Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome

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Received 3 September 2014; accepted 11 February 2015
Available online 13 April 2015

KEYWORDS
Lynch syndrome
Surveillance
Café-au-lait macules
Polyposis
Turcot’s syndrome
Colon cancer

Abstract
Lynch syndrome, the most common inherited colorectal cancer syndrome in adults, is an autosomal dominant condition caused by heterozygous germ-line mutations in DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2. Inheriting biallelic (homozygous) mutations in any of the MMR genes results in a different clinical syndrome termed biallelic mismatch repair deficiency (BMMR-D) that is characterised by gastrointestinal tumours, skin lesions, brain tumours and haematologic malignancies. This recently described and under-recognised syndrome can present with adenomatous polyps leading to early-onset small bowel and colorectal adenocarcinoma. An important clue in the family history that suggests underlying BMMR-D is consanguinity. Interestingly, pedigrees of BMMR-D patients typically show a paucity of Lynch syndrome cancers and most parents are unaffected. Therefore, a family history of cancers is often non-contributory. Detection of BMMR-D can lead to more appropriate genetic counselling and the implementation of targeted surveillance protocols to achieve earlier tumour detection that will allow surgical resection. This review describes an approach for diagnosis and management of these patients and their families.
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1. Introduction

Lynch syndrome is the most common inherited colorectal cancer syndrome in adults. It is an autosomal dominant condition caused by heterozygous germ-line mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2. However, inheriting biallelic (homozygous) mutations in any of the MMR genes results in a different clinical syndrome termed biallelic mismatch repair deficiency (BMMR-D). The more severe BMMR-D phenotype presents with cancer during childhood and is characterised by gastrointestinal tumours, brain tumours and haematologic malignancies [1]. Colorectal and small bowel adenomatous polyps are a phenotypic feature of BMMR-D. Children surviving the initial malignancy and adults presenting with BMMR-D can develop gastrointestinal malignancies most commonly, colorectal and small bowel cancers, which is the presenting tumour in up to two-thirds of patients with BMMR-D [2]. Individuals with BMMR-D have café-au-lait (CAL) macules and other features more typically associated with neurofibromatosis type 1 (NF-1).

BMMR-D is an under-recognised clinical syndrome that can present with advanced disease. In contrast to juvenile inflammatory polyps, which commonly present with painless rectal bleeding, adenomatous polyps are often asymptomatic [7]. Furthermore, the progression from adenoma to carcinoma can be rapid in BMMR-D. Consequently, patients with BMMR-D can present with intestinal cancer and metastatic disease before the onset of any relevant intestinal or systemic symptoms [8].

Many patients labelled as having Turcot syndrome were noted to have café-au-lait macules and then were reclassified as BMMR-D because they carry biallelic mutations in MMR genes [4]. Turcot syndrome was characterised by the joint occurrence of a brain tumour and multiple colorectal adenomas. Turcot syndrome was originally considered to be a phenotypic variant of either familial adenomatous polyposis (FAP) or Lynch syndrome, with medulloblastomas associated with the former and glioblastomas associated with the latter [3]. Other patients with multiple colonic adenomatous polyps, some with café-au-lait macules, but in the absence of brain tumours, were previously characterised as having FAP or attenuated FAP even though no APC gene mutation is identified [5,6]. It is now evident that all such patients should undergo genetic evaluation for the possible underlying diagnosis of BMMR-D.

In order to better define the clinical and genetic characteristics of BMMR-D, an international consortium has been formed to collect clinical data, obtain tumour tissue and provide genetic testing to increase current understanding of BMMR-D and, ultimately, improve patient outcomes. Specialists in internal medicine, pediatrics, clinical genetics, dermatology, gastroenterology and haematology/oncology are each in a position to recognise probable BMMR-D patients so that appropriate surveillance can be offered and families referred for genetic counselling.

Here we review data from published case series and the BMMR-D consortium over the last decade. Special emphasis is given to important clues for the treating physician who manages such individuals and families.

2. Clinical presentations

Café-au-lait skin macules are the most common feature reported in the majority of BMMR-D patients [1]. Health care providers should recognise characteristic features of café-au-lait macules observed in BMMR-D; within the hyper-pigmented macules there are frequently areas of hypopigmentation and the borders of the skin lesions in BMMR-D are more diffuse and irregular than in classic CAL (Fig. 1). Number of skin lesions is variable, ranging from only one or two focal areas to more diffuse areas of skin pigmentation. Of the 34 BMMR-D patients followed by the consortium, 97% have CAL from early childhood.

Due to these dermatologic features, some children with BMMR-D are misdiagnosed as having NF-1 and are subsequently followed with this presumed diagnosis by either dermatologists, geneticists, paediatricians or internists. Although other features of NF-1, such as axillary freckling, Lisch nodules and plexiform neurofibromas, are also reported in BMMR-D, only a small subset of these meet established NF-1 diagnostic criteria [8]. Moreover, documented germ-line NF1 mutations are unusual. We performed exome sequencing of 17 BMMR-D patients and none were identified to have germline NF-1 mutations including two patients who fulfilled clinical criteria. Individuals mis-classified as NF-1 will inappropriately undergo NF-1 surveillance protocols, and, more importantly, early detection of the malignant tumours occurring in BMMR-D may be missed.

3. Family history

An important clue in the family history that suggest underlying BMMR-D is parental consanguinity, which is present in more than half of BMMR-D families [1,2]. BMMR-D is more common in families originating from south Asia where consanguinity is common. Pedigrees of BMMR-D patients typically show a paucity of Lynch syndrome cancers and most parents are unaffected. Out of 20 families followed by the consortium, none of the parents had a history of or developed a Lynch related tumour during surveillance. Therefore, as the family history of cancers is often non-contributory, a high index of suspicion is required. Indications to advance to genetic testing for BMMR-D are
D include a child from a consanguineous family presenting with a malignant brain tumour, haematological malignancy or early-onset gastrointestinal (GI) cancer. Adults can present with uterine or GI cancer and café-au-lait macules without any family history suggestive of a familial predisposition syndrome. Less specific but important is evidence of café-au-lait macules in a highly consanguineous family even without a malignancy.

4. Characterisation of the gastrointestinal phenotype

The phenotypic spectrum of BMMR-D is wide [2]. Adenomatous polyps have been identified in both the small intestine and large bowel of BMMR-D patients. The number of polyps is extremely variable ranging from less than five to 50. Gastric polyps have been described [2,9]. Both duodenal and jejunal carcinomas also can occur [6,8,10]. These observations highlight the need for comprehensive GI tract surveillance, including both upper and lower endoscopies, and possibly capsule endoscopy, in patients with BMMR-D [11].

The Colorectal cancer is the initial cancer diagnosed in up to two-thirds of patients with BMMR-D [2,6]; 40% with a colorectal cancer alone. Among those patients presenting with either rectal or colon cancer, the mean age at first diagnosis was just 16.4 years (range 5–28 years) with more than half classified as paediatric-onset colorectal cancer [2].

Site-specific locations of the colorectal cancer are not always specified in published case reports. In contrast to the right-sided colonic lesions characteristic of Lynch syndrome, preliminary findings on patients with BMMR-D suggest that left-sided colorectal cancers is more prevalent in this syndrome [6].

5. Brain tumours

Brain tumours are common cancers in BMMR-D [1] especially during the first two decades. Data gathered from the consortium suggest that malignant brain cancers are the most common presentation of the syndrome during childhood [12]. Some authors suggest that there is an association of brain tumours with PMS2/MSH6 mutations [1]. The spectrum of brain cancers in BMMR-D are most commonly high-grade gliomas followed by primitive neuroectodermal tumour and medulloblastoma. A central pathology review of a large series of these tumours revealed a high rate of atypical cells resembling pleomorphic xanthoastrocytoma, including tumours initially diagnosed as primitive neuroectodermal lesions [12]. Furthermore, several low-grade glial neoplastic lesions were diagnosed, suggesting a role for early detection in tumour surveillance and clinical management [12]. Of note, optic nerve gliomas and flair-associated subcortical intensities, which are common in NF-1 patients, are not observed in BMMR-D. This observation further highlights differences in the clinical spectrum between BMMR-D and NF-1.

6. Haematological malignancies

All major types of leukaemias and lymphomas have been reported in BMMR-D; however, there is a high prevalence of lymphoid malignancies, most commonly T-cell lymphomas [1]. This may be relevant since patients
with BMMR-D have immunoglobulin inefficient class-switch changes and can have sub-clinical immune deficiency [13]. Although less common, myeloid leukaemias are also reported in BMMR-D. Chronic myelomonocytic leukaemia, which is observed in children with NF-1, has not been reported in BMMR-D carriers.

7. Extra-intestinal Lynch-associated tumours

Eight patients with uterine cancer have been reported in BMMR-D. These patients ranged in age between 23 and 35 years [1,14–16]. To date, three patients (10–21 years of age) have been diagnosed with ureteric, renal pelvis, and bladder cancer respectively [6,10]. A number of these patients presented with a first malignancy in adulthood, consistent with a milder BMMR-D phenotype. Clinicians caring for patients with uterine and specific urologic malignancies must closely evaluate patients for café-au-lait macules as diagnosing BMMR-D would allow implementation of surveillance.

8. Emerging phenotypes

As BMMR-D becomes better recognised and more patients are genotyped, systematic data collection will allow for a more comprehensive understanding of the cancer spectrum, as well as genotype:phenotype relationships. Survival of the brain with magnetic resonance imaging reveal other central nervous system anomalies such as agenesis of the corpus callosum, the first congenital abnormality associated with BMMR-D and vascular anomalies [17,18]. Data gathered from the consortium and other case series expand the tumour spectrum of BMMR-D, to include tumours of embryonal tissue origin such as neuroblastoma, Wilms tumour and rhabdomyosarcoma [19].

Hepatic adenomas have been described in patients with BMMR-D. Sporadic hepatic adenomas are caused by somatic HNF1A mutations, and were identified in three unrelated children with BMMR-D [20]. Hamilton reported a three centimetre hepatic adenoma found at autopsy in one of the original Turcot siblings who had a history of brain tumour, colorectal cancer and café-au-lait macules [3]. These lesions are important to recognise, since hepatic adenomas may be misdiagnosed as metastatic disease resulting in inappropriate interventions, including surgery or chemotherapy [20].

Taken together, these additional clinical and oncological manifestations of BMMR-D highlight the need for international consortia to better define the phenotypic spectrum of BMMR-D.

9. Diagnostic evaluation

Tumours with MMR deficiency demonstrate a high frequency of somatic microsatellite instability (MSI). MSI is the hallmark of MMR-deficient colon cancer and serves as a screening tool for diagnosing Lynch syndrome [21]. In contrast to Lynch syndrome, the role of tumour microsatellite instability (MSI) in screening for BMMR-D remains controversial [22,23]. Data gathered from the consortium on more than 31 tumours reveal stable microsatellite in the vast majority of brain tumours and haematological malignancies from BMMR-D patients [12]. This is in agreement with previous reports [22–24]. Patients with multiple cancers – such as colon carcinoma, lymphoma and brain tumours – exhibit a different MSI genotype in different tumour tissues [12]. Since different MSI genotypes are observed in different tumours from patients affected by multiple cancers, MSI status may be tumour-specific and not mutation related. Gastrointestinal lesions reveal MSI stability in low-grade polyps and MSI-high in polyps with high-grade dysplasia and cancers. Therefore in contrast to Lynch syndrome, MSI should not be used as an initial screening test for BMMR-D.

The initial diagnostic screening for BMMR-D includes immunohistochemical (IHC) analysis for MLH1, MSH2, MSH6 and PMS2 protein expression in tumours. Additionally, loss of expression of the same protein is seen in normal cells contained within tumours. Consortium results on a large cohort of tumours (n = 33) confirm tumour immunohistochemistry as 100% sensitive and specific in diagnosing MMR deficiency of the corresponding gene [12]. By contrast, MSI was neither sensitive nor specific as a screening tool [12].

Although confirmation of a diagnosis of BMMR-D must be done through identification of a germ-line mutation in one of the MMR genes, immunohistochemistry on normal and tumour tissues can assist in both screening and direct genetic testing. We evaluated IHC in normal colonic mucosa and skin biopsies from five BMMR-D patients with mutations identified [12]. All normal tissues studied revealed negative IHC for the mutated gene while staining was positive for the other MMR genes. The high sensitivity and specificity of IHC, and its availability in clinical pathology laboratories supports the role of this assay as an initial functional diagnostic screening tool (Fig. 2).

10. Functional tests in challenging cases

In some kindred it can be difficult to identify the specific gene mutation despite evidence of a convincing BMMR-D phenotype and an absence of tumour protein staining. Skin biopsies can be evaluated in kindred in this setting. We studied skin biopsies from a kindred of six individuals with a proband suspected of having BMMR-D with possible PMS2 mutation based on negative tumour staining. IHC of these skin biopsies revealed positive staining in family members and no staining in
skin biopsies from the proband and one unaffected sister. Subsequent genetic testing confirmed that these two children harboured a homozygous \( PMS2 \) mutation (BMMR-D), while the rest of the kindred carried a heterozygote mutation [12]. Skin biopsy has the advantage of results being available in less than 48 h. Therefore IHC on skin biopsy can be useful when treatment decisions must be made before conclusive genetic testing is available. Data from the consortium supports testing of normal tissue biopsies, including colonic mucosa and skin biopsy as a highly specific and sensitive tool that can precede the final genetic diagnosis, and allows for earlier implementation of surveillance protocols [12]. For evaluation of normal tissue when genetic testing is contraindicated for religious or cultural reasons.

11. Tumour surveillance

Evidence-based gastrointestinal screening and surveillance recommendations in Lynch syndrome were developed based on prospective trials involving large series of patients. By contrast, there is limited experience and, therefore, no evidence-based screening guidelines for BMMR-D. There is also no literature evaluating long-term outcomes in patients with BMMR-D. Clinical surveillance strategies aimed at early detection of a diverse tumour spectrum has been successfully implemented for other cancer susceptibility syndromes, including Beckwith–Wiedemann syndrome [25], von Hippel–Lindau disease [26] and Li–Fraumeni syndrome [27].

In the setting of Lynch syndrome, colonoscopy screening reduces the risk of developing colorectal cancer, prevents cancer-associated deaths, and substantially decreases overall mortality [28]. Cancer risks appear to be striking in BMMR-D patients. In view of the high mortality in subjects with BMMR-D presenting with advanced disease, frequent surveillance is likely to prove important in enabling earlier detection of resectable cancers.

Over a decade ago we developed a feasible surveillance protocol focused on the prevention of gastrointestinal malignancies and brain tumours that includes: blood testing, imaging modalities and endoscopy [11] (Table 1). Colonoscopy, beginning at 6 years and upper

Table 1
Surveillance protocol for biallelic mismatch repair deficiency (BMMR-D) individuals.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Surveillance strategy</th>
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<tbody>
<tr>
<td>Children-colon</td>
<td>Colonoscopy annually(^a)</td>
</tr>
<tr>
<td>Upper GI tract and small bowel</td>
<td>EGD annually(^a)</td>
</tr>
<tr>
<td>Brain(^b)</td>
<td>Ultrasound at birth then MRI brain every 6 months</td>
</tr>
<tr>
<td>Adults(^d) uterus</td>
<td>Ultrasound annually</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Ultrasound annually</td>
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\(^a\) Beginning at 6 years of age.
\(^b\) EGD, esophagogastroduodenoscopy, beginning at 8 years of age.
\(^c\) Brain screening should commence at birth if diagnosed prenatally.
\(^d\) In adulthood continue gastrointestinal and brain surveillance.

Fig. 2. Algorithm for evaluation of patients with suspected biallelic mismatch repair deficiency (BMMR-D). * Once familial adenomatous polyposis and \( MYH \)-associated adenomatous polyposis is ruled out.
endoscopy and video capsule endoscopy commencing at 8 years, are performed annually. Brain MRI every 6 months starting at 3 years of age or at diagnosis [11]. Importantly, this protocol over the past 12 years has detected more than 45 tumours, which were amenable for complete surgical resection. Most of these resectable tumours did not require aggressive chemotherapy or radiation, modalities usually employed in advanced cancers. All tumours, both benign and malignant, identified by screening were asymptomatic. The most encouraging data from this surveillance protocol are a high survival rate for these patients. Of the patients undergoing surveillance one died.

Recently Vasen et al. has proposed similar surveillance guidelines with gastrointestinal screening beginning at 8 years of age [29]. As additional data are collected from patients around the world undergoing surveillance at many centres, more precise long-term outcomes will be determined. It will also be crucial to monitor psychosocial implications for patients and their families participating in intensive surveillance protocols. Psychosocial supports for BMMR-D patients and their families also will be an exceedingly important component of the long-term management.

12. Genetic counselling

The genetic counsellor plays a key role in the management of families with BMMR-D. As in any clinical encounter, counsellors must be sensitive to the diverse cultural and religious beliefs held by families. There may be a cultural acceptance of consanguineous marriage and discussions of inheritance as a result of such a relationship must be handled with great care and considerable sensitivity. For cultural or religious reasons, some families may not be comfortable with genetic testing. Despite hesitation to proceed with genetic testing, these families can elect to undergo cancer surveillance.

Future reproductive decisions are important for parents of affected children and for patients in their reproductive years. Identification of biallelic MMR mutations may provide families options including, for example, pre-implantation genetic diagnosis or prenatal testing through chorionic villous sampling or amniocentesis. Parents can be presented with options of selective implantation of unaffected embryos, termination of pregnancy or introduction of cancer surveillance at the birth of the child.

13. Summary

BMMR-D is a newly recognised syndrome for which both phenotypic and genotypic data are still emerging. The presence of café-au-lait macules and other signs of NF-1 in a patient with BMMR-D related tumours, particularly in consanguineous kindred, must raise the suspicion of a possible underlying diagnosis of BMMR-D. Molecular and genetic tests aid in screening and diagnosis of this rare, yet clinically and genetically informative, syndrome. Detection of BMMR-D can lead to more appropriate genetic counselling and the implementation of targeted surveillance protocols to achieve earlier tumour detection that will allow surgical resection. Clinical research collaboration on an international scale, with prospective clinical and biological data collection, will advance current understanding of the biology, clinical course and benefits of a surveillance protocol. These findings should ultimately lead to better targeted therapies and improve clinical outcomes for affected patients.

Funding

The Zane Cohen Center for Digestive Diseases. BRAINchild Canada and Canadian Institute of Health Research.

Conflict of interest statement

None declared.

References


