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Constitutional Mismatch Repair Deficiency, the Most Aggressive Cancer Predisposition Syndrome : Clinical Presentation, Surveillance, and Management

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Constitutional mismatch repair deficiency (CMMRD) is a rare and highly aggressive cancer predisposition syndrome caused by biallelic germline mutations in mismatch repair genes. This condition is characterized by early-onset malignancies across multiple organ systems, including central nervous system tumors, hematological cancers, and gastrointestinal malignancies. CMMRD-associated tumors exhibit hypermutation and microsatellite instability, resulting in a high tumor mutation burden and rendering these malignancies responsive to immune checkpoint inhibitors (ICIs). ICIs targeting programmed cell death protein-1 and programmed cell death ligand 1 have demonstrated remarkable efficacy, particularly in hypermutated tumors, providing durable responses and improving survival outcomes. Advances in genetic and molecular diagnostics have enhanced the ability to identify CMMRD early, allowing for the implementation of comprehensive surveillance programs and improved management strategies. A multidisciplinary and individualized approach is essential for managing CMMRD patients. This review underscores the importance of early diagnosis, surveillance, and emerging therapeutic approaches to improve outcomes and quality of life for individuals and families affected by this devastating syndrome.

Key Words : Neoplastic syndromes · Hereditary · DNA mismatch repair · Brain neoplasms.

OVERVIEW OF CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD) SYNDROME

DNA polymerase enzymes facilitate DNA replication during the S-phase of the cell cycle, a process that, despite its remarkable efficiency, is inherently prone to errors[35]. During replication, two primary types of errors can occur : single-nucleotide variations, resulting from incorrect base incorporation, and insertions or deletions (indels), often caused by polymerase slippage. This slippage is particularly frequent in repetitive genomic segments known as microsatellites[8,31]. Replication fidelity, which is essential for maintaining genomic stability and preventing mutations that contribute to cancer and other genetic disorders, is governed by several mechanisms (Fig. 1). These in-

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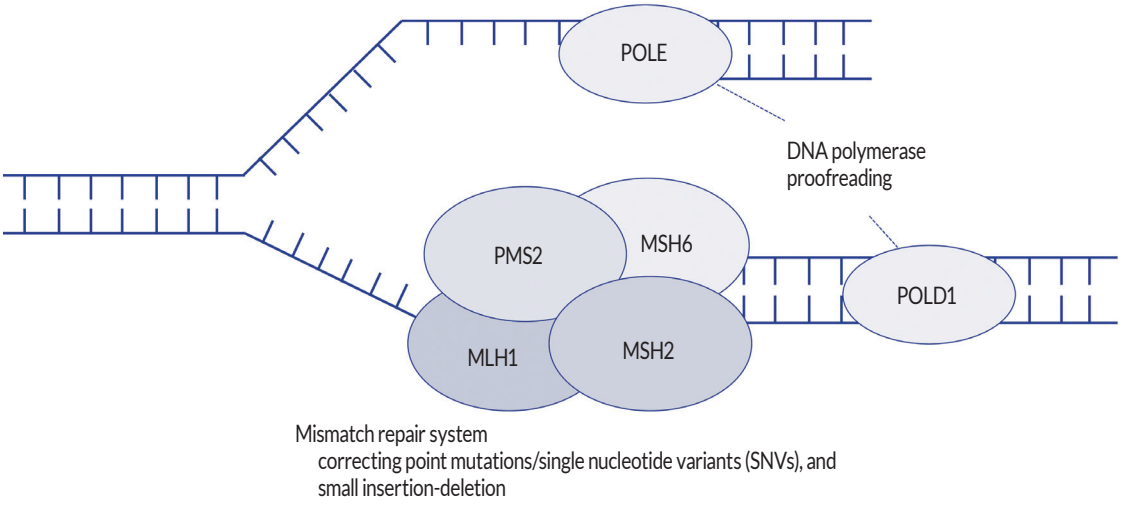

Fig. 1. Polymerase-proofreading and mismatch repair system. Replication fidelity is maintained through multiple mechanisms, including DNA polymerase selectivity, exonuclease proofreading activity encoded by the *POLD1* and *POLE* genes, and the mismatch repair (MMR) system. The MMR system plays a critical role in correcting mismatches and small insertion-deletion loops that evade polymerase proofreading, thereby maintaining genomic stability and preventing mutagenesis. POLE : DNA polymerase epsilon, catalytic subunit, PMS2 : postmeiotic segregation increased 2, MSH : mutS homolog, MLH1 : mutL homolog 1, POLD1 : DNA polymerase delta 1, catalytic subunit.

clude DNA polymerase selectivity, the exonuclease proofreading activity of polymerases encoded by the *POLD1* and *POLE* genes, and the mismatch repair (MMR) system[27].

CMMRD syndrome is a rare, autosomal recessive, highly penetrant cancer predisposition syndrome caused by biallelic germline mutations in one of the four MMR genes; *MLH1*, *MSH2*, *MSH6*, or *PMS2*[36,51]. The MMR system plays a critical role in maintaining genomic stability, particularly by correcting base-base mismatches and insertion-deletion loops during DNA replication, particularly in repetitive sequences known as microsatellites[29]. Loss of MMR function results in uncontrolled mutagenesis and genomic instability, characterized by a high tumor mutation burden (TMB) as well as microsatellite instability (MSI), the hallmark of MMR-deficient tumors. CMMRD cancers are classified as hypermutated (TMB ≥10 mutations per megabase), and in some cases, an additional polymerase proofreading defect leads to ultramutated tumors (TMB ≥100 mutations/MB) that evade conventional MSI tests but can be detected by more sensitive methods[1,23,42]. Hypermutated MMR-deficient tumors produce immunogenic neoantigens, rendering them responsive to immune checkpoint inhibitors (ICIs), which have shown clinical benefit in CMMRD patients with gastrointestinal (GI) and brain tumors[39]. However, MMR deficiency can also confer resistance to certain chemotherapies, notably temozolomide, which is commonly used to treat brain tumors[18].

The incidence of CMMRD is estimated at 1 in a million births in non-consanguineous populations, though the prevalence can be higher in populations with high rates of consanguinity and/or founder mutations[30,33]. Approximately 60% of CMMRD patients have a biallelic *PMS2* pathogenic variant, followed by over 20% with a biallelic *MSH6* pathogenic variant, and less than 20% with a biallelic pathogenic variant in either *MLH1* or *MSH2*[16,53]. Owing to lower penetrance of monoallelic *PMS2* and *MSH6* variants, CMMRD patients often lack a strong family history of Lynch syndrome-associated cancers. Lynch syndrome, an autosomal dominant cancer predisposition syndrome caused by heterozygous mutations in the MMR genes, typically manifests as MSI-high colorectal, endometrial, gastric, and ovarian cancers in mid to late adulthood. In contrast, patients with CMMRD have a very high risk for a broad spectrum of malignancies, including central nervous system (CNS), hematological, GI, and other cancer types, often leading to death within the first two or three decades of life[16,45]. CMMRD is also associated with non-malignant phenotypes, including café-au-lait spots resembling those seen in neurofibromatosis, and other developmental abnormalities[54].

Early identification of CMMRD is crucial for implementing effective surveillance strategies, determining appropriate treatment options, and providing genetic counseling for affected families[2,9]. Recent advances in molecular diagnostics have sig-

nificantly improved the diagnosis of CMMRD. However, the rarity of the condition, coupled with its variable clinical presentation and often delayed diagnosis, underscores the need for increased awareness. This review aims to provide a comprehensive overview of CMMRD syndrome, encompassing its clinical manifestations, diagnostic approaches, surveillance guidelines, and management strategies. By this review, we hope to facilitate a deeper understanding of this condition and highlight emerging insights that may improve outcomes for affected individuals.

CLINICAL PRESENTATION OF CMMRD

A distinctive feature of CMMRD is the early onset of malignancies, often affecting multiple organ systems (Table 1). Cancers associated with CMMRD typically arise at a median age of less than 10 years, with a cumulative cancer incidence exceeding 90% by the age of 18 years and approaching 100% by the age of 40 years[2,11,16]. With a significantly higher incidence of primary and subsequent cancers at young ages compared to other predisposition syndromes, and patients developing new tumors approximately every 2 years, CMMRD represents one of the most aggressive and highly penetrant human cancer predisposition syndromes[16,24]. The hallmark tumors in CMMRD include glioma or CNS embryonal tumors diagnosed before the age of 25 years, hematological cancer (excluding Hodgkin's lymphoma) diagnosed before the age of 18 years, and GI adenocarcinoma diagnosed before the age of 25 years[2]. The presence of over 10 adenomatous GI polyps before 18 years, after ruling out other polyposis conditions, is also a suggestive feature. In addition, Patients with CMMRD have been reported to develop cancers typically seen in adults, such as breast, prostate, pancreatic, and genitourinary cancers, which present at significantly earlier ages than in the general population.

CNS tumors are the most frequent malignancies, accounting for up to 51% of cases in the CMMRD cohort[5,15,16,30,52]. High-grade gliomas, including glioblastomas, are particularly common and often represent the initial manifestation of the disease. Other CNS tumors, such as medulloblastomas and ependymomas, are also observed, though less frequently. The median age at diagnosis for CNS tumors is 9.7 years (interquartile range [IQR], 6.9–12.9), with a cumulative incidence of 82% (95% confidence interval [CI], 76–88%) by age 20. The 10-year overall survival rate following a cancer diagnosis is significantly worse for CNS tumors at 39% (95% CI, 30–52%), making

Table 1. Tumor spectrum and incidence in CMMRD (n=339 tumors in 201 patients with CMMRD)[16]

	Value	Age at diagnosis (years)
Central nervous system	173 (51.0)	9.7 (6.9–12.9)
Glioblastoma	115 (66.0)	
Anaplastic astocytoma	25 (14.0)	
Medulloblastoma	18 (10.0)	
Low-grade glioma	5 (3.0)	
Embryonal tumor	7 (4.0)	
Ependymoma	1 (1.0)	
Diffuse midline glioma	1 (1.0)	
Anaplastic pleomrophic xanthoastrocytoma	1 (1.0)	
Gastrointestinal	75 (22.0)	20.1 (13.9–24.9)
Colorectal carcinoma	59 (79.0)	
Small bowel adenocarcinoma	12 (16.0)	
Gastric adenocarcinoma	3 (4.0)	
Pancreatic cancer	1 (1.0)	
Hematological	61 (18.0)	9.7 (5.3–13.4)
T-cell lymphoblastic lymphoma	26 (43.0)	
B-cell lymphoma	14 (23.0)	
Precursor B-ALL	9 (15.0)	
T-ALL	3 (5.0)	
Acute myeloid leukemia	4 (7.0)	
Mixed-phenotype acute leukemia	1 (2.0)	
Histiocytic sarcoma	1 (2.0)	
Non-Hodgkin lymphoma	1 (2.0)	
Hodgkin lymphoma	1 (2.0)	
Other cancers	30 (9.0)	14.9 (7.7–23.9)
Genitourinary	10 (33.0)	
Pilomatrical neoplasms	10 (33.0)	
Melanoma	3 (10.0)	
Breast cancer	2 (7.0)	
Retinoblastoma	1 (3.0)	
Neuroblastoma	1 (3.0)	
Osteochondroma	1 (3.0)	
Sebaceous carcinoma of the eyelid	1 (3.0)	
Sarcoma	1 (3.0)	

Values are presented as median (interquartile range) or number (%).
CMMRD : constitutional mismatch repair deficiency, ALL : acute lymphoblastic leukemia

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them a leading cause of mortality in CMMRD patients.

Hematologic malignancies, including T-cell lymphoblastic lymphoma, B-cell lymphoma, and leukemia (both lymphoid and myeloid), account for approximately 18% of reported cancers in CMMRD[5,15,16,30,52]. These malignancies typically occur during childhood or adolescence, with a median age at diagnosis of 9.7 years (IQR, 5.3–13.4) and a cumulative incidence of 33% (95% CI, 24–41%) by age 20. They are often aggressive in nature, with a 10-year overall survival rate following a cancer diagnosis of 67% (95% CI, 55–82%).

GI cancers, particularly colorectal adenocarcinomas, are another common feature of CMMRD[5,15,16,30,52]. Small intestinal adenocarcinomas and other GI tract tumors are also observed. The risk of GI cancers begins in early adolescence and continues to increase throughout life, with a median age at diagnosis of 20.1 years (IQR, 13.9–24.9) and a cumulative incidence of 42% (95% CI, 30–54%) by age 20. Multiple adenomatous polyps may be detectable as early as 6 years of age.

CMMRD syndrome is often associated with café-au-lait macules (CALM), neurofibromas, and axillary freckling, though only a minority of patients meet the National Institutes of Health diagnostic criteria for neurofibromatosis type 1 (NF1)[16,49,54]. CMMRD should also be considered in children suspected of sporadic NF1 but lacking *NF1* or *SPRED1* mutations, particularly if they exhibit features like Lynch syndrome-related cancers in the family, childhood cancers in siblings, or atypical skin lesions. CALMs in CMMRD typically present with irregular, jagged borders and variable pigmentation, distinguishing them from those in NF1, and hypochromic spots, which are absent in NF1, are observed in 16–29% of patients with CMMRD[16,30]. Other features include venous anomalies, pilomatrixomas, grey matter heterotopia, and systemic conditions such as lupus erythematosus and renal angiomyolipomas[3,7,40,41,47]. These manifestations, although not routinely evaluated at the time of diagnosis, can provide essential clues when a diagnosis is uncertain.

DIAGNOSIS OF CMMRD

CMMRD testing is indicated for all patients with clinical and genetic features suggestive of the syndrome[9,45,53]. Table 2 presents the revised Care for CMMRD consortium (C4CMMRD) indication criteria outlined in the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) guidelines. Testing should be considered in cancer patients scoring at least 3 points on the C4CMMRD scoring system, which incorporates malignancies, non-malignant manifestations, and family history. Testing is also recommended for all cancer patients under 18 years of age with a tumor exhibiting pediatric-high TMB, regardless of the presence of somatic *POLE* or *POLD1* pathogenic variants, and for those with tumors demonstrating loss of expression of one or more MMR proteins in neoplastic and non-neoplastic cells as identified by immunohistochemical (IHC) staining[21]. Furthermore, CMMRD testing should be performed in cancer patients under 18 years with a heterozygous (likely) pathogenic variant in one of the MMR genes detected by germline sequencing[28]. A family history assessment and physical examination are essential for patients meeting these indication criteria for CMMRD testing. Additionally, it may be considered for children suspected of having sporadic NF1 or Legius syndrome without cancer and no germline *NF1* or *SPRED1* pathogenic variant, particularly in patients with additional features outlined by the C4CMMRD guidelines[44].

Any testing strategy for CMMRD should aim to provide a definitive diagnosis by confirming or ruling out the syndrome while simultaneously identifying the causative variants in the relevant MMR gene. In patients with (pre-)malignancies, testing should include IHC staining of all four MMR proteins in tumor tissue to evaluate protein expression in both neoplastic and non-neoplastic cells, including tumor-infiltrating leukocytes and endothelial cells. Laboratories performing genetic testing for CMMRD should be equipped to offer transcript analysis of all four MMR genes (*PMS2*, *MSH6*, *MSH2*, and *MLH1*) and utilize assays that address diagnostic challenges posed by the high homology between *PMS2* and its pseudogene *PMS2CL*. Furthermore, for index patients with or without (pre-)malignancies, laboratories should have validated ancillary assays available to confirm or rule out CMMRD in cases where genetic testing yields inconclusive results, as described by the currently available ancillary assays for CMMRD listed in Table 3[6,17,20,22,25,43].

Germline testing of MMR genes (*PMS2, MSH6, MSH2*, and *MLH1*) is crucial for diagnosing CMMRD. The American College of Medical Genetics (ACMG) categorizes variants into five classifications : pathogenic (P), likely pathogenic (LP), variants of unknown significance (VUS), likely benign (LB), and benign (B)[37]. Only P/LP variants are considered actionable for clinical

Table 2. Revised Care for CMMRD consortium indication criteria for CMMRD testing in cancer patients

Category	Criteria	Point
C4CMMRD scoring points assigned to (pre-) malignancies in the patient (at least 1 point is mandatory)	Carcinoma of the Lynch syndrome (LS) spectrum* and/or a high-grade dysplastic adenoma of the digestive tract at age <25 years	3
	Multiple colorectal adenomas at age <25 years and no genetic diagnosis/explanation upon testing for polyposis syndromes	3
	T-cell lymphoblastic lymphoma at age <18 years	2
	WHO grade III or IV glioma at age <25 years	2
	Any other malignancy at age <18 years	1
C4CMMRD scoring points assigned to additional features in the patient (optional)	Clinical sign of neurofibromatosis type 1 (NF1) and/or ≥4 hyperpigmented and/or hypopigmented skin alterations with Ød >1 cm	2
	2 or 3 hyperpigmented and/or hypopigmented skin alterations with Ø >1 cm (do not count if two points are already given for "clinical sign of NF1 and/or ≥4 hyperpigmented and/or hypopigmented skin alterations with diameter >1 cm")	1
	Multiple pilomatrixomas	2
	One pilomatrixoma	1
	Agenesis of the corpus callosum	1
	Non-therapy-induced cavernoma†	1
	Multiple developmental venous anomalies (DVAs, also known as cerebral venous angiomas) in separate regions of the brain†	2
	Pediatric systemic lupus erythematosus†	1
	Deficiency/reduced levels of IgG2/4 and/or IgA	1
C4CMMRD scoring points assigned to additional features in the family (optional)	Consanguineous parents	1
	Diagnosis of LS in a first-degree or second-degree relative	2
	Carcinoma from LS spectrum* before the age of 60 years in a first-degree, second-degree, and/or third-degree relative	1
	A sibling with a (pre-)malignancy assigned two or three C4CMMRD scoring points	2
	A sibling with any type of childhood malignancy	1

CMMRD testing is indicated in a patient with cancer ≥ 3 points[9]. *Colorectal, endometrial, small bowel, urothelial, gastric, ovarian, and biliary tract cancer. †Included as a new feature in the revised C4CMMRD indication criteria within the European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) guidelines. CMMRD : constitutional mismatch repair deficiency, WHO : World Health Organization, C4CMMRD : European Consortium Care for CMMRD, IgG : immunoglobulin G, IgA : immunoglobulin A

decision-making, while VUS are not actionable due to insufficient evidence, and LB/B variants are assumed not to contribute to the phenotype. However, challenges arise in cases of non-definitive results, such as biallelic VUS or monoallelic VUS combined with a P/LP variant, as these may still impact protein function and lead to CMMRD[30,32,34]. For example, a study described a patient with homozygous *MSH6* VUS who exhibited clinical and ancillary findings consistent with CMMRD, highlighting the importance of functional assays in such cases[46]. In a study of 12 CMMRD families, 67% had biallelic P/LP variants, 17% had biallelic VUS, 8% had monoallelic pathogenic variants, and 8% had no variants detected, while similar findings were observed in the C4CMMRD consortium study of brain tumor patients[4,22]. These results underscore the need for ancillary testing, such as immunohistochemistry or MSI analysis, to confirm the diagnosis when germline results are inconclusive. Germline testing, complemented by ancillary methods, is essential for accurate diagnosis and the careful interpretation of variant pathogenicity in suspected CMMRD cases. The diagnostic criteria for CMMRD are based on a combination of germline testing, ancillary testing, and clinical manifestations (Table 4)[2]. Seven criteria have been established by experts, with four providing strong evidence for a definitive diagnosis and three offering moderate evidence for a likely diagnosis, all of which warrant CMMRD surveillance.

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Table 3. Comprehensive overview of Ancillary tests available for CMMRD diagnosis

Test	Description	Advantages	Limitations
Immunohistochemistry of non-neoplastic tissue	Immunohistochemical staining of MMR proteins in non-cancerous tissue (e.g., skin or normal colon biopsy)	Widely available, low cost, high specificity (~100%) and sensitivity (>90%) in experienced labs	Interpretation can be subjective; obtaining normal tissue may be invasive; pathogenic missense variants may lead to false-positive and negative results
Germline microsatellite instability (MSI)	Analysis of "stutter" peaks in non-neoplastic tissue PCR products	Rapid results, routinely used in some European countries	Insensitive to *MSH6* deficiency; not widely available outside Europe; ~16% uninterpretable results
Ex vivo MSI (evMSI)	Combines tolerance to methylating agents and MSI analysis in lymphoblastoid cell lines	High sensitivity and specificity; concordant results strengthen interpretation	Requires ~120 days for cell immortalization and culture; limited clinical accessibility, especially in North America
In vitro repair assay	Quantifies MMR activity from patient-derived lymphoblastoid cell lines and identifies defective protein complexes	High specificity and sensitivity; identifies specific defective MMR complexes	Requires live cell cultures; limited scalability; not yet clinically approved
NGS-based MSI testing	Detects low MSI levels using next-generation sequencing from constitutional tissue	Highly sensitive and specific; cost-effective; scalable without requiring live cell cultures	Not yet widely commercially available; requires expertise in NGS analysis

CMMRD : constitutional mismatch repair deficiency, MMR : mismatch repair, PCR : polymerase chain reaction, *MSH6* : mutS homolog 6, NGS : next generation sequencing

Table 4. the recommended CMMRD diagnostic criteria from the international consensus working group[2)]

Criterion		Germline result	Positive Ancillary testing	Clinical phenotype
Definitive diagnosis (strong evidence of CMMRD)	1	Biallelic pathogenic variants (P/P)*, confirmed in trans‡	Not required unless unaffected >25 years, then one required†	Not required if under age 25 (if no malignancy over age 25, ancillary testing required)
	2	Biallelic P/LP or LP/LP* variants, confirmed in trans‡	One required† for hallmark CMMRD¶. Two required† for C4CMMRD criteria**.	Hallmark CMMRD cancer diagnosis¶ or C4CMMRD criteria of 3 points** (then two ancillary tests required)
	3	Heterozygous P or LP variant (±VUS* or likely benign variants)	One required†	Hallmark CMMRD cancer diagnosis¶
	4	No P or LP MMR variants (including VUS/VUS)††. Or no testing available (i.e., deceased proband).	Two required†	Hallmark CMMRD cancer diagnosis¶
Likely diagnosis (moderate evidence of CMMRD)	5	Biallelic P/LP* or LP/LP variants, confirmed in trans§	Not required	C4CMMRD criteria of 3 points**
	6	No P or LP MMR variants (including VUS/VUS)††. Or no testing available (i.e., deceased proband).	One required†	Hallmark CMMRD cancer diagnosis¶
	7‡‡	Heterozygous P or LP variant or no testing available (i.e., deceased proband)	Two required†	C4CMMRD criteria of 3 points**. Individuals aged <18 with NF1 features (i.e., no malignancy or polyposis history). Malignancy under 30.

*Biallelic-impacts same gene on both parental alleles (i.e., *PMS2*/*PMS2*); P, pathogenic (ACMG C5); LP, likely pathogenic (ACMG C4); VUS (ACMG C3). Multigene panel testing is recommended to investigate overlapping conditions. Consider phenotype of individual to rule out overlapping syndromes. All families should be assessed in a specialized center for diagnosis. †Ancillary testing is described in further detail in main text of rationale for criteria. Does not include tumor mutation burden and signature at this time. Functional testing should be published with proven high sensitivity and specificity performed in an accredited (e.g., CAP-inspected) laboratory authorized to give a clinically usable report. If discrepancy occurs among tests, multiple ancillary tests should be used to reach more conclusive decision. ‡In trans variants can be proven by testing parents, offspring or other relatives. If unavailable to confirm variants in trans, individual should fulfil criterion 3. §If unavailable to confirm variants in trans, individual should fulfil criterion 6. ¶Hallmark CMMRD cancer : glioma or CNS embryonal tumours <25 years, haematological cancer (excluding Hodgkin's lymphoma) <18 years, GI adenocarcinoma <25 years, or >10 adenomatous GI polyps <18 years (after ruling out polyposis conditions). **C4CMMRD criteria outlined in Table 2. ††Consanguinity further supports a diagnosis of CMMRD due to a homozygous MMR gene mutation that is unidentifiable. ‡‡Individuals with two positive ancillary tests for CMMRD in the absence of the described phenotype can be assessed on a case-by-case basis, but these are atypical CMMRD cases and additional assessment is required to determine surveillance. CMMRD : constitutional mismatch repair deficiency, C4CMMRD : European Consortium Care for CMMRD, MMR : mismatch repair, NF1 : neurofibromatosis type 1, ACMG : American College of Medical Genetics, CAP : College of American Pathologist, CNS : central nervous system, GI : gastrointestinal

GENETIC COUNSELING OF CMMRD

Genetic counseling for CMMRD should be provided by a multidisciplinary team including a medical geneticist, pediatric oncologist, and psychologist, ensuring that both medical and psychosocial aspects of the condition are addressed[9]. Parents of a child diagnosed with CMMRD should undergo genetic testing to confirm their carrier status and identify the specific pathogenic variants involved, thus enabling accurate risk assessment and informed family planning. Cascade genetic testing should be extended to all relatives in both parental branches to identify individuals at risk and facilitate early surveillance and prevention strategies. All siblings of a CMMRD patient, irrespective of age or clinical features, should be tested because of the early-onset nature of cancers associated with CMMRD. If CMMRD is not confirmed by identifying two pathogenic MMR variants but rather through ancillary tests, siblings should likewise receive these ancillary tests to exclude CMMRD. Reproductive counseling, including discussion of prenatal and preimplantation genetic testing, is essential for parents of reproductive age and couples in which both partners carry a pathogenic variant in the same MMR gene, or where consanguinity, founder mutations, or a significant family history exist. Children of Lynch syndrome carriers who exhibit clinical features suggestive of CMMRD should undergo testing to assess their risk.

Recent large-scale analyses of patients with CMMRD have revealed genotype-phenotype associations[16]. *MLH1* and *MSH2* mutations, most of which are homozygous missense mutations, are associated with more aggressive phenotypes, including early onset, higher penetrance, and poorer overall outcomes. Conversely, *PMS2* variants, generally associated with a milder phenotype, exhibited heterogeneity; frameshift or truncating variants are associated with earlier cancer onset, and worse survival than missense variants. Notably, even within the same gene mutation, variant type (truncating vs. missense) significantly impacts cancer onset and prognosis. Current guidelines do not offer tailored recommendations due to limited evidence on genotype-specific differences in screening and treatment. However, while surveillance and immunotherapy improve survival across all genotypes, their efficacy varies by affected genes and variants, emphasizing the need for personalized surveillance strategies based on both the specific MMR gene and variant type.

SURVEILLANCE PROGRAM OF CMMRD

CMMRD is associated with a significantly increased risk of developing multiple malignancies from a young age, emphasizing the importance of comprehensive surveillance. Table 5 summarizes the surveillance recommendations[9,13,14,19,45,50]. A key aspect of surveillance involves educating patients and their parents about the broad spectrum of CMMRD-associated tumors, which is critical for shared decision-making about participating in a surveillance program. They should be also informed the specific symptoms associated with main tumors,

Table 5. Surveillance recommendations for patients with CMMRD

Tumor type	Screening tool	Frequency
All tumors	- Clinical examination - Education on signs/symptoms - Whole-body MRI (WBMRI)	- Clinical exam : every 6 months from diagnosis - WBMRI : at diagnosis or when anesthesia no longer required; optional annual imaging thereafter
Brain tumors	- Brain MRI	Every 6 months from age 2–20, annually after age 20
Digestive tumors	- Colonoscopy (ileocolonoscopy) - Upper GI endoscopy - Video capsule endoscopy	Annually : from age of 6 for colonoscopy and from age 10 for upper GI and video capsule endoscopy
Leukemias	- Blood count	Every 6 months after age 1
Lymphomas	- Abdominal ultrasonography	Every 6 months (optional) after age 1
Gynecological	- Clinical exam & transvaginal ultrasound – Prophylactic hysterectomy	Annually from age 20, prophylactic surgery once family planning is completed
Urological	- Urine cytology & dipstick - Abdominopelvic ultrasound	Annually: from age 10 for cytology/dipstick From age 20 for abdominopelvic ultrasound

CMMRD : constitutional mismatch repair deficiency, MRI : magnetic resonance imaging, GI : gastrointestinal

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including dyspnea or superior vena cava syndrome for mediastinal lymphomas, signs of pancytopenia for leukemia, neurological deficits for brain tumors, and rectal bleeding for colorectal lesions.

Regular clinical examinations are recommended every 6 months for both children and adults. The cornerstone of the surveillance program is bran magnetic resonance imaging (MRI), which should begin at diagnosis or by age 2, continue every 6 months until age 20, and then at least annually thereafter. Colonoscopy is another essential component of surveillance, starting at age 6 and performed at least annually. Upper GI endoscopy, ensuring visualization of the entire duodenum and ampullary region, should be performed at least annually, beginning simultaneously with colonoscopy or at least by age 10. Video capsule endoscopy is recommended annually from the age of 10. Once polys are detected, the frequency of examination can increase to every 6 months. Ideally, these GI examinations should be conducted at centers with gastroenterologists who have experience in Lynch syndrome surveillance. Gynecological surveillance, including clinical examination and transvaginal ultrasonography, as well as abdominopelvic ultrasonography for gynecological and urinary tract tumor screening is recommended annually from age 20. Prophylactic hysterectomy can be discussed once family planning is complete.

Whole-body MRI is recommended at least once at diagnosis or when anesthesia is no longer necessary, to detect asymptomatic low-grade tumors or malformations. Annual whole-body MRI may also be considered as a surveillance option, although current evidence for its efficacy in CMMRD screening remains limited[14]. The roles of blood counts and abdominal ultrasounds in screening for hematologic malignancies and lymphomas are still under debated. Breast cancer screening for CMMRD patients generally follows the guidelines for the general population.

CLINICAL MANAGEMENT OF CMMRD

A multidisciplinary, individualized approach that accounts for the high risk of multiple malignancies should be emphasized in the management of CMMRD patients to optimize care, and enrollment in clinical trials is encouraged whenever possible[9]. In general, standard protocols for each tumor type are followed. For resectable high-grade gliomas, surgery remains the mainstay of treatment. Also, CMMRD associated low-grade gliomas should be considered to be resected whenever possible without excessive neurologic risks. Radiotherapy and hematopoietic stem cell transplantation are not contraindicated if indicated, and chemotherapy for lymphomas and leukemia should not differ from the standard treatment for sporadic cases[38]. Multiple colonic adenomas should be surgically managed in line with general practice for other polyposis syndromes.

Temozolomide is no longer recommended in CMMRD-associated high-grade glioma, given preclinical evidence that MMR defects are a major mechanism of temozolomide resistance and the observed hypermutated phenotype in recurrent glioblastomas after temozolomide treatment[18,48]. Immunotherapy using ICIs has emerged as a particularly promising treatment modality for CMMRD-related tumors. The defective MMR mechanism in these tumors leads to the accumulation of numerous neoantigens, making them highly immunogenic and responsive to ICIs. Programmed cell death protein 1 (PD-1) inhibitors (pembrolizumab, nivolumab) and programmed cell death ligand 1 (PD-L1) inhibitors (atezolizumab, durvalumab), which are widely used in the treatment of CMMRD-related tumors, enhance the immune response against tumors by blocking the inhibitory signaling pathways that prevent T-cells from attacking tumor cells[11]. Several studies have reported high response rates with these agents in CMMRD-related malignancies, including high-grade gliomas and advanced colorectal cancer[10,12,24]. These immune activation caused by ICI, at the same time, can incur immune-related adverse events (irAEs). A study of 75 pediatric patients with chemo-radiation refractory CMMRD high-grade glioma who were treated with combined ICI reported that 50% of patients underwent irAEs to interrupt ICI. Hepatitis (60%) and colitis (33%) were most common. Higher incidences of irAEs were evaluated in patients in CMMRD than Lynch syndrome[10]. Further studies are required due to the limited data on the long-term side effects of ICIs in pediatrics, including growth impairments and other endocrine abnormalities.

Unlike other DNA damage repair syndromes, CMMRD primarily affects DNA replication rather than the repair of damage induced by external genotoxic agents. Consequently, in cases of CMMRD, the response of normal tissues to chemotherapy and radiotherapy remains largely intact. As such, there is no evidence to support dose reduction of standard chemotherapy

or radiotherapy regimens in these patients, as they do not exhibit the excessive treatment-related toxicity seen in other DNA repair disorders[11]. Interestingly, a study of chemo-radiation refractory CMMRD high-grade gliomas, which was previously referred to, reported patients who received ICI with radiotherapy had better survival outcomes, even after prior radiation exposure[10]. However, a larger clinical study should be performed to confirm these findings about radiation effects on patients with CMMRD patients.

For malignancies in the Lynch syndrome spectrum (e.g., colorectal cancers), ICIs are now the standard of care for metastatic or advanced disease, yielding significant clinical benefits[26]. Given the multiple and aggressive nature of CMMRD-associated tumors, immunotherapy is recommended as first-line therapy for large, unresectable, or metastatic lesions. Beyond these high-incidence tumor types, ICIs may also be considered for non-Lynch-related malignancies in CMMRD patients[9]. For tumors that have only a limited chance of cure or are poorly responsive to standard therapies, ICIs may be used after interdisciplinary discussions, although evidence regarding specific indications and optimal treatment timing remains limited.

CONCLUSION

CMMRD is a rare, but highly aggressive cancer predisposition syndrome characterized by early-onset malignancies in multiple organ systems. Advances in genetic and molecular diagnostics have significantly improved the identification and management of this condition. Comprehensive surveillance programs, including brain MRI and GI endoscopy, are crucial for early detection and management of tumors, while genetic counseling plays a pivotal role in supporting affected families and guiding their decisions.

Recent studies on ICIs have revolutionized the therapeutic landscape for CMMRD-associated malignancies. ICIs have demonstrated remarkable efficacy, particularly in hypermutated and immunogenic tumors, providing durable responses and significantly improving outcomes for many patients. However, several challenges remain, including treatment resistance, the complexity of managing synchronous and metachronous tumors, and optimizing care across a broad spectrum of cancers. Multidisciplinary, individualized approaches to care, combined with ongoing research and clinical trials, are essential to advancing the management of this devastating syndrome and alleviating the burden of CMMRD on patients and their families.

AUTHORS' DECLARATION

Conflicts of interest

Sang-Dae Kim has been editorial board of JKNS since May 2017. He was not involved in the review process of this original article. No potential conflict of interest relevant to this article was reported.

Informed consent

This type of study does not require informed consent.

Author contributions

Conceptualization : EK, JKS, SDK; Data curation : EK; Formal analysis : EK, JKS, SDK; Methodology : EK, JKS; Project administration : EK; Visualization : EK; Writing - original draft : EK, JKS; Writing - review & editing : EK, JKS, SDK

Data sharing

None

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