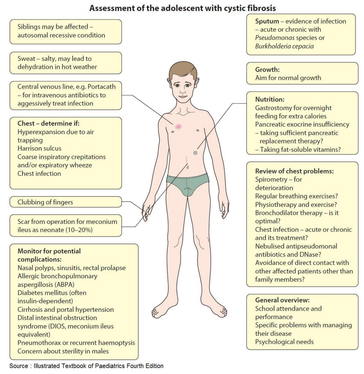
Comparative risks of cancer types of general population and patients with *MLH1* and *MSH2* mutation, and mean age of onset of each cancer with patients with *MLH1* and *MSH2* mutations. [5]

CASE PRESENTATION

- A 42-year-old man with colon cancer consulted for pre-test genetic counselling before having genetic testing. There is a history of colon cancer in the proband's paternal uncle and paternal cousin brother.
- Following extensive genetic counselling, the proband underwent lynch syndrome panel testing, which identified a pathogenic variation in the *MSH2* gene (c.1216C>T; p.Arg406Ter).
- The proband's 10-year-old son has a history of a rare feature, abdominal migraine (chronic pain). After googling, the proband discovered a few cases of paediatric lynch syndrome and sought genetic counselling to rule out the cause of abdominal migraine considering reported cases of paediatric lynch syndrome and family history of lynch syndrome.
- However, there are ethical concerns around testing minors for adult-onset cancers. Additionally, the proband's wife provided a history cystic fibrosis heterozygosity in her family.
- After discussing with a medical oncologist about the unusual abdominal migraines, reported cases, family history of lynch syndrome, and history of cystic fibrosis heterozygosity, whole exome sequencing (WES) was offered for the proband's son.
- The WES did not detect the familial *MSH2* variant. However, the child was found to have a compound heterozygous mutation in the *CFTR* gene (c.1521_1523del; p.Phe508del and c.1291A>G; p.Ser431Gly), which was inherited from his parents.
- Following this, testing was offered to additional family members for lynch syndrome with comprehensive pre-test counselling and consent. The proband's wife also provided a family history of breast cancer on her side and was apprehensive about testing. Her test results for hereditary breast and ovarian cancer panel were negative.

GENETIC COUNSELLING & FAMILY TESTING

- Initially, the proband underwent pre-test genetic counselling, during which he was provided with detailed information about the genetic tests, their limitations, potential results, and the importance of testing. Subsequently, the proband chose to undergo lynch syndrome gene panel testing.
- During the post-test counselling session, the proband was briefed on the report, potential risks to his offspring, and testing for at-risk family members.
- The proband and his wife were apprehensive to test their 10-year-old son in view of a few reported cases of paediatric lynch syndrome and a history of abdominal migraine in him. However, there were challenges in testing an asymptomatic minor for adult-onset cancers. Genetic testing for adult-onset conditions generally should be deferred until adulthood or until an adolescent interested in testing has developed mature decision-making capacities.
- Whole exome sequencing (WES) was later offered to the child, with synchronized discussion with a medical oncologist due to the rare presentation of abdominal migraines, history of lynch syndrome, cystic fibrosis heterozygotes, and a few reported cases of paediatric lynch syndrome.
- Individuals with bronchiectasis, allergic bronchopulmonary aspergillosis, asthma, chronic rhinosinusitis/nasal polyposis, atypical mycobacterial infections, and aquagenic palmoplantar keratoderma are more likely to be carriers of a *CFTR* pathogenic variant. [6]
- WES revealed that the child did not inherit the *MSH2* gene mutation but was found to have a compound heterozygous mutation in the *CFTR* gene (c.1521_1523del; p.Phe508del; c.1291A>G, p.Ser431Gly).



Assessments of adolescents with cystic fibrosis [8]

- The *CFTR* variant (c.1521_1523del; p.Phe508del) is a common pathogenic variant and is present in the proband's son and his wife.
- *CFTR* variants are linked to varying disease severity and reduced penetrance. Cystic fibrosis screening can also identify the 5T/7T/9T variants in the *CFTR* gene. While not causing disease on their own, these variants may be associated with milder forms of disease and male infertility in individuals who are carriers of certain *CFTR* gene mutations.[7]
- The child did not exhibit classic symptoms of cystic fibrosis, and his sweat chloride test results were normal.
- Most gastrointestinal symptoms of Cystic Fibrosis (CF) present with localized abdominal pain along with other symptoms.
- A study conducted by the CF Centre at Jena University collected data on Abdominal symptoms in CF patients over the last three months, as shown in table 1. The most common symptoms were lack of appetite (99%) and loss of taste (91%), followed by abdominal pain (79%), flatulence (78%), and abdominal distention (63%). Interestingly, children reported experiencing more abdominal pain than adults (87% vs. 70%), while adults more frequently reported abdominal distention (79% vs. 51%) and heartburn (61% vs. 22%).
- However, in this case, the presentation is milder. It can be suggested that the rare presentation of abdominal migraine might be linked to cystic fibrosis. Regular follow-ups and monitoring of new symptoms will be necessary.

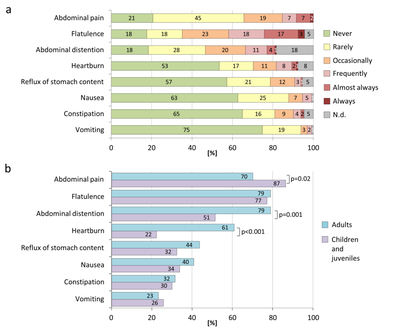


Table 1 - Frequencies of abdominal symptoms in CF patients of all ages (Fig a) and in children compared with adults (Fig b) [1]

CONCLUSION

- This case showcases the intricate relationship between genetic predisposition and disease presentation. It highlights the significance of correlating the rare presentation of abdominal migraine with cystic fibrosis, challenges in minor testing, comprehensive genetic testing strategies, and appropriate genetic counseling for accurate diagnosis and risk assessment. This case also shows how important it is for people to get advice about genetic study.

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