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Review

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

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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 underling 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, paediatrics, 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 underling 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-