Genetic and clinical aspects of inherited syndromes associated with adenomatous polyposis

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CHAPTER 6

High Yield of Surveillance in Patients Diagnosed with Constitutional Mismatch Repair Deficiency

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ABSTRACT

Background: Constitutional Mismatch Repair Deficiency (CMMRD) is a rare autosomal recessively inherited syndrome that is caused by bi-allelic pathogenic variants of the mismatch repair genes. It is characterized by the development of multiple tumors in the first and second decade of life including brain, gastrointestinal and hematological tumors often resulting in early death. In order to improve the prognosis of these patients, the European collaborative group "Care for CMMRD" (C4CMMRD) developed a surveillance program in 2014 and established a registry of CMMRD patients in Paris. The aim of the study was to evaluate the outcome of this program.

Methods: Twenty-two patients with a definitive diagnosis of CMMRD and with at least one follow-up study were selected from the registry. Medical data on the outcome of surveillance were collected from these patients.

Results: During a mean follow-up of four years, the program detected eight malignant tumors including three brain tumors, three upper gastrointestinal cancers, and two colorectal cancers. Most tumors could successfully be treated. In addition, many adenomas were detected in the duodenum, and colorectum and subsequently removed. Seven patients developed a symptomatic malignancy, including two brain tumors, one small bowel cancer, and four hematological malignancies. At the end of the follow-up, 16 out of 22 patients (73%) who participated in the surveillance program were still alive.

Conclusion: The study suggests a beneficial effect of surveillance of the digestive tract and brains.

INTRODUCTION

One of the most frequent inherited forms of cancer is Lynch syndrome (LS), which is characterised by high risks of developing colorectal cancer (CRC), endometrial cancer and other cancers. LS is an autosomal dominant inherited syndrome caused by pathogenic monoallelic variants in the mismatch repair (MMR) genes including *MLH1, MSH2, MSH6* and *PMS2*.[1] Biallelic pathogenic germline variants of the MMR genes result in a very rare syndrome usually referred to as constitutional mismatch repair deficiency (CMMRD). CMMRD is an autosomal recessive syndrome characterised by multiple cancers that develop in childhood including brain tumours, cancers of the digestive tract, haematological malignancies and other tumours.[2]

In CMMRD, brain tumours and haematological malignancies are often diagnosed in the first decade of life. If the patients survive these cancers, they may develop cancers of the digestive tract including CRC, small bowel cancer (SBC) and other tumours associated with LS in the second decade of life or later.[2 3] One of the most striking features is the very high risk of developing multiple tumours, synchronously or metachronously.

The life expectancy of patients with CMMRD is very limited as many patients will die in the first or second decade of life frequently due to brain tumours. Early detection and treatment is the only way to improve the prognosis. Identification of CMMRD is therefore of utmost importance because it allows implementation of preventative strategies including genetic counselling of parents and tumour surveillance for the patient.

Currently, various guidelines are available that can be used to guide the management of these patients.[4–7] In 2012, Durno *et al* reported the successful outcome of a surveillance protocol for the first time implemented in a kindred with CMMRD.[4] Two years later, the European collaborative group (C4CMMRD), collected data on the natural history of the tumours involved in this syndrome and developed a new protocol using this information.[2 5] In 2017, the US Multi-Society Task Force on CRC with invited experts developed a consensus statement and recommendations for the management of patients with CMMRD.[7] The aims of the present study are (1) to assess the effectiveness of the C4CMMRD

surveillance programme and (2) to discuss possible improvements of the protocol.

METHODS

At the meeting of the C4CMMRD group in 2014, the collaborative group decided to set up an European Registry of patients with CMMRD to enable various research projects. One of the purposes of the registry was to collect prospective data to better understand the natural history of the disease; another purpose was to investigate the effectiveness of surveillance in patients that underwent periodic examination. Only patients with a definitive diagnosis of CMMRD are registered. The registry, based in Paris, includes medical data, family history of cancer, previous malignancies, genetic tests results and outcome. All data are pseudonymised.

For the present study, patients were selected from the Paris registry who underwent at least one surveillance examination. Anonymous medical data were retrospectively collected. The observation time is between the first examination and the last screening examination or date of death.

RESULTS

Basic characteristics

A total of 22 patients (11 females and 11 males) were included in the study. The most common underlying biallelic pathogenic variants were in *PMS2*, detected in 15 patients, followed by biallelic *MSH6* pathogenic variants in 4 patients and biallelic *MSH2* pathogenic variants in 3 patients. Eighteen of the 22 patients had developed 27 malignancies before start of the surveillance programme including 12 CRCs, 8 lymphomas, 2 leukaemia, 4 brain tumours and 1 patient was diagnosed with a pilomatricial carcinoma. The characteristics of the patients are summarised in table 1.

TABLE 1. Detailed information of the study group of CMMRD patients

Pt No.	*Sex*	*Gene*	*Age @ first screening (years)*	*Previous cancers (Age, if known)*
1	M	*PMS2*	10	Lymphoma
2	F	*PMS2*	7	-
3	M	*PMS2*	27	-
4	F	*PMS2*	21	Two synchronous CRC (19)
5	F	*MSH2*	22	CRC (22)
6	M	*PMS2*	14	Lymphoma (8), Lymphoma (14)
7	F	*PMS2*	17	Two synchronous CRC (17)
8	F	*PMS2*	12	BT- glioblastoma (12)
9	F	*MSH6*	7	-
10	M	*PMS2*	8	Lymphoma
11	M	*MSH6*	9	Leukemia (3), Lymphoma (7)
12	M	*MSH2*	12	CRC (12)
13	M	*PMS2*	5	Lymphoma (3)
14	M	*MSH2*	24	CRC (23)
15	F	*PMS2*	18	BT- Glioblastoma (18)
16	M	*PMS2*	13	Leukemia, Pilomatrix carcinoma, CRC
17	F	*MSH6*	10	BT- Glioblastoma (9)
18	M	*PMS2*	17	Lymphoma, CRC (17)
19	F	*MSH6*	7	CRC (7)
20	F	*PMS2*	27	Two synchronous CRC, Lymphoma
21	M	*PMS2*	12	-
22	F	*PMS2*	17	BT-Medulloblastoma (4)

BT, brain tumour; CMMRD, constitutional mismatch repair deficiency; CRC, colorectal cancer

TABLE 2: Characteristics and management of cancers detected during the screening program

Site	*Type of Tumor (Stage)*	*Mode of diagnosis*	*Age at dx (yrs)*	*Treatment/Outcome*
Brain	Glioblastoma	Symptomatic	8	Surgery, radiotherapy & chemotherapy; Local recurrence after 11 months; Deceased due to liver failure after 16 months.
	Glioblastoma	Symptomatic	31	Surgery, radiotherapy & chemotherapy; Deceased after 2 years due to complications of the tumor.
	Astrocytoma (grade 3)	Screen-detected	8	Surgery and radiotherapy; Alive at his last follow-up, 3.5 years after the diagnosis.
	Anaplastic Oligodendro-glioma (grade 3)	Screen-detected	11	Surgery and radiotherapy; Alive at her last follow-up, 2 years after the diagnosis.
	Glioblastoma	Screen-detected	19	Right frontal resection; Local recurrence one month after the initial diagnosis. Deceased due to increased cerebral pressure.
Upper GI	Gastric Cancer (T3N1)	At first screening	23	Neo-adjuvant chemotherapy and surgery; Alive 3 years after diagnosis with no abnormalities detected on the follow-up endoscopies.
	Gastric Cancer	Screen-detected	10	Future treatment refused because of advanced metastatic disease CRC; The patient died less than 2 months after gastric cancer diagnosis

	Esophageal Cancer (T1aN0)	At first screening	18	Neo-adjuvant chemotherapy and surgery; The patient died after 16 months due to the complications of glioblastoma.
Small Bowel	Small Bowel Cancer (T3N2M1)	Symptomatic	26	Palliative chemotherapy Alive 4 years after diagnosis
Colorectum	Pouch Adenocarcinoma (T2N2)	Screen-detected	28	Pouch resection; no adjuvant treatment. Alive 27 months after diagnosis
	Colorectal Carcinoma (T1N0)	Screen-detected	19	Endoscopic resection; additional subtotal colectomy; No residual malignancy in colectomy specimen. The patient died after 10 months due to the complications of glioblastoma.
Hematolog-ical	Myelodysplastic Syndrome	Symptomatic	15	Pt deceased shortly after diagnosis
	T-Cell Lymphoma (Ann Arbor Stage IV)	Symptomatic	8	Conventional chemotherapy Mediastinal & testicular CR ; persistent MRD
	Acute Lymphoblastic Leukemia	Symptomatic	12	no additional information
	Acute Lymphoblastic Leukemia	Symptomatic	14	Chemotherapy plus allogenic HSCT Complete remission

CR, complete remission; CRC, colorectal cancer; GI, gastrointestinal; HSCT, haematopoietic stem cell transplantation; MRD, minimal residual disease.

Outcome of surveillance

The median age at the first screening examination was 13.2 years (range: 5.9–27.6). The mean follow-up time between the first screening examination until the last follow-up was 48.2 months (SD=21.8). Six (27%) of the 22 patients died during follow-up. Causes of death included brain tumour in three patients, myelodysplastic syndrome in one patient, metastatic GI tumour in another patient and liver failure in a patient diagnosed with local recurrence of glioblastoma. The outcome of surveillance is summarised in table 2.

Surveillance for brain tumours

The programme recommended by the C4CMMRD group includes an MRI at intervals of 6–12 months starting from the age of 2 years. All patients except one patient who refused screening of the brain, underwent biannual or annual MRI.

A total of five brain tumours were diagnosed during follow-up of which three were detected by screening, one tumour was a symptomatic interval cancer and one patient who refused MRI surveillance developed a symptomatic brain tumour. In addition, one other patient was found to have a suspicious finding on his last screening MRI which was under diagnostic workup.

A glioblastoma was detected in a woman aged 19 years while she was under yearly MRI surveillance. She underwent a right frontal resection. Already 1 month after treatment, she developed a local recurrence. Shortly thereafter, the patient died due to increased cerebral pressure. Seven years earlier, the patient had been treated for another primary brain tumour.

An anaplastic oligodendroglioma (grade 3) was detected by MRI screening in a girl aged 11 years. The patient was undergoing biannual MRI screening and there were few intracerebral hyperintense foci without postcontrast enhancement or diffusion restriction which were stable in the previous 4 years of screening. The patient underwent block-resection and radiotherapy and she was alive at her last follow-up, 2 years after the diagnosis.

An astrocytoma (grade 3) was detected in a boy aged 8 years, detected with screening 5.5 months after the previous normal MRI. The patient underwent complete resection and radiotherapy and was alive until his last follow-up, 3.5

years after the diagnosis. However, a suspicious mass (6 mm) was detected after 27 months in the left frontal lobe (gyrus) but was not biopsied because of the location (too close to the speech zone) and risk of aphasia. The mass progressed to 13 mm after 12 months. He is still alive 15 months after the diagnosis of this irresectable mass.

A girl aged 8 years developed a symptomatic glioblastoma, 8 months after a normal MRI. She underwent surgery, radiotherapy and chemotherapy. There was a local recurrence 11 months after the initial diagnosis which was treated with radiotherapy. The patient developed liver failure after 4 months with a suspected diagnosis of haemophagocytic lymphohistiocytosis and died due to the complications of progressive liver failure. One patient accepted surveillance of the digestive tract but refused MRI screening of the brain. After 4 years of follow-up, he developed a glioblastoma at the age of 31 years and underwent surgery, radiotherapy and chemotherapy. He died from the complications of the tumour, 22 months after initial diagnosis.

Surveillance of the digestive tract

The protocol recommendations comprise annual gastroduodenoscopy and video capsule endoscopy (VCE) from the age of 10 years and annual colonoscopy from age 8 years. Twenty of the 22 patients underwent regular colonoscopies and 19 regular upper gastrointestinal (GI) endoscopy. Eight patients had at least one VCE.

Upper digestive tract

Duodenal adenoma with low-grade dysplasia were detected in five patients with maximal size of 20 mm which were endoscopically resected. Another two patients had hyperplastic duodenal polyps. One patient had multiple adenomatous polyps of maximal 20 mm with high-grade dysplasia and mucosectomy was planned for the patient. The median age of duodenal polyp diagnosis was 18.6 years (range: 10.1–28.1).

Two upper GI cancers were detected at the first screening. In one patient aged 23 years, a T3N1 gastric cancer was found. The patient underwent neo-adjuvant

chemotherapy and surgery and is still alive 3 years after diagnosis with no abnormalities detected on follow-up endoscopies. In the second patient, a T1N0 oesophageal cancer was diagnosed at the age of 18 years. She underwent neo-adjuvant chemotherapy and an oesophageal-cardia resection with gastric tube reconstruction but the patient died after 16 months due to the complications of glioblastoma. In another patient aged 10 years, gastric cancer of 4.2 cm located in the antrum was diagnosed during screening 16 months after the previous upper GI endoscopy. The patient was diagnosed with colon cancer with metachronous liver metastases 3 years earlier, before the diagnosis of CMMRD and start of the screening programme. The family refused treatment of the gastric cancer and the patient died <2 months after the diagnosis.

VCE detected polyps in two patients. Because the polyps were small, no additional diagnostic examinations were performed. During follow-up, one patient not under VCE surveillance developed a symptomatic SBC at age 26 (stage: pT3N2M1) located in the jejunum. The patient underwent surgery and chemotherapy and was alive at last follow-up, 4 years after the diagnosis.

Lower digestive tract

Multiple adenomas in the colon were found in 12 patients at the median age of 16.3 years (range: 9.0–29.6). The number of adenomas varied from 1 to 30 adenomas. The adenomas were equally distributed in the colon. In three patients, adenomas showed high-grade dysplasia. All polyps were endoscopically removed. The programme detected CRC in two patients. In one patient at the age of 19 years, a malignant polyp was endoscopically removed. She subsequently underwent a subtotal colectomy and no residual malignancy was detected (TNM: pT1N0). She died due the complications of a glioblastoma 10 months after the diagnosis of CRC. In another patient aged 28 years with a history of simultaneous rectal and colon malignancies 12 years ago, multiple adenomas were resected from the pouch, 11 months after the previous coloscopy followed by resection of the pouch. Pathological examination revealed an adenocarcinoma (TNM: pT2N2).

Tumours that develop at other sites

In our programme, there are no specific tools for the early detection of haematological disorders except checking medical history and blood investigation during the regular 6 monthly visits and optional abdominal ultrasound. One patient developed a myelodysplastic syndrome and died due to the syndrome at age 15 years. Two other patients were diagnosed with acute lymphoblastic leukaemia (ALL) at age 12 and 14 years and another patient with T-cell lymphoma (Ann Arbor stage IV) at the age of 8 years. T-cell lymphoma (mediastinal, testicular and medullar) was treated by conventional chemotherapy. After treatment, there was complete remission of testicular and mediastinal locations but persistent minimal residual disease detected by immunophenotyping. One of the patients with ALL (precursor B) underwent chemotherapy (according to AIEOP-BFM ALL 2017 protocol) plus allogenic haematopoietic stem cell transplantation and complete remission was achieved. All patients were alive and under treatment during the last follow-up screening.

DISCUSSION

In the current study, we present the outcome of surveillance of 22 patients with CMMRD. During a mean follow-up of 4 years, the programme detected eight malignant tumours including three brain tumours, three upper GI cancers and two CRCs. Most tumours could successfully be treated. In addition, adenomas were detected and subsequently removed involving colorectal adenomas in 12 patients and duodenal adenomas in 6 patients. Seven patients developed a symptomatic malignancy, comprising two brain tumours, one SBC and four haematological malignancies. At the end of the follow-up of 4 years, 16 out of 22 patients (73%) who participated in the surveillance programme were still alive.

The International Replication Repair Deficiency Consortium recently reported the results of surveillance in 53 patients with CMMRD who were prospectively followed in centres all over the world.[8] The study demonstrated that the 5-year overall survival significantly increased when cancers were detected asymptomatically (90% in asymptomatic vs 50% in symptomatic cancers).

In our surveillance programme, five patients were diagnosed with brain tumours including two patients diagnosed after presentation with symptoms. Two patients with a screen-detected tumour are still alive 2.5 and 3 years, respectively, after diagnosis. In the International Consortium cohort, a total of 20 brain tumours were diagnosed, including 5 patients with symptomatic tumours. The 5-year survival was twice as high (72% vs 33%) in patients with asymptomatic brain tumours compared with those with symptomatic tumours. In conclusion, both studies suggest that intensive surveillance with MRI scanning improves the prognosis and that not all tumours can be detected at an early stage and cured.

In the prospective cohort followed by the International Consortium, all GI cancers were detected in asymptomatic patients. The 5-year survival of the patients with asymptomatic tumours was 100%. The type of GI cancers was not specified in this study.[8] In the present European study, two patients were diagnosed with early stage gastric and oesophageal cancers on first screening. In a third patient, advanced gastric cancer was detected in a patient already diagnosed with liver metastases of CRC. In addition, benign duodenal lesions were detected and removed endoscopically in 27% of our patients. In the recent Consortium studies, no cancers of oesophagus or stomach were reported.[9, 10] We are not able to make conclusions on the value of VCE in the present study because in only 2 of 10 patients who underwent this procedure small polyps were detected and 1 patient developed a symptomatic SBC outside the programme. However, the role of VCE in CMMRD surveillance has recently been studied in 17 patients by Shimamura *et al*.[10] Polypoid lesions were detected in 63 % of VCEs (24/38) conducted on nine patients. Further investigation of three patients led to the detection of one adenocarcinoma in the jejunum in a patient aged 16 years. During the programme, two other patients were diagnosed with SBC detected with magnetic resonance enterography and upper GI endoscopy, respectively. The investigators concluded that although VCE was found to be effective to detect neoplasia of the small intestine, incomplete studies in 28%, false negative and positive results were found to be limiting factors of this screening modality.[10]

Colonoscopic surveillance in our cohort led to the detection and removal of many adenomas including adenomas with high-grade dysplasia. One early asymptomatic CRC as well as one advanced CRC were found. In a previous Consortium study by Aronson *et al*, the results of GI surveillance were reported for 24 patients.[9] Two CRC and two SBC were detected during surveillance. None of the patients undergoing surveillance died of GI malignancy. Levi *et al* reported the outcome of colonoscopy in 11 patients with CMMRD. Two patients were found to have CRC, three multiple (polyposis-like) polyps, four a few polyps and two no polyps, demonstrating the high yield of such a programme.[11] In conclusion, the benefits and effectiveness of colorectal surveillance are supported by our observations and previous studies.

Regarding haematological disorders, all of our cases were diagnosed after the presentation of symptoms. In the Consortium study, most (10 out of 12) haematological disorders were symptomatic.

An important question is, how the results of our and other recent studies can be used to improve the current surveillance protocols? [4–7]

For brain tumours, it is currently recommended to start the MRI scanning at 2 years of age.[5-7] Guerrini-Rousseau *et al* reported that among 49 patients with brain tumours known in the European C4CMMRD database, there was only one patient diagnosed with a brain tumour (medulloblastoma at age 1 year) before age 2.[12] In the present study, and also in the International Consortium study,[8] all tumours were detected beyond this age. In conclusion, all studies suggest that the current starting age limit is appropriate. Regarding the interval of MRI surveillance, in two of our patients, an astrocytoma and oligodendroglioma were detected within 6 months after the last MRI and both tumours could successfully be resected. Both patients are still alive. In two other patients, the brain tumours, both glioblastomas, were diagnosed at an interval longer than 6 months after 8 and 12 months, respectively. Both patients developed local recurrences within 12 months. In the prospective cohort of the International Consortium, 20 brain tumours were diagnosed of which 15 were asymptomatic and 5 were symptomatic. One of the five patients with symptomatic tumours had an surveillance interval of 1.5 years and in four of the five patients, the MRI schedule

was disrupted because of access or availability to surveillance modalities. It is unclear whether all asymptomatic tumours were detected within the 6 months interval. In conclusion, the few data available may suggest that a surveillance interval of 6 months should be recommended but in clinical practice, it may be challenging to perform MRI scans at such short intervals.

In our study, the four patients that developed gastric, oesophageal and SBC were between 10 and 26 years of age. In the VCE study by Shimamura *et al*,[10] three SBC were diagnosed at age 12, 15 and 20 years. The information on all known patients in the International Consortium study revealed that there were 10 patients with SBC of which 1 patient was diagnosed at age 9 and 2 patients with gastric cancer, of which 1 was diagnosed at age 9.[8] In our previous study, all 18 SBC were diagnosed >10 years.[5] In view of the rarity of upper GI and SBCs diagnosed before age 10, starting upper GI endoscopy and VCE from this age appears to be appropriate. However, if colonoscopy is performed under general anaesthesia (which is recommended in children), it may be considered to start performing upper GI endoscopy together with colonoscopy from the age of 8 years (see below) because there is no additional burden for the patients. There are insufficient data to evaluate the recommended interval of upper GI surveillance of 1 year, but experience suggests that this is appropriate.

Recommendations regarding the annual interval of colonoscopic screening and shorter intervals in case of multiple or advanced polyps seem also justified. However, there is discrepancy regarding the starting age for colonoscopic surveillance. In previous guidelines, colorectal surveillance as early as 3 and 6 years was recommended.[4-7] In our 2014 study, among 59 patients with CRC, there were no cases diagnosed below the age of 8 years.[5] Also in our current study and in the International Consortium study, there were no cases of CRC below age 8 years which suggest that starting surveillance at this age is appropriate.

In view of cancers that may develop outside the usual sites of tumours, whole body MRI (WBMRI) has been recommended by the International Consortium. In the recently published study, all brain tumours were detected by the brain MRI as well as the total body scan. In addition, one malignant tumour (type of tumour

not specified) was detected by WBMRI.[8] In our study, we did not observe the development of tumours outside the usual sites. More studies are needed to prove the effectiveness of total body MRI.

The present study has advantages and disadvantages. Advantages were the prospective collection of the data, the availability of detailed findings and the relatively long follow-up. A disadvantage might be the low number of patients participating in the programme primary due to the rarity of the syndrome. However, despite this low number, the patients developed a very high number of 15 tumours during follow-up.

CMMRD is one of the most lethal and devastating forms of hereditary cancer. Surveillance programmes may alleviate the tumour burden and improve the prognosis as demonstrated in the present and other studies. Future studies are needed to evaluate whether the adjustments of the surveillance protocol as suggested will lead to further increase of life expectancy.

ETHICS STATEMENTS

Ethics approval

The study was approved by the members of the C4CMMRD group at their meeting in Innsbruck, Austria, on 1 February 2014. The C4CMMRD database has been assessed by the local data protection officer at Gustave Roussy Institute to be in accordance with the reference methodology of (MR004) of the Commission Nationale Informatique et liberté (CNIL) and approved by the ethics committee 'CEEI Inserm' (IRB00003888). All living patients gave signed informed consent to use their data in the context of care, including international collaborations. For deceased patients, the ethics commission authorised the use of the data subject to a non-opposition which has been verified with their referring physician.

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