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FAMILY MATTERS IN WALDENSTROM MACROGLOBULINEMIA

by Mary McMaster, MD

Dr. Mary McMaster received her medical degree from the Wake Forest University Bowman Gray School of Medicine, followed by training in internal medicine and medical oncology at Vanderbilt University Medical Center, where she began to study the genetics of lymphoma. Following postdoctoral training in cellular biology and genetics at the University of North Carolina, she joined the National Institutes of Health. She completed a residency in clinical medical genetics with the National Human Genome Research Institute before moving to the National Cancer Institute (NCI).

At NCI, Dr. McMaster has pursued her long-term interest in cancer genetics. She is especially interested in understanding the basis of susceptibility of certain rare cancers including Waldenström macroglobulinemia (WM) and related blood and lymph node cancers. In 2000 she established a national registry for familial WM, which continues actively to enroll patients and their families. She is active in research consortia related to lymphoid malignancies, and her research encompasses family, genetic, epidemiological, and population-based registry studies. She and her group have characterized the familial risk of WM, identified environmental exposures associated with both familial and non-familial WM, established IgM MGUS as an important component of the familial WM phenotype, and discovered new genetic determinants of susceptibility to WM.

INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare form of malignant lymphoma that arises from a type of immune cell called a B-cell. Only about five persons in one million are diagnosed with this disease each year in the US. WM was first described by Professor Jan Waldenström in 1944. It is very interesting, then, that the first family having more than one relative diagnosed with WM was described less than 20 years later, in 1962. Family studies have been informing our understanding of WM ever since. Families often provide the first clues about aspects of WM biology that have inspired important research about WM in the general population. Over the years we have learned not only about how WM behaves in families but also about susceptibility to WM overall.

IS FAMILY HISTORY A RISK FACTOR FOR WALDENSTRÖM MACROGLOBULINEMIA?

Following the description of the original family in 1962, more families were reported in the medical literature. These families usually included multiple relatives with WM, and some families included relatives who had other B-cell tumors. In addition, some families included relatives who had other conditions such as autoimmune diseases. Some natural questions arose. First, is the familial occurrence of WM a coincidence, or does a family history of it increase a person's risk to develop WM? Second, if family history of WM increases risk, does that risk include other B-cell cancers as well as WM? Third, are other diseases part of the familial WM spectrum? A series of studies has addressed these questions in large populations. Population-based registries in Scandinavia have been useful because they link information about cancer diagnoses, other medical conditions, and family relationships for the entire population. These

studies have shown that close relatives (parents, siblings, and children) of WM patients are at increased risk to develop WM or other B-cell cancers, including chronic lymphocytic leukemia, other non-Hodgkin lymphomas, and Hodgkin lymphoma. On the other hand, studies disagree about whether the risk for other forms of leukemia or multiple myeloma is increased in relatives of WM patients. Additional registry-based studies have shown that relatives of WM patients are more likely to be diagnosed with certain autoimmune diseases than relatives of patients without WM. Registry studies are records-based. Researchers have also used other types of study designs to answer these questions. One study directly asked both WM patients ("cases") and people without WM ("controls") about family history. This case-control study also found that WM patients were more likely to report a family history of hematologic (blood) cancers and certain autoimmune diseases than individuals without WM. Finally, when WM patients seen in a large referral hospital were asked about their family history, nearly 20% reported another family member with either WM or a related B-cell cancer. It is important to point out that all these studies have included predominantly white patients with Northern European ancestry. No similar studies have looked at other demographic groups.

HOW DOES IgM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (IgM MGUS) FIT INTO THE WM PICTURE?

The original WM family consisted of two brothers who developed WM. While studying the family, researchers discovered the brothers' mother had IgM monoclonal gammopathy (today termed "monoclonal gammopathy of undetermined significance" or "MGUS"). This was the first indication that IgM MGUS is part of the familial WM spectrum. After that initial finding, researchers began to screen apparently unaffected relatives for MGUS in other families. Several studies reported finding MGUS in otherwise healthy relatives. Whereas IgG MGUS is the most common form of MGUS in the general population, these relatives usually had IgM MGUS. To determine whether this observation was statistically significant and not a coincidence, researchers used the population-based registry studies described above. They found that relatives of WM patients are at significantly increased risk of developing MGUS compared to relatives of people without WM.

A new development began in 1966, when researchers reported a family where one patient had WM and two of his siblings had IgM MGUS. The family was followed over time, and eventually both siblings progressed to WM. This was the first clue that IgM MGUS might be a precursor to WM. Not long afterward, Dr. Robert Kyle confirmed this suggestion by showing that a proportion of all patients with IgM MGUS in his Minnesota study progressed to WM or related B-cell cancers. Further studies have shown that when IgM MGUS occurs in the general population, it progresses to WM at a rate of about 1-2% per year. There are three important points to remember about these results. First, most patients with IgM MGUS do not go on to develop a cancer. Second, these studies again were conducted largely in white Northern European populations, so we cannot generalize the findings globally. Third, we do not yet know whether the rate of progression is different for an IgM MGUS patient who has a family history of WM.

A WORD ABOUT RISK AND INTERPRETATION OF RISK RESEARCH

Interpreting risk-related data is challenging. Unfortunately, most risk data are presented as a "relative risk." In family history studies, this means the risk that person A with a family history of WM will develop WM, compared to the risk that person B without a family history will develop WM. This can be misleading. In contrast, "absolute risk" means the actual risk that a given person will develop WM during his or her lifetime. Clearly, absolute risk is a more meaningful indicator of individual risk. Absolute risk is influenced by the frequency of a condition in the general population. To relate this to cancer risk, consider how relative risk affects absolute risk for a common cancer (e.g., breast cancer) and a rare cancer such as WM. In the US, about 12% of women will develop breast cancer. Suppose a hypothetical risk factor is associated with a relative risk of 2 (twice as likely to develop cancer). For breast cancer, a relative risk of 2 raises this number to nearly 25%, or 1 in 4 women. In contrast, that same relative risk of 2 increases a person's absolute risk of developing WM next year from about 5 in 1,000,000 to 10 in 1,000,000. The actual calculation is a bit more complicated, but the concept is valid.

ARE THERE GENETIC RISK FACTORS FOR DEVELOPING WM?

The accumulated evidence suggests that there are genetic risk factors for developing WM. Pinpointing those factors has been difficult, however. Genetics could contribute to susceptibility to WM in two main ways. In one scenario, a rare change in a gene important for cell growth and survival could occur. Such a change (called a "variant") would be expected to lead to a high risk for WM and would be present in most or all patients who had an inherited susceptibility to WM. When large-scale genomic sequencing technologies became available, there was hope that it would be possible to discover such a rare "big-effect" gene variant. Instead, WM patients within families share many rare gene variants (as expected), but the same gene variants are not found in different families. This disappointing result caused researchers to change our thinking.

In the second scenario, WM susceptibility might be due to variants in the genome that are more common in the general population. Each common genomic variant would contribute only a small increase in risk ("small-effect") in this scenario. A person would need to have several such variants or a combination of genomic variants and specific environmental exposures to develop WM. To search for small-effect, common variants, researchers use a technique to analyze thousands of known common variants to see whether there are differences between WM patients and persons without WM ("controls"). Recently, two regions of the genome were found to be associated with risk for WM. These regions contained common "small-effect" variants that were much more likely to occur in WM patients than in controls. One region is near several genes that are known to be important in B-cell development and function. Laboratory studies showed that the variant influences cells' ability to grow and divide and affects the function of nearby genes. Importantly, although these regions were discovered in a group that contained many familial WM patients, they were also associated with risk for WM in nonfamilial patients.

WHAT DO THESE RESULTS MEAN FOR ME AND MY FAMILY?

Over the years, I have found patients, families, and caregivers are interested in several questions:

1. Can WM run in families? The answer is clearly yes. We now have over 50 years of data in both family and population studies supporting this conclusion. However, because familial WM is an uncommon feature of a rare disease, most WM patients will have no other family members with WM or another B-cell cancer.
2. What is my family member's risk to develop WM now that I have been diagnosed? We know that the close relatives of a WM patient are at increased risk to develop WM or another B-cell cancer at some point in their lifetime. We do not know exactly by how much this risk is increased, but the available data suggest that the absolute risk (see discussion of risk, above) for any given individual with a family history of WM is small. We also know that risk increases with age—even with a family history, it is rare for a person to be diagnosed before age 40 and extremely rare for a person to be diagnosed before age 30.
3. Can or should my family have a genetic test for WM? As of 2018, the answer is no. The MYD88 gene variant that is characteristic of WM is present only in the WM tumor cells and has never been shown to be passed down from one generation to the next. To date, no single rare "big-effect" gene variant has been conclusively proven to cause WM or found in more than one family, so no gene test of this type is available clinically. The common "small-effect" variants recently discovered are not within genes but may regulate gene function. However, we do not yet understand exactly how they modulate risk or whether they can increase risk by themselves or need additional gene changes or environmental exposures to influence risk.
4. Should my family members be screened for monoclonal gammopathy of undetermined significance? This question is the most difficult, and the answer may be evolving over time. An important consideration is what one wants to accomplish by such testing. We know that MGUS can progress to WM. However, we also know progression can take many years and most MGUS patients will never progress. Moreover, in 2018 there is no treatment that can prevent progression to WM or cure WM once it develops. Meanwhile, the pace of drug discovery is accelerating, and we expect treatment to improve over time. Further, we know that MGUS, even when part of the familial spectrum, is age-dependent and is virtually never found in childhood, adolescence, or young adulthood. Thus, a family member who does not have MGUS at a young age may be falsely reassured, because they might develop it later in life. These lines of evidence favor an argument to not screen healthy family members for MGUS, except in a research setting. On the other hand, our understanding of MGUS is evolving also. By definition, MGUS has no associated symptoms. However, there is growing evidence that monoclonal gammopathy may have health consequences and in some patients is no longer "of undetermined significance." Therefore, in 2018, it is reasonable to consider screening for monoclonal gammopathy in adult family members over age 40 who desire screening. However, in general, screening is most appropriate in the research setting.

Clearly, family studies have played a pivotal role in our understanding of Waldenström macroglobulinemia. We owe a huge debt of gratitude to all the WM patients, familial and nonfamilial, who have contributed—and continue to contribute—to WM research!

This article was published in the IWMF *Torch*, volume 18.4 (October 2017) pages 1-2, 26-28.