Coexistence of Constitutional Mismatch Repair Deficiency syndrome and Lynch syndrome in a family of seven : MSH6 mutation and childhood colorectal cancer – a case series

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Abstract

***Purpose* : To present a case series of two fraternal twin girls who passed away from brain and colorectal cancers attributed to Constitutional Mismatch Repair Deficiency syndrome (CMMRD). A review of literature for CMMRD-related pediatric malignancies is also presented.**

***Methods* : The two girls were diagnosed with cancer at the age of 11 and 13 respectively. The early onset of multiple malignancies in the family raised clinical suspicion for a potential genetic mutation. The presence of café-au-lait spots at clinical examination led to further investigations for neurofibromatosis.**

***Results* : Neurofibromatosis type 1 testing was negative in both children. Genetic analysis turned out positive for biallelic MSH6 mutations in the two girls, leading to CMMRD syndrome diagnosis. Both parents and two out of three alive siblings were diagnosed with Lynch syndrome.**

***Conclusions* : Colorectal cancer is a very rare finding in childhood and should raise suspicion for CMMRD syndrome and should be followed by regular screening.** (Acta gastroenterol. belg., **2020**, 83, **479-481**).

Key words : CMMRD, Lynch syndrome, MHS6 mutation, colorectal cancer, pediatric oncology.

1. Introduction

Lynch syndrome is an autosomal dominant inherited cancer predisposition syndrome, linked with colorectal, endometrial and a variety of extracolonic malignancies. Lynch syndrome is caused by heterozygous germline mutations in one of the four mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6* and *PMS2*. Homozygous germline mutations on these genes cause the Constitutional Mismatch Repair Deficiency syndrome (CMMRD). CMMRD includes mainly hematologic, brain and colorectal cancers with remarkably early onset that are seen in patients with Lynch syndrome at a later age. (1) Lynch syndrome predisposes in the development of colorectal cancer at the age of 40-45 years old, while CMMRD at the age of 13 years old.

2. Case history

2.1 Case series presentation

Case 1

A 11-year-old girl presented with a one-month history of morning occipital headaches accompanied with nausea. The MRI scan revealed a medulloblastoma. The management included two operations, so as radiotherapy and eight cycles of adjuvant chemotherapy, with cisplatin and vincristine. However, 6 months after the last chemotherapy, the MRI revealed metastatic lesions at the vertebral column. Following that, salvage chemotherapy was administered, but unfortunately the girl passed away two years after the initial diagnosis.

Case 2

The twin sister of patient in case 1, at the age of 13, presented with seizures, progressive right hemiparesis, speech difficulties and motor dysphasia. For almost a year before she was experiencing intermittent headaches, nausea and episodes of unsteadiness that got worse with time. Lumbar puncture was performed and revealed IgG oligoclonal bands at CSF, suggesting systematic inflammation and blood brain barrier dysregulation. Antibiotics and immunoglobulins were prescribed with mild relief of symptoms. Antibodies for many viral/bacterial agents, along with neurofibromatosis type 1 (NF1) testing were negative, while the ultrasound revealed an enlarged spleen. The physical examination revealed café-au-lait spots. MRI showed a space-occupying lesion of the left frontal lobe and the subsequent stereotactic biopsy led to glioblastoma multiforme diagnosis. The pre-surgery workup included functional MRI and fasciculography. The operation included complete excision of the mass via a left frontal craniotomy guided with

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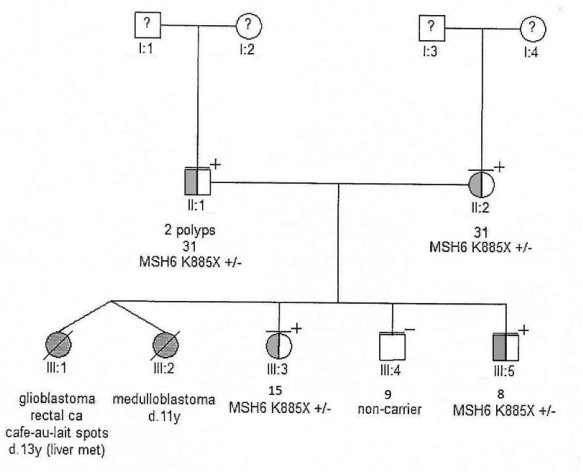

Fig. 1

real-time ultrasound and neuro-navigation. The post-operative period was uncomplicated, and the girl was discharged with levetiracetam, ranitidine and dexamethasone. Subsequently, radiotherapy along with per os chemotherapy was administered. However, two months later our patient presented hematochezia and was eventually diagnosed with a rectal adenocarcinoma with pericolic invasion and liver metastasis. Thus, she underwent only a palliative resection of the rectal tumour. Unfortunately, the patient passed away, five months after the initial diagnosis.

2.2 Genetic analysis

Under the presence of early-observed pediatric cancers in two members of the family, the suspicion for an underlying genetic mutation was increased. Parents and the three alive children were tested for a variety of gene mutations and eventually were found positive and heterozygous for the ***MSH6*** mutation. Fortunately, the third child, a 10-year-old boy, was negative for the mutation. (Fig. 1)

Children undergo screening colonoscopy, along with brain and abdominal MRI scans every 6 months, in order to detect any potential malignancy at an early stage. Parents denied screening for themselves.

3. Discussion

In terms of childhood malignancy, colorectal cancer is by all means a very rare clinical manifestation, whereas brain cancer remains a common site of pediatric malignancy in both CMMRD and non-CMMRD families. In our cases, we observed an early onset of both brain cancer and colorectal cancer at the age of 11 and 13 respectively. In CMMRD patients the mean age at diagnosis for brain cancer is 9 years old, while for colorectal cancer it is 17 years old. (1) During the literature review (PubMed) 7 cases of pediatric patients with *MSH6*-related CMMRD and colorectal cancer were tracked (2-6) and are summarized at Table 1. We should highlight the fact that in our case, the tumour was rectal, while all the other papers present cases of colon adenocarcinomas.

Individuals with Lynch syndrome should undergo annual screening colonoscopy every 1 to 2 years, starting at the age of 20-25 years, or every 2 to 5 years prior to the age of colorectal cancer diagnosis in a family member. *MLH1* and *MSH2* mono-allelic mutations, in Lynch syndrome patients, are responsible for 90% of and colorectal cancer cases (7) while

PMS2 and *MSH6* mutations have a lower and colorectal cancer risk and an older age of manifestation. Thus, screening for *PMS2* and *MSH6* mutations can begin 5 years later than the other MMR mutations. (8)

On the other hand, as CMMRD patients with *PMS2* and *MSH6* mutations are more prone to develop and colorectal cancer, they demand an earlier screening, (9) ideally before the age of 13, which is the mean age of and colorectal cancer manifestation. Judging by the presentation of and colorectal cancer in a 8-year-old patient, the age limit of screening could be even lower. (6) Our patients undergo screening more regularly than the suggested guidelines due to the aggressiveness of their siblings' cancers.

As suggested by a model of decision analysis, screening colonoscopy in Lynch syndrome and CMMRD patients is associated with a gain of roughly 14 quality-adjusted life years for every screened individual compared with no screening. (10)

Furthermore, in the literature, there is a correlation between brain cancer, neurofibromatosis type 1 and *MSH6* mutation. However, no family member turned to be NF1-positive, despite the *MSH6*-positive mutation and the detection of few café-au-lait spots at clinical examination. Neurofibromatosis type 1, an autosomal dominant disorder caused by germline mutations occurring de novo in up to 50%, predisposes to a variety of

Table 1. — **MSH6-related colorectal cancer cases referred in the literature**

Study	Type of CRC	Age at diagnosis of CRC	Mutation
Hegde et al. 2005	**Colon adenocarcinoma**	**8**	**MSH6**
Scott et al. 2007	**Colon adenocarcinoma**	**13**	**MSH6**
Ripperger et al. 2010	**Colon adenocarcinoma**	**13**	**MSH6**
Hoell et al. 2014	**Colon adenocarcinoma**	**13**	**MSH6**
Lavoine et al. 2015	**Colon adenocarcinoma** **Colon adenocarcinoma** **Colon adenocarcinoma**	**11** **14** **17**	**MSH6** **MSH6/MSH2** **MSH6**

benign and malignant neoplasms in childhood. CMMRD belongs to the differential diagnosis of NF1, due to phenotypic similarities between them. Neurofibromatosis type 1 should definitely be excluded under the presence of Lynch syndrome-associated malignancies. (9)

Brain cancer belongs to the most frequent manifestations of CMMRD. Both our patients developed brain cancers, glioblastoma multiforme and medulloblastoma in particular. High-grade gliomas are the most common types of brain cancer in CMMRD syndrome.

3. Conclusion

Clinical suspicion for the presence of Constitutional Mismatch Repair Deficiency syndrome should be raised in any patient with colorectal cancer below the age of 25 years old. High-grade gliomas should also be accounted as highly suggestive for CMMRD, as they represent 26% of CMMRD-related malignancies, compared to 5% of all pediatric malignancies. (1) Therefore, patients with CMMRD, and their relatives with confirmed MMR mutations should be encouraged to join close surveillance programs, in order to reduce mortality and to prevent the development of another malignancy in the future.

Conflict of interest

The authors have no conflict of interest to declare.

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