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MSH6 Mutation and Early-Onset Multicentric Glioma: A Paediatric Case Report of Lynch Syndrome

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ABSTRACT

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), arises from mutations in DNA repair genes such as MLH1, MSH2, MSH6, and PMS2. These genetic alterations impede the body's ability to mend DNA damage, elevating the likelihood of various cancers, particularly colorectal and endometrial cancers. Individuals affected by Lynch syndrome are at an increased lifetime risk of developing colorectal cancer, as well as other types including endometrial, ovarian, stomach, small intestine, hepatobiliary tract, urinary tract, brain, and skin cancers. Diagnosis typically entails genetic testing, followed by routine screenings and vigilant surveillance to catch cancer at its earliest stages. Management strategies may involve frequent colonoscopies, endometrial biopsies, and other screening procedures tailored to the specific genetic mutation and familial background of every one. Some individuals may choose risk-reducing surgeries such as prophylactic removal of the colon, uterus, or ovaries. Genetic counseling is paramount in aiding individuals to comprehend their risks, make well-informed decisions regarding testing, and devise personalized plans for screening and prevention. This overview highlights the multifaceted challenges and complications associated with Lynch syndrome, emphasizing the importance of comprehensive management strategies and support systems for affected individuals and families.

INTRODUCTION:

Lynch syndrome, also referred to as hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited genetic disorder associated with an elevated susceptibility to specific types of cancers, notably colorectal and endometrial cancer. [1] It results from inherited mutations in genes responsible for DNA repair, most frequently involving the MLH1, MSH2, MSH6, and PMS2 genes. These mutations hinder the body's capacity to mend DNA damage, consequently heightening the probability of cancer development. Inheritance of Lynch syndrome follows an autosomal dominant pattern, indicating that an affected individual carries a 50% likelihood of transmitting the mutated gene to their offspring. Individuals with Lynch syndrome tend to manifest cancer at an earlier age compared to those unaffected by the condition and face an escalated risk of developing multiple cancers over their lifespan. Managing Lynch syndrome entails regular screenings and vigilant surveillance to detect cancer in its nascent stages, alongside genetic counseling and consideration of risk-mitigating strategies like prophylactic surgery.[3]

Aetiology of Lynch syndrome

Lynch syndrome predominantly arises from hereditary mutations occurring in specific genes responsible for DNA repair. Among the most implicated genes linked to Lynch syndrome are:

1. MLH1 (Mut L Homolog 1)
2. MSH2 (Mut S Homolog 2)
3. MSH6 (Mut S Homolog 6)
4. PMS2 (Post meiotic Segregation Increased 2)

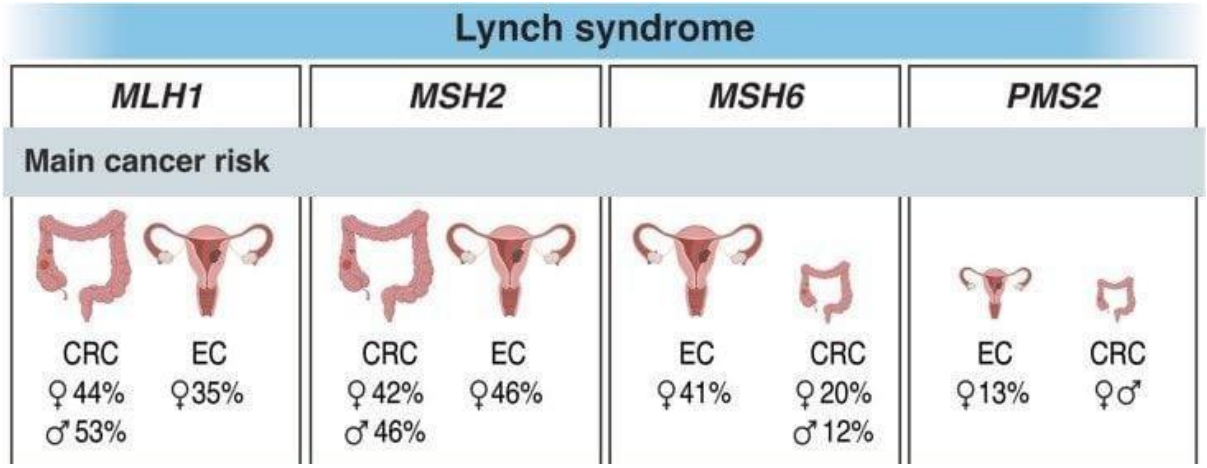

Fig 1. Different genes in Lynch syndrome [3]

These genes encode proteins crucial for DNA mismatch repair (MMR), a process vital for preserving the accuracy of the genetic code by rectifying errors during DNA replication. Mutations in these genes disrupt MMR, resulting in a condition called microsatellite instability (MSI), thereby heightening susceptibility to certain cancers. Approximately 70-80% of individuals diagnosed with Lynch syndrome exhibit mutations in either the MLH1 or MSH2 genes, whereas mutations in MSH6 and PMS2 are less prevalent, each accounting for around 10-20% of cases. In rare instances, Lynch syndrome may also stem from mutations in other genes within the MMR pathway, such as EPCAM (EPCAM-MSH2) or MLH3, although these represent fewer common aetiologies.[4]

It's crucial to recognize that Lynch syndrome follows an autosomal dominant inheritance pattern, meaning an individual needs to inherit just one copy of the mutated gene from either parent to manifest the condition. Consequently, each child of an affected individual carries a 50% chance of inheriting the mutation.[5]

While Lynch syndrome predominantly results from inherited genetic mutations, sporadic mutations in these MMR genes can also occur spontaneously (de novo) rather than being passed down from a parent. Nevertheless, the majority of Lynch syndrome cases stem from inherited mutations transmitted through familial lines.

Epidemiology of lynch syndrome

Lynch syndrome's epidemiology encompasses its prevalence, incidence, associated cancers, and public health implications:

1. Prevalence: Lynch syndrome contributes to approximately 2-4% of colorectal cancers and 3-5% of endometrial cancers, though underdiagnosis suggests a potentially higher prevalence.

2. Incidence: Lynch syndrome is relatively rare, with an estimated incidence ranging from 1 in 250 to 1 in 2,000 individuals in the general population.

3. Age of Onset: Cancers linked to Lynch syndrome typically occur before age 55, with colorectal cancer potentially emerging in one's 20s or 30s.

4. Cancer Risk: Those with Lynch syndrome face significantly elevated risks of colorectal and other cancers, with lifetime risks of colorectal cancer reaching 70-80%. These cancers often manifest at a younger age compared to sporadic cases.

5. Hereditary Transmission: Lynch syndrome follows autosomal dominant inheritance, with a 50% chance of inheriting the mutated gene from an affected parent.

6. Diagnosis: Identification typically occurs around age 44 for colorectal cancer and age 46 for endometrial cancer, emphasizing the need for enhanced screening to improve early detection and intervention.

7. Public Health Implications: Identifying individuals with Lynch syndrome and implementing suitable screening and surveillance strategies can lead to earlier detection of cancers, potentially reducing associated morbidity and mortality.[6]

Pathophysiology of lynch syndrome

Normal DNA Mismatch Repair (MMR): Lynch syndrome manifests with mutations in MMR genes, notably MLH1, MSH2, MSH6, and PMS2, disrupting the typical operation of the MMR mechanism. These mutations can result in a loss of function or diminished activity of the MMR proteins encoded by these genes, resulting in microsatellite instability (MSI). This MSI heightens susceptibility to cancer by enabling the accumulation of mutations in crucial genes, contributing to various cancer types like colorectal, endometrial, ovarian, gastric, and urinary tract cancers.[7]

Evaluation:

Two methods used to screen for Lynch syndrome are immunohistochemical staining and microsatellite instability testing. *Immunohistochemical staining* examines protein expression

from mismatch repair genes in a tumor sample, with negative staining indicating potential mismatch repair deficiency. *Microsatellite instability* testing identifies variations in repetitive DNA sequences due to loss of mismatch repair activity. However, neither method alone is sufficient for diagnosing Lynch syndrome; germline mutation testing through DNA sequencing and large rearrangement analysis is required. Screening colonoscopies should begin at ages 20 to 25 for individuals with Lynch syndrome, followed by biennial screenings unless indicated otherwise by specific findings.[8]

Diagnostic criteria of lynch syndrome

Diagnosing Lynch syndrome entails a multifaceted approach, combining clinical criteria, tumour characteristics, and genetic testing. The Amsterdam criteria and Bethesda guidelines serve as standard frameworks for clinical diagnosis, while tumour testing for microsatellite instability (MSI) and immunohistochemistry (IHC) analysis of MMR proteins aid in identifying individuals warranting genetic testing. Here are the key diagnostic criteria for Lynch syndrome:

1. Amsterdam Criteria: These criteria were formulated to identify individuals and families with Lynch syndrome based on clinical presentations. The original Amsterdam criteria comprise:

- Presence of three or more relatives with Lynch syndrome-associated cancers (e.g., colorectal, endometrial, small bowel, ureter/renal pelvis cancers) across two successive generations.

- Diagnosis of at least one affected relative before the age of 50 and exclusion of Lynch syndrome in families with hereditary polyposis syndromes.

Subsequently, revised Amsterdam criteria (Amsterdam II) were introduced, incorporating extracolonic cancers associated with Lynch syndrome.[9]

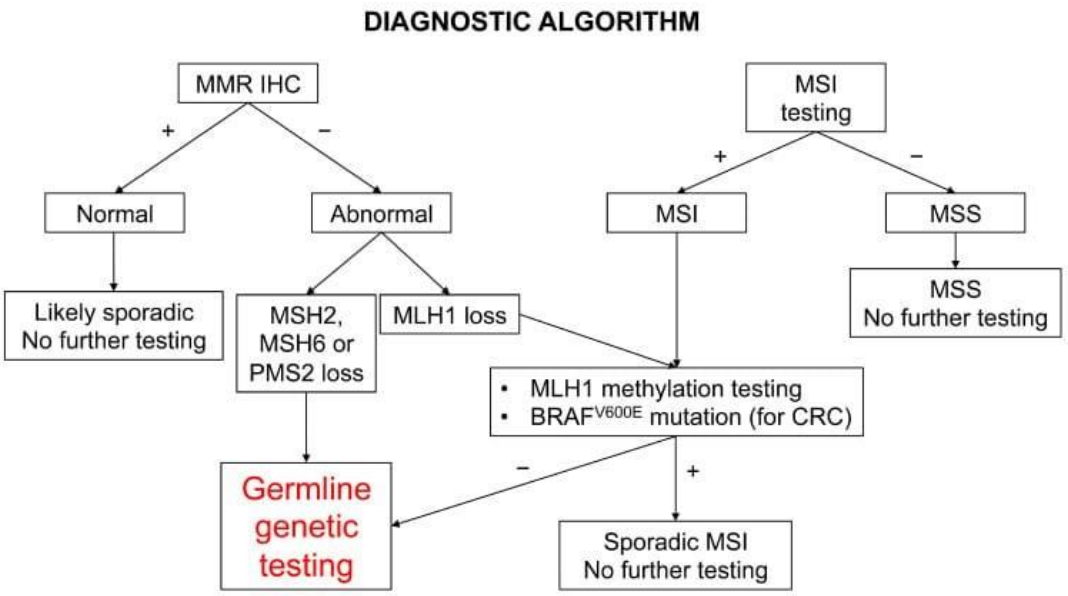

Fig. 2. Diagnostic logarithm of lynch syndrome [6]

Table 1: Revised Amsterdam and Bethesda criteria

Table 1: Amsterdam Criteria II	**Table 2: Revised Bethesda Guidelines for Colorectal Cancers for Microsatellite Instability Testing**
Criterion for identifying Lynch syndrome based on Amsterdam Criteria II involves the presence of at least three relatives with Lynch syndrome-associated cancers (colorectal, endometrial, small bowel, ureter, or renal pelvic cancer), meeting the following conditions:	Indications for microsatellite instability (MSI) testing in colorectal cancer (CRC) patients are outlined in the Revised Bethesda Guidelines as follows:
- One must be a first-degree relative of the other two.	- Diagnosis of CRC in a patient under 50 years of age.
- Affected individuals should span at least two successive generations.	- Presence of synchronous or metachronous colorectal tumours or other Lynch syndrome (LS)-associated tumours, irrespective of age.
- At least one diagnosis should occur before the age of 50 years.	- Diagnosis of CRC with the MSI-H phenotype in a patient under 60 years of age.
- Familial adenomatous polyposis must be ruled out.	- Diagnosis of CRC in a patient with at least one first-degree relative with an LS-associated tumour, with one cancer diagnosed before the age of 50 years.
- Histopathological examination must confirm the tumour diagnosis.	- Diagnosis of CRC in two or more first- or second-degree relatives with LS-associated tumours, regardless of age.

Investigations for diagnosing Lynch syndrome typically involve a comprehensive approach, incorporating clinical evaluation, tumour testing, and genetic analysis. Here are the main investigative procedures used:

1. Clinical Assessment:

- Family History: A thorough inquiry into familial cancer history is crucial to identify patterns suggestive of Lynch syndrome across multiple generations.

- Clinical Criteria: The Amsterdam criteria and Bethesda guidelines help evaluate if individuals or families meet clinical criteria indicative of Lynch syndrome.

2. Tumour Testing:

- Microsatellite Instability (MSI) Testing: This examines the stability of microsatellite sequences in tumour DNA. Lynch syndrome-associated cancers often display high-frequency microsatellite instability (MSI-H), detectable through PCR-based MSI testing.

- Immunohistochemistry (IHC): Analysis of mismatch repair (MMR) protein expression in tumour tissue can indicate deficient MMR function, suggestive of Lynch syndrome.[10]

3. Genetic Testing:

- Germline Genetic Testing: Analysis of peripheral blood or saliva samples identifies germline mutations in Lynch syndrome-associated genes like MLH1, MSH2, MSH6, PMS2, and EPCAM, commonly utilizing next-generation sequencing (NGS) techniques for comprehensive gene panel testing.

- Tumour DNA Testing: Inconclusive or unavailable germline testing may prompt tumour DNA testing to identify somatic mutations in MMR genes or other Lynch syndrome-associated genes.

4. Additional Investigations:

- Endoscopic Evaluation: Colonoscopy and other endoscopic procedures assess the colon, rectum, and other gastrointestinal sites for polyps or tumours.

- Gynaecological Assessment: Women with Lynch syndrome may undergo endometrial biopsies, pelvic ultrasounds, or other gynaecological evaluations to detect abnormalities in the endometrium or ovaries.[11]

- Imaging Studies: Modalities like computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound may survey for tumours in Lynch syndrome-affected organs.[12]

Risks and complications:

Complications associated with Lynch syndrome primarily involve increased cancer risks and related consequences:

- Colorectal Cancer: Heightened risk with potential complications like bowel obstruction, bleeding, and metastasis.

- Endometrial Cancer: Elevated risk in women with possible progression to metastatic disease.

- Other Associated Cancers: Increased susceptibility to various cancers, each with unique complications.

- Secondary Cancers: Greater likelihood of developing secondary cancers, necessitating careful surveillance.

- Psychological Impact: Diagnosis may lead to emotional distress, anxiety, and depression.

- Surgical Complications: Risk-reducing surgeries entail surgical risks and potential long-term consequences.

- Financial and Social Impacts: Management imposes financial burdens and affects social and occupational aspects of life.[13]

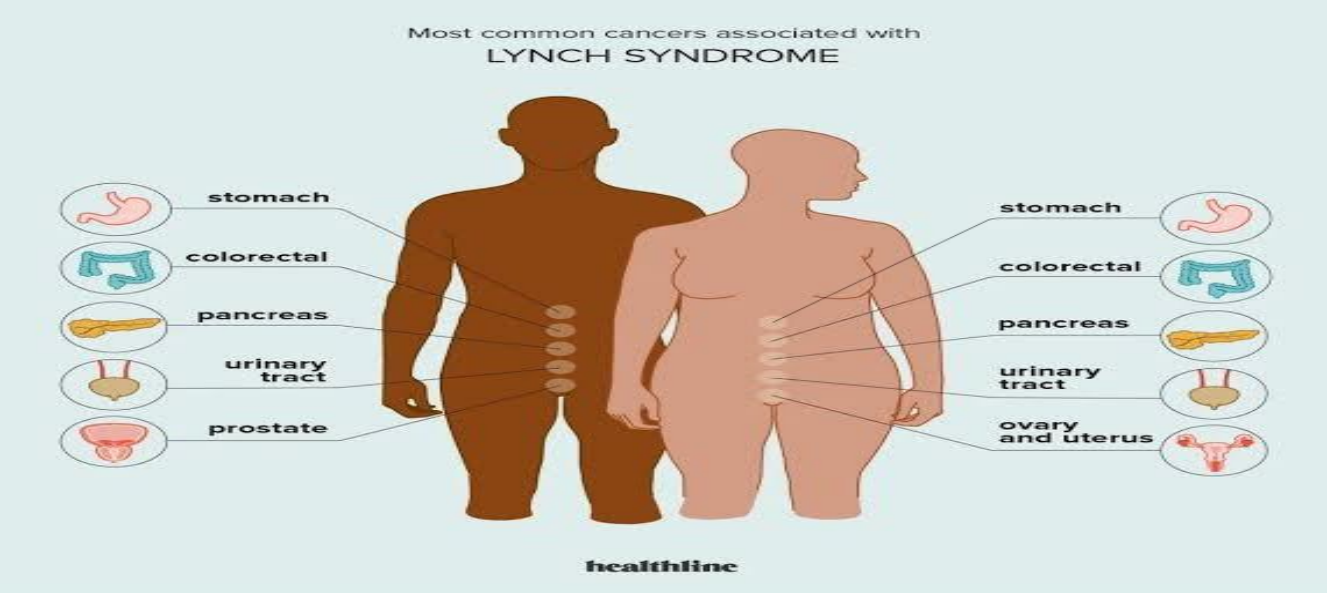

Fig 3. Most common cancers associated with lynch syndrome [8]

Differential diagnosis:

Several conditions resembling Lynch syndrome can lead to misdiagnosis based on clinical and genetic testing results:

1. Sporadic Colorectal Cancer:

- MSI or loss of MMR protein expression may be present.

- Lacks a strong family history and germline mutations in MMR genes.

2. Serrated Polyposis Syndrome (SPS):

- Characterized by multiple serrated polyps.

- Some cases may show MSI or MLH1 promoter methylation, but distinct diagnostic criteria differentiate it from Lynch syndrome.

3. Familial Colorectal Cancer Type X:

- Families with a significant colorectal cancer history.

- Lacks identifiable mutations in known Lynch syndrome genes and does not meet diagnostic criteria.

4. Polyposis Syndromes (e.g., FAP, MAP):

- Association with colorectal cancer, but distinct clinical features, genetic mutations, and management compared to Lynch syndrome.

5. Endometrial Hyperplasia and Endometrial Cancer:

- Lynch syndrome presents with these conditions, but they can also arise sporadically or due to other factors.

6. Other Hereditary Cancer Syndromes:

- Syndromes like hereditary breast and ovarian cancer or Li-Fraumeni syndrome may share features with Lynch syndrome, including an increased risk of certain cancers.[14]

Signs and symptoms of lynch syndrome

Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), is a genetic predisposition to certain cancers, notably colorectal and endometrial cancers. While Lynch syndrome typically lacks specific signs or symptoms, individuals affected by it may exhibit the following:

1. Symptoms of Colorectal Cancer:

- Alterations in bowel habits, such as diarrhoea, constipation, or stool narrowing
- Rectal bleeding or presence of blood in the stool
- Abdominal discomfort, cramps, or pain
- Unintended weight loss.

2. Symptoms of Endometrial Cancer:

- Irregular vaginal bleeding, including bleeding between menstrual cycles, heavy menstruation, or postmenopausal bleeding
- Pelvic discomfort or pain
- Unintended weight loss
- Vaginal discharge that is watery or tinged with blood.

3. Symptoms of Other Associated Cancers:

- Ovarian Cancer: Abdominal or pelvic pain, bloating, difficulty eating, urinary urgency or frequency
- Stomach Cancer: Indigestion, abdominal pain, nausea, vomiting, unexplained weight loss
- Urinary Tract Cancers: Haematuria (blood in the urine), urinary urgency or frequency, dysuria (pain during urination)
- Small Bowel Cancer: Abdominal pain, cramps, nausea, vomiting, changes in bowel habits

4. Family History:

- Lynch syndrome is characterized by a robust family history of certain cancers, particularly colorectal and endometrial cancers, spanning multiple generations. Affected individuals often have relatives diagnosed with cancer at an earlier age than sporadic cases.[15]

It is crucial to recognize that Lynch syndrome may remain asymptomatic until cancer emerges or may exhibit nonspecific symptoms that resemble those of other conditions.[16]

Non-pharmacological management of Lynch syndrome focuses on cancer prevention, early detection, and risk reduction:

1. **Lifestyle Adjustments:**

- Healthy Diet**:** Embrace a diet rich in fruits, vegetables, whole grains, and lean proteins.
- Regular Exercise: Commit to regular physical activity for weight maintenance and overall well-being.

2. **Screening and Surveillance:**

- Colonoscopy: Frequent screenings from an earlier age for identifying and removing precancerous lesions.
- Endometrial Biopsies: Periodic assessments for women to detect precancerous changes or early-stage endometrial cancer.
- Additional Cancer Screenings: Tailored screenings based on individual risk factors and genetic mutations.[17]

3. **Risk-Reducing Surgeries:**

- Prophylactic Colectomy: Considered by some to reduce the risk of colorectal cancer.
- Hysterectomy and Bilateral Salpingo-Oophorectomy: Options for women post-childbearing age to mitigate endometrial and ovarian cancer risks.

4. **Genetic Testing:**

- Identification: Genetic testing aids in personalized risk assessment and management based on individual genetic mutations.

5. **Patient Education and Support:**

- Comprehensive Information: Empower individuals and families with detailed information about Lynch syndrome, inheritance patterns, associated cancer risks, and available management options.[18]

Therapeutic management and surgical management of lynch syndrome

The therapeutic and surgical management of Lynch syndrome is primarily focused on cancer prevention, early detection, and risk reduction strategies. Here's an overview of the approaches used:

1. Therapeutic Management:

a. Chemoprevention: While specific medications for Lynch syndrome-related cancer prevention aren't approved, studies have explored aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) for colorectal cancer prevention in high-risk individuals. However, further research is needed to evaluate their efficacy and safety.

b. Targeted Therapies: Targeted therapies, including immune checkpoint inhibitors or agents targeting specific molecular pathways, may be utilized in Lynch syndrome-associated cancer treatment, particularly for advanced or metastatic cases.

c. Chemotherapy and Radiation: Standard treatments like surgery, chemotherapy, and radiation therapy are employed based on cancer stage and type. Multidisciplinary management ensures tailored treatment plans.[19]

2. Surgical Management:

a. Prophylactic Colectomy: Prophylactic removal of the colon (proctocolectomy) with ileorectal anastomosis reduces colorectal cancer risk in Lynch syndrome.

b. Hysterectomy and Bilateral Salpingo-Oophorectomy: Women with Lynch syndrome may opt for prophylactic removal of the uterus and ovaries to reduce endometrial and ovarian cancer risk.

c. Risk-Reducing Mastectomy: Women with Lynch syndrome and mutations in BRCA1/BRCA2 genes may consider risk-reducing mastectomy to lower breast cancer risk [20].

3. Genetic Testing: Testing confirms the diagnosis, identifies mutations, and guides personalized management strategies.[21]

4. Screening and Surveillance:

a. Regular Screening: Lynch syndrome individuals require frequent screenings like colonoscopies and endometrial biopsies to detect cancers early.

b. Multidisciplinary Care: A team of healthcare professionals collaborates for comprehensive care, including genetic counsellors, gastroenterologists, oncologists, gynaecologists, and surgeons.[22]

Case Report:

The patient, a 14-year-old female, presented with left upper limb weakness persisting for the past 7 days. She had a known history of multiple colonic polyps due to hereditary polyposis syndrome and had undergone evaluation for abdominal pain and haematochezia at another hospital. Endoscopic examination revealed mild villous atrophy without an increase in lymphocytes, with no evidence of parasites, granuloma, dysplasia, or malignancy. Colonoscopy confirmed the presence of multiple colonic polyps. EMR Polypectomy and colonic biopsy indicated mucosal lymphoid hyperplasia. Earlier this year, patient was advised to get whole genome sequencing, which in result showed mutations in MSH6 secondary to Lynch syndrome, as well in KRAS and ERB2 genes. CT Enteroclysis showed no significant abnormalities in the small bowel loops. Additionally, the patient was diagnosed with Stargardt's disease. Cardiac examination revealed S1 and S2 sounds, while neurological

examination showed left upper motor neuron (UMN) facial weakness and left upper limb weakness. Brain MRI revealed multiple abnormalities and vasculitis. Multicentre glioma was suspected.

Discussion:

The patient, a 14-year-old female, presented with left upper limb weakness over the past 7 days. She has a known history of multiple colonic polyps due to hereditary polyposis syndrome and had previously sought evaluation for abdominal pain and haematochezia at another medical facility. Endoscopic examination revealed mild villous atrophy without an increase in lymphocytes, and no evidence of parasites, granuloma, dysplasia, or malignancy was found. Colonoscopy confirmed the presence of multiple colonic polyps. Subsequent EMR polypectomy and colonic biopsy showed mucosal lymphoid hyperplasia. CT enteroclysis showed no significant abnormalities in the small bowel loops.

In January 2024, she underwent whole-genome sequencing, which revealed mutations in the MSH6, KRAS, and ERB2 genes secondary to Lynch syndrome. Additionally, she is diagnosed with Stargardt's disease. Cardiac examination showed normal S1 and S2 sounds, while neurological examination revealed left upper motor neuron (UMN) facial weakness and left upper limb weakness. Brain MRI demonstrated multifocal abnormalities with vasculitis. Neuronavigational-guided right frontal burr holes and biopsy of the right frontal intra-axial lesion were performed earlier in the years, with suspected multi-centric glioma present.

The patient's clinical presentation aligns with the diagnostic criteria for Lynch syndrome, leading to a provisional diagnosis of Lynch Syndrome, with predisposition of cancer in brain, bladder, reproductive organs, and pancreas.

The therapeutic regimen encompassed the administration of T. Clobazam 5mg before bedtime and T. Levetiracetam 250mg twice daily for seizure prophylaxis. T. Pantoprazole 40mg was prescribed once daily for ulcer prophylaxis, complemented by intravenous hydration using normal saline at a rate initially set at 50ml/hr, subsequently adjusted to 25ml/hr. Additionally, intravenous injections of Dexamethasone 2mg were provided thrice daily to address cerebral edema, and Inj. Ceftriaxone 1g was administered twice daily for antibiotic coverage. Inj. Zofer 4mg was dispensed at 5 am, and T. Acetaminophen 650mg was administered post-lunch, accompanied by intravenous vit B complex with vit B12 ampoule once daily.

The patient's condition remained stable, and she was discharged with oral medications including T. Levetiracetam 250mg twice daily, T. Clobazam 5mg once daily, Pantoprazole 40mg once daily, T. Naxdom twice daily, and T. Dexamethasone 4mg thrice daily.

In conclusion, Lynch syndrome necessitates comprehensive management strategies encompassing prevention, early detection, and personalized treatment to mitigate cancer risk and enhance outcomes for affected individuals and their families.

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