A New Type of Lynch Syndrome: Childhood Cancers and Café-au-Lait Spots

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Several of these articles have discussed Lynch syndrome (LS) and its general features, including increased colon and uterine cancer risk, amongst others. As you know, LS is a dominantly-inherited cancer syndrome, with only 1 copy of a mismatch repair gene mutation (MLH1,MSH2,MSH6,PMS2) needed to cause increased lifetime cancer risk (otherwise known as monoallelic mutation). In this month’s article, we will focus on a recessively-inherited form of LS, where an individual has 2 copies of a LS-related gene with a mutation (otherwise known as biallelic mutations).

Monoallelic mutations in MLH1 and PMS2 were reported in individuals with colorectal cancer and brain tumors at excessively young ages in 1995, with additional biochemical evidence that led researchers to believe an additional gene mutation was contributing to the phenotype. It was only in 2004 when the biallelic mutation was discovered in the affected individuals. These patients are characterized by development of childhood cancers, including hematological malignancies and/or brain tumors, which are not typical for LS. Some also have earlier-onset colorectal cancers when compared to monoallelic LS mutation carriers, and almost all show characteristics similar to those of neurofibromatosis I (NF1, mainly café-au-lait spots). It has been suggested that any child presenting with multiple café-au-lait spots and early-onset malignancy that is not clearly NF1 associated should be tested for mismatch repair gene mutations.

Unlike other DNA repair deficiency syndromes (i.e. Fanconi Anemia, etc.), growth parameters are usually within the normal range. Affected children typically have not required medical attention prior to onset of malignancy. This diagnosis can be missed, delayed, or mistaken for other conditions, particularly NF1. It can also be missed when the monoallelic mutation carriers may not manifest the pathognomonic LS cancers until after an affected biallelic carrier has.

A review by Wimmer and Etzler in 2008 examined the genetic, clinical and pathological findings per gene as documented in 78 patients from 46 families. The largest group (43 patients) carried biallelic PMS2 mutations, while 14 patients carried biallelic MLH1 mutations and 8 carried biallelic MSH2 and MSH6 mutations. Tumors documented could be classified into 4 groups: hematologic, brain, LS, and other (neuroblastoma, Wilms tumor, ovarian neuroectodermal tumor, sarcoma, etc.). The most prevalent brain tumors are astrocytomas (primarily glioblastomas), and 4 patients developed medulloblastoma. Interestingly, 5 patients developed supratentorial primitive neuroectodermal tumors (SPNET), all of whom were PMS2 biallelics. The most common hematological malignancies are non-Hodgkin lymphoma and acute lymphoblastoid leukemia, and acute myeloid leukemia was noted in 3 patients (one as a first malignancy).

Overall, hematological malignancies seem to arise in infancy or early childhood (~5.5 years), while brain tumors tend to arise in later childhood (~8 years). LS tumors, primarily colorectal cancer, usually arise in adolescents (~16 years). Colorectal cancer can be the second or third malignancy in patients that survived their first tumor. MLH1 and MSH2 biallelic mutation carriers tend to have an earlier age of malignancy onset (mean 3.5 years) in comparison with MSH6 or PMS2 biallelic mutation carriers (mean 9 years).
Hematologic tumor prevalence has been higher in patients with *MLH1* or *MSH2* biallelics, and the incidence of brain and LS-associated tumors has been higher in *MSH6* or *PMS2* biallelics. The likelihood of surviving the first tumor and to develop a different second (or third) cancer is higher in *MSH6* or *PMS2* biallelics. This trend follows monoallelic LS carriers, where those with *MLH1/MSH2* mutations tend to have a more severe and earlier presentation than *MSH6/PMS2* carriers.

As discussed in previous articles, microsatellite instability (MSI) in tumor tissue is a hallmark criterion of LS. In biallelic patients, various tumor tissues were analyzed for MSI. In all LS-related tumors in biallelic patients analyzed so far, MSI has been reported. MSI was also tested in eight of the brain tumors (7 glioblastomas and 1 oligodendroglioma), and only 3 displayed MSI. Immunohistochemical (IHC) testing on tumor tissues is another diagnostic exam for LS discussed in previous articles. IHC testing was also performed on tumor tissue from biallelics, all of which showed lack of protein expression (therefore, an abnormal test result, indicative of mismatch repair gene dysfunction). This leads us to believe that IHC would be the preferable test on tumor tissue in those where biallelic mutations are suspected.

There is evidence from in vitro data that monoallelic mismatch repair gene mutations may confer resistance to certain chemotherapeutics and may increase their mutagenic potential. Practically speaking, certain chemotherapy agents are not useful in treating LS-related tumors and can even cause increased risk of secondary cancers. This article suggests that avoidance of certain chemotherapeutics, such as O-methylating agents, may be considered when defining treatment options for patients with biallelic mutations.

To date, there is not a consensus statement regarding surveillance for known biallelic mutation carriers. These children have increased risk for a wide spectrum of malignancies, which makes delineating a surveillance program difficult. Research is ongoing in this respect to provide a pragmatic approach for screening affected individuals. This information is also useful for the relatives of affected individuals, as siblings would have a 25% risk for this condition. Given the known childhood onset of malignancies in this case, prenatal diagnosis and preimplantation genetic diagnosis (PGD) would be appropriate options to discuss with these families if they are interested.

The similar presentation in biallelics (and distinct difference in presentation from LS) has prompted some to call this ‘mismatch repair-deficiency syndrome’, ‘constitutional mismatch repair-deficiency syndrome’, or ‘Lynch syndrome 3’. Whatever its name, this newly defined syndrome is important to be aware of when evaluating patients with LS or children with café-au-lait spots and malignancies. As always, if you have any questions regarding this or evaluation of your patients, please contact my office at 817-838-4871.

References:

1. Wimmer and Etzler. Constitutional mismatch repair-deficiency syndrome: have we so far seen only the tip of an iceberg? Hum Genet 2008; 124:105-22.