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Clinical Management and Tumor Surveillance Recommendations of Inherited Mismatch Repair Deficiency in Childhood

Uri Tabori[1], Jordan R. Hansford[2], Maria Isabel Achatz[3], Christian P. Kratz[4], Sharon E. Plon[5], Thierry Frebourg[6], and Laurence Brugières[7]

Abstract

Replication proofreading is crucial to avoid mutation accumulation in dividing cells. In humans, proofreading and replication repair is maintained by the exonuclease domains of DNA polymerases and the mismatch repair system. Individuals harboring germline mutations in genes involved in this process are at increased risk of early cancers from multiple organs. Biallelic mutations in any of the four mismatch repair genes *MSH2*, *MSH6*, *MLH1*, and *PMS2* result in one of the most aggressive childhood cancer predisposition syndromes, termed constitutional mismatch repair deficiency or constitutional mismatch repair deficiency syndrome (CMMRD). Data gathered in the last decade allow us to better define the clinical manifestations, tumor spectrum, and diagnostic algorithms for CMMRD. In this article, we summarize this information and present a comprehensive consensus surveillance protocol for these individuals. Ongoing research will allow for further definition of replication repair–deficient cancer syndromes, assessing the cost-effectiveness of such surveillance protocols and potential therapeutic interventions for these children and families. *Clin Cancer Res; 23(11); e32–e37. ©2017 AACR.*

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Introduction

DNA replication is a highly conserved and controlled process during the cell cycle. DNA polymerases, which replicate the DNA during the S-phase, are not mistake free. Single-nucleotide variations (SNV) represent incorporated base errors, whereas slippages of the polymerase will result in insertions and deletions, especially in repetitive elements termed microsatellites. Indeed, point mutations and microsatellite instability (MSI) are the hallmarks of replication repair deficiency. Replication fidelity is governed by the exonuclease domains in the DNA polymerases and the mismatch repair (MMR) system (ref. 1; Fig. 1).

In humans, germline mutations in the four MMR genes (*MSH2*, *MSH6*, *MLH1*, and *PMS2*) result in known specific types of cancers and predisposition patterns. In addition, germline deletions of the *EPCAM* gene (2), located just upstream of *MSH2*, result in hypermethylation of the *MSH2* promoter in epithelial tissues and MSH2 deficiency. Recently, germline mutations in *MSH3* (3) were reported, further expanding the spectrum of MMR deficiency in humans. Germline mutations in the DNA polymerases *epsilon* and *delta* have also been reported to cause cancer predisposition in adults (4) and children (5). However, because the clinical manifestations of the latter conditions are still relatively unknown, we will focus on the MMR system in this article.

Inherited heterozygous mutations in the MMR genes result in a cancer condition termed Lynch syndrome (LS; refs. 6, 7). LS is characterized by gastrointestinal and genitourinary cancers in mid- to late adulthood, and large datasets allow for risk stratification, molecular and diagnostic genetic tests, and implementation of surveillance protocols [see National Comprehensive Cancer Network (NCCN) guidelines, 2016; ref. 8].

Although growing evidence suggests presentation of LS during childhood including gastrointestinal and brain tumors, these are rare and, therefore, are beyond the scope of this article.

In contrast, biallelic germline mutations in the MMR genes result in a distinct phenotypically defined constitutional mismatch repair deficiency syndrome (CMMRD). Children with CMMRD are affected by a large variety of malignant neoplasms, and most do not reach adulthood. CMMRD is a devastating and penetrant cancer predisposition syndrome, and urgent interventions are needed.

In this consensus statement, we discuss current issues in the tumor spectrum, clinical characteristics, diagnosis, and management of these children. On the basis of these ongoing observations, we suggest criteria for diagnosis and implementation of a surveillance protocol for early tumor detection and potentially improve survival for these individuals and family members.

Clinical Presentation of CMMRD

The association of childhood tumors with biallelic MMR-gene germline mutations was firstly described in 1999 (9). Although

[1]Division of Hematology/Oncology, The Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada. [2]Children's Cancer Centre, Royal Children's Hospital, Murdoch Children's Research Institute, University of Melbourne, Melbourne, Australia. [3]Clinical Genetics Branch, National Cancer Institute, Bethesda, Maryland. [4]Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany. [5]Texas Children's Cancer Center, Baylor College of Medicine, Houston, Texas. [6]Department of Genetics, Rouen University Hospital, Rouen, France. [7]Child and Adolescent Cancer Department, Gustave Roussy Cancer Campus, Villejuif, France.

Corresponding Author: Uri Tabori, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G1X8, Canada. Phone: 416-813-7654, ext. 1503; Fax: 416-813-5024; E-mail: uri.tabori@sickkids.ca

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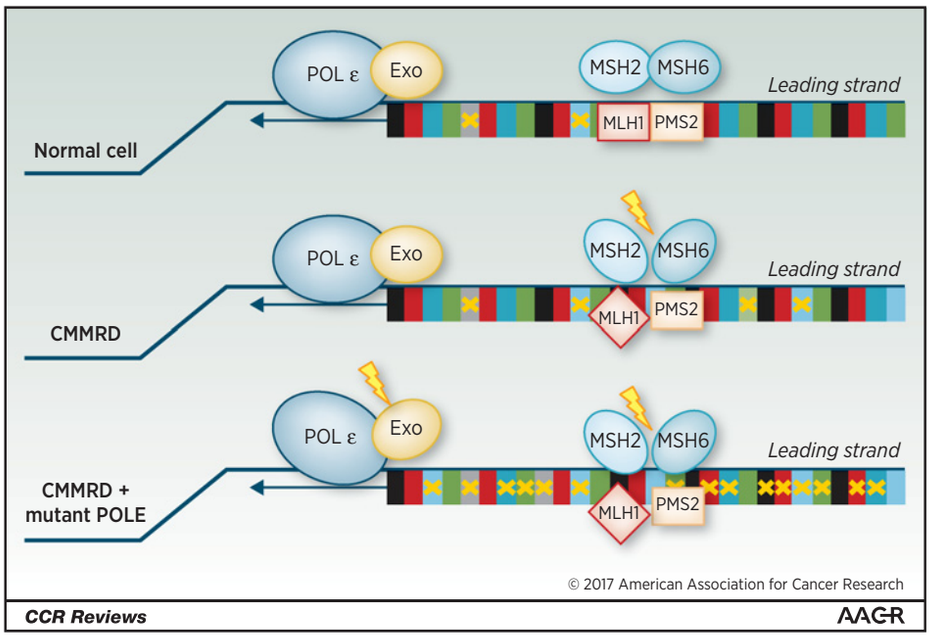

Figure 1.
A model of replication repair deficiency. Both the internal proofreading capability of the DNA polymerases and the mismatch repair systems are key to preventing replication errors in dividing cells. Inherited mismatch repair defect or mutations in DNA polymerases lead to the gradual accumulation of mutations and, thus, increased cancer risk during adulthood. However, combination of mutations in mismatch repair and the exonuclease domains of *POLE* or *POLD1* DNA polymerases results in an extremely rapid accumulation of mutations and onset of cancer in young children. CMMRD, constitutional mismatch repair deficiency syndrome.

first termed Turcot syndrome, other labels were inconsistently used. Consequently, based on the underlying pathomechanisms, the syndrome was subsequently designated as CMMRD (10).

The hallmark of the disease is early onset cancer, most often in childhood or young adulthood. The median age of onset of the first tumor is 7.5 years, with a wide range observed (0.4–39; ref. 11). The spectrum of tumors in CMMRD is expanding and is distinct from those of LS. The most common are malignant brain tumors, followed by gastrointestinal and hematologic malignancies. The median ages at diagnosis of hematologic malignancies and brain tumors have been estimated to be 6.6 and 10.3 years, respectively (12). Most brain tumors are malignant gliomas, although low-grade lesions have been observed. The morphologic features of these gliomas include large, multinucleated giant cells with clumped nuclei and cells with many smaller, eccentrically placed nuclei mimicking pleomorphic xanthroastrocytomas (13). Central nervous system (CNS) embryonal tumors and medulloblastomas have also been reported (11, 14).

The most commonly observed hematopoietic malignancies are non-Hodgkin lymphomas (NHL) and, in particular, T-lymphoblastic NHL. T-cell acute lymphoblastic leukemia (T-ALL) and acute myeloid leukemia have also been reported (11, 15). Patients with CMMRD also develop LS-associated malignancies, the vast majority being colorectal carcinoma, although cancers of the small bowel, endometrium, ovary, and urinary tract have also been seen. Remarkably, a large proportion of CMMRD patients develop multiple synchronous adenomas ranging from a few up to >100 polyps, mimicking attenuated familial adenomatous polyposis. All patients will have polyposis by the third decade of life (16). Furthermore, recent data reveal a large variety of other cancers and multi-organ involvement. These include childhood sarcomas such as osteosarcoma and rhabdomyosarcoma (12), other childhood cancers such as neuroblastoma and Wilms tumor, and genitourinary cancers usually seen in adults with LS. These tumors occur even in the first decade of life, although sarcomas and genitourinary cancers are also observed in the second decade. CMMRD may present with synchronous or metachronous malignancies of different types (17). Overall, most patients will be affected during childhood (11, 12), and the median survival after diagnosis of the primary tumor is less than 30 months (12).

The rate of consanguinity varies according to the countries of origin. A high rate of consanguinity is observed especially among homozygous cases (17), whereas in Western countries, most of the cases are associated with composite heterozygous mutation in families with no consanguinity (12). In contrast to family members with LS, many of the heterozygous parents will not be affected, especially among families with *PMS2* or *MSH6* mutations (14, 18).

Nonneoplastic manifestations of diagnostic importance include features of NF1, in particular café au lait macules (CALMs), and other hyper- and hypopigmented skin alterations. Most children will have this feature (19). Other features include developmental venous anomalies, pilomatricomas (benign skin lesions that usually appear in the first two decades of life; ref. 20), agenesis of the corpus callosum, and mild immunodeficiency with decreased levels of immunoglobulins IgG2/4 and IgA, among others (11).

Clinical Genetics

CMMRD mode of inheritance is consistent with an autosomal recessive pattern. Biallelic mutations have been reported in all LS-associated MMR genes (*MSH2*, *MLH1*, *MSH6*, and *PMS2*). Importantly, the frequency is strikingly different than in LS. The most commonly involved genes are *PMS2* and *MSH6*, whereas *MSH2* and *MLH1* mutations are rare (11, 14), which might be explained by the lower penetrance and clinical severity of *PMS2* and *MSH6* heterozygous mutations on the one hand and the lethality of homozygous-null mutations in *MSH2* on the other. Genotype:phenotype correlations are difficult to assess due to

the rarity of the syndrome and are complicated by the high rate of potential hypomorphic *MLH1* and *MSH2* mutations among CMMRD patients.

Family history often is noncontributory, although both parents are obligate carriers. Penetrance of monoallelic *MSH6* and *PMS2* mutations is lower than that of *MSH2* and *MLH1*; therefore, it is not uncommon for affected children to have unaffected parents. Nevertheless, the cancer risk in children with CMMRD is higher than the risk in children with most other childhood cancer syndromes (14).

Diagnosis

A high index of suspicion and awareness of CMMRD are prerequisites for rapid diagnosis of the syndrome. This is due to the aggressiveness of CMMRD and the need to adjust treatment to the underlying MMR defect and to adapt follow-up evaluations aimed at the high risk of subsequent malignancies. Despite the wide range of clinical presentations, a few signs are highly suggestive of CMMRD. These especially include the combination of tumors belonging to the spectrum (high-grade gliomas, T-lymphoblastic lymphoma, or colorectal carcinomas) associated with CALMs and/or depigmented spots. Because CMMRD has several unique clinical phenotypic features, a clinical diagnostic protocol was developed by the European "Care for CMMRD (C4CMMRD)" consortium (Table 1; ref. 11). The scoring system is highly sensitive for CMMRD and suggests genetic counselling and testing for patients fulfilling these criteria. CMMRD should be suspected in all individuals who reach a score of three or more points.

Genetic testing for the presence of biallelic mutations in one of the four MMR genes is recommended to genetically confirm the diagnosis of CMMRD. This is complicated by the large number of variants of unknown significance in these genes and the difficulties in sequencing *PMS2*, which has multiple pseudogenes. Because the diagnosis is urgent and will affect both surveillance and therapeutic decisions, several diagnostic screening algorithms and pretests have been developed.

Immunohistochemistry (IHC) revealing loss of the corresponding MMR protein in both normal and malignant cells is highly concordant with a diagnosis of CMMRD. It is also available in most pathology laboratories in the world, as it is a part of the workup for colon cancers in adults. Because normal cells are usually positively stained in Lynch tumors and are negative in CMMRD, this simple tool can distinguish between the two syndromes. The high sensitivity and specificity of this test support its role as an initial screening tool in both nonmalignant and cancer tissues (11, 14). Furthermore, it guides subsequent mutation analysis in the four MMR genes and may contribute to diagnosis when the latter is controversial. In most cases, this can be performed on the tumor biopsy. It is important to emphasize that negative IHC staining in neoplastic and surrounding normal cells should not be interpreted as a failure of proper staining, as is usually the case for LS. In cases in which no tumor tissue is available for immunostaining, such as hematologic malignancies or in a healthy individual suspected of CMMRD, immunostaining for MMR can be performed on a skin biopsy (14). In general, biallelic truncating mutations in *PMS2* or *MSH6* will result in isolated loss of these proteins, whereas mutations in *MLH1* or *MSH2* will lead to concurrent loss of MLH1/PMS2 or MSH2/MSH6, respectively. Of note, some missense mutations will result in retained staining of the protein. Therefore, a positive stain does not preclude a diagnosis of CMMRD (11).

Importantly, MSI, which is extremely sensitive and specific for LS tumors, may be negative in CMMRD cancers, especially in non-gastrointestinal cancers (12, 14). Therefore, the opinion of the committee is that MSI should not be a part of diagnostic tools used for CMMRD, whereas IHC for the four common MMR genes should be used on any index and family members, as it can inform both genetic testing and contribute to diagnosis when the latter is controversial.

Assays based on lymphocytes from patients with CMMRD are being developed as tools to examine the degree of MSI (21), response to treatment, and repair of specific mutations for diagnosis in problematic cases (22, 23).

Recently, high mutational burden in the tumor with mutation rates of 100/MB as compared with <10/MB in most childhood cancers has been described to be extremely specific to CMMRD (23) and may play a role in future diagnostic

Table 1. C4CMMRD scoring system for a clinical suspicion of CMMRD in cancer patients (11)

Indication for CMMRD testing in cancer patients	≥3 points
Malignancies/premalignancies: one is mandatory; if more than one is present in the patient, add the points	
Carcinoma from the LS spectrum[a] at age <25 years	3 points
Multiple bowel adenomas at age <25 years and absence of APC/MUTYH mutation(s) or a single high-grade dysplasia adenoma at age <25 years	3 points
WHO grade III or IV glioma at age <25 years	2 points
NHL of T-cell lineage or sPNET at age <18 years	2 points
Any malignancy at age <18 years	1 point
Additional features: optional; if more than one of the following is present, add the points	
Clinical sign of NF1 and/or ≥2 hyperpigmented and/or hypopigmented skin alterations Ø >1 cm in the patient	2 points
Diagnosis of LS in a first-degree or second-degree relative	2 points
Carcinoma from LS spectrum[a] before the age of 60 in first-degree, second-degree, or third-degree relative	1 point
A sibling with carcinoma from the LS spectrum[a], high-grade glioma, sPNET, or NHL	2 points
A sibling with any type of childhood malignancy	1 point
Multiple pilomatricomas in the patient	2 points
One pilomatricoma in the patient	1 point
Agenesis of the corpus callosum or non-therapy–induced cavernoma in the patient	1 point
Consanguineous parents	1 point
Deficiency/reduced levels of IgG2/4 and/or IgA	1 point

Abbreviations: sPNET, supratentorial primitive neuroectodermal tumors; WHO, World Health Organization.
[a]Colorectal, endometrial, small bowel, ureter, renal pelvis, biliary tract, stomach, bladder carcinoma.

algorithms. This increased genomic instability and underlying DNA repair defect may lead to tumor responses to specific drugs, as discussed below.

Surveillance Protocol

The two major international groups, C4CMMRD and International BMMRD Consortium, have designed surveillance protocols based on available data on tumor frequency at specific ages. Specific surveillance of the gastrointestinal tract, the CNS, and hematopoietic system is performed from early childhood, whereas additional surveillance of the genitourinary tract is reserved to older ages (14, 17, 24).

Because the known spectrum of CMMRD cancers during childhood is increasing, suggestions for the addition of whole-body MRI (WBMRI) are being considered, as for Li–Fraumeni syndrome (25). Several reports demonstrate early detection and survival benefit, especially in brain tumors and gastrointestinal tumors by WBMRI, brain MRI, and endoscopy, respectively (16, 26). However, prospective screening data will be critical to fully evaluate the efficacy of these protocols.

Due to the above, modifications in the current surveillance protocols were discussed in the AACR Childhood Cancer Predisposition Workshop. Because CNS tumors are observed in CMMRD patients during infancy, appropriate imaging is recommended from diagnosis even in the first year of life. Expert opinion from neuroradiologists highlighted the lack of sensitivity and efficacy of ultrasonographic assessment of the CNS in infants with open fontanelle. Therefore, brain MRI is suggested to be implemented at diagnosis and then every 6 months and upon any clinical warning sign. Gastrointestinal surveillance with colonoscopy has been effective in identification of polyps amenable to polypectomy. Once polyps are identified, colonoscopy every 6 months is recommended. Due to reports of colonic polyps as early as 6 years of age, the recommendation is to start colonic surveillance at 6 years of age. Annual endoscopy is recommended until polyps are identified. Patients with polyps with high-grade dysplasia are at significant risk of carcinoma. Colectomy should be considered in patients with high-grade dysplasia or too many polyps to be excised endoscopically. Age of onset of small bowel polyps is later than for colonic adenoma in CMMRD. Small bowel polyps develop in the second decade of life. Upper endoscopy and video capsule endoscopy are recommended commencing at 8 years of age.

Although lymphoid and other hematologic malignancies are the third most common malignancies observed in children with CMMRD and can be observed in early childhood, lack of current effective tools limits the enthusiasm of the panel for recommendation. Nevertheless, both repeated complete blood count (CBC) and abdominal ultrasounds may be considered by the treating physician, and the panel recommends a frequency of every 6 months. Reports of young CMMRD patients with Wilms tumors and neuroblastoma may contribute to future suggestions of ultrasound in young age. Importantly, educating parents on early suspicion of both abdominal masses and general symptoms and signs of hematologic malignancies will prompt early interventions with these tests.

Perhaps the most important modification to the current protocols is the implementation of WBMRI as an important surveillance modality for CMMRD. This recommendation is based on several key observations. First is the emerging evidence of other "non-canonical" tumors in 10% to 15% of patients. These include bone and soft-tissue sarcomas, genitourinary cancer, and other cancers occurring more frequently from the latter part of the first decade of life. Second is the encouraging data from the implementation of WBMRI in patients with Li–Fraumeni syndrome (3, 25) and the high feasibility of the tool in children who do not require anesthesia, which give strong consideration for its use in CMMRD. The current suggestion is to implement WBMRI once a year at 6 year of age or when anesthesia is not needed. This method should not replace the need for ultrasound and brain MRI. This is since the latter is more sensitive for detection of CNS lesions and should continue at a frequency of 6 months.

Genitourinary cancers are observed in patients with CMMRD at a much younger age than in patients with LS. Although these cancers appear even in the second decade, considering the aggressiveness of LS guidelines for these cancers and the potential benefits from WBMRI and ultrasound, the recommendation remains to include the genitourinary-specific monitoring from age 20, as previously suggested by the European consortium (17). The overall surveillance protocol and times are displayed in Table 2.

Preventive colectomy is recommended on the basis of the degree of dysplasia and numbers of polyps observed during endoscopies. These are similar to other polyposis syndromes in childhood. These considerations are complicated by the high prevalence of upper gastrointestinal polyps and cancers.

Overall, examination of the efficacy and cost-effectiveness of surveillance protocols for CMMRD will require a prospective collaborative approach.

Therapeutic Considerations

Several issues exist with the management of CMMRD cancers. These include potential toxicity to the host, resistance to therapy, and application of novel targeted approaches.

Table 2. Surveillance protocol for patients with CMMRD

Examination	Start age	Frequency	Tumors	Comment
MRI brain	At diagnosis	Q 6 months	Brain tumors	Should not be replaced with WBMRI
WBMRI	6 years	Once a year	All tumors	Should not replace dedicated CNS imaging
CBC	1 year	Q 6 months	Leukemia	May be considered
Abdominal U/S	1 year	Q 6 months	Lymphoma	May be considered Can be alternated with WBMRI
Upper gastrointestinal endoscopy; VCE, ileocolonoscopy	4 to 6 years	Once a year	Gastrointestinal tumors	Upper and lower endoscopy, to increase once polyps are found
GYN exam, transvaginal U/S, pipelle curettage, urine cytology, dipstick	20 years	Once a year	Genitourinary cancers	As per LS guidelines

Abbreviations: GYN, gynecologic; Q, every; U/S, ultrasound; VCE, visual capsule endoscopy.

Whereas in other DNA damage repair syndromes, chemotherapy and radiotherapy can result in unacceptable toxicity, mismatch repair deficiency primarily affects replication. Therefore, normal tissue response to external genotoxic agents and radiotherapy is preserved. Currently, there is no information of extensive toxicity to these patients as a result of chemoradiation therapies.

In contrast, CMMRD tumor resistance to therapy is a known issue (1, 27, 28). Several common chemotherapeutic agents require adequate mismatch repair to exert their tumor damage. These include mercaptopurine and temozolomide, which are commonly used in hematopoietic and glioma treatment. Importantly, there is no obvious lack of efficacy of other therapeutic agents such as alkylating agents or anthracyclines. Treatment protocols that avoid those drugs should be considered for CMMRD patients with cancer.

Finally, the hypermutation phenotype, which is universal for CMMRD malignant cancers (29), offers opportunities for novel approaches to the treatment of these patients. Specifically, immune checkpoint inhibition has been shown to have significant effect in prolonging survival for two patients with CMMRD recurrent glioblastoma (29). Tumor sequencing commonly identifies mutations in targetable genes for available compounds and can potentially offer a precision medicine approach to these patients.

Chemoprevention may potentially be the most effective intervention for this highly penetrant cancer syndrome. Several compounds have been suggested including anti-inflammatory agents such as aspirin, which has been shown to reduce the risk of cancer in LS (30). Tumor-maturing agents such as retinoids and, more recently, checkpoint inhibitors can be considered as "tumor preventive tools." These promising therapies should be assessed through prospective trials.

Summary

Heterozygous and homozygous mutations in genes associated with the mismatch repair system share a common tumor phenotype and both diagnostic and therapeutic challenges. Although LS tumors during childhood are rare, they are more commonly uncovered with the availability of genomic analysis of childhood cancers and may require future considerations. CMMRD is highly penetrant, and most patients will be affected during childhood with an expanding range of cancers. Recent data gathered by international and national consortia allow for potential diagnostic screening tools and installation of early surveillance protocols that may improve survival for these patients. Emerging data of specific resistance to common therapeutic agents and potential benefit from novel therapies may result in uniquely designed protocols for the management of both primary and recurrent mismatch repair–deficient cancers. Prospective international surveillance and clinical therapeutic trials may help to improve the medical care for these individuals.

Disclosure of Potential Conflicts of Interest

S.E. Plon is a consultant/advisory board member for Baylor Genetics. No potential conflicts of interest were disclosed by the other authors.

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