“Familial Mediterranean Fever”

For

Professor Brutlag

BIO84

16 March 2011

Three months ago, I received the "results are ready" e-mail I had been eagerly anticipating since the moment I spit into that infamous test tube. As if I were going to see a fortune teller whose palm readings had a 100% confidence level, I entered my password with great apprehension. At first, I looked through "Traits." Yes, I have brown eyes. No, I do not smell asparagus when I urinate. Next, I took a tour of my ancestry; there were a few surprises, but nothing too challenging. And then, before opening up Pandora's Box of "Disease Risk," I clicked on "Carrier Status." As a female who is at an age where childbearing is not far from the picture, I was terrified of what the results would say. And there it was…Familial Mediterranean Fever. Familial Mediterranean Fever? I was stumped. I was uncertain of the implications this had on my life or the life of my hypothetical children. I was left wondering: What is it? Have I ever experienced it? How is this passed on? Should I be concerned? Throughout my research, I have found answers to my questions regarding Familial Mediterranean Fever's classical diagnosis and treatment, genetic tapestry, and the uses of genetics for future diagnosis and treatment of this disease.

Classical Diagnosis & Treatment

Familial Mediterranean Fever is a Mendelian autosomal recessive disease, also categorized as the most prevalent hereditary periodic fever syndrome ("Periodic Fever Syndrome"). An affected Familial Mediterranean Fever (FMF) patient may experience recurring attacks that include fever, peritonitis (inflammation of the abdomen, specifically the "thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs"), rashes, chest pain (pleuritis), arthritis attacks, and joint effusion (build up of joint fluid) (Kastner, "Peritonitis"). These attacks, which are experienced by phenotype 1 of FMF (Type 1 FMF), typically last one to three days, but can last as long as one week (*Merck Manuals Online Medical Library*).

Symptoms

95% of FMF patients will feel intense pain and bloating in the abdomen caused by peritonitis; doctors often note that the abdomen appears "board-like" and feels firm to the touch (*Merck Manuals Online Medical Library*, "Peritonitis"). A laparoscopy can reveal adhesions (scar tissue) caused by the recurring episodes of peritonitis; these adhesions can eventually lead to bowel obstruction, infertility in women, and a 1 in 3 chance of spontaneous abortion (Kastner,

Better Health Channel, *Merck Manuals Online Medical Library*). For some FMF patients, recurring peritonitis may be the only sign of FMF.

Another complication from FMF is pleuritis, an "inflammation of the lining of the lungs and chest" ("Pleurisy"). Pleuritis, which causes difficulty in breathing, is experienced by 40% of patients, mostly those who are homozygous for the M694V mutation (Shinawi). Additionally, 70% of patients experience "nondestructive acute monoarthritis" (Shinawi).

In extreme cases where the disease is unnoticed, misdiagnosed, or treated improperly, systemic amyloidosis (protein deposits) may form and eventually lead to a dialysis, kidney transplant, or even death (Dabestani). In Type 2 FMF, amyloidosis is "the first clinical manifestation of FMF in an otherwise asymptomatic individual," which can prove to be the most detrimental case of FMF (*NCBI Bookshelf*).

The window between attacks is not predictable, making life truly unstable for untreated FMF patients; however, this unpredictability is what differentiates FMF from other hereditary periodic fever syndromes, which share many symptomatic similarities. Additionally, blood tests administered during a periodic episode can reveal increased levels of specific markers, such as white blood cell count, that may reveal "an inflammatory condition in the body" (*Mayo Clinic*).

Symptoms of FMF are likely to start between the ages of five and fifteen, but could potentially start as early as infancy, or even appear later in life (*Merck Manuals Online Medical Library*). In fact, 90% of people experiencing FMF have been diagnosed before age twenty, and children under age ten make up 60% of FMF patients (Shinawi). FMF is most predominant in Sephardic Jews, Armenians, North Africans, Arabs, Italians, and Turks (*Mayo Clinic*, Kastner). 1 in 250 people to 1 in 1,000 people in this population will be affected by FMF, and 1 in 4 people will simply carry it ("Familial Mediterranean Fever," Shinawi).

Diagnosis & Treatment

Properly diagnosing FMF early-on by closely evaluating the types / patterns of symptoms, family health history, and ethnic background, can make this a completely tolerable disease. In cases

where the disease has already attacked the body due to improper diagnosis / treatment or Type 2 FMF, chronic renal failure can result from amyloid protein deposition in the kidneys (*Merck Manuals Online Medical Library*).

Currently, the only treatment for FMF is life-long use of the drug colchicine, which came out in 1972 (Shinawi). If started early-on, colchicine can both alleviate symptoms associated with recurrent attacks and prevent further complications, such as amyloidosis. This drug works best as a preventative medication, rather than as treatment during / after attacks (*Mayo Clinic*). Colchicine, taken orally each day, is an "anti-gout agent" which prevents swelling and other negative effects resulting from FMF ("Colchicine"). Colchicine completely prevents attacks in 60% of patients, partially prevents attacks in 33% of patients, and is not effective in 5% of patients ("Periodic Fever Syndrome"). Regardless of its potential lack of effectiveness, patients must continue to use colchicine as it prevents amyloidosis in 100% of patients. Colchicine can be taken by small children and even pregnant women. It has minimal side effects, including diarrhea and lactose intolerance, but its overall effectiveness outweighs the negative side effects of taking the medication.

Genetics of Familial Mediterranean Fever

In 1997, it was discovered that the culprit of FMF was a mutation in the MEFV gene on chromosome 16, specifically at location 16p13.3 ("Familial Mediterranean Fever," Medlej-Hashim). MEFV "carries the genetic code for a protein called pyrin, which is involved in regulating inflammation" (*Mayo Clinic*). This protein was named "pyrin," meaning "fever" by the International Familial Mediterranean Fever Consortium and named "marenostrin," Latin for "Mediterranean Sea," by the French Familial Mediterranean Fever Consortium (Shinawi, Kastner). Normally, pyrin behaves as a wall, blocking inflammation from occurring in the body; however, with the MEFV mutation, pyrin is not as effective and can no longer prevent inflammation (*Genetic Home Reference*). As a result of the ongoing inflammatory response, the aforementioned symptoms associated with Type 1 FMF (fever, peritonitis, joint inflammation, etc) all occur. "To date, more than forty missense mutations are known to exist. The diversity of mutations identified has provided insight into the variability of clinical presentation and disease progression" (Fisher).

Currently, clinical tests are predominantly used to identify FMF in children. However, genetic tests are being used simultaneously to identify the presence of the gene mutation. Because FMF is an autosomal recessive disorder, a child is at risk for carrying FMF if both parents have the recessive, mutated MEFV gene, although neither parent will necessarily have the disease. FMF can be a confirmed diagnosis with this genetic information (*Mayo Clinic*). It is less likely but still possible that FMF can come from only one gene copy, from only one affected parent ("pseudodominance"), or from no mutations at all (*Genetic Home Reference*). In this scenario, colchicine is used as an indicator to determine whether or not the child has FMF ("Periodic Fever Syndrome"). If the patient responds well to colchicine, and subsequently, attacks are minimized or eliminated, then a diagnosis of FMF can be confirmed. The patient would also continue to have an annual urinalysis to determine if protein is present, as this would be a sign of amyloidosis.

Additionally, genetic testing can be used to determine whether the patient carries the SAA1 gene. The SAA1 gene is known to elevate the risk of amyloidosis in FMF patients (*Genetic Home Reference*). Eventually, by decoding the gene mutations, a basic diagnostic blood test will effectively be able to determine FMF, determine "environmental triggers" leading to the recurrent attacks, and lead to alternative treatments ("Familial Mediterranean Fever"). Because individuals who are asymptomatic (Type 2 FMF) eventually face the biggest threat, amyloidosis, patients with relatives who have FMF should take preventative measures by getting genetically tested for mutations in MEFV. This can also be done as a prenatal diagnosis (*NCBI Bookshelf*). "In untreated individuals, amyloidosis can occur in 60% of individuals of Turkish heritage and in up to 75% of North African Jews" (*NCBI Bookshelf*). The presence of mutation p.Met694Val should also be determined, as FMF is especially dangerous to individuals with this mutation since amyloidosis is directly related to it.

Novel Diagnoses / Treatments Resulting from Genetic Information

Although colchicine is currently the most valuable drug for sufferers of FMF, 5-15% of patients who regularly take colchicine still experience bouts of symptoms and / or may not tolerate colchicine's side effects ("Rilonacept for Treatment of Familial Mediterranean Fever"). Therefore, The Cleveland Clinic began an ongoing study in December of 2007 to determine

whether Rilonacept could work to treat FMF; Rilonacept works by binding and neutralizing IL-1, "an important pro-inflammatory cytokine" ("Rilonacept"). The Cleveland Clinic's hypothesis is that "Rilonacept will decrease the number of acute FMF attacks and will be safe to use" ("Rilonacept"). The study is set to be completed in July 2011. The number one criteria for participants in this study is that subjects must be genetically tested in order to determine whether there is a definite diagnosis of FMF. This is just one of the many studies that uses genetics to aid in advancing FMF treatment.

Conclusion

"Once regarded simply as an inflammatory, autosomal recessive disease of unknown etiology, the spectrum of FMF has evolved as a complex genetic puzzle during the genomic era" (Fisher). The advancements in genetics that have enabled the ability to diagnose a disease that could easily be misdiagnosed as another hereditary periodic fever syndrome, has truly made life more tolerable for those affected by FMF. Further, with ancestry paintings provided by genetic testing, patients who may not have previously their own ethnicities can now trace their lineage and discover their ethnic link to FMF. Given my European and Cuban decent (some FMF cases have surfaced in Cubans), I am no longer surprised that I am susceptible to carrying a disease like FMF. Similarly, my genetic test results determined that I am a carrier of FMF, but that the disease will not likely manifest.

As we continue to make genetic discoveries, my hope is that doctors continue to use this information to treat diseases before they manifest, understand the code behind these diseases, and ultimately find ways to eliminate them all together. Echoing the words of Huang Dee from 2600 B.C., my hope is that doctors will embrace genetic information as a means towards becoming "superior doctors" who prevent diseases before the diseases even begin.

Works Cited

"Colchicine." *PubMed Health*. 1 February 2010. 15 March 2011. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000756>.

Dabestani, Noble, Child, Krivokapich and Schwabe. "Pericardial disease in Familial Mediterranean Fever: an echocardiographic study." *Chest*. 5 May 1982. 12 March 2011. <http://chestjournal.chestpubs.org/content/81/5/592.full.pdf>.

"Familial Mediterranean Fever." *Genetic Home Reference*. September 2008. 12 March 2011. <http://ghr.nlm.nih.gov/condition/familial-mediterranean-fever>.

"Familial Mediterranean Fever." *Mayo Clinic*. 22 July 2010. 12 March 2011. <http://www.mayoclinic.com/health/familial-mediterranean-fever/DS00766>.

"Familial Mediterranean Fever." *Merck Manuals Online Medical Library*. January 2009. 12 March 2011. <http://www.merckmanuals.com/professional/print/sec19/ch297/ch297b.html>.

"Familial Mediterranean Fever." *NCBI Bookshelf*. 12 March 2011. <http://www.ncbi.nlm.nih.gov/books/NBK22235>.

"Familial Mediterranean Fever." *NCBI Bookshelf*. 30 April 2009. 12 March 2011. <http://www.ncbi.nlm.nih.gov/books/NBK1227>.

Fisher, et al. "Familial Mediterranean Fever, Inflammation and Nephrotic Syndrome: Fibrillary Glomerulopathy and the M680I Missense Mutation." 11 August 2003. 12 March 2011. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC194618/>.

Kastner, Daniel. "Fevers, Genes, and Histories: Adventures in the Genomics of Inflammation." *The NIH Wednesday Afternoon Lecture Series*. 18 November 2009. 13 March 2011. <http://www.youtube.com/watch?v=Q37tFM7jEnM>.

Medlej-Hashim, Myrna, et al. "1 Novel MEFV transcripts in Familial Mediterranean Fever Patients and Controls." *BioMed Central Medical Genetics.* 9 June 2010. 12 March 2011. <http://www.biomedcentral.com/1471-2350/11/87>.

"Periodic Fever Syndrome." *Cleveland Clinic*. 12 March 2011. <http://my.clevelandclinic.org/disorders/periodic_fever_syndrome/rheumatology_overview.aspx>.

"Peritonitis." *Better Health Channel*. May 2009. 12 March 2011. <http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Peritonitis>.

"Peritonitis." *PubMed Health*. 10 June 2010. 15 March 2011. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002311>.

"Pleurisy." *PubMed Health*. 28 August 2009. 12 March 11. <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002347>.

"Rilonacept for Treatment of Familial Mediterranean Fever." *Clinicaltrials.gov*. 2 August 2010. 12 March 2011. <http://clinicaltrials.gov/ct2/show/NCT00582907?term=familial+mediterranean+fever&rank=1>.

Shinawi, Marwan, MD. "Hereditary Periodic Fever Syndromes" *eMedicine for WebMD*. 8 November 2010. 12 March 2011. <http://emedicine.medscape.com/article/952254-overview>.